Health Evidence Review Commission's Value-based Benefits Subcommittee

May 16, 2024

8:00 AM - 1:00 PM

Clackamas Community College
Wilsonville Training Center, Room
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

Agenda
Value-based Benefits Subcommittee (VbBS)
May 16, 2024

8:00 am–1:00pm

Hybrid meeting

Register in advance for this webinar

All agenda items are subject to change and times listed are approximate.

Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed.

	Time	Topic
I.	8:00 AM	**Call to Order, Roll Call, Approval of Minutes**
II	8:05 AM	**Previous Discussion Topics** **Vulvodynia** A surgery that removes a part of a female's genitals (vulva) for a condition (vulvodynia) that causes burning, pain and discomfort even when there is no sign of injury or infection
III.	8:30 AM	**Staff report** A. Conflict of interest declaration policy B. March 2024 listening session C. Legislative update D. Membership update
IV.	8:45 AM	**Straightforward/Consent Agenda** Consent table Straightforward guideline note changes Hemorrhoid coding changes **OHAP report consent vote** A report about dental care **1) Fluoride varnish frequency** A type of special teeth coating (fluoride varnish) that is brushed onto teeth to prevent tooth decay 2) **CDT code change recommendations** Dental treatment codes MRI in MS guideline clarification
V	9:00 AM	**New Codes**

	Time	Topic
		A. July HCPCS
VI	9:05 AM	**Previous Discussion Topics Continued** A. **CGM guideline clarifications** Proposed guideline updates for a device that measures blood sugar throughout the day
VII	9:15 AM	**New Discussion Topics** A. **Basivertebral nerve ablation** A treatment for pain caused by nerves in the back B. **Percutaneous tibial nerve stimulation** A treatment that stimulates a nerve to help with overactive bladder C. **Deep brain stimulation for essential tremor** A treatment that sends the brain electrical pulses to reduce symptoms for a condition that causes unintended shaky movements (tremors) happen D. **X-ray motional analysis for low back pain** A motion x-ray to see how the spine moves as a person bends or twists
	10:15 AM	**BREAK**
VIII	10:30 AM	**New Discussion Topics Continued** A. **Actigraphy** A device used to measure sleep patterns and movements **B. Next Generation sequencing of malignancy guideline edits for circulating tumor DNA testing** A test to check tumor cells for changes that may have caused cancer **C. Leadless pacemakers** Small devices (pacemaker), implanted directly into the heart (without wires, called leads), that help regulate the heartbeat when the heart is not beating regularly **D. Perirectal spacer for prostate cancer radiation therapy** A dissolvable spacer for prostate radiation therapy **E. Periurethral injection of bulking agents for urinary incontinence** A shot to control when urine is passed **F. Percutaneous ultrasound guided tenotomy** A shot to control when urine is passed
IX	12:00 PM	**2026 Biennial Review** **A. Neonatal circumcision** Removing the loose skin covering at the end of a boy's penis (foreskin)
X	12:55 PM	**Public comment on topics not on the agenda**
XI	1:00 PM	**Adjournment**

Value-based Benefits Subcommittee (VbBS) Summary

For Presentation to:
Health Evidence Review Commission on 3/14/2024

For specific coding recommendations and guideline wording, please see the text of the 3/14/24 VbBS minutes.

Recommended Code Movement (Changes to the 10/1/24 Prioritized List unless otherwise noted):

- Diagnosis and treatment codes for hemorrhoids were move to a covered line with a new guideline
- The procedure code for drug induced sleep endoscopy was added to the covered obstructive sleep apnea line and removed from a non-covered line with changes to the obstructive sleep apnea guideline
- The procedure code for coronary lithotripsy was added to a non-covered line
- The diagnosis code for benign positional vertigo was added to a covered line along with procedure codes for canalith repositioning and vestibular rehabilitation with a new guideline
- Several new HCPCS codes were added to the Prioritized List
- The procedure code for stereotactic body radiation therapy was added to the covered line for prostate cancer and the uncovered line for oligometastatic disease of unknown primary
- Several straightforward coding changes were made

Item Considered but No Recommendations for Changes Made:

- No coverage was added for self-management programs for chronic pain

Recommended Guideline Changes (Changes to the 10/1/24 Prioritized List unless otherwise noted):

- A new guideline was adopted allowing treatment of hemorrhoids with significant bleeding
- The diagnosis of sleep apnea guideline was modified to specific that drug induced sleep apnea is only covered for pre-surgical evaluation of children with high risk conditions
- A new guideline was adopted regarding when various procedures for benign paroxysmal positional vertigo must be covered
- The guideline regarding electronic tumor treatment fields was modified to conform with updated NCCN guidelines
- The guideline regarding stereotactic body radiation therapy was modified to require a multi-disciplinary team evaluation and to add coverage for prostate cancer and, through exceptions if medical appropriate, for oligometastatic disease of unknown primary tumors
- The guideline for newer interventions for osteoarthritis of the knee was modified to specify that genicular artery embolization is not a covered procedure.
- Several straightforward guideline note changes were made

Biennial review changes (effective 1/1/2026):

- The current unfunded complicated hernia line will be deleted

Minutes
Value-based Benefits Subcommittee (VbBS)

Online meeting
March 14,2024

Committee Members Present: Holly Jo Hodges, MD, VbBS Chair; Lucy Langer, MD; Cristina Pinzon, MSN, RN; Antoinette Awuakye, JD; Max Kaiser, MD; Mary Beth Engrav, MD; Adriane Irwin, PharmD; Sara Love, ND

Committee Members Absent: Brian Duty, MD, VbBS Vice-Chair; David Saenger, MD; Kathryn Schabel, MD

Staff Present: Jason Gingerich; Liz Walker, PhD, MPH; Ariel Smits, MD; Jessica Malstrom, Daphne Peck.

Also Attending: Lewis Backus, Jason Daniels (OHA); Valerie King; Marcus Bachhuber, Shauna Durbin, Firozeh Darabi (Center for Evidence-based Policy); Daniel Herzig; Rodrigo Pedraza; Derek Lam, MD; Jae Hong, MD; Richard Sohn, MD; Stephanie Asher; Rebecca Gale; Carissa Bishop; Laura Briggs; Renee Doan; Lavinia Goto; Angelina Guinto; Michelle Strausbaugh; Kristina Nelson; Scott Brown; Liz Brown; Paula Granger; Gabriel Rivera; Paul Terdal; Janeen McBride; Lillia Rogers; June Wilson; Siobhan Hess

Call to Order, Minutes Approval, Staff Report

The meeting was called to order at 8:00 am and roll was called. A quorum of members was present at the meeting. Minutes from the 1/18/2024 VbBS meeting were reviewed and approved with no modifications.

MOTION: To approve the minutes as presented. CARRIES 5-0 (Kaiser and Langer abstained, Engrav not present).

Jason Gingerich gave the staff report. A scope statement on surgical treatment of obstructive sleep apnea in adults has been posted for public comment. He also gave a legislative update on HB 4011, which would have expanded coverage for continuous glucose monitors beyond the expansions approved by HERC in 2023, which did not pass. Additionally, SB 1508, which has several requirements for HERC, including a requirement that HERC not rely on quality-adjusted life years (QALYs) in decision making, passed both chambers. It is awaiting the governor's signature. Staff will prepare an action plan and give a fuller description of its impacts if it is signed by the governor.

Straightforward/Consent Agenda

Discussion: There was no discussion about the consent agenda items.

Recommended Actions:

1) Add I97.89 (Other postprocedural complications and disorders of the circulatory system, not elsewhere classified) to line 419 LYMPHEDEMA
2) Modify GN 43 as shown in Appendix A
3) Add a new diagnostic guideline regarding lipoprotein(a) as shown in Appendix B
4) Modify GN 106 as shown in Appendix A
5) Delete the diagnostic guideline for CAD mammography as shown in Appendix A
6) Modify GN 35 as shown in Appendix A
7) Modify GN 7 as shown in Appendix A
8) Modify GN 36 as shown in Appendix A

MOTION: To approve the recommendations as presented in the consent agenda. CARRIES 8-0.

Hemorrhoids

Discussion: Smits presented the meeting materials.

Dr. Dan Herzig from OHSU Colorectal Surgery expressed understanding that HERC needs to limit coverage to the patients most in need of hemorrhoid care so as not to overwhelm the system. Office banding is safe in many cases, but there are cases where injection sclerotherapy or operative treatment is needed due to the anatomic location of the hemorrhoid or a patient not being able to stop anticoagulation therapy.

Dr. Rodrigo Pedraza, a community colorectal surgeon, agreed that lack of coverage for significant hemorrhoid bleeding is a significant problem. He agreed with the staff recommendations but suggested not covering CPT 45350 (hemorrhoid banding by sigmoidoscope) or 45398 (hemorrhoid banding by colonoscopy) for non-bleeding hemorrhoids as banding by anoscopy is much less expensive and works well. These procedures should be only be covered if performed during sigmoidoscopy or colonoscopy for other indications or for evaluation of a gastrointestinal bleed, and were appropriately placed on the gastrointestinal bleeding line.

Pinzon asked the experts if step therapy was appropriate. The experts agreed with step therapy. They try banding first, and if not effective, move on to operative treatment. Both types of procedures should be covered.

Coverage of painful hemorrhoids was then discussed. Pedraza stated that pain is a problematic indication as it is so subjective. Herzig stated that he felt the pain from hemorrhoids had a similar mechanism to pain from anal fissures, which are not covered. The experts only recommended coverage for significant bleeding and prolapse.

Hodges asked whether the guideline should define the degree of hemorrhoids. The experts did not think so. While these degrees are well defined in colorectal surgery, treatment should be based more on whether there is significant bleeding. Small hemorrhoids that bleed are just as important to treat as large bleeding hemorrhoids.

Engrav spoke in support of coverage. She felt the risk of overutilization or abuse is low. She noted that this is an equity issue, as other payers in the state all cover these treatments. PCPs are not even referring patients to surgeons as surgeons decline to see OHP patients due to lack of coverage.

Pedraza noted that some of the CPT codes may not be appropriate. HERC staff will consult with him and bring any suggested coding changes back to a future meeting as a consent agenda item.

The decision was to adopt coverage of significant bleeding hemorrhoids beginning 10/1/24. The subcommittee did not recommend covering hemorrhoids that are just painful. The only biennial review change will be to delete line 471, since all the relevant codes will appear on the other two hemorrhoid lines.

Recommended Actions:
Effective 10/1/24

1) Add ICD-10-CM K64.0 (First degree hemorrhoids), K64.1 (Second degree hemorrhoids), K64.2 (Third degree hemorrhoids), K64.3 (Fourth degree hemorrhoids) and K64.8 (Other hemorrhoids) to line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
2) Remove ICD-10-CM K64.5 (Perianal venous thrombosis) from line 471 THROMBOSED AND COMPLICATED HEMORRHOIDS and add to line 614 UNCOMPLICATED HEMORRHOIDS
3) Remove the following CPT codes from lines 471 and 614
    a. 45350 Banding of hemorrhoids using a flexible endoscope (sigmoidoscope)
    b. 45398 Banding of hemorrhoids using a flexible endoscope (colonoscope)
4) Add the following CPT codes to line 56

CPT Code	Code Description
45350	Banding of hemorrhoids using a flexible endoscope (sigmoidoscope)
45398	Banding of hemorrhoids using a flexible endoscope (colonoscope)
46221	Removal of external hemorrhoids by rubber banding
46250	Removal of multiple external hemorrhoids
46255	Removal of single external and internal hemorrhoid group
46257	Removal of single external and internal hemorrhoid group and chronic tear in anus
46258	Removal of single external and internal hemorrhoid group with removal of abnormal drainage tract in anus

46260	Removal of multiple hemorrhoid groups
46261	Removal of multiple hemorrhoid groups and chronic tear in anus
46262	Removal of multiple hemorrhoid groups with removal of abnormal drainage tract from anus
46320	Removal of external hemorrhoid with blood clot
46500	Injection of hemorrhoid
46930	Destruction of internal hemorrhoids using heat
46945	Tying of single internal hemorrhoid group
46946	Tying of multiple internal hemorrhoid groups
46947	Stapling of internal hemorrhoid
46948	Tying of arteries to multiple internal hemorrhoid groups

5) Change the line title of line 471 ~~THROMBOSED AND~~ COMPLICATED HEMORRHOIDS
6) Adopt a new guideline for lines 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE, 471 COMPLICATED HEMORRHOIDS, and 614 UNCOMPLICATED HEMORRHOIDS as shown in Appendix B
7) Remove the following CPT codes from lines 417 and line 614. If there is significant bleeding, these procedures are available on line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE using ICD-10-CM K62.5 (Hemorrhage of anus and rectum).

44391	Control of bleeding of large bowel using an endoscope inserted through surgically created opening from large bowel to skin
45317	Control of bleeding of lower large bowel using an endoscope
45320	Destruction of multiple polyps or growths of lower large bowel using an endoscope
45334	Control of bleeding of lower large bowel using a flexible endoscope
45335	Injection beneath lining of lower large bowel using a flexible endoscope
45381	Injection beneath lining of large bowel using a flexible endoscope
45382	Control of bleeding of upper large bowel using a flexible endoscope
46610	Removal of anal polyps or growths using an endoscope with electrical cautery
46611	Removal of single anal polyp or growth using an endoscope with mechanical snare
46612	Removal of multiple anal polyps or growths using an endoscope with electrical cautery or mechanical snare
46615	Destruction of anal polyp or growth using an endoscope

Effective 1/1/26

1) Delete line 471 and remove line reference from the new hemorrhoid guideline
2) Add ICD-10-CM K64.2 (Fourth degree hemorrhoids) to line 614

~~Line: 471~~
~~Condition: THROMBOSED AND COMPLICATED HEMORRHOIDS~~
~~Treatment: HEMORRHOIDECTOMY, INCISION~~
~~ICD-10: K64.3,K64.5~~
~~CPT: 44391,45317,45320,45334,45335,45350,45381,45382,45398,46083,46220,46221,46250-46262,46320,46500,46610-46615,46930,46945-46948,98966-98972,99051,99060,99070,99078,99184,99202-99239,99281-99285,99291-99404,99411-99449,99451,99452,99468-99472,99475-99480,99487-99491,99495-99498,99605-99607~~
~~HCPCS: C7900-C7902,G0019-G0024,G0068,G0071,G0088,G0090,G0140,G0146,G0248-G0250,G0316-G0318,G0323,G0406-G0408,G0425-G0427,G0463,G0466,G0467,G0490,G0508-G0511,G2012,G2211,G2212,G2214,G2251-G3003,S9563~~

MOTION: To approve the recommendations as amended. CARRIES 8-0.

DISE for sleep apnea

Discussion: Smits reviewed the staff summary. Dr. Derek Lam from OHSU ENT gave a presentation on DISE. He reviewed the literature in the staff summary and argued that these studies show that DISE provides better outcomes, though the studies were not powered to achieve statistical significance. He also noted flaws in the various study designs and selection bias in the participants that may make interpretation of their findings more difficult. Dr. Lam feels that DISE is the best technique to select the appropriate surgery for a patient. It is a quick and easy outpatient procedure.

Pinzon asked about the cost of DISE, and what percent of patients require it. Lam replied that the majority of his patients require DISE, as he is at a referral center that sees patients that have already failed other treatments such as CPAP. He did not have cost information. He noted that he is one of the few providers in the state doing DISE as he does the most complicated airway surgery cases. He does not think that there will be a sudden increase in utilization if DISE is covered.

Engrav stated that she felt the literature supports the use of DISE in children, and that the few adults that need this can be approved as exceptions. Kaiser pointed out that OHP doesn't cover any OSA surgeries for adults, so DISE would not be indicated in OHP adults. King noted that the evidence in this space appears to be of very low quality.

The group agreed that the evidence did not support the use of DISE in adults. There was discussion regarding the evidence in children. Irwin felt that children constitute a vulnerable population, and that she was compelled by the systematic review that found a 30% change in surgical plan in children after DISE. The other members were in agreement regarding adding DISE for use in children with underlying conditions before consideration for surgery for OSA.

Recommended Actions:

1) Remove CPT 42975 (Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic) from line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS and delete the entry from GN 173 as shown in Appendix A
    a. Advise HSD to add CPT 42975 to the DIAGNOSTIC PROCEDURES file
2) Modify Diagnostic Guideline D8 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 8-0.

Intravascular lithotripsy

Discussion: Smits reviewed the summary document.

Dr. Richard Sohn, an interventional cardiologist from Providence, testified. He stated that a third of cardiac catheterization cases involve coronary artery calcium, which makes stenting the artery difficult. The amount of difficulty in stenting depends on the location of the calcium in the artery. Without intravascular lithotripsy (IVL), circumferential calcium lesions cannot be stented and the patient would need a coronary artery bypass graft (CABG), which is a more invasive surgery. Other interventions exist, but they are all high risk. Some involve high pressures that can lead to life threatening tears in the artery walls. IVL breaks up the calcium with lower risks to the artery and works in cases where balloons and other interventions do not work. IVL is safer than many other types of interventions. Expert group algorithms include IVL. He expressed understanding that there is not much data behind IVL but states that he feels it is an important tool to have available. He also said that because IVL is safe and easy to use, there is some risk of overutilization. The billing code for IVL (CPT 92972) is an "add on code," and increases the cost of the coronary catheterization by 22-28%. In addition, there is a facility charge that is about $4,700 per device.

Engrav expressed concerns about the manufacturer (Shockwave) being a private equity firm and the data from CMS that Oregon providers are getting payments from Shockwave. Sohn and Hong stated that these payments are small amounts for food or beverage when the representatives visit the catheterization labs.

Dr. Jae Hong, an interventional cardiologist who practices in Medford, then gave a presentation. In her group, 4.6% of cases in 2023 used IVL and to her knowledge may not have been reimbursed due to lack of insurance coverage. She states that IVL is useful for bifurcation lesions, severe calcified vessels where further vessel prep is needed post rotational atherectomy, calcified ostial lesions with tortuous take over where coaxial catheter engagement is difficult, and acutely under expanded stent despite high pressure balloon dilation. Hong was asked about why this technology has not been studied in comparative trials with other technologies. She said that IVL is used for different kinds of lesions than other

technologies like high-pressure balloons. She said IVL is usually used as a last resort, after several other technologies have been used, which adds increased costs. She had some payment data from her group. He said that rotational atherectomy costs $5,144 while IVL costs about $6,000. There is also a cost for the additional catheterization lab time. Both Hong and Sohn noted that while the studies to date are small, it takes time to accumulate enough cases to publish a report. Hong noted that Medi-Cal has begun to cover IVL.

Pinzon expressed some support for IVL coverage, noting that the population requiring this procedure is relatively small, the procedure has a low risk of overutilization, and that comparison data will likely not be generated.

Engrav stated that she does not feel that the current literature supports use of IVL and that she is concerned about reports of company payments to hospitals for use of the device. Irwin expressed concern about lack of other payer coverage and recommended continuing non-coverage with a plan to revisit the evidence and payer policies on IVL in one year. Langer concurred that she would like more evidence on efficacy and on long term outcomes.

Sohn noted that his group will continued to use IVL even if not covered by OHP, though it will be at their own cost. The decision was made to continue non-coverage and readdress this topic in one year.

Recommended Actions:

1) Place CPT 92972 (Percutaneous transluminal coronary lithotripsy (List separately in addition to code for primary procedure)) on line 654
2) Add an entry to GN173 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 7-1 (Pinzon nay).

Benign paroxysmal vertigo

Discussion: Smits reviewed the summary document. Members expressed concern with the staff recommendation to have a patient have 4 months of symptoms prior to vestibular rehabilitation. This time period was shorted to 6 weeks, which members thought was realistic given current limits in access to PT/OT services.

Recommended Actions:

1) Add ICD-10-CM H81.1 family (Benign paroxysmal vertigo) to line 290 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
    a. Will pair with CPT 95992 (Repositioning exercises of head for treatment of dizziness, each day) and CPT 97112 (Therapy procedure to re-educate brain-to-nerve-to-muscle function, each 15 minutes)
2) Add HCPCS S9476 (Vestibular rehabilitation program, non-physician provider, per diem) to line 290

3) Add a new guideline to lines 290 and 505 as shown in Appendix B

MOTION: To approve the recommendations as amended. CARRIES 8-0.

April HCPCS codes

Discussion: Three HCPCS codes were reviewed and approved without discussion.

Recommended Actions:

1) Add HCPCS C9796 (Repair of enterocutaneous fistula small intestine or colon (excluding anorectal fistula) with plug (e.g., porcine small intestine submucosa [sis])) to line 29 REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE
2) Add HCPCS C9797 (Vascular embolization or occlusion procedure with use of a pressure-generating catheter (e.g., one-way valve, intermittently occluding), inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction) to lines 312 CANCER OF LIVER and 401 UTERINE LEIOMYOMA
3) Add HCPCS S4988 (Penile contracture device, manual, greater than 3 lbs traction force) to line 650 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

MOTION: To approve the recommendations as presented. CARRIES 8-0.

Fluoride varnish frequency

Discussion: Smits reviewed the summary and noted that no vote can be taken on this topic today as it was not included on the public notice for the meeting. All VBBS members were in support of the OHAP/staff recommended changes.

Recommended Actions:

1) This item will be brought back to the May VBBS meeting for formal voting as a consent agenda item

CDT code review

Discussion: Smits reviewed the summary, and noted that no vote can be taken on this topic today as it was not included on the public notice for the meeting. All VBBS members were in support of the OHAP/staff recommended changes.

Recommended Actions:

1) This item will be brought back to the May VBBS meeting for formal voting as a consent agenda item

Electronic tumor treatment fields

Discussion: Smits introduced the summary document. Langer noted that adding IDH mutant wording (as proposed in the staff recommendation) would require IDH mutation testing. Smits replied that this testing is already covered as diagnostic.

Recommended Actions:

1) Modify GN55 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 8-0.

Stereotactic body radiation therapy

Discussion: Smits introduced the summary document. There was discussion about whether to include the SBRT code on the non-covered line for poorly differentiated cancer. The medical directors in attendance felt that including it was not confusing and could be helpful in terms of the exceptions review process. The group agreed to keep the recommendation to add to the uncovered line. There was a question about why central nervous system (CNS) cancer was not included in the guideline; Smits noted that there are different billing codes for CNS cancers and other CNS indications. These codes are currently covered without guideline limitations.

Recommended Actions:

1) Add CPT 32701 (Delineation of thoracic targets for radiation therapy), CPT 77373 (Delivery of radiation therapy per dose to 1 or more lesions not to exceed 5 doses), and CPT 77435 (Stereotactic body diation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions) to the following lines:
    a. 326 CANCER OF PROSTATE GLAND
    b. 586 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS
2) Modify GN 142 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 8-0.

Genicular artery embolization

Discussion: There was minimal discussion on this topic. Kaiser noted that genicular nerve procedures are also not covered for knee osteoarthritis.

Recommended Actions:

1) Modify GN104 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 8-0.

Basivertebral nerve ablation

Discussion: Tabled until the May 2024 VBBS meeting

Multisector interventions report: Self-management programs for chronic pain

Discussion: Bachhuber presented the report developed by the Evidence-based Guidelines Subcommittee (EbGS). Smits reported that the subcommittee recommended no changes to the Prioritized List. There was discussion regarding general disappointment that the evidence in this area was so poor.

Recommended Actions:

1) Do not add self-management program procedure codes to any additional lines on the Prioritized List

MOTION: To approve the recommendations as presented. CARRIES 8-0.

Public Comment

No additional public comment was received.

Issues for next meeting

- Basivertebral nerve ablation
- Voting on the OHAP recommendations as a consent agenda item

Next meeting

May 16, 2024, Hybrid meeting

Adjournment

The meeting adjourned at 12:55 PM.

Appendix A
Revised Guideline Notes

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA)

For adults over the age of 18 years:

A) For patients with clinical signs and symptoms consistent with obstructive sleep apnea (OSA), a home sleep study is the first-line diagnostic test for most patients, when available.
   1) For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type I-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line.

B) Polysomnography in a sleep lab is indicated as a first-line test for patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to a neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia.

C) If a patient has had an inconclusive (or negative) home sleep apnea test and a clinical suspicion for OSA remains, then attended polysomnography is included on this line. Split night diagnostic protocols are required when a diagnosis of OSA is confirmed in the first portion of the night.

D) Repeat sleep studies are covered up to twice a year when one of the following has occurred since the most recent test:
   1) recurrence of OSA symptoms
   2) weight change of more than 10% of body weight
   3) new or worsening health conditions related to OSA
   4) upper airway surgical procedures or initial treatment with oral appliances

For children age of 18 or younger:

Obstructive sleep apnea (OSA) must be diagnosed by

1) nocturnal polysomnography with an AHI >5 episodes/h or AHI >1 episodes/h with history and exam consistent with OSA, OR

2) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR

3) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR

4) consultation with a sleep medicine specialist.

B) Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

1) high-risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)

2) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing), children younger than three years of age

C) Drug-induced sleep endoscopy (CPT 42975) is only covered only when ALL of the following criteria are met:

1) The patient is under 21 years of age; AND
2) The patient has OSA diagnosed by polysomnography; AND
3) The patient is being evaluated for upper airway surgery for OSA; AND
4) The patient has at least one of the following:
   a) a high-risk condition including but not limited to trisomy 21 (Down's syndrome), craniofacial anomalies, hypotonia, or neurological disorder; OR
   b) a known physical airway anomaly.

Appendix A
Revised Guideline Notes

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

~~**DIAGNOSTIC GUIDELINE D15, COMPUTER-AIDED MAMMOGRAPHY**~~

~~Computer-aided mammography is not intended to be a covered service.~~

GUIDELINE NOTE 7, ERYTHROPOIESIS-STIMULATING AGENT (ESA) GUIDELINE

Lines 12,59,92,94,111-115,125,133,135,157,158,161,162,178,190,198,199,207,209,213,214,216, 228,233,236,237,256-260,269,274,284-286,292,293,311-313,326,336,393,394,398,416,432,552, 567,586

A) Indicated for anemia (Hgb < 10gm/dl or Hct < 30%) induced by cancer chemotherapy given within the previous 8 weeks or in the setting of myelodysplasia.
   1) Reassessment should be made after 8 weeks of treatment. If no response, treatment should be discontinued. If response is demonstrated, ESAs should be discontinued once the hemoglobin level reaches 10, unless a lower hemoglobin level is sufficient to avoid the need for red blood cell (RBC) transfusion.

B) Indicated for anemia (Hgb < 10gm/dl or HCT < 30%) associated with HIV/AIDS.
   1) An endogenous erythropoietin level < 500 IU/L is required for treatment, and patient may not be receiving zidovudine (AZT) > 4200 mg/week.
   2) Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl.

C) Indicated for anemia (Hgb < 10 gm/dl or HCT <30%) associated with chronic renal disease, with or without dialysis, in the absence of iron deficiency.
   1) Reassessment should be made after 12 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl. In those not on dialysis, the Hgb level should not exceed 10gm/dl.

GUIDELINE NOTE 35, SINUS SURGERY

Lines 285,463,499

Sinus surgery (other than adenoidectomy) is indicated when at least one of the following circumstances occur (A-G):

A) Recurrent acute rhinosinusitis, defined as 4 or more episodes of acute bacterial rhinosinusitis in one year without signs or symptoms of rhinosinusitis between episodes and have failed optimal medical management defined as nasal steroid therapy and nasal saline therapy, in patients who are compliant with oral antibiotics and/or oral corticosteroids for management of acute episodes of rhinosinusitis

OR

1) Chronic sinusitis defined as 12 weeks of continuous symptoms without improvement after appropriate medical therapy (defined as two or more courses of antibiotics with adequate doses AND a trial of 2 or more adequate doses of inhaled and/or oral steroids unless one or more of these therapies are contraindicated) and one or more ~~one~~ of the following (1-3):
   1) Findings of obstruction ~~of~~ or active infection on CT scan OR
   2) Symptomatic mucocele OR
   3) Negative CT scan but significant disease found on nasal endoscopy
   ~~AND~~
   ~~Failure of medical therapy defined as (1-2)~~
   ~~4) Two or more courses of antibiotics with adequate doses AND~~
   ~~5) Trial of inhaled and/or oral steroids (2 or more courses of adequate doses of one or both)~~

OR

B) Nasal polyposis causing or contributing to sinusitis

OR

C) Complications of sinusitis including subperiosteal or orbital abscess, Pott's puffy tumor, brain abscess or meningitis

OR

D) Invasive or allergic fungal sinusitis

OR

F) Tumor of nasal cavity or sinuses

OR

G) CSF rhinorrhea

Adenoidectomy (CPT 42830, 42835) is included on Line 463 only for treatment of children with chronic sinusitis who fail appropriate medical therapy.

GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA

Lines 42,47,365,544

Tonsillectomy/adenotonsillectomy is an appropriate treatment for patients with one of the following (either A, B or C):

A) Individuals with a history of recurrent throat infection (both 1 and 2):
   1) Throat infections must occur with a frequency of at least:
      i) Seven episodes in the past year; or
      ii) Five episodes per year for 2 years; or
      iii) Three episodes per year for 3 years;
      and
   ~~a)~~ 2) Documentation in the medical record for each episode of sore throat which includes at least one of the following:
      i) Temperature greater than 38.3 Celsius (100.9 Fahrenheit); or
      ii) Cervical adenopathy; or
      iii) Tonsillar exudates or erythema; or
      iv) Positive test for Group A Beta-hemolytic streptococcus (GABHS); OR

B) A history of two or more peritonsillar abscesses OR when general anesthesia is required for the surgical drainage of a peritonsillar abscess and tonsillectomy is performed at the time of the surgical drainage; ~~or,~~ OR
C) Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

ICD-10-CM J35.1 and J35.3 are included on Line 365 only for 1) unilateral tonsillar hypertrophy in adults and 2) unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy. Bilateral tonsillar hypertrophy and unilateral tonsillar hypertrophy in children without other symptoms suggestive of malignancy are included only on Line 544.

See Guideline Notes D8 and 27 for diagnosis and treatment of obstructive sleep apnea in children.

GUIDELINE NOTE 43, LYMPHEDEMA

Line 283, 419

Lymphedema treatments are included on this line when medically appropriate. These services are to be provided by a licensed practitioner who is

1) Certified by Lymphology Association of North America (LANA, http://www.clt-lana.org), OR
2) CLT-LANA eligible (graduates from a minimum 135-hour lymphedema program that meet the LANA eligibility requirements).

Services should be provided by a LANA certified therapist if available.

Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

ICD-10-CM I97.89 (Other postprocedural complications and disorders of the circulatory system, not elsewhere classified) is only included on line 419 for post-operative lymphedema.

It is the intent of the HERC that compression dressings/garments and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,622

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2022.
   1) https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations/
      a) ~~Treatment of falls prevention with exercise interventions is included on Line 292.~~
   2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.

B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   1) http://brightfutures.aap.org. Periodicity schedule available at https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf
      a) Bright Futures is the periodicity schedule for screening for EPSDT for the Oregon Health Plan.
   2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.

C) Health Resources and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines (revised January 2022). Available at https://www.hrsa.gov/womens-guidelines as of July 28, 2022.

D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: https://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf
   1) COVID-19 vaccines are intended to be included on this line even if the specific administration code(s) do not yet appear on the line when the vaccine has both 1) FDA approval or FDA emergency use authorization (EUA) and 2) ACIP recommendation.
   2) Other ACIP recommended vaccines not on the routine vaccine schedule are included on Line 3 when administered according to recommendations specified in the Morbidity and Mortality Weekly Review (MMWR) as required by federal law: https://www.cdc.gov/vaccines/hcp/acip-recs/index.html (retrieved 8/8/2023).

Colorectal cancer screening is included on Line 3 for average-risk adults aged 45 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
B) Flexible sigmoidoscopy every 5 years
C) Fecal immunochemical test (FIT) every year
D) Guaiac-based fecal occult blood test (gFOBT) every year

CT colonography (CPT 74263), FIT-DNA (CPT 81528) and mSEPT9 (HCPCS G0327) are included on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS.

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered after informed decision making between patients and clinicians which includes consideration of the patient's overall health, prior screening history, and preferences.

Supervised evidence-based exercise programs for fall prevention for persons aged 65 or older OR younger patients who are at increased risk of falls are included on Line 3 using CPT 98961 or 98962 or HCPCS S9451. HCPCS S9451 is only included on Line 3 for the provision of supervised exercise therapy for fall prevention. Programs should be culturally tailored/culturally appropriate when feasible.

Appendix A
Revised Guideline Notes

Note: CPT 96110 (Developmental screening (e.g., developmental milestone survey, speech and language delay screen), with scoring and documentation, per standardized instrument) can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 104, NEWER INTERVENTIONS FOR OSTEOARTHRITIS OF THE KNEE

Lines 429,461

The following treatments are not included on this line for osteoarthritis of the knee:

- Whole body vibration
- Glucosamine/chondroitin (alone, or in combination)
- Platelet rich plasma
- Viscosupplementation
- Transcutaneous electrical stimulation (TENS)
- Genicular artery embolization

CPT 20610 and 20611 are included on these lines only for interventions other than viscosupplementation for osteoarthritis of the knee.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 142, STEREOTACTIC BODY RADIATION THERAPY

Line 260,326,586

Stereotactic body radiation therapy (CPT 32701, 77373, 77435) is included on these lines ~~on Line 260 for early stage non-small cell lung cancer in medically inoperable patients.~~ only when

1) Evaluation includes multidisciplinary team analysis (e.g., tumor board) including a surgical specialist and radiation oncologist; AND
2) The patient has one of the following:
    a. Very low, low, and intermediate risk prostate cancer, as defined by NCCN based on stage, Gleason score, and PSA level; OR
    b. Non-Small Cell Lung Cancer (NSCLC) when:
        1. Stage I and Stage II (node negative), and
        2. Tumor is deemed to be unresectable, or patient is deemed too high risk, or the patient declines operative intervention; OR
    c. Small Cell Lung Cancer (SCLC) when:
        1. Stage I and Stage II (node negative) and
        2. Tumor is deemed to be unresectable, or patient is deemed too high risk, or the patient declines operative intervention; OR

d. Oligometastatic disease when each of the following conditions are met:
    i. Five or fewer total metastatic lesions (maximum 3 per organ), and
    ii. Controlled primary tumor.

GUIDELINE NOTE 155, ELECTRIC TUMOR TREATMENT FIELDS FOR GLIOBLASTOMA

Line 292

Electric tumor treatment fields (HCPCS E0766) are included on this line only when

A) Used for the initial treatment of either a
    a. supratentorial glioblastoma OR
    b. supratentorial IDH-mutant WHO grade 4 astrocytoma; AND
B) Used in combination with temozolomide and standard radiation therapy; AND
C) The patient is age 22 or older.

Electric tumor treatment fields are not included on this line for recurrent glioblastoma or astrocytoma or any other indication.

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 654

The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~42975~~	~~Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic~~	~~Insufficient evidence of effectiveness~~	~~November 2021~~
92972	Coronary intravascular lithotripsy	Insufficient evidence of effectiveness	March 2024

Appendix B
NEW GUIDELINE NOTES

DIAGNOSTIC GUIDELINES DX LIPOPROTEIN(A) TESTING
Repeat lipoprotein(a) testing (CPT 83695) is not medically necessary.

GUIDELINE NOTE XXX COMPLICATED HEMORRHOIDS
Lines 56,471,614
First through fourth degree hemorrhoids (ICD-10-CM K64.0, K64.1, K64.2, K64.3) are included on line 56 only when

A) The patient has not responded to conservative management, including topical medications and dietary management; AND
B) There is recurrent hemorrhoidal bleeding resulting in anemia (hemoglobin less than 10 g/dL or hemoglobin less than 11 g/dL if use of iron is documented).

Otherwise, first through fourth degree hemorrhoids are included on lines 417 or 614.

For first and second degree hemorrhoids only: treatment is limited to office-based procedures (for example, banding and sclerotherapy). Other surgical procedures are only included on line 56 for third and fourth degree hemorrhoids.

ICD-10-CM K64.8 (Other hemorrhoids) is only included on line 56 when representing strangulated hemorrhoids.

GUIDELINE NOTE XXX TREATMENT OF BENIGN PAROXYSMAL POSITIONING VERTIGO
Lines 290,505
Canalith repositioning maneuvers (CPT 95992) is included on line 290 for treatment of benign paroxysmal positioning vertigo (BPPV) for up to 2 visits per year for education by a physical therapist or an otolaryngologist, with no requirement for conservative therapy or a waiting period prior to these visits.

Vestibular rehabilitation (CPT 97112 and HCPCS S9476) is included on line 290 only when ALL of the following criteria are met:

1) The patient has benign paroxysmal positioning vertigo (BPPV); AND
2) The patient has tried and failed canalith repositioning maneuvers (CPT 95992) or has contradictions to canalith repositioning maneuvers; AND one or more of the following applies:
    a. The patient is aged 65 or older; OR
    b. The patient is under age 65 and is at increased risk of falls; OR
    c. The patient has symptoms (for example, vertigo and imbalance) for more than 6 weeks

Section 2.0

Plain Language Summaries

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
May 16, 2024

This plain language summary provides a short and non-technical explanation of the topics that will be discussed at the meeting, along with the staff recommendations. Decisions are not final unless approved by the Health Evidence Review Commission (which usually meets later on the same day). The Commission may approve, modify, or not approve staff recommendations.

Vulvectomy and Other Treatments for Vulvodynia

Plain Language Summary:

Coverage question:
1. Should OHP cover a surgery that removes a part of a female's genitals (vulva) for a condition (vulvodynia) that causes burning, pain and discomfort even when there is no sign of injury or infection?
2. Should OHP cover one or two conditions that make vaginal sex painful or, in some cases, impossible (dyspareunia and vaginismus)?

Should OHP cover this treatment?
1. Yes. Surgery and physical therapy can help this condition.
2. Based on expert input, staff recommends a discussion on these topics.

Fluoride Varnish Frequency

Plain Language Summary:

Coverage question: Should OHP change the guideline about a special teeth coating (fluoride varnish) to add more times a year it is covered?

Should OHP cover this treatment? Yes, medical studies show that for higher risk people under 21 years old, more fluoride coatings lead to fewer cavities. The Oral Health Advisory Panel recommends up to 4 fluoride treatments a year for members who are at higher risk for cavities.

MRI for Monitoring in Multiple Sclerosis Clarification

Plain Language Summary:

Coverage question: Should the OHP provide more clear direction about covering MRI imaging tests for multiple sclerosis, a condition causing symptoms such as fatigue, muscle weakness and struggling to do tasks??

Should OHP make this change? Yes. OHP covers this testing for all reasons for multiple sclerosis.

Continuous Glucose Monitor (CGM) Guideline Updates March 2024

Plain Language Summary:

Coverage question: Should HERC change OHP's rules about when to cover a device that measures blood sugar throughout the day (continuous glucose monitors or CGM)?

Recommendation? Yes:
1) Change the rules for getting a CGM for the first time
2) Change the rules for getting re-approval for a CGM
3) Add coverage for people with a condition where the body has trouble storing and using a type of blood sugar called glycogen (glycogen storage disease)
4) Clearly explain real-time CGM is covered and retrospective (professional) CGM is not covered
5) Clarify that type 2 diabetes includes diabetes caused by other conditions such as cystic fibrosis

Basivertebral Nerve Ablation for Back Pain

Plain Language Summary:

Coverage question: Should OHP cover a treatment for chronic low back pain that destroys some nerves (basivertebral nerve ablation)?

Should OHP cover this treatment?
Option 1: No, there are not enough quality medical studies.
Option 2: Yes, add limited coverage with a guideline, since other insurance companies cover this treatment.

Posterior Tibial Nerve Stimulation

Plain Language Summary:

Coverage question: Should OHP cover a treatment that stimulates a nerve to help with overactive bladder, especially when other treatments haven't helped?

Should OHP cover this treatment? Yes, this treatment should be covered when other treatments haven’t helped.

Brain Stimulation for Essential Tremor

Deep Plain Language Summary:

Coverage question: Should OHP cover a treatment that sends the brain electrical pulses to reduce symptoms for a condition that causes unintended shaky movements (tremors)?

Should OHP cover this treatment? Studies have shown this treatment helps people who have extreme tremors and medications are no longer working.

X-ray Motion Analysis for Back Pain

Plain Language Summary:

Coverage question: Should OHP cover a certain x-ray to see how the spine moves as a person bends or twists?

Should OHP cover this treatment? No, this test has not been studied enough to show it is helpful for choosing the best treatment for a person’s spine problem.

Actigraphy

Plain Language Summary:

Coverage question: Should OHP cover a device used to measure sleep patterns and movements? The device is worn overnight.

Should OHP cover this treatment? No, limited medical studies show that using the device does not help tell if a person has sleeping problems.

Next Generation Sequencing of Malignancies with Liquid Biopsy

Plain Language Summary:

Coverage question: Should OHP cover a blood test to check for DNA changes from a person's cancer?

Should OHP cover this treatment? Yes, in certain cases:
1) When the patient is not well enough to give tumor samples OR
2) When the tumor sample taken isn't big enough to study closely

Leadless Pacemaker Review 2024

Plain Language Summary:

Coverage question: Should OHP cover a specific pacemaker, implanted directly into the heart? This type is called "leadless" because it doesn't have wires, called leads, that connect to the heart like traditional pacemakers do.

Should OHP cover this treatment? No, it's not clear if the benefits outweigh the harms.

Absorbable Perirectal Spacer for Prostate Cancer Radiation Therapy

Plain Language Summary:

Coverage question: Should OHP cover a dissolvable spacer for prostate radiation therapy?

Should OHP cover this treatment? No, medical studies found the risks did not outweigh the harms.

Periurethral injection of bulking agents for urinary incontinence—2024 review

Plain Language Summary:

Coverage question: Should OHP cover a shot to control when urine is passed? The shot contains bulking agents (tiny balls, bone-like material, silicone bits) that help keep the urethra closed.

Should OHP cover this treatment? No, the medical studies that show this treatment does not work well.

Ultrasound Guided Percutaneous Tenotomy

Plain Language Summary:

Coverage question: Tendinosis happens when a tendon gets damaged or worn out from over-use or injury and doesn't heal properly. Should a treatment using soundwaves to break down the injured area (ultrasound) be covered for any type of injury?

Should OHP cover this treatment? No, there is very little evidence that this treatment is helpful.

2026 Biennial Review: Neonatal Circumcision

Plain Language Summary:

Coverage question: Should OHP cover removing the loose skin covering the end of a boy's penis (foreskin)? If so, for what ages?

Should OHP cover this treatment? Unknown. The Commission is seeking written and verbal public comments. VbBS and HERC will discuss this topic at the May 16, 2024 meetings.

Section 3.0

Previously Discussed Items

Vulvectomy and Other Treatments for Vulvodynia

Plain Language Summary:

Coverage question:

1. Should OHP cover a surgery that removes a part of a female's genitals (vulva) for a condition (vulvodynia) that causes burning, pain and discomfort even when there is no sign of injury or infection?
2. Should OHP cover one or two conditions that make vaginal sex painful or, in some cases, impossible (dyspareunia and vaginismus)?

Should OHP cover this treatment?

1. Yes. Surgery and physical therapy can help this condition.
2. Based on expert input, staff recommends a discussion on these topics.

Changes to issue summary after public comment period:

HERC staff further worked with experts to refine the staff recommendations. Based on these discussions, HERC staff have added a recommendation to discuss coverage for vaginismus and vulvodynia.

Coverage Question: Should vulvectomy be added as a treatment for vulvodynia?

Question source: Medical Management Committee of OHA

Background: Vulvodynia is persistent pain in the vulvar area (the area around the vaginal opening). When no specific cause is found for the vulvar pain, it is referred to as vulvodynia. It is diagnosed by ruling out conditions that can cause vulvar pain, such as yeast infections, bacteria vaginosis, lichen sclerosis, etc. Treatments include topical anesthetics, pudendal nerve blocks, botulinum toxin injections, tricyclic antidepressants, anticonvulsants, biofeedback, pelvic floor physical therapy, TENS, and in severe cases vulvectomy (removal of the vulva).

Coverage of vulvodynia, particularly vulvectomy, was discussed at the January 2024 VBBS and HERC meetings. Experts testified that this condition can be successfully treated with a combination of pelvic floor physical therapy, surgery, and counseling.

The subcommittee members discussed how this is a difficult condition to treat, and that surgery is likely to not be overutilized as studies show a high rate of patient refusal of surgery. Several members noted that this was an area where the literature does not give a strong signal of effectiveness, but noted that this is a difficult condition to recruit persons into clinical trials. In this type of case, members rely more on expert opinion. There was discussion about the need to cover counseling, although this might be accomplished through using PTSD or anxiety diagnoses. Some concern was noted about covering a condition associated with sexual dysfunction, as sexual dysfunction is an unfunded line on the OHP Prioritized List. However, it was noted that this condition causes significant pain as well as sexual dysfunction. All of the conditions mentioned by the experts are on uncovered lines (for example, ICD-10-CM N94.2 vaginismus, F52.5 Vaginismus not due to a substance or known physiological condition and

N94.1 dyspareunia). The general consensus was that some coverage for vulvodynia should be considered. HERC staff were directed to work with experts to identify the needed diagnosis and procedure codes, and bring back a refined proposal to a future VBBS/HERC meeting.

HERC staff have received coding information from the OHSU vulvar health program. The details of the coding as shown below.

HERC staff have further discussed coverage of this condition with experts, and feel that coverage of vaginismus and dyspareunia should be considered. Both of these conditions cause significant pain as well as sexual dysfunction. Vaginismus is defined as recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina, which interferes with coitus and causes distress and interpersonal difficulty. Treatments include sex therapy, education, hypnosis and drug treatments.

Current Prioritized List/Coverage status:

ICD-10 Code	Code Description	Current Line(s)	Used for
N94.810	Vulvar vestibulitis	525 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA	Primary diagnosis
N94.818	Other vulvodynia	525	Primary diagnosis
N94.819	Vulvodynia, unspecified	525	Primary diagnosis
N94.89	Other specified conditions associated with female genital organs and menstrual cycle	515	
N94.1X	Dyspareunia	525	Primary diagnosis, PT
N94.2	Vaginismus	525	Physical therapy (PT)
N81.82	Incompetence or weakening of pubocervical tissue	465 UTERINE PROLAPSE; CYSTOCELE	PT
N81.83	Incompetence or weakening of rectovaginal tissue	465	PT
N81.84	Pelvic muscle wasting	465	PT
M79.10	Myalgia, unspecified site	597 DISORDERS OF SOFT TISSUE	PT
M79.18	Myalgia, other site	597	PT
F52.5	Vaginismus not due to a substance or known physiological condition	516 SEXUAL DYSFUNCTION	PT
F52.6	Dyspareunia not due to a substance or known physiological condition	516	Mental health services
F52.8	Other sexual dysfunction not due to a substance or known physiological condition	516	Mental health services
F52.69	Unspecified sexual dysfunction not due to a	516	Mental health services

	substance or known physiological condition		
K59.4	Anal spasm	522 ISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS	PT
M63.838	Other muscle spasm	651 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	PT

CPT code	**Code description**	**Current line(s)/lists**
14040	Repair of wound of forehead, cheeks, chin, mouth, neck, underarms, genitals, hands, or feet by transferring skin, 10.0 sq cm or less	ANCILLARY PROCEDURES
14041	10.1-30.0 sq cm	ANCILLARY PROCEDURES
56620	Vulvectomy simple; partial	284 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS 309 GENDER AFFIRMING TREATMENT 433 PRECANCEROUS VULVAR CONDITIONS
97140, 97161-97164	Physical therapy	Multiple lines, including 465 UTERINE PROLAPSE; CYSTOCELE

New code effective April 2024
HCPCS S9002 Intra-vaginal motion sensor system, provides biofeedback for pelvic floor muscle rehabilitation device

Evidence:

Treatment of vaginismus

1) **Melnik 2012**, Cochrane review of treatments for vaginismus
    a. N=5 studies (282 patients)
        i. All moderate to high risk of bias
    b. There is no clinical or statistical difference between systematic desensitization and any of the control interventions (either waiting list control, systematic desensitization combined with group therapy or in vitro (with women under instruction by the therapist) desensitization) for the treatment of vaginismus.
    c. Authors' conclusions A clinically relevant effect of systematic desensitization when compared with any of the control interventions cannot be ruled out. None of the included trials compared other behavior therapies (e.g. cognitive behavior therapy, sex therapy) to pharmacological interventions. The findings are limited by the evidence

available and as such conclusions about the efficacy of interventions for the treatment of vaginismus should be drawn cautiously

HERC staff summary: The evidence supporting topical or oral medications, TENS, botulinum injection and CBT for treatment of vulvodynia is very weak and in controlled studies show little to no effect. Acupuncture showed some effectiveness in small clinical trials. CBT studies have found inconsistent results. Pelvic floor physical therapy is considered first line therapy, but there is insufficient evidence supporting its use. Vulvectomy appears to be more effective than other therapies for vulvodynia, but this is based on case series and a single RCT with a high refusal rate in the surgical arm. The complications of vulvectomy have not been well studied.

Ten public comments were received on this topic from patients and providers. All recommended coverage of vulvodynia, and of pelvic PT and vulvectomy in particular. ACOG also recommends pelvic PT, vulvectomy, topical medications, and biofeedback for treatment of vulvodynia.

Based on previous discussion at VBBS and HERC as well as expert input and expert guidelines, HERC staff recommend adding coverage of vulvodynia. Paired treatments should include physical therapy and vulvectomy.

HERC staff recommend discussion of adding coverage for dyspareunia and vaginismus based on expert input.

HERC staff recommendations:

1) Add ICD-10-CM N94.810 (Vulvar vestibulitis), N94.818 (Other vulvodynia) and N94.819 (Vulvodynia, unspecified) to line 324 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION and remove from line 532 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA
    a. Delete these codes from line 525 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA
    b. Do not add ICD-10-CM N94.1X family of codes (dyspareunia) as these codes are specified to be on line 525.
2) Add CPT 56620 (Vulvectomy simple; partial) to line 324
    a. Physical therapy CPT codes are already on line 324
    b. Will not pair with botulinum injections, acupuncture, biofeedback or CBT codes
    c. Wound repair codes are Ancillary and will be covered if primary diagnosis is covered
    d. Medications would be covered as Ancillary
3) Discuss adding dyspareunia and vaginismus to line 324
    a. If coverage of these conditions is desired:
        i. Add ICD-10-CM N94.1X family of codes to line 324
        ii. Add N94.2 (Vaginismus) to line 324
        iii. Delete these codes from line 525 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA
        iv. Change the title of line 525 to CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME~~, DYSPAREUNIA~~
        v. Would allow use for physical therapy but not for CBT or other mental health treatments

Vulvectomy and Other Treatments for Vulvodynia

Appendix A
OHSU Vulvar Health billing information, by payer type

For financial class MEDICAID for FY22-FY24, with quantities.

CPT Code	Proc Name	DX1	FY22	FY23	FY24	Grand Total
14040	PR ADJACENT TISSUE TRANSFER/REARRANGEMENT F/C/C/M/N/AX/G/H/F 10.0 SQ CM/<	D07.1	1			1
		L90.0			1	1
		N94.810	2	2		4
		N94.819			1	1
		R10.2		1	1	2
14040 Total			**3**	**3**	**3**	**9**
14041	PR ADJACENT TISSUE TRANSFER/REARRANGEMENT F/C/C/M/N/AX/G/H/F 10.0 SQ CM TO 30.0 SQ CM	N90.4		1		1
		N94.810	2	1		3
14041 Total			**2**	**2**		**4**
56620	PR PART SIMPLE REMV VULVA	D07.1	3	1		4
		D28.0			1	1
		L90.0			2	2
		N76.2	2			2
		N81.11		1		1
		N90.0		1		1
		N90.4		2		2
		N90.60		1		1
		N90.813		1		1
		N90.89	1			1
		N94.10		1		1
		N94.810	7	6		13
		N94.819	1		2	3
		R10.2		2	1	3
56620 Total			**14**	**16**	**6**	**36**

For comparison here is financial class MEDICARE for FY22-FY24, with QTYs.

CPT Code	Proc Name	DX1	FY22	FY23	FY24	Grand Total

Vulvectomy and Other Treatments for Vulvodynia

14040	**PR ADJACENT TISSUE TRANSFER/REARRANGEMENT F/C/C/M/N/AX/G/H/F 10.0 SQ CM/<**	L90.0			1	1
		N89.5		1		1
		N94.810	1	3	1	5
14040 Total			**1**	**4**	**2**	**7**
14041	**PR ADJACENT TISSUE TRANSFER/REARRANGEMENT F/C/C/M/N/AX/G/H/F 10.0 SQ CM TO 30.0 SQ CM**	L43.9	1			1
		N94.818		1		1
14041 Total			**1**	**1**		**2**
56620	**PR PART SIMPLE REMV VULVA**	A63.0			1	1
		C51.9	5	2	1	8
		D07.1	7	2	7	16
		L43.9	2			2
		L90.0	2	1	2	5
		N76.4	2	1		3
		N90.1		2	1	3
		N90.4	1	2		3
		N90.7			1	1
		N90.89	6	5		11
		N94.810	1	6	2	9
		N94.818		2		2
56620 Total			**26**	**23**	**15**	**64**

Here is the financial class all others (BCBS, Managed Care, Commercial and Self Pay) for FY22-FY24, with QTYs.

CPT Code	Proc Name	DX1	FY22	FY23	FY24	Grand Total
14040	**PR ADJACENT TISSUE TRANSFER/REARRANGEMENT F/C/C/M/N/AX/G/H/F 10.0 SQ CM/<**	D07.1	2			2
		L43.9	1			1
		L90.0	3	1	2	6
		N76.2		1		1
		N89.5		1		1
		N90.4	1	2		3
		N90.89	1			1
		N94.810	13	17	10	40

		N94.818			1	1
		N94.819	2	2		4
		O71.89		1		1
14040 Total			**23**	**25**	**13**	**61**
14041	**PR ADJACENT TISSUE TRANSFER/REARRANGEMENT F/C/C/M/N/AX/G/H/F 10.0 SQ CM TO 30.0 SQ CM**	D07.1		1		1
		N76.3			1	1
		N90.4		1		1
		N94.810	4	9	4	17
14041 Total			**4**	**11**	**5**	**20**
56620	**PR PART SIMPLE REMV VULVA**	A63.0		2		2
		C51.9	1			1
		D06.9	2			2
		D07.1	9	7	2	18
		L43.9	2			2
		L73.2	2			2
		L90.0	5	4	4	13
		N76.2		2		2
		N76.3		2	2	4
		N76.4	1	2		3
		N84.3			1	1
		N89.5	2	4		6
		N90.1	2	2		4
		N90.4	4	8	2	14
		N90.60		4		4
		N90.810	2			2
		N90.89	2			2
		N94.10		0		0
		N94.810	34	53	27	114
		N94.818			2	2
		N94.819	3	4		7
		O71.89		2		2
		O71.9			2	2
56620 Total			**71**	**96**	**42**	**209**

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Review

Continuing Education

Evaluation and Treatment of Vulvodynia: State of the Science

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Vulvodynia affects 7% of American women, yet clinicians often lack awareness of its presentation. It is underdiagnosed and often misdiagnosed as vaginitis. The etiology of vulvodynia remains unknown, making it difficult to identify or develop effective treatment methods. The purpose of this article is to (1) review the presentation and evaluation of vulvodynia, (2) review the research on vulvodynia treatments, and (3) aid the clinician in the selection of vulvodynia treatment methods. The level of evidence to support vulvodynia treatment varies from case series to randomized controlled trials (RCTs). Oral desipramine with 5% lidocaine cream, intravaginal diazepam tablets with intravaginal transcutaneous electric nerve stimulation (TENS), botulinum toxin type A 50 units, enoxaparin sodium subcutaneous injections, intravaginal TENS (as a single therapy), multimodal physical therapy, overnight 5% lidocaine ointment, and acupuncture had the highest level of evidence with at least one RCT or comparative effectiveness trial. Pre to posttest reduction in vulvar pain and/or dyspareunia in non-RCT studies included studies of gabapentin cream, amitriptyline cream, amitriptyline with baclofen cream, up to 6 weeks' oral itraconazole therapy, multimodal physical therapy, vaginal dilators, electromyography biofeedback, hypnotherapy, cognitive behavioral therapy, cold knife vestibulectomy, and laser therapy. There is a lack of rigorous RCTs with large sample sizes for the treatment of vulvodynia, rendering it difficult to determine efficacy of most treatment methods. Clinicians will be guided in the selection of best treatments for vulvodynia that have the highest level of evidence and are least invasive.
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Keywords: pain management, pharmacology, patient education

INTRODUCTION

Vulvodynia is chronic vulvar pain of unknown etiology lasting at least 3 months in duration and may be accompanied by other potentially associated factors.[1] Vulvodynia can severely impact the lives of women and of individuals assigned female sex at birth. Vulvodynia often affects the ability to have sexual intercourse, devastating intimate relationships.[2,3] Even with adjuvant drugs and opioids, women with vulvodynia reported an average pain intensity score of 6.7 out of 10; 60% of women drank alcohol and 43% used analgesics (including opioids) and alcohol together to reduce their pain.[4] Vulvodynia can cause severe chronic pain resulting in physical disability[5] and can lead to suicidal ideation.[6]

Vulvodynia pain can be localized to one area, generalized to multiple areas, or mixed (localized and generalized). Pain can be either provoked (by vaginal penetration or contact to the vulva), spontaneous, or mixed (provoked and spontaneous). The onset of pain is either primary (with first intercourse or tampon insertion) or secondary (occurring later). The pain pattern can be either continuous or constant, rhythmic or intermittent, and transient or brief.[7] The 2 most common types of vulvodynia are provoked vestibulodynia (PV) and generalized vulvodynia. PV is localized pain confined to the vulvar vestibule and vaginal introitus that is provoked or triggered by touch.[7,8] Generalized vulvodynia is unprovoked or spontaneous diffuse pain of the vulva and may extend into the inner thighs and perineum.[7,8] Terms used for PV are not standardized and include *localized provoked vestibulodynia*, *vestibulodynia*, *provoked vestibulodynia*, *vulvar vestibulitis*, *provoked vulvodynia*, and *localized vulvodynia*. Some published studies do not differentiate between vulvodynia types (provoked and generalized vulvodynia) and report findings on unspecified vulvodynia. The purpose of this article was to (1) review the presentation and evaluation of vulvodynia, (2) review the research on vulvodynia treatments, and (3) aid the clinician in the selection of vulvodynia treatment methods.

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Quick Points

- A cotton swab test of the vulva should be performed to diagnose vulvodynia.
- Clinicians should prescribe treatments that are the least invasive and have the highest level of evidence.
- There is an urgent need to perform high-quality randomized controlled trials of treatments for vulvodynia.

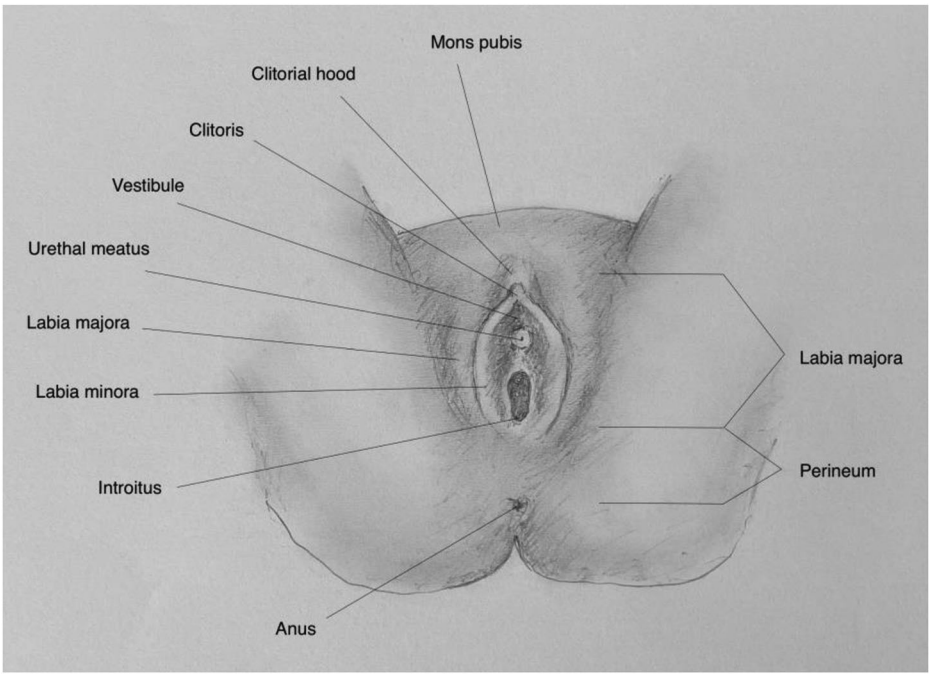

Figure 1. Vulvar Anatomy.

Source: Image courtesy of Pavlina Vagoun-Gutierrez.

SIGNS AND SYMPTOMS OF VULVODYNIA

The pain of vulvodynia may be described as itching, burning, or stabbing and is often accompanied by dyspareunia.[1] Women frequently present with a report of long-standing or recurring vaginitis, with negative laboratory findings, that does not resolve despite receiving a myriad of treatments. Often, women with vulvodynia cannot tolerate anything touching their vulva, such as underclothing or tight-fitting pants, or sitting for prolonged periods, all of which may trigger pain.

HISTORY OF THE PRESENT ILLNESS AND VULVODYNIA

When vulvodynia is suspected, the clinical evaluation focuses on whether women have the following clinical signs and symptoms that may be implicated in, associated with, or lead to the development of vulvodynia: (1) vulvar pain that started while on combined oral contraceptives (COCs), as COCs may promote changes in the vulvar morphology;[9] (2) allergic reactions, chronic infections, and yeast infections, as there may be an exaggerated immune response to common pathogens such as *Candida albicans*;[10] and (3) urinary frequency, urgency, hesitancy, feeling of incomplete emptying of the bladder, or constipation, which may be signs of hypertonic pelvic floor muscles associated with vulvodynia.[1,11]

The clinician should also inquire about other associated factors that can be associated with vulvodynia such as (1) lower back pain, which may constrict muscles, vessels, and nerves with referred pain to the vulva;[12] (2) hip, groin, or buttock pain, which may be due to a torn labrum resulting in pelvic floor muscle dysfunction and vulvar pain;[13] (3) traumatic childbirth or long bicycle trips, which can lead to pudendal neuralgia and can similarly present with vulvar pain; (4) vulvar burning, soreness, or itching, which may be due to nerve damage that may or may not be associated with low back pain, sciatica, and spinal pathology; and/or (5) genitourinary syndrome of menopause, which may present with vaginal/vulvar pain and/or dyspareunia.

CLINICAL EXAMINATION TO DIAGNOSE VULVODYNIA

Dyspareunia associated with vulvodynia is superficial and occurs at the vaginal introitus, fourchette, and/or outer one-third of the vagina. There is no cervical motion tenderness because the dyspareunia is superficial and not a sign of a peritoneal mass or infection.

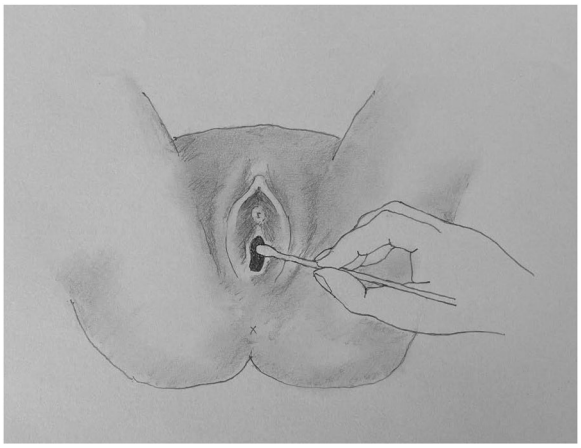

Figure 2. Cotton Swab Test to Assess for Vulvar Allodynia.

Source: Image courtesy of Pavlina Vagoun-Gutierrez.

If vulvodynia is suspected, a detailed gynecologic examination of the vulvar anatomy should be performed for allodynia (painful response to an unpainful stimulus) using a cotton swab test (Figure 1). Allodynia, a symptom of neuropathic pain, is caused by a lesion or disease of the nervous system and reflects peripheral or central nervous system changes that may occur in chronic pain conditions.[14] The pain of vulvodynia may have a neuropathic component.[7,15] To assess for allodynia, the examiner should perform a cotton swab test (Figure 2). Gentle pressure is applied with a cotton swab starting at the thigh and moving medially to the labia majora, interlabial sulcus, clitoral hood, labia minora, and sites within the vulvar vestibule at 2, 4, 6, 8, 10, and 12 o'clock.[16] Pain is recorded on a 0 to 10 numeric ratings scale (NRS). If the pain is confined to the vulvar vestibule, the diagnosis is localized vestibulodynia; if the pain extends to areas outside the vulvar vestibule, the diagnosis is generalized vulvodynia.

Pelvic floor muscle dysfunction is caused by hypertonic muscles with tenderness and can be present in women with vulvodynia.[1,11] Tenderness can be elicited with firm digital pressure to both the levator ani muscle group and the obturator internus in women with vulvodynia. The levator ani muscle group (puborectalis, pubococcygeus, and the iliococcygeus) comprises most of the pelvic floor (Figure 3) that supports the bladder and rectum. The obturator internus muscle in the pelvic wall (Figure 3) connects to the pelvic floor via the arcuate tendon levator ani. Both the levator ani and the obturator internus should be palpated by applying even pressure with the index and middle finger of the examining hand during the digital examination, and the pain should be recorded on a 0 to 10 NRS.

TREATMENTS FOR VULVAR PAIN AND DYSPAREUNIA

The goal of this review is to present the myriad of vulvodynia treatments that patients of midwives are prescribed by other clinicians. All dosages and treatment regimens can be found in Tables 1 to 10. There is a paucity of research on vulvodynia, and many of the studies reviewed are almost 2 decades old with few newer treatment studies that demonstrated efficacy. Our initial search for research articles revealed anecdotal reports and individual case reports of women with vulvodynia, but they were not high quality and were not included in this review. Forty-one studies with the highest level of evidence for each treatment including case series were ultimately included in this review. The level of evidence was evaluated with the rating system from the Centre for Evidence-Based Medicine at the University of Oxford (Table 11).[17]

Overall, there is great variability in treatments prescribed for vulvodynia. Results from the National Vulvodynia Registry[18] showed that a total of 78 different treatments were

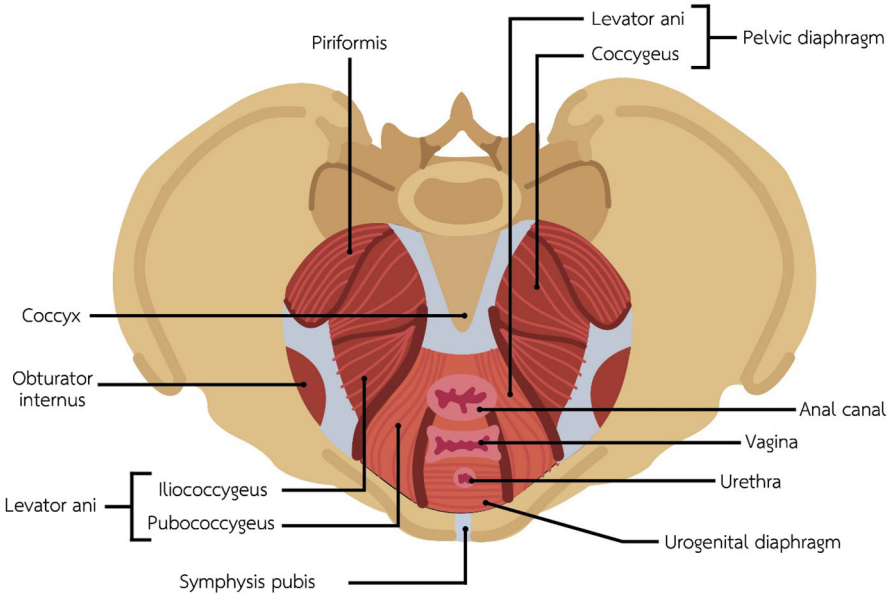

Figure 3. Pelvic Floor and Pelvic Wall Musculature

Table 1. Topical Treatments for Vulvodynia

Treatment	Author, Year, Sample Size, Conditions	Level of Evidence	Study Design, Treatment Groups, Dosages	Results
Lidocaine	Zolnoun et al[23] 2003 N = 61 Vulvar vestibulitis	2c	Prospective cohort uncontrolled 5% lidocaine ointment applied generously to the vulvar vestibule and also to a cotton ball that was kept in vulvar vestibule overnight	Ability to have intercourse increased from 36% to 76% posttreatment ($P = .002$). Daily vulvar pain (VAS 0-100) reduced from 27.4 to 17.0 ($P = .004$). Dyspareunia (VAS 0-100) reduced from 76.2 to 37.0 ($P = .001$).
Corticosteroid vs GCBT	Bergeron et al[26] 2016 N = 97 PV	2b	Uncontrolled randomized trial 2 groups: (1) Hydrocortisone 1% cream every d for 13 wk (2) GCBT, 10 2-h sessions for 13 wk	Hydrocortisone reduced mean (SD) dyspareunia (MPQ PPI, NRS 0-10) from 7.7 (2.1) to 5.6 (3.3) at 13 wk ($P < .01$) and to 5.9 (3.1) ($P < .01$) at 6-mo follow-up. GCBT reduced mean (SD) dyspareunia from 7.3 (2.5) at baseline to 5.5 (2.7) at 13 wk ($P < .01$) and to 5.2 (2.9) ($P < .01$) at 6-mo follow-up. GCBT significantly reduced dyspareunia compared with hydrocortisone at 6 mo ($P < .01$).
Gabapentin cream	Boardman et al[28] 2008 N = 51 LV, n = 32 GV, n = 19	2c	Retrospective chart review 3 arms: (1) 2% gabapentin cream: LV (n = 9), GV (n = 9) (2) 4% gabapentin cream: LV (n = 7), GV (n = 3) (3) 6% gabapentin cream: LV (n = 16), GV (n = 6) Used for 8 wk but did not state how often was applied	Mean (SD) vulvar pain (VAS 0-10) in LV reduced significantly from 7.9 (2.0) to 2.7 (1.6) ($P < .001$). Mean (SD) vulvar pain in GV reduced significantly from 5.8 (1.7) to 2.0 (2.3) ($P < .001$). Pain improved at least 50% in 80% participants with 29% having complete pain relief in at least 8 wk. Varying doses of gabapentin cream were not accounted for in the statistical analysis.
2% amitriptyline cream	Pagano and Wong[30] 2012 N = 150 Vulvodynia	2c	Prospective, uncontrolled study 2% amitriptyline cream twice daily for 30 d	Dyspareunia (Marinoff dyspareunia scale, 1-3) response: 84 (56%) responded positively to treatment, 15 (10%) participants reported excellent improvement, 44 (29.3%) reported moderate improvement, 25 (16.7%) reported slight but noticeable improvement, 66 (44%) no improvement. 16 participants ceased treatment due to skin irritation. No analysis for significance or posttreatment grading was reported.

(*Continued*)

Table 1. Topical Treatments for Vulvodynia

Treatment	Author, Year, Sample Size, Conditions	Level of Evidence	Study Design, Treatment Groups, Dosages	Results
2% amitriptyline cream with 2% baclofen cream	Nyirjesy et al[29] 2009 N = 38 PV	2c	Retrospective study, uncontrolled 2% amitriptyline cream with 2% baclofen cream twice daily for 4-6 wk and up to 33 wk	Dyspareunia (NRS 1-5) significantly reduced from 4 to 2 ($P = .05$).
Amitriptyline-ketamine gel	Poterucha et al[31] 2012 N = 13 Women with genital, rectal, perineal pain	4	Retrospective chart review Amitriptyline-ketamine gel applied to vulva, perineum, rectum, or groin 2-4 times per d Duration unspecified	Of the 13 women using amitriptyline-ketamine gel, 2 (15%) had no response, 4 (31%) had less than 50% relief, 6 (46%) had 50%-99% relief, and 1 (8%) had complete relief ($P = .84$). Pain was measured by asking participants which of the categories listed they fell into. No significance testing was reported.
Equine conjugated estrogen cream 0.3 mg	Langlais et al[33] 2017 N = 20 Vulvodynia	2b	Double-blind RCT Equine conjugated estrogen cream 0.3 mg or placebo cream applied at bedtime for 8 wk	Equine conjugated estrogen significantly reduced global dyspareunia (VAS 0-10) 27% (95% CI, −1% to 55%) ($P < .05$). Placebo reduced global estrogen 3% (95% CI, −8% to 14%). The difference between the 2 groups was not significant ($P = .29$). Means for each treatment methods were not reported.
Topical estradiol 0.03% and testosterone 0.01% cream	Burrows and Goldstein[32] 2013 N = 50 Vestibulodynia	2c	Retrospective database chart review of 50 consecutive premenopausal women on combined contraceptive pills Topical estradiol 0.03% and testosterone 0.01% cream applied to the vulvar vestibule twice daily for 20 wk	Cotton swab test vulvar pain (NRS 0-10) reduced from 7.5 to 2 ($P = .001$). Long-term use of testosterone in premenopausal women has not been evaluated.
Nifedipine cream	Bornstein et al[35] N = 30 Localized PV	2b	Double-blind RCT 3 arms of 10 participants: (1) 0.2% nifedipine cream (2) 0.4% nifedipine cream (3) Placebo cream Each cream applied 4 times per d for 6 wk	Nifedipine 0.2% significantly reduced mean (SD) dyspareunia (NRS 0-100) from 90.5 (9.0) to 61.9 (34.2) ($P = .01$). Nifedipine 0.4% significantly reduced mean (SD) dyspareunia from 92.5 (7.2) to 72.5 (27.6) ($P = .06$). Placebo significantly reduced mean (SD) dyspareunia from 88.0 (12.9) to 48.1 (42.8) ($P = .04$). Treatment methods were not compared with each other.

Abbreviations: GCBT, group cognitive behavioral therapy; GV, generalized vulvodynia; LV, localized vulvodynia; MPQ PPI, McGill Pain Questionnaire Present Pain Index; NRS, numeric ratings scale; RCT, randomized controlled trial; PV, provoked vestibulodynia; VAS, visual analog scale.

Table 2. Diazepam Vaginal Suppositories and Tablets for the Treatment of Hypertonic Pelvic Floor Dysfunction

Treatment	Author, Year, Sample Size, Conditions	Level of Evidence	Study Design, Treatment Groups, Dosages	Results
Diazepam intravaginal suppository	Crisp et al[46] 2013 N = 21 Hypertonic pelvic floor dysfunction	1b	Double-blind RCT Diazepam 10 mg or placebo intravaginal suppository at bedtime for 28 d	Diazepam significantly reduced mean (SD) muscle tone (EMG) from 3.16 (0.88) microvolts to 2.77 (0.91) microvolts ($P = .02$). Placebo significantly reduced mean (SD) muscle tone from 2.7 (0.328) microvolts to 1.87 (1.3) microvolts ($P = .02$). The difference between the diazepam and placebo group was not significant. Diazepam significantly reduced mean (SD) worst pelvic pain (VAS 10 cm) from 8.42 (1.02) to 8.5 (1.22) at 2 wk to 8.0 (1.9) at 4 wk. *P* values not reported. Placebo reduced mean (SD) worst pelvic pain from 8.86 (1.07) to 7.29 (2.14) at 2 wk, and to 6.71 (2.69) at 4 wk. *P* values not reported. The difference between the diazepam and placebo group was not significant ($P = 0.431$).
Diazepam intravaginal capsules	Holland et al[47] 2019 N = 35 Hypertonic pelvic floor dysfunction	1b	Double-blind RCT 10 mg diazepam capsules or placebo 1-2 times d intravaginally for 4 wk	Diazepam reduced pelvic pain and levator ani spasm median pain scores (VAS 100 mm) from 59 (95% CI, 50-80) to 50 (95% CI, 20-75). Placebo reduced pelvic pain and levator ani spasm median pain scores from 58 (95% CI, 35-75) to 39 (95% CI, 5-55). Diazepam had 0 median change in the VAS score (100 mm). The placebo group had a 12-point median change. There was not a significant difference in the improvement between the groups ($P = .53$).

(*Continued*)

Table 2. (Continued)

Treatment	Author, Year, Sample Size, Conditions	Level of Evidence	Study Design, Treatment Groups, Dosages	Results
Diazepam and intravaginal TENS	Murina et al[48] 2018 N = 42 Vestibulodynia	1b	Double-blind RCT 10 mg diazepam tablet at bedtime and intravaginal TENS 3 times per wk for 60 d Placebo tablet at bedtime and intravaginal TENS 3 times per wk for 60 d	Diazepam and TENS reduced mean (SD) cotton swab test vulvar pain (VAS 10 cm) from 7.5 (2) to 4.7 (no SD). Placebo and TENS reduced cotton swab test vulvar pain from 7.2 (1.7) to 4.3 (no SD). No significant difference in pain reduction between groups. *P* value not provided. Diazepam and TENS reduced mean (SD) dyspareunia (Marinoff dyspareunia scale 0-3) from 2.5 (0.5) to 1.6 (no SD). Placebo and TENS reduced mean (SD) pain from 2.0 (1.3) to 1.3 (no SD). Within-group significance testing was not calculated. Diazepam significantly improvement in dyspareunia compared with the placebo group ($P < .01$).

Abbreviations: EMG, electromyography; RCT, randomized controlled trial; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

prescribed to 282 women to reduce their vulvodynia symptoms. Importantly, 72% had been prescribed more than one treatment. Findings highlighted that clinicians may need to prescribe multiple therapies for vulvodynia and that studies may need to replicate real-life conditions.[18] Because the etiology of vulvodynia remains unclear, multiple therapies with different mechanisms of action can either potentiate one another or target different pain mechanisms.[18]

Although the following treatments may have been tested in women with unspecified vulvodynia or for one type of vulvodynia, considering the state of the science, clinicians may consider treating women with either type of vulvodynia. The first 3 treatment groups reviewed are topical, intravaginal, and oral therapies. Topical and intravaginal treatments are localized pharmacologic treatments that are commonly prescribed first. If there is inadequate pain relief, oral therapies are often added. The fourth group of therapies, pelvic floor physical therapy, multimodal therapies, and acupuncture, are minimally invasive and non-pharmacologic. They are prescribed if there is an inadequate response to previously attempted therapies. Unfortunately, third-party insurance, Medicaid, and Medicare reimbursement for these therapies is limited or unavailable, which limits their accessibility.[19]

The fifth group is injection therapies. They are more invasive and may be prescribed when there is a poor response to the previous therapies. Some clinicians may prescribe them in lieu of pelvic floor physical therapy and particularly acupuncture if they practice within a strict biomedical model. The sixth group, psychological interventions, are presented next, as they are not commonly prescribed because of availability and access issues and are often not considered by the clinician who practices within a strict biomedical model. The seventh group, surgical interventions, are the most invasive therapies and may be prescribed when all other treatment options have failed. The authors reviewed medical cannabis last to update clinicians on progress in this area. There is great interest in treating chronic pain conditions and pelvic pain with medical cannabis.[20] The following medications or devices are being used off-label for the treatment of vulvodynia: amitriptyline, desipramine, nifedipine, milnacipran, botulinum toxin type A, low-molecular-weight heparin, and electromyography (EMG) biofeedback.

Topical Treatments

Topical treatments (Table 1) are attractive because they can be applied to the targeted area and have little systemic

absorption. Topical treatments for vulvodynia include 5% lidocaine ointment,[21–23] capsaicin,[24,25] corticosteroids,[26,27] antiepileptics,[28] tricyclic antidepressants (TCAs),[29–31] hormones,[32,33] mast cell stabilizers,[34] and calcium channel blockers.[35]

Lidocaine, a local anesthetic, is prescribed as a gel, ointment, or cream and is used to numb the burning pain of vulvodynia. In PV, there is an increase in unmyelinated C-fibers that transmit dull, delayed, diffuse, achy, and burning pain and in calcitonin gene–related peptide that promotes nerve irritation.[36,37] Lidocaine blocks the conduction of C-fibers, but it also can block calcitonin gene–related peptide and calm irritable nociceptors (peripheral sensory neurons) when it is used continuously.[38] One large multicenter parallel group randomized trial,[22] one randomized controlled trial (RCT),[21] and one uncontrolled study[23] showed that lidocaine applied to the vulvar vestibule reduced vulvar pain and dyspareunia either alone or with oral desipramine (a TCA) in women with PV.

Capsaicin is the active ingredient found in chili peppers and has been used in many over-the-counter pain preparations. The adverse-effect profile does not warrant prescribing capsaicin for women, as it can cause vulvar burning and can result in vulvar nerve damage.[39]

One percent hydrocortisone cream decreases inflammation. Long-term use of hydrocortisone causes thinning of skin and vulvar mucosa. In an uncontrolled randomized trial, pre- to post-treatment, 1% hydrocortisone reduced dyspareunia in women with PV, but it did not significantly reduce dyspareunia compared with group cognitive behavioral therapy (CBT).[26] Triamcinolone, a medium potency topical steroid, along with oral amitriptyline, did not reduce vulvar pain in women with PV.[27] Even though rapid pain relief is unpredictable and rarely possible,[16] there are no data on the long-term use of corticosteroid creams for management of vulvodynia.

Gabapentin, an antiepileptic, exerts its effect on the voltage-dependent calcium ion channels at the postsynaptic terminal of the spinal cord dorsal horn,[40] resulting in reduced neuropathic pain. In a retrospective chart review,[28] gabapentin cream reduced vulvar pain in PV and generalized vulvodynia pre- to post-treatment. Gabapentin cream must be obtained through a compounding pharmacy. Efficacy of gabapentin cream needs to be tested in future RCTs. Amitriptyline is a TCA that treats chronic neuropathic pain.[41] Amitriptyline cream alone[30] and amitriptyline cream with baclofen cream, an antispasmotic,[29] showed a reduction in dyspareunia in unspecified vulvodynia and in PV. These studies had no control group. Ketamine is used to treat neuropathic pain.[42] A case series of 7 women[31] showed relief of genital, perineal, and rectal pain after applying amitriptyline-ketamine cream to affected areas. Efficacy of amitriptyline cream, baclofen cream, and amitriptyline-ketamine cream needs to be tested in RCTs.

Conjugated equine estrogen[33] and estradiol/testosterone cream[32] increase the elasticity, thickness, and moisture of the vulvar epithelium. In a small-sample double-blind RCT of 20 women with PV,[33] equine conjugated estrogen showed no reduction in dyspareunia compared with the placebo cream control group. In a retrospective chart review of estradiol/testosterone cream for premenopausal women with PV,[32] vulvar pain was reduced pre- to post-treatment. Efficacy of both conjugated equine estrogen cream and estradiol/testosterone cream need to be tested in RCTs. The health effects of long-term hormone creams in premenopausal women have not been studied.

Diazepam Vaginal Suppositories and Tablets

Diazepam is an antispasmodic and anticonvulsant that acts on gamma-amino butyric acid (GABA) receptors located in the brain (Table 2).[43] GABA is the main inhibitory neurotransmitter in the central nervous system. Diazepam vaginal suppositories and tablets have been prescribed to treat vulvodynia[18] and vulvar pain related to hypertonic pelvic floor muscles.[11,43–45] Studies conducted on the use of vaginal diazepam have targeted women with pelvic pain related to hypertonic pelvic floor muscles[46–48] but not specifically vulvodynia. There were 2 small-sample double-blind RCTs[46,47] of vaginal diazepam for hypertonic pelvic floor dysfunction that showed no reduction in vulvar pain. A third double-blinded RCT[48] of diazepam with intravaginal transcutaneous electrical nerve stimulation (TENS) versus placebo with TENS for PV also showed no reduction in vulvar pain but did show a significant reduction in dyspareunia. All 3 studies were underpowered. Efficacy of diazepam vaginal suppositories and tablets with or without TENS needs to be tested in larger RCTs.

Oral Medications

Oral medications (Table 3) are often prescribed if topical and intravaginal treatments offer incomplete relief. Oral antifungals are initially prescribed for women's common symptoms of vulvar burning and itching with or without confirmatory laboratory testing for vulvar vaginitis. It is only after there is little relief that the clinician may suspect a diagnosis of vulvodynia.[49] In an uncontrolled retrospective chart review, women reporting vulvar burning and itching were given 6 to 8 weeks of daily fluconazole with subsequent negative fungal cultures and an insufficient reduction in vulvar pain.[49] Women then began a regimen of oral daily itraconazole for 5 to 6 weeks. There was a 70% reduction in vulvar burning and itching. Efficacy of daily fluconazole followed by itraconazole needs to be tested in an RCT. Caution must be exercised if prescribing 5 to 6 weeks of itraconazole therapy for women with vulvodynia that is refractory to fluconazole, even with negative fungal cultures. Because of the risk of hepatotoxicity, liver function needs to be monitored every 3 to 4 weeks during itraconazole therapy.

Oral TCAs, serotonin norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and antiepileptics are prescribed for chronic neuropathic pain. TCAs, SNRIs, SSRIs, and antiepileptics can reduce neuropathic pain by influencing neurotransmitters affecting pain in the central and peripheral nervous systems.[41] Their ability to reduce pain in women with vulvodynia has been inconsistent.[21,27,45,50]

One 4-arm double-blind RCT used oral desipramine (a TCA) and 5% lidocaine cream for dyspareunia.[21] Desipramine compared with placebo did not reduce dyspareunia, but

Table 3. Oral Medications for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Fluconazole and itraconazole	Rothenberger et al[49] 2021 N = 106 PV	2c	Retrospective cohort chart review with no control 200 mg fluconazole daily for 6-8 wk. If there was insufficient reduction of vulvar pain and a negative fungal culture, itraconazole therapy 200 mg twice daily was used for at least 5 wk Due to risk of hepatotoxicity; liver function tests were carried out every 3-4 wk during treatment period	Mean (SD) decrease in cotton swab test vulvar vestibule pain (NRS 0-10) from baseline to 9 wk was 60.7% (39%). 66.0% of participants had significant pain reduction of >50% reduction ($P = 0.043$). The optimal window for pain improvement was 5-6 wk with an average reduction of 69.6%. 5 women discontinued, 3 due to gastrointestinal adverse effects, 1 due to elevated liver function, 1 after seizure during treatment.
Oral desipramine with topical lidocaine vs oral desipramine only vs topical lidocaine only	Foster et al[21] 2010 N = 133 PV	1b	Double-blind placebo RCT 4 arms, 12 wk: (1) 25 mg oral desipramine daily with a 25 mg increase every wk until 150 mg daily; 5% lidocaine cream applied 4 times daily to painful areas (2) Placebo desipramine and placebo topical lidocaine (3) Oral desipramine protocol with placebo topical lidocaine (4) Placebo desipramine with topical lidocaine protocol	Desipramine with lidocaine cream reduced tampon test pain (NRS 0-10) significantly by 36% ($t = -2.13$; $P = .04$). Oral desipramine and placebo topical lidocaine reduced pain by 24% ($t = 0.90$; $P = .37$). Placebo desipramine and topical lidocaine cream reduced pain by 20% ($t = 1.27$; $P = .21$). Placebo oral desipramine and placebo topical cream reduced pain by 33% (no *t*-score provided). There was no significant reduction in pain when interventions were used singularly. Pain scores were not provided.
Oral amitriptyline vs oral amitriptyline and topical triamcinolone	Brown et al[27] 2009 N = 43 Vulvodynia	2b	RCT (1) Oral amitriptyline: 10-20 mg daily (2) Oral amitriptyline: 10-20 mg daily and 0.1% topical triamcinolone at bedtime (3) Self-management control 12-wk intervention	Oral amitriptyline reduced mean (SD) vulvar pain (MPQ PPI, 0-5) by 1.4 (1.6) points. Oral amitriptyline and triamcinolone reduced mean (SD) pain by 0.8 (1.9) points. Self-management reduced mean (SD) pain by 0.7 (1.6) points. No significant difference between self-management, oral amitriptyline, and oral amitriptyline and triamcinolone at 12 wk. No *P* values reported.

(*Continued*)

Table 3. Oral Medications for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Amitriptyline vs amitriptyline and PT	Bardin et al[45] 2020 N = 57 PV	2b	RCT (1) Daily home PT and amitriptyline 25 mg at bedtime for 8 wk (2) Amitriptyline 25 mg at bedtime for 8 wk	Amitriptyline only reduced cotton swab test mean (SD) vulvar pain (NRS 0-10) significantly from 6.6 (2.0) to 4.4 (2.5) ($P = .018$). PT and amitriptyline reduced mean (SD) vulvar pain significantly from 6.3 (2.0) to 2.9 (2.06) ($P < .001$). Amitriptyline only increased mean (SD) pain during intercourse (NRS 0-10) from 2.4 (2.6) to 2.5 (2.5) ($P = .91$). PT and amitriptyline reduced mean (SD) pain during intercourse significantly from 7.5 (3.1) to 3.1 (2.6) ($P < .001$).
Milnacipran	Brown et al[50] 2015 N = 22 PV	2c	Clinical intervention with no control group Milnacipran from 12.5 to 200 mg/d over 6 wk followed by 6 wk on maximum dose	Milnacipran reduced mean (SD) pain (MPQ PRI 0-45) significantly from 20 (8.9) to 12.3 (13.3) ($P = .001$). Mean (SD) coital pain (NRS 0-10) reduced from 6.94 (2.51) to 3.43 (2.82) ($P = .001$).
PEA, transpolydatin, and TENS vs TENS	Murina et al[52] 2013 N = 20 Vestibulodynia	1b	RCT (1) PEA 400 mg and transpolydatin 40 mg twice daily with intravaginal TENS self-administered at home for 60 d (2) Placebo and intravaginal TENS self-administered at home for 60 d	PEA, transpolydatin, intravaginal TENS significantly reduced mean (SD) pain intensity (VAS 10 cm) from 5.8 (1.1) to 2.2 (1.6) ($P < .05$). Placebo and intravaginal TENS significantly reduced mean (SD) pain intensity from 6.2 (1.1) to 2.3 (1.5) ($P < .05$). No significant reduction between groups ($P = .57$). PEA, transpolydatin, intravaginal TENS reduced mean (SD) dyspareunia (Marinoff dyspareunia scale 0-3) from 2.8 (0.4) to 1.0 (0.9); not significant; no *P* value provided. Placebo and intravaginal TENS reduced mean (SD) dyspareunia from 2.6 (0.5) to 1.1 (0.9); not significant; no *P* value provided. No significant reduction between groups ($P = .38$). PEA and transpolydatin found to be more effective than placebo in cases with more recent onset (VAS, $P < .01$, Marinoff $P < .01$).

(*Continued*)

Table 3. Oral Medications for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Gabapentin	Brown et al[89] 2018 N = 89 PV	1b	Double-blind RCT with crossover over 16 wk Gabapentin 1200-3000 mg/d or placebo, increasing dose over 4 wk followed by 2 wk maintenance, then 2 wk taper down (wash out); then switch to other therapy	Gabapentin reduced mean dyspareunia (tampon test, NRS 0-10) by 3.9 (95% CI, 3.4-4.5) points. Placebo reduced mean pain scores by 4.3 (95% CI, 3.7-4.9). Difference −0.3 (95% CI, −0.7 to 0.1) ($P = .07$).
Gabapentin	Bachmann et al[90] 2019 N = 66 PV	1b	Double-blind RCT with crossover 16-wk study Gabapentin 1200-3000 mg/d or placebo, increasing dose over 4 wk followed by 2 wk maintenance, then 2 wk taper down (wash out); then switch to other therapy	Gabapentin did not significantly improve dyspareunia (FSFIp 0-5) ($P = .23$).

Abbreviations: FSFIp Female Sexual Function Index Sensory Pain Subscale; MPQ PPI, McGill Pain Questionnaire Present Pain Index; MPQ PRI, McGill Pain Questionnaire Pain Rating Index; NRS, numeric ratings scale; PEA, palmitoylethanolamide; PT, physical therapy; PV, provoked vestibulodynia; RCT, randomized controlled trial; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

desipramine with 5% lidocaine did reduce dyspareunia in women with PV. One RCT using amitriptyline alone and amitriptyline with triamcinolone cream did not reduce vulvar pain in women with PV.[27] A second RCT of amitriptyline, and amitriptyline with physical therapy,[45] showed amitriptyline alone reduced vulvar pain but not dyspareunia. Amitriptyline with physical therapy reduced vulvar pain and dyspareunia.

There is only one study that used SNRIs and no studies that used SSRIs for vulvodynia even though they are commonly prescribed.[18,50] Milnacipran (an SNRI) reduced pain and dyspareunia in one uncontrolled study.[50] Efficacy of SSRIs and SNRIs need to be tested in RCTs.

Women with vulvodynia can have an increased number of vulvar mast cells, which are part of the inflammatory response.[51] Palmitoylethanolamide (PEA) is an endogenous fatty acid amide that targets mast cell infiltration, and trans-polydatin is a natural antiinflammatory compound found in foods.[52] An RCT of PEA with trans-polydatin and intravaginal TENS compared with oral placebo and intravaginal TENS (Figure 4) showed no reduction of vulvar pain and dyspareunia except for in newly diagnosed women.[52] Both PEA and trans-polydatin are natural food supplements. There is evidence to support the use of PEA and TENS only in women who are newly diagnosed with vulvodynia.

Figure 4. Intravaginal Probe Used with Transcutaneous Electrical Nerve Stimulation.

Source: Vaginal probe courtesy of BEACMED s.r.l, Portalbera (PV), Italy.

Pelvic Floor Physical Therapy and Multimodal Therapy

Pelvic floor physical therapy is used to treat pelvic floor dysfunction and hypertonic pelvic floor muscles associated with vulvodynia (Table 4).[45,53,54] Pelvic floor physical therapy includes dilators, EMG biofeedback, and TENS.

Dilators desensitize the vulva to touch and pressure and stretch hypertonic pelvic floor muscles and the vagina.[54] One uncontrolled prospective study showed dilators[55] reduced dyspareunia. Dilators as a standalone therapy are a cost-effective, self-administered at home, and noninvasive intervention with a low adverse-effect profile. Efficacy of dilators as a single therapy needs to be tested in RCTs.

EMG biofeedback offers women immediate visual feedback regarding their pelvic floor muscle tonus. By watching a monitor, women learn how it feels when their pelvic floor

Table 4. Pelvic Floor Physical Therapy for the Treatment of Pelvic Floor Dysfunction and Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Dilators	Murina et al[55] 2008 N = 15 Vestibulodynia	2c	Uncontrolled observational prospective 4 sizes of sequentially larger vaginal dilators over 8 wk	Mean (SD) dyspareunia (Marinoff dyspareunia scale 0-3) reduced significantly from 2.2 (0.4) to 1.1 (0.9) ($P < .001$).
EMG biofeedback vs topical lidocaine	Danielsson et al[58] 2006 N = 46 Vulvar vestibulitis	2b	Randomized prospective cohort study 2 arms, no control group: (1) EMG biofeedback 3 times per d with intravaginal probe (2) 2% topical lidocaine gel applied 5-7 times per d for 2 mo, then 5% topical lidocaine ointment applied 5-7 times per d for 4 mo Follow-up at 6 mo and 12 mo	Both treatments showed significant improvement in vestibular pressure pain threshold (grams) (biofeedback group $P = .02$, lidocaine group $P = .007$) and pain threshold intensity (VAS 0-100) (biofeedback group $P = .001$, lidocaine group $P = .002$) at 12 mo. Neither the pain nor pain intensity had significant improvement when compared with one another. Compliance for 3 sessions of biofeedback per d was low.
TENS	Murina et al[60] 2008 N = 40 Vestibulodynia	1b	Double-blind placebo controlled RCT 2 arms: (1) TENS 2 times per wk with electrodes placed at the introitus for 10 wk (2) TENS placebo 2 times per wk with electrodes placed at the introitus for 10 wk 60- and 90-d follow-up	TENS reduced mean (SD) vulvar pain (VAS 0-10) significantly from 6.2 (1.9) to 2.1 (2.7) ($P = .004$) at 60 d posttest, and to 2.8 (2.5) ($P = .004$) at 90 d posttest. TENS placebo reduced mean (SD) vulvar pain from 6.7 (2.0) to 5.7 (2.2) at 60 d posttest, and to 5.6 (2.1) at 90 d posttest. Placebo pain reductions were statistically significant; no P value provided. Between-group comparisons were not conducted. TENS reduced mean (SD) dyspareunia (Marinoff dyspareunia scale 0-3) significantly from 2.7 (0.4) to 1.1 (0.9) ($P = .001$) at 60 d posttest, and to 1.1 (0.9) ($P = .001$) at 90 d posttest. TENS placebo reduced mean (SD) dyspareunia from 2.7 (0.4), to 2.4 (0.8) at 60 d posttest, and to 2.4 (0.8) at 90 d posttest. Neither reduction in pain due to placebo was significant; P values not provided. Between-group comparisons were not conducted.

(*Continued*)

Table 4. Pelvic Floor Physical Therapy for the Treatment of Pelvic Floor Dysfunction and Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Multimodal approach	Brotto et al[2] 2015 N = 116 PV	2b	Uncontrolled prospective study Multimodal approach Each participant received (1) 2 educational informational sessions on PV, (2) 3 educational psychological sessions, (3) 3 pelvic floor education sessions including home exercises and in office biofeedback, (4) final session with gynecologist to discuss skills acquired, referrals needed, and community resources All sessions over 10-12 wk	Dyspareunia (VAS 0-10) reduced significantly from pretreatment to posttreatment ($\beta = -5.3$, $P < .001$).
Multimodal physical therapy vs lidocaine	Morin et al[22] 2021 N = 212 PV	2c	Multicenter parallel group randomized trial 1:1 (1) Multimodal physical therapy: (a) education, (b) pelvic floor muscle exercises with biofeedback, (c) manual therapy, (d) dilation (2) Overnight lidocaine 5% ointment vestibule with gauze soaked in lidocaine applied to vulvar vestibule Baseline, posttreatment (10 wk), and 6-mo follow-up	Physical therapy significantly reduced mean (SD) dyspareunia (NRS 0-10) from 7.3 (0.2), to 2.7 (0.2) at 10 wk ($P <$ .01), with results maintained through follow-up at 6 mo 3.0 (0.2). Overnight lidocaine significantly reduced mean (SD) dyspareunia from 7.3 (0.2), to 4.5 (0.2) at 10 wk ($P < .01$), with results maintained through 6-mo follow-up 4.8 (0.2). Physical therapy significantly reduced dyspareunia compared with lidocaine from baseline to 10 wk, and through follow-up at 6 mo ($P < .001$).

Abbreviations: EMG, electromyography; NRS, numeric ratings scale; PV, provoked vestibulodynia; RCT, randomized controlled trial; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

muscles contract and relax. Three uncontrolled studies of EMG biofeedback[56–58] all showed a reduction in vulvar pain. EMG biofeedback is a noninvasive intervention with a low adverse-effect profile. Efficacy of biofeedback needs to be tested in RCTs.

TENS inhibits pain by (1) blocking pain signals at the injury from being propagated to larger afferent fibers in the central nervous system for processing (gate control theory)[59] and (2) stimulating the release of endogenous opioids.[60] A double-blind placebo RCT compared intravaginal TENS with a TENS sham.[60] TENS significantly reduced pain and dyspareunia.

There are 2 studies that have tested an interprofessional multimodal combined therapy approach. In the first study, which was uncontrolled,[2] 116 women received educational sessions on PV, psychology, pelvic floor exercises and biofeedback as well as a session with a gynecologist. Findings showed a significant decrease in dyspareunia at 3 months. In the second, a large multicenter parallel group randomized trial,[22] 212 women with PV were randomized to either multiple modality physical therapy (physical therapy, education, pelvic floor exercises with biofeedback, manual therapy, and dilation) or overnight 5% lidocaine ointment applied to the vulva. Findings showed a significant reduction in dyspareunia in both groups that was maintained at 6 months. Participants in the multimodal physical therapy group had significant improvement in all the measured outcomes; moreover, there was a significant reduction in pain and treatment effectiveness in women who received multimodal physical therapy compared with lidocaine.

Acupuncture

Women often turn to acupuncture to relieve vulvodynia (Table 5).[16] According to acupuncture theory, when

Table 5. Acupuncture for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Acupuncture	Schlaeger et al[64] 2015 N = 36 Vulvodynia	1b	RCT 1:1 Standardized acupuncture protocol twice per wk for 5 wk, total 10 sessions compared with waitlist control group Women in the waitlist control group received 10 sessions free acupuncture upon study completion	Acupuncture reduced mean (SD) pain (SF-MPQ, VAS 0-10) from 5.6 (1.9) to 2.7 (1.7). Usual care control reduced mean (SD) pain from 5.7 (2.3) to 5.1 (2.9). Acupuncture significantly reduced pain compared with usual care ($P = .003$). Acupuncture improved mean (SD) dyspareunia (FSFIp, 0-5) from 1.9 (1.3) to 3.2 (1.9). Usual care control improved dyspareunia from 1.7 (1.8) to 1.4 (1.8). Acupuncture significantly improved care compared with usual care ($P = .003$).

Abbreviations: FSFIp, Female Sexual Function Index Sensory Pain Subscale; RCT, randomized controlled trial; SF-MPQ, Short Form McGill Pain Questionnaire; VAS, visual analog scale.

the vital energy (*qi*) is blocked in vulvodynia, there is resultant pain and heat (felt as vulvar burning, stinging, and/or itching).[61] Acupuncture is applied to acupoints on the abdomen, suprapubically, and the extremities, but not directly to the vulva. Acupuncture moves blocked *qi*, relax pelvic floor muscles, and reduce pain and heat in the vulva. The physiologic mechanisms of acupuncture include increased release of mu opioids[62] and beta endorphins, both important in reducing the sensation of pain.[63] Acupuncture in an RCT[64] significantly reduced vulvar pain and dyspareunia in vulvodynia compared with a waitlist control. This standardized acupuncture guideline is currently being replicated in a National Institutes of Health (NIH)–funded double-blind sham placebo–controlled RCT of acupuncture for vulvodynia;[65,66] results will be reported in 2023. Acupuncture is a minimally invasive, non-pharmacologic intervention with a low adverse-effect profile.

Injections

Botulinum toxin type A injections[67–69] and low-molecular-weight-heparin[70] have been used to treat vulvodynia (Table 6). Botulinum toxin type A prevents the release of acetylcholine at the neuromuscular junction resulting in muscle paralysis and has been used in the prevention of migraine headaches.[71] Botulinum toxin type A is injected into trigger points (painful areas on the vulvar vestibule) and/or into hypertonic pelvic floor muscles. Out of 3 studies,[67–69] one double-blind RCT[67] showed that 50 units of botulinum toxin type A reduced dyspareunia but not vulvar pain in women with vulvodynia. The second double-blind RCT[69] showed no difference in vulvar pain between botulinum toxin type A 20 units and placebo at 3 and 6 months. The third study was uncontrolled.[68] Efficacy of botulinum toxin type A 50 units needs to be replicated in a larger RCT.

Low-molecular-weight heparin reduces pain by increasing blood flow to the vulvar stroma, reducing the release of nerve growth factor from mast cells, and decreasing inflammation.[70] In a single-blind RCT,[70] enoxaparin sodium administered subcutaneously to the abdomen by self-injection every day for 90 days showed a significant reduction in vulvar pain at 180 days compared with placebo.[70] Coagulation monitoring is not necessary with low-molecular-weight heparin, but women should be taught self-monitoring for bleeding and bruising. Evidence suggests low-molecular-weight heparin be used up to 90 days' duration.

Psychological Interventions

Cognitive Behavioral Therapy

CBT is used as a non-pharmacologic option for the management of PV (Table 7).[72] There were 2 uncontrolled studies of group CBT and other psychological modalities.[73,74] The first showed a reduction of dyspareunia in women with PV receiving group CBT.[73] The second showed a non-significant reduction in vulvar pain on a scale of 0 to 6, from 2.6 to 1.5 at 10 weeks posttreatment, and to 1.3 at one year posttreatment in unspecified vulvodynia compared with supportive psychotherapy.[74] There were 5 separate randomized uncontrolled studies of CBT with non-psychological interventions: 1% hydrocortisone cream,[26] physical therapy,[72] vestibulectomy plus EMG biofeedback,[56,57] and 5% lidocaine.[75] In the first uncontrolled randomized study, CBT significantly

Table 6. Injections for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Botulinum toxin type A	Diomande et al[67] 2019 N = 33 PV	1b	Double-blind RCT 3 arms: (1) Botulinum toxin type A 50 units (2) Botulinum toxin type A 100 units (3) Saline injections 1 injection subcutaneously into the dorsal vulvar vestibulum Pain assessed at 3 mo	Botulinum toxin type A 50 units reduced mean (SD) pain (VAS 0-10 cm) from 6.6 (2.0) to 0.2 (2.6) but not significantly more than the placebo ($P = .4$). Botulinum toxin type A 100 units reduced cotton swab test mean (SD) vulvar pain from 7.4 (1.9) to 6.0 (1.8) but not significantly more than the placebo ($P = .2$). Saline reduced mean (SD) pain from 7.0 (2.2) to 0.5 (1.3). Botulinum toxin type A 50 units reduced (Marinoff dyspareunia scale 0-3) dyspareunia from 2.0 to 1.5, significantly more than the placebo ($P = .03$). Botulinum toxin 100 units reduced dyspareunia from 2.5 to 1.5, but not significantly more than the placebo ($P = .3$). Saline dyspareunia pain score remained the same from before to after treatment: 2.0.
Botulinum toxin type A diluted in saline	Petersen et al[69] 2009 N = 60 PV	1b	Double-blind RCT 1 injection in to bulbospongiosus of botulinum toxin type A 20 units diluted in 0.5 mL normal saline or 0.5 mL placebo saline 6-mo follow-ups	Botulinum toxin 20 units and the placebo significantly reduced pain (VAS 10 cm) from baseline (botulinum toxin type A, 7.5; placebo, 7.6) to 6 mo (6-mo values not provided) ($P < .001$). There was not a significant difference between improvement in the botulinum toxin 20 units group compared with the placebo group ($P = .984$).
Botulinum toxin type A	Hansen et al[68] 2019 N = 109 PV	2b	Prospective uncontrolled trial 100 units botulinum toxin type A 50 units to each side	Cotton swab test vulvar pain (NRS 0-10) (n = 63) reduced significantly from 6.8 to 5.5, at 6 mo ($P < .01$). Dyspareunia (NRS 0-10) (n = 44) reduced significantly from 7.8 to 5.8 ($P < .01$). 30 participants dropped before follow-up.

(*Continued*)

Table 6. (Continued)

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Enoxaparin	Farajun et al[70] 2012 N = 40 PV	1b	Single-blinded RCT Self-administered 40 mg enoxaparin (low-molecular-weight heparin) or placebo saline self-administered subcutaneously to the abdomen every d for 90 d Pain measured at 90 and 180 d Enoxaparin sodium requires daily self-injections and may promote bruising and bleeding	Enoxaparin reduced cotton swab test vulvar pain (NRS 0-10) from 8.2 to 6.25 at end of treatment and to 5.8 at 180-d follow-up. Saline reduced pain from 7.5 to 6.6 at end of treatment However, pain increased to 6.8 at 180-d follow-up. Enoxaparin reduced pain significantly compared with saline from baseline to 180-d follow-up ($P = .004$). Enoxaparin sodium significantly reduced pain during intercourse (percentage reduced) 28.9% at 90 d ($P = .057$). Placebo reduced pain by 4.4%; P value not provided.

Abbreviations: NRS, numeric ratings scale; PV, provoked vestibulodynia; RCT, randomized controlled trial; VAS, visual analog scale.

reduced dyspareunia compared with 1% hydrocortisone cream at 6 months.[26] In the second uncontrolled randomized study, CBT and physical therapy[72] showed a decrease in vulvar pain and dyspareunia. Physical therapy significantly reduced vulvar pain more than CBT, but there was no significant difference between CBT's and physical therapy's reduction in dyspareunia. In the third uncontrolled randomized study, CBT compared with vestibulectomy compared with EMG biofeedback[56,57] showed reduced vulvar pain and dyspareunia in all 3 groups at 6 months for women with PV. In a continuation of the same study at 2.5 years, vestibulectomy had a greater reduction in vulvar pain, but all groups had a sustained reduction in pain. Both CBT and vestibulectomy reduced dyspareunia at 2.5 years. However, women in the CBT group were significantly more satisfied with their treatment than women who received vestibulectomy, suggesting that women may prefer less invasive treatments. In the fourth uncontrolled randomized study, both cognitive behavioral couples therapy and 5% overnight lidocaine ointment[75] reduced dyspareunia at 12-week and 6-month follow-up in women with PV, but treatment groups were not compared with one another. Use of CBT can be limited by a lack of CBT providers and access to CBT for women with low income. Efficacy of CBT needs to be tested in RCTs.

Hypnosis

Hypnosis for vulvodynia has only been evaluated in one uncontrolled study[76] that showed a significant reduction of vulvar pain and dyspareunia (Table 7). Because hypnosis is a noninvasive therapy for the treatment of chronic pain conditions,[77] it may be considered a viable treatment option for women with PV. Efficacy of hypnosis needs to be tested in RCTs.

Surgical Interventions

Cold Knife Vestibulectomy and Laser Therapy

It is unknown why vestibulectomy reduces vulvar pain and dyspareunia (Table 8). Two studies[56,57,78] on vestibulectomy found significant reduction in vulvar pain and dyspareunia, one of which was compared with group CBT and EMG biofeedback[56] that continued 2.5 years postoperatively.[57] Twenty-seven percent of women declined to participate after they had been randomized to the vestibulectomy group, suggesting that not all women may view vestibulectomy as an acceptable treatment option.[56] Vestibulectomy is not widely used because of limited patient acceptability. Because of its invasive nature, vestibulectomy should be considered a treatment of last resort.

KTP-Nd Yag laser uses a deep depth of ablation, may assist in remodeling collagen and vasculature, and may destroy pain fibers. There was a non-randomized case series[79] of 67 women who were self-selected to receive an interprofessional treatment program including up to 3 Yag laser treatments (35 women) at least one month apart compared with 32 women receiving usual care for vulvodynia without laser therapy. Baseline differences were not controlled. There was a significant reduction in pain at one-month follow-up in women receiving laser therapy, but no difference in pain at

Table 7. Psychological Interventions for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
M-gCBT vs education support group	Guillet et al[73] 2019 N = 32 Localized provoked vulvodynia	2b	Randomized uncontrolled prospective cohort study 2 arms: (1) M-gCBT once per wk for 8 wk (2) Education support group therapy, 3 sessions in 8 wk	Education support group's dyspareunia (tampon test, Likert 0-10) reduced significantly from baseline to 3 mo ($P = .012$), and from baseline to 6 mo ($P < .001$). M-gCBT group's dyspareunia reduced significantly from baseline to 3 mo ($P < .001$), and from baseline to 6 mo ($P < .001$). There was no significant difference between dyspareunia scores in the education support group and M-gCBT group ($P = .427$).
CBT	Masheb et al[74] 2009 N = 50 Vulvodynia	2b	Randomized uncontrolled prospective cohort study CBT 1 session/wk for 10 wk Supportive psychotherapy 1 session/wk for 10 wk Baseline, posttreatment at 10 wk and 3, 6, and 12-mo follow-up	CBT reduced mean (SE) vulvar pain severity (Yale–New Haven Multidimensional Pain Severity scale, 0-6) from 2.6 (0.2) to 1.5 (0.3) at 10 wk posttreatment, and to 1.3 (0.3) at 1 y posttreatment. Supportive psychotherapy reduced mean (SE) vulvar pain severity from 3.0 (0.6) to 1.9 (0.3) at 10 wk posttreatment, and 1.3 (0.3) at 1 y posttreatment. There was not a significant difference improvement of vulvar pain severity between groups at 1 y ($F = 2.63$ $P = .053$).
CBT vs PT	Goldfinger et al[72] 2016 N = 20 PV	2b	Randomized uncontrolled CBT or PT 8 1.5-h one-on-one sessions of CBT or PT and homework activities Pain measured at baseline, posttreatment, and 6-mo follow-up	CBT reduced cotton swab test mean (SD) vulvar pain (NRS 0-10) from 3.94 (2.3) at pretreatment to 3.26 (2.69) at posttreatment ($P = .144$) and 2.62 (2.88) at follow-up (pretreatment to follow-up, $P = .009$). PT significantly reduced cotton swab test mean (SD) vulvar pain from 4.16 (1.53) at pretreatment to 1.28 (1.05) at posttreatment ($P = .001$) and 1.86 (2.22) at follow-up (pretreatment to follow-up, $P = .008$). PT reduced average cotton swab test vulvar pain significantly compared with CBT ($P = 0.009$). CBT significantly reduced mean (SD) pain intensity with intercourse (dyspareunia) from 5.2 (1.4) to 2.6 (1.43) at posttreatment ($P = .004$) to 2.1 (1.37) at 6 mo (pretreatment to follow-up, $P = .001$). PT significantly reduced mean (SD) pain intensity with intercourse from 5.05 (1.86) at pretreatment to 2.7 (2.36) at posttreatment ($P = .004$) to 2.4 (2.63) at follow-up (pretreatment to follow-up, $P < .001$). There was not a significant difference between the 2 groups; *P* value not provided.

(*Continued*)

Table 7. Psychological Interventions for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
CBCT Lidocaine	Bergeron et al[75] 2021 N = 108 women and their partners PV	2b	Randomized uncontrolled trial 2 arms: (1) CBCT 1, 75-min session per wk for 12 wk (2) 5% lidocaine ointment overnight to vulvar vestibule	CBCT reduced mean (SD) pain intensity during intercourse (NRS 0-10) from 6.8 (1.8) at baseline to 4.7 (2.2) at 12 wk posttreatment, and to 4.5 (2.5) at 6 mo posttreatment. 5% overnight lidocaine reduced mean (SD) pain intensity during intercourse from 6.5 (1.8) at baseline to 4.7 (2.2) at 12 wk posttreatment, and to 4.7 (2.6) at 6 mo posttreatment. No significant difference between the treatment effect of CBCT vs 5% overnight lidocaine.
Hypnosis	Pukall et al[76] 2007 N = 8 Vulvar vestibulitis	2c	Case series with no control group Hypnotherapy, 6 sessions Follow-up at 1 mo and 6 mo posttreatment	Cotton swab test vulvar pain scores (NRS 0-10) significantly reduced from pretreatment to 1 and 6 mo posttreatment ($P \leq .01$). Cotton rub test vulvar pain scores (NRS 0-10) significantly reduced from pretreatment to 6 mo ($P \leq .05$) but not pretreatment to 1 mo posttreatment. Intercourse pain measured (MPQ PPI, 0-5) improved significantly between baseline and 1-mo follow-up, and baseline and 6-mo follow-up ($P = .006$); and intercourse-/nonintercourse-related pain frequency ($P = .03$). Nonintercourse vulvar pain severity MPQ PPI improved significantly between baseline and 1-mo follow-up, and baseline and 6-mo follow-up ($P = .002$).

Abbreviations: CBCT, cognitive behavioral couples therapy; CBT, cognitive behavioral therapy; M-gCBT, mindfulness-based group cognitive behavioral therapy; MPQ PPI, McGill Pain Questionnaire Present Pain Index; NRS, numeric ratings scale; PT, physical therapy.

9-to-12–month follow-up. There was a second case series[80] using fractional CO_2 laser (used for skin resurfacing at a superficial level) for PV; 67.6% of women with PV reported improvement, and all patients completed the therapy. Efficacy of both KTP-Nd Yag laser and CO_2 laser need to be tested in RCTs.

Arthroscopic Hip Surgery

Orthopedists, physiatrists, and physical therapists have observed a relationship between generalized vulvodynia and intra-articular hip disorders, such as femoro-acetabular impingement syndrome and labral tears (Table 8). The labrum is the connective tissue lining of the acetabulum (the hip socket) where the head of the femur inserts and aids in smooth movement and increases stability of the hip joint.[13,81] In a case series[13] of 26 individuals with femoro-acetabular impingement syndrome and vulvodynia, arthroscopic correction improved vulvar pain postoperatively in 6 (23%) women under the age of 30. Clinicians may consider an orthopedic source of vulvar pain and referral to an orthopedist and/or physical therapist as warranted.

Cannabis

Medical cannabis has been used to treat chronic neuropathic pain conditions (Table 9).[82] Cannabis has anti-inflammatory properties.[83] Medical cannabis is not legal in all states and remains illegal at the federal level. Therefore there are few federal funding mechanisms supporting studies on the pain-relieving properties of cannabis.[84] An online survey of 38 women with vulvodynia found that cannabis reduced vulvar pain and dyspareunia; however, the route of administration was not reported.[85] There have been no rigorous studies on the use of medical cannabis, including utility and safety profiles, for vulvodynia.

DISCUSSION

Vulvodynia research is in its infancy. Most studies lack control groups, have small sample sizes, and do not compare

Table 8. Surgical Treatments for Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Cold knife vestibulectomy vs GCBT vs EMG biofeedback	Bergeron et al[56,57] 2001 and 2008 N = 78 Vulvar vestibulitis	2b	2001: Prospective uncontrolled randomized trial 3 arms: (1) Cold knife vestibulectomy with a 6-wk postoperative visit (2) GCBT, 8 sessions over 12 wk (3) Surface EMG biofeedback 8 sessions over 12 wk with twice daily practice sessions All treatment methods had a posttreatment and 6-mo follow-up 2008: 2.5-y follow-up study conducted in 2008	2001: 7 of 26 (27%) of women randomized to the vestibulectomy group declined participation ($P < .01$). All 3 treatment groups had significant reduction in cotton swab test vulvar pain (average of 2 test scores, scale not provided) at posttreatment, 6 mo, and 2.5 y ($P < .01$). Vestibulectomy reduced vulvar pain by 70%, GCBT by 28.6%, and biofeedback by 23.7%. Vestibulectomy reduced vulvar pain significantly from baseline to posttreatment, and through 6-mo follow-up compared with GCBT and to EMG biofeedback ($P < .01$). All 3 groups had significant improvement in pain intensity during intercourse (NRS 0-10) ($P < .01$). Vestibulectomy reduced intercourse pain by 52.5%, GCBT by 37.5%, and biofeedback by 35%. Vestibulectomy significantly improved pain intensity during intercourse from baseline to 6-mo follow-up compared with GCBT and EMG biofeedback ($P <0.01$). Pain (MPQ PRI 0-78) significantly reduced in all treatment groups ($P < .01$). Vestibulectomy reduced pain by 46.8%, GCBT by 27.7%, and biofeedback by 22.8%. Between-group comparison was not reported. 2008: 68% of women participated at 2.5-y follow-up. All groups had a significant reduction in pain at 2.5 y ($P < .01$). Vestibulectomy group had significantly lower cotton swab test vulvar pain from 6 mo to 2.5 y as compared with biofeedback $F(62,75) = 8.96$ ($P < .01$), and GCBT $F(2,75) = 10.38$ ($P < .01$). Vestibulectomy group had significantly lower pain during intercourse than the biofeedback group $F(2,75) = 3.50$ ($P < .05$) but was not compared with the GCBT group. Vestibulectomy group pain (MPQ PRI) was significantly lower than biofeedback ($P < .05$) and GCBT groups ($P < .05$).

(*Continued*)

Table 8. (Continued)

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Cold knife posterior vulvectomy	Tommola et al[78,93] 2011 N = 57 Vulvar vestibulitis	2c	Prospective descriptive cohort study Cold knife posterior vulvectomies performed from 1995 to 2007 Long-term follow-up performed for a median of 36 mo (range 5 to 158 mo) No set time points for data collection	19 (35.2%) of participants reported they were cured by vulvectomy (complete response); 30 (55.6%) had partial response, and 5 (9.3%) had no response. Dyspareunia (VAS 0-10) reduced from 9 to 3 (66.7% decrease; $P < .001$). 7 (13%) women reported dyspareunia that required topical anesthetic postoperatively. Posterior vestibular tenderness measured with the cotton swab test (0-10) was absent in 34 (64.2%) participants, 14 (25.9%) reported some degree of constant vulvar pain, and 21% had complications (bleeding, hematoma, infection, Bartholin's cyst, vulvar fissure). Duration of wound pain was 14 d (range = 0-90 d). Duration of sick leave for postoperative recovery was 10.5 d (range 3-24 d).
Yag laser Multidisciplinary Treatment	Trutnovsky et al[79] 2021 N = 67 Vulvodynia	1c	Case study 2 arms: (1) Yag laser up to 3 sessions with 1 session per mo along with a multidisciplinary treatment program (n = 35) (2) Interprofessional treatment program that did not include Yag laser (n = 32)	Yag laser significantly reduced mean (SD) pain during a vulvar cotton swab test (NRS 0-10) from 6.1 (2.6) to 3.1 (2.6) 1-mo posttreatment ($P < .001$). At 9-12 mo Yag laser group participants reported 26% were a lot better, 17% better, 23% a little better and 34% unchanged. Multidisciplinary group reported 13% a lot better, 41% better, 28% a little better, and 19% unchanged. At 9-12 mo there was 73% overall improvement with no significant difference between groups ($P = .6$).
Fractional CO_2 laser	Murina et al[80] 2016 N = 70 Vestibulodynia, n = 37 Genitourinary syndrome of menopause, n = 33	4	Case series Women underwent 3 fractional CO_2 laser treatments Data collected at baseline, 4, 8, 12 wk, and 4 mo	Using analysis of covariance, there was a statistically significant difference in vulvar pain scores (VAS 0-10) in both groups ($P < .05$) through 4-mo follow-up. No statistical results reported, only discussion of results. 13 (35.2%) of the vestibulodynia group reported dyspareunia (Marinoff dyspareunia scale 0-3) symptoms were very improved, 12 (32.4%) reported symptoms improved, and 12 (32.4%) reported no change in dyspareunia.

(*Continued*)

Table 8. (Continued)

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Arthroscopic surgery	Coady et al[13] 2015 N = 26 Femoral acetabular impingement syndrome and generalized vulvodynia or clitorodynia	4	Case series Uncontrolled observational Arthroscopic surgery to remove impingement between acetabular rim and femoral head	Vulvar pain (NRS 0-10) was reduced from 6.7 to 3 postoperatively in the improvement group. Pain was reduced from 6.7 to 4.8 postoperatively in the non-improvement group. There was a significant reduction in pain between groups ($P = .03$). Only 6 (23%) had significant reduction in pain after arthroscopy, and they were all under 30 y old. 1 woman had worse pain.

Abbreviations: EMG, electromyography; GCBT, group cognitive behavioral therapy; MPQ PRI, McGill Pain Questionnaire Pain Rating Index; NRS, numeric ratings scale; VAS, visual analog scale

Table 9. Cannabis for the Treatment of Vulvodynia

Treatment	Author/ Year/ Sample Size	Level of Evidence	Study Design/Treatment Groups/Dosages	Results
Cannabis	Barach et al[85] 2020 N = 38 Vulvodynia	2c	Online survey Pain relief of vulvodynia symptoms from cannabis use. Average use 17.3 d/mo Route of consumption not stated	Using cannabis significantly improved sharp/stabbing, dyspareunia, soreness, burning, stinging, throbbing, rawness, itching, and pain with sitting, exercise, and tight pants (Likert −2 to 2) ($P = .002$) as well as tampon insertion pain ($P < .001$) using two-tailed t-test.

multiple treatment groups with one another. These design flaws limit validity, rigor, reproducibility, and generalizability, which makes it difficult for clinicians to prescribe therapies for vulvodynia that are evidence-based. Also, measures of pain and dyspareunia are not standardized between studies, making it difficult to compare study results.[86] There is little evidence supporting the efficacy of treatments for vulvodynia, singularly or together. Most vulvodynia studies were performed in a clinical setting with women expecting treatment and not expecting to be randomized to a non-treatment or placebo control group.[2] It is unknown what the effect of a control group would have had on study treatment outcomes for vulvar pain and dyspareunia. For example, several RCTs[21,46,47] found no reduction in dyspareunia compared with placebo controls. Placebo treatments can have a therapeutic effect of up to 58%.[87] Without a control group it cannot be determined if findings are due to the treatment or other influencing factors. Placebo groups allow for the true treatment effect to be determined. Also, in studies testing multiple treatments, the benefit of using multiple modalities compared with individual treatments has not been tested.[2]

Recommended Treatments for Vulvodynia

There is uncertainty as to how to afford relief to women who suffer from the debilitating pain of vulvodynia. Clinicians tend to prescribe empirically, based on treatments that have worked for women or recommendations from colleagues. The authors recommend that once women are diagnosed with vulvodynia, clinicians teach women to evaluate their vulvar pain and dyspareunia on a 0 to 10 NRS, keeping a log of their pain ratings and treatments attempted. Tracking this information will enable the clinician and woman to develop a personalized treatment plan.

Once diagnosed, women can be referred to the National Vulvodynia Association (nva.org), which has resources and listings for local support groups, as well as a quarterly newsletter summarizing the latest research. The National Vulvodynia Association also has clinician resources. There are also support groups on social media, including Facebook and Reddit.

Changes in sexual position, vaginal lubricants, and good hygiene will not reduce the pain of vulvodynia. Suggestions that women need "to just relax" during intercourse or get more

Table 10. Treatment Recommendations for Vulvodynia Based on Level of Evidence	
Line	**Treatment Recommendation**
First line: RCT or comparative effectiveness	
Non-pharmacologic	Multimodal physical therapy[22]
	Acupuncture[64]
	Intravaginal TENS as a single therapy[60]
Pharmacologic	Overnight 5% lidocaine cream applied with gauze to vulvar vestibule[22]
	Oral desipramine with 5% lidocaine cream[21]
	Intravaginal diazepam tablets with intravaginal TENS[48]
Invasive pharmacologic	Botulin toxin type A 50 units[67]
	Enoxaparin sodium (low-molecular-weight heparin) subcutaneous injections[70]
Second line: Non-pharmacologic; pre to posttest or group comparison without a control group	Vaginal dilators as a single therapy[55]
	EMG biofeedback[56–58]
	Hypnotherapy[76]
	Cognitive behavioral therapy[26,56,57,72–75]
Third line: Topical pharmacologic; pre to posttest without a control group	Gabapentin cream[28]
	Amitriptyline cream[30]
	Amitriptyline with baclofen cream[29]
	Ketamine-amitriptyline cream[31]
	Conjugated equine estrogen cream[33]
	Estradiol/testosterone cream[32]
Fourth line: Case studies or prospective descriptive studies or invasive	Milnacipran[50]
	Laser therapy[79,80]
	Cold knife vestibulectomy[56,57,78]

Abbreviations: EMG, electromyography; RCT, randomized controlled trial; TENS, transcutaneous electrical nerve stimulation

"turned on" in response to reports of dyspareunia are patronizing, dismissive, and not therapeutic. It is the authors' opinion that these comments may be offered by the clinician because women may not respond to treatments and clinicians may feel helpless.

There are 8 treatments that have the highest level of evidence for reduction of pain and/or dyspareunia based on either RCTs or a comparative effectiveness trial. The authors recommend clinicians first prescribe these 8 treatments. Therapies that are non-pharmacologic and least or minimally invasive can be attempted first with additional treatments as needed: (1) multimodal physical therapy (education, pelvic floor muscle exercises with biofeedback, manual therapy, and vaginal dilators),[22] (2) acupuncture,[64] (3) intravaginal TENS (as a single therapy),[60] (4) overnight 5% lidocaine ointment soaked in a gauze and applied to the vulvar vestibule,[22] (5) oral desipramine with 5% lidocaine cream,[21] (6) intravaginal diazepam tablets with intravaginal TENS,[48] (7) botulinum toxin type A 50 units,[67] and (8) enoxaparin sodium (low-molecular-weight heparin) subcutaneous injection.[70]

The following non-pharmacologic treatments have shown reduction in pain and/or dyspareunia in pre to posttest studies or group comparisons without a control group. This group includes vaginal dilators (as a single therapy),[55] EMG biofeedback,[56–58] hypnotherapy,[76] and CBT.[26,56,57,72–75]

If further treatment is warranted, there is low-quality evidence for the following topical treatments that were shown to reduce pain in pre to posttest studies (without a control group): gabapentin cream,[28] amitriptyline cream,[30] amitriptyline with baclofen cream,[29] ketamine-amitriptyline cream,[31] conjugated equine estrogen cream,[33] and estradiol/testosterone cream.[32]

There is also low-quality evidence for the use of oral milnacipran (reduced pain pre to posttest studies without a control group)[50] and laser therapy (reduced pain in a case series).[79,80] Because of the invasive nature of cold knife vestibulectomy,[56,57,78] it should be used after other treatment options have been exhausted. See Table 10 for a quick guide to treatment recommendations.

Treatments That Have No Support for Use in Vulvodynia

Cromolyn sodium, a mast cell stabilizer, reduces chronic urticaria, inflammation, and hypersensitivity reactions. A small-sample double-blind study in women with PV showed that cromolyn sodium cream did not reduce vulvar pain compared with placebo.[34] There is no evidence to support prescribing cromolyn sodium for vulvodynia. Nifedipine, a calcium channel blocker, relaxes smooth muscles, decreases inflammatory infiltrates, and reduces hypertonicity of the

Table 11. Level of Evidence for Appraising Research	
Level	**Description**
1a	Systematic review of randomized controlled trials
1b	Randomized controlled trials
1c	Case series
2a	Systematic review of cohort studies
2b	Cohort study or subpar randomized controlled trials
2c	Ecological or outcomes research
3a	Systematic review of case control studies
3b	Case control study
4	Case series and subpar cohort or case control studies

Adapted from the Oxford Centre for Evidence-Based Medicine: Levels of Evidence (2009).[17]

internal anal sphincter in patients with chronic anal fissures.[88] In a double-blind RCT,[35] nifedipine showed no reduction in dyspareunia in women with PV as compared with placebo. Antiepileptics treat vulvodynia by calming the central nervous system and are used to treat neuropathic pain conditions.[89,90] In a multicenter double-blind crossover RCT, oral gabapentin did not reduce dyspareunia.[90] There is no evidence to support the use of oral gabapentin for vulvodynia.

Future of Vulvodynia Treatments

Because the etiology of vulvodynia remains unknown, it has been virtually impossible to develop effective treatments for the 7% of American women suffering from vulvodynia. Vulvodynia treatments are still based largely on case and anecdotal reports. As of late, vulvodynia specialists are beginning to focus more on uncovering the etiologic factors of vulvodynia and their potential associations that may guide future vulvodynia treatments. This scientific progress is reflected in emerging new diagnostic subcategories of vulvodynia based on etiology.[91] These diagnostic subcategories have not been validated. Most are based on either histological findings from vulvar biopsy or response to expensive or invasive testing such as 3 Tesla magnetic resonance imaging and serial pudendal nerve blocks. Currently, expert clinicians have started to use these diagnostic subcategories to guide their management of women with vulvodynia.[91] These subcategories may be subject to change and are based on specific clinical findings. They are (1) hormonally associated vestibulodynia, (2) inflammatory vestibulodynia, (3) congenital neuroproliferative vestibulodynia, (4) acquired neuroproliferative vestibulodynia, and (5) overactive (hypertonic) pelvic floor muscle dysfunction. Other factors associated with vulvodynia that have been identified include (1) pudendal neuralgia, (2) spinal pathology and vulvar dysesthesia, and (3) persistent genital arousal disorder. There are no plans at this time to issue a new set of definitions and guidelines for the diagnosis and treatment of vulvodynia. An NIH-sponsored study, "Vestibulodynia: Understanding Pathophysiology and Determining Appropriate Treatments (VBD UPDATe)," is currently underway.[92] The investigators have identified 2 distinct subtypes of vestibulodynia that may benefit from 2 distinct types of treatments. The subtypes differ based on patient-reported outcomes, physical and mental health, production of cytokines involved with inflammation, and expression of microRNAs that regulate gene expression. The study is in its third of 5 years.

CONCLUSION

It is remarkable how many treatments, including vestibulectomy, women are willing to undergo to obtain relief from the symptoms of vulvodynia.[18] Because current treatments for vulvodynia only focus on symptom amelioration, there is a need for research that focuses on the etiology and characterization of vulvodynia. This article provides a framework for clinicians to understand, diagnose, and treat women with vulvodynia using evidence-based approaches. The authors encourage clinicians to avail themselves of changes in the state of the science when treating women with vulvodynia. Importantly, there is an urgent need to conduct rigorous controlled trials to identify the most effective treatments for this difficult condition.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

REFERENCES

1. Bornstein J, Goldstein AT, Stockdale CK, et al. 2015 ISSVD, ISSWSH and IPPS consensus terminology and classification of

persistent vulvar pain and vulvodynia. *Obstet Gynecol*. 2016;127(4):745-751.
2. Brotto LA, Yong P, Smith KB, Sadownik LA. Impact of a multidisciplinary vulvodynia program on sexual functioning and dyspareunia. *J Sex Med*. 2015;12(1):238-247.
3. Basson R. The recurrent pain and sexual sequelae of provoked vestibulodynia: a perpetuating cycle. *J Sex Med*. 2012;9(8):2077-2092.
4. Schlaeger JM, Pauls HA, Powell-Roach KL, et al. Vulvodynia, "a really great torturer": a mixed methods pilot study examining pain experiences and drug/non-drug pain relief strategies. *J Sex Med*. 2019;16(8):1255-1263.
5. Masheb RM, Brondolo E, Kerns RD. A multidimensional, case-control study of women with self-identified chronic vulvar pain. *Pain Med*. 2002;3(3):253-259.
6. Young AL, Miller AD. "This girl is on fire": sensemaking in an online health community for vulvodynia. Presented at: CHI Conference on Human Factors in Computing Systems; May 4-9, 2019; Glasgow, Scotland.
7. Schlaeger JM, Patil CL, Steffen AD, et al. Sensory pain characteristics of vulvodynia and their association with nociceptive and neuropathic pain: an online survey pilot study. *Pain Rep*. 2019;4(2):e713.
8. Goldstein AT, Pukall CF, Brown C, Bergeron S, Stein A, Kellogg-Spadt S. Vulvodynia: assessment and treatment. *J Sex Med*. 2016;13(4):572-590.
9. Johannesson U, Blomgren B, Hilliges M, Rylander E, Bohm-Starke N. The vulval vestibular mucosa—morphological effects of oral contraceptives and menstrual cycle. *Br J Dermatol*. 2007;157(3):487-493.
10. Falsetta ML, Foster DC, Woeller CF, et al. Identification of novel mechanisms involved in generating localized vulvodynia pain. *Am J Obstet Gynecol*. 2015;213(1):38.e1-38.e12.
11. Morin M, Binik YM, Bourbonnais D, Khalife S, Ouellet S, Bergeron S. Heightened pelvic floor muscle tone and altered contractility in women with provoked vestibulodynia. *J Sex Med*. 2017;14(4):592-600.
12. Lev-Sagie A, Witkin SS. Recent advances in understanding provoked vestibulodynia. *F1000Res*. 2016;5:2581.
13. Coady D, Futterman S, Harris D, Coleman SH. Vulvodynia and concomitant femoro-acetabular impingement: long-term follow-up after hip arthroscopy. *J Low Genit Tract Dis*. 2015;19(3):253-256.
14. Terminology. International Association for the Study of Pain. Updated 2017. Accessed May 17, 2021. https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Neuropathicpain
15. Reed BD, Sen A, Harlow SD, Haefner HK, Gracely RH. Multimodal vulvar and peripheral sensitivity among women with vulvodynia: a case-control study. *J Low Genit Tract Dis*. 2017;21(1):78-84.
16. Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. *J Low Genit Tract Dis*. 2005;9(1):40-51.
17. Howick J, Chalmers I, Glasziou P, et al. The Oxford Levels of Evidence 2. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence. Published 2011. Accessed 12/19/2021
18. Lamvu G, Alappattu M, Witzeman K, Bishop M, Robinson M, Rapkin A. Patterns in vulvodynia treatments and 6-month outcomes for women enrolled in the National Vulvodynia Registry—an exploratory prospective study. *J Sex Med*. 2018;15(5):705-715.
19. Mao JJ, Davis RT, Coeytaux R, et al. Acupuncture for chronic low back pain: recommendations to Medicare/Medicaid from the Society for Acupuncture Research. *J Altern Complement Med*. 2019;25(4):367-369.
20. Liang AL, Gingher EL, Coleman JS. Medical cannabis for gynecologic pain conditions: a systematic review. *Obstet Gynecol*. 2022;139(2):287-296.
21. Foster DC, Kotok MB, Huang L-S, et al. Oral desipramine and topical lidocaine for vulvodynia: a randomized controlled trial. *Obstet Gynecol*. 2010;116(3):583.
22. Morin M, Dumoulin C, Bergeron S, et al. Multimodal physical therapy versus topical lidocaine for provoked vestibulodynia: a multicenter, randomized trial. *J Obstet Gynecol*. 2021;224(2):189.e1-189.e12.
23. Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. *Obstet Gynecol*. 2003;102(1):84-87.
24. Murina F, Radici G, Bianco V. Capsaicin and the treatment of vulvar vestibulitis syndrome: a valuable alternative? *MedGenMed*. 2004;6(4):48.
25. Steinberg AC, Oyama IA, Rejba AE, Kellogg-Spadt S, Whitmore KE. Capsaicin for the treatment of vulvar vestibulitis. *Am J Obstet Gynecol*. 2005;192(5):1549-1553.
26. Bergeron S, Khalifé S, Dupuis MJ, McDuff P. A randomized clinical trial comparing group cognitive-behavioral therapy and a topical steroid for women with dyspareunia. *J Consult Clin Psychol*. 2016;84(3):259-268.
27. Brown CS, Wan J, Bachmann G, Rosen R. Self-management, amitriptyline, and amitripyline plus triamcinolone in the management of vulvodynia. *J Womens Health (Larchmt)*. 2009;18(2):163-169.
28. Boardman LA, Cooper AS, Blais LR, Raker CA. Topical gabapentin in the treatment of localized and generalized vulvodynia. *Obstet Gynecol*. 2008;112(3):579-585.
29. Nyirjesy P, Lev-Sagie A, Mathew L, Culhane JF. Topical amitriptyline-baclofen cream for the treatment of provoked vestibulodynia. *J Low Genit Tract Dis*. 2009;13(4):230-236.
30. Pagano R, Wong S. Use of amitriptyline cream in the management of entry dyspareunia due to provoked vestibulodynia. *J Low Genit Tract Dis*. 2012;16(4):394-397.
31. Poterucha TJ, Murphy SL, Rho RH, et al. Topical amitriptyline-ketamine for treatment of rectal, genital, and perineal pain and discomfort. *Pain Physician*. 2012;15:485-488.
32. Burrows LJ, Goldstein AT. The treatment of vestibulodynia with topical estradiol and testosterone. *Sex Med*. 2013;1(1):30-33.
33. Langlais EL, Lefebvre J, Maheux-Lacroix S, Bujold E, Fortier M, Bouchard C. Treatment of secondary vestibulodynia with conjugated estrogen cream: a pilot, double-blind, randomized placebo-controlled trial. *J Obstet Gynaecol Can*. 2017;39(6):453-458.
34. Nyirjesy P, Sobel JD, Weitz MV, Leaman DJ, Small MJ, Gelone SP. Cromolyn cream for recalcitrant idiopathic vulvar vestibulitis: results of a placebo controlled study. *Sex Transm Infect*. 2001;77(1):53-57.
35. Bornstein J, Tuma R, Farajun Y, Azran A, Zarfati D. Topical nifedipine for the treatment of localized provoked vulvodynia: a placebo-controlled study. *J Pain*. 2010;11(12):1403-1409.
36. Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Increased intraepithelial innervation in women with vulvar vestibulitis syndrome. *Gynecol Obstet Invest*. 1998;46(4):256-260.
37. Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. *Gynecol Obstet Invest*. 1999;48(4):270-275.
38. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiol Dis*. 1998;5(4):209-227.
39. Akel R, Cohen C, Fuller C. Caution with topical capsaicin. *Clin Exp Dermatol*. 2020;45(6):739-739.
40. Rose M, Kam P. Gabapentin: pharmacology and its use in pain management. *Anaesthesia*. 2002;57(5):451-462.
41. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol*. 2005;96(6):399-409.
42. Yang Y, Maher DP, Cohen SP. Emerging concepts on the use of ketamine for chronic pain. *Expert Rev Clin Pharmacol*. 2020;13(2):135-146.

43. Stone RH, Abousaud M, Abousaud A, Kobak W. A systematic review of intravaginal diazepam for the treatment of pelvic floor hypertonic disorder. *J Clin Pharmacol*. 2020;60:S110-S120.
44. Graziottin A, Murina F, Gambini D, et al. Vulvar pain: the revealing scenario of leading comorbidities in 1183 cases. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:50-55.
45. Bardin MG, Giraldo PC, Martinho N. Pelvic floor biometric changes assessed by 4D translabial ultrasound in women with vulvodynia submitted to physical therapy: a pilot study of a randomized controlled trial. *J Sex Med*. 2020;17(11):2236-2246.
46. Crisp CC, Vaccaro CM, Estanol MV, et al. Intra-vaginal diazepam for high-tone pelvic floor dysfunction: a randomized placebo-controlled trial. *Int Urogynecol J*. 2013;24(11):1915-1923.
47. Holland MA, Joyce JS, Brennaman LM, Drobnis EZ, Starr JA, Foster Sr RT. Intravaginal diazepam for the treatment of pelvic floor hypertonic disorder: a double-blind, randomized, placebo-controlled trial. *Female Pelvic Med Reconstr Surg*. 2019;25(1):76-81.
48. Murina F, Felice R, Di Francesco S, Oneda S. Vaginal diazepam plus transcutaneous electrical nerve stimulation to treat vestibulodynia: a randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol*. 2018;228:148-153.
49. Rothenberger R, Jones W, MacNeill C. Itraconazole improves vulvodynia in fungus culture-negative patients post fluconazole failure. *Sex Med*. 2021;9(4):100383.
50. Brown C, Bachmann G, Foster D, Rawlinson L, Wan J, Ling F. Milnacipran in provoked vestibulodynia: efficacy and predictors of treatment success. *J Low Genit Tract Dis*. 2015;19(2):140-144.
51. Bornstein J, Goldschmid N, Sabo E. Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. *Gynecol Obstet Invest*. 2004;58(3):171-178.
52. Murina F, Graziottin A, Felice R, Radici G, Tognocchi C. Vestibulodynia: synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation. *J Low Genit Tract Dis*. 2013;17(2):111-116.
53. Morin M, Carroll MS, Bergeron S. Systematic review of the effectiveness of physical therapy modalities in women with provoked vestibulodynia. *Sex Med Rev*. 2017;5(3):295-322.
54. Gentilcore-Saulnier E, McLean L, Goldfinger C, Pukall CF, Chamberlain S. Pelvic floor muscle assessment outcomes in women with and without provoked vestibulodynia and the impact of a physical therapy program. *J Sex Med*. 2010;7(2 pt 2):1003-1022.
55. Murina F, Bernorio R, Palmiotto R. The use of Amielle vaginal trainers as adjuvant in the treatment of vestibulodynia: an observational multicentric study. *Medscape J Med*. 2008;10(1):23.
56. Bergeron S, Binik YM, Khalifé S, et al. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain*. 2001;91(3):297-306.
57. Bergeron S, Khalifé S, Glazer HI, Binik YM. Surgical and behavioral treatments for vestibulodynia: two-and-one-half–year follow-up and predictors of outcome. *Obstet Gynecol*. 2008;111(1):159-166.
58. Danielsson I, Torstensson T, Brodda-Jansen G, Bohm-Starke N. EMG biofeedback versus topical lidocaine gel: a randomized study for the treatment of women with vulvar vestibulitis. *J Low Genit Tract Dis*. 2007;11(3):194.
59. Melzack R, Torgerson WS. On the language of pain. *Anesthesioloy*. 1971;34(1):50-59.
60. Murina F, Bianco V, Radici G, Felice R, Di Martino M, Nicolini U. Transcutaneous electrical nerve stimulation to treat vestibulodynia: a randomised controlled trial. *BJOG*. 2008;115(9):1165-1170.
61. Schlaeger JM, Cai HY, Nenggui X, Steffens AD, Lin W, Wilkie DJ. Do vulvodynia TCM patterns differ by pain types? Beginning evidence supporting the concept. *J Altern Complement Med*. 2017;23(5):380-384.
62. Harris RE, Zubieta JK, Scott DJ, Napadow V, Gracely RH, Clauw DJ. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on μ-opioid receptors (MORs). *Neuroimage*. 2009;47(3):1077-1085.
63. Ren XX, Guo MW, Zhao YF, et al. Effects of electroacupuncture on pain reactions, expression of spinal kappa-opioid receptor and contents of enkephalin and beta-endorphin in periaqueductal gray of midbrain in dysmenorrhea model rats. Article in Chinese. *Zhen Ci Yan Jiu*. 2012;37(1):1-7.
64. Schlaeger JM, Xu N, Mejta CL, Park CG, Wilkie DJ. Acupuncture for the treatment of vulvodynia: a randomized wait-list controlled pilot study. *J Sex Med*. 2015;12(4):1019-1027.
65. Schlaeger JM, Takakura N, Yajima H, et al. Double-blind acupuncture needles: a multi-needle, multi-session randomized feasibility study. *Pilot Feasibility Stud*. 2018;4(1):72.
66. Steffen AD, Burke LA, Pauls HA, et al. Double-blinding of an acupuncture randomized controlled trial optimized with clinical translational science award resources. *Clin Trials*. 2020;17(5):545-551.
67. Diomande I, Gabriel N, Kashiwagi M, et al. Subcutaneous botulinum toxin type A injections for provoked vestibulodynia: a randomized placebo-controlled trial and exploratory subanalysis. *Arch Gynecol Obstet*. 2019;299(4):993-1000.
68. Hansen TH, Guldberg R, Meinert M. Botulinum toxin-treatment of localized provoked vulvodynia refractory to conventional treatment. *Eur J Obstet Gynecol Reprod Biol*. 2019;234:6-9.
69. Petersen CD, Giraldi A, Lundvall L, Kristensen E. Botulinum toxin type A—a novel treatment for provoked vestibulodynia? Results from a randomized, placebo controlled, double blinded study. *J Sex Med*. 2009;6(9):2523-2537.
70. Farajun Y, Zarfati D, Abramov L, Livoff A, Bornstein J. Enoxaparin treatment for vulvodynia: a randomized controlled trial. *Obstet Gynecol*. 2012;120(3):565-572.
71. Park MY, Ahn KY. Scientific review of the aesthetic uses of botulinum toxin type A. *Arch Craniofac Surg*. 2021;22(1):1.
72. Goldfinger C, Pukall CF, Thibault-Gagnon S, McLean L, Chamberlain S. Effectiveness of cognitive-behavioral therapy and physical therapy for provoked vestibulodynia: a randomized pilot study. *J Sex Med*. 2016;13(1):88-94.
73. Guillet AD, Cirino NH, Hart KD, Leclair CM. Mindfulness-based group cognitive behavior therapy for provoked localized vulvodynia: a randomized controlled trial. *J Low Genit Tract Dis*. 2019;23(2):170-175.
74. Masheb RM, Kerns RD, Lozano C, Minkin MJ, Richman S. A randomized clinical trial for women with vulvodynia: cognitive-behavioral therapy vs. supportive psychotherapy. *Pain*. 2009;141(1-2):31-40.
75. Bergeron S, Vaillancourt-Morel MP, Corsini-Munt S, et al. Cognitive-behavioral couple therapy versus lidocaine for provoked vestibulodynia: a randomized clinical trial. *J Consult Clin Psychol*. 2021;89(4):316-326.
76. Pukall C, Kandyba K, Amsel R, Khalifé S, Binik Y. Sexual pain disorders: effectiveness of hypnosis for the treatment of vulvar vestibulitis syndrome: a preliminary investigation. *J Sex Med*. 2007;4(2):417-425.
77. Dillworth T, Mendoza ME, Jensen MP. Neurophysiology of pain and hypnosis for chronic pain. *Transl Behav Med*. 2012;2(1):65-72.
78. Tommola P, Unkila-Kallio L, Paavonen J. Long-term follow up of posterior vestibulectomy for treating vulvar vestibulitis. *Acta Obstet Gynecol Scand*. 2011;90(11):1225-1231.
79. Trutnovsky G, Bliem B, Greimel E, Tamussino K, Gold D. Microablative erbium: YAG laser therapy for vulvodynia–a report on efficacy, safety, and treatment satisfaction. *Sex Med*. 2021;9(6):100432.
80. Murina F, Karram M, Salvatore S, Felice R. Fractional CO_2 laser treatment of the vestibule for patients with vestibulodynia and

genitourinary syndrome of menopause: a pilot study. *J Sex Med*. 2016;13(12):1915-1917.
81. Prather H, Dugan S, Fitzgerald C, Hunt D. Review of anatomy, evaluation, and treatment of musculoskeletal pelvic floor pain in women. *PM R*. 2009;1(4):346-358.
82. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol*. 2015;10(2):293-301.
83. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology*. 2006;45(1):50-52.
84. State medical marijuana laws. National Conference of State Legislatures. Updated April 5, 2021. Accessed May 12, 2021. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx
85. Barach E, Slavin MN, Earleywine M. Cannabis and vulvodynia symptoms: a preliminary report. *Cannabis*. 2020;3(2):139-147.
86. Dargie E, Holden RR, Pukall CF. The vulvar pain assessment questionnaire inventory. *Pain*. 2016;157(12):2672-2686.
87. Tavel ME. The placebo effect: the good, the bad, and the ugly. *Am J Med*. 2014;127(6):484-488.
88. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum*. 2003;46(6):805-808.
89. Brown CS, Bachmann GA, Wan J, Foster DC. Gabapentin for the treatment of vulvodynia: a randomized controlled trial. *Obstet Gynecol*. 2018;131(6):1000-1007.
90. Bachmann GA, Brown CS, Phillips NA, et al. Effect of gabapentin on sexual function in vulvodynia: a randomized, placebo-controlled trial. *Am J Obstet Gynecol*. 2019;220(1):89.e1-89.e8.
91. Goldstein AT. Diagnostic and treatment algorithm for women with vulvodynia and sexual pain disorders. In: Goldstein AT, Pukall CF, Goldstein I, Krapf JM, Goldstein SW, Goldstein G, eds. *Female Sexual Pain Disorders: Evaluation and Management*. 2nd ed. Wiley; 2020:157-162.
92. Vestibulodynia: Understanding Pathophysiology and Determining Appropriate Treatments (VBD UPDATe). ClinicalTrials.gov identifier: NCT03844412. Updated November 24, 2021. Accessed July 6, 2022. https://clinicaltrials.gov/ct2/show/NCT03844412
93. Tommola P, Unkila-Kallio L, Paavonen J. Surgical treatment of vulvar vestibulitis: a review. *Acta Obstet Gynecol Scand*. 2010;89(11):1385-1395.

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CME REVIEW ARTICLE 14

CHIEF EDITOR'S NOTE: This article is part of a series of continuing education activities in this Journal through which a total of 36 *AMA/PRA Category 1 Credits™* can be earned in 2011. Instructions for how CME credits can be earned appear on the last page of the Table of Contents.

Vulvodynia Interventions—Systematic Review and Evidence Grading

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Introduction: State of the art guidance exists for management of vulvodynia, but the scientific basis for interventions has not been well described. Although there are many interventional therapies, and their use is increasing, there is also uncertainty or controversy about their efficacy.

Objective: To systematically assess benefits and harms of interventional therapies for vulvodynia and vestibulodynia.

Methods: The following databases were searched, using MeSH terms for studies related to the treatment of vulvodynia or vulva pain/pruritus/dysesthesia/hyperesthesia/hypersensitivity: MEDLINE, PsycINFO, Scopus, Cochrane Library, EBSCO Academic, and Google Scholar. Using Medical Subject Reference sections of relevant original articles, reviews, and evidence-based guidelines were screened manually. Manual searching for indirect evidence supporting interventions was done whenever no direct evidence was found for a treatment described within a review or guideline. Each modality is assessed with a grading system similar to the Grades of Recommendation, Assessment, Development, and Evaluation system. The grading system assesses study quality, effect size, benefits, risks, burdens, and costs.

Results: For improvement of pain and/or function in women with vestibulodynia (provoked localized vulvodynia), there was fair evidence that vestibulectomy was of benefit, but the size of the effect cannot be determined with confidence. There was good evidence of a placebo effect from multiple studies of nonsurgical interventions. There was fair evidence of lack of efficacy for several nonsurgical interventions. There were several interventions for which there were insufficient evidence to reliably evaluate. There was insufficient evidence to judge harms or to judge long-term benefits.

For clinically meaningful improvement of pain in women with generalized unprovoked vulvodynia, there was insufficient evidence for benefit of any intervention. There was fair evidence of a placebo effect in people with neuropathic pain and functional pain syndromes, from multiple studies of interventions. Based on indirect evidences from studies of patients with other pain disorders, interventions may be selected for future research.

Conclusion: There is fair evidence for effectiveness of vestibulectomy for vestibulodynia; however, there is uncertainty about the size of the absolute effect, because of the risk of bias inherent in studies of pain interventions without a placebo control group. Providers and patients looking for evidence-based interventions for generalized unprovoked vulvodynia may need to rely on indirect evidences from studies of neuropathic pain and functional pain syndromes.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this educational activity, the obstetrician/gynecologist should be better able to identify potential causes of vulvar pain to facilitate diagnosis of vulvodynia and vestibulodynia, distinguish between the symptoms of localized, provoked vulvodynia and generalized unprovoked vulvodynia to select the most appropriate therapies, evaluate the efficacy of surgical and nonsurgical interventions for the treatment of generalized unprovoked and localized, provoked vulvodynia. In addition, assess the benefits and risks of interventional therapies for vulvodynia and vestibulodynia to improve patient care.

The author, faculty, and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interest in, any commercial organizations pertaining to this educational activity.

Dr. Andrews has disclosed that the U.S. Food and Drug Administration has not approved the use of botulinum toxin, Interferon, Cromolyn, Nifedipine, Montelukast, TENS, Nitroglycerin, Photodynamic therapy, and Magnetic field therapy for the treatment of vestibulodynia as discussed in this article. Please consult the product's labeling for approved information.

The author is solely responsible for the content of this article and the decision to submit for publication. No statement in this article should be construed as an official position of the Vanderbilt Evidence Practice Center, the International Society for the Study of Vulvovaginal Disease, nor the GRADE Working Group.

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GUIDELINE

2021 European guideline for the management of vulval conditions

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Conflicts of interest

Dr Boffa is President, Maltese Association of Dermatology & Venereology and Elected member of Malta Medical Council. Dr Lewis has received royalties for contribution to textbooks A Practical Guide to Vulval Disease. Ridley's 'The Vulva' 3rd edition and honoraria for teaching on dermatology. She is a Council member of the European College for the Study of Vulval Disease. Professor Tiplica has received lecture honoraria from Antibiotice SA and Novartis Pharma. He is chair of IUSTI Europe and president of the Romanian Association of Dermato-Venereologists. Dr Sherrard is a Member of the European Sexually Transmitted Infections Guidelines Editorial Board; and she is an officer of the International Union against Sexually Transmitted Infections (membership secretary). She is UK representative to the EBDV at UEMS. The other authors declare no conflict of interest.

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Changes to this guideline since the 2015 version:

- Evaluation scale for genital psoriasis lesions
- Use of ixekizumab, secukinumab and ustekinumab in treating genital psoriasis
- Diagnostic criteria for vulval lichen planus
- Changed first line management recommendations for vulvodynia

Search strategy

- Guidelines produced by the British Association for Sexual Health and HIV (www.bashh.org) were reviewed.
- Searched libraries: MEDLINE, MEDLINE process, Embase, Cochrane library.
- Search up to June 2021 with no date limitation. The search strategy comprised the following terms in the title or abstract: Vulval lichen sclerosus, Vulval lichen planus, Vulval eczema, Vulval lichen simplex, Vulval psoriasis, Vulval intraepithelial neoplasia, High-grade SIL of the vulva, vulval HSIL, Vulval pain syndromes/vulvodynia.

Scope

This guideline covers the more common conditions affecting the vulva:

1 Vulval dermatitis (eczema)
2 Psoriasis
3 Lichen simplex chronicus
4 Lichen sclerosus
5 Lichen planus
6 Vulvodynia
7 Vulval intraepithelial neoplasia (VIN)

General advice for delivery of vulval care

Vulval conditions may present to a variety of clinicians including dermatologists, genitourinary medicine physicians, gynaecologists and primary care physicians or general practitioners (GP). Investigations and management span across this spectrum, so women with vulval conditions are best managed by a multidisciplinary approach, which includes clear referral pathways between disciplines or access to a specialist multidisciplinary

[Intervention Review]

Interventions for vaginismus

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ABSTRACT

Background

Vaginismus is an involuntary contraction of the vaginal muscles which makes sexual intercourse difficult or impossible. It is one of the more common female psychosexual problems. Various therapeutic strategies for vaginismus, such as sex therapy and desensitisation, have been proposed, and uncontrolled case series appear promising.

Objectives

To assess the effects of different interventions for vaginismus.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Group's Specialised Register (CCDANCTR-Studies and CCDANCTR-References) to August 2012. This register contains relevant randomised controlled trials from: The Cochrane Library (all years), EMBASE (1974 to date), MEDLINE (1950 to date) and PsycINFO (1967 to date). We searched reference lists and conference abstracts. We contacted experts in the field regarding unpublished material.

Selection criteria

Controlled trials comparing treatments for vaginismus with another treatment, a placebo treatment, treatment as usual or waiting list control.

Data collection and analysis

The review authors extracted data which we verified with the trial investigator where possible.

Main results

Five studies were included, of which four with a total of 282 participants provided data. No meta-analysis was possible due to heterogeneity of comparisons within included studies as well as inadequate reporting of data. All studies were considered to be at either moderate or high risk of bias. The results of this systematic review indicate that there is no clinical or statistical difference between systematic desensitisation and any of the control interventions (either waiting list control, systematic desensitisation combined with group therapy or in vitro (with women under instruction by the therapist) desensitisation) for the treatment of vaginismus. The drop-out rates were higher in the waiting list groups.

Authors' conclusions

A clinically relevant effect of systematic desensitisation when compared with any of the control interventions cannot be ruled out. None of the included trials compared other behaviour therapies (e.g. cognitive behaviour therapy, sex therapy) to pharmacological interventions. The findings are limited by the evidence available and as such conclusions about the efficacy of interventions for the treatment of vaginismus should be drawn cautiously.

PLAIN LANGUAGE SUMMARY

Interventions for vaginismus

Vaginismus is when the muscles in the vagina tighten and prevent a woman having (vaginal) intercourse. It can cause distress, relationship problems and also infertility. Many treatments have been tried including sex therapy, education, hypnosis and drug treatments. Sex therapy may involve relaxation techniques and gradually inserting a dilator or finger into the vagina (this may be called systematic desensitisation).

This review found five poor to moderate quality studies, of which four with a total of 282 women provided data. There was not enough evidence to say if systematic desensitisation worked better than another treatment. Further studies including larger numbers of women are needed to show if systematic desensitisation if effective for the treatment of women with vaginismus.

Section 4.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—May 2024

HmCode	Code Description	Line(s) Involved	Issue	Recommendation(s)
38205-38215 38230 38243	Collection and preparation of stem cells Harvest of donor bone marrow for transplantation Transplantation of donor stem cells	113 APLASTIC ANEMIAS; AGRANULOCYTOSIS; SICKLE CELL DISEASE Treatment: Bone Marrow Transplant	Multiple bone marrow transplant and stem cell transplant CPT codes are missing from line 113. These codes appear on other BMT lines.	Add 38205-38215, 38230 and 38243 to line 113
17110	Destruction of skin growth, 1-14 growths	274 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA	Multiple denied claims were found pairing CPT 17110 with ICD-10-CM D48.5 (Neoplasm of uncertain behavior of skin) which is on line 274. CPT 17110 is on multiple covered lines	Add 17110 to line 274
45385	Removal of polyps or growths of large bowel using an endoscope with mechanical snare	56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE	Multiple denied claims were found for pairing CPT 45385 with GI hemorrhage ICD-10-CM codes. Similar code 45384 (Removal of polyps or growths of large bowel using a flexible endoscope with electrical cautery) is on line 56	Add 45385 to line 56
B58.01	Toxoplasma chorioretinitis	357 CHORIORETINAL INFLAMMATION	Multiple denied claims were found for ophthalmology services for ICD-10-CM B58.01. This code is currently only on line 230 MYCOBACTERIA, FUNGAL INFECTIONS, TOXOPLASMOSIS, AND OTHER OPPORTUNISTIC INFECTIONS	Add B58.01 to line 357
58120	Dilation and scraping of uterus	63 SPONTANEOUS ABORTION; MISSED ABORTION	Multiple denied claims were found for D&C with missed abortion diagnosis codes. 58120 is on multiple covered gynecologic lines.	Add 58120 to line 63
26440 26442 26445	Release of tendon of palm or finger Release of tendon of palm and finger Release of tendon of top of hand or finger	290 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	Various denied claims for tendon release in the hand for hand contractures were identified.	Add 26440, 26442, and 26445 to line 290

Consent Agenda Issues—May 2024

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
10060 10061 15002-15005 15275 15276 15277 15278	Simple or single drainage of skin abscess Complicated or multiple drainage of skin abscess Preparation of skin graft site Application of skin substitute graft to wound of face, scalp, eyelids, mouth, neck, ears, around eyes, genitals, hands, feet, fingers, or toes, 25.0 sq cm or less of wound 100.0 sq cm or less each additional 25.0 sq cm of wound 100.0 sq cm or less Skin substitute graft to wound 100.0 sq cm or more of face, scalp, eyelids, mouth, neck, ears, around eyes, genitals, hands, feet, fingers, or toes, 100.0 sq cm or 1% body area for infants and children, or less each additional 100.0 sq cm or 1% body area for infants and children, or less	415 MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA	Multiple denied claims were found for pairing abscess drainage CPT codes with hidradenitis suppurativa. Abscess drainage codes are on the severe acne line but not line 415. Additionally, skin graft codes are missing from line 415 and have multiple denied claims.	Add 10060, 10061, 15002-15005, 15275-15278 to line 415
38747	Removal of lymph nodes of abdominal organ	269 CANCER OF BLADDER AND URETER	Denied claims were identified pairing 38747 with bladder cancer. 38747 is on other abdominal cancer lines	Add 38747 to line 269
44130	Creation of connection between 2 segments of small bowel	79 INJURY TO INTERNAL ORGANS	Denied claims were identified pairing 44130 with small intestine injury diagnosis codes, which appear on line 79. 44130 is on multiple covered lines. Many similar CPT codes are on line 79	Add 44130 to line 79

Consent Agenda Issues—May 2024

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
28805 28810 28820 28825 26910- 26952 69120	Amputation of foot across instep Amputation of toe and midfoot bone Amputation of toe at joint between forefoot and toes Amputation of toe at toe joint Finger amputation Excision external ear; complete amputation	180 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	Denied claims were identified pairing frostbite with necrosis to toe and foot amputation. These are unlikely to be abused procedures. These procedures codes are on multiple covered lines. HERC staff identified other amputation codes that should also be on line 180	Add 28805, 28810, 28820, 28825, 26910-26952 and 69120 to line 180
29916	Arthroscopy, hip, surgical; with labral repair	373 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT	Kaiser Permanente is requesting pairing of arthroscopic labral repair with ICD-10-CM S73.191 (Ischiocapsular ligament sprain of right hip) which represents hip labral tears. Open labral repair (CPT 29862 Arthroscopy, hip, surgical; with debridement/shaving of articular cartilage (chondroplasty), abrasion arthroplasty, and/or resection of labrum) pairs with this condition. The HERC intends to cover arthroscopic procedures when the open procedure is covered for the condition on line 373.	Add 29916 to line 373
90589	Chikungunya virus vaccine, live attenuated, for intramuscular use	3 PREVENTIVE SERVICES WITH EVIDENCE OF EFFECTIVENESS	90589 was added to the Excluded file with the 2024 CPT code review in November 2023 as there was no approved vaccine. There is now an FDA approved ACIP recommended vaccine	Add 90589 to line 3

Consent Agenda Issues—May 2024

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
97530 97535	Therapy procedure using functional activities Training for self-care or home management, each 15 minutes	73 DERMATOMYOSITIS, POLYMYOSITIS 200 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS 252 CHRONIC OSTEOMYELITIS 405 EPIDERMOLYSIS BULLOSA 464 BRACHIAL PLEXUS LESIONS	Five lines were found with some but not all physical therapy codes. These lines are attached to the physical therapy guideline (GN6).	Add 97530 and 97535 to lines 73, 200, 252, 405, 464

Straightforward Guideline Note Changes

Trigger finger and trigger thumb guideline clarification

Coverage was added for treatment of trigger finger as well as expanded for treatment of trigger thumb in October 2023. Reviewers have raised concerns about the current guideline wording. First, many of these procedures are done on young children, who cannot have the procedure done in the office setting as the current guideline requires. This would also be the case for any age person with conditions such as developmental delay. No private payers restrict surgical procedures to the office setting and HERC staff recommend removing this clause from the guideline.

Second, the current guideline is confusing. Reviewers are unclear on which parts relate to trigger thumb and which to trigger fingers. There are also questions about whether the different surgical clauses are stand alone situations or not.

Third, HERC staff have concerns about requiring a 48 month waiting period for pediatirc trigger thumb/finger surgery. Based on the most recent study staff identified (Dittmer 2020), current recommendations are for no more than a one year observation period. Given EPSDT, HERC staff recommend removing timing constraints on pediatric surgery.

HERC staff recommendation:

1) Modify GN 120 as shown below

GUIDELINE NOTE 120, TRIGGER THUMB AND TRIGGER FINGER
Lines 373,583
Trigger finger and trigger thumb (ICD-10-CM M65.3 code family) are included on Line 373 only when there is documented interference with function of the hand. Up to 3 steroid injections are covered per digit.

Surgery for trigger finger or trigger thumb is ~~limited to~~ included on line 373 only in ONE of the following situations:
A) ~~Open surgical procedures under local anesthesia; AND~~
B) ~~Only a~~The triggering persists or recurs after at least one steroid injection or a minimum of 3 weeks of splinting has been tried ~~and the triggering persists or recurs~~; OR
C) The patienthas diabetes; OR
D) The finger or thumb is permanently locked in the palm; OR
E) The patient is a child up to age 21 who has a trigger thumb or trigger finger ~~that does not spontaneously resolve within 48 months of diagnosis. Immediate surgery may be considered for bilateral trigger thumb or trigger thumb with locking symptoms in children.~~

Otherwise, trigger finger and trigger thumb are included on Line 583.

Pulling the Trigger: Recommendations for Surgical Care of the Pediatric Trigger Thumb

Alison J. Dittmer, MD, Olivia Grothaus, BA,* Ryan Muchow, MD,† and Scott Riley, MD†*

Background: Despite being a common pediatric hand condition, there are few clear guidelines regarding the optimal management of pediatric trigger thumb. Our primary aim was to help guide surgical management of this disorder by establishing a treatment algorithm on the basis of our institution's experience.

Methods: This is an institutional review board-approved retrospective study of all patients with idiopathic trigger thumbs from 2005 to 2015 at a single institution. Demographics and treatment course were recorded for all patients including duration of follow-up, observation, surgical intervention, and complications. All children were classified according to the Sugimoto classification.

Results: A total of 149 patients with 193 thumbs met inclusion and exclusion criteria. 16.5% of patients had stage II thumbs, 10.3% of patients with stage III, and 73% of patients with stage IV thumbs. Of all patients with stage IV thumbs, 3.5% were locked in extension for an overall incidence of 2.6%. In total, 46% of patients failed observation and underwent surgical treatment. Only 14% of stage IV trigger thumbs resolved when observed, compared with 53% of stage II and 25% of stage III trigger thumbs. Stage IV thumbs were 4.6 times more likely to fail conservative treatment and go on to surgery than stage II or III thumbs (odds ratio, 4.6; $P = 0.006$). Thirty-two percent of patients underwent surgery without an observation period. Older children with bilateral stage 3 thumbs were the most likely to go straight to the odds ratio instead of being observed ($P = 0.002$, $r^2 = 0.17$). Of the total amount of patients who underwent surgery (116), there were 4 complications for a rate of 3.4% with a recurrence rate of 1.7%.

Conclusions: On the basis of the data in this study, the authors would recommend that stage IV thumbs undergo surgery without an observational period. Second, stage II and stage III thumbs can be safely observed for at least 1 year before surgery. Finally, our study concurs with the literature that surgery can be successful with low rates of complications and recurrence.

Level of Evidence: Level IV.

Key Words: pediatric trigger thumb, trigger thumb, thumb flexion deformity

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The authors declare no conflicts of interest.

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Pediatric trigger thumb is a common condition with an overall incidence of 1 to 3 in 1000.[1] Despite the fact that pediatric trigger thumb is relatively common, there is no consensus for the treatment of this disorder. Throughout the literature, evidence exists for both nonoperative and surgical management of this condition with heterogeneous results.[1–7] Rates of resolution of pediatric trigger thumb with nonoperative management range from 10% to 89%, whereas surgical treatment has been demonstrated to be effective in 95% of children on the basis of a systematic review.[2] However, the question of which patients to observe, and for how long, has not been definitively answered.

Multiple studies have reported on their institution's length of observation, which ranges from 3 months to ≥ 7 years.[2,4,6,7] In addition, the exact nature of nonoperative management is also debated and can include simple observation, passive stretching exercises by family, and the use of static splinting.[4] Issues with nonoperative management include lack of compliance secondary to need for daily maintenance and difficulty with splint-wear because of young patient ages.[2] Despite this, there seems to be an age-related rate of success with nonoperative management with younger patients responding more effectively to conservative treatment.[3,6]

Alternatively, surgical treatment of pediatric trigger thumb has been demonstrated to be safe and effective for this condition, yet consensus for surgical treatment is limited by the lack of clear guidelines for operative management. Therefore, treatment often varies on the basis of family and surgeon preference.[1–3,5] Furthermore, although surgical release has been proven to be effective, complications can occur, including recurrent triggering. Despite these known complications, there are few reports of rates for recurrence, surgical site infection, and range of motion abnormalities after surgery.[8–11]

Trigger thumb in children has varied presentations and can present with a palpable Notta's nodule, dynamic triggering, or fixed flexion deformity of the thumb. It is most commonly categorized on the basis of the Sugimoto classification with stages I to IV (Table 1).[6,12] However, the traditional classification fails to categorize those patients who present with a fixed *extension* deformity of the thumb with only one study reporting an incidence of thumbs with fixed extension deformity.[13] Given this variation in the severity of pediatric trigger thumb, we sought to develop treatment criteria that could encompass the entire range of this disease process.

2026 Biennial Review: Hemorrhoids

Issue: At the March 2024 VBBS/HERC meetings, coverage of treatment of hemorrhoids resulting in significant bleeding was added to the 10/1/24 Prioritized List. HERC staff were directed to work with Dr. Rodrigo Pedraza Rosales regarding the CPT codes proposed for addition to the GI bleeding line. Dr. Pedraza Rosales has completed his review of the proposed codes and recommends not adding two of the proposed codes to line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE.

From Dr. Pedraza Rosales:

> After reviewing the CPT's. I still believe 45350 and 45398 should not be covered, as they add resources (endoscopy) to the procedure of hemorrhoidal ligation. Moreover, they are not commonly performed.
>
> Also, since the coverage would be for bleeding hemorrhoids, I would remove 46320 and 46250. While these codes are use in clinical practice, commonly by some, they are done for external hemorrhoids, therefore not matching with the ICD-10 codes of internal hemorrhoids and bleeding/anemia.

The endoscopic procedures referenced by Dr. Pedraza Rosales were removed from the current two hemorrhoid lines at the March meeting.

HERC staff recommendations:

1) **Do not add** the following CPT codes to line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE effective 10/1/24

CPT Code	Code Description
45350	Banding of hemorrhoids using a flexible endoscope (sigmoidoscope)
45398	Banding of hemorrhoids using a flexible endoscope (colonoscope)
46250	Removal of multiple external hemorrhoids
46320	Removal of external hemorrhoid with blood clot

2) **Return** the following CPT codes to lines 471 ~~THROMBOSED AND~~ COMPLICATED HEMORRHOIDS and 614 UNCOMPLICATED HEMORRHOIDS

CPT Code	Code Description
45350	Banding of hemorrhoids using a flexible endoscope (sigmoidoscope)—remove from hemorrhoid lines (471 and 614)
45398	Banding of hemorrhoids using a flexible endoscope (colonoscope) —remove from hemorrhoid lines (471 and 614)

Fluoride Varnish Frequency

Plain Language Summary:

Coverage question: Should OHP change the guideline about a special teeth coating (fluoride varnish) to add more times a year it is covered?

Should OHP cover this treatment? Yes, medical studies show that for higher risk people under 21 years old, more fluoride coatings lead to fewer cavities. The Oral Health Advisory Panel recommends up to 4 fluoride treatments a year for members who are at higher risk for cavities.

Changes to issue summary after public comment period:

One public comment was received on this topic. The commentor supported the staff recommendation. No changes to the staff recommendation were made based on this comment.

Coverage Question: Should the guideline regarding fluoride varnish be updated to clarify the number of covered applications per year?

Question source: Metrics and Scoring Committee

Background:

The Metrics & Scoring Committee is looking at possibly including topical fluoride varnish for kids. It's a national measure and requires two applications. Currently, the guideline on fluoride varnish allows two applications per year for average risk children and up to 4 per year for high risk children. It was discussed at OHAP in the past that Medicaid eligibility (i.e. low socioeconomic status) is one of the qualifying definitions of moderate to high risk for which varnish is indicated. All patients under OHP would thus meet this definition of risk. Metrics and Scoring would like clarification of the number of covered applications per year.

This topic was discussed at the March 2024 VBBS/HERC meetings and no changes in the OHAP/staff recommendations were suggested.

Fluoride Varnish Frequency

HERC staff summary:

Systematic reviews from a highly trusted source (USPSTF) found evidence of reduced caries incidence with the use of fluoride varnish. The studies included in these reviews generally applied varnish every 6 months. Expert guidelines all recommend the use of fluoride varnish "at least every 6 months" in children, with the ADA recommending varnish "at least every 3 to 6 months."

One public comment was received in support of the OHAP/HERC staff recommendation.

OHAP and HERC staff recommend modifying guideline note 17 to clarify that coverage of fluoride varnish four times a year for people up to age 21.

OHAP/HERC staff recommendation:

1) Modify GN17 as shown below

GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE

Lines 3,53

Dental cleaning is limited to once per 12 months for adults and twice per 12 months for children up to age ~~19~~ 21 (D1110, D1120). More frequent dental cleanings may be required for high-risk individuals ~~certain higher risk populations~~ when dentally appropriate.

Fluoride varnish (99188) is included on Line 3 for use with children ~~18~~ up to age 21 ~~and younger~~ during well child preventive care visits. Fluoride treatments (D1206 and D1208) are included on Line 53 PREVENTIVE DENTAL SERVICES for use with adults and children during dental visits. The total number of fluoride applications provided in all settings is not to exceed four per twelve months for children under age 21 ~~a child at high risk for dental caries and two per twelve months for a child not at high risk~~. The number of fluoride treatments is limited to once per 12 months for average risk adults and up to four times per 12 months for high-risk adults when dentally appropriate.

Fluoride Varnish

Disposition of Public Comments

Table of Contents

Discussion Table

IDs/#s	Summary of Issue	HERC Staff Response

Commenters

Identification	Stakeholder
A	Geraldine Kempler MD FAAP, OHP provider *[Submitted April 5, 2024]*
B	*[Submitted December 19, 2023]*

Public Comments

ID/#	Comment	Disposition
A	Fluoride varnish is an evidence based treatment to prevent dental carries. Pediatricians take advantage of routine check ups to apply varnish to the teeth of high-risk children. This should be covered every three months to match the ADA guidelines.	*Thank you for your comments. This frequency is the HERC staff recommended frequency for fluoride varnish.*

References Provided by Commenters

ID	References
A	None provided
B	None provided

Dental Coding Review

Coverage Question: Should any changes be made in the current placement of various dental codes?

Question source: multiple stakeholders

Background: At the request of multiple stakeholders, OHA convened the Oral Health Forum (OHF), which is a workgroup that reviewed the placement of current CDT codes and their relationship to dental rules. This workgroup has completed their review of codes and has made recommendation for addition of some previously excluded codes and for movement of some currently covered codes.

OHAP input: OHAP members agreed with HERC staff recommendations. HERC staff were directed to conduct an evidence review regarding cone beam CT for possible coverage. This review will be discussed at a future OHAP.

HERC staff summary:

OHAP agree with the HERC staff compilation of the OHA dental code workgroup recommendations. Codes recommended for movement (covered line to covered line or excluded to covered line) are shown in the first two spreadsheets and will be the focus of the VBBS/HERC discussion. A complete list of all reviewed codes are included in the second two spreadsheets; any member may call out one or more additional codes for review if desired.

These codes were reviewed at the March 2024 VBBS and HERC meetings and no changes were suggested at that time.

OHAP/HERC staff recommendation:

1) Make the code changes presented in the covered codes and the excluded codes review documents

OHF recommended changes to covered codes (with HERC staff recommendations)						
Code	**Code description**	**Current Placement**	**HERC Staff Recommended**	**Rationale/Notes from OHA workgroup**	**OAR update, other comments**	**OHAP input**
D0190	Screening of a patient	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	Diagnostic Procedures File	to align w/CDT groupings; per CDT line is Diagnostic File (align w/D0191 3,53)		
D4346	Scaling in presence of generalized moderate or severe gingival inflammation - full	53 PREVENTIVE DENTAL SERVICES	217 DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE)	Periodontal code		
D4355	Full mouth debridement to enable a comprehensive	53	217	Periodontal code		
D9920	Behavior management, by report	53	Ancillary	D9920 - behavior management was established as a means to assure comprehensive oral health care for persons with developmental disabilities (DD). This code allows for additional compensation to a dentist who is treating persons with developmental disabilities due to the increased time, staffing, expertise, and adaptive equipment required for treatment	define in OAR when code is appropriate	
D7997	Appliance removal (not by dentist who placed appliance), includes removal of archbar	54	265 DENTAL CONDITIONS (TIME SENSITIVE EVENTS) Treatment URGENT DENTAL SERVICES			

OHF recommended changes to covered codes (with HERC staff recommendations)						
Code	**Code description**	**Current Placement**	**HERC Staff Recommended**	**Rationale/Notes from OHA workgroup**	**OAR update, other comments**	**OHAP input**
D7280	Exposure of an unerupted tooth	254 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION 611 DENTAL CONDITIONS (E.G., MALOCCLUSION)	254, 341	618 = uncovered by dental; is covered for HCM should also be on a covered dental line 341 (in addition to 256)		Request for clarificaiton in rule
D7283	Placement of device to facilitate eruption of impacted tooth	254,636	254, 341	618 = uncovered by dental; is covered for HCM should also be on a covered dental line 344 (in addition to 254)		Request for clarificaiton in rule

OHF codes recommended for movement from Excluded file to Prioritized List (with HERC staff recommendations)					
Code	**Code description**	**Current placement**	**HERC staff recommended placement**	**Rationale/OHA workgroup Notes/other comments**	**OHAP input**
D0171	Re-evaluation - post-operative office visit	Excluded (Group 1118)	341 DENTAL CONDITIONS (E.G., SEVERE CARIES, INFECTION) Treatment ORAL SURGERY	Possibly "not to be billed separately" as this service is included in treatment/service provided. (410-123-1200 not eligible for separate reimbursement) 1. Exam code, should be moved to be consistent w/OARs. 2.	
D0391	Interpretation of diagnostic image by a practitioner not associated with capture of the image, including report	Excluded (Group 1118)	53 PREVENTIVE DENTAL SERVICES	Possibly "not to be reimbursed separately" as this service is included in treatment/service provided. (410-123-1200 not eligible for separate reimbursement)	
D0460	Pulp vitality tests	Excluded (Group 1118)	54 DENTAL CONDITIONS (E.G., INFECTION, PAIN, TRAUMA)	Diagnostic	Already in rule as "not to be reimbursed separately"
D4921	Gingival irrigation with a medicinal agent - per quadrant	Not open for pymt	217 DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE)	Is this open for encounter data? (update OAR? Can be billed) "not to be billed separately"	

OHF codes recommended for movement from Excluded file to Prioritized List (with HERC staff recommendations)					
Code	**Code description**	**Current placement**	**HERC staff recommended placement**	**Rationale/OHA workgroup Notes/other comments**	**OHAP input**
D7922	Placement of intra-socket biological dressing to aid in hemostasis or clot stabilization, per site	Excluded (Group 1118)	341	Clinical need. Part of procedure, not separately reimbursed. Dr. Geisler input: Used for bleeding, may reduce ED visits and other complications. These materials are	
D7993	Surgical placement of craniofacial implant - extra oral	Excluded (Group 1118)	612 DENTAL CONDITIONS (E.G., MISSING TEETH) Treatment IMPLANTS	implant Dr. Geisler input: May be used for treatment of severe facial trauma or congentital defects that require extensive reconstruction.	
D7994	Surgical placement: zygomatic implant	Excluded (Group 1118)	612	Dr. Geisler input: May be used for creation of substrate for dentures in a person who had all teeth pulled as a young person	
D9210	Local anesthesia not in conjunction with operative or surgical procedures	Excluded (Group 1118)	54	Palliative, could be urgent, or emergent (needs GN). Add situation to 123-1200 re: local anesthesia	

OHF codes recommended for movement from Excluded file to Prioritized List (with HERC staff recommendations)					
Code	**Code description**	**Current placement**	**HERC staff recommended placement**	**Rationale/OHA workgroup Notes/other comments**	**OHAP input**
D9219	Evaluation for moderate sedation, deep sedation or general anesthesia	Excluded (Group 1118)	54, 341	add to "not to be reimbursed separately" (bundle w/oral surgery procedures)	
D9613	Infiltration of sustained release therapeutic drug, per quadrant	Excluded (Group 1118)	341	gets billed, but not paid. Should be either "not paid separate" or have a guideline (e.g. Exporel)	

MRI for Monitoring in Multiple Sclerosis Clarification

Plain Language Summary:

Coverage question: Should the OHP provide more clear direction about covering MRI imaging tests for multiple sclerosis, a condition causing symptoms such as fatigue, muscle weakness and struggling to do tasks??

Should OHP make this change? Yes. OHP covers this testing for all reasons for multiple sclerosis.

Coverage Question: What is the best method to clarify coverage of MRI in multiple sclerosis (MS)?

Question source: HSD staff

Background: In May 2022, HERC reviewed MRI for monitoring disease in MS. At that time, the staff summary concluded the "MRI lesion changes have become a standard diagnostic criteria for initiating or changing disease modifying therapy in multiple sclerosis. All major expert groups use MRI lesion activity as criteria in their guidelines for treatment of MS. All major expert groups recommend at least yearly MRI for monitoring, with more frequent MRIs during DMT changes. No new literature is expected to be produced looking at whether routine MRI affects clinical outcomes as routine MRI is now standard of care. HERC staff recommends deletion of the MRI in MS guideline." The MRI in MS guideline was deleted, but HERC members expressed a desire to ensure that the intent of the HERC to cover MRI of the brain and spine in MS was clear. HSD staff have reached out due to lack of clarity of HERC intent for MRI of the spine in MS, as there is an MRI of the spine guideline that does not include MS as an indication.

Current Prioritized List/Coverage status:

ICD-10-CM G35 (Multiple sclerosis) is on line 249 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM and the dysfunction lines

Multiple diagnostic guidelines for MRI exist on the Prioritized List, for back pain, breast MRI, neuroimaging in dementia, prostate cancer, and MRI of the spine

DIAGNOSTIC GUIDELINE D11, MRI OF THE SPINE (CERVICAL AND THORACIC)

MRI of the cervical and thoracic spine is covered in the following situations:

A) Recent onset of major or progressive neurologic deficit (objective evidence of markedly abnormal reflexes, dermatomal muscle weakness, dermatomal sensory loss, EMG or NCV evidence of nerve root impingement), suspected cauda equina syndrome (loss of bowel or bladder control or saddle anesthesia), or neurogenic claudication in patients who are potential candidates for surgery;
B) Clinical or radiological suspicion of neoplasm; or,

C) Clinical or radiological suspicion of infection.

The former MRI in MS guideline:

~~DIAGNOSTIC GUIDELINE D10, MRI IN MULTIPLE SCLEROSIS~~
~~MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.~~

~~MRI may be considered in the following circumstances:~~

~~A) Suspected drug failure in the setting of clinical relapse in patients with objective changes in neurological status or documented new clinical symptoms such as urinary urgency or cognitive changes~~

~~B) Evaluation of a clear objective progression in clinical symptoms in patients with previously relapsing disease to rule out ongoing inflammatory disease when conversion to secondary progressive MS is suspected~~

~~C) Patients who require enhanced pharmacovigilance, including~~

~~1) Yearly monitoring for patients treated with natalizumab who are JCV seropositive~~

~~2) One MRI for patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate) one year after the switch from natalizumab~~

HERC staff summary:

Stakeholders are requesting clarification of coverage of MRI of the brain and spine in MS. HERC staff recommend adding a short guideline.

HERC staff recommendation:

1) Add a new Diagnostic Guideline as shown below

DIAGNOSTIC GUIDELINE DX, MRI IN MULTIPLE SCLEROSIS
MRI of the brain and spine is covered for diagnosis of MS and for monitoring of disease.

Section 5.0

New Codes

HCPCS	LONG DESCRIPTION	Recommended Placement	Comments
C1605	Pacemaker, leadless, dual chamber (right atrial and right ventricular implantable components), rate-responsive, including all necessary components for implantation	654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	See leadless pacemaker topic
C9901	Endoscopic defect closure within the entire gastrointestinal tract, including upper endoscopy (including diagnostic, if performed) or colonoscopy (including diagnostic, if performed), with all system and tissue anchoring components	DIAGNOSTIC PROCEDURES	Added for billing of clip closure after procedures such as polypectomy or for closure of a GI perforation from an endoscopy. As may be used during diagnostic procedures, convention is to place on the DIAGNOSTIC PROCEDURES file
G0519	Management of new patient-caregiver dyad with dementia, low complexity, for use in cmmi model	200 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS	For use in the GUIDE model for dementia care through CMS https://www.cms.gov/priorities/innovation/innovation-models/guide
G9037	Interprofessional telephone/internet/electronic health record clinical question/request for specialty recommendations by a treating/requesting physician or other qualified health care professional for the care of the patient (i.e. not for professional education or scheduling) and may include subsequent follow up on the specialist's recommendations; 30 minutes	All lines with E&M codes	
G9038	Co-management services with the following elements: new diagnosis or acute exacerbation and stabilization of existing condition; condition which may benefit from joint care planning; condition for which specialist is taking a co-management role; condition expected to last at least 3 months; comprehensive care plan established, implemented, revised or monitored in partnership with co-managing clinicians; ongoing communication and care coordination between co-managing clinicians furnishing care	All lines with E&M codes	

Section 6.0

Previously Discussed Items

Continuous Glucose Monitor (CGM) Guideline Updates March 2024

Plain Language Summary:

Coverage question: Should HERC change OHP's rules about when to cover a device that measures blood sugar throughout the day (continuous glucose monitors or CGM)?

Recommendation? Yes:
1) Change the rules for getting a CGM for the first time
2) Change the rules for getting re-approval for a CGM
3) Add coverage for people with a condition where the body has trouble storing and using a type of blood sugar called glycogen (glycogen storage disease)
4) Clearly explain real-time CGM is covered and retrospective (professional) CGM is not covered
5) Clarify that type 2 diabetes includes diabetes caused by other conditions such as cystic fibrosis

Changes to issue summary after public comment period:

One public comment was received on this topic. The commentor requested that diabetes due to cystic fibrosis be covered for CGMs. HERC staff modified the recommended changes to the CGM guideline to clarify that DM caused by other conditions is covered for CGMs for patients that otherwise meet criteria for CGMs.

Coverage Question: How should the newly updated guideline on continuous glucose monitoring be updated?

Question source: HERC staff; Holly Jo Hodges, CCO medical director

Background: Various updates were done to the continuous glucose monitoring guideline in November 2023 in response to a coverage guidance on this technology. Since that time, several issues have come to HERC staff attention:

1) Glycogen storage disease type 1a patients require continuous glucose monitoring. This came to staff attention based on proposed legislation during the 2024 short session.
    a. This condition is a very rare inborn error of metabolism that results in frequent hypoglycemia events
    b. There appear to be only 5 patients on OHP with this condition
2) Initial criteria for CGM approval appear to be mixed with criteria for CGM continuation. These should be separated for clarity
3) It is unclear if the continuation criteria for CGM coverage applies to type 1, type 2 or both types of patients with diabetes;
4) For type 2 diabetes the approved language does not pose a meaningful restriction since two six-month trials per year are approved.

Continuous Glucose Monitor (CGM) Guideline Updates March 2024

Current Prioritized List/Coverage status:

GUIDELINE NOTE 108, CONTINUOUS GLUCOSE MONITORING

Lines 1,8,27,60

Real-time (personal) continuous glucose monitoring (CGM) is included on Line 8 for:

A) Adults with type 1 diabetes mellitus not on insulin pump management:
   1) Who have received or will receive diabetes education specific to the use of CGM AND
   2) Who have used the device for at least 50% of the time at their first follow-up visit AND
   3) Who have baseline HbA1c levels greater than or equal to 8.0%, frequent or severe hypoglycemia, or impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM).

B) Adults with type 1 diabetes on insulin pump management (including the CGM-enabled insulin pump):
   1) Who have received or will receive diabetes education specific to the use of CGM AND
   2) Who have used the device for at least 50% of the time at their first follow-up visit.

C) Women with type 1 diabetes who are pregnant or who plan to become pregnant within six months without regard to HbA1c levels.

D) Children and adolescents under age 21 with type 1 diabetes:
   1) Who have received or will receive diabetes education specific to the use of CGM AND
   2) Who have used the device for at least 50% of the time at their first follow-up visit

CPT 95250 and 95251 (Ambulatory continuous glucose monitoring) are included on these lines for services related to real-time continuous glucose monitoring but not retrospective (professional) continuous glucose monitoring.

Therapeutic continuous glucose monitors are included on Lines 1 and 27 for individuals with type 2 diabetes or gestational diabetes who use short- or intermediate-acting insulin injections when ALL of the following criteria are met:

A) Have received or will receive diabetes education specific to the use of CGM, AND

B) Have used the device for at least 50% of the time for a 90-day period by their first follow-up visit (within 3-6 months), AND

C) Have one of the following at the time of CGM therapy initiation:
   1) Baseline HbA1c levels greater than or equal to 8.0%, OR
   2) Frequent or severe hypoglycemia, OR
   3) Impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM), OR
   4) Diabetes-related complications (for instance, peripheral neuropathy, end-organ damage)

D) Every 6 months following the initial prescription for CGM, the prescriber must conduct an in-person or telehealth visit with the member to document adherence to their CGM regimen to ensure that CGM is used for diabetes treatment planning.

Two trials per year of CGM are allowed to meet adherence for continuation of coverage.

Continuous Glucose Monitor (CGM) Guideline Updates March 2024

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports-Blog.aspx?View={DE654D2C-76D6-4607-B754-C7862C05B54F}&SelectedID=5

Continuous Glucose Monitor (CGM) Guideline Updates March 2024

HERC staff summary:

Several edits need to be made to the CGM guideline.

HERC staff recommendations:

1) Modify GN108 as shown below:
    a. Differentiate the criteria for initial approval from that from reapproval criteria and collapse it so it is stated in one place for all indications
    b. Add an indication for glycogen storage disease
    c. Clarify that type 2 DM includes DM due to other causes
    d. Add specific HCPCS codes for CGM

GUIDELINE NOTE 108, CONTINUOUS GLUCOSE MONITORING

Lines 1,8,27,60,147

Real-time (personal) continuous glucose monitoring (CGM) is included on Line 8 for:

A) Adults with type 1 diabetes mellitus not on insulin pump management:
    1) Who have received or will receive diabetes education specific to the use of CGM AND
    ~~2) Who have used the device for at least 50% of the time at their first follow-up visit AND~~
    3) Who have baseline HbA1c levels greater than or equal to 8.0%, frequent or severe hypoglycemia, or impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM).

B) Adults with type 1 diabetes on insulin pump management (including the CGM-enabled insulin pump)~~:~~ ~~W~~who have received or will receive diabetes education specific to the use of CGM ~~AND~~
~~1) Who have used the device for at least 50% of the time at their first follow-up visit.~~

C) Women with type 1 diabetes who are pregnant or who plan to become pregnant within six months without regard to HbA1c levels.

D) Children and adolescents under age 21 with type 1 diabetes~~:~~ ~~W~~who have received or will receive diabetes education specific to the use of CGM ~~AND~~
~~1) Who have used the device for at least 50% of the time at their first follow-up visit~~

~~CPT 95250 and 95251 (Ambulatory continuous glucose monitoring) are included on these lines for services related to real-time continuous glucose monitoring but not retrospective (professional) continuous glucose monitoring.~~

Real-time (personal) continuous glucose monitoring (CGM) is included on Line 147 for children or adults with glycogen storage disease type 1a (ICD-10-CM E74.00)

Therapeutic continuous glucose monitors (HCPCS A4239 and E2103) are included on Lines 1 and 27 for individuals with type 2 diabetes (including diabetes due to underlying conditions and drug or chemical induced diabetes), or gestational diabetes who use short- or intermediate-acting insulin injections when ALL of the following criteria are met:

A) Have received or will receive diabetes education specific to the use of CGM, AND
~~B) Have used the device for at least 50% of the time for a 90-day period by their first follow-up visit (within 3-6 months), AND~~
C) Have one of the following at the time of CGM therapy initiation:
    1) Baseline HbA1c levels greater than or equal to 8.0%, OR
    2) Frequent or severe hypoglycemia, OR

3) Impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM), OR
4) Diabetes-related complications (for instance, peripheral neuropathy, end-organ damage)

Requirements for continued CGM coverage:

A) Every 6 months following the initial prescription for CGM, the prescriber must conduct an in-person or telehealth visit with the member to document adherence to their CGM regimen to ensure that CGM is used for diabetes treatment planning. Continued coverage of CGM requires documentation of use of the device for at least 50% of the time since the last visit.
B) Two trials per year of CGM are allowed to meet adherence for continuation of coverage.

CPT 95250 and 95251 (Ambulatory continuous glucose monitoring) are included on these lines for services related to real-time continuous glucose monitoring but not retrospective (professional) continuous glucose monitoring.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports-Blog.aspx?View={DE654D2C-76D6-4607-B754-C7862C05B54F}&SelectedID=5

Continuous Glucose Monitors Guideline Updates

Disposition of Public Comments

Table of Contents

Discussion Table

IDs/#s	Summary of Issue	HERC Staff Response
All	Add cystic fibrosis related diabetes to the coverage criteria for CGM, and consider adding CGMs as a diagnostic test for diabetes in the CF population.	The current continuous glucose monitor (CGM) guideline should have wording added to clarify that type 2 diabetes mellitus includes diabetes mellitus caused by other diseases or medication. HERC staff have proposed additional wording modifications to the CGM guideline to clarify that such types of diabetes mellitus are covered similarly to general type 2 diabetes mellitus. There is insufficient evidence that CGM is superior to other screening modalities for the diagnosis of diabetes mellitus in the CF population.

Commenters

Identification	Stakeholder
A	Jennifer Bass, MD OHP provider*[Submitted April 14, 2024]*

Continuous Glucose Monitors Guideline Updates

Disposition of Public Comments

Public Comments

ID/#	Comment	Disposition
A	Please consider adding Cystic Fibrosis Related Diabetes to your indications for CGM. Because of damage to the pancreas, individuals with cystic fibrosis are at high risk for developing pancreatic endocrine dysfunction and diabetes that is insulin dependent. Glucose dysregulation impacts overall health including pulmonary function and leads to more rapid decline in lung function which negatively impacts survival. Many of these patients will have both hyperglycemia and reactive hypoglycemia even before insulin therapy. The literature supports the use of CGMs for CFRD to improve blood sugar management, nutritional status, and lung health	Thank you for your comments. Diabetes due to cystic fibrosis is coded with an ICD-10-CM code in the E08 family (diabetes mellitus related to underlying condition), which is on line 27 TYPE 2 DIABETES MELLITUS and pairs with CGMs. One additional code that can be used for patients with CF who develop diabetes is ICD-10-CM E84.8 (Cystic fibrosis with other manifestations), which does not currently pair with CGMs. CGMs would be covered for patients with CF who also have diabetes on insulin therapy. The submitted articles give information on the utility of CGMs in patients with CF who have diabetes. Specifically: 1) Kumar 2023 included 24 studies, all of which included CF patients already using either multiple daily insulin injections or insulin pumps, who would qualify for CGMs based on the current guideline. 2) Elidottir 2021 is a small cohort study of 32 patients examining whether CGM was a better diagnostic tool for detecting diabetes that a 1 hour GTT. The study concluded that "CGM can be a valuable addition to OGTT in

Disposition of Public Comments

ID/#	Comment	Disposition
		evaluating glucose abnormalities in CF although its clinical implications are not fully understood and standardization of its use is required." 3) Ng 2020 is a small cohort study of 5 patients on the utility of using CGM to diagnose diabetes in patients with CF. All patients had diabetes mellitus based on 1 hour GTT values; therefore addition of CGM would like have had no change in the diagnosis of these patients. 4) Scully 2021 is a prospective observational study of 77 adults with CF to compare hemoglobin a1c vs CGM for the diagnosis of CF related diabetes mellitus. 25 patients had pre-existing diabetes mellitus and an additional 6 were diagnosed with a 1 hour GTT at study onset. The remaining 44 patients (2 patients had no CGM data) did not have data reporting whether a1c or CGM led to a diagnosis of diabetes mellitus. The CMG values were reported to correlate well with a1c values. The study concluded: "Further large-scale, prospective studies are needed to explore how CGM measures can predict pulmonary and nutritional decline and microvascular complications in patients with CF and to investigate the use of CGM as

Disposition of Public Comments

ID/#	Comment	Disposition
		a screening strategy in this patient population." Based on the studies submitted, HERC staff do not feel that there is evidence to support the use of CGM to diagnose diabetes in the CF population. 1 hour GTT and hemoglobin a1c values continue to be useful for this purpose. The use of CGMs in CF patients with diabetes mellitus on insulin has been shown, and is already included in the new CGM coverage.

References Provided by Commenters

ID	References
A	1. Kumar S et al. Continuous glucose monitoring versus self-monitoring of blood glucose in the management of cystic fibrosis related diabetes: A systemic review and meta-analysis. Journal of Cystic Fibrosis 22 (2023); 39-49. 2. Elidottir H et al. Abnormal glucose tolerance and lung function in children with cystic fibrosis. Comparing oral glucose tolerance test and continuous glucose monitoring. Journal of Cystic Fibrosis 21 (2021): 779-784. 3. Ng S and Ogundiya A. Use of Continuous Glucose Monitoring in Diagnosis and Management of Cystic Fibrosis-related Diabetes in Children. Journal of Diabetology 2020; 11: 86-9. 4. Scully K et al. Continuous Glucose Monitoring and HbA1c in Cystic Fibrosis: Clinical Correlations and Implications for CFRD Diagnosis. J Clinical Endocrinology and Metabolism 2022: 107 (4); e1444-e 1454

Section 7.0

New Discussion Items

Basivertebral Nerve Ablation for Back Pain

Plain Language Summary:

Coverage question: Should OHP cover a treatment for chronic low back pain that destroys some nerves (basivertebral nerve ablation)?

Should OHP cover this treatment?
Option 1: No, there are not enough quality medical studies.

Option 2: Yes, add limited coverage with a guideline, since other insurance companies cover this treatment.

Changes to issue summary after public comment period:
No public comment was received on this topic. This document contains no changes from the version released with the early VBBS/HERC packet.

Coverage Question: Should basivertebral nerve ablation be covered for treatment of chronic low back pain not responsive to conservative therapy?

Question source: Matthew Kaul MD, chief of physiatry, Kaiser Permanente

Background: The sensory nerves within the center of the vertebral body converge to form the basivertebral nerve (BVN). The BVN exits the vertebral body posteriorly via the basivertebral foramen. In patients with vertebrogenic back pain, utilizing therapeutic radiofrequency (RF) ablation of the BVN has been proposed as a method of treating low back pain.

Low back pain is a common condition that has many available treatments, including physical therapy, NSAIDs, spinal fusion, disc procedures, chiropractic procedures, exercise programs, and cognitive behavioral therapy.

Basivertebral nerve ablation was reviewed as a new CPT code in 2021, and only two small RCTs were identified with only short-term outcomes. No private payer was covering the procedure. Based on this review, basivertebral nerve ablation was added to line 662 (now line 654). Dr. Kaul has reached out to request a re-review of this procedure based on CMS adding coverage for the procedure recently.

Previous HSC/HERC reviews:
This procedure is relatively new. It was reviewed as a new CPT code in November 2021. At that time the staff summary was: “Basivertebral nerve ablation is a new treatment for chronic low back pain, with

an evidence base consisting of two RCTs (N=320 patients) which reported only short term outcomes. All private payers surveyed consider it experimental." The code was added to line 662 (now line 654).

Current Prioritized List/Coverage status:

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 654
The following Interventions are prioritized on Line 654CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
64628-64629	Thermal destruction of intraosseous basivertebral nerve	Insufficient evidence of effectiveness	November 2021

Evidence:

Khalil 2019 (the INTRACEPT trial) was reviewed in 2021. RCT comparing basivertebral nerve ablation to usual care. N=104 patients, 3 month follow up

Fischgrund 2018 (the SMART trial) was also reviewed in 2021. RCT comparing basivertebral nerve ablation to sham treatment. N=225 patients, 12 month follow up

1) **Conger 2022**, systematic review and meta-analysis of basivertebral nerve ablation (BVN)
    a. N=6 studies (in 12 publications), 414 patients total
        i. Studies
            1. One RCT comparing BVN RFA with sham, with outcomes reported at up to 1, 2, and 5 years (SMART trial)
            2. One RCT comparing BVN RFA with standard care treatment, with outcomes reported at up to 3, 6, 12, and 24 months (INTRACEPT trial)
            3. Four single-group cohort studies, with outcomes reported between 3 and 12 months (De Vivo 2021, Fishchenko 2021, Becker 2017, Macadaeg 2020)
        ii. Inclusion criteria in all studies was low back pain for 6 or more months and Modic 1 (MC1) and Modic 2 (MC2) changes in at least one of the L3-S1 vertebral bodies
            1. Modic type 1 change represents bone marrow edema and inflammation on MRI
            2. Modic type 2 change represents marrow ischemia and the conversion of normal red haemopoietic bone marrow into yellow fatty marrow
    b. Meta-analysis of the two RCTs

i. a single-arm meta-analysis of outcomes after treatment with BVN RFA was performed to examine the percentage of responders, defined by the ≥ 50% VAS/NRS and ≥ 15-point ODI improvement thresholds at 6 and 12 months. For ≥ 50% pain improvement at 6 and 12 months, the calculated success rates were 65% (95% CI 51–78%) and 64% (95% CI 43–82%), respectively. Rates of ≥ 15-point ODI improvement were 75% (95% CI 63–86%) and 75% (95% CI 63–85%) at 6 and 12 months, respectively.

ii. Meta-analysis was also performed to calculate the success rates based on an intention-to-treat analysis (including lost to follow-up, protocol deviations, targeting failure, etc.) for the RCTs and a "worst-case" scenario (unreported patients were categorical failures) for cohort studies, which demonstrated slightly lower success rates for pain and functional improvement: At 6, 12, 24, and 60 months 61% (95% CI 48–74%), 59% (95% CI 40–77%), 49% (95% CI 43–56%), and 50% (95% CI 41–58%) of participants reported ≥50% pain improvement. Rates of ≥15-point ODI improvement at these same time points were 71% (95% CI 59–82%), 70% (95% CI 57–81%), 57% (95% CI 50–64%), and 57% (95% CI 49–65%

iii. The evidence from these two RCTs was downgraded from "high quality" because of the risk of bias in the form of selective outcome reporting and the inability to blind participants effectively. The possibility of publication bias was also considered, given that the majority of studies have been industry funded; however, two recently performed independent studies have shown similar results. According to GRADE, there is moderate-quality evidence that intraosseous BVN RFA effectively reduces LBP and related disability in those with vertebrogenic LBP, compared with sham RFA and continued standard care treatment

c. Conclusion: According to GRADE, there continues to be "moderate"-quality evidence that BVN RFA effectively reduces chronic LBP and associated disability in individuals with chronic vertebrogenic LBP associated with MC1 and MC2 in the L3 to S1 vertebral bodies. Between 65% and 75% of such patients report clinically significant pain and functional improvement at 6 and 12 months after BVN RFA, with similar success rates up to 5 years. S60 Conger et al. Further high-quality studies will likely improve our understanding of the effectiveness of this procedure

Expert guidelines:

1) **North American Spine Society 2023** (as reported in CMS LCD; proprietary document)
    a. **B**VN is indicated when:
        i. Patients are skeletally mature and have CLBP for at least 6 months, and lower back pain is their main symptom.
        ii. Patients have failed to adequately improve despite attempts at nonsurgical management.
        iii. Patients have Type 1 or Type 2 Modic changes on MRI — endplate hypo-intensity (Type 1) or hyperintensity (Type 2) on T1 images plus hyperintensity on T2 images (Type 1) involving in the endplates between L3 and S1.
2) **International Society for the Advancement of Spine Surgery 2020**, guideline for basivertebral nerve ablation for low back pain

a. Intraosseous ablation of the BVN from the L3 through S1 vertebrae may be considered medically indicated for individuals with CLBP when all the following criteria are met:
    i. Chronic low back pain of at least 6 months duration,
    ii. Failure to respond to at least 6 months of nonsurgical management, and
    iii. MRI-demonstrated MC1 or MC2 in at least 1 vertebral endplate at 1 or more levels from L3 to S1

Other payer policies:

1) Regence BCBS 2023
    a. Intraosseous basivertebral nerve ablation (BVNA) is considered **medically necessary** when all of the following criteria are met:
        i. Individual is skeletally mature; **and**
        ii. Chronic unremitting low back pain of at least 6 months duration is present; **and**
        iii. Has failed to respond to at least 6 months of supervised conservative medical management (for example, exercise, nonsteroidal and/or steroidal medication [unless contraindicated], physical therapy, including passive and active treatment modalities, and activity/lifestyle modification); **and**
        iv. Diagnosis of vertebrogenic pain meeting the following criteria:
            1. Documented by history and physical examination; **and**
            2. Magnetic resonance imaging (MRI)-demonstrated Modic Type 1 or 2 changes in at least one vertebral endplate, at one or more levels from L3 to S1, including the following:
                a. Fibrovascular bone marrow changes are present (hypointense MRI signal for Modic Type 1); **or**
                b. Fatty bone marrow changes are present (hyperintense MRI signal for Modic Type 2);
                and
        v. Qualifying Modic changes are exhibited at each level to be treated; **and**
        vi. Documentation that other causes of low back pain have been excluded (including, but not limited to: chronic lumbar strain, lumbar stenosis, degenerative scoliosis, facet arthropathy and disc disease).
2) CMS LCD, Intraosseous Basivertebral Nerve Ablation 2023
    a. Current evidence suggests BVN ablation offers short- to intermediate-term improvements in function and pain. Prospective single-arm studies have reported clinically significant improvements in Oswestry Disability Index (ODI) and Visual Analog Scale (VAS) from baseline, while Level 1 randomized controlled trials (RCTs) have demonstrated superiority over standard care at 3 months and 12 months and over sham control at 12 months.
    b. Thermal ablation of the intraosseous Basivertebral Nerve (BVN) is considered medically reasonable and necessary for the treatment of Chronic Low Back Pain (CLBP) in patient who meet ALL the following criteria for coverage and reimbursement.
        i. Individual is skeletally mature and has had CLBP for at least 6 months, with lower back pain as the dominant symptom.
        ii. Has failed to adequately improve despite documented non-surgical management, to include at least 3 or more of the following modalities:
            1. Avoidance of activities that aggravate pain.

2. Course of physical therapy or professionally directed therapeutic exercise program.
3. Chiropractic manipulation
4. Cognitive therapy
5. Pharmacotherapy, including narcotic and non-narcotic analgesics, muscle relaxants, neuroleptics, and anti-inflammatories.
6. Injection therapy of epidural or facet joint implicated pain sources in the region of concern

c. Type 1 or Type 2 Modic changes on MRI: Endplate hypointensity (Type 1) or hyperintensity (Type 2) on T1 images plus hyperintensity on T2 images (Type1) involving the endplates between L3 and S1
d. Absence of additional vertebral pathology by physical, history, radiologic or clinical assessment including, but not limited to, fracture, tumor, infection, deformity, trauma, or post-surgical change which could cause the patient's symptoms or complicate the procedure and outcome.
e. Physical and psychological assessment of patient's ability to tolerate and benefit from BVN ablation.

3) Cigna 2023
   a. Intraosseous radiofrequency nerve ablation of the basivertebral nerve (i.e., INTRACEPT® Intraosseous Nerve Ablation System) is considered medically necessary for treatment of chronic, vertebrogenic low back for at least 12 months duration and at no more than three adjacent vertebral bodies (i.e., between L3-S1), during which time ALL of the following criteria have been met:
      i. Unremitting back pain and significant functional impairment continues despite at least six (6) consecutive months of structured*, physician supervised conservative medical management, including ALL of the following components:
         1. exercise, including core stabilization exercises
         2. nonsteroidal and/or steroidal medication (unless contraindicated)
         3. physical therapy, including passive and active treatment modalities
         4. activity/lifestyle modification
         5. participation in 3 or more individual or group cognitive behavioral therapy (CBT) sessions provided by a licensed healthcare professional (e.g., physical therapist, [PT], occupational therapist [OT], psychiatrist, psychologist, social worker, psychiatric nurse, other licensed professional) with competence in principles and practice of CBT and providing individualized treatment that includes ALL of the following elements
            a. disease education
            b. activity and lifestyle modification
            c. stress management (stress management typically also includes strategies to deal with emotions such as fear, anxiety, sadness that can interfere with pain management)
      ii. Imaging studies confirm Modic Type I changes on MRI report (i.e., hypointense T1 and hyperintense T2 in the vertebral endplates) at a maximum of three vertebrae between L3 and S1) or Type I and Type II changes on MRI (hyperintense T1 and hyperintense T2 in the vertebral endplates) at a maximum of three vertebrae between L3 and S1)

iii. Statement from a primary care physician, neurologist, physiatrist, psychiatrist, psychologist, or other licensed behavioral and/or medical health care provider not involved with the recommended plan of treatment attesting to the absence of untreated, underlying mental health conditions/issues (e.g., depression, drug, alcohol abuse) as a major contributor to chronic back pain.
iv. *Note: Structured medical management consists of medical care that is delivered through regularly scheduled appointments, including follow-up evaluation, with licensed healthcare professionals

4) Aetna 2023
    a. Considers BVN to be experimental
5) United Healthcare 2024
    a. Considers BVN to be experimental

Basivertebral Nerve Ablation for Back Pain

HERC staff summary: Since the 2021 HERC review of basivertebral nerve ablation, only 1 new RCT has been published (N=77). A recent systematic review (Conger 2021) found moderate quality evidence that this procedure is effective at reducing pain and disability in highly selected patients, but recommended larger, non-industry funded studies to confirm this. National and international spine surgery expert guidelines recommend use of this procedure in selected patients. Multiple private payers as well as CMS are now covering this procedure. it appears that many private payers are now covering this procedure.

HERC staff remain concerned about the lack of large RCTs examining the efficacy of this procedure. However, expert guidelines recommend use in selected patients and many other payers are covering this procedure. The HERC should discuss whether adding coverage is desirable. Two options are presented below, one to continue non-coverage until more evidence is published while the second adds limited coverage based on other payer coverage policies.

HERC staff recommendation:

1) **Option 1:** continued non-coverage
    a. Update the BVN entry date of last review in GN173

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Line 654
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Procedure Code	Intervention Description	Rationale	Last Review
64628-64629	Thermal destruction of intraosseous basivertebral nerve	Insufficient evidence of effectiveness	~~November 2021~~ March 2024

2) **Option 2**: Add limited coverage for basivertebral nerve ablation
    a. Add the following CPT codes to lines 343 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS and 523 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
        i. 64628 Heat destruction of intraosseous basivertebral nerve in bones of spine in lower back, first two bones
        ii. 64629 Heat destruction of intraosseous basivertebral nerve in additional bone of spine in lower back
    b. Delete the entry in GN173 for BVN

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 654
The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Basivertebral Nerve Ablation for Back Pain

Procedure Code	Intervention Description	Rationale	Last Review
~~64628-64629~~	~~Thermal destruction of intraosseous basivertebral nerve~~	~~Insufficient evidence of effectiveness~~	~~November 2021~~

c. Add a new guideline for lines 343 and 523 as shown below

GUIDELINE NOTE XXX BASIVERTEBRAL NERVE ABLATION
Lines 343,523

Intraosseous basivertebral nerve ablation (CPT 64628, 64629) is included on line 343 when all of the following criteria are met:

1) The patient has chronic unremitting low back pain of at least 6 months duration; AND
2) The patient has failed to respond to at least 6 months of conservative medical management, which must include at least 3 of the following:
    a. A course of physical therapy or professionally directed therapeutic exercise program,
    b. Chiropractic manipulation,
    c. Pharmacotherapy (for example, narcotic and non-narcotic analgesics, muscle relaxants, neuroleptics, and anti-inflammatories),
    d. Cognitive behavioral therapy,
    e. Activity/lifestyle modification; AND
3) The patient has magnetic resonance imaging (MRI)-demonstrated Modic Type 1 or 2 changes in at each one vertebral endplate proposed for treatment, at one or more levels from L3 to S1, including the following:
    a. Fibrovascular bone marrow changes are present (hypointense MRI signal for Modic Type 1); OR
    b. Fatty bone marrow changes are present (hyperintense MRI signal for Modic Type 2); AND
4) Documentation that other causes of low back pain have been excluded (including, but not limited to: chronic lumbar strain, lumbar stenosis, degenerative scoliosis, facet arthropathy and disc disease).

Otherwise, basivertebral nerve ablation is included on line 523.

Pain Medicine, 23(S2), 2022, S50–S62
https://doi.org/10.1093/pm/pnac070
Review Article

The Effectiveness of Intraosseous Basivertebral Nerve Radiofrequency Ablation for the Treatment of Vertebrogenic Low Back Pain: An Updated Systematic Review with Single-Arm Meta-analysis

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Disclosures and Conflicts of interest: Dr. Aaron Conger and Dr. Zachary L. McCormick have received investigator-initiated research funding from Relievant MedSystems (paid directly to the University of Utah).

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Study registration: PROSPERO (ID:CRD42020192001).

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Abstract

Objective. To provide an estimate of the effectiveness of basivertebral nerve (BVN) radiofrequency ablation (RFA) to treat vertebrogenic low back pain (LBP). **Design**. Systematic review with single-arm meta-analysis. **Population**. Persons ≥18 years of age with chronic LBP associated with type 1 or 2 Modic changes. **Intervention**. Intraosseous BVN RFA. **Comparison**. Sham, placebo procedure, active standard care treatment, or none. **Outcomes**. The proportion of patients treated with BVN RFA who reported ≥50% pain score improvement on a visual analog scale or numeric rating scale. The main secondary outcome was ≥15-point improvement in Oswestry Disability Index score. **Methods**. Three reviewers independently assessed articles published before December 6, 2021, in MEDLINE and Embase. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework was used to evaluate the overall quality of evidence. **Results**. Of the 856 unique records screened, 12 publications met the inclusion criteria, representing six unique study populations, with 414 participants allocated to receive BVN RFA. Single-arm meta-analysis showed a success rate of 65% (95% confidence interval [CI] 51–78%) and 64% (95% CI 43–82%) for ≥50% pain relief at 6 and 12 months, respectively. Rates of ≥15-point Oswestry Disability Index score improvement were 75% (95% CI 63–86%) and 75% (95% CI 63–85%) at 6 and 12 months, respectively. **Conclusion**. According to GRADE, there is moderate-quality evidence that BVN RFA effectively reduces pain and disability in most patients with vertebrogenic LBP. Further high-quality studies will likely improve our understanding of the effectiveness of this procedure.

Key Words: Endplate; Vertebrogenic, Discogenic; Modic; Ablation

Introduction

Intraosseous basivertebral nerve (BVN) radiofrequency ablation (RFA) has gained attention as a target-specific treatment for pain arising from pathological degeneration of the vertebral endplates (VEPs) of the lumbosacral spine. At lumbar levels, the BVN is a paired branch of the bilateral sinuvertebral nerves that passes through the basivertebral foramen at the posterior aspect of the vertebral body

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International Society for the Advancement of Spine Surgery Guideline—Intraosseous Ablation of the Basivertebral Nerve for the Relief of Chronic Low Back Pain

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RATIONALE

This International Society for the Advancement of Spine Surgery guideline is generated to respond to growing requests for background, supporting literature and evidence, and proper coding for intraosseous ablation of the basivertebral nerve for chronic low back pain.

Testing & Regulatory Affairs

Keywords: intraosseous ablation, basivertebral nerve, chronic low back pain, vertebrogenic pain

INTRODUCTION

Prevalence and Clinical Presentation

Low back pain (LBP) is the most expensive occupational disorder in the United States and the leading cause of disability worldwide.[1–3] Thirty percent of Americans have LBP at any given time, leading to approximately 50 million physician visits in the US annually. Although many of these patients improve with little to no treatment, an estimated 30 million adults in the US currently suffer from chronic LBP (CLBP), defined as pain lasting for greater than 12 weeks.[4–10] These CLBP patients have direct yearly costs of over $90 billion/year.[11] As is the case with many medical conditions, a minority of CLBP patients consume the majority of health care resources. Analyses of commercial payer and Medicare claims databases reveals that 15% of CLBP patients account for 75% of health care costs, with average claims of $24 700 over a 3-year period in the high health care use group (MarketScan, Truven Health Analytics from October 2011 to September 2016).

Disc degeneration (DD) is a strong risk factor for CLBP,[12–14] and the disc has been the target of many treatments. Recent scientific research has reexamined CLBP sources, and there is evidence suggesting that the disc and adjacent endplates act as 1 functional unit and that the vertebral endplate is a source of pathologic innervation that occurs with DD.

Indeed, the endplates must balance conflicting requirements of being strong to prevent vertebral fracture and being porous to facilitate transport between disc cells and vertebral capillaries. Consequently, endplates are particularly susceptible to damage leading to inflammation and nerve proliferation.

The sensory nerves within the center of the vertebral body converge to form the basivertebral nerve (BVN).[15,16] The BVN exits the vertebral body posteriorly via the basivertebral foramen before communicating with the sinuvertebral nerve then the ventral rami of the spinal nerves or by nerves derived from the gray rami communicantes[16] When the density of pain fibers between normal endplates and degenerated endplates is compared, the BVN density is considerably higher in patients with degenerated endplates, further suggesting the role of pain transmission via the BVN in patients with CLBP.[16] The pain transmission of the endplates toward the BVN has been named of "vertebrogenic" origin.[14,15] Patients with vertebrogenic pain are thought to present with LBP, with or without referral into the buttocks or thighs (somatic referred pain).

Traditional Treatments for CLBP

CLBP may lead to a compromised quality of life, strained societal and familial relationships, and increased absenteeism or work-related disability

Posterior Tibial Nerve Stimulation

Plain Language Summary:

Coverage question: Should OHP cover a treatment that stimulates a nerve to help with overactive bladder, especially when other treatments haven't helped?

Should OHP cover this treatment? Yes, this treatment should be covered when other treatments haven't helped.

Changes to issue summary after public comment period:

One public comment was received on this topic. The commentor recommended coverage of Percutaneous Tibial Nerve Stimulation (PTNS) for overactive bladder. The commenter provided four additional studies, one of which found a clinically meaningful change in quality of life for women with OAB with PTNS compared to pelvic PT. In another study, the group of patients randomized to PTNS had clinically meaningful improvement of quality of life at 6 weeks and 3 months but not at longer time periods. The staff recommendation was already to add coverage for PTNS for OAB; therefore, no change was made in the staff recommendation based on this public comment.

Coverage Question: Should posterior tibial nerve stimulation be covered for any urinary or other indications?

Question source: Holly Jo Hodges, CCO medical director

Background: Posterior tibial nerve stimulation (PTNS) is a technique of electrical neuromodulation for the treatment of voiding dysfunction in patients who have failed behavioral and/or pharmacologic therapies. The aim of neuromodulation is to target the innervation system of the lower urinary tract. The posterior tibial nerve is a distal branch of the sciatic nerve that originates in the pelvis (L5–S3 spinal roots) and descends towards the lower extremities. Stimulation of the posterior tibial nerve delivers retrograde neuromodulation to the sacral nerve plexus that controls the bladder function.

PTNS is used for treatment of overactive bladder. Overactive bladder is a condition in which causes frequent urination, urge incontinence, and sudden need to urinate. Other treatments for overactive bladder are lifestyle changes, bladder retraining, medications, botulinum injections, pelvic floor physical therapy and sacral nerve stimulation.

PTNS has also been proposed as a treatment for neurogenic bladder, fecal incontinence and pelvic dysfunction.

A new HCPCS code was published effective April 2024 for transcutaneous tibial nerve stimulator devices.

Previous HSC/HERC reviews:

Posterior Tibial Nerve Stimulation

PTNS was last reviewed as a new CPT code in December 2010. At that time, a 2010 NICE review found that long term efficacy of PTNS for treatment of overactive bladder had not been established. Most private insurers considered PTNS experimental. The CPT code for PTNS was added to the Excluded File. It was later moved to line 495/GN172.

Current Prioritized List/Coverage status:

64566 (Insertion of lower leg neurostimulator electrode) is on line 495 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS

64590 (Insertion or replacement of peripheral, sacral, or gastric neurostimulator generator or receiver) is on lines 324 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION, 454 URINARY INCONTINENCE, and 522 STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

ICD-10-CM N32.81 (Overactive bladder) is on line 324

ICD-10-CM N31.X (neurogenic bladder) is on lines 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES and 324

ICD-10-CM R33.8 (Other retention of urine) is on the Diagnostic Workup File and line 324

HCPCS E0736 (Transcutaneous tibial nerve stimulator) is a new code for April 2024

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 495

The following interventions are prioritized on Line 495 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
64566	Posterior tibial neurostimulation	Minimally effective, no evidence of long-term effectiveness	December, 2010

GUIDELINE NOTE 192, SACRAL NERVE STIMULATION FOR URINARY CONDITIONS

Lines 324,454

Sacral nerve stimulation is included on these lines only for urinary incontinence, non-obstructive urinary retention, and overactive bladder AND only when all of the following criteria are met:

A) The patient has had symptoms for at least 12 months and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities); AND

Posterior Tibial Nerve Stimulation

B) Documented failure or intolerance to pharmacotherapies and behavioral treatments (e.g., pelvic floor exercise, timed voids, and fluid management) and, for non-obstructive urinary retention, intermittent catheterization; AND
C) The patient must be an appropriate surgical candidate such that implantation with anesthesia can occur; AND
D) The patient does not have stress incontinence, urinary obstruction, or specific neurologic diseases (e.g., diabetes with peripheral nerve involvement, spinal cord injury, or multiple sclerosis); AND
E) Patient must have had a successful test stimulation, defined as a 50% or greater improvement in symptoms.

Evidence:

PTNS for overactive bladder

1) **Stewart 2016**, Cochrane review of electrical stimulation (ES) for overactive bladder (OAB) in adults
    a) N=63 trials (4424 patients)
        i) The majority of trials were deemed to be at low or unclear risk of selection and attrition bias and unclear risk of performance and detection bias. Lack of clarity with regard to risk of bias was largely due to poor reporting
        ii) For perception of improvement in OAB symptoms, moderate-quality evidence indicated that ES was better than pelvic floor muscle training (PFMT) (risk ratio (RR) 1.60, 95% confidence interval (CI) 1.19 to 2.14; n = 195), drug treatment (RR 1.20, 95% 1.04 to 1.38; n = 439). and placebo or sham treatment (RR 2.26, 95% CI 1.85 to 2.77, n = 677) but it was unclear if ES was more effective than placebo/sham for urgency urinary incontinence (UUI)(RR 5.03, 95% CI 0.28 to 89.88; n = 242). Drug treatments included in the trials were estrogen cream, oxybutynin, propantheline bromide, probanthine, solifenacin succinate, terodiline, tolterodine and trospium chloride
        iii) Low- or very low-quality evidence suggested no evidence of a difference in perception of improvement of UUI when ES was compared to PFMT with or without biofeedback
        iv) Low-quality evidence indicated that OAB symptoms were more likely to improve with ES than with no active treatment (RR 1.85, 95% CI 1.34 to 2.55; n = 121)
        v) Low-quality evidence suggested participants receiving ES plus PFMT, compared to those receiving PFMT only, were more than twice as likely to report improvement in UUI (RR 2.82, 95% CI 1.44 to 5.52; n = 51)
        vi) There was inconclusive evidence, which was either low- or very low-quality, for OAB-related quality of life when ES was compared to no active treatment, placebo/sham or biofeedback-assisted PFMT, or when ES was added to PFMT compared to PFMT-only. There was very low-quality evidence from a single trial to suggest that ES may be better than PFMT in terms of OAB-related quality of life
        vii) There was a lower risk of adverse effects with ES than tolterodine (RR 0.12, 95% CI 0.05 to 0.27; n = 200) (moderate-quality evidence) and oxybutynin (RR 0.11, 95% CI 0.01 to 0.84; n = 79) (low-quality evidence)

viii) Due to the very low-quality evidence available, we could not be certain whether there were fewer adverse effects with ES compared to placebo/sham treatment, magnetic stimulation or solifenacin succinate. We were also very uncertain whether adding ES to PFMT or to drug therapy resulted in fewer adverse effects than PFMT or drug therapy alone Nor could we tell if there was any difference in risk of adverse effects between different types of ES.

ix) There was insufficient evidence to determine if one type of ES was more effective than another or if the benefits of ES persisted after the active treatment period stopped.

x) Authors' conclusions Electrical stimulation shows promise in treating OAB, compared to no active treatment, placebo/sham treatment, PFMT and drug treatment. It is possible that adding ES to other treatments such as PFMT may be beneficial. However, the low quality of the evidence base overall means that we cannot have full confidence in these conclusions until adequately powered trials have been carried out, measuring subjective outcomes and adverse effects

PTENS for idiopathic nonobstructive urinary retention

1) **Coolen 2020**, systematic review
    a. N=8 studies (N=227 patients)
        i. 6 prospective cohort studies
        ii. 2 prospective studies comparing PTENS to other treatments (only one randomized patients)
    b. Objective success was defined as a ≥50% decrease in the number of catheterizations per 24 h or in the total catheterized volume in 24 h. The objective success rate of PTNS ranged from 25% to 41%. Subjective success was defined as the patient's request for continued chronic treatment with PTNS, and ranged from 46.7% to 59%.
    c. Conclusions: The efficacy of TENS and PTNS in the treatment of idiopathic NOUR is limited and should be verified in larger randomized studies before application in clinical practice.

PTENS for neurogenic bladder

1) **Schneider 2015**, systematic review
    a. N=16 studies (4 randomized controlled trials [RCTs], 9 prospective cohort studies, 2 retrospective case series, and 1 case report) enrolling 469 patients
        i. Patients had Parkinson's disease, stroke, or spinal cord injuries
    b. In acute and chronic TNS, the mean increase of maximum cystometric capacity ranged from 56 to 132 mL and from 49 to 150 mL, and the mean increase of bladder volume at first detrusor overactivity ranged from 44 to 92 mL and from 93 to 121 mL, respectively. In acute and chronic TNS, the mean decrease of maximum detrusor pressure during the storage phase ranged from 5 to 15 cm H2O and from 4 to 21 cm H2O, respectively. In chronic TNS, the mean decrease in number of voids per 24 h, in number of leakages per 24 h, and in postvoid residual ranged from 3 to 7, from 1 to 4, and from 15 to 55 mL, respectively. No TNS-related adverse events have been reported. Risk of bias and confounding was high in most studies.
    c. No TNS-related adverse events have been reported.

d. Conclusions: Although preliminary data of RCTs and non-RCTs suggest TNS might be effective and safe for treating NLUTD, the evidence base is poor, derived from small, mostly noncomparative studies with a high risk of bias and confounding. More reliable data from well-designed RCTs are needed to reach definitive conclusions

Submitted literature:

1) Lashin 2021, RCT of tibial nerve stimulation (PTNS) vs sham
    a. N=25 in the PTNS group, N=25 in the sham group
    b. 6 week study
    c. A significant improvement in the PTNS group at the 7th week, 3rd and 6th month, based on Overactive Bladder Symptom Score (OABSS) was noted in the active group compared to sham group (P=0.001)
        i. Actual change in scores not presented, unable to determine if clinically important change
    d. Conlcusions:
    e. A shortened 6-week treatment protocol with PTNS appears to be successful and more effective than sham in the treatment of refractory OAB. PTNS therapy is safe and effective in treating OAB symptoms with 52% success rate following a shortened 6-week protocol
    f. HERC staff conclusion: unable to determine if PTNS resulted in a clinically important change in quality of life
2) Vecchioli Scaldazza 2017, RCT of tibial nerve stimulation (PTNS) vs pelvic floor muscle training
    a. N=60 women with overactive bladder syndrome (OAB)
        i. 30 in the pelvic floor muscle training group: 10 sessions of pelvic floor PT with vaginal electrical stimulation done 3x a week
        ii. 30 in the PTNS group: 6 weeks of 2x a week sessions
    b. Overactive Bladder questionnaire Short Form (OAB-q SF) used to assess impact on quality of life
        i. Pelvic PT change -7.47; PTNS change -19.55
        ii. MCID for the OABSS core is -10
    c. Urgency was assessed by the Patient Perception of Intensity of Urgency Scale (PPIU-S)
        i. Pelvic PT change -0.77; PTNS change -1.25
        ii. Studies reviewed reported being unable to determine a MCID for PPIU-S
    d. Improvement was evaluated with the Patient Global Impression of Improvement questionnaire (PGI-I).
        i. Pelvic PT change -7.47; PTNS change -19.55
        ii. No MCID found for PGI-I
    e. A statistically significant reduction in the number of daily micturitions, episodes of nocturia and urge incontinence was found in the two groups but the difference was more substantial in women treated with PTNS; voided volume increased in both groups. Quality of life improved in both groups, whereas patient perception of urgency improved only in women treated with PTNS. Global impression of improvement revealed a greater satisfaction in patients treated with PTNS
    f. Conclusion: This study demonstrates the effectiveness of PTNS and ES with PFMT in women with OAB, but greater improvements were found with PTNS
    g. HERC staff conclusion: PTNS resulted in a clinically significant improvement in quality of life compared to pelvic PT

Posterior Tibial Nerve Stimulation

3) Vecchioli Scaldazza 2018, RCT of solifenacin vs tibial nerve stimulation (PTNS)
    a. N=94 women with overactive bladder syndrome (OAB)
        i. N=27 patients in the solifenacin group, received medication for 12 weeks
        ii. N=34 women in the PTNS group, treated for 12 weeks
        iii. N=33 women in the solifenacin + PTNS group, treated with both for 8 weeks
        iv. 12 week study
    b. Change in OAB-q SF 6 quality of life measure
        i. PTNS change -1.1; solifenacin change -0.77
        ii. MCID for the OABSS core is -4.8
    c. Change in OAB-q SF 13 quality of life measure
        i. PTNS change -1.26; solifenacin change -0.76
        ii. MCID for the OABSS core is -4.8
    d. Change in OABSS day time frequency score
        i. PTNS change -0.77; solifenacin change -0.86
        ii. MCID for the OABSS core is -3
    e. Change in OABSS night time frequency
        i. PTNS change -1.3; solifenacin change -0.48
        ii. MCID for the OABSS core is -3
    f. Change in OABSS urgency score
        i. PTNS change -1.35; solifenacin change -0.86
        ii. MCID for the OABSS core is -3
    g. Change in OABSS urge incontinence score
        i. PTNS change -1.76; solifenacin change -1.04
        ii. MCID for the OABSS core is -3
    h. Author reported results: All treatments were effective on symptoms. PTNS showed a greater effectiveness than solifenacin, but PTNS + solifenacin was more effective than solifenacin and PTNS. Furthermore, PTNS + solifenacin showed a greater duration of effectiveness than PTNS and solifenacin
    i. HERC staff conclusions: no clinically important difference was found between PTNS and soifenacin
4) Sherif 2017: RCT of PTNS compared to botulinum toxin injection for OAB
    a. N=60 women with OAB
        i. N=30 women in the PTNS group, 12 week course
        ii. N=30 women in the botulinum toxin group, given 1 injection
    b. PTNS group: OABSS score change -8.2 at 6 weeks, -8.9 at 3 months, -3.1 at 6 months, and -1.5 at 9 months
        i. MCID for the OABSS core is -4.8
    c. Patients in the PTNS group had significant improvements in OAB symptom score and urgency score at 6 months comparted to baseline, but the improvements were not significant at 9 months. However, they had a significant improvement in quality-of-life that persisted until 9 months

Expert guidelines:

1) **Lightner 2019,** amendment to the AUA/SUFU guideline

a) The 2019 amendment was based on the inclusion of combination therapy for the treatment of OAB. All other statements in the previous guideline iteration remain unchanged.
   i) The only change in this guideline appears to be review of combinations of medications rather than "anti-muscarinics or oral β3-adrenoceptor agonists"
b) The treatment algorithm begins with behavioral therapies, then moves to pharmacologic therapies, and then moves to other therapies such as PTNS.
c) The text contains the following comment: "The clinician should bear in mind that the treatment framework does not require that every patient go through each line of treatment in order. There are many factors to consider when identifying the best treatment for a particular patient, including information regarding allergies, sensitivity to various adverse drug events, patient ability and motivation to comply, and availability of and access to specific treatments."

2) **American Urology Association 2015**, guideline on the diagnosis and treatment of overactive bladder in adults
   a) Clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first line therapy to all patients with OAB. Standard (Evidence Strength Grade B)
   b) Behavioral therapies may be combined with pharmacologic management. Recommendation (Evidence Strength Grade C)
   c) Clinicians should offer oral anti-muscarinics or oral β3-adrenoceptor agonists as second-line therapy. Standard (Evidence Strength Grade B)
   d) Clinicians may offer peripheral tibial nerve stimulation (PTNS) as third line treatment in a carefully selected patient population. Recommendation (Evidence Strength Grade C)
      i) The Panel interpreted these data to indicate that PTNS can benefit a carefully selected group of patients characterized by moderately severe baseline incontinence and frequency and willingness to comply with the PTNS protocol. Patients must also have the resources to make frequent office visits both during the initial treatment phase and to obtain maintenance treatments in order to achieve and maintain treatment effects obtain treatment because treatment effects dissipate once treatment ceases. Reported adverse events were minor; the most frequently reported events were painful sensation during stimulation that did not interfere with treatment and minor bleeding at the insertion site. In the Panel's view, benefits outweigh risks/burdens for the use of PTNS in the thoughtfully-selected and counseled patient who is highly-motivated to make the required office visits.
      ii) As a group, the PTNS studies constitute Grade C evidence because of the predominant observational designs, varying patient inclusion criteria, small sample sizes, and short follow-up durations for most studies.

Other payer policies:

1) Wellmark BCBS
   a. Percutaneous Posterior Tibial Nerve Stimulation (PTNS) for an initial 12-week course may be considered medically necessary for individuals with non-neurogenic urinary dysfunction (see Policy Guidelines) including overactive bladder (OAB) who have both:

i. failed behavioral therapy following an appropriate duration of 8 to 12 weeks without meeting treatment goals; and
ii. failed pharmacologic therapy following 4 to 8 weeks of treatment without meeting treatment goals

b. Maintenance therapy using monthly percutaneous PTNS may be considered medically necessary for individuals following a 12-week initial course of posterior tibial nerve stimulation that resulted in improved urinary dysfunction meeting treatment goals.
c. Percutaneous PTNS not meeting the above criteria and for all other indications is considered not medically necessary. Implantable PTNS (e.g., eCoin) is considered investigational for all indications, including individuals with non-neurogenic urinary dysfunction including overactive bladder.

2) Aetna 2023
   a. Aetna considers percutaneous tibial nerve stimulation (PTNS) (e.g., the eCoin Peripheral Neurostimulator System, and Urgent PC Neuromodulation System, Uroplasty, Inc., Minneapolis, MN) medically necessary for the treatment of members with urge UI or urge-frequency when they meet the first 2 criteria listed for Implantable Sacral Nerve Stimulators (e.g., Axonics and InterStim) (policy section I.B.3a and I.B.3b for the treatment of urge urinary incontinence or symptoms of urge-frequency).
      i. The member has experienced urge UI or symptoms of urge-frequency for at least 6 months and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities); *and*
      ii. Pharmacotherapies (i.e., at least 2 different anti-cholinergic drugs or an anti-cholinergic and a beta-3 adrenergic receptor agonist (mirabegron)) as well as behavioral treatments (e.g., pelvic floor exercise, biofeedback, timed voids, and fluid management) have failed;
   b. In general, 12 treatments (once-weekly) with PTNS are needed for symptom relief. If the member fails to improve after 12 PTNS treatments, continued treatment is considered not medically necessary. If the member improves after 12 PTNS treatments, continued monthly treatments are considered medically necessary as long as the member's symptoms remain improved.
   c. Aetna considers percutaneous tibial nerve stimulation experimental and investigational when criteria are not met.

3) Cigna 2023
   a. Percutaneous Tibial Nerve Stimulation (PTNS) Overactive Bladder A standard treatment regimen of 30-minute weekly sessions for 12 weeks of percutaneous tibial nerve stimulation (PTNS) is considered medically necessary for the treatment of overactive bladder (OAB) symptoms when there is failure, intolerance, or contraindication to conservative medical management (e.g., bladder training, pharmacotherapy)

Expert input:

Dr. Tom Gregory, OHSU Chief of Urogynecology

Thank you for taking this on! Our patients on OHP will benefit from this expansion of coverage. I have no edits/suggestions to your summary…I am happy that you use the term "intolerance to pharmacotherapies" – rather than spelling out that they must have not responded to antimuscarinics/anticholinergics. As you are likely aware, evolving literature is demonstrating

that that class of medications is deleterious with prolonged use – particularly in the elderly. Most of my colleagues are pushing to remove the requirement for that medication to be used in pathways – in favor of beta 3 agonists such as mirabegron and vibegron (or moving directly to 3rd line therapies such as PTNS/SNS and Botox).

Posterior Tibial Nerve Stimulation

HERC staff summary:

A recent Cochrane review found that tibial nerve stimulation had moderate quality evidence that it improved perception of improvement in overactive bladder symptoms (OAB) compared to pelvic floor PT or placebo/sham treatment. There was insufficient evidence to conclude whether tibial nerve stimulation improved urinary incontinence or OAB-related quality of life. There was also insufficient evidence regarding comparative adverse effects between tibial nerve stimulation and other treatments of OAB.

Private payers are covering PTNS for OAB. Expert guidelines recommend PTNS as a third line treatment option for overactive bladder, after a trial of medications and behavioral therapies.

Recent systematic reviews did not find evidence of efficacy of PTNS for treatment of neurogenic bladder or idiopathic nonobstructive urinary retention.

One public comment was received on this topic. The commenter provided 4 additional RCTs, all of which were small and of poor quality. One of these studies found a clinically significant improvement in quality of life for women with OAB with PTNS compared to pelvic PT. An additional study did not find a clinically meaningful difference between PTNS and one medication.

Based on expert guidelines and Oregon expert recommendations, HERC staff recommends adding coverage of PTNS for treatment of overactive bladder as a third line therapy with a new guideline.

HERC staff recommendations:

1) Add CPT 64566 (Insertion of lower leg neurostimulator electrode) to line 324 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
2) Remove CPT 64566 from line 495 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS and delete the GN172 entry as shown below
3) Add the new HCPCS code E0736 (Transcutaneous tibial nerve stimulator) to line 324
4) Adopt a new guideline for line 324 as shown below
    a. Criteria are from the sacral nerve stimulator guideline

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 495

The following interventions are prioritized on Line 495 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
~~64566~~	~~Posterior tibial neurostimulation~~	~~Minimally effective, no evidence of long-term effectiveness~~	~~December, 2010~~

Posterior Tibial Nerve Stimulation

GUIDELINE NOTE XXX POSTERIOR TIBIAL NERVE STIMULATION

Line 324

Posterior tibial nerve stimulation (CPT 64566, 64590, HCPCS E0736) is included on line 324 only when all of the following criteria are met:

A) The patient has overactive bladder syndrome; AND
B) The patient has had symptoms for at least 6 months and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities); AND
C) Documented failure or intolerance to pharmacotherapies and behavioral treatments (e.g., pelvic floor exercise, timed voids, and fluid management).

Initial coverage is limited to 12 once-weekly treatments. If the member improves after 12 posterior tibial nerve stimulation treatments, continued monthly treatments are considered medically necessary as long as the member’s symptoms remain improved.

Posterior Tibial Nerve Stimulation

Disposition of Public Comments

Table of Contents

Discussion Table

IDs/#s	Summary of Issue	HERC Staff Response
A	PTNS should be covered for overactive bladder treatment.	This change is already in the staff recommendation; no changes to the staff recommendation were made based on this comment.
A	PTNS should be offered "when there is documented failure or intolerance to pharmacotherapies and behavioral treatments and criteria are met."	This wording is in the current staff guideline draft.

Commenters

Identification	Stakeholder
A	Wendy Chan, Medtronic *[Submitted April 15, 2024]*

Public Comments

ID/#	Comment	Disposition
A1	Medtronic is the world's leading medical technology company, specializing in implantable and interventional therapies that alleviate pain, restore health,	Thank you for your comments. HERC staff propose coverage PTNS for OAB in the current meeting

Disposition of Public Comments

ID/#	Comment	Disposition
	and extend life. We are committed to the continual research and development necessary to provide high-quality products and innovative therapies that improve the health outcome for all patients. Specifically, with our posterior tibial nerve stimulation (PTNS) therapy, we provide relief for patients who suffer from urinary incontinence as a treatment option when multiple first line therapies have failed in providing patients with improved relief and increased quality of life to support their daily activities. Medtronic wishes to submit public comments to support the Oregon Health Authority's proposed coverage of posterior tibial nerve stimulation. Medtronic is the manufacturer of the NEURO™ PTNS which is intended to treat patients with overactive bladder (OAB) and associated symptoms of urinary urgency, urinary frequency, and urge incontinence. We agree with the Oregon Health Evidence Review Commission (HERC) in adding this as an option for line 324 supporting PTNS as a treatment option. Medicare and the large commercial payers already support coverage of this treatment when there is documented failure or intolerance to pharmacotherapies and behavioral treatments and criteria are met. The American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Guideline Amendment in 2019 states that "This clinical framework does not require that every patient go through each line of treatment in order as there are many factors to consider when identifying the best treatment for a particular patient." This should also be considered in relation to the evidence framework.	materials. However, the staff recommendation includes step therapy as the AUA guideline amendment specifically includes notation that PTNS and similar therapies be tried after behavioral and medication therapies. There is wording in the proposed guideline that would allow a patient to forgo pharmacotherapy and behavioral treatments if intolerant to these therapies, which appears to be the intent of the AUA guideline.
A2	Since the 2016 Cochrane review on electrical stimulation using non-implantable devices, there are four PTNS randomized clinical trials that have	The submitted articles give information on the utility of PTNS for treatment of OAB.

Disposition of Public Comments

ID/#	Comment	Disposition
	been published in 2016 or later not included in the review. They are as follows: • Lashin 2021. Int Urol Nephrol. • Vecchioli-Scaldazza 2016. Int Braz J Urol. • Vecchioli-Scaldazza 2017. Int Braz J Urol. • Sherif 2017. Can J Urol. A table summarizing the studies are included as a separate attachment to facilitate your review. These recent randomized clinical trials help support the continued safety and effectiveness of PTNS as a treatment option for OAB. We request that the proposal be finalized with this recommendation and support amending the criteria for PTNS to reflect this to ensure that it continues to be an available treatment option for patients who suffer from OAB	1) Lashin 2021 is a small, poorly conducted RCT of PTNS vs sham. No actual clinical data was presented on the quality of life score changes; therefore, staff were not able to determine if PTNS resulted in a clinically important change in symptoms 2) Vercchioli Scaldazza 2017 (listed here as 2016) is a small, poorly conducted RCT of PTNS vs pelvic floor PT. This study found a clinically meaningful difference favoring PTNS over pelvic floor PT in quality of life 3) Vercchioli Scaldazza 2018 (listed here as 2017) is a small, poorly conducted RCT of PTNS vs solifenacin. Based on the data presented, it did not appear that there was a clinically important difference between these two treatments in various measurements of bladder symptoms. 4) Sherif 2017 was an RCT comparing PTNS to botulinum toxin injection for OAB. The group assigned to PTNS had clinically significant improvement in bladder related quality of life in short term assessments but not long term (>3 months).

Disposition of Public Comments

ID/#	Comment	Disposition
		Based on the studies submitted, HERC staff are not recommending any changes to the current staff recommendations.

References Provided by Commenters

ID	References
A	• Lashin 2021. Int Urol Nephrol. • Vecchioli-Scaldazza 2016. Int Braz J Urol. • Vecchioli-Scaldazza 2017. Int Braz J Urol. • Sherif 2017. Can J Urol.

Cochrane Library

Cochrane Database of Systematic Reviews

Electrical stimulation with non-implanted electrodes for overactive bladder in adults (Review)

Stewart F, Gameiro LF, El Dib R, Gameiro MO, Kapoor A, Amaro JL

Stewart F, Gameiro LF, El Dib R, Gameiro MO, Kapoor A, Amaro JL.
Electrical stimulation with non-implanted electrodes for overactive bladder in adults.
Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD010098.
DOI: 10.1002/14651858.CD010098.pub4.

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[Intervention Review]

Electrical stimulation with non-implanted electrodes for overactive bladder in adults

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Editorial group: Cochrane Incontinence Group.
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ABSTRACT

Background

Several options exist for managing overactive bladder (OAB), including electrical stimulation (ES) with non-implanted devices, conservative treatment and drugs. Electrical stimulation with non-implanted devices aims to inhibit contractions of the detrusor muscle, potentially reducing urinary frequency and urgency.

Objectives

To assess the effects of ES with non-implanted electrodes for OAB, with or without urgency urinary incontinence, compared with: placebo or any other active treatment; ES added to another intervention compared with the other intervention alone; different methods of ES compared with each other.

Search methods

We searched the Cochrane Incontinence Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, ClinicalTrials.gov, WHO ICTRP and handsearching of journals and conference proceedings (searched 10 December 2015). We searched the reference lists of relevant articles and contacted specialists in the field. We imposed no language restrictions.

Selection criteria

We included randomised or quasi-randomised controlled trials of ES with non-implanted devices compared with any other treatment for OAB in adults. Eligible trials included adults with OAB with or without urgency urinary incontinence (UUI). Trials whose participants had stress urinary incontinence (SUI) were excluded.

Data collection and analysis

Two review authors independently screened search results, extracted data from eligible trials and assessed risk of bias, using the Cochrane 'Risk of bias' tool.

Main results

We identified 63 eligible trials (4424 randomised participants). Forty-four trials did not report the primary outcomes of perception of cure or improvement in OAB. The majority of trials were deemed to be at low or unclear risk of selection and attrition bias and unclear risk of performance and detection bias. Lack of clarity with regard to risk of bias was largely due to poor reporting.

For perception of improvement in OAB symptoms, moderate-quality evidence indicated that ES was better than pelvic floor muscle training (PFMT) (risk ratio (RR) 1.60, 95% confidence interval (CI) 1.19 to 2.14; n = 195), drug treatment (RR 1.20, 95% 1.04 to 1.38; n = 439). and placebo or sham treatment (RR 2.26, 95% CI 1.85 to 2.77, n = 677) but it was unclear if ES was more effective than placebo/sham for urgency urinary incontinence (UUI) (RR 5.03, 95% CI 0.28 to 89.88; n = 242). Drug treatments included in the trials were oestrogen cream, oxybutynin, propantheline bromide, probanthine, solifenacin succinate, terodiline, tolterodine and trospium chloride.

Low- or very low-quality evidence suggested no evidence of a difference in perception of improvement of UUI when ES was compared to PFMT with or without biofeedback.

Low-quality evidence indicated that OAB symptoms were more likely to improve with ES than with no active treatment (RR 1.85, 95% CI 1.34 to 2.55; n = 121).

Low-quality evidence suggested participants receiving ES plus PFMT, compared to those receiving PFMT only, were more than twice as likely to report improvement in UUI (RR 2.82, 95% CI 1.44 to 5.52; n = 51).

There was inconclusive evidence, which was either low- or very low-quality, for OAB-related quality of life when ES was compared to no active treatment, placebo/sham or biofeedback-assisted PFMT, or when ES was added to PFMT compared to PFMT-only. There was very low-quality evidence from a single trial to suggest that ES may be better than PFMT in terms of OAB-related quality of life.

There was a lower risk of adverse effects with ES than tolterodine (RR 0.12, 95% CI 0.05 to 0.27; n = 200) (moderate-quality evidence) and oxybutynin (RR 0.11, 95% CI 0.01 to 0.84; n = 79) (low-quality evidence).

Due to the very low-quality evidence available, we could not be certain whether there were fewer adverse effects with ES compared to placebo/sham treatment, magnetic stimulation or solifenacin succinate. We were also very uncertain whether adding ES to PFMT or to drug therapy resulted in fewer adverse effects than PFMT or drug therapy alone Nor could we tell if there was any difference in risk of adverse effects between different types of ES.

There was insufficient evidence to determine if one type of ES was more effective than another or if the benefits of ES persisted after the active treatment period stopped.

Authors' conclusions

Electrical stimulation shows promise in treating OAB, compared to no active treatment, placebo/sham treatment, PFMT and drug treatment. It is possible that adding ES to other treatments such as PFMT may be beneficial. However, the low quality of the evidence base overall means that we cannot have full confidence in these conclusions until adequately powered trials have been carried out, measuring subjective outcomes and adverse effects.

PLAIN LANGUAGE SUMMARY

Non-invasive electrical stimulation for overactive bladder in adults

Background

People with overactive bladder (OAB) have a frequent and compelling desire to urinate, which has a significant impact on quality of life. Many people with OAB also have urinary incontinence. OAB affects around 17% of the world's population and is particularly common in elderly people. Treatment for OAB includes pelvic floor muscle training, drug therapy and electrical stimulation.

Non-invasive electrical stimulation works by passing an electrical current through the bladder muscles, via a vaginal or anal probe, or through a fine needle inserted into the tibial nerve around the ankle. The current is intended to reduce (inhibit) contractions of the detrusor muscle (the bladder muscle which squeezes out urine); this should reduce the number of times a person will need to urinate. Invasive electrical stimulation involves implanting electrodes within the body and requires a surgical procedure.

Aim

We investigated whether electrical stimulation was better than no treatment at all or better than any other treatment available for OAB. We also investigated which type of electrical stimulation was better for OAB and whether or not electrical stimulation was safe.

Results

We identified 63 studies (4424 people altogether) comparing electrical stimulation to no treatment or any other available treatment. We found that electrical stimulation is probably better than sham electrical stimulation or pelvic floor muscle training at reducing the main symptoms of OAB.

Electrical stimulation may be better than no active treatment or drug treatment at reducing OAB symptoms but we are less certain about these results because the available evidence was less reliable.

Similarly, there was not enough evidence to tell if adding electrical stimulation to pelvic floor muscle training or to drug treatment helped to reduce OAB symptoms. Nor could we tell which type of electrical stimulation was better.

We did not find enough information to know whether or not electrical stimulation was safer than other treatments, or if one type of electrical stimulation was safer than others.

Many of the studies we identified did not report whether or not the treatment improved OAB symptoms or whether there were any side effects caused by any of the treatments.

Finally, we could not tell from the evidence whether or not any benefits of electrical stimulation continued after the course of electrical stimulation stopped.

The evidence in this review is current up to December 2015.

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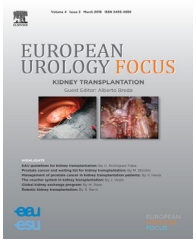

Review – Voiding Dysfunction

Transcutaneous Electrical Nerve Stimulation and Percutaneous Tibial Nerve Stimulation to Treat Idiopathic Nonobstructive Urinary Retention: A Systematic Review

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Abstract

Context: Transcutaneous electrical nerve stimulation (TENS) and percutaneous tibial nerve stimulation (PTNS) provide minimally invasive ways to treat idiopathic nonobstructive urinary retention (NOUR).
Objective: To assess the efficacy of TENS and PTNS for treating idiopathic NOUR.
Evidence acquisition: A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Embase, Medline, Web of Science Core Collection, and the Cochrane CENTRAL register of trials were searched for all relevant publications until April 2020.
Evidence synthesis: A total of 3307 records were screened based on the title and abstract. Eight studies met the inclusion criteria and none of the exclusion criteria. Five studies, all from the same group, reported the efficacy of PTNS and two that of TENS in adults with idiopathic NOUR. One study reported the efficacy of TENS in children with idiopathic NOUR. Objective success was defined as a $\geq$50% decrease in the number of catheterizations per 24 h or in the total catheterized volume in 24 h. The objective success rate of PTNS ranged from 25% to 41%. Subjective success was defined as the patient's request for continued chronic treatment with PTNS, and ranged from 46.7% to 59%. Eighty percent of women who underwent transvaginal stimulation reported an improvement such as a stronger stream when voiding. TENS in children reduced postvoid residual and urinary tract infections.
Conclusions: The efficacy of TENS and PTNS in the treatment of idiopathic NOUR is limited and should be verified in larger randomized studies before application in clinical practice.
Patient summary: The outcomes of transcutaneous electrical nerve stimulation and percutaneous tibial nerve stimulation for the treatment of urinary retention of unknown origin were reviewed. Whether these treatments are superior to other treatments could not be established.

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European Association of Urology

Review – Neuro-urology

Tibial Nerve Stimulation for Treating Neurogenic Lower Urinary Tract Dysfunction: A Systematic Review

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Systematic review

Abstract

Context: Tibial nerve stimulation (TNS) is a promising therapy for non-neurogenic lower urinary tract dysfunction and might also be a valuable option for patients with an underlying neurological disorder.
Objective: We systematically reviewed all available evidence on the efficacy and safety of TNS for treating neurogenic lower urinary tract dysfunction (NLUTD).
Evidence acquisition: The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.
Evidence synthesis: After screening 1943 articles, 16 studies (4 randomized controlled trials [RCTs], 9 prospective cohort studies, 2 retrospective case series, and 1 case report) enrolling 469 patients (283 women and 186 men) were included. Five studies reported on acute TNS and 11 on chronic TNS. In acute and chronic TNS, the mean increase of maximum cystometric capacity ranged from 56 to 132 mL and from 49 to 150 mL, and the mean increase of bladder volume at first detrusor overactivity ranged from 44 to 92 mL and from 93 to 121 mL, respectively. In acute and chronic TNS, the mean decrease of maximum detrusor pressure during the storage phase ranged from 5 to 15 cm H_2O and from 4 to 21 cm H_2O, respectively. In chronic TNS, the mean decrease in number of voids per 24 h, in number of leakages per 24 h, and in postvoid residual ranged from 3 to 7, from 1 to 4, and from 15 to 55 mL, respectively. No TNS-related adverse events have been reported. Risk of bias and confounding was high in most studies.
Conclusions: Although preliminary data of RCTs and non-RCTs suggest TNS might be effective and safe for treating NLUTD, the evidence base is poor, derived from small, mostly noncomparative studies with a high risk of bias and confounding. More reliable data from well-designed RCTs are needed to reach definitive conclusions.
Patient summary: Early data suggest tibial nerve stimulation might be effective and safe for treating neurogenic lower urinary tract dysfunction, but more reliable evidence is required.

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Voiding Dysfunction

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019

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From the American Urological Association Education and Research, Inc., Linthicum, Maryland and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction, Schaumburg, Illinois

Abbreviations and Acronyms

AHRQ = Agency for Healthcare Research and Quality

AUA = American Urological Association

ICS = International Continence Society

OAB = overactive bladder

RCT = randomized controlled trial

TEAE = treatment-emergent adverse event

UUI = urgency urinary incontinence

Accepted for publication April 22, 2019.

The complete unabridged version of the amendment is available at https://www.jurology.com.

This document is being printed as submitted independent of editorial or peer review by the editors of *The Journal of Urology®*.

Purpose: The purpose of this guideline is to provide a clinical framework for the diagnosis and treatment of non-neurogenic overactive bladder (OAB).

Materials & Methods: The primary source of evidence for the original version of this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment Number 187 titled *Treatment of Overactive Bladder in Women* (2009). That report was supplemented with additional searches capturing literature published through December 2011. Following initial publication, this guideline underwent amendment in 2014 and 2018. The current document reflects relevant literature published through October 2018.

Results: When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate), or C (low). Such statements are provided as Standards, Recommendations, or Options. In instances of insufficient evidence, additional guidance information is provided as Clinical Principles and Expert Opinions.

Conclusions: The evidence-based statements are provided for diagnosis and overall management of OAB, as well as for the various treatments. Diagnosis and treatment methodologies can be expected to change as the evidence base grows and as new treatment strategies become obtainable.

Key Words: urinary bladder, overactive; urinary bladder; urinary incontinence; nocturia; guideline

OAB is a clinical diagnosis characterized by the presence of bothersome urinary symptoms. Most studies of OAB, including this guideline, exclude individuals with symptoms related to neurologic conditions. The International Continence Society (ICS) defines OAB as the presence of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection or other obvious pathology."[1] OAB studies have used varying combinations of these symptoms to identify patients for study inclusion and to define treatment response.

Urgency is defined by the ICS as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer."[1] Urgency is considered the hallmark symptom of OAB, but it has proven difficult to precisely define or to characterize for research or clinical purposes. Therefore, many studies of OAB treatments have relied upon

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Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment

E. Ann Gormley, Deborah J. Lightner, Martha Faraday and Sandip Prasan Vasavada*

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Abbreviations and Acronyms

AE = adverse event

AHRQ = Agency for Healthcare Research and Quality

FDA = U.S. Food and Drug Administration

OAB = overactive bladder

PTNS = peripheral tibial nerve stimulation

PVR = post-void residual

QoL = quality of life

SNS = sacral neuromodulation

UTI = urinary tract infection

UUI = urgency urinary incontinence

Accepted for publication January 16, 2015.

The complete guideline is available at http://www.auanet.org/content/media/OAB_guideline.pdf.

This document is being printed as submitted independent of editorial or peer review by the Editors of *The Journal of Urology*®.

* Financial interest and/or other relationship with Allergan, Boston Scientific, Medtronic.

For another article on a related topic see page 1692.

Purpose: The purpose of this guideline amendment, herein referred to as the amendment, is to incorporate relevant newly published literature to better provide a clinical framework for the diagnosis and treatment of patients with non-neurogenic overactive bladder.

Materials and Methods: The primary source of evidence for this guideline is the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality Evidence Report/Technology Assessment Number 187 titled Treatment of Overactive Bladder in Women (2009). That report searched PubMed, MEDLINE®, EMBASE and CINAHL for English language studies published from January 1966 to October 2008. The AUA conducted additional literature searches to capture populations and treatments not covered in detail by the AHRQ report and relevant articles published through December 2011. The review yielded 151 treatment articles after application of inclusion/exclusion criteria. An additional systematic review conducted in February 2014 identified 72 additional articles relevant to treatment and made up the basis for the 2014 amendment.

Results: The amendment focused on four topic areas: mirabegron, peripheral tibial nerve stimulation, sacral neuromodulation and BTX-A. The additional literature provided the basis for an update of current guideline statements as well as the incorporation of new guideline statements related to the overall management of adults with OAB symptoms.

Conclusions: New evidence-based statements and expert opinion supplement the original guideline published in 2012, which provided guidance for the diagnosis and overall management of OAB in adults. An integrated presentation of the OAB guideline with the current amendments is available at www.auanet.org.

Key Words: urinary bladder, urinary incontinence, nocturia

INTRODUCTION

The purpose of this guideline is to direct specialist and non-specialist clinicians and educate patients regarding how to recognize non-neurogenic overactive bladder, conduct a valid diagnostic process and establish treatment goals that maximize symptom control and patient quality of life while minimizing adverse events and patient burden. The strategies and approaches discussed in this document were derived from evidence-based and consensus-based processes derived from a continually expanding body of literature on OAB. The Panel notes that this document constitutes a clinical strategy and is not intended to be

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Deep Brain Stimulation for Essential Tremor

Plain Language Summary:

Coverage question: Should OHP cover a treatment that sends the brain electrical pulses to reduce symptoms for a condition that causes unintended shaky movements (tremors)?

Should OHP cover this treatment? Studies have shown this treatment helps people who have extreme tremors and medications are no longer working.

Changes to issue summary after public comment period:

Two public comments were received on this topic. Both commentors recommended coverage of deep brain stimulation for essential tremor (ET). The commentors provided 11 additional articles on this topic. Three of these articles were systematic reviews providing evidence that DBS reduces tremor severity in ET and were added to the staff evidence summary. One study was a review article that concluded that DBS is "likely efficacious" for treatment of ET. The other studies were generally case series that found DBS to be efficacious for ET. The HERC staff recommendation is to add coverage of DBS for ET; therefore, no changes were made to the staff recommendation based on this public comment.

Coverage Question: Should deep brain stimulation be covered for treatment of severe essential tremor?

Question source: Ruben Halperin, CCO medical director

Background:

Essential tremor is a common movement disorder afflicting 5 to 10 million Americans. It is characterized primarily by an action and postural tremor most often affecting the arms, but it can also affect other body parts. Essential tremor is a progressive neurological disorder and can result in severe disability in some individuals. Although there is no cure for essential tremor, pharmacotherapy and surgery can provide some relief. Primidone and propranolol are first-line treatments. Other medications include benzodiazepines, gabapentin, and topiramate. Patients with medication-resistant tremor may benefit from thalamotomy or deep brain stimulation (DBS) of the thalamus.

Deep brain stimulation can be carried out on structures within the brain. that are responsible for modifying movements. The function of these brain nuclei is altered during deep brain stimulation through the application of an electrical current.

Previous HSC/HERC reviews:

Deep brain simulation was reviewed in January 2018 for treatment of Parkinson's disease.

Deep brain stimulation for refractory epilepsy was reviewed as a coverage guidance in 2021.

Deep Brain Stimulation for Essential Tremor

Current Prioritized List/Coverage status:

GROUP	CODES	DESCRIPTION	
		CPT Codes	**Current Placement**
Lead implantation or replacement	61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array	173 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY 247 PARKINSON'S DISEASE
	61864	Each additional array (List separately in addition to primary procedure)	173,247
	61867	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array	173,247
	61868	Each additional array	173,247
Generator implantation or replacement	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array	173,247 283 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays	173,247,283
Revision or removal	61880	Revision or removal of intracranial neurostimulator electrodes	173,247,283
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver	173,283
Intraoperative stimulation with microelectrode recording	95961	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify vital brain structures; initial hour of attendance by physician or other qualified healthcare professional	DIAGNOSTIC PROCEDURES
	95962	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify	DIAGNOSTIC PROCEDURES

Deep Brain Stimulation for Essential Tremor

GROUP	CODES	DESCRIPTION	
		vital brain structures; each additional hour of attendance by physician or other qualified healthcare professional (List separately in addition to code for primary procedure)	
Analysis and Programming	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional, with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming	DIAGNOSTIC PROCEDURES
	95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional, with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional	173,247,283
	95984	With brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)	173,247,283
ICD-10-CM Diagnosis Codes			
Essential tremor	G25.0	Essential tremor	359 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM

HCPCS Code	Code Description	Current Placement
C1767	Generator, neurostimulator (implantable), nonrechargeable	173,247,290, 324,343,439,454,522, 523

Deep Brain Stimulation for Essential Tremor

C1778	Lead, neurostimulator (implantable)	71,173,247,290,324,343,439,454,522, 523
C1816	Receiver and/or transmitter, neurostimulator (implantable)	71,173,247,290,343,439,523
C1897	Lead, neurostimulator test kit (implantable)	173,247,290,324,343,439,454,522,523
L8680	Implantable neurostimulator electrode, each	71,324,454,522
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only	324,454,522
L8682	Implantable neurostimulator radiofrequency receiver	71,324,454,522
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver	71,324,454,522
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension	324,454,522
L8686	Implantable neurostimulator pulse generator, single array, non-hyphenrechargeable, includes extension	324,454,522
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension	324,454,522
L8688	Implantable neurostimulator pulse generator, dual array, non-hyphenrechargeable, includes extension	324,454,522
L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only	324,454,522

GUIDELINE NOTE 177, DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

Line 247

Unilateral or bilateral deep brain stimulation (DBS) is included on this line only for treatment of intractable tremors due to Parkinson's disease (PD) when all of the following conditions are met:

A) For thalamic ventrointermediate nucleus (VIM) DBS, patients must meet all of the following criteria:
   1) A diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor- dominant form
   2) Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.
   3) Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings.

B) For subthalamic nucleus (STN) or globus pallidus interna (GPi) DBS, patients must meet all of the following criteria:
   1) Diagnosis of PD based on the presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia).

2) Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.
3) L-dopa responsive with clearly defined "on" periods.
4) Persistent disabling Parkinson's symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling "off" periods) despite optimal medical therapy.
5) Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings.

C) DBS is not included on this line for PD patients with any of the following:
1) Non-idiopathic Parkinson's disease or "Parkinson's Plus" syndromes.
2) Cognitive impairment, dementia or depression which would be worsened by or would interfere with the patient's ability to benefit from DBS
3) Current psychosis, alcohol abuse or other drug abuse.
4) Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.
5) Previous movement disorder surgery within the affected basal ganglion.
6) Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation.

GUIDELINE NOTE 221, DEEP BRAIN STIMULATION FOR TREATMENT OF REFRACTORY EPILEPSY

Line 173

Deep brain stimulation for treatment of refractory epilepsy is included on this line only when

A) The surgery is performed at a Level 4 epilepsy center, AND
B) The patient has failed two or more anti-seizure medications, AND
C) The patient is ineligible for resective surgery OR has failed vagus nerve stimulation or resective surgery.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

Deep Brain Stimulation for Essential Tremor

Evidence:

1) **Giammalva 2022**: systematic review of treatments for ET
    a. N=15 studies on DBS (N=580 patients)
        i. 12 retrospective case series, 3 prospective trials
        ii. Mean follow up 34.51 months
    b. Post-treatment symptomatic improvement, i.e., reduction or resolution of presenting symptoms, occurred in 63.01% of DBS patients
    c. Each of these three techniques was related to a substantial improvement of post-treatment Quality of Life, with increased patient independency in ADLs and functional status and improved self-perceived Quality of Life.
    d. **I**n DBS, the most frequent adverse events were speech (88 patients, 15.3%) and gait disturbance (67 patients, 11.48%). DBS was rarely associated with intracranial hemorrhages (1 patient)
2) **Giordano 2020**: systematic review of DBS vs magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy on treatment of essential tremor
    a. N=45 articles (1202 patients treated with DBS vs 477 treated with MRgFUS thalamotomy
        i. 15 retrospective studies, 30 prospective studies
    b. The average percentage improvement in terms of tremor severity was 60.1% (SD: ±9.7) for the DBS group and 55.6% (SD: ±8.2) for the MRgFUS group
        i. Studies varied on scale used
    c. Data regarding peri-interventional and postinterventional complications were available for 29 studies out of 45, including 1208 operated patients (731 treated with DBS and 477 with MRgFUS). There were 517 complications reported in the DBS group and 484 complications reported in the MRgFUS group.
    d. Persistent complications were significantly more common in the MRgFUS group (p=0.042)
3) **Lu 2020**, systematic review of DBS for ET
    a. N=46 studies (439 patients)
        i. 4 RCTs, 42 observational studies
    b. The percentage change in any objective TRS score in all included studies was 61.3% (P <0.001)
    c. The incidence of stimulation-related AEs (23.6%) was higher than the incidence of device-related AEs (11.5%) and the incidence of surgical AEs (6.4%). The most common stimulation-related AEs were dysarthria (10.5%), paresthesia (6.3%), hemiparesis/paresis (6.3%), and headache (6.7%).
4) **Wharen 2017**, controlled trial of DBS for essential tremor (ET)
    a. N=76 patients, randomized to stimulator-on or stimulator-off for 6 months after insertion
    b. the mean improvement in target extremity CTRS score between the DBS stimulation-off and stimulation-on states was 1.25 ± 1.26 ($p < 0.001$; 95% CI -1.54, -0.96), which represents an improvement of 60%. Additionally, the mean change in target extremity CTRS score from baseline to the DBS stimulation-on state at 180 days, as assessed by the blinded reviewer, improved by 65% to 1.62 ± 1.05 ($p < 0.001$; 95% CI -1.87, -1.36)
    c. N=127 patients initially randomized who received DBS
        i. Thirty-four serious adverse events occurred, including three hemorrhages (2.4%), three infections (2.4%), and three deaths (2.4%).

   ii. A total of 288 adverse events (AEs) occurred during the one-year study. The majority of AEs were classified by the Data Safety Monitoring Board (DSMB) in the stimulation-related category, and most of these events were resolved with reprogramming of the device parameters.
- d. Patients with medication refractory ET implanted with a constant-current device met the primary efficacy and safety outcomes for this study. There were improvements in mood and quality-of-life measures. Unilateral and bilateral ET DBS is a useful therapeutic option for patients with disabling, medically refractory ET

5) **Flora 2010**, systematic review of deep brain stimulation for essential tremor
   a. N=17 studies (case series)
   b. Safety
      i. Most reported adverse events were relatively mild and could potentially be resolved by changing the stimulation settings. Many events were related to the stimulation such as paresthesia, dysarthria, and headache
   c. Effectiveness
      i. Generally, in all studies, there was a significant improvement in outcomes following DBS compared with baseline scores. In addition, where reported, DBS was significantly better in testing when the stimulation was on compared with off or baseline. Meta-analysis of the overall outcomes was not possible
   d. Based on Level IV evidence, it appears that DBS may be a safe and effective therapy for essential tremor. However, the included studies in this review only reported short-term safety outcomes. Further comparative studies and randomized controlled trials will enable more confident assessments of the safety and efficacy of DBS to be made; however, it is unlikely that these will become available. DBS should be considered an invasive procedure, which will not be chosen lightly by patients. Most patients will endure symptoms until they have significant impairment in quality of life (i.e., unable to independently feed or go to toilet) and, at this point, will have failed all alternative treatments. The potential for treatment with DBS should be assessed on a case-by-case basis. An expert committee comprising a movement disorder surgeon and a neurologist can assess the extent of disability and the likelihood of benefit. This will ensure that the procedure is warranted, may provide an estimate of potential benefit to the patient, and determine any comorbidities that may reduce the effectiveness of the DBS.

6) **NICE 2006**, deep brain stimulation for essential tremor and dystonia
   a. N=4 case series (N=17, 52, 19, 22 patients)
   b. A case–control series found that, in up to 27 months' follow-up, total tremor score improved in 17 patients treated with deep brain stimulation, but there was no significant improvement in most other efficacy outcomes. A case series of 52 patients with essential tremor who underwent deep brain stimulation reported a significant improvement in activities of daily living at 3 months' follow-up, with scores improving from 17.8 points to 6.5 points ($p < 0.001$). Another case series of 19 patients found that deep brain stimulation produced an improvement in tremor score (Fahn–Tolosa–Marin scale) from 3.3 points at baseline to 0.8 points at 27 months' follow-up ($p < 0.005$).
   c. A case series of 22 patients with dystonia who underwent deep brain stimulation reported that the total score on the Burke–Fahn–Marsden dystonia rating scale improved significantly from a mean of 46.3 points at baseline to 24.3 points at 3 months' follow-up. This improvement was maintained to 12 months' follow-up, with a score of 21.0 points ($p < 0.001$ for both comparisons with baseline). Similarly, global

disability score improved from 11.6 points at baseline to 7.6 points at 3 months' follow-up

d. Safety
    i. One case series reported that the pulse generator failed in 50% (6/12) of patients. Across three case series where it was reported as an outcome, displacement of the stimulating electrode occurred in 6% (1/18), 8% (1/ 12) and 15% (8/52) of patients. The incidence of lead fracture or failure in three studies was 4% (2/52), 5% (1/22) and 6% (1/18). These complications sometimes required further surgery
    ii. One case series of 22 patients who underwent deep brain stimulation for dystonia reported transient oedema of the frontal lobe, cutaneous necrosis of the scalp, localized skin infection and hematoma near the neurostimulator, in one patient each. However, none of these events had permanent sequelae
e. Conclusion: Current evidence on the safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) appears adequate to support the use of this procedure

Submitted literature:

1) Della-Flora 2010: already included in evidence review above
2) Giammalva 2022: added to evidence review above
3) Giordano 2020: added to evidence review above
4) Lu 2020: added to evidence review above
5) Wang 2020 was a device review
6) Dallapiazza 2019: study of stereotactic surgery for ET, not DBS
7) Ferreira 2019: review of various therapies for ET
    a. N=7 studies on DBS
        i. 1 RCT, 6 case series
    b. For upper limb tremor, unilateral Vim-DBS was considered likely efficacious (efficacy recommendation). There was an acceptable risk with specialized monitoring (safety recommendation). Unilateral Vim-DBS was considered possibly useful for clinical practice
8) Zhang 2010, case series of DBT for ET
    a. N=34 patients
        i. N=22 for first follow up
        ii. N=12 for second follow up
    b. Of the 34 patients, the mean preoperative Fahn-Tolosa-Marin TRS tremor score was 3.27 ± 0.87
        i. MCID was not able to be determined for this scale
    c. For the 22 patients assessed in 2006 the stimulation-off tremor score was 3.00 ± 0.88 and the stimulation-off handwriting score was 2.50 ± 0.97.
    d. For the 12 patients assessed in 2008 the stimulation-off tremor score was 3.33 ± 0.72 and the stimulation-off handwriting score was 2.80 ± 1.32. With the stimulation on the tremor score improved to 0.67 ± 0.72 and the handwriting score improved to 1.30 ± 1.16

e. Adverse events usually observed during postoperative programming included tingling, numbness of an extremity, eye movement disorders, weakness, gait instability, slurring of speech, and drooling.

9) Paschen 2019, case series of DBT for ET
   a. N=20 patients
   b. Tremor severity worsened considerably over time in both in the nonstimulated and stimulated conditions. Vim-DBS improved the TRS in the short term and long term significantly
   c. However, the stimulation effect was negatively correlated with time since surgery
   d. Conclusion Vim-DBS loses efficacy over the long term
10) Rodriguez Cruz 2017, case series of DBT for ET
   a. N=14 patients
   b. The mean reduction in FTM-TRS score was 73.4% at 6 months after VIM-DBS surgery ($P < 0.001$) and 50.1% at the last visit ($P < 0.001$). The gradual worsening of FTM-TRS scores over time fit a linear regression model (coefficient of determination [$R2$] = 0.887; $P < 0.001$)
   c. Conclusions: The current findings suggest that the waning effect of VIM-DBS over time in patients with essential tremor may be the consequence of a combination of factors. Superimposed on the progression of the disease, tolerance can occur during the early years of stimulation.
11) Kundu 2017, retrospective cohort study of DBS on voice tremor
   a. Not an outcome of interest in this review

Expert guidelines:

1) **American Academy of Neurology 2011**, guideline for treatment of essential tremor
   a. DBS of the VIM of the thalamus
      i. **Level C –** effectively treats contralateral limb tremor in ET that is refractory to medication management

Other payer policies:

1) United Health Care 2023
   a. Deep brain stimulation is proven and medically necessary for treating the following indications: Dystonia, Essential Tremor, Parkinson's disease, Refractory Epilepsy for a partial or focal seizure disorder
2) Anthem BCBS 2023
   a. *Essential tremor:* Unilateral or bilateral deep brain stimulation is considered **medically necessary** for individuals with medically refractory essential tremor.
3) Aetna 2023
   a. Aetna considers unilateral or bilateral deep brain stimulators (e.g., stimulation of the ventral intermediate thalamic nucleus, globus pallidus, and subthalamic nucleus) medically necessary durable medical equipment (DME) for the treatment of intractable tremors as a consequence of Parkinson's disease or essential tremor when *all* of the following criteria are met:

i. Member does not have dementia, severe depression, cerebral atrophy, or Hoehn and Yahr stage V Parkinson's disease (see Note below) *and*
ii. Member does not have other independent diagnoses that could explain the failure to respond to medical treatment, *and*
iii. Member suffers from disabling upper extremity essential tremor that is not responding satisfactorily to drug therapy or suffers from a disabling tremor of idiopathic Parkinson's disease that is refractory to pharmacotherapy, *and*
iv. There is no focal lesion of the basal ganglia (e.g., a space occupying lesion or lacunae) at the target site that would negate the result of thalamic stimulation, *and*
v. There is sufficient residual motor function in the upper extremity so that it is reasonable to expect an improvement following the surgery.

1) **CMS 2003**, National Coverage Determination (https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=21)

a. Medicare will cover *unilateral or bilateral thalamic VIM DBS* for the treatment of essential tremor (ET) and/or Parkinsonian tremor and *unilateral or bilateral STN or GPi DBS* for the treatment of Parkinson's disease only under the following conditions:
i. Medicare will only consider DBS devices to be reasonable and necessary if they are Food and Drug Administration (FDA) approved devices or devices used in accordance with FDA approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials.
ii. For thalamic VIM DBS to be considered reasonable and necessary, patients must meet all of the following criteria:
1) Diagnosis of essential tremor (ET) based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor- dominant form
2) Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.
3) Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings.

b. DBS is not reasonable and necessary and is not covered for ET or PD patients with any of the following:
i. Non-idiopathic Parkinson's disease or "Parkinson's Plus" syndromes.
ii. Cognitive impairment, dementia or depression which would be worsened by or would interfere with the patient's ability to benefit from DBS
iii. Current psychosis, alcohol abuse or other drug abuse.
iv. Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.
v. Previous movement disorder surgery within the affected basal ganglion.
vi. Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation.

c. Patients who undergo DBS implantation should not be exposed to diathermy (deep heat treatment including shortwave diathermy, microwave diathermy and ultrasound

diathermy) or any type of MRI which may adversely affect the DBS system or adversely affect the brain around the implanted electrodes.

d. DBS should be performed with extreme caution in patients with cardiac pacemakers or other electronically controlled implants which may adversely affect or be affected by the DBS system.
e. For DBS lead implantation to be considered reasonable and necessary, providers and facilities must meet all of the following criteria:
    1) Neurosurgeons must: (a) be properly trained in the procedure; (b) have experience with the surgical management of movement disorders, including DBS therapy; and (c) have experience performing stereotactic neurosurgical procedures.
    2) Operative teams must have training and experience with DBS systems, including knowledge of anatomical and neurophysiological characteristics for localizing the targeted nucleus, surgical and/or implantation techniques for the DBS system, and operational and functional characteristics of the device.
    3) Physicians specializing in movement disorders must be involved in both patient selection and postprocedure care.
    4) Hospital medical centers must have: (a) brain imaging equipment (MRI and/or CT) for pre-operative stereotactic localization and targeting of the surgical site(s); (b) operating rooms with all necessary equipment for stereotactic surgery; and (c) support services necessary for care of patients undergoing this procedure and any potential complications arising intraoperatively or postoperatively.

Since long-term safety, effectiveness and optimal targeting for DBS have not been established, CMS will review the appropriateness of Medicare coverage as pertinent new evidence becomes available. This review will include clinical follow-up and targeting information from the ongoing, randomized VA/NINDS Cooperative Trial comparing best medical therapy with DBS of the STN and GPi for PD, as well as longer term clinical results from mandatory annual progress reports and final report to the FDA of Medtronic's bilateral DBS PMA postapproval study.

Expert input:

None received

Deep Brain Stimulation for Essential Tremor

HERC staff summary:

Deep brain stimulation for essential tremor has mainly been studied in case series, with one controlled trial. However, these studies have consistently showed benefit for patients who have severe essential tremor that is interfering with activities of daily living and not responding to medications or other standard therapies. DBS has significant risks, making RCTs or other more rigorous trial designs not feasible. One trusted evidence-based source (NICE) recommends coverage, and DBS is included in expert guidelines as a last line therapy for essential tremor. Private payers and CMS cover DBS for essential tremor in severe cases. Because of the serious risks involved in DBS, this technology is not at risk of being overused for essential tremor.

Two public comments were received on this topic. Both commentors recommended coverage of deep brain stimulation for essential tremor. The commentors provided 11 additional articles on this topic. Three of these articles were systematic reviews providing evidence that DBS reduces tremor severity in ET and were added to the staff evidence summary. One study was a review article that concluded that DBS is "likely efficacious" for treatment of ET. The other studies were generally case series that found DBS to be efficacious for ET. The HERC staff recommendation is to add coverage of DBS for ET; therefore, no changes were made to the staff recommendation based on this public comment.

HERC staff recommend adding coverage of deep brain stimulation for essential tremor with a new guideline based on CMS criteria.

Additionally, some HCPCS codes for DBS are missing from the Parkinson's disease and seizure disorder lines.

HERC staff recommendations:

1) Add the following CPT codes to line 359 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM
    a. CPT 61863-61868 Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array
    b. CPT 61885 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
    c. CPT 61880 Revision or removal of intracranial neurostimulator electrodes
    d. CPT 61886 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays
    e. CPT 61888 Revision or removal of cranial neurostimulator pulse generator or receiver
    f. CPT 95983 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional, with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
    g. CPT 95984 With brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional
2) Add the following HCPCS codes to line 359
    a. C1767 Generator, neurostimulator (implantable), nonrechargeable
    b. C1778 Lead, neurostimulator (implantable)

   c. C1816 Receiver and/or transmitter, neurostimulator (implantable)
   d. C1897 Lead, neurostimulator test kit (implantable)

3) Add the following HCPCS codes to lines 173 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY, 247 PARKINSON'S DISEASE, and 359
   a. L8680 Implantable neurostimulator electrode, each
   b. L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
   c. L8682 Implantable neurostimulator radiofrequency receiver
   d. L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
   e. L8685 Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
   f. L8686 Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
   g. L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
   h. L8688 Implantable neurostimulator pulse generator, dual array, non-hyphenrechargeable, includes extension
   i. L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
4) Add a new guideline to line 359 as shown below

GUIDELINE NOTE XXX DEEP BRAIN STIMULATION FOR TREATMENT OF REFRACTORY EPILEPSY
Line 359
Deep brain stimulation for treatment of essential tremor is included on this line only when ALL of the following criteria are met:

1) Diagnosis of essential tremor based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor- dominant form; AND
2) Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy; AND
3) Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings; AND
4) Lack of contraindications, including but not limited to cognitive impairment, dementia or depression which would be worsened by or would interfere with the patient's ability to benefit from DBS, current psychosis, alcohol abuse or other drug abuse, structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder, or previous movement disorder surgery within the affected basal ganglion.

Deep Brain Stimulation for Essential Tremor

Disposition of Public Comments

Table of Contents

Discussion Table

IDs/#s	Summary of Issue	HERC Staff Response
All	Deep brain stimulation should be covered for treatment of essential tremor.	This change is already in the staff recommendation; no changes to the staff recommendation were made based on this comment.

Commenters

Identification	Stakeholder
A	Cyndy Novak, Medtronic *[Submitted April 16, 2024]*
B	Delaram Safarpour, MD, OHP provider *[Submitted April 17, 2024]*

Public Comments

ID/#	Comment	Disposition
A	Oregon HERC Public Comments on Deep Brain Stimulation for Essential Tremor Medtronic is the world's leading medical technology company, specializing in implantable and interventional therapies that alleviate pain, restore health,	Thank you for your comments. HERC staff currently recommend addition of deep brain stimulation for treatment of essential tremor.

Disposition of Public Comments

ID/#	Comment	Disposition
	and extend life. We are committed to the continual research and development necessary to provide high-quality products and innovative therapies that improve the health outcome for all patients. Specifically, with our deep brain stimulator (DBS) for essential tremor. Deep brain stimulation should be considered when a patient with essential tremor has disabling symptoms and medications are ineffective or have intolerable side effects. Medtronic wishes to submit public comments to support the Oregon Health Authority's proposed coverage of deep brain stimulation for essential tremor, a treatment that sends the brain electrical pulses to reduce symptoms for a condition that causes unintended shaky movements (tremors). Medtronic is the manufacturer of the PerceptTM PC and RC neurostimulators which are intended to treat essential tremor. Parkinson's disease, epilepsy, and dystonia. We agree with the Oregon Health Evidence Review Commission (HERC) in adding DBS as a treatment option for essential tremor to line 359 of the DBS policy. Medicare and the majority, if not all, commercial payers already support coverage of this treatment in line with the HERC proposed coverage criteria. In addition to the publications listed in the Evidence section, there have been 6 additional, high quality, studies that have been published in the past 5 years. A document summarizing this evidence is provided as a separate attachment. These publications help support the safety and effectiveness of DBS for essential tremor as well as support DBS as a preferred treatment option for this indication.	The submitted articles give information on the use of deep brain stimulation for essential tremor. Specifically: 1) Della 2010 is already included in the staff summary as Flora 2010 2) Giammalva 2022 is a systematic review of treatments for ET and was added to the staff evidence review 3) Giordano 2020 is a systematic review comparing DBS to magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy and was added to the staff evidence review 4) Lu 2020 is a systematic review examining the effects of DBS on ET and was added to the staff evidence review 5) Wang 2020 was a device review 6) Dallapiazza 2010 was a study on stereotactic surgery, not DBS 7) Ferreira 2019 was a review of treatments for ET. DBS was found to be "likely efficacious" for treatment of ET

Disposition of Public Comments

ID/#	Comment	Disposition
	We request that the proposal be finalized with this recommendation and support the additional of essential tremor as a covered indication for deep brain stimulation.	
B	Deep Brain Stimulation (DBS) surgery for Essential Tremor (ET) has been a game-changer for many patients and their families. Unfortunately, only about 50% of ET patients find relief through pharmacologic therapy. Even more concerning is that nearly half of those who do benefit from medications eventually discontinue treatment due to limited efficacy or dose-dependent side effects. Research has shown that DBS significantly enhances the quality of life for ET patients. After undergoing DBS surgery, there's a notable reduction in the need for centrally acting medications, which not only reduces the burden of side effects but also minimizes polypharmacy. With improved tremor control post-surgery, patients become more self-reliant in their daily activities, thereby reducing the caregiver burden. For younger patients with ET, improved tremor control can extend their ability to work and reduce disability. In the older population, DBS promotes greater independence and diminishes the need for medications like propranolol and primidone, thereby reducing the risk of falls. Medicaid coverage for DBS surgery is truly transformative, offering hope and improved quality of life for ET patients across different age groups.	Thank you for your comments. HERC staff currently recommend addition of deep brain stimulation for treatment of essential tremor. The submitted articles give information on the use of deep brain stimulation for essential tremor. Specifically: 1) Zhang 2010, Paschen 2019, and Rodriguez Cruz 2017 were all small case series that found that DBS was effective for treatment of ET. However, 2 of these studies found that the effectiveness of DBS decreased over time 2) Kundu 2017 did not report on the outcome of interest in this review 3) Flora 2010 is already included in the staff summary

References Provided by Commenters

ID	References
A	1. Della FE, Perera CL, Cameron AL, Maddern GJ. Deep brain stimulation for essential tremor: A systematic review. Movement Disorders. 2010;25(11):1550-1559. doi:10.1002/mds.23195

Disposition of Public Comments

ID	References
	2. Giammalva G, Maugeri R, Umana G, et al. DBS, tcMRgFUS, and gamma knife radiosurgery for the treatment of essential tremor: a systematic review on techniques, indications, and current applications. Journal of neurosurgical sciences. 2022;66(6):476-484. doi:10.23736/S0390-5616.22.05524-2 3. Giordano M, Caccavella VM, Zaed I, et al. Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: A systematic review and pooled analysis of functional outcomes. Journal of Neurology, Neurosurgery and Psychiatry. 2020;91(12):1270-1278. doi:10.1136/jnnp-2020-323216 4. Lu G, Luo L, Liu M, et al. Outcomes and Adverse Effects of Deep Brain Stimulation on the Ventral Intermediate Nucleus in Patients with Essential Tremor. Neural Plast. 2020;2020:2486065. doi:10.1155/2020/2486065 5. Wang KL, Ren Q, Chiu S, et al. Deep brain stimulation and other surgical modalities for the management of essential tremor. Expert Review of Medical Devices. 2020;17(8):817-833. doi:10.1080/17434440.2020.1806709 6. Dallapiazza R, Lee D, Vloo PD, et al. Outcomes from stereotactic surgery for essential tremor. Journal of neurology, neurosurgery, and psychiatry. 2019;90(4):474-482. doi:10.1136/jnnp-2018-318240 7. Ferreira JJ, Mestre TA, Lyons KE, et al. MDS evidence-based review of treatments for essential tremor. Movement Disorders. 2019;34(7):950-958. doi:10.1002/mds.27700
B	1. Zhang K, Bhatia S, Oh MY, et al. Long-term results of thalamic deep brain stimulation for essential tremor. J. Neurosurg 2010; 112:1271–1276. 2. Paschen S, Forstenpointner J, Becktepe J, et al. Long-term efficacy of deep brain stimulation for essential tremor: An observer-blinded study. Neurology. 2019;92: e1378–e1386. 3. Rodríguez Cruz PM, Vargas A, Fernández-Carballal C, et al. Long-term Thalamic Deep Brain Stimulation for Essential Tremor: Clinical Outcome and Stimulation Parameters. Mov Disord Clin Pract. 2016; 3: 567–572. 4. Kundu B, Schrock L, Davis T, et al. Thalamic Deep Brain Stimulation for Essential Tremor Also Reduces Voice Tremor: THALAMIC DBS REDUCES VOICE TREMOR. Neuromodulation: Technology at the Neural Interface. 2018; 21: 748–754 5. Flora ED, Perera CL, Cameron AL, et al. Deep brain stimulation for essential tremor: A systematic review. Movement Disorders. 2010; 25:1550–1559

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REVIEW

NEUROSURGICAL SYSTEMATIC REVIEWS AND META-ANALYSES FOR A DAILY PRACTICE - PART II

DBS, tcMRgFUS, and gamma knife radiosurgery for the treatment of essential tremor: a systematic review on techniques, indications, and current applications

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ABSTRACT

INTRODUCTION: Essential tremor (ET) may severely impact patient's Quality of Life. Several techniques such as radiofrequency, deep brain stimulation (DBS), gamma knife (GK) radiosurgery and high-intensity focused ultrasound may be used for the surgical treatment of ET. The aim of this paper is to summarize the most recent available literature on DBS, transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) and GK, and to compare indications, targets, and effectiveness of these surgical techniques for the treatment of ET.

EVIDENCE ACQUISITION: A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was performed on the three largest medical databases (PubMed, Scopus, and Web of Science). This systematic review is focused on the effectiveness and safety of GK, DBS, and tcMRgFUS as functional neurosurgical techniques for the treatment of ET. The aim of this study was to compare these techniques by evaluating mode, target, effectiveness in improving motor outcomes, and rates of adverse effects.

EVIDENCE SYNTHESIS: Articles meeting the predetermined criteria were included. Data for DBS, tcMRgFUS, and GK were analyzed and compared for indications, patient selection, advantages *vs*. disadvantages, and treatment targets for essential tremor.

CONCLUSIONS: DBS, tcMRgFUS and GK are effective techniques for the treatment of ET. Despite different functioning principles, all three surgical techniques require a proper functional diagnosis to define accurate indications for patient selection. Their indication depends upon the patient's neurological condition and their effectiveness relies on proper targeting.

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KEY WORDS: Deep brain stimulation; Radiosurgery; Essential tremor.

Introduction

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part.[1, 2] It is widely associated with multiple conditions including neurodegenerative diseases (*e.g.*, essential tremor (ET), Parkinson disease (PD), multiple system atrophy and spinocerebellar ataxias), inflammatory diseases (*e.g.*, multiple sclerosis (MS)), drug toxicity, stroke, trauma, and many others.[3-5] ET and non-ET disorders could severely impact patient's Quality of Life, especially in patients with severe disabling tremors who usually have difficulty in completing daily tasks

such as eating, drinking, taking showers, dressing, and writing.[5-7] Thalamotomy is the gold-standard treatment, usually performed with several techniques, such as radiofrequency, gamma knife (GK) radiosurgery and high intensity focused ultrasound.[4, 5, 7, 8] Along lesioning technique, deep brain stimulation (DBS) has been widely used in the past two decades for patients with severe clinical impairment due to medical refractory ET and non-ET disorders. DBS consists in a non-lesioning inactivation of specific thalamic nuclei or basal ganglia obtained by positioning one or two electrodes through a burr hole approach. In the last years, transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) has emerged as a new lesioning procedure for the treatment of ET and non-ET disorders. This procedure consists of an incisionless brain lesion obtained with focused ultrasound guided by brain MRI. The advantages of tcMRgFUS are the opportunity of using the MR imaging both for planning the best lesioning target, the real-time monitoring of lesioning procedure, and the possibility to repeat the procedure in case of recurrence since it does not adopt ionizing radiations.[1, 5, 7-9] Along with DBS and tcMRgFUS, GK has been reported as an effective lesioning technique for the treatment of several movement disorders such as PD and ET.[10, 11] GK lesioning relies on the delivery of high doses of radiation to selected targets. The delivery of radiation suddenly reduces to non-target structures, thus GK is an attractive technique by safely targeting eloquent deep neural structures. The current literature on GK for the treatment of ET and PD is scarce, encouraging future studies to investigate and validate targets with aim to better understand GK's efficacy, related risks, and complications.[12] In the whole scenario of lesioning and non-lesioning surgical techniques for the treatment movement disorders, the purpose of this paper is to summarize the most recent literature on DBS, tcMRgFUS, and GK, further comparing indications, targets, and effectiveness for the treatment of ET. The final goal is to better define the correct indications for each therapeutic option in these fragile patients.

Evidence acquisition

Search strategy

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The literature search was performed on the three largest medical databases (PubMed, Scopus, and Web of Science). In regards of the large number of studies on DBS and tcMRgFUS for ET, the search was limited from 2015 onward for retrieving studies on DBS and tcMRgFUS. In contrast, due to limited evidence on GK for ET, no temporal criteria were set for studies describing the use of GK. The following medical subject headings (MeSH) and free text terms were combined: "essential tremor AND DBS," "essential tremor AND MRgFUS," "essential tremor AND neurosurgery," "MRgFUS AND tremor," "HIFU AND tremor," "focused ultrasound AND Tremor;" "([gammaknife OR gamma knife OR stereotactic radiosurgery] AND [essential tremor])." Collected studies were retrieved; duplicates were removed.

Study selection

We performed a subgroup analysis screening all surgical series on ET for a qualitative synthesis. Studies were eligible if they met the following criteria, defined "*a priori*." Studies were included if they: 1) involved one or more patients with ET receiving GK, tcMRgFUS or DBS treatments; 2) report clinical data on treatment protocols and outcomes; and 3) were written in English. Studies were excluded if they were: 1) editorials, letters, non-human studies, or books; 2) studies lacking sufficient clinical data on treatment protocols and outcomes; 3) studies reporting the use of radiosurgery strategies different than GK; and 4) studies reporting the use of ultrasound techniques different than HIFU for tcMRgFUS. In case of studies from the same institution with overlapping populations, only the studies with largest cohort size were included. As regards the subgroup analysis on tcMRgFUS and DBS, three experienced neurosurgeons with more than 5 years of experience in functional neurosurgery screened titles and abstracts upon the predetermined inclusion criteria. If a title and abstract met the inclusion criteria, then full text copies of all articles were retrieved for further investigation. Eligibility was independently assessed by two authors (F.M. and F.P.) and differences were resolved with the help of a third author (G.R.G.). As regards the subgroup analysis on GK, two authors (P.P. and G.E.U.) independently screened the titles and abstracts of all extracted papers, and then appraised full texts of studies that met inclusion criteria. Disagreements were settled by a third author (G.S.). This process also permitted to assess the study risk of bias. The data collection process was conducted without using any automated tools. No ethical approval was required for this study. Eligible articles were included based on the predefined criteria, and references were searched to retrieve additional relevant studies.

Data extraction

As regards the subgroup analysis on tcMRgFUS and DBS, one author (L.B.) extracted data from included articles. Extracted data were then confirmed by an additional author (G.R.G.). Data about tcMRgFUS and DBS included: authors, year of publication, study design, cohort size, patient's age and gender, disease, primary symptoms and duration, DBS or tcMRgFUS anatomical target and laterality, post-treatment clinical improvement, recurrence of primary symptoms, DBS, or tcMRgFUS-related adverse event (ADE; either transient or permanent), follow-up. Data on post-treatment clinical improvements referred to reported rates of decreased motor symptoms and ameliorated quality-of-life for patients included in each study. As regards the subgroup analysis on GK, one author (P.P.) extracted data from included articles, then confirmed independently by two additional authors (G.E.U. and G.S.). Where available, data about GK included: authors, year of publication, country, study design, cohort size, patient's age and gender, disease, primary symptoms and duration, GK anatomical target and laterality, time interval between first and second operation in case of bilateral GK treatments, maximal GK dose (Gy), post-treatment clinical improvement, time interval between GK and clinical improvement, recurrence of primary symptoms, GK-related adverse event (ADE; transient and permanent), time interval between GK and ADE onset, follow-up. Data on post-treatment clinical improvements referred to reported rates of decreased motor symptoms and ameliorated quality-of-life/activity of daily living (ADL) for patients included in each study. Data on quality-of-life was collected only from studies using validated quantitative scales.

Synthesis methods

The processes used to decide which studies were eligible for each synthesis were based on clinical indications, treatment protocols, and clinical outcomes of patients with ET treated by DBS, tcMRgFUS, or GK.

General study characteristics

From the whole literature review, 2602 studies were identified, of which 42 were included for this systematic review after a proper screening according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1). Their general characteristics are listed in Supplementary Digital Material 1 (Supplementary Table I-III). Most studies were monocenter retrospective case series.

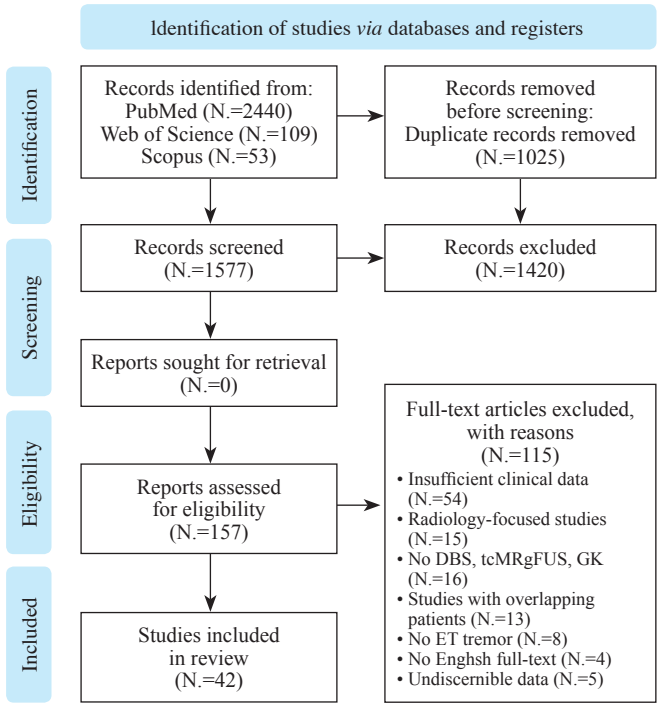

Figure 1.—PRISMA 2020 flow diagram.[13]

Studies

A total of 15 studies on DBS were included, 12 were retrospective case series and 3 were prospective trials[14-28] (Supplementary Table I). A total of 16 studies on tcMRgFUS were included, 8 were retrospective case series and 8 were prospective trials (Supplementary Table II). 14 studies included only patients with ET-and 2 studies included ET and non-ET patients.[4, 24, 26, 27, 29-40] A total of 13 studies on GK were included, 11 were retrospective series and 2 were prospective series[41-53] (Supplementary Table III).

Demographics, clinical characteristics, and treatment protocols

Patients were divided into three cohorts based on treatment technique (Table I). In total 1768 patients treated with DBS, tcMRgFUS, and GK were analyzed. Mean ages were >60 years in both cohorts with a male proportion significantly higher than females. Disease duration was on average >10 years. The duration of general follow-up ranged from 1 to 120 months. Considering the different surgical techniques, in total, 580 patients treated with DBS were analyzed (Table I). Mean age was 64.4 years (SD±4.61), with a male proportion of 55.17%. As regard tcMRgFUS, 741 patients were analyzed. Mean age was

67,97 years (SD±3.44), with a male proportion of 68,69%. Mean disease duration before DBS or tcMRgFUS was >15 years: 23,05 years in DBS patients (SD±7.52), 19.73 years in tcMRgFUS patients (SD±5.04). As regards GK, 447 patients with ET were analyzed. Mean age was 73.2 (SD ±8.6; range 18-93, with a male proportion of 49%. Mean disease duration before GK was 20,2 years (SD±4.5; range: 2-38). DBS, tcMRgFUS, and GK were proposed to patients not responding to available medications, and GK was also offered to patients not eligible or refusing to undergo other surgical/radiosurgical treatments. In DBS the ventral intermediate nucleus of the thalamus (VIM) represented the most common anatomical target for neurostimulation in ET patients. The posterior subthalamic area (PSA) and cZi (caudal zona incerta) were other targets associated with various outcomes and side effect profiles. In tcMRgFUS, VIM represented the most common anatomical target. In GK, VIM was the most common anatomical target, followed by the ventral lateral nucleus of the thalamus (VL). As regards laterality of treatment, tcMRgFUS was performed unilaterally in most cases (717 unilateral *vs*. 24 bilateral, 97.1%); similarly, DBS implantation was often unilateral (332 unilateral *vs*. 248 bilateral, 57.2%). In case of GK, unilateral treatments were performed in 329 patients (73,6%), while 118 patients (24,6%) underwent bilateral GK. In patients receiving bilateral GK, time intervals between the first and the second operation averaged 17,5 months (SD±4.2; range: 7–70) (Table I).

Treatment outcomes and adverse events

Table I summarizes treatment outcomes and adverse events related to DBS, tcMRgFUS, and GK. In DBS, the most frequent adverse events were speech (88 patients, 15.3%) and gait disturbance (67 patients, 11.48%), whereas gait disturbance was the most common adverse event in tcMRgFUS (246 patients, 33.1%) followed by paresthesia (195 patients, 26.3%), which was almost always transient. TcMRgFUS was associated with a higher rate of reversible headache, nausea, and vomiting (71 patients, 9.5%). DBS was rarely associated with intracranial hemorrhages (1 pa-

TABLE I.—*Summary of demographics, treatment characteristics, target, and outcomes of all pooled patients with Essential Tremor grouped per treatment.*

Variables	DBS	tcMRgFUS	GK
Cohort size (N.)	580	741	447
Gender (male)	320 (55.17%)	509 (68.69%)	219 (49%)
Mean Age (year) and SD	64.4±4.61	67.97±3.44	73.2±8.6
Mean disease duration and SD*	23.05±7.52	19.73±5.04	20.2±4.5
Pathology			
Essential tremor	580 (100%)	724 (97.7%)	447 (100%)
Other type of tremor syndromes	0 (0%)	17 (2.29%)	0 (0%)
	Target DBS (N.)	Target tcMRgFUS (N.)	Target GK (N. %)
VIM	483 (83.28%)	720 (97.17%)	442 (98.9%)
PSA	31 (5.34%)	0 (0%)	0 (0%)
cZi	66 (11.38%)	0 (0%)	0 (0%)
VL	0 (0%)	0 (0%)	4 (0.9%)
Undefined thalamic region	0 (0%)	0 (0%)	0 (0%)
CMT	0 (0%)	0 (0%)	1 (0.2%)
CTT	0 (0%)	21 (2.83%)	0 (0%)
Laterality (N., %)			
Unilateral	332 (57.24%)	717 (96.76%)	329 (73.6%)
Bilateral	248 (42.76%)	24 (3.24%)	118 (26.4%)
Mean % improvement and SD of motor symptoms in ET	63.01±15.63	67.21±10.37	79.62±22.87
ADE (N. of case)			
Paresthesia	20 (3.4%)	195 (26.3%)	8 (1.8%)
Intracranial Hemorrhage	1 (0.1%)	0 (0%)	0 (0%)
Gait disturbance/ataxia	67 (11.48%)	246 (33.1%)	2 (0.5%)
Speech disturbance/Dysarthria	88 (15.3%)	27 (3.6%)	10 (2.2%)
Na&Vo	1 (0.1%)	29 (3.9%)	0 (0%)
Transitory paresis	6 (1.02%)	15 (2.0%)	14 (3.4%)
Others	12 (2.04%)	42 (5.6%)	3 (0.7%)
Dysmetria	0 (0%)	105 (14.1%)	0 (0%)
Mean follow-up and SD (months)	34.51±35.89	17.05±11.58	26.6±5.2

DBS: deep brain stimulation; tcMRgFUS: transcranial magnetic resonance-guided focused ultrasound; GK: gamma knife radiosurgery; cZi: caudal zona incerta; VIM: ventral intermediate nucleus of thalamus; VL: ventral lateral nucleus of thalamus; PSA: posterior subthalamic area;-CTT: cerebellothalamic tract.

tient, 0.1%). GK-related adverse events were described in 37 patients (over 413 with available data, 8,9%), occurring within an average time of 8,9 months (SD±3; range: 6–16). Transient adverse events related to GK resolved at later follow-ups in 27 patients (6.5%). The most common adverse events were hemiparesis (14 patients, 3.4%) and dysarthria (7 patients, 1.7%). Permanent adverse events referred to GK lasting up to the last available follow-ups were reported in 10 patients (2.4%). The most frequent were paresthesia (4 patients, 1%) and dysarthria (3 patients, 0.7%). Mean postsurgical follow-ups ranged from 2 to 120 months. On average, post-DBS follow-up was 34.51 months (SD±35.89) and post-tcMRgFUS follow-up was 17.05 months (SD±11.58). Average post-GK follow-ups was 26.6 months (SD±5.2). For each patient, treatment outcomes were assessed at first and last available follow-up. Post-treatment symptomatic improvement, *i.e.*, reduction or resolution of presenting symptoms, occurred in 67.21% of tcMRgFUS patients and 63,01% of DBS patients. As regards GK, post-treatment symptomatic improvement occurred in 341 patients (76.3%). Each of these three techniques was related to a substantial improvement of post-treatment Quality of Life, with increased patient independency in ADLs and functional status and improved self-perceived Quality of Life.

Evidence synthesis

Deep brain stimulation

Deep Brain Stimulation is a widely accepted surgical strategy aimed at improving symptoms of several movement disorders. It consists of an implant of a stimulation electrode to obtain a reversible suppression of defined target. Efficacy of DBS is strictly related to the accuracy of electrode location and to the stimulation parameters. As regard DBS programming, no universally accepted guidelines are available, and scientific evidence is really scarce.[5, 54] As reported in previous studies, despite no major differences in tremor severity between DBS and other lesioning techniques, patients undergoing DBS showed a greater improvement in Quality of Life than other subgroups.[1, 8]

Indications and patient selection

Drug-resistant PD was the first indication to DBS.[9] Nowadays, indications involve a large scale of tremor syndromes. In particular, ET, dystonic tremor, MS-associated tremor and other less common tremor syndromes can be treated by DBS after a proper selection which relies on the balancing of risk/benefit ratio.[7] As regards timing of DBS in case of medical refractory tremor, there is not yet a consensus, but "early DBS" for the treatment of tremor disorders is strongly debated in recent literature.[55]

Advantages vs. *disadvantages*

On choosing the most appropriate strategy to treat patients, risk/benefit ratio must be considered.[1, 3, 14] DBS has several advantages: it is a reversible procedure with lower risk of severe complications;[5] DBS patients generally have a long-time follow-up and their adaptation to DBS can be modified by DBS setting.[3] On the other hand, DBS is an invasive technique likely to cause infection, hemorrhage, and stroke; it requires general anesthesia in case of dysfunction, lead or battery replacement;[7] during long time follow-up a large percentage of patients develop tolerance or "habituation," with worsening of tremor control.[3]

Targets

DBS targets are several depending upon the movement disorder to treat. VIM is the target of choice in case of tremor-dominant PD and commonly in case of ET. As regards the treatment of ET, the ventral portion of VIM could be the target of choice, followed by other potential targets such as Pedunculopontine nucleus (PPn), cZi, or cerebellothalamic tract (CTT).[15, 54, 56, 57] VIM DBS could also be associated to Ventral Oral Nucleus (Vo) DBS.[3, 7] As regards potential adverse events, in a small percentage of patients VIM DBS entails the risk of irreversible gait ataxia mostly imputable to a permanent lesion, even in case of turning "OFF" DBS generator.[21, 56, 58] PSA and its anterior zone are recently used targets for the treatment of ET. Results are really promising, but few available studies seem to show a deterioration in tremor control at long-term follow-up. PSA could allow physicians to obtain the highest risk/benefit ratio, because it requires a lower stimulation current thus limiting side effects.[56, 59] Besides PD and ET, DBS has been used also for the treatment of non-ET tremor such as dystonic tremor, MS-associated tremor, post-stroke tremors, lesion-related tremors, and post-traumatic tremors, and other indications may arise from introduction of newer DBS implants.[8, 9, 60-63] Few studies are available, in almost totality of them VIM is the target of choice, but level of evidence is still low.[3, 64]

TcMRgFUS

TcMRgFUS uses focused ultrasound energy to obtain focal lesions in specific target, under the guidance of brain

MRI. The focused lesioning of tcMRgFUS follows the stereotactic principles of GK, but it is non-invasive since it does not adopt ionizing radiations.[65]

Indications and patient selection

TcMRgFUS was accepted by FDA in 2016. The first treated syndrome was ET, followed by other movement disorder such as PD, Fragile X associated tremor, ataxic syndromes, and dystonic tremor.[66, 67] Despite being non-invasive, tcMRgFUS is still a surgical intervention, so an accurate patient selection is essential. Presence of uncorrelated coagulopathy, high anesthesiology risk score, claustrophobia, dementia, PLT count <100.000, and intolerance to MRI contrast agent are absolute contraindications. Psychiatric disease, intracranial calcifications, scalp lesions, and hyperostosis frontalis are relative contraindications.[5, 30] TcMRgFUS feasibility and effectiveness mostly rely on the skull morphology. In particular, Skull Density Ratio (SDR) affects sonication energy, and it is strongly correlated to tremor improvement at 1-month and 6-months follow-up and to the risk of adverse events.[35]

Advantages vs. *disadvantages*

TcMRgFUS has specific advantage on other surgical techniques: it is non-invasive, and it does not require hardware implantation and programming; the procedure is planned and controlled by MRI; it does not require anesthesia; it is repeatable several times and it seems to be preferred by patients since their perception of avoiding surgery. On the other hand, tcMRgFUS is a relatively novel technique and lacks long-term follow-ups; its effectiveness is variable among different series and its application is limited by patient's skull characteristics.[5-7, 68-73]

Targets

ET was the first tcMRgFUS treated pathology by targeting VIM, since ET could be easily assessed during procedure and the VIM position allows an easy access of ultrasound beams.[4, 7, 34, 68, 74] Some of the common side effects of VIM tcMRgFUS thalamotomy are paresthesia, numbness of limbs, dysarthria, gait disturbance, dysmetria, and disequilibrium. Adverse events usually appear within 1 week after the treatment and they are often completely reversible within 3 months.[4, 6, 35, 71, 75, 76] Considering the possible pathophysiological involvement of cerebellar circuits, the CTT and its entry point in the PSA have been recently targeted with a good tremor control, but also related to a high incidence of gait disturbance.[40, 68] Besides ET, VIM is the target of choice even for the treatment of PD. Indication of tcMRgFUS for the treatment of PD are now limited to tremor-dominant PD and L-DOPA-induced dyskinesia.

Gamma knife

GK treatment represents a non-invasive procedure with several benefits compared to other surgical techniques in functional neurosurgery.

Indications and patient selection

GK has been used for movement disorders since the 1960s, with constantly growing number of treated patients.[77] Hence, GK is a good therapeutic option for movements disorders, with improvement rates ranging from 60-90%, and side effects lower than 8%, better than DBS.[42, 49, 50, 78-89] A peculiarity of GK treatment is the sustained radiobiological effects, which are delayed in contrast with the acute effects of thermocoagulation or DBS treatments.[49, 81] GK energy delivery induces parenchymal effects characterized by a necrotic lesion at the level of the target and with a mean diameter of 4 mm, associated to vascular alterations and gliosis in its proximity.[88] Previous studies reported that these peri-target modifications may induce a wide range of therapeutic effects compared to DBS, thus responsible for the prolonged benefits of GK treatment.[49, 79-81]

Advantages vs. *disadvantages*

In GK, the acute risks related to surgery and general anesthesia are avoided: no craniotomy is required with no cosmetic damage, no risk of hemorrhage or infection, no cardiac or pulmonary complications related to injectable opioid treatment, and nor risk of leads misplacement. The avoidance of such complications is of particular interest in fragile and elderly patients, especially with comorbidities or in treatment with lifesaving therapies like anti platelets/anticoagulant therapy for cardiological disorders, whose suspension is associated to higher thromboembolic risk in the postoperative period. Moreover, the pharmacological therapy usually taken from those patients needs to be reduced before general anesthesia, and the therapeutic range must be individualized on patient basis. This pharmacological assessment represents a critical moment in the management of those patients and a strict collaboration with neurologist is of paramount importance. Compared to DBS, GK shows a shorter hospital stay of about 48 h.

Targets

The VIM thalamotomy represented the most frequent target for GK treatment of ET. GK offers the opportunity to

deliver high energy in those deep sited neural brain structures, with a sharp fall of dose to the no-target area. In addition to the lesional effects, GK induces neuromodulative effects that could be even of greater benefit, although yet not fully documented.

Limitations of the study

The present study is a systematic review of the current literature about DBS, tcMRgFUS and GK for the treatment of ET. Due to the descriptive nature of the study, no quantitative data have been compared; thus, no statistical analysis could be performed. Despite this review represents a comprehensive summary about indications, targets and effectiveness of DBS, tcMRgFUS and GK for the treatment of ET, further studies and meta-analyses are necessary in order to statistically compare quantitative data about these three surgical techniques.

Conclusions

Tremor represents a condition that can deeply affect patient's functional status and Quality of Life. Among different etiologies, ET represents one of the most frequent and disabling one, and DBS, tcMRgFUS, and GK are three effective techniques for its treatment. Despite different functioning principles, DBS, tcMRgFUS, and GK require a proper functional diagnosis to define the correct indications. Their indications depend on patients' neurological conditions, and their effectiveness relies on the anatomical target chosen on the basis of patients' neurological examinations, so to obtain the most achievable control on patient's movement and to improve patients' Quality of Life.

References

1. Ferreira JJ, Mestre TA, Lyons KE, Benito-León J, Tan EK, Abbruzzese G, *et al.*; MDS Task Force on Tremor and the MDS Evidence Based Medicine Committee. MDS evidence-based review of treatments for essential tremor. Mov Disord 2019;34:950–8.

2. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, *et al.*; Tremor Task Force of the International Parkinson and Movement Disorder Society. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord 2018;33:75–87.

3. Iorio-Morin C, Fomenko A, Kalia SK. Deep-brain stimulation for essential tremor and other tremor syndromes: A narrative review of current targets and clinical outcomes. Brain Sci 2020;10:1–17.

4. Fukutome K, Kuga Y, Ohnishi H, Hirabayashi H, Nakase H. What factors impact the clinical outcome of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor? J Neurosurg 2020;134:1618–23.

5. Wang KL, Ren Q, Chiu S, Patel B, Meng FG, Hu W, *et al.* Deep brain stimulation and other surgical modalities for the management of essential tremor. Expert Rev Med Devices 2020;17:817–33. [Internet]

6. Varma-Doyle AV, Villemarette-Pittman NR, Copeland BJ. Hemi-parkinsonism and return of essential tremors after MRgFUS thalamotomy: case report and review of procedural complications affecting ventral thalamic nuclei. eNeurologicalSci 2021;23:100339.

7. Elble RJ, Shih L, Cozzens JW. Surgical treatments for essential tremor. Expert Rev Neurother 2018;18:303–21.

8. Altinel Y, Alkhalfan F, Qiao N, Velimirovic M. Outcomes in Lesion Surgery versus Deep Brain Stimulation in Patients with Tremor: A Systematic Review and Meta-Analysis. World Neurosurg 2019;123:443–452.e8.

9. Fasano A, Lozano AM, Cubo E. New neurosurgical approaches for tremor and Parkinson's disease. Curr Opin Neurol 2017;30:435–46.

10. Higuchi Y, Matsuda S, Serizawa T. Gamma knife radiosurgery in movement disorders: indications and limitations. Mov Disord 2017;32:28–35.

11. Bond AE, Shah BB, Huss DS, Dallapiazza RF, Warren A, Harrison MB, *et al.* Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant Parkinson disease a randomized Clinical trial. JAMA Neurol 2017;74:1412–8.

12. Gonzalez-Martinez J, Hernandez L, Zamorano L, Sloan A, Levin K, Lo S, *et al.* Gamma knife radiosurgery for intracranial metastatic melanoma: a 6-year experience. J Neurosurg 2002;97:494–8.

13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

14. Sun X, Huang L, Pan Y, Zhang C, Wang T, Li H, *et al.* Bilateral Posterior Subthalamic Area Deep Brain Stimulation for Essential Tremor: A Case Series. Front Hum Neurosci 2020;14:16.

15. Barbe MT, Reker P, Hamacher S, Franklin J, Kraus D, Dembek TA, *et al.* DBS of the PSA and the VIM in essential tremor: A randomized, double-blind, crossover trial. Neurology 2018;91:e543–50.

16. De Jesus S, Almeida L, Shahgholi L, Martinez-Ramirez D, Roper J, Hass CJ, *et al.* Square biphasic pulse deep brain stimulation for essential tremor: the BiP tremor study. Parkinsonism Relat Disord 2018;46:41–6.

17. Cury RG, Fraix V, Castrioto A, Pérez Fernández MA, Krack P, Chabardes S, *et al.* Thalamic deep brain stimulation for tremor in Parkinson disease, essential tremor, and dystonia. Neurology 2017;89:1416–23.

18. Eisinger RS, Wong J, Almeida L, Ramirez-Zamora A, Cagle JN, Giugni JC, *et al.* Ventral Intermediate Nucleus Versus Zona Incerta Region Deep Brain Stimulation in Essential Tremor. Mov Disord Clin Pract (Hoboken) 2017;5:75–82.

19. Diaz A, Cajigas I, Cordeiro JG, Mahavadi A, Sur S, Di Luca DG, *et al.* Individualized Anatomy-Based Targeting for VIM-cZI DBS in Essential Tremor. World Neurosurg 2020;140:e225–33. . [Internet]

20. Wang S, Wang X, Zhao M, Li T, Zhang C, Wang M, *et al.* Long-term efficacy and cognitive effects of voltage-based deep brain stimulation for drug-resistant essential tremor. Clin Neurol Neurosurg 2020;194:105940.

21. Paschen S, Forstenpointner J, Becktepe J, Heinzel S, Hellriegel H, Witt K, *et al.* Long-term efficacy of deep brain stimulation for essential tremor: an observer-blinded study. Neurology 2019;92:e1378–86.

22. Becker J, Thies T, Petry-Schmelzer JN, Dembek TA, Reker P, Mücke D, *et al.* The effects of thalamic and posterior subthalamic deep brain stimulation on speech in patients with essential tremor - A prospective, randomized, doubleblind crossover study. Brain Lang 2020;202:104724.

23. Degeneffe A, Kuijf ML, Ackermans L, Temel Y, Kubben PL. Comparing deep brain stimulation in the ventral intermediate nucleus versus the posterior subthalamic area in essential tremor patients. Surg Neurol Int 2018;9:244.

24. Kim M, Jung NY, Park CK, Chang WS, Jung HH, Chang JW. Comparative Evaluation of Magnetic Resonance-Guided Focused Ultrasound Surgery for Essential Tremor. Stereotact Funct Neurosurg 2017;95:279–86.

25. Chen T, Mirzadeh Z, Chapple K, Lambert M, Dhall R, Ponce FA. "Asleep" deep brain stimulation for essential tremor. J Neurosurg 2016;124:1842–9.

26. Harary M, Segar DJ, Hayes MT, Cosgrove GR. Unilateral Thalamic Deep Brain Stimulation Versus Focused Ultrasound Thalamotomy for Essential Tremor. World Neurosurg 2019;126:e144–52.

27. Huss DS, Dallapiazza RF, Shah BB, Harrison MB, Diamond J, Elias WJ. Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy. Mov Disord 2015;30:1937–43.

28. Tsuboi T, Jabarkheel Z, Zeilman PR, Barabas MJ, Foote KD, Okun MS, *et al.* Longitudinal follow-up with VIM thalamic deep brain stimulation for dystonic or essential tremor. Neurology 2020;94:e1073–84.

29. Chang JW, Park CK, Lipsman N, Schwartz ML, Ghanouni P, Henderson JM, *et al.* A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: results at the 2-year follow-up. Ann Neurol 2018;83:107–14.

30. Iacopino DG, Gagliardo C, Giugno A, Giammalva GR, Napoli A, Maugeri R, *et al.* Preliminary experience with a transcranial magnetic resonance-guided focused ultrasound surgery system integrated with a 1.5-T MRI unit in a series of patients with essential tremor and Parkinson's disease. Neurosurg Focus 2018;44:E7.

31. Ito H, Yamamoto K, Fukutake S, Odo T, Kamei T. Two-year follow-up results of magnetic resonance imaging-guided focused ultrasound unilateral thalamotomy for medication-refractory essential tremor. Intern Med 2020;59:2481–3.

32. Park YS, Jung NY, Na YC, Chang JW. Four-year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. Mov Disord 2019;34:727–34.

33. Halpern CH, Santini V, Lipsman N, Lozano AM, Schwartz ML, Shah BB, *et al.* Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. Neurology 2019;93:e2284–93.

34. Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, *et al.* A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. N Engl J Med 2016;375:730–9.

35. Sinai A, Nassar M, Eran A, Constantinescu M, Zaaroor M, Sprecher E, *et al.* Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. J Neurosurg 2019;133:1–8.

36. Krishna V, Sammartino F, Cosgrove R, Ghanouni P, Schwartz M, Gwinn R, *et al.* Predictors of Outcomes After Focused Ultrasound Thalamotomy. Neurosurgery 2020;87:229–37.

37. Jung NY, Park CK, Chang WS, Jung HH, Chang JW. Effects on cognition and quality of life with unilateral magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. Neurosurg Focus 2018;44:E8.

38. Boutet A, Ranjan M, Zhong J, Germann J, Xu D, Schwartz ML, *et al.* Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. Brain 2018;141:3405–14.

39. Zaaroor M, Sinai A, Goldsher D, Eran A, Nassar M, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. J Neurosurg 2018;128:202–10.

40. Gallay MN, Moser D, Rossi F, Pourtehrani P, Magara AE, Kowalski M, *et al.* Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. J Ther Ultrasound 2016;4:5.

41. Rand RW, Jacques DB, Melbye RW, Copcutt BG, Fisher MR, Levenick MN. Gamma Knife thalamotomy and pallidotomy in patients with movement disorders: preliminary results. Stereotact Funct Neurosurg 1993;61:65–92.

42. Friedman DP, Goldman HW, Flanders AE, Gollomp SM, Curran WJ Jr. Stereotactic radiosurgical pallidotomy and thalamotomy with the gamma knife: MR imaging findings with clinical correlation—preliminary experience. Radiology 1999;212:143–50.

43. Niranjan A, Raju SS, Kooshkabadi A, Monaco E 3rd, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for essential tremor: retrospective analysis of a 19-year experience. Mov Disord 2017;32:769–77.

44. Tuleasca C, Witjas T, Najdenovska E, Verger A, Girard N, Champoudry J, *et al.* Assessing the clinical outcome of Vim radiosurgery with voxel-based morphometry: visual areas are linked with tremor arrest! Acta Neurochir (Wien) 2017;159:2139–44.

45. Tuleasca C, Najdenovska E, Régis J, Witjas T, Girard N, Champoudry J, *et al.* Clinical response to Vim's thalamic stereotactic radiosurgery for essential tremor is associated with distinctive functional connectivity patterns. Acta Neurochir (Wien) 2018;160:611–24.

46. Siderowf A, Gollump SM, Stern MB, Baltuch GH, Riina HA. Emergence of complex, involuntary movements after gamma knife radiosurgery for essential tremor. Mov Disord 2001;16:965–7.

47. Elaimy AL, Demakas JJ, Arthurs BJ, Cooke BS, Fairbanks RK, Lamoreaux WT, *et al.* Gamma knife radiosurgery for essential tremor: a case report and review of the literature. World J Surg Oncol 2010;8:20.

48. Lim SY, Hodaie M, Fallis M, Poon YY, Mazzella F, Moro E. Gamma knife thalamotomy for disabling tremor: a blinded evaluation. Arch Neurol 2010;67:584–8.

49. Young RF, Li F, Vermeulen S, Meier R. Gamma knife thalamotomy for treatment of essential tremor: Long-term results: Clinical article. J Neurosurg 2010.

50. Ohye C, Higuchi Y, Shibazaki T, Hashimoto T, Koyama T, Hirai T, *et al.* Gamma knife thalamotomy for Parkinson disease and essential tremor: a prospective multicenter study. Neurosurgery 2012;70:526–35, discussion 535–6.

51. Young RF, Hesselgesser RD, Ahn E, Vermeulen S, Li F, Lee J. Bilateral gamma knife thalamotomy for treatment of axial tremor. Transl Cancer Res 2014.

52. Witjas T, Carron R, Krack P, Eusebio A, Vaugoyeau M, Hariz M, *et al.* A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology 2015;85:1562–8.

53. Niranjan A, Raju SS, Monaco EA, Flickinger JC, Lunsford LD. Is staged bilateral thalamic radiosurgery an option for otherwise surgically ineligible patients with medically refractory bilateral tremor? J Neurosurg 2018;128:617–26.

54. Yousif N, Mace M, Pavese N, Borisyuk R, Nandi D, Bain P. A Network Model of Local Field Potential Activity in Essential Tremor and the Impact of Deep Brain Stimulation. PLOS Comput Biol 2017;13:e1005326.

55. Munhoz RP, Picillo M, Fox SH, Bruno V, Panisset M, Honey CR, *et al.* Eligibility Criteria for Deep Brain Stimulation in Parkinson's Disease, Tremor, and Dystonia. Can J Neurol Sci 2016;43:462–71.

56. Wong JK, Hess CW, Almeida L, Middlebrooks EH, Christou EA, Patrick EE, *et al.* Deep brain stimulation in essential tremor: targets, technology, and a comprehensive review of clinical outcomes. Expert Rev Neurother 2020;20:319–31.

57. Holslag JA, Neef N, Beudel M, Drost G, Oterdoom DL, Kremer NI, *et al.* Deep Brain Stimulation for Essential Tremor: A Comparison of Targets. World Neurosurg 2018;110:e580–4.

58. Sandström L, Blomstedt P, Karlsson F. Long-term effects of unilateral deep brain stimulation on voice tremor in patients with essential tremor. Parkinsonism Relat Disord 2019;60:70–5.

59. Hidding U, Schaper M, Moll CK, Gulberti A, Köppen J, Buhmann C, *et al.* Mapping stimulation-induced beneficial and adverse effects in the subthalamic area of essential tremor patients. Parkinsonism Relat Disord 2019;64:150–5.

60. Shao MM, Liss A, Park YL, DiMarzio M, Prusik J, Hobson E, *et al.* Early Experience With New Generation Deep Brain Stimulation Leads in Parkinson's Disease and Essential Tremor Patients. Neuromodulation 2020;23:537–42.

61. Steffen JK, Reker P, Mennicken FK, Dembek TA, Dafsari HS, Fink GR, *et al.* Bipolar Directional Deep Brain Stimulation in Essential and Parkinsonian Tremor. Neuromodulation 2020;23:543–9.

62. He S, Debarros J, Khawaldeh S, Pogosyan A, Mostofi A, Baig F, *et al.* Closed-loop DBS triggered by real-time movement and tremor decoding based on thalamic LFPs for essential tremor. Annu Int Conf IEEE Eng Med Biol Soc 2020;2020:3602–5.

63. Bruno S, Nikolov P, Hartmann CJ, Trenado C, Slotty PJ, Vesper J, *et al.* Directional Deep Brain Stimulation of the Thalamic Ventral Intermediate Area for Essential Tremor Increases Therapeutic Window. Neuromodulation 2021;24:343–52.

64. Mendonça MD, Meira B, Fernandes M, Barbosa R, Bugalho P. Deep brain stimulation for lesion-related tremors: A systematic review and meta-analysis. Parkinsonism Relat Disord 2018;47:8–14.

65. Giammalva GR, Gagliardo C, Marrone S, Paolini F, Gerardi RM, Umana GE, *et al.* Focused ultrasound in neuroscience. State of the art and future perspectives. Brain Sci 2021;11:84.

66. Meng Y, Jones RM, Davidson B, Huang Y, Pople CB, Surendrakumar S, *et al.* Technical Principles and Clinical Workflow of Transcranial MR-Guided Focused Ultrasound. Stereotact Funct Neurosurg 2021;99:329–42.

67. Fasano A, Llinas M, Munhoz RP, Hlasny E, Kucharczyk W, Lozano AM. MRI-guided focused ultrasound thalamotomy in non-ET tremor syndromes. Neurology 2017;89:771–5.

68. Rohani M, Fasano A. Focused ultrasound for essential tremor: review of the evidence and discussion of current hurdles. Tremor Other Hyperkinet Mov (N Y) 2017;7:462.

69. Krishna V, Sammartino F, Rezai A. A Review of the Current Therapies, Challenges, and Future Directions of Transcranial Focused Ultrasound Technology: Advances in Diagnosis and Treatment. JAMA Neurol 2018;75:246–54.

70. Alshaikh J, Fishman PS. Revisiting bilateral thalamotomy for tremor. Clin Neurol Neurosurg 2017;158:103–7.

71. Mohammed N, Patra D, Nanda A. A meta-analysis of outcomes and complications of magnetic resonance-guided focused ultrasound in the treatment of essential tremor. Neurosurg Focus 2018;44:E4.

72. Giammalva GR, Gagliardo C, Maugeri R, Midiri M, Iacopino DG. Letter to the Editor. Transcranial MRgFUS for movement disorder: toward a wider and affordable employment for functional neurosurgery through 1.5-T MRI? J Neurosurg 2018;129:843–4.

73. Valentino F, Cosentino G, Maugeri R, Giammalva R, Iacopino GD, Marrale M, *et al.* Is Transcranial Magnetic Resonance Imaging-Guided Focused Ultrasound a Repeatable Treatment Option? Case Report of a Retreated Patient With Tremor Combined With Parkinsonism. Oper Neurosurg (Hagerstown) 2020;18:577–82.

74. Su JH, Choi EY, Tourdias T, Saranathan M, Halpern CH, Henderson JM, *et al.* Improved Vim targeting for focused ultrasound ablation treatment of essential tremor: A probabilistic and patient-specific approach. Hum Brain Mapp 2020;41:4769–88.

75. Kapadia AN, Elias GJ, Boutet A, Germann J, Pancholi A, Chu P, *et al.* Multimodal MRI for MRgFUS in essential tremor: post-treatment radiological markers of clinical outcome. J Neurol Neurosurg Psychiatry 2020;91:921–7.

76. Fishman PS, Elias WJ, Ghanouni P, Gwinn R, Lipsman N, Schwartz M, *et al.* Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor. Mov Disord 2018;33:843–7.

77. Campbell AM, Glover J, Chiang VL, Gerrard J, Yu JB. Gamma knife stereotactic radiosurgical thalamotomy for intractable tremor: a systematic review of the literature. Radiother Oncol 2015;114:296–301.

78. Young RF, Jacques S, Mark R, Kopyov O, Copcutt B, Posewitz A, *et al.* Gamma knife thalamotomy for treatment of tremor: long-term results. J Neurosurg 2000;93:128–35.

79. Ohye C, Shibazaki T, Zhang J, Andou Y. Thalamic lesions produced by gamma thalamotomy for movement disorders. J Neurosurg 2002;97:600–6.

80. Kondziolka D, Ong JG, Lee JY, Moore RY, Flickinger JC, Lunsford LD. Gamma Knife thalamotomy for essential tremor. J Neurosurg 2008;108:111–7.

81. Kooshkabadi A, Lunsford LD, Tonetti D, Flickinger JC, Kondziolka D. Gamma Knife thalamotomy for tremor in the magnetic resonance imaging era. J Neurosurg 2013;118:713–8.

82. Lindquist C, Steiner L, Hindmarsh T. Gamma knife thalamotomy for tremor: report of two cases. Radiosurgery 1992:237–43.

83. Young RF. Functional neurosurgery with the Leksell Gamma knife. Stereotact Funct Neurosurg 1996;66:19–23.

84. Duma CM, Jacques DB, Kopyov OV, Mark RJ, Copcutt B, Farokhi HK. Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: a five-year experience. J Neurosurg 1998;88:1044–9.

85. Young RF, Shumway-Cook A, Vermeulen SS, Grimm P, Blasko J, Posewitz A, *et al.* Gamma knife radiosurgery as a lesioning technique in movement disorder surgery. J Neurosurg 1998;89:183–93.

86. Duma CM, Jacques D, Kopyov OV. The treatment of movement disorders using Gamma Knife stereotactic radiosurgery. Neurosurg Clin N Am 1999;10:379–89.

87. Niranjan A, Jawahar A, Kondziolka D, Lunsford LD. A comparison of surgical approaches for the management of tremor: radiofrequency thalamotomy, gamma knife thalamotomy and thalamic stimulation. Stereotact Funct Neurosurg 1999;72:178–84.

88. Ohye C, Shibazaki T, Ishihara J, Zhang J. Evaluation of gamma thalamotomy for parkinsonian and other tremors: survival of neurons adjacent to the thalamic lesion after gamma thalamotomy. J Neurosurg 2000;93:120–7.

89. Niranjan A, Kondziolka D, Baser S, Heyman R, Lunsford LD. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor. Neurology 2000;55:443–6.

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REVIEW

Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: a systematic review and pooled analysis of functional outcomes

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ABSTRACT

The current gold standard surgical treatment for medication-resistant essential tremor (ET) is deep brain stimulation (DBS). However, recent advances in technologies have led to the development of incisionless techniques, such as magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy. The authors perform a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to compare unilateral MRgFUS thalamotomy to unilateral and bilateral DBS in the treatment of ET in terms of tremor severity and quality of life improvement. PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and SCOPUS databases were searched. 45 eligible articles, published between 1990 and 2019, were retrieved. 1202 patients were treated with DBS and 477 were treated with MRgFUS thalamotomy. Postoperative tremor improvement was greater following DBS than MRgFUS thalamotomy ($p<0.001$). A subgroup analysis was carried out stratifying by treatment laterality: bilateral DBS was significantly superior to both MRgFUS and unilateral DBS ($p<0.001$), but no significant difference was recorded between MRgFUS and unilateral DBS ($p<0.198$). Postoperative quality of life improvement was significantly greater following MRgFUS thalamotomy than DBS ($p<0.001$). Complications were differently distributed among the two groups ($p<0.001$). Persistent complications were significantly more common in the MRgFUS group ($p=0.042$). While bilateral DBS proves superior to unilateral MRgFUS thalamotomy in the treatment of ET, a subgroup analysis suggests that treatment laterality is the most significant determinant of tremor improvement, thus highlighting the importance of future investigations on bilateral staged MRgFUS thalamotomy.

INTRODUCTION

Essential tremor (ET) is a progressive neurological disorder that affects about 0.9% of adults, with a known increasing of prevalence with age (4% in adults older than 65).[1] Pathophysiology is still undetermined, although several possible mechanisms have been highlighted.[2 3] Even though the pattern of inheritance is still unknown, there are the evidences of a strong familial linkage.[2 3]

ET is characterised by postural and/or kinetic tremor, affecting the upper limbs, head and possibly voice; there is evidence that other neurological disturbances ('non-motor' symptoms) such as mild cognitive changes, depression and olfactory and hearing deficiencies occur more frequently in patients with ET compared with age-matched controls.[1]

Several pharmacological options are available; first line treatment consists of a combination of propranolol and primidone, which obtains a 50% reduction in tremor severity in 70% of patients; benzodiazepines, topiramate and gabapentin have been suggested as second-line therapy.[4]

Even though pharmacological treatment is sufficient in symptoms control for most patient, a significant cohort is medically refractory and may benefit from surgery.[5] Indications to surgery include failure to respond to, intolerance of or medical contraindication to use of at least two medications for ET, one of which must be a first-line medication, and appendicular tremor that interferes with quality of life (QoL) based on clinical history.[6] Surgical ablation targeting the ventral intermedius nucleus of the thalamus (VIM) was among the first stereotactic procedures and proved highly effective for treating medication-resistant tremor related to Parkinson's disease and ET.[4] Ablative approaches to the VIM have been gradually supplanted by deep brain stimulation (DBS).[7] The abundance of studies showing the superior safety profile of DBS compared with thalamotomy has made DBS the new golden standard for the treatment of ET.[8–15]

The recent approval of magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy for the treatment of ET has ignited the debate surrounding the use of incisionless thalamotomy.[16 17]

Being a novel technique, the results of MRgFUS in the treatment of medication-refractory ET ought to be compared with the gold standard technique, that is DBS. Comparison, however, is scarce. The authors performed a systematic review and pooled analysis of the present literature.

MATERIALS AND METHODS

Search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18] A search of PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and SCOPUS databases was conducted to identify articles of interest. These

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Review Article

Outcomes and Adverse Effects of Deep Brain Stimulation on the Ventral Intermediate Nucleus in Patients with Essential Tremor

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Objective. This study was aimed at identifying the potential outcome predictors, comparing the efficacy in patients with different tremor characteristics, and summarizing the adverse effect rates (AERs) of deep brain stimulation on the ventral intermediate nucleus (VIM-DBS) for essential tremor (ET). *Methods*. An extensive search of articles published to date in 2019 was conducted, and two main aspects were analyzed. Improvement was calculated as a percentage of change in any objective tremor rating scale (TRS) and analyzed by subgroup analyses of patients' tremor characteristics, laterality, and stimulation parameters. Furthermore, the AERs were analyzed as follows: the adverse effects (AEs) were classified as stimulation-related, surgical-related, or device-related effects. A simple regression analysis was used to identify the potential prognostic factors, and a two-sample mean-comparison test was used to verify the statistical significance of the subgroup analyses. *Results*. Forty-six articles involving 1714 patients were included in the meta-analysis. The pooled improvement in any objective TRS score was 61.3% (95% CI: 0.564-0.660) at the mean follow-up visit (20.0 ± 17.3 months). The midline and extremity symptoms showed consistent improvement ($P = 0.440$), and the results of the comparison of postural and kinetic tremor were the same ($P = 0.219$). In addition, the improvement in rest tremor was similar to that in action tremor (OR = 2.759, $P = 0.120$). In the simple regression analysis, the preoperative Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) scores and follow-up time were negatively correlated with the percentage change in any objective TRS score ($P < 0.05$). The most common adverse event was dysarthria (10.5%), which is a stimulation-related AE (23.6%), while the rates of the surgical-related and device-related AEs were 6.4% and 11.5%, respectively. *Conclusion*. VIM-DBS is an efficient and safe surgical method in ET, and the efficacy was not affected by the body distribution of tremor, age at surgery, and disease duration. Lower preoperative FTM-TRS scores likely indicate greater improvement, and the effect of VIM-DBS declines over time.

1. Introduction

Essential tremor (ET), also known as primary tremor, is defined as an isolated tremor syndrome consisting of a bilateral upper extremity action tremor for at least 3 years with or without tremor in other locations and without other neurological signs [1]. Currently, the management of this disorder focuses on controlling the symptoms, and pharmacotherapy is the primary therapy. Unfortunately, drug therapy is only effective in 50% of ET patients [2]. Surgical options include stereotactic radiofrequency thalamotomy, gamma knife thalamotomy, and deep brain stimulation [3–5] Among these options, deep brain stimulation in the ventral intermediate nucleus (VIM-DBS) is more easily reversed than thalamotomy and can effectively suppress tremors while avoiding the common complications of thalamotomies [6, 7]. The posterior subthalamic area/caudal zona incerta and subthalamic nucleus, except for the VIM, are also targets of DBS; however, thus far, studies are still limited with a short follow-up period compared to that in studies investigating VIM [8].

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Thalamic DBS with a constant-current device in essential tremor: A controlled clinical trial☆

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ABSTRACT

Introduction: This study of thalamic deep brain stimulation (DBS) investigated whether a novel constant-current device improves tremor and activities of daily living (ADL) in patients with essential tremor (ET).
Methods: A prospective, controlled, multicenter study was conducted at 12 academic centers. We investigated the safety and efficacy of unilateral and bilateral constant-current DBS of the ventralis intermedius (VIM) nucleus of the thalamus in patients with essential tremor whose tremor was inadequately controlled by medications. The primary outcome measure was a rater-blinded assessment of the

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change in the target limb tremor score in the stimulation-on versus stimulation-off state six months following surgery. Multiple secondary outcomes were assessed at one-year follow-up, including motor, mood, and quality-of-life measures.
Results: 127 patients were implanted with VIM DBS. The blinded, primary outcome variable ($n = 76$) revealed a mean improvement of 1.25 ± 1.26 points in the target limb tremor rating scale (TRS) score in the arm contralateral to DBS ($p < 0.001$). Secondary outcome variables at one year revealed significant improvements ($p \leq 0.001$) in quality of life, depression symptoms, and ADL scores. Forty-seven patients had a second contralateral VIM-DBS, and this group demonstrated reduction in second-sided tremor at 180 days ($p < 0.001$). Serious adverse events related to the surgery included infection ($n = 3$), intracranial hemorrhage ($n = 3$), and device explantation ($n = 3$).
Conclusion: Unilateral and bilateral constant-current VIM DBS significantly improves upper extremity tremor, ADL, quality of life, and depression in patients with severe ET.

1. Introduction

Deep brain stimulation (DBS) is an effective therapy for reducing tremor in appropriately selected patients with essential tremor (ET) [1–13]. Most trials have reported substantial improvement in tremor of the contralateral limb following DBS implants in the unilateral ventralis intermedius (VIM) nucleus of the thalamus with improvements varied between 18% and 88%. This variation likely reflects differences in patient selection, placement techniques of the DBS leads, and methods of outcome assessments. A recent literature review [14] cited the need for more prospective VIM DBS studies, with consistent preoperative baseline assessments, blinded evaluations, and long-term follow-up, inclusive of quality-of-life evaluations. Further, all previous studies of VIM DBS have used voltage-controlled devices. Recently, devices that deliver constant-current stimulation have become an option [15]. These devices may provide more accurate and consistent delivery of electricity to the brain by compensating for variations in electrode impedance over time. This technology reduces voltage fluctuations, but comparative studies will be needed to determine if there are any additional benefits with outcomes employing these new devices [16].

Here we assessed for the first time the safety and efficacy of unilateral constant-current thalamic DBS in patients with ET. Additionally, we evaluated the safety and efficacy of bilateral VIM DBS in a subset of patients electing a second-side implant.

2. Methods

2.1. Study design

A prospective, controlled, multicenter, blinded study of a constant-current DBS device was conducted at 12 academic centers that specialize in the care of patients who have tremor and movement disorders. Eligibility to participate in the study was determined according to the inclusion/exclusion criteria (Supplemental Table 1).

The study protocol was approved by the United States Food and Drug Administration (FDA), and the study was registered with clinicaltrials.gov (NCT02087046). All sites received Institutional Review Board approval prior to consenting patients for the study. Written informed consent was obtained from all patients prior to study procedures and device implantation.

2.2. Unilateral versus second-side implants

After screening, each patient underwent a baseline evaluation, followed by unilateral or bilateral implantation of the DBS system. A unilateral or bilateral approach was determined based on a discussion between the clinical team and the patient about the potential risks and benefits of unilateral versus simultaneous bilateral stimulation. For unilateral cases, the DBS system was most often implanted on the side of the brain contralateral to the most affected extremity with a CTRS score 3 or higher. This was based on patient's dominant hand or worse side. For patients undergoing bilateral simultaneous implants, the target extremity for primary data analysis was determined prospectively by the site investigator.

2.3. Surgical procedures

Implantation of the Libra DBS system (St. Jude Medical Neuromodulation Division, Plano, TX, USA) was performed according to the standard surgical procedures at each center. Patients in the clinical trial were treated with a single-channel implantable pulse generator (IPG), which was placed in the subclavicular area of the chest wall (or subcutaneously in the abdomen) on the same day as the lead implant or during a separate surgical procedure within four weeks. Patients who underwent staged or bilateral simultaneous placement of a second lead on the opposite side of the brain had an additional IPG placed in the same area on the other side of the body.

2.4. Clinical assessments

All patients were evaluated at baseline (presurgery), at day 90 (±14 days), day 180 (±14 days), and day 365 (±30 days) following surgery. Device programming was conducted as per routine care in as many clinic visits as were needed to optimize tremor control. Evaluations at each of these visits included CTRS [5]. The motor scale measures the maximum tremor severity in various body regions in different positions (rest, postural, kinetic). Each body area is scored from 0 to 4, with 4 representing maximal tremor. The total motor score is calculated by summation of the individual scores. The most severe (postural or kinetic) tremor in the target limb (arm) at baseline was designated as the primary outcome variable for each patient. Patients also completed the disability scale, the CTRS Activities of Daily Living (ADL) sub-scale (questions 15–21) of the CTRS, the Quality of Life in Essential Tremor (QUEST) scale [17], and the Patient Satisfaction Ratings. The Mini-mental State Exam (MMSE) was used to assess cognitive function. The Beck Depression Inventory II (BDI-II) score [18] was used to assess depressive symptoms.

At follow-up assessments, patients were instructed to deactivate their DBS system for 4 h prior to the clinic visit while continuing their ET medications on the day of visit. The CTRS evaluation was performed first in the stimulation-off state and was repeated following activation of the DBS system for approximately

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Deep Brain Stimulation for Essential Tremor: A Systematic Review

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Abstract: Deep brain stimulation (DBS) is a neurosurgical treatment, which has proven useful in treating Parkinson's disease. This systematic review assessed the safety and effectiveness of DBS for another movement disorder, essential tremor. All studies concerning the use of DBS in patients with essential tremor were identified through searching of electronic databases and hand searching of reference lists. Studies were categorized as before/after DBS or DBS stimulation on/off to allow the effect of the stimulation to be analyzed separately to that of the surgery itself. A total of 430 patients who had received DBS for essential tremor were identified. Most of the reported adverse events were mild and could be treated through changing the stimulation settings. Generally, in all studies, there was a significant improvement in outcomes after DBS compared with baseline scores. In addition, DBS was significantly better in testing when the stimulation was turned on, compared with stimulation turned off or baseline. Based on Level IV evidence, DBS is possibly a safe and effective therapy for essential tremor. © 2010 Movement Disorder Society

Key words: deep brain stimulation; essential tremor; systematic review

Essential tremor (ICD-10 G25.0) is one of the most common neurological disorders.[1] A key feature of this disorder is kinetic tremor of the arms during voluntary movement, which in severe cases can spread to other body parts or occur at rest.[1,2] Patients may have significant physical impairment and a markedly decreased quality of life.

Among the general population, the prevalence of essential tremor has been conservatively estimated at between 0.4% and 5%, although it is expected that the true prevalence is much higher due to the absence of uniform methodology by which to diagnose the disorder.[3–5]

Existing Procedures

To date, no curative treatment exists for essential tremor. Management of the disorder is focused on controlling the symptoms, with pharmacotherapy as the primary therapy. However, it is estimated that between 25% and 55% of patients will have medication-refractory essential tremor.[6] For these patients, surgical options include stereotactic radiofrequency thalamotomy, gamma knife thalamotomy, or deep brain stimulation (DBS).[2,4,7] Thalamotomy is rarely conducted in Australia because of its association with increased morbidity and mortality.[8,9] This procedure is effective in 73% to 93% of patients with medication-refractory

Guy J. Maddern, as corresponding author, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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incapacitating tremor but is accompanied by permanent complications in 9% to 23% of patients.[10] Tremor recurs in ~20% of thalamotomy cases.[11]

DBS is an alternative to lesional surgery and may be an effective treatment for a wide range of movement disorders including Parkinson's disease, essential tremor, and dystonia. Although the precise mechanism of DBS is still not understood, the procedure is thought to have several effects including stimulation of neural tracts and disruption of neural networks.[12] DBS is more easily reversed than thalamotomy, and side effects of treatment may often be minimized by altering stimulation settings.

The DBS Procedure

DBS is a nondestructive surgical treatment, which involves the placement of electrodes into one or both sides of the basal ganglia of the brain. The target is generally the thalamic ventralis intermedius nucleus.[4] The DBS procedure is generally performed in two separate steps. First the electrodes and leads are implanted, with placement determined by the patient's response to stimulation and interpretation of the microelectrode recording data. This stage is performed under local anesthesia assisted with sedation. Second, the neurostimulator/implantable pulse generator (IPG) is implanted below the clavicle while the patient is fully anesthetized. The IPG, to which the leads are connected, delivers electrical pulses and contains a battery that needs to be replaced at intervals of 2 to 5 years. Patients are instructed to turn off their IPG at night to prevent habituation.[13] This also conserves the battery, which may then last between 7 and 10 years. Stimulation elicits an immediate response in patients with essential tremor, and an external programming unit is used to adjust the stimulation settings to the patient's needs.

Assessing patients for potential treatment with DBS involves several complex decisions. To be considered for the procedure, patients should have failed all alternative treatments and have severe symptoms that affect daily activities such as the inability to independently feed or go to toilet. As this can often be subjective, relevant validated rating scales should be used to assess these symptoms. Some patients with other comorbidities may be unsuitable for the procedure. Further, because of the nature of the surgery, some patients may not accept DBS or may delay DBS until the symptoms become so extreme that they are unable to look after themselves.

METHODS

Data Origin

The population considered was patients suffering from medically refractory essential tremor. For these patients, the alternative treatment to DBS is considered to be thalamotomy, an ablative intervention that is not recommended for use in Australia.[14] Thus, for the purposes of this Australian systematic review, the comparator with DBS was no treatment. In patients with essential tremor, DBS has an almost instantaneous effect when the IPG is switched on or off. Consequently, there are two distinct aspects of no treatment: no surgical intervention and no stimulation intervention (stimulation turned off). The study of patients with the stimulation turned on and off allows the effect of the stimulation to be seen, whereas the study of patients before and after implantation allows the effect of the implantation alone to be seen. Because of the different nature of these two sets of studies, they were reported separately.

All outcomes relating to safety or clinical effectiveness of DBS were considered. The nature of the procedure and the population who are refractory to other treatment make it difficult to conduct comparative studies of a high level of evidence. Therefore, randomized controlled trials, comparative studies, and studies of Level IV evidence were considered for inclusion in this systematic review.

Inclusion Criteria

Articles were obtained on the basis of the abstract containing safety and efficacy data on the use of DBS to treat essential tremor.

Search Strategy and Selection Criteria

Searches of the published and unpublished literature were conducted without language restriction in August 2007. On advice from clinical experts, searches were date limited to studies published after 1990 as DBS is a relatively new and evolving procedure in Australia. The bibliographies of all retrieved publications were hand searched for any relevant references. Two reviewers independently applied the inclusion criteria, and any differences were resolved by discussion and expert advice sought where appropriate. The search terms used and databases searched are included in Table 1.

Data were extracted by one researcher and checked by a second using standardized data extraction tables developed a priori. Included studies were assigned a level of evidence according to the Hierarchy of Evi-

TABLE 1. *Databases searched and search terms used*

Databases	MeSH terms	Textword terms
AustHealth—including: Australian Medical Index, APAIS Health CINAHL Cochrane Library Current contents connect EMBASE Medline PubMed Web of science—science citation index expanded	Dystonia; tremor; spasmodic torticollis; hemifacial spasm; dysphonia; Brueghel's syndrome; hemidystonia; myoclonus; blepharospasm; dyskinesia; Meige syndrome; status dystonicus; Hallervorden Spatz; PKAN; deep brain stimulation	Dystonia; tremor; spasmodic torticollis; hemifacial spasm; dysphonia; Breughel's syndrome; hemidystonia; myoclonus; blepharospasm; dyskinesia; Meige syndrome; status dystonicus; Hallervorden spatz; PKAN; (thalam* OR pallid* OR deep brain) AND stimulat*; deep brain stimulation

The truncation symbol (*) is used in many databases to allow retrieval of search terms with common word stems.
APAIS, Australian Public Affairs Information Service.

dence table (Table 2) developed by the National Health and Medical Research Council of Australia[15] and examined for design or execution factors that may have introduced bias.

Description of Studies

A total of 17[16–32] studies met the inclusion criteria and were included for review (Table 3). All included studies were National Health and Medical Research Council Level IV evidence in which data were provided for the same cohort of patients, hence, the evidence is subject to a degree of bias and should be interpreted accordingly.

The identified studies were analyzed in two separate groups for effectiveness outcomes. The first group reported the outcomes of DBS treatment when stimulation was switched on and when stimulation was switched off. The second group reported outcomes before and after DBS implantation.

Study Quality

There was a relative homogeneity to the patient pool because, where reported, the studies had similar inclusion criteria for patient recruitment. The patient pool typically included those with clinically diagnosed essential tremor who received DBS. Where reported, the mean age at surgery ranged from 60 to 73.8 years. Age at onset of symptoms was reported by only one study,[22] with onset at a mean age of 38.4 years (range, 20–58 years).

Three studies reported on patients with comorbidities. One patient had a thalamotomy contralateral to implant,[16] one patient had atrial fibrillation and congestive cardiac failure,[22] one patient had lung cancer,[24] and one patient had colon cancer.[24]

A total of 96 losses to follow-up were reported.[16,18–20,23,25,28–30] Several of these losses were not adequately reported on. Most notably, 22 of the participants in one study[28] were lost with no discussion on the reasons why these patients were not followed up. Seven studies[18,19,21–25] reported a preoperative baseline (Table 3). These studies may be regarded as higher quality than those which did not provide a preoperative baseline as they provide a clearer estimate of the effect of the stimulation. Those studies that did not clearly nominate a preoperative baseline may be subject to more bias through possible mistaken estimation of the effect of the stimulation.

TABLE 2. *NHMRC hierarchy of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomized controlled trials
II	Evidence obtained from at least one properly designed randomized controlled trial
III-1	Evidence obtained from well-designed pseudorandomized controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either posttest or pretest/posttest

Source: NHMRC 1999.

TABLE 3. *Included studies*

Study ID	N	Follow-up	Previous treatment	Blinding of assessors	Medication during study	Level of evidence	Study type
Assessors were blinded							
Koller et al.[18]	38[a]	12 mo	NR	Yes at 3-mo evaluations for 24 patients	10/38 patients used medication 30 d before study and for first 3 mo of study	IV	DBS on/off[b]
Koller et al.[19]	49[c]	3, 12, and 40 mo	Previous pharmacologic treatment	Yes at 3-mo evaluations	9/49 patients used medication	IV	DBS on/off[b]
Lyons et al.[20]	22[d]	Mean 11 mo (3–30 mo)	NR	Yes	2/22 patients used medication	IV	DBS on/off
Pahwa et al.[22]	9	3 months	NR	Yes at 3-mo evaluations	No	IV	DBS on/off[b]
Assessors either not blinded or not reported to be blinded							
Bryant et al.[16]	23[e]	Mean 13 mo (4.5–22 mo)	NR	No	No	IV	DBS on/off
Carpenter et al.[17]	7	Mean 18 mo (1–32 mo)	NR	NR	2 patients (1 male, 1 female) used medication as part of their management of hand tremor	IV	DBS on/off
Obwegeser et al.[21]	27	3 mo	Propranolol, primidone and gabapentin at maximum tolerable doses	NR	9/27 patients used medication at baseline examination	IV	DBS on/off[b]
Pahwa et al.[23]	26[f]	5 yr	NR	NR	NR	IV	DBS on/off[b]
Putzke et al.[24]	22[g]	3 mo, 2 yr, 3 yr	Propranolol, primidone and gabapentin at maximum tolerable doses	NR	No	IV	DBS on/off[b]
Sydow et al.[25]	37[h]	6 yr	Propranolol, primidone and/or benzodiazepines at maximum tolerable doses	NR	8/37 patients used medication	IV	DBS on/off[b]
Ushe et al.[26]	11	NR	NR	NR	Patients discontinued medication overnight, tested next morning	IV	DBS on/off
Vaillancourt et al.[27]	6 ET, 6 control	Immediate on/off, at least 3 mo after surgery	NR	NR	All patients taken off medication during the study	IV	DBS on/off
Assessors were blinded							
Fields et al.[28]	62[i]	3 and 12 mo	Inadequately controlled by medication	Yes at postoperative evaluation to preoperative evaluation results, operative complications, tremor ratings, stimulation parameters	Yes throughout the study	IV	DBS before/after
Hariz et al.[29]	27	Mean 12.5 mo	Failed pharmacologic treatment, 4 patients had VIM thalamotomy, 1 patient had VIM thalamotomy then VIM DBS contralateral to study DBS	Yes at postoperative evaluation to preoperative evaluation results	NR	IV	DBS before/after
Troster et al.[30]	40	Mean 3.0 ± 0.7 mo	Tremor inadequately controlled by medication	Yes	NR	IV	DBS before/after
Assessors either not blinded or not reported to be blinded							
Lee and Kondziolka[31]	19[j]	Mean 27 mo (10–75 mo)	Failed propranolol or mysoline therapy	NR	NR	IV	DBS before/after
Murata et al.[32]	8	Median 22 mo (8–42 mo)	Various medications providing slight improvement, 1 patient had thalamotomy	NR	NR	IV	DBS before/after

[a]Originally 38 patients at baseline, 22 at 6-mo follow-up, and 20 at 12-mo follow-up.
[b]Reported a presurgical baseline.
[c]Originally 49 patients at baseline, only 25 patients were evaluated with follow-up ≥2 yr.
[d]Originally 22 patients at baseline, 2 refused to switch stimulation to off.
[e]Originally 23 patients at baseline, only 16 completed the study.
[f]Originally 26 patients, only 23 patients remaining at 5 yr.
[g]Originally 22 patients, 18 at follow-up.
[h]Originally 37 patients at baseline, 18 lost to follow-up.
[i]Originally 62 patients, only 40 at 1-yr follow-up.
[j]Originally 19 patients, 18 at follow-up.
DBS, deep brain stimulation; NR, not reported; VIM, ventralis intermedius.

Seven studies[18–20,22,28–30] reported that outcomes assessors were blinded to treatment, which may be regarded as higher quality than those which either did not blind outcome assessors or where this was not reported. In addition, some studies did not record that all patients failed medical therapy before DBS (Table 3). Hence, it is possible that some included patients may have responded to medical therapy as well as to DBS.

RESULTS

Safety

Most reported adverse events were relatively mild and could potentially be resolved by changing the stimulation settings. Many events were related to the stimulation such as paresthesia, dysarthria, and headache; however, the resolution and consequences of these events were generally not reported. The more severe events were relatively rare, although the studies poorly reported the overall long-term outcomes related to these events. Three separate instances of stroke were reported.[25] One of these was as a result of hemorrhage during implantation, which resulted in hemiparesis, and the overall outcome was not reported. The other two strokes were ischemic, and one resolved spontaneously, whereas the outcome of the second was not reported. There was one mild case of syncope, which was easily managed with a change in stimulation.[19] Four cases of dystonia appeared during stimulation,[18,19,25] and the outcome and consequence of three cases were not reported whereas one case was reported to be ongoing. There were few complications related to the DBS equipment such as lead breakage and electrode migration.

Two studies did not report on adverse events; however, there may have been some variation in the way that adverse events were reported between the studies and some minor adverse events may not have been reported. In summary, from this group of Level IV studies, DBS is a relatively safe treatment for essential tremor (Table 4). Most adverse events were mild and could potentially be treated through changing the stimulation settings. The more severe events were relatively rare and may not affect long-term outcomes; however, the studies poorly reported the overall long-term outcomes related to these events.

Effectiveness

The two study types (on/off and before/after) were analyzed separately. Most of the included studies used the Fahn-Tolosa-Marin (FTM) tremor rating scale to assess the effectiveness of DBS for essential tremor. Generally, in all studies, there was a significant improvement in outcomes following DBS compared with baseline scores. In addition, where reported, DBS was significantly better in testing when the stimulation was on compared with off or baseline. Meta-analysis of the overall outcomes was not possible as many studies did not clearly define the specific subscores of the FTM that were used. Unfortunately, none of the included studies reported directly on quality of life outcomes after DBS, thus preventing a useful assessment of the impact of DBS on the patient.

DBS On/Off

Twelve studies reported outcomes for patients when DBS was switched on compared with off. Ten of these studies[16,18–26] used the FTM to assess the effectiveness of DBS, of which seven studies[18,19,21–25] also reported outcomes for patients at baseline before the implantation of DBS equipment (Table 5). The remaining three studies[16,20,26] that used the FTM to assess patients did not report preoperative patient assessment scores. The length of follow-up ranged from at least 3 months postoperatively[19] to mean 6 years postoperatively.[25]

The subscores of FTM used to report on patients varied between studies; however, there was consistently a significant improvement when the stimulator was switched on compared with when it was switched off (Table 5). Six of the seven studies that reported a preoperative baseline showed that essential tremor was significantly improved after DBS.[18,19,21,23–25]

Three studies followed up patients for 3 years or more.[23–25] Each of these studies reported that FTM scores were significantly improved when the stimulator was switched on compared with when it was switched off.

Generally, where reported, there was a significant improvement in FTM scores when the IPG was switched on compared with scores when the IPG was off and with baseline measurements. In addition, where reported, bilateral stimulation seemed more effective than unilateral surgery.[21,23]

DBS lead implantation can in the first instance be unilateral or bilateral, and for most of the included studies, it was bilateral. In a single study,[24] most patients had unilateral implantation initially, with all receiving eventual bilateral implantation. Unilateral outcomes were intermediate, and the full clinical response was gained from bilateral implantation. The average DBS on percentage change from the unilateral

TABLE 4. *Adverse events reported in 430 patients who received DBS*

Adverse event	N patients affected				
	With adverse event	Rate (%)	Reported as resolved	Reported as unresolved	No outcome provided
Severe					
Syncope	1	0.23	1	–	0
Stroke/hemiparesis	3	0.7	1	–	2
Dystonia	4	0.93	–	1	3
Movement associated					
Disequilibrium	17	3.95	–	–	17
Gait disorder	9	2.09	3	–	6
Incoordination	6	1.4	–	–	6
Paresis	13	3.02	1	–	12
Facial weakness	5	1.16	–	–	5
Dyspraxia	2	0.47	–	–	2
Asthenia	6	1.4	–	–	6
Hypertonia	1	0.23	–	–	1
Accidental injury	4	0.93	–	–	4
Bone fracture	5	1.16	2	–	3
Motor disturbance	3	0.7	–	–	3
Psychologic					
Depression	5	1.16	–	–	5
Anxiety	1	0.23	–	–	1
Abnormal thinking	4	0.93	–	–	4
Hallucinations	2	0.47	–	–	2
Other					
Headache	31	7.21	–	2	29
Dysarthria	38	8.84	2	–	36
Word finding difficulty	2	0.47	–	–	2
Attention/cognitive deficits	4	0.93	–	–	4
Hypophonia	5	1.16	–	–	5
Speech disorder	4	0.93	–	–	4
Nausea	5	1.16	–	–	5
Dizziness	3	0.7	–	–	3
Vomiting during programming	1	0.23	–	–	1
Choking	1	0.23	–	–	1
Increased salivation	2	0.47	–	–	2
Dysphagia	2	0.47	–	–	2
Insomnia	3	0.7	–	–	3
Somnolence	3	0.7	–	–	3
Paraesthesia	81	18.84	3	3	75
Diplopia	1	0.23	1	–	0
Pain	4	0.93	4	–	0
Hand-tingling during stimulation	3	0.7	–	–	3
Unsuccessful trial stimulation	1	0.23	–	1	0
Lead breakage	1	0.23	–	1	0
Electrode migration	1	0.23	1	–	0
Temporary erythema of the incision	1	0.23	1	–	0
Miscellaneous stimulation-related events (all minor events)	15	3.49	–	–	15
Total	303		20	8	275

to the various bilateral follow-up periods was 81% (range, 59–100%) and the average effect size estimate was 1.3 (range 0.77–1.95), representing a large effect size difference. However, absolute change was not reported.

Of the 10 studies that reported FTM outcomes for patients when DBS was switched on compared with off, six studies[16,20,22–25] reported activities of daily living (ADL) scores. All six studies reported that ADL scores improved after stimulation was switched on. Three studies also reported preoperative baseline ADL scores, and each reported an improvement from preoperative ADL scores to last follow-up.[22,24,25]

The remaining DBS on/off studies[17,27] did not use the FTM to assess patients. One study[17] used voice measures to measure the effectiveness of DBS for their patients, with the degree of improvement ranging from a 1- to a 3-point change on the severity scale and 24% to 60% difference in relative amplitude. One study[27] used surface electromyography and accelerometry to

TABLE 5. *DBS on/off FTM tremor rating scale*

Study ID	N	Preoperative score	Follow-up (mo) (mean)	Off (mean ± SD)	ON (mean ± SD)	Improvement
Studies that reported a preoperative baseline						
Koller et al.[18a]	38	Tremor Motor Score: 24.0 ± 7.0 Head Tremor Score: 2.7 ± 1.8	12	TMS: 24.0 ± 6.5 HTS: 2.2 ± 1.0	TMS: 15 ± 6 HTS: 1.2 ± 1.0	$P < 0.01$ compared with baseline for both TMS and HTS
Koller et al.[19a]	49	Tremor Motor Score: 20 ± 7.5	3, 12, and 40	3 mo: 20 ± 7.5 12 mo: 20 ± 7.5 40 mo: 15 ± 7	3 mo: 12 ± 5.5 12 mo: 12.5 ± 5.5 40 mo: 10 ± 5	$P < 0.001$ vs baseline at 3 mo, 12 mo, and 40 mo
Obwegeser et al.[21a,c]	27	Total contralateral arm tremor: 6.7 ± 2.3 Midline tremor: 5.3 ± 5.1	3	Total contralateral arm tremor: 5.5 ± 2.5 Midline tremor: 3.6 ± 3.5	Total contralateral arm tremor: 1.2 ± 2.2 Midline tremor: 1.8 ± 2.3	All scores significantly improved ($P < 0.05$ to $P < 0.01$) for off vs activated; on vs baseline and vs first surgery
Pahwa et al.[22]	9[d]	Motor scores: 20.8 ± 4.1 Postural and kinetic hand tremor side 1: 6.0 ± 0.7 Postural and kinetic hand tremor side 2: 5.6 ± 0.9	3	Motor scores: 23.6 ± 10.3 Side 1: 6.0 ± 2.5 Side 2: 5.2 ± 1.9	Motor scores: 7.3 ± 2.5 Side 1: 2.0 ± 1.0 Side 2: 2.0 ± 0	Motor scores 30.1% mean improvement Side 1: 66.7% mean improvement Side 2: 61.5% mean improvement
Pahwa et al.[23]	23	Combined groups: 23.9 ± 7.8	5 yr	Combined groups: 21.6 ± 6.7	Combined groups: 10.0 ± 4.9	Stimulation off or on vs baseline $P = 0.21$, stimulation off vs stimulation on $P < 0.01$
Putzke et al.[24a,e]	22	Ipsilateral UE Tremor: 6.4 (2.2) Contralateral: 6.75 ± 2.5 Midline: 5.9 ± 5.1	3 mo, 2 yr, 3 yr[f]	Ipsilateral UE 36 mo: 4.0(2.0) Contralateral 36 mo: 5.0 ± 1.3 Midline 24 mo: 2.8 ± 2	Ipsilateral UE 36 mo: 1.0 (0.7) Contralateral 36 mo: 0.2 ± 0.3 Midline 24 mo: 1.0 ± 1.2	All scores $P < 0.05$ for off vs baseline, on vs baseline and on vs off at 3 mo and 2 yr
Sydow et al.[25]	37	ETRS: 17.6 (7.5)	6 yr	ETRS: 19.4 (9.2)	ETRS: 10.4 (5.4)	$P < 0.001$ vs baseline; $P < 0.001$ vs off
Studies that did not report a preoperative baseline						
Bryant et al.[16]	23	NR	13 (4.5–22)	32.7	21.6	33.9%[b]
Lyons et al.[20]	22	NR	11 (3–30)	20.1 ± 6.7	12.2 ± 4.3	39.3% improvement, $P < 0.001$
Ushe et al.[26]	11	NR	NR	65.2 ± 12.7 (47–83)	24.4 ± 13.3 (4–44)	Mean 62.8 ± 19.8% reduction (range, 26.3–93%)

[a]Approximated from figures, not specified in text.

[b]High patient-clinician correlation of rs = 0.91 (Spearman rank order correlation), FTM scores were highly correlated with patient-rated TADLS (rs = 0.80 on, rs = 0.78 off) and clinician-rated TADLS (rs = 0.88 on, rs = 0.86 off).

[c]Contralateral, midline, and ipsilateral scores are provided for unilateral and bilateral stimulation.

[d]Performed in 8 of 9 patients using the motor subscale of the TRS.

[e]Some patients had two sets of surgery (one unilateral, one bilateral), and the authors provide data for unilateral patients at 1 and 3 mo. For consistency, the tables examine these same follow-up periods for bilateral (ie, 1 and 3 mo). Yr 3 is the furthest follow-up and has been included to ascertain the full clinical effect at long-term follow up.

[f]Mean duration between placement of the first and second lead = 223 d, most being undertaken ≤5 mo (n = 17, 77%) following initial surgery. Mean time between initial lead placement and last available follow-up= 29 mo.

FTM, Fahn-Tolosa-Marin scale; TMS, Total Motor Score; HTS, Head Tremor Score; UE, upper extremity; ETRS, Essential Tremor Rating Scale; NR, not reported; rs, Spearman rank order correlation; SD, standard deviation.

TABLE 6. *DBS before/after FTM tremor rating scale*

Study ID	N	Tremor rating score* (before DBS)	Mean follow-up (mo)	Tremor rating score* (after DBS)	Percent improvement	Statistical significance
Assessors were blinded						
Hariz et al.[29]	27	Total score: 57 ± 3.0[a]	12	30 ± 2.0	47.4	Statistically significant improvements ($P < 0.0001$)
Assessors either not blinded or not reported to be blinded						
Lee and Kondziolka.[31]	19	Action Score: 3.3 ± 0.5 Writing Score: 2.8 ± 0.9	27	Action: 0.8 ± 0.4 Writing: 1.0 ± 0.6	Action: 75.8 Writing: 64.3	Significant differences between pre- and postoperative scores for both action tremor and writing score ($P < 0.005$)
Murata et al.[32]	8	Mean total score: 21.4 ± 4.9[b]	22[c]	Mean total score: 7.4 ± 10.2[a]	65.4	Statistically significant improvements from before treatment to after treatment ($P < 0.01$)

*Mean ± standard deviation.
[a]Approximate data based on estimations from bar graphs in text.
[b]Raw data provided by authors when requested via e-mail.
[c]Median value.
DBS, deep brain stimulation; FTM, Fahn-Tolosa-Marin scale; N, total patient cohort.

assess patients. All patients had clinically reduced tremor and reported reductions in the amplitude of tremor, and for all values, tremor was decreased in favour of DBS on.

DBS Before/After

Five studies reported outcomes for patients before and after receiving DBS.[28–32] However, this systematic review only included effectiveness outcomes for three of these studies.[29,31,32] The two remaining before/after studies[28,30] did not indicate consecutive patient inclusion, and hence effectiveness outcomes were excluded as they may have been subject to significant bias. Only one of the three studies reported that outcome assessors were blinded.[29] The mean length of follow up ranged from 12.5[29] to 27 months.[31]

The FTM scale was used in each of the three studies (Table 6). Tremor scores significantly improved after DBS treatment with mean P values varying from $P < 0.01$ to $P < 0.0001$. A significant improvement was also found in the study that reported the longest patient follow-up (mean, 27 months; $P < 0.005$).[31]

One study[29] also used ADL to assess patients before and after receiving DBS. Of the 47 items on the ADL scale, eight items had significant improvements after DBS, and no items had significant deterioration after DBS. Unfortunately, because of the relatively short follow-up of patients, it is unclear whether these outcomes would persist in the longer term.

DISCUSSION

Depending on the specific indication, patients with essential tremor can receive numerous medications in treatment of the disorder; however, these treatments have limited success and can become ineffective over time. For medication-refractory patients, alternative treatment is limited to thalamotomy or DBS.

Many issues were identified during the completion of this systematic review. The quality of the available evidence was very limited. In the absence of high quality evidence, case series and case reports were used to assess the safety and effectiveness of DBS, which may introduce bias and limit the generalizability of the results. Further bias may have been introduced into this systematic review as appropriate effectiveness scales were not identified a priori.

Although several included studies had followed up patients for 3 years or more, none reported on replacement of the IPG or battery. Replacement of either component requires a further surgical procedure, performed under general anesthesia. Although none of the included studies reported on the length of battery life, additional literature suggests that battery replacement may be required at ~3.9 years, although this may vary according to the condition which the DBS aims to treat.[33]

There was a great variety in the manner in which studies reported the use of DBS for movement disorders. Some studies reported outcomes pre- and postintervention, whereas others reported outcomes of stimu-

lation compared with no stimulation. In this systematic review, where possible, clinically relevant conditions and outcomes were reported separately.

It is unclear whether or not the beneficial effect of DBS for essential tremor changes over time. Three studies following up patients for 3 years or more found significant improvements in FTM when DBS was switched on compared with off. The remaining studies included relatively short patient follow-up, and all included studies had small patient numbers.

None of the included studies reported on quality of life outcomes for patients receiving DBS. As such, this systematic review cannot inform on the impact of DBS on the patient, such as the ordeal of the surgery and frequency of hospital visitations.

There were numerous issues surrounding the nature of the conditions investigated. Patients with essential tremor generally experience a low rate of mortality but a high level of morbidity and decreased quality of life. Essential tremor may also represent an economic burden on the welfare and hospital systems.

CONCLUSION

Based on Level IV evidence, it appears that DBS may be a safe and effective therapy for essential tremor. However, the included studies in this review only reported short-term safety outcomes. Further comparative studies and randomized controlled trials will enable more confident assessments of the safety and efficacy of DBS to be made; however, it is unlikely that these will become available. DBS should be considered an invasive procedure, which will not be chosen lightly by patients. Most patients will endure symptoms until they have significant impairment in quality of life (i.e., unable to independently feed or go to toilet) and, at this point, will have failed all alternative treatments.

The potential for treatment with DBS should be assessed on a case-by-case basis. An expert committee comprising a movement disorder surgeon and a neurologist can assess the extent of disability and the likelihood of benefit. This will ensure that the procedure is warranted, may provide an estimate of potential benefit to the patient, and determine any comorbidities that may reduce the effectiveness of the DBS.

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Author Roles: Eliana Della Flora: research project organization, research project execution, statistical analysis design, statistical analysis execution, statistical analysis review and critique, review and critique of the manuscript; Caryn Perera: research project execution, statistical analysis review and critique, writing of the first draft of the manuscript; Alun Cameron: research project design, research project execution, statistical analysis review and critique, review and critique of the manuscript; and Guy Maddern: research project conception, statistical analysis review and critique, review and critique of the manuscript.

REFERENCES

1. Louis ED. Essential tremor. Lancet Neurol 2005;4:100–110.
2. Rincon F, Louis ED. Benefits and risks of pharmacological and surgical treatments for essential tremor, disease mechanisms and current management. Expert Opin Drug Saf 2005;4:899–913.
3. Louis ED. A new twist for stopping the shakes? Revisiting GABAergic therapy for essential tremor. Arch Neurol 1999; 56:807–808.
4. Zesiewicz T, Elble R, Louis ED, et al. Practice parameter, therapies for essential tremor. Report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2005;64:2008–2020.
5. Louis ED. Essential tremor. Clin Geriatr Med 2006;22:843–857.
6. Louis ED. Clinical practice. Essential tremor. N Engl J Med 2001;345:887–891.
7. Kondziolka D, Ong JG, Lee JYK, Moore, RY, Flickinger JC, Lunsford LD. A gamma knife thalamotomy for essential tremor, J Neurosurg 2008;108:111–117
8. Pahwa R, Lyons KE. Essential tremor, differential diagnosis and current therapy. Am J Med 2003;115:134–142.
9. Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C, Yamamoto T. Difference in surgical strategies between thalamotomy and thalamic deep brain stimulation for tremor control. J Neurol 2005;252:IV17–IV22.
10. Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Eng J Med 2000;342:461–468.
11. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991;337:403–406.
12. Putzke JD, Uitti RJ, Obwegeser AA, Wszolek ZK, Wharen RE. Bilateral thalamic deep brain stimulation: midline tremor control. J Neurol Neurosurg Psych 2005;76:684–690.
13. Plaha P, Patel NJ, Gill SS. Stimulation of the subthalamic region for essential tremor. J Neurosurg 2004;101:48–54.
14. Medical Services Advisory Committee. Deep brain stimulation for dystonia and essential tremor. MSAC Application 1109. Canberra, Australia: MSAC; 2008.
15. NHMRC. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra, Australia: National Health and Medical Research Council; 1999.

16. Bryant JA, De Salles A, Cabatan C, Frysinger R, Behnke E, Bronstein J. The impact of thalamic stimulation on activities of daily living for essential tremor. Surg Neurol 2003;59:479–484.
17. Carpenter MA, Pahwa R, Miyawaki KL, Wilkinson SB, Searl JP, Koller WC. Reduction in voice tremor under thalamic stimulation. Neurology 1998;50:796–798.
18. Koller WC, Lyons KE, Wilkinson SB, Pahwa R. Efficacy of unilateral deep brain stimulation of the VIM nucleus of the thalamus for essential head tremor. Mov Disord 1999;14:847–850.
19. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 2001;16: 464–468.
20. Lyons KE, Pahwa R, Busenbark KL, Tröster AI, Wilkinson S, Koller WC. Improvements in daily functioning after deep brain stimulation of the thalamus for intractable tremor. Mov Disord 1998;13:690–692.
21. Obwegeser AA, Uitti RJ, Turk MF, Strongosky AJ, Wharen RE. Thalamic stimulation for the treatment of midline tremors in essential tremor patients. Neurology 2000;54:2342–2344.
22. Pahwa R, Lyons KL, Wilkinson SB, et al. Bilateral thalamic stimulation for the treatment of essential tremor. Neurology 1999;53:1447–1450.
23. Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. J Neurosurg 2006;104:506–512.
24. Putzke JD, Wharen RE Jr, Obwegeser AA, et al. Thalamic deep brain stimulation for essential tremor, recommendations for long-term outcome analysis. Can J Neurol Sci 2004;31:333–342.
25. Sydow O, Thobois S, Alesch F, Speelman JD. Multicentre European study of thalamic stimulation in essential tremor. A six year follow up. J Neurol Neurosurg Psychiatry 2003;74:1387–1391.
26. Ushe M, Mink JW, Tabbal SD, et al. Postural tremor suppression is dependent on thalamic stimulation frequency. Mov Disord 2006;21:1290–1292.
27. Vaillancourt DE, Sturman MM, Verhagen Metman L, Bakay RA, Corcos DM. Deep brain stimulation of the VIM thalamic nucleus modifies several features of essential tremor. Neurology 2003;61: 919–925.
28. Fields JA, Troster AI, Woods SP, et al. Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor. J Neurol Neurosurg Psychiatry 2003;74:305–311.
29. Hariz GM, Lindberg M, Bergenheim AT. Impact of thalamic deep brain stimulation on disability and health-related quality of life in patients with essential tremor. J Neurol Neurosurg Psychiatry 2002;72:47–52.
30. Troster AI, Fields JA, Pahwa R, et al. Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. Neurology; 199953:1774–1780.
31. Lee JY, Kondziolka D. Thalamic deep brain stimulation for management of essential tremor. J Neurosurg 2005;103:400–403.
32. Murata J, Kitagawa M, Uesugi H, et al. Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. J Neurosurg 2003;99:708–715.
33. Bin-Mahfoodh M, Hamani C, Sime E, et al. Longevity of batteries in internal pulse generators used for deep brain stimulation. Stereotact Funct Neurosurg 2003;80:56–60.

NICE National Institute for Health and Care Excellence

NICE guidance

Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease)

Interventional procedures guidance
Published: 23 August 2006

www.nice.org.uk/guidance/ipg188

1 Guidance

1.1 Current evidence on the safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance.

1.2 Patient selection and management should be carried out in the context of a multidisciplinary team specialising in the long-term care of patients with movement disorders.

2 The procedure

2.1 Indications

2.1.1 Tremor and dystonia are symptoms arising from a number of different neurological diseases, including essential tremor, multiple sclerosis and primary generalised dystonia. Tremor and dystonia associated with Parkinson's disease are not covered by this guidance.

2.1.2 Tremor is an involuntary rhythmic repetitive movement, most frequently affecting the upper limbs. It can occur at rest or can be brought on (or exacerbated) by posture or intentional movement. Severe tremor can be disabling because it affects fine-movement coordination.

2.1.3 Dystonia is the simultaneous uncoordinated contraction of opposing antagonistic muscles. It may be limited to a particular group of muscles, or it may be generalised.

2.1.4 Tremor can be treated by rehabilitation and drug therapy, and early appropriate treatment may minimise functional disability. Anti-tremor drugs reduce the amplitude but not the frequency of tremor, and this does not always translate into functional improvement. Surgery, which often involves ablation of the thalamic nucleus, is usually reserved for patients with severe disabling tremor and functional disability that interferes with activities of daily living, and for tremor that is refractory to the highest tolerated doses of medication.

2.1.5 Dystonia can be treated conservatively or surgically. Currently available conservative management options for dystonia improve the symptoms but do not cure the underlying neurological disorder. The severity of dystonia may progress over time as part of the underlying neurological condition. Surgical options include thalamotomy and pallidotomy; however, benefits may not be maintained in the long term.

2.2 Outline of the procedure

2.2.1 Deep brain stimulation can be carried out on structures within the brain

that are responsible for modifying movements, such as the thalamus, the globus pallidus and the subthalamic nucleus, which interact functionally with the substantia negra (nigra). These structures are all bilateral, and surgery can be performed on one or both sides. The function of these brain nuclei is altered during deep brain stimulation through the application of an electrical current.

2.2.2 The procedure involves inserting fine needles into the brain through small holes in the skull under imaging guidance, to determine the exact position of the targeted nucleus, which may be different in each patient. One or more permanent electrodes are subsequently placed into this nucleus. Wires are tunnelled subcutaneously to the anterior chest wall, where they are connected to an implanted pulse generator. Local or general anaesthetic may be used in this procedure.

2.2.3 Further operations may be required for replacement of the pulse generator.

2.3 Efficacy

2.3.1 A case–control series found that, in up to 27 months' follow-up, total tremor score improved in 17 patients treated with deep brain stimulation, but there was no significant improvement in most other efficacy outcomes. A case series of 52 patients with essential tremor who underwent deep brain stimulation reported a significant improvement in activities of daily living at 3 months' follow-up, with scores improving from 17.8 points to 6.5 points ($p < 0.001$). Another case series of 19 patients found that deep brain stimulation produced an improvement in tremor score (Fahn–Tolosa–Marin scale) from 3.3 points at baseline to 0.8 points at 27 months' follow-up ($p < 0.005$).

2.3.2 A case series of 22 patients with dystonia who underwent deep brain stimulation reported that the total score on the Burke–Fahn–Marsden dystonia rating scale improved significantly from a mean of 46.3 points at baseline to 24.3 points at 3 months' follow-up. This improvement was maintained to 12 months' follow-up, with a score of 21.0 points ($p < 0.001$ for both comparisons with baseline). Similarly, global disability score improved from 11.6 points at baseline to 7.6 points at 3 months' follow-up

and 6.5 points at 12 months' follow-up ($p < 0.001$).

2.3.3 Very few data are available on the use of deep brain stimulation for tremor in multiple sclerosis. Three case series reported significant improvements in tremor secondary to multiple sclerosis at 12–22 months; however, two of these studies found that improvements in tremor did not necessarily correlate with improvements in functional ability. For more details, refer to the 'Sources of evidence' section.

2.3.4 The Specialist Advisers noted that there are concerns about the long-term efficacy of the procedure, because tremor may become resistant to stimulation.

2.4 Safety

2.4.1 One case series reported that the pulse generator failed in 50% (6/12) of patients. Across three case series where it was reported as an outcome, displacement of the stimulating electrode occurred in 6% (1/18), 8% (1/12) and 15% (8/52) of patients. The incidence of lead fracture or failure in three studies was 4% (2/52), 5% (1/22) and 6% (1/18). These complications sometimes required further surgery.

2.4.2 One case series of 22 patients who underwent deep brain stimulation for dystonia reported transient oedema of the frontal lobe, cutaneous necrosis of the scalp, localised skin infection and haematoma near the neurostimulator, in one patient each. However, none of these events had permanent sequelae. For more details, refer to the 'Sources of evidence' section.

2.4.3 The Specialist Advisers noted that adverse events relating to this procedure include infection, haemorrhage (possibly causing hemiparesis), hardware failure, dysarthia, speech disturbance, cerebral oedema and death. They also noted that theoretical complications include stroke, speech impairment, cognitive impairment, depression, suicide and risk of injury during subsequent magnetic resonance imaging.

2.5 Other comments

2.5.1 There are variations in the technique of deep brain stimulation. In addition, the procedure may be used concurrently or sequentially with other surgery or drug therapies. Different rehabilitation methods may also have an effect on outcome.

2.5.2 Further information on the long-term effects of this procedure in patients undergoing surgery at a young age would be useful.

3 Further information

3.1 The Institute has published interventional procedures guidance on deep brain stimulation for Parkinson's disease and a clinical guideline on Parkinson's disease.

Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the following document.

'Interventional procedure overview of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease)', February 2006.

Information for patients

NICE has produced information on this procedure for patients and carers. It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

4 About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is

for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedure guidance process.

We have produced a summary of this guidance for patients and carers. Information about the evidence it is based on is also available.

Changes since publication

19 January 2012: minor maintenance.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

SPECIAL ARTICLE

Evidence-based guideline update: Treatment of essential tremor

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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ABSTRACT

Background: This evidence-based guideline is an update of the 2005 American Academy of Neurology practice parameter on the treatment of essential tremor (ET).

Methods: A literature review using MEDLINE, EMBASE, Science Citation Index, and CINAHL was performed to identify clinical trials in patients with ET published between 2004 and April 2010.

Results and Recommendations: Conclusions and recommendations for the use of propranolol, primidone (Level A, established as effective); alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective); nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation, thalamotomy (Level C, possibly effective); and gamma knife thalamotomy (Level U, insufficient evidence) are unchanged from the previous guideline. Changes to conclusions and recommendations from the previous guideline include the following: 1) levetiracetam and 3,4-diaminopyridine probably do not reduce limb tremor in ET and should not be considered (Level B); 2) flunarizine possibly has no effect in treating limb tremor in ET and may not be considered (Level C); and 3) there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozapine as treatment for ET (Level U). *Neurology*® 2011;77:1752–1755

GLOSSARY

AAN = American Academy of Neurology; **DBS** = deep brain stimulation; **ET** = essential tremor; **FTM** = Fahn-Tolosa-Marin; **TRS** = Tremor Rating Scale.

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Supplemental data at www.neurology.org

Supplemental Data

Podcast

CME

Essential tremor (ET) is the most common tremor disorder and often affects activities of daily living, including writing and eating.[1] The head and voice are commonly affected. Diagnostic criteria for ET may be found in the Consensus Statement of the Movement Disorder Society on Tremor.[2]

Propranolol and primidone are the medications used most frequently and successfully to treat ET, and propranolol is the only medication approved by the US Food and Drug Administration to treat ET. Unfortunately, 30% to 50% of patients will not respond to either primidone or propranolol.[3] This evidence-based guideline is an update of the American Academy of Neurology (AAN) 2005 practice parameter regarding treatment of ET[4] and includes relevant research published since the 2005 publication.

DESCRIPTION OF THE ANALYTIC PROCESS

The AAN invited neurologists with expertise in ET to perform the review. Computer-assisted literature searches were conducted for relevant English-language articles pertinent to the treatment of ET. The MEDLINE, EMBASE, Science Citation Index, and CINAHL databases were searched from the years 2004 to 2010. Appendix e-1 on the *Neurology*® Web site at www.neurology.org lists the key words and phrases used in the search.

The search identified 589 articles pertaining to the treatment of ET, the titles and abstracts of which were each reviewed by at least 2 committee members. Articles were accepted for further review if they consisted of controlled trials, observational studies, cohort studies, open-label studies, or case series. Of the

From the University of South Florida (T.A.Z., K.L.S.), Tampa; Department of Neurology (R.J.E.), Southern Illinois University School of Medicine, Springfield; Neurological Institute (E.D.L.), Columbia University, New York, NY; University of Kansas (G.S.G.), Kansas City; Department of Neurology (W.G.O.), Baylor College of Medicine, Houston, TX; University of Texas Southwestern Medical School (R.B.D.), Dallas; Departments of Neurology and Neurosurgery (M.S.O.), Movement Disorders Center, University of Florida, Gainesville; and University of Maryland School of Medicine (W.J.W.), Baltimore.

Study funding: This evidence-based guideline was funded by the American Academy of Neurology. No author received honoraria or financial support to develop this document.

Approved by the Quality Standards Subcommittee on November 13, 2010; by the Practice Committee on May 23, 2011; and by the AAN Board of Directors on August 13, 2011.

Disclosure: Author disclosures are provided at the end of the article.

Table e-2: Surgical conclusions and recommendations

Recommendations for use	Treatment
Level C – effectively treats contralateral limb tremor in ET that is refractory to medication management	Unilateral thalamotomy DBS of the VIM of the thalamus[23–27]
Level U – insufficient evidence to support or refute efficacy in treating ET	Superiority of DBS or thalamotomy for the treatment of ET Relative advantages and disadvantages of unilateral vs bilateral DBS in the treatment of limb tremor Direct subthalamic stimulation and/or zona incerta/prelemniscal stimulation Gamma knife thalamotomy

DBS = deep brain stimulation, VIM = ventral intermediate nucleus.

X-ray Motion Analysis for Back Pain

Plain Language Summary:

Coverage question: Should OHP cover a certain x-ray to see how the spine moves as a person bends or twists?

Should OHP cover this treatment? No, this test has not been studied enough to show it is helpful for choosing the best treatment for a person's spine problem.

Changes to issue summary after public comment period:

No public comment was received on this topic. This document contains no changes from the version released with the early VBBS/HERC packet.

Coverage Question: Should x-ray motion analysis of the spine be a covered service?

Question source: Bhavesh Rajani, CCO medical director

Background:

Dynamic spinal visualization is a way to see how the spine moves as a person bends or twists. It is thought that looking at moving images could help a healthcare professional diagnose the cause of neck or back pain or other problems with the spine. There are several different ways to create moving images as the spine twists or turns. Most techniques use x-ray to create images on film, a video monitor, or computer screen. Several x-rays are taken, assembled in order, and then played to create a moving image. Other technologies use fluoroscopy and magnetic resonance imaging

Dr. Rajani has been getting requests for x-ray motion analysis from several chiropractic offices, using a generic CPT code for unlisted radiologic procedures.

Previous HSC/HERC reviews:

No previous review has been conducted of x-ray motion analysis of the spine

Current Prioritized List/Coverage status:

CPT code	Code description	Current list/line(s)
0693 T	Comprehensive full body computer-based markerless 3D kinematic and kinetic motion analysis and report	Never reviewed—temporary CPT code
96000	Test to evaluate gait using 3D, video, and computer technology	654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE

		UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
96001	Test to evaluate gait using 3D, video, and computer technology with measurement of foot pressure distribution	654
96004	Physician review of gait analysis test	654
95851	Measurement of range of motion in arm, leg or each spine section	DIAGNOSTIC PROCEDURES
72110-72120	Xray lumbar spine	DIAGNOSTIC PROCEDURES
76499	Other diagnostic imaging procedure	DIAGNOSTIC PROCEDURES

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 654

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
96000-96004	Comprehensive computer-based motion analysis by video-taping and 3D kinematics Dynamic surface electromyography	Insufficient evidence of effectiveness	March 2022

Evidence:

1) **Wang 2022**, systematic review of diagnosing lumbar segmental instability
    a. N=39 articles
    b. The execution of dynamic X-rays (DXR) in flexion and extension is the most commonly used in clinical practice and widely recognized as an effective method to detect the presence of lumbar segmental instability (LSI). The range of segmental vertebral mobility is relatively wide, it is widely be accepted by many authors that sagittal translation of segmental vertebral ≥4mm or ≥8% and a sagittal rotation ≥10° in L1 to L5 and ≥20° in L5 to S1 are pathological for LSI. Patient can evocate a greater segmental slip in the standing position compared to the recumbent position, so it may not reflect the degree of LSI sensitively and accurately. At the same time, its clinical significance is still controversial and there is not a unanimous consensus on this technique.
    c. Overall, there have been a variety of researches to develop the diagnosing methodology for LSI, and many have been successful, although no consensus has been reached yet.
2) **Papi 2018**, systematic review of kinetic measures in low back pain
    a. N=62 articles

        i. Generally small sample sizes
        ii. Common biases identified were lack of assessor blinding and sample size calculation, use of samples of convenience, and poor experimental protocol standardization.
    b. Based on the studies included within this review, no conclusive statements can be drawn regarding what kinematic and/or kinetic measures should be used to assess LBP
    c. Interpretation: The literature to date offers limited and inconsistent evidence of kinematic/kinetic measures in low back pain patients that could be used clinically
3) **Negrini 2016**, systematic review of trunk motional analysis
    a. N=45 studies
        i. All studies were quite small, including 1 to 113 participants
    b. The results of these few studies are difficult to summarize, since the differences are so high in terms of methodology and sample studied
    c. This study has shown that the literature on trunk motion analysis today is relative scarce
    d. The use of optoelectronic systems in the evaluation of spine movement is a growing research area. Nevertheless, no standard protocols have been developed so far, making its clinical application hard at present time. Future research is needed with the aim of defining a precise protocol in terms of number and position of markers along the spine and movements and tasks to be evaluated

Expert guidelines:

1) **NICE 2016**, Low back pain and sciatica in over 16s: assessment and management
    a. Do not routinely offer imaging in a non-specialist setting for people with low back pain with or without sciatica
2) **Chou 2011**, American College of Physicians clinical guideline for diagnostic imaging of low back pain
    a. Kinetic analysis not mentioned
    b. Immediate imaging (standard 2 or 3 view xray) is recommended in patients with acute low back pain who have major risk factors for cancer, risk factors for spinal infection, risk factors for or signs of the cauda equina syndrome, or severe or progressive neurologic deficits
    c. Imaging after a trial of therapy is recommended in patients with minor risk factors for cancer, risk factors for inflammatory back disease, risk factors for vertebral compression fracture, signs or symptoms of radiculopathy, or risk factors for or symptoms of symptomatic spinal stenosis
    d. Repeated imaging is only recommended in patients with new or changed low back symptoms
    e. Routine imaging does not improve clinical outcomes but increases costs and may lead to potentially unnecessary invasive treatments, such as surgery
    f. Imaging abnormalities are extremely common, especially in older adults, but most are poorly correlated with symptoms In most cases, treatment plans do not change after imaging studies
    g. Back imaging is associated with radiation exposure, which can increase the risk for cancer in the case of lumbar radiography and computed tomography

X-ray Motion Analysis for Back Pain

Other payer policies:

1) Aetna 2023: The following procedures are considered experimental and investigational because the effectiveness of these approaches has not been established:
    a. Computerized motion diagnostic imaging for evaluation of the spine or any other indications
    b. DARI scan (functional motion analysis)
    c. Vertebral motion analysis for evaluation of the spine or any other indications.
2) Premara BCBS 2023
    a. The following dynamic spinal visualization techniques are considered investigational, including, but not limited to:
        i. Digital motion x-ray of the spine
        ii. Cineradiography/videofluoroscopy
        iii. Dynamic magnetic resonance imaging
3) United Healthcare 2023
    a. The following dynamic spinal visualization techniques when used to visualize movement of the back or spine are unproven and not medically necessary due to insufficient evidence of efficacy
        i. Digital motion x-ray of the spine
        ii. Cineradiography/videofluoroscopy
    b. ECRI (2023) performed a clinical evidence assessment for Dynamic Spinal Visualization for assessing Lumbar Spine Abnormalities. They concluded that evidence from one cohort study and two diagnostic cohorts on dynamic MRIs compared with flexion/extension radiography provide no evidence that dynamic spinal visualization improves patient outcomes or diagnoses for patients with lumbar spine abnormalities. The studies suggests that dynamic spinal visualization may identify lumbar abnormalities; however, too few data exist per dynamic visualization technique, and the studies are of too low quality to provide conclusive evidence

Expert input:

Lisa Kouzes, DC

To my knowledge there are no established normative values and no evidence it is superior to flexion/extension or lateral flexion films, such as in a 7-view Davis series for the cervical spine; for which CPT Codes are already established.

Clinical guidelines and diagnostic criteria for instability are based on static views of end range motion, not an assessment of movement between neutral and end range.

I could see this technology being utilized as fluoroscopy during a surgical procedure or intervention, but not as diagnostic imaging, as it offers no cost-effective advantage over plain films.

HERC staff summary: Xray motion analysis of the spine has been poorly studied. Several recent systematic reviews found only small studies, and no standard protocol exists. Such testing has not been shown to have a health impact. NICE and the ACP do not recommend even routine standard x-rays for

low back pain without risk factors for cancer, ankylosing spondylitis or vertebral compression fracture. Major insurers consider this type of testing to be experimental.

HERC staff recommend adding a diagnostic guideline that specifies that x-ray motional analysis is not a covered diagnostic service.

HERC staff recommendation:

1) Adopt a new diagnostic guideline as shown below

DIAGNOSTIC GUIDELINE DX X-RAY MOTION ANALYSIS OF THE SPINE
X-ray motion analysis, kinematic analysis or similar testing of the spine is not a covered diagnostic service.

Systematic Review and Meta-Analysis

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Research progress of diagnosing methodology for lumbar segmental instability

A narrative review

Yingfeng Wang, DO, MD[b], Kai Huang, DO, MD[a,*]

Abstract

Objective: Lumbar segmental instability (LSI) is due to a pathologic movement of the vertebral body on the vertebra below and often causes clinical symptoms. The study was to achieve the research progress of diagnosing methodology for lumbar segmental instability and help clinicians make treatment choices.

Methods: The data for this study were collected from the MEDLINE, Springer, Web of Science, PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, Evidence Based Medicine Reviews, VIP, and CNKI. The search terms were integrated as follows: "(*lumbar instability* OR *lumbar spondylolisthesis*) and (*image* or *diagnosis*)". Studies without clear radiographic instable criteria, case reports, letter, and basic research were excluded.

Result: In total, 39 articles published met our inclusion criteria. The various modalities were used to diagnosis LSI in these studies included radiographs, facet joint degeneration and physical examination tests.

Conclusion: Overall, there have been a variety of researches to develop the diagnosing methodology for LSI, and many have been successful, although no consensus has been reached yet. However, it is believed that the diagnosis of LSI will become easier and more accurate in the near future.

Abbreviations: DXR = dynamic X-rays, F/E = flexion-extension, LSI = lumbar segmental instability.

Keywords: diagnosing methodology, literature review, lumbar segmental instability, research progress

1. Introduction

Lumbar segmental instability (LSI) is due to a pathologic movement of the vertebral body on the vertebra below and often causes clinical symptoms. Spondylolisthesis is a main factor causing low back pain. The topic of chronic instability of the lumbar spine is subject to much debate as to the exact nature of the problem, the correlation with symptoms, or the relevance to patient management.[1–4] Some authors refer to the concept of instability also considering the so-called "clinical" or "functional" instability, in which no defect of the body architecture of the lumbar spine, and no excessive detectable translation or rotation are shown. So, we consider that lumbar instability is an evolving and challenging concept.[4–9]

Previous reviews separately investigated the diagnostic accuracy or the reliability of the instability tests, but a complete vision about their diagnostic validity to detect lumbar instability is lacking. The objective of this literature review is to achieve the research progress of diagnosing methodology for lumbar segmental instability and help clinicians make treatment choices.

2. Materials and methods

2.1. Search criteria

We conducted a comprehensive computerized literature search through multiple electronic databases without date limits up until August, 2020 by using combinations of key search terms. MEDLINE, Springer, Web of Science, PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, Evidence Based Medicine Reviews, VIP, and CNKI were searched for any potential studies. The search terms were integrated as follows: "(*lumbar instability* OR *lumbar spondylolisthesis*) and (*image* or *diagnosis*)". This is a review that does not require an ethics committee review board approval and informed consent.

2.2. Inclusion and exclusion criteria

Articles for potential selection were screened using inclusion and exclusion criteria. Inclusion criteria include studies published in

Editor: Gopal Nambi.

The manuscript submitted does not contain information about medical device(s)/drug(s). No funds were received in support of this work. No relevant financial activities outside the submitted work. This is a review that does not require an ethics committee review board approval and informed consent.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Review

Is there evidence to use kinematic/kinetic measures clinically in low back pain patients? A systematic review

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ARTICLE INFO

Keywords:
Low back pain
Movement
Functional assessment
Motion analysis
Objective measure

ABSTRACT

Background: Currently, there is a widespread reliance on self-reported questionnaires to assess low back pain patients. However, it has been suggested that objective measures of low back pain patients' functional status should be used to aid clinical assessment. The aim of this study is to systematically review which kinematic /kinetic parameters have been used to assess low back pain patients against healthy controls and to propose clinical kinematic/kinetic measures.

Methods: PubMed, Embase and Scopus databases were searched for relevant studies. Reference lists of selected studies and hand searches were performed. Studies had to compare people with and without non-specific low back pain while performing functional tasks and report body segment/joint kinematic and/or kinetic data. Two reviewers independently identified relevant papers.

Findings: Sixty-two studies were included. Common biases identified were lack of assessor blinding and sample size calculation, use of samples of convenience, and poor experimental protocol standardization. Studies had small sample sizes. Range of motion maneuvers were the main task performed (33/62). Kinematic/kinetic data of different individual or combination of body segments/joints were reported among the studies, commonest was to assess the hip joint and lumbar segment motion (13/62). Only one study described full body movement. The most commonly reported outcome was range of motion. Statistically significant differences between controls and low back pain groups were reported for different outcomes among the studies. Moreover, when the same outcome was reported disagreements were noted.

Interpretation: The literature to date offers limited and inconsistent evidence of kinematic/kinetic measures in low back pain patients that could be used clinically.

1. Introduction

Treatment for low back pain (LBP) aims to restore normal movement function and relieve pain. Measurements of movement function and measures of pain reduction, should, therefore, be the focus of LBP evaluation (Newman et al., 1996). This review is focused on measures of movement function. Movement analysis, allowing quantification of human movement, provides a means to objectify impairments from which clinical decisions can be made (Andriacchi and Alexander, 2000). However, clinical assessment of LBP relies predominately on self-reported questionnaires and scores, which depend on the patients' perception of their pain and functional capacity (Smeets et al., 2011). In many cases of LBP, the origin of pain cannot be identified, with diagnosis occurring in only 5–10% of cases (Krismer and van Tulder, 2007). This relates to the multifactorial and complex nature of LBP. Psychosocial factors, such as fear avoidance, dissatisfaction at work and pain beliefs as well as mechanical factors due to daily movement contribute to LBP development and occurrence (Clays et al., 2007). The interaction among these factors makes non-specific LBP difficult to classify and leaves clinicians facing significant challenges during its evaluation and management with consequences on patients' recovery. Imaging techniques, such as X-rays, computed tomography and magnetic resonance imaging, are employed in clinical practice but do not increase clinicians' ability to assess function and provide few if any indicators on how to manage non-specific LBP (Newman et al., 1996). Conversely, the ability to objectively assess the extent of movement impairments due to LBP has the potential to aid clinical assessment and, combined with psychosocial intervention, may provide important treatment targets.

The use of objective measures of LBP patients' movement function, alongside self-reported questionnaires, has been recently encouraged (Sanchez-Zuriaga et al., 2011; Smeets et al., 2011), yet definition of functional motion and what should be measured is lacking. Lumbar

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SYSTEMATIC REVIEW
MOTION ANALYSIS

Trunk motion analysis: a systematic review from a clinical and methodological perspective

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ABSTRACT

INTRODUCTION: This systematic literature review aims to check the current state of affairs of non-gait-related optoelectronic trunk movement analysis; results have been analyzed from a clinical and a methodological perspective.
EVIDENCE ACQUISITION: Extensive research was performed on all papers published until December 31st, 2015, dealing with trunk movement analysis assessed by optoelectronic systems, excluding those related to gait. The research was performed on the 14th of January 2016 on three databases: Scopus, Science Direct and Pubmed. A reference search and expert consultation were also performed.
EVIDENCE SYNTHESIS: Out of a total number of 8431 papers, 45 were deemed relevant: they included 1334 participants, 57.9% healthy, with age range 8-85. Few studies considered the whole trunk, and none focused on each vertebra independently: the trunk was almost always divided into three segments. Thirteen studies included 20 or more markers. Most of the papers focused mainly on the biomechanics of various movements; the lumbar area and low back pain were the most studied region and pathology respectively.
CONCLUSIONS: This study has shown the relative scarcity of current literature focusing on trunk motion analysis. In clinical terms, results were sparse. The only quite well represented group of papers focused on the lumbar spine and pathologies, but the scarcity of individuals evaluated make the results questionable. The use of optoelectronic systems in the evaluation of spine movement is a growing research area. Nevertheless, no standard protocols have been developed so far. Future research is needed to define a precise protocol in terms of number and position of markers along the spine and movements and tasks to be evaluated.

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Key words: Spine - Motion - Torso.

Introduction

Motion analysis has developed greatly during the last 30 years, focusing mainly on gait. There are several reasons for this; the quite standard activity of walking, for example, but also the importance of gait impairment in neurological and orthopedic diseases both in adults and children. The development of movement essentially in the sagittal plane has allowed the development of standard protocols.[1] As regards the upper limbs, there are many more difficulties in the way of defining a standard for motion analysis, the result mainly of the different tasks and functions of this body segment.[2] Trunk activity can be considered more similar to the upper than the lower extremities in terms of complexity. Trunk movements play an important role in many human activities, contributing to the movement of the whole body:[3-5] in fact the trunk offers stability to the limbs, allowing them to operate properly.[6] For these reasons, the trunk has been studied in relation to

NICE National Institute for Health and Care Excellence

NICE guideline

Low back pain and sciatica in over 16s: assessment and management

NICE guideline
Published: 30 November 2016
www.nice.org.uk/guidance/ng59

Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guideline replaces CG88.

This guideline is the basis of QS155.

Overview

This guideline covers assessing and managing low back pain and sciatica in people aged 16 and over. It outlines physical, psychological, pharmacological and surgical treatments to help people manage their low back pain and sciatica in their daily life. The guideline aims to improve people's quality of life by promoting the most effective forms of care for low back pain and sciatica.

The recommendations in this guideline were developed before the COVID-19 pandemic.

For advice on neuropathic pain not related to sciatica, see the NICE guideline on neuropathic pain in adults.

In **December 2020**, we reviewed our guidance on opioids for non-cancer pain in response to a Public Health England evidence review on dependence on, and withdrawal from, prescribed medicines. To support discussion with patients about opioid prescribing, and safe withdrawal management, we are developing guidance on safe prescribing and withdrawal management of prescribed drugs associated with dependence and withdrawal and shared decision making. In the meantime, we have added links in this guideline to other NICE guidelines and other resources that support this aim.

Who is it for?

- Healthcare professionals
- Commissioners and providers of healthcare
- People with low back pain or sciatica, and their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Assessment of low back pain and sciatica

Alternative diagnoses

1.1.1 Think about alternative diagnoses when examining or reviewing people with low back pain, particularly if they develop new or changed symptoms. Exclude specific causes of low back pain, for example, cancer, infection, trauma or inflammatory disease such as spondyloarthritis. If serious underlying pathology is suspected, refer to relevant NICE guidance on:

- metastatic spinal cord compression in adults
- spinal injury
- spondyloarthritis in over 16s
- suspected cancer. [2016]

Risk assessment and risk stratification tools

1.1.2 Consider using risk stratification (for example, the STarT Back risk assessment tool) at first point of contact with a healthcare professional for each new episode of low back pain with or without sciatica to inform shared decision-making about stratified management. [2016]

1.1.3 Based on risk stratification, consider:

- simpler and less intensive support for people with low back pain with or without sciatica likely to improve quickly and have a good outcome (for example, reassurance, advice to keep active and guidance on self-management)
- more complex and intensive support for people with low back pain with or without sciatica at higher risk of a poor outcome (for example, exercise programmes with or without manual therapy or using a psychological approach). [2016]

Imaging

1.1.4 Do not routinely offer imaging in a non-specialist setting for people with low back pain with or without sciatica. [2016]

1.1.5 Explain to people with low back pain with or without sciatica that if they are being referred for specialist opinion, they may not need imaging. [2016]

1.1.6 Consider imaging in specialist settings of care (for example, a musculoskeletal interface clinic or hospital) for people with low back pain with or without sciatica only if the result is likely to change management. [2016]

1.2 Non-invasive treatments for low back pain and sciatica

Non-pharmacological interventions

Self-management

1.2.1 Provide people with advice and information, tailored to their needs and capabilities, to help them self-manage their low back pain with or without sciatica, at all steps of the treatment pathway. Include:

- information on the nature of low back pain and sciatica
- encouragement to continue with normal activities. [2016]

Exercise

1.2.2 Consider a group exercise programme (biomechanical, aerobic, mind–body or a combination of approaches) within the NHS for people with a specific episode or flare-up of low back pain with or without sciatica. Take people's specific needs,

preferences and capabilities into account when choosing the type of exercise. [2016]

Orthotics

1.2.3 Do not offer belts or corsets for managing low back pain with or without sciatica. [2016]

1.2.4 Do not offer foot orthotics for managing low back pain with or without sciatica. [2016]

1.2.5 Do not offer rocker sole shoes for managing low back pain with or without sciatica. [2016]

Manual therapies

1.2.6 Do not offer traction for managing low back pain with or without sciatica. [2016]

1.2.7 Consider manual therapy (spinal manipulation, mobilisation or soft tissue techniques such as massage) for managing low back pain with or without sciatica, but only as part of a treatment package including exercise, with or without psychological therapy. [2016]

Acupuncture

1.2.8 Do not offer acupuncture for managing low back pain with or without sciatica. [2016]

Electrotherapies

1.2.9 Do not offer ultrasound for managing low back pain with or without sciatica. [2016]

1.2.10 Do not offer percutaneous electrical nerve simulation (PENS) for managing low back pain with or without sciatica. [2016]

1.2.11 Do not offer transcutaneous electrical nerve simulation (TENS) for managing low back pain with or without sciatica. [2016]

1.2.12 Do not offer interferential therapy for managing low back pain with or without sciatica. [2016]

Psychological therapy

1.2.13 Consider psychological therapies using a cognitive behavioural approach for managing low back pain with or without sciatica but only as part of a treatment package including exercise, with or without manual therapy (spinal manipulation, mobilisation or soft tissue techniques such as massage). [2016]

Combined physical and psychological programmes

1.2.14 Consider a combined physical and psychological programme, incorporating a cognitive behavioural approach (preferably in a group context that takes into account a person's specific needs and capabilities), for people with persistent low back pain or sciatica:

- when they have significant psychosocial obstacles to recovery (for example, avoiding normal activities based on inappropriate beliefs about their condition) **or**
- when previous treatments have not been effective. [2016]

Return-to-work programmes

1.2.15 Promote and facilitate return to work or normal activities of daily living for people with low back pain with or without sciatica. [2016]

Pharmacological management of sciatica

1.2.16 Do not offer gabapentinoids, other antiepileptics, oral corticosteroids or benzodiazepines for managing sciatica as there is no overall evidence of benefit and there is evidence of harm. [2020]

1.2.17 Do not offer opioids for managing chronic sciatica. [2020]

1.2.18 If a person is already taking opioids, gabapentinoids or benzodiazepines for sciatica, explain the risks of continuing these medicines. [2020]

1.2.19 As part of shared decision making about whether to stop opioids, gabapentinoids or benzodiazepines for sciatica, discuss the problems associated

with withdrawal with the person.

To support discussions with patients about the benefits and harms of opioid treatment, and safe withdrawal management, see:

- the NICE guideline on patient experience in adult NHS services for recommendations on shared decision making
- the NICE guideline on medicines optimisation for recommendations on structured medication reviews
- the key therapeutic topic on medicines optimisation in chronic pain, the opioids aware website and the section in the BNF on controlled drugs and drug dependence. [2020]

NICE is developing a guideline on medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management.

1.2.20 Be aware of the risk of harms and limited evidence of benefit from the use of non-steroidal anti-inflammatory drugs (NSAIDs) in sciatica. [2020]

1.2.21 If prescribing NSAIDs for sciatica:

- take into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age
- think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment
- use the lowest effective dose for the shortest possible period of time. [2020]

For a short explanation of why the committee made the 2020 recommendations and how they might affect practice, see the rationale and impact section on pharmacological management of sciatica.

The committee have also made research recommendations on opioids for the management of acute sciatica, and antidepressants for the management of sciatica.

Full details of the evidence and the committee's discussion are in evidence review A: pharmacological management of sciatica.

Pharmacological management of low back pain

1.2.22 Consider oral NSAIDs for managing low back pain, taking into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age. **[2016]**

1.2.23 When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. **[2016]**

1.2.24 Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time. **[2016]**

1.2.25 Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective. **[2016]**

1.2.26 Do not offer paracetamol alone for managing low back pain. **[2016]**

1.2.27 Do not routinely offer opioids for managing acute low back pain (see recommendation 1.2.25). **[2016]**

1.2.28 Do not offer opioids for managing chronic low back pain. **[2016]**

1.2.29 Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants for managing low back pain. **[2016]**

1.2.30 Do not offer gabapentinoids or antiepileptics for managing low back pain. **[2016, amended 2020]**

1.3 Invasive treatments for low back pain and sciatica

Non-surgical interventions

Spinal injections

1.3.1 Do not offer spinal injections for managing low back pain. **[2016]**

Radiofrequency denervation

1.3.2 Consider referral for assessment for radiofrequency denervation for people with chronic low back pain when:

- non-surgical treatment has not worked for them **and**
- the main source of pain is thought to come from structures supplied by the medial branch nerve **and**
- they have moderate or severe levels of localised back pain (rated as 5 or more on a visual analogue scale, or equivalent) at the time of referral. **[2016]**

1.3.3 Only perform radiofrequency denervation in people with chronic low back pain after a positive response to a diagnostic medial branch block. **[2016]**

1.3.4 Do not offer imaging for people with low back pain with specific facet join pain as a prerequisite for radiofrequency denervation. **[2016]**

Epidurals

1.3.5 Consider epidural injections of local anaesthetic and steroid in people with acute and severe sciatica. **[2016]**

1.3.6 Do not use epidural injections for neurogenic claudication in people who have central spinal canal stenosis. **[2016]**

Surgical interventions

Surgery and prognostic factors

1.3.7 Do not allow a person's BMI, smoking status or psychological distress to influence the decision to refer them for a surgical opinion for sciatica. **[2016]**

Spinal decompression

1.3.8 Consider spinal decompression for people with sciatica when non-surgical treatment has not improved pain or function and their radiological findings are consistent with sciatic symptoms. **[2016]**

Spinal fusion

1.3.9 Do not offer spinal fusion for people with low back pain unless as part of a randomised controlled trial. [2016]

Disc replacement

1.3.10 Do not offer disc replacement in people with low back pain. [2016]

Terms used in this guideline

This section defines terms that have been used in a particular way for this guideline. For other definitions see the NICE glossary and the Think Local, Act Personal Care and Support Jargon Buster.

Acute

Less than 3 months duration.

Chronic

A 3-month duration or longer. The intensity of pain may fluctuate over time.

Weak opioids

See the information on weak opioids in the analgesics section of the British National Formulary.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Pharmacological therapies

What is the clinical and cost effectiveness of opioids for the management of acute sciatica? [2020]

2 Pharmacological therapies

What is the clinical and cost effectiveness of antidepressants for the management of sciatica? [2020]

For a short explanation of why the committee made the 2020 recommendations for research, see the rationale and impact section on pharmacological management of sciatica.

Full details of the evidence and the committee's discussion are in evidence review A: pharmacological management of sciatica.

3 Pharmacological therapies

What is the clinical and cost effectiveness of benzodiazepines for the management of acute low back pain? [2016]

4 Pharmacological therapies

What is the clinical and cost effectiveness of codeine with and without paracetamol for the management of acute low back pain? [2016]

5 Radiofrequency denervation

What is the clinical and cost effectiveness of radiofrequency denervation for chronic low back pain in the long term? [2016]

6 Epidurals

What is the clinical and cost effectiveness of image-guided compared with non-image-guided epidural injections for people with acute sciatica? **[2016]**

7 Spinal fusion

Should people with low back pain be offered spinal fusion as a surgical option? **[2016]**

Full details of the 2016 research recommendations are in the full guideline.

Rationale and impact

This section briefly explains why the committee made the recommendations and how they might affect practice. They link to details of the evidence and a full description of the committee's discussion.

Pharmacological management of sciatica

Recommendations 1.2.16 to 1.2.21

Why the committee made the recommendations

The evidence showed that gabapentinoids did not improve sciatica symptoms, and oral corticosteroids did not improve pain or function, but may have an impact on quality of life. Both increased the risk of adverse events in the long-term. While there was no evidence of increased risk of adverse events associated with benzodiazepines, there was evidence of poorer response than placebo in terms of pain reduction. The committee considered:

- the evidence reviewed,
- knowledge of the potential longer-term harms, and
- the reclassification of gabapentin and pregabalin as Schedule 3 controlled drugs (April 2019 UK Government drug safety update) because of the evidence for risk of abuse and dependence of these drugs.

The committee agreed that although the evidence about lack of effectiveness was limited, the harms would outweigh the benefits for most people with sciatica and therefore agreed to recommend against the use of gabapentinoids, oral corticosteroids and benzodiazepines for sciatica.

There was no evidence on the use of antiepileptics (other than gabapentinoids) for sciatica. Given the lack of evidence, and the committee's knowledge of potential harms, they agreed to recommend that antiepileptics (including gabapentinoids) should not be used for sciatica.

There was no evidence on the use of opioids for sciatica. Given the lack of evidence and the committee's knowledge of potential harms when used long term, the committee agreed to recommend against the use of opioids for chronic sciatica. However, the committee discussed

whether opioids might be effective when used short term for acute sciatica, so made a research recommendation on this topic.

There was no evidence on the use of antidepressants for sciatica. The committee agreed that antidepressants were commonly prescribed for sciatica, and clinical experience suggests they may be of benefit in some people. The committee considered the potential for harm to be less than the harms of prolonged use of opioids. On this basis, the committee made a research recommendation to determine if there was any clinical benefit for their use to treat sciatica.

Limited evidence showed no benefit from NSAIDs for sciatica. The committee discussed that there were also known risks of harms from NSAIDs that most clinicians were aware of so they were unlikely to be continued if they were not helpful. They agreed there was not sufficient evidence to make a recommendation for or against the use of NSAIDs for sciatica, but agreed to include a recommendation highlighting the risk of harms and lack of evidence of benefit as well as a research recommendation on this topic.

The committee were aware that some people may already be using opioids, antiepileptics (including gabapentinoids) and benzodiazepines for long periods for sciatica. Given the potential harms from sudden withdrawal of these medicines, based on consensus, they recommended discussing with the person the potential harms of long-term use and the need to withdraw safely if they chose to do so.

No evidence was identified for paracetamol, nefopam or muscle relaxants other than benzodiazepines for the management of sciatica. The committee agreed that none of these are widely prescribed for sciatica. They noted that advice is already included in this guideline for the use of paracetamol for people with low back pain. Therefore no further recommendations were made regarding management of sciatica alone, and these medicines do not warrant further research.

How the recommendations might affect practice

These recommendations are expected to reduce the use of gabapentinoids and other antiepileptics, corticosteroids, benzodiazepines and long-term opioid analgesics for sciatica. This will reduce the chance of adverse events and dependence on medicines that are unlikely to provide clinical benefit. It might lead to an increased use of other recommended treatments.

Full details of the evidence and the committee's discussion are in evidence review A: pharmacological management of sciatica.

Return to recommendations

Context

Low back pain that is not associated with serious or potentially serious causes has been described in the literature as 'non-specific', 'mechanical', 'musculoskeletal' or 'simple' low back pain. For consistency, we have used the term 'low back pain' throughout this guideline. However, 'non-specific low back pain' was used when creating the review questions. Worldwide, low back pain causes more disability than any other condition. Episodes of back pain usually do not last long, with rapid improvements in pain and disability seen within a few weeks to a few months. Although most back pain episodes get better with initial primary care management, without the need for investigations or referral to specialist services, up to one-third of people say they have persistent back pain of at least moderate intensity a year after an acute episode needing care, and episodes of back pain often recur.

One of the greatest challenges with low back pain is identifying risk factors that may predict when a single back pain episode will become a long-term, persistent pain condition. When this happens, quality of life is often very low and healthcare resource use high.

This guideline gives guidance on the assessment and management of both low back pain and sciatica from first presentation onwards in people aged 16 years and over.

We use 'sciatica' to describe leg pain secondary to lumbosacral nerve root pathology rather than the terms 'radicular pain' or 'radiculopathy', although they are more accurate. This is because 'sciatica' is a term that patients and clinicians understand, and it is widely used in the literature to describe neuropathic leg pain secondary to compressive spinal pathology.

This guideline does not cover the evaluation or care of people with sciatica with progressive neurological deficit or cauda equina syndrome. All clinicians involved in the management of sciatica should be aware of these potential neurological emergencies and know when to refer to an appropriate specialist.

A review of the NICE guideline on neuropathic pain in adults, triggered by an MHRA safety update of the reclassification of gabapentin and pregabalin as controlled drugs, highlighted the need for reconsideration of these as suitable treatments for sciatica. It was decided that update should sit within the guideline for low back pain and sciatica, alongside other treatment recommendations for sciatica.

Finding more information and committee details

You can see everything NICE says on this topic in the NICE Pathway on low back pain and sciatica.

To find NICE guidance on related topics, including guidance in development, see the NICE webpage on low back pain.

For full details of the evidence and the guideline committee's discussions, see the evidence review and 2016 full guideline. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

Update information

December 2020: we reviewed our guidance on opioids for non-cancer pain in response to a Public Health England evidence review on dependence on, and withdrawal from, prescribed medicines. We added links in recommendation 1.2.19 to other NICE guidelines and resources that support discussion with patients about opioid prescribing, and safe withdrawal management.

September 2020: We have reviewed the evidence and made new recommendations on pharmacological management for people with sciatica. These recommendations are marked **[2020]**.

We have also updated a recommendation to bring it in line with current terminology. This recommendation is marked **[2016, amended 2020]**.

Recommendations marked **[2016]** last had an evidence review in 2016. In some cases minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

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Accreditation

ACP American College of Physicians
Best Practice Advice

CLINICAL GUIDELINE

Diagnostic Imaging for Low Back Pain: Advice for High-Value Health Care From the American College of Physicians

Roger Chou, MD; Amir Qaseem, MD, PhD, MHA; Douglas K. Owens, MD, MS; and Paul Shekelle, MD, PhD, for the Clinical Guidelines Committee of the American College of Physicians*

Diagnostic imaging is indicated for patients with low back pain only if they have severe progressive neurologic deficits or signs or symptoms that suggest a serious or specific underlying condition. In other patients, evidence indicates that routine imaging is not associated with clinically meaningful benefits but can lead to harms. Addressing inefficiencies in diagnostic testing could minimize potential harms to patients and have a large effect on use of resources by reducing both direct and downstream costs. In this area, more testing does not equate to better care. Implementing a selective approach to low back imaging, as suggested by the American College of Physicians and American Pain Society guideline on low back pain, would provide better care to patients, improve outcomes, and reduce costs.

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For author affiliations, see end of text.

Low back pain is very common (1, 2), and many patients with low back pain receive routine spinal imaging (lumbar radiography, computed tomography [CT], or magnetic resonance imaging [MRI]) (3, 4), despite evidence-based recommendations from the American College of Physicians (ACP) and the American Pain Society (APS) that call for imaging only for patients who have severe or progressive neurologic deficits or signs or symptoms that suggest a serious or specific underlying condition (5). This is problematic, because routine imaging does not seem to improve clinical outcomes and exposes patients to unnecessary harms (6, 7).

The overuse of imaging also contributes to the high and growing costs associated with low back pain. In 1998, total U.S. health care expenditures for low back pain were estimated at $90 billion (8). Average total health expenditures for patients with back and neck problems increased from $4795 per year in 1997 to about $6096 per year in 2005, an inflation-adjusted increase of 65% (in 2005 U.S. dollars) (9). This rate was higher than that observed for overall health expenditures. Low back pain also incurs high indirect costs due to lost productivity (10). Reducing unnecessary tests or ineffective treatments (11) is an obvious way to decrease the costs associated with low back pain.

Imaging is an important driver of low back pain costs, not only because of the direct costs of the procedures (**Table 1**) (12, 13) but also the downstream effects (14). Imaging can lead to additional tests, follow-up, and referrals and may result in an invasive procedure of limited or questionable benefit. Of note, the rate of spine MRI increased sharply at the same time as that of lumbar surgeries (7, 15).

Despite increased spending on low back pain, U.S. adults with spine problems reported similar or worse scores for mental health, physical functioning, work or school limitations, and social limitations in 2005 than in 1997 (9). In North Carolina, the proportion of persons who reported chronic low back pain that impaired activity more than doubled between 1992 and 2006, from 3.9% to 10.2% (16).

The appropriateness of many of the low back imaging studies obtained in clinical practice has long been questioned (17), but clinicians are subject to many pressures that promote excessive imaging. This report, based on a systematic review (18) conducted for the 2007 ACP/APS low back pain guideline and a subsequent meta-analysis (6), aims to help clinicians practice high-value health care by following a more rational and cost-conscious diagnostic approach.

See also:

Print
Related article 174
Summary for Patients I-36

Web-Only
CME quiz
Conversion of graphics into slides
ACP Foundation Health TiPS

* This paper, written by Roger Chou, MD; Amir Qaseem, MD, PhD, MHA; Douglas K. Owens, MD, MS; and Paul Shekelle, MD, PhD, was developed for the Clinical Guidelines Committee of the American College of Physicians: Paul Shekelle, MD, PhD (*Chair*); Roger Chou, MD; Paul Dallas, MD; Thomas D. Denberg, MD, PhD: Nick Fitterman, MD; Mary Ann Forciea, MD; Robert H. Hopkins Jr., MD; Linda L. Humphrey, MD, MPH; Tanvir P. Mir, MD; Douglas K. Owens, MD, MS; Holger J. Schünemann, MD, PhD; Donna E. Sweet, MD; and David S. Weinberg, MD, MSc. Approved by the ACP Board of Regents on 20 November 2010.

Table 1. **Costs of Low Back Imaging**

Intervention	Reimbursement, $*	Range of Estimated Charges, $†
Lumbar spine radiography	50	204–286 (in network), 404–565 (out of network)
Lumbar spine computed tomography	381 (without contrast), 459 (with contrast)	1082–1517 (in network), 2091–2928 (out of network)
Lumbar spine magnetic resonance imaging	715 (without contrast), 863 (with contrast)	877–1226 (in network), 1762–2467 (out of network)

* From reference 12.
† From reference 13.

WHAT ARE THE EVIDENCE-BASED RECOMMENDATIONS FOR USE OF IMAGING TESTS IN PATIENTS WITH LOW BACK PAIN?

The ACP/APS low back pain guideline (5) recommends selective imaging for patients in whom it is clinically indicated. Appropriateness criteria from the American College of Radiology (19) are consistent with this guideline. The evidence supporting these recommendations includes the findings of randomized trials of spine imaging strategies; this is one of the relatively few areas of diagnostic imaging for which data are available from multiple randomized trials that reported clinical outcomes. Most studies of diagnostic tests estimate their accuracy at identifying a disease or condition, but even accurate tests may not improve patient outcomes. Well-conducted, randomized trials of diagnostic studies that evaluate patient outcomes provide the most direct information about the benefits and harms of alternative testing strategies (**Table 2**) (20–23).

A meta-analysis of 6 randomized trials (6), which comprised 1804 patients with primarily acute or subacute low back pain and no clinical or historical features that suggested a specific underlying condition, found no differences between routine lumbar imaging (radiography, MRI, or CT) and usual care without routine imaging in terms of pain, function, quality of life, or overall patient-rated improvement (**Table 3**). For short-term outcomes (<3 months), trends slightly favored usual care without routine imaging. Routine imaging was also not associated with psychological benefits (6), despite the perception that it can help alleviate patient anxiety about back pain (24). These results can probably be generalized to some degree to patients with or without radiculopathy, because most of the trials enrolled at least some patients with radiculopathy. The conclusions of the meta-analysis did not seem to be affected by whether radiography or advanced imaging (MRI or CT) was evaluated. On the basis of the systematic review, routine imaging can be considered a low-value health care intervention; because it is more costly than usual care without routine imaging and offers no clear clinical advantages, it cannot be cost-effective (11, 25).

Several factors may explain why routine imaging does not seem beneficial. Most lumbar imaging abnormalities are common in persons without low back pain and are only loosely associated with back symptoms. One systematic review (26) reported odds ratios that ranged from 1.2 to 3.3 for the association between low back pain and disc degeneration on radiography and no association with spondylosis or spondylolisthesis. A randomized trial (27) showed no incremental value of rapid MRI over radiography for evaluating low back pain, which suggests that although advanced imaging can detect more and smaller abnormalities, these abnormalities are not necessarily clinically relevant. Many abnormalities detected with advanced imaging are so common in asymptomatic persons that they could be viewed as normal signs of aging (28–30). In a cross-sectional study (31), 36% of asymptomatic persons aged 60 years or older had a herniated disc, 21% had spinal stenosis, and more than 90% had a degenerated or bulging disc. A prospective study (32) found that among patients with lumbar imaging abnormalities before the onset of low back pain, 84% had unchanged or improved findings after symptoms developed. Thus, it is important to understand that the presence of imaging abnormalities need not mean that the abnormalities are responsible for symptoms.

Routine imaging might also be ineffective because acute low back pain has such a favorable natural history and because the expected yield of routine imaging is low. Most patients with acute back pain, with or without radiculopathy, have substantial improvements in pain and function in the first 4 weeks (33, 34); routine imaging is unlikely to improve on this. About 0.7% of patients with low back pain in primary care settings have metastatic cancer, 0.01% have spinal infection, and 0.04% have the cauda equina syndrome (35, 36). Vertebral compression fractures (4%) and inflammatory back disease (≤5%) may also cause back pain, but these conditions typically carry lower diagnostic urgency (36, 37). Of the small proportion of patients with any of these conditions, almost all have an identifiable risk factor. In a retrospective study of 963 patients with acute low back pain (38), the 8 patients with tumors or fractures all had clinical risk factors. A prospective study (39) found no cases of cancer in 1170 patients younger than 50 years with acute low back pain and no history of cancer, weight loss, other sign of systemic illness, or lack of improvement. Similarly, 4 trials that enrolled 399 patients without risk factors found no missed serious conditions (6).

Routine imaging may have little effect on clinical outcomes because imaging results rarely affect treatment plans. A review of 68 000 lumbar radiographs (40) estimated that clinically unsuspected findings occurred in 1 of every 2500 patients between 20 and 50 years of age. In 2 studies of

about 100 patients each (41, 42), lumbar radiography affected management in only 1 or 2 patients. Similarly, a randomized trial of routine advanced imaging versus no imaging (43) found no differences in diagnoses or treatment plans. The limited therapeutic effect could be due to the largely unknown clinical significance of most imaging abnormalities. No evidence suggests that selecting therapies on the basis of the presence of the most common imaging findings improves outcomes compared with a generalized approach (5).

Any potential benefits of routine imaging may also be offset by potential harms. Lumbar radiography and CT contribute to cumulative low-level radiation exposure, which could promote carcinogenesis. Lumbar spine CT is associated with an average effective radiation dose of 6 mSv (44). On the basis of the 2.2 million lumbar CT scans performed in the United States in 2007, 1 study (45) projected 1200 additional future cases of cancer. Another study (46) estimated 1 additional case of cancer for every 270 women aged 40 years who had coronary angiography, a procedure associated with a radiation dose similar to that of lumbar spine CT (44). A woman aged 20 years would have an approximately doubled risk. Lumbar CT also involves the use of iodinated contrast, which is associated with hypersensitivity reactions and nephropathy.

Because lumbar radiography is performed much more frequently than lumbar CT, it accounts for a greater proportion of the total radiation dose from medical imaging procedures in the United States (3.3% vs. 0.7%), despite having a lower average effective radiation dose (1.5 mSv) (44). The average radiation exposure from lumbar radiography is 75 times higher than for chest radiography (44). This is of particular concern in young women because of the proximity to the gonads, which are difficult to effectively shield. The amount of female gonadal irradiation from lumbar radiography has been estimated as equivalent to having chest radiography daily for several years (36).

Telling patients that they have a back imaging abnormality could result in unintended harms related to labeling (47). In an acute low back pain trial that performed lumbar spine MRI on all patients (48), patients randomly assigned to routinely receive their results reported smaller improvements in general health than those who were blinded to their results. In another trial (49), patients with back pain of at least 6 weeks' duration who had routine radiography reported more pain and worse overall health status after 3 months than those who did not have radiography and were more likely to seek follow-up care. Knowledge of clinically irrelevant imaging findings might hinder recovery by causing patients to worry more, focus excessively on minor back symptoms, or avoid exercise or other recommended activities because of the fear that they could cause more structural damage (47).

Imaging might also lead to unnecessary procedures. Visual evidence can be very compelling, despite the uncertainties related to interpretation of most spinal imaging abnormalities, and imaging abnormalities may be viewed as targets for surgery or other interventions (50). The association between rates of advanced spinal imaging and rates of spinal surgery seems strong (15), although causality is difficult to establish. In a randomized trial, patients with low back pain who had rapid MRI had spine surgery about twice as often as those who had radiography, although the difference did not reach statistical significance (risk difference, 0.34 [95% CI, −0.06 to 0.73]) (27). One observational study (7) showed that variation in rates of spinal MRI accounted for 22% of the variability in overall spinal surgery rates among Medicare beneficiaries, or more than double the variability accounted for by differences in patient characteristics. Another study (51) found that for work-related acute low back pain, MRI within the first month was associated with more than an 8-fold increase in risk for surgery and more than a 5-fold increase in subsequent total medical costs compared with propensity-matched control patients who did not have early MRI.

Does Practice Follow the Evidence?

Although clinicians vary substantially in how frequently they obtain low back pain imaging (7, 52), some

Table 2. **Types of Diagnostic Evaluation Research, From Least to Most Informative, for Understanding Effects of Diagnostic Tests on Patient Outcomes**

Question Addressed by Diagnostic Studies	Low Back Pain Imaging Example
Does the test meet technical standards in laboratory settings? (technological efficacy)	What are the technical standards needed to obtain high-quality lumbar radiographs?
Does the test distinguish asymptomatic from symptomatic patients? (diagnostic accuracy)	What is the relative risk of lumbar radiography to detect or rule out facet joint arthritis in persons with versus persons without low back pain?
Does the test accurately distinguish persons with a disorder from those without among those in whom it is clinically reasonable to suspect the disorder? (diagnostic accuracy)	In patients with low back pain, what is the sensitivity and specificity of lumbar radiography for detecting or ruling out facet joint arthritis in patients with pain that originates from the facet joint?
Do the test results help guide management decisions? (therapeutic impact)	Do patients with low back pain who undergo routine radiography for low back pain receive different treatments from those who receive usual care without routine imaging?
Do patients who undergo the test fare better than similar untreated patients? (clinical efficacy)	Do patients with low back pain who undergo routine radiography for low back pain experience better pain or functional outcomes than those who receive usual care without routine imaging?

Table 3. **Results From Meta-analysis of Randomized, Controlled Trials of Routine Imaging Versus Usual Care Without Routine Imaging***

Outcome	Short Term (<3 Months)		Long Term (>6 Months to ≤1 Year)	
	Results, by Specific Scale	Analysis (95% CI)	Results, by Specific Scale	Analysis (95% CI)
Pain	SF-36 bodily pain (0 to 100 scale): 3.0 (−2.0 to 8.0), 2 trials; VAS (0 to 10 scale): 1.0 (0.46 to 1.54), 1 trial	Pooled SMD: 0.19 (−0.01 to 0.39); 3 trials	SF-36 bodily pain: −2.1 (−5.1 to 0.80), 3 trials; VAS: 0.08 (−0.02 to 0.18), 1 trial	Pooled SMD: −0.04 (−0.15 to 0.07); 4 trials
Function	RDQ (0 to 24 scale): 0.48 (−1.4 to 2.3), 3 trials	Pooled SMD: 0.11 (−0.29 to 0.50); 3 trials	RDQ: 0.34 (−0.65 to 1.3), 3 trials; Aberdeen low back score (0 to 100 scale): −3.1 (−4.2 to −2.0), 1 trial	Pooled SMD: 0.01 (−0.17 to 0.19); 4 trials
Quality of life	EQ-5D (0 to 1 scale): −0.10 (−0.17 to −0.03), 1 trial; EuroQoL subjective score (0 to 100 scale): 2.0 (−1.5 to 5.5), 1 trial	Pooled SMD: −0.10 (−0.53 to 0.34); 2 trials	EQ-5D: −0.005 (−0.06 to 0.05), 2 trials; EuroQoL subjective score: −7.0 (−10 to −3.7), 1 trial	Pooled SMD: −0.15 (−0.33 to 0.04); 3 trials
Mental health	SF-36 mental health (0 to 100 scale): 2.3 (−6.3 to 11), 2 trials	Pooled SMD: 0.12 (−0.37 to 0.62); 2 trials	SF-36 mental health: 0.61 (−4.4 to 5.6), 3 trials	Pooled SMD: 0.01 (−0.32 to 0.34); 3 trials
Overall improvement†	Risk difference: −7.8% (−14% to −1.3%)	Relative risk: 0.83 (0.65 to 1.06); 4 trials	Risk difference: −7.8% (−17% to 1.8%)	Relative risk: 0.82 (0.64 to 1.05); 1 trial

EQ-5D = European Quality of Life—5 Dimensions; EuroQoL = European Quality of Life; RDQ = Roland Disability Questionnaire; SF-36 = Short Form-36; SMD = standardized mean difference; VAS = visual analogue scale.
* From reference 6. Negative results favor routine imaging for pain and function, whereas positive results favor routine imaging for quality of life and mental health.
† Dichotomous outcome, defined as back pain resolved, normal activities resumed, and patient rating of "symptoms much improved" or at least "very pleased."

continue to order imaging routinely or without a clear clinical indication. In a survey (3), about 40% of family practice and 13% of internal medicine physicians reported ordering routine diagnostic imaging for acute low back pain. Another survey (4) found that in the absence of any worrisome features, 22% of physicians would obtain lumbar spine radiography for acute low back pain without sciatica and 62% would do so for low back pain with sciatica. Data on actual imaging practices support these survey results. Among 35 000 Medicare beneficiaries with acute low back pain and no diagnostic code indicating a serious underlying condition, nearly 30% had lumbar radiography within 28 days (53), even though the ACP/APS guideline (5) suggests a trial of management without imaging in adults with no risk factors other than older age. An Australian study (54) showed a slight increase in imaging rates in general practice for patients with new low back pain, despite the publication of guidelines that recommend against routine imaging.

Use of advanced spinal imaging, which is far more expensive than lumbar radiography (**Table 1**), is increasing rapidly. Among Medicare Part B beneficiaries, lumbar MRI scans increased by about 4-fold between 1994 and 2005 (55). Similarly, the rate of MRI tripled between 1997 and 2006 in a large health care organization (46). In North Carolina, more than one third of patients with chronic low back pain received either MRI or CT in the past year (56), and other studies show even higher rates (57).

What Forces Promote the Overuse of Imaging in Patients With Low Back Pain?

Patient expectations and preferences about diagnostic testing, when communicated to physicians, can affect clinical decisions (24). Patients expect a clear diagnosis for their low back pain (58). They want to know what is causing their symptoms and may equate a decision to not obtain imaging or provide a precise diagnosis with low-quality care (59) or as a message that their pain is not legitimate or important (50). Wanting diagnostic testing is a frequent reason for repeated office visits for chronic back pain (60). In 1 study (61), use of low back pain imaging was strongly associated with how intensely patients believed imaging was necessary. A survey of U.S. physicians (62) found that more than one third would order lumbar MRI for uncomplicated acute low back pain if a patient insisted on it even after the physician explained that it was unnecessary.

Linking financial performance incentives to patient satisfaction could augment such tendencies. In randomized trials, patients expressed more satisfaction when they received routine lumbar imaging (49) or advanced imaging instead of radiography (27), even when their clinical outcomes were no better. A study of Medicare beneficiaries found earlier use of imaging and more advanced imaging when clinician incentives were based on patient satisfaction (53). A trial showed that patients randomly assigned to receive routine imaging became more likely to believe it was necessary, despite experiencing no clinical benefit (63).

Greater availability of imaging resources seems to correlate with increased use. One study (64) found a strong correlation between the number of MRI units added in a geographic area and the number of MRI scans performed, with about 40 additional lumbar MRI scans for each new unit over a 5-year period. The number of MRI scanners in the United States tripled from 2000 to 2005, from 7.6 to 26.6 per million persons (64). In 2006, about 7000 U.S.

sites offered MRI (65), almost twice as many per capita as any other industrialized country and more than 4 times as many as Canada or the United Kingdom (65). In 2006, western Pennsylvania had almost as many MRI machines (140 units) as all of Canada (151 units) (66).

Financial incentives can also influence imaging decisions. Top-of-the-line MRI units can cost at least $2 million to purchase and about $800 000 a year to operate (64, 66). However, advanced imaging offers a high profit margin. Relative to actual costs, Medicare provides far greater reimbursement for MRI than for conventional radiography (reimbursement–cost ratio, 2.3 vs. 0.9) (67). A 2009 report from the Medicare Payment Advisory Commission (68) reported an association between physician ownership or investment in imaging facilities and rates of use. An earlier study of worker's compensation cases (69) found more inappropriate imaging requests from physicians who self-referred.

In addition, the overuse of back imaging could be related to the perceived risk for missing a serious diagnosis. *Defensive medicine* refers to alteration of clinical behavior owing to concerns over malpractice liability. In 1 study (70), more than 90% of Pennsylvania physicians from 6 specialties reported defensive medicine practices, and almost one half of those with positive responses reported unnecessary imaging as their most recent defensive act. When a legal claim related to the back pain is more likely or when patients express dissatisfaction, the likelihood of such practices probably increases. Low back pain imaging is a typical part of the evaluation in worker's compensation and disability cases, despite the absence of evidence that it improves outcomes in these situations.

Finally, clinicians are pressed for time. Ordering an imaging test may be viewed as more expedient than explaining to a patient why imaging is not necessary (23, 71).

How Can Physicians Reduce Overuse of Imaging for Low Back Pain?

Adhering to the ACP/APS recommendations on use of imaging could reduce overuse. Most patients do not need immediate imaging, and an initial trial of therapy before imaging is warranted in many cases (**Table 4**). A key principle of the guideline is that a thorough history and physical examination are necessary to guide imaging decisions. No randomized trial data are available to guide optimal diagnostic strategies for patients with clinical risk factors. However, imaging is recommended when features suggest the cauda equina syndrome or vertebral infection. Although these conditions are rare and the prevalence of risk factors is low (72), timely diagnosis may prevent serious sequelae related to compression of the spinal cord or cauda equina. Key clinical features include new urine retention, saddle anesthesia, fecal incontinence, or fever (especially in patients with risk factors for bacteremia). Imaging is also indicated for severe or progressive neurologic deficits (such as objective or progressive motor weakness at a single level or deficits at multiple spinal levels).

Other risk factors are associated with specific conditions, such as cancer, vertebral compression fracture, ankylosing spondylitis, herniated disc, or symptomatic spinal stenosis (**Table 4**). The traditional approach has been to use imaging to act on all clinical risk factors. However, this would result in high imaging rates with low positive pre-

Table 4. **Suggestions for Imaging in Patients With Acute Low Back Pain***

Imaging Action and Clinical Situation	Suggestions for Initial Imaging
Immediate imaging	
Radiography plus erythrocyte sedimentation rate†	Major risk factors for cancer (new onset of low back pain with history of cancer, multiple risk factors for cancer, or strong clinical suspicion for cancer)
Magnetic resonance imaging	Risk factors for spinal infection (new onset of low back pain with fever and history of intravenous drug use or recent infection) Risk factors for or signs of the cauda equina syndrome (new urine retention, fecal incontinence, or saddle anesthesia) Severe neurologic deficits (progressive motor weakness or motor deficits at multiple neurologic levels)
Defer imaging after a trial of therapy	
Radiography with or without erythrocyte sedimentation rate	Weaker risk factors for cancer (unexplained weight loss or age >50 y) Risk factors for or signs of ankylosing spondylitis (morning stiffness that improves with exercise, alternating buttock pain, awakening because of back pain during the second part of the night, or younger age [20 to 40 y]) Risk factors for vertebral compression fracture (history of osteoporosis, use of corticosteroids, significant trauma, or older age [>65 y for women or >75 y for men])
Magnetic resonance imaging	Signs and symptoms of radiculopathy (back pain with leg pain in an L4, L5, or S1 nerve root distribution or positive result on straight leg raise or crossed straight leg raise test) in patients who are candidates for surgery or epidural steroid injection Risk factors for or symptoms of spinal stenosis (radiating leg pain, older age, or pseudoclaudication) in patients who are candidates for surgery
No imaging	No criteria for immediate imaging and back pain improved or resolved after a 1-mo trial of therapy Previous spinal imaging with no change in clinical status

* Adapted from reference 5.
† Consider magnetic resonance imaging if the initial imaging result is negative but a high degree of clinical suspicion for cancer remains.

Figure. **American College of Physicians best practice advice: diagnostic imaging for low back pain.**

ACP American College of Physicians *Best Practice Advice*

Summary of the American College of Physicians Best Practice Advice: Diagnostic Imaging for Low Back Pain

Disease or condition	Imaging for low back pain
Target audience	Internists, family physicians, and other clinicians
Target patient population	Adults with low back pain
Interventions	Radiography Computed tomography Magnetic resonance imaging
Indications for diagnostic imaging	Immediate imaging is recommended in patients with acute low back pain who have major risk factors for cancer, risk factors for spinal infection, risk factors for or signs of the cauda equina syndrome, or severe or progressive neurologic deficits Imaging after a trial of therapy is recommended in patients with minor risk factors for cancer, risk factors for inflammatory back disease, risk factors for vertebral compression fracture, signs or symptoms of radiculopathy, or risk factors for or symptoms of symptomatic spinal stenosis Repeated imaging is only recommended in patients with new or changed low back symptoms
Evidence that expanding imaging to patients without these indications does not improve outcomes	Randomized trials of routine imaging versus usual care without routine imaging in patients without indications for diagnostic imaging suggest no clinically meaningful benefits on outcomes related to pain, function, quality of life, or mental health Other supporting evidence includes the weak correlation between most imaging findings and symptoms, the favorable natural history of acute low back pain with or without imaging, the low prevalence of serious or specific underlying conditions, and unclear effects of imaging on treatment decisions
Harms of unnecessary imaging	Radiation exposure (for lumbar radiography and computed tomography) Labeling Hypersensitivity reactions and contrast nephropathy (for iodinated contrast with computed tomography) Potential association with subsequent unnecessary, invasive, and expensive procedures
Approaches to overcome barriers to evidence-based practice	Patient expectations or preferences for routine imaging: Use talking points based on evidence-based guidelines to aid in patient education Time constraints: Use evidence-based online or print education material to supplement face-to-face education Clinician uncertainty: Recognize the low likelihood of serious conditions in the absence of clinical risk factors and the evidence that shows no benefit associated with routine imaging Clinician incentives based on patient satisfaction: Advocate for incentives that are based on providing appropriate care
Talking points for clinicians when discussing low back pain imaging with patients	Risk factor assessment can almost always identify patients who require imaging The prevalence of serious underlying conditions is low in patients without risk factors The natural history of acute low back pain is quite favorable, but patients require reevaluation if they are not better after about 1 month Routine imaging does not improve clinical outcomes but increases costs and may lead to potentially unnecessary invasive treatments, such as surgery Imaging abnormalities are extremely common, especially in older adults, but most are poorly correlated with symptoms In most cases, treatment plans do not change after imaging studies Back imaging is associated with radiation exposure, which can increase the risk for cancer in the case of lumbar radiography and computed tomography

dictive values (38, 73). One study of 1172 patients with acute back pain in primary care (73) found that one quarter were older than 55 years, about one quarter had morning back stiffness, and about one third had pain that improved with exercise. All are considered risk factors for cancer or ankylosing spondylitis, but no cases of either condition were identified.

A more efficient strategy would be to use likelihood ratios to inform imaging decisions. For instance, the prevalence, or pretest probability, of cancer in a primary care population is about 0.7% (39). A history of cancer is the strongest risk factor for a spinal tumor (positive likelihood ratio, 15) (39). Unexplained weight loss, lack of improvement after 1 month, and age older than 50 years are weaker

risk factors (positive likelihood ratio, 2.7 to 3.0). On the basis of these likelihood ratios, the probability of cancer in a patient with a history of cancer would increase to approximately 9%, or high enough to warrant immediate imaging (a strong clinical suspicion for cancer would give a similar result [72]). In patients with any of the other 3 risk factors, the posttest probability increases only marginally, to 1.2%. Imaging could be reasonably deferred in most cases unless symptoms did not improve after several weeks (38, 74). For patients with no signs of neurologic compromise who have risk factors for vertebral compression fracture, ankylosing spondylitis, herniated disc, or spinal stenosis, a trial of therapy before imaging would also be warranted. Diagnostic rules based on the evaluation of multiple risk factors could help better inform imaging decisions, but they are in the early stages of development (72).

Advanced imaging should be reserved for situations in which findings are more likely to affect clinical decision making, such as major trauma, severe neurologic compromise, or vertebral infection (5). If available, MRI is usually preferred over CT because it involves less radiation exposure and has better soft-tissue visualization. In cases in which only weak risk factors for cancer and no neurologic signs are present, initial imaging with lumbar radiography and evaluation of erythrocyte sedimentation rate is a reasonable approach (74). For persistent radicular symptoms or spinal stenosis without severe neurologic compromise, advanced imaging should be performed after a 1-month trial of therapy in candidates for surgery or an epidural steroid injection (5). For suspected vertebral compression fracture or ankylosing spondylitis, lumbar radiography is recommended. Decisions regarding repeated imaging should be based on the development of new or changed clinical features, such as new or progressive neurologic symptoms or recent trauma.

Although patient expectations regarding back imaging are frequently at odds with the evidence (58), this need not be the case. Most patients do not want unnecessary or potentially harmful tests. Patient education could help bring expectations more in line with the evidence. In addition, effective education may be less burdensome than assumed. One randomized trial (63) found that a brief educational intervention regarding back imaging took fewer than 5 minutes and resulted in similar satisfaction with overall care (and similar clinical outcomes) to that of routine radiography. Supplementing face-to-face information with patient handouts, self-care education books (75), online materials (76, 77), mass media educational campaigns (78), or other methods could be an efficient strategy for reinforcing or expanding on key points.

Efforts to decrease imaging overuse should also address external barriers to change. For example, clinician incentives based on patient satisfaction could reward unnecessary testing and be counterproductive (53). Incentives should instead be based on whether clinicians deliver appropriate care. Efforts are under way to curb overuse related to physician self-referral and to revise reimbursement schedules to provide fair compensation without excessive incentives for advanced imaging (65, 68, 79).

Active and individualized methods will probably be more effective at changing clinician behavior than passive ones, such as distributing guidelines (80, 81). Many health insurers have imposed authorization requirements for advanced imaging, but these are often viewed as onerous (65). As a potential alternative, a randomized trial (82) found that an educational session by local clinical leaders followed by individualized clinician audit and feedback was more effective than no intervention for reducing inappropriate lumbar imaging. Another promising method is a computer-based decision support tool (65) that provides information at the time of ordering, such as whether the patient has had a recent imaging study, and compares a physician's ordering patterns with that of his or her peers.

CONCLUSION

Health care practices associated with high costs and limited or no benefits provide little value (11). Good evidence indicates that routine back imaging is not associated with clinically meaningful benefits and exposes patients to unnecessary harms, but imaging remains overused. Implementation of the ACP/APS recommendations on judicious and selective low back imaging would improve patient care while reducing costs. To be most effective, efforts to reduce use of imaging should be multifocal and address clinician behaviors, patient expectations, and financial incentives. The mindset that more testing means better care must be abandoned in favor of a more evidence-based approach.

ACP BEST PRACTICE ADVICE

The ACP has found strong evidence that routine imaging for low back pain by using radiography or advanced imaging methods is not associated with a clinically meaningful effect on patient outcomes. Unnecessary imaging exposes patients to preventable harms, may lead to additional unnecessary interventions, and results in unnecessary costs. Diagnostic imaging studies should be performed only in selected, higher-risk patients who have severe or progressive neurologic deficits or are suspected of having a serious or specific underlying condition. Advanced imaging with MRI or CT should be reserved for patients with a suspected serious underlying condition or neurologic deficits, or who are candidates for invasive interventions. Decisions about repeated imaging should be based on development of new symptoms or changes in current symptoms. Patient education strategies should be used to inform patients about current and effective standards of care. The **Figure** summarizes this advice.

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References

1. **Deyo RA, Mirza SK, Martin BI.** Back pain prevalence and visit rates: estimates from U.S. national surveys, 2002. Spine (Phila Pa 1976). 2006;31:2724-7. [PMID: 17077742]
2. **Hart LG, Deyo RA, Cherkin DC.** Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns from a U.S. national survey. Spine (Phila Pa 1976). 1995;20:11-9. [PMID: 7709270]
3. **Di Iorio D, Henley E, Doughty A.** A survey of primary care physician practice patterns and adherence to acute low back problem guidelines. Arch Fam Med. 2000;9:1015-21. [PMID: 11115201]
4. **Webster BS, Courtney TK, Huang YH, Matz S, Christiani DC.** Physicians' initial management of acute low back pain versus evidence-based guidelines. Influence of sciatica. J Gen Intern Med. 2005;20:1132-5. [PMID: 16423103]
5. **Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, et al; Clinical Efficacy Assessment Subcommittee of the American College of Physicians.** Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-91. [PMID: 17909209]
6. **Chou R, Fu R, Carrino JA, Deyo RA.** Imaging strategies for low-back pain: systematic review and meta-analysis. Lancet. 2009;373:463-72. [PMID: 19200918]
7. **Lurie JD, Birkmeyer NJ, Weinstein JN.** Rates of advanced spinal imaging and spine surgery. Spine (Phila Pa 1976). 2003;28:616-20. [PMID: 12642771]
8. **Luo X, Pietrobon R, Sun SX, Liu GG, Hey L.** Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. Spine (Phila Pa 1976). 2004;29:79-86. [PMID: 14699281]
9. **Martin BI, Deyo RA, Mirza SK, Turner JA, Comstock BA, Hollingworth W, et al.** Expenditures and health status among adults with back and neck problems. JAMA. 2008;299:656-64. [PMID: 18270354]
10. **Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R.** Lost productive time and cost due to common pain conditions in the US workforce. JAMA. 2003;290:2443-54. [PMID: 14612481]
11. **Owens DK, Qaseem A, Chou R, Shekelle P; Clinical Guidelines Committee of the American College of Physicians.** High-value, cost-conscious health care: concepts for clinicians to evaluate benefits, harms, and costs of medical interventions. Ann Intern Med. 2011;154:174-80.
12. 2009 Medicare reimbursement fee schedule. Baltimore: Centers for Medicare & Medicaid Services; 2009. Accessed at www.trailblazerhealth.com/Tools/Fee%20Schedule/MedicareFeeSchedule.aspx on 8 December 2010.
13. Anthem Health Care Advisor. Estimated total costs before insurance benefits. WebMD Health Services Group; 2008. Accessed at www1.subimo.com/hca/app/abch/View/TreatmentCostAdvisor/Index on 14 December 2010.
14. **Deyo RA.** Cascade effects of medical technology. Annu Rev Public Health. 2002;23:23-44. [PMID: 11910053]
15. **Verrilli D, Welch HG.** The impact of diagnostic testing on therapeutic interventions. JAMA. 1996;275:1189-91. [PMID: 8609687]
16. **Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, et al.** The rising prevalence of chronic low back pain. Arch Intern Med. 2009;169:251-8. [PMID: 19204216]
17. **Hall FM.** Overutilization of radiological examinations. Radiology. 1976;120:443-8. [PMID: 778913]
18. **Chou R, Huffman LH.** Evaluation and Management of Low Back Pain: Evidence Review. Glenview, IL: American Pain Society; 2009. Accessed at www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf on 30 November 2010.
19. **American College of Radiology.** ACR Appropriateness Criteria. Low Back Pain. Reston, VA: American College of Radiology; 2008. Accessed at www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonneurologicImaging/LowBackPainDoc7.aspx on 30 November 2010.
20. **Fryback DG, Thornbury JR.** The efficacy of diagnostic imaging. Med Decis Making. 1991;11:88-94. [PMID: 1907710]
21. **Guyatt GH, Tugwell PX, Feeny DH, Haynes RB, Drummond M.** A framework for clinical evaluation of diagnostic technologies. CMAJ. 1986;134:587-94. [PMID: 3512062]
22. **Sackett DL, Haynes RB.** The architecture of diagnostic research. BMJ. 2002;324:539-41. [PMID: 11872558]
23. **Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al; GRADE Working Group.** Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336:1106-10. [PMID: 18483053]
24. **Schers H, Wensing M, Huijsmans Z, van Tulder M, Grol R.** Implementation barriers for general practice guidelines on low back pain a qualitative study. Spine (Phila Pa 1976). 2001;26:E348-53. [PMID: 11474367]
25. How to read clinical journals: VII. To understand an economic evaluation (part B). Can Med Assoc J. 1984;130:1542-9. [PMID: 6428730]
26. **van Tulder MW, Assendelft WJ, Koes BW, Bouter LM.** Spinal radiographic findings and nonspecific low back pain. A systematic review of observational studies. Spine (Phila Pa 1976). 1997;22:427-34. [PMID: 9055372]
27. **Jarvik JG, Hollingworth W, Martin B, Emerson SS, Gray DT, Overman S, et al.** Rapid magnetic resonance imaging vs radiographs for patients with low back pain: a randomized controlled trial. JAMA. 2003;289:2810-8. [PMID: 12783911]
28. **Jarvik JJ, Hollingworth W, Heagerty P, Haynor DR, Deyo RA.** The Longitudinal Assessment of Imaging and Disability of the Back (LAIDBack) study: baseline data. Spine (Phila Pa 1976). 2001;26:1158-66. [PMID: 11413431]
29. **Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS.** Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med. 1994;331:69-73. [PMID: 8208267]
30. **Wiesel SW, Tsourmas N, Feffer HL, Citrin CM, Patronas N.** A study of computer-assisted tomography. I. The incidence of positive CAT scans in an asymptomatic group of patients. Spine (Phila Pa 1976). 1984;9:549-51. [PMID: 6495024]
31. **Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW.** Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am. 1990;72:403-8. [PMID: 2312537]
32. **Carragee E, Alamin T, Cheng I, Franklin T, van den Haak E, Hurwitz E.** Are first-time episodes of serious LBP associated with new MRI findings? Spine J. 2006;6:624-35. [PMID: 17088193]
33. **Pengel LH, Herbert RD, Maher CG, Refshauge KM.** Acute low back pain: systematic review of its prognosis. BMJ. 2003;327:323. [PMID: 12907487]
34. **Vroomen PC, de Krom MC, Knottnerus JA.** Predicting the outcome of sciatica at short-term follow-up. Br J Gen Pract. 2002;52:119-23. [PMID: 11887877]
35. **Deyo RA, Rainville J, Kent DL.** What can the history and physical examination tell us about low back pain? JAMA. 1992;268:760-5. [PMID: 1386391]
36. **Jarvik JG, Deyo RA.** Diagnostic evaluation of low back pain with emphasis on imaging. Ann Intern Med. 2002;137:586-97. [PMID: 12353946]

37. **Underwood MR, Dawes P.** Inflammatory back pain in primary care. Br J Rheumatol. 1995;34:1074-7. [PMID: 8542211]
38. **Suarez-Almazor ME, Belseck E, Russell AS, Mackel JV.** Use of lumbar radiographs for the early diagnosis of low back pain. Proposed guidelines would increase utilization. JAMA. 1997;277:1782-6. [PMID: 9178791]
39. **Deyo RA, Diehl AK.** Cancer as a cause of back pain: frequency, clinical presentation, and diagnostic strategies. J Gen Intern Med. 1988;3:230-8. [PMID: 2967893]
40. **Nachemson A.** The lumbar spine: an orthopaedic challenge. Spine. 1976;1: 59-71.
41. **Halpin SF, Yeoman L, Dundas DD.** Radiographic examination of the lumbar spine in a community hospital: an audit of current practice. BMJ. 1991;303: 813-5. [PMID: 1932970]
42. **Rockey PH, Tompkins RK, Wood RW, Wolcott BW.** The usefulness of x-ray examinations in the evaluation of patients with back pain. J Fam Pract. 1978;7:455-65. [PMID: 151124]
43. **Gillan MG, Gilbert FJ, Andrew JE, Grant AM, Wardlaw D, Valentine NW, et al; Scottish Back Trial Group.** Influence of imaging on clinical decision making in the treatment of lower back pain. Radiology. 2001;220:393-9. [PMID: 11477242]
44. **Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, et al.** Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med. 2009;361:849-57. [PMID: 19710483]
45. **Berrington de González A, Mahesh M, Kim KP, Bhargavan M, Lewis R, Mettler F, et al.** Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med. 2009;169:2071-7. [PMID: 20008689]
46. **Smith-Bindman R, Miglioretti DL, Larson EB.** Rising use of diagnostic medical imaging in a large integrated health system. Health Aff (Millwood). 2008;27:1491-502. [PMID: 18997204]
47. **Fisher ES, Welch HG.** Avoiding the unintended consequences of growth in medical care: how might more be worse? JAMA. 1999;281:446-53. [PMID: 9952205]
48. **Ash LM, Modic MT, Obuchowski NA, Ross JS, Brant-Zawadzki MN, Grooff PN.** Effects of diagnostic information, per se, on patient outcomes in acute radiculopathy and low back pain. AJNR Am J Neuroradiol. 2008;29:1098-103. [PMID: 18467522]
49. **Kendrick D, Fielding K, Bentley E, Kerslake R, Miller P, Pringle M.** Radiography of the lumbar spine in primary care patients with low back pain: randomised controlled trial. BMJ. 2001;322:400-5. [PMID: 11179160]
50. **Rhodes LA, McPhillips-Tangum CA, Markham C, Klenk R.** The power of the visible: the meaning of diagnostic tests in chronic back pain. Soc Sci Med. 1999;48:1189-203. [PMID: 10220019]
51. **Webster BS, Cifuentes M.** Relationship of early magnetic resonance imaging for work-related acute low back pain with disability and medical utilization outcomes. J Occup Environ Med. 2010;52:900-7. [PMID: 20798647]
52. **Cherkin DC, Deyo RA, Wheeler K, Ciol MA.** Physician variation in diagnostic testing for low back pain. Who you see is what you get. Arthritis Rheum. 1994;37:15-22. [PMID: 8129759]
53. **Pham HH, Landon BE, Reschovsky JD, Wu B, Schrag D.** Rapidity and modality of imaging for acute low back pain in elderly patients. Arch Intern Med. 2009;169:972-81. [PMID: 19468091]
54. **Williams CM, Maher CG, Hancock MJ, McAuley JH, McLachlan AJ, Britt H, et al.** Low back pain and best practice care: A survey of general practice physicians. Arch Intern Med. 2010;170:271-7. [PMID: 20142573]
55. **Deyo RA, Mirza SK, Turner JA, Martin BI.** Overtreating chronic back pain: time to back off? J Am Board Fam Med. 2009;22:62-8. [PMID: 19124635]
56. **Carey TS, Freburger JK, Holmes GM, Castel L, Darter J, Agans R, et al.** A long way to go: practice patterns and evidence in chronic low back pain care. Spine (Phila Pa 1976). 2009;34:718-24. [PMID: 19282797]
57. **Weiner DK, Kim YS, Bonino P, Wang T.** Low back pain in older adults: are we utilizing healthcare resources wisely? Pain Med. 2006;7:143-50. [PMID: 16634727]
58. **Verbeek J, Sengers MJ, Riemens L, Haafkens J.** Patient expectations of treatment for back pain: a systematic review of qualitative and quantitative studies. Spine (Phila Pa 1976). 2004;29:2309-18. [PMID: 15480147]
59. **Carman KL, Maurer M, Yegian JM, Dardess P, McGee J, Evers M, et al.** Evidence that consumers are skeptical about evidence-based health care. Health Aff (Millwood). 2010;29:1400-6. [PMID: 20522522]
60. **McPhillips-Tangum CA, Cherkin DC, Rhodes LA, Markham C.** Reasons for repeated medical visits among patients with chronic back pain. J Gen Intern Med. 1998;13:289-95. [PMID: 9613883]
61. **Wilson IB, Dukes K, Greenfield S, Kaplan S, Hillman B.** Patients' role in the use of radiology testing for common office practice complaints. Arch Intern Med. 2001;161:256-63. [PMID: 11176741]
62. **Campbell EG, Regan S, Gruen RL, Ferris TG, Rao SR, Cleary PD, et al.** Professionalism in medicine: results of a national survey of physicians. Ann Intern Med. 2007;147:795-802. [PMID: 18056665]
63. **Deyo RA, Diehl AK, Rosenthal M.** Reducing roentgenography use. Can patient expectations be altered? Arch Intern Med. 1987;147:141-5. [PMID: 2948466]
64. **Baras JD, Baker LC.** Magnetic resonance imaging and low back pain care for medicare patients. Health Aff (Millwood). 2009;28:w1133-40. [PMID: 19828486]
65. **Iglehart JK.** Health insurers and medical-imaging policy—a work in progress. N Engl J Med. 2009;360:1030-7. [PMID: 19264694]
66. **Snowbeck C.** Region still rich with MRI machines. Pittsburgh Post-Gazette. 11 June 2005.
67. **Gray DT, Hollingworth W, Blackmore CC, Alotis MA, Martin BI, Sullivan SD, et al.** Conventional radiography, rapid MR imaging, and conventional MR imaging for low back pain: activity-based costs and reimbursement. Radiology. 2003;227:669-80. [PMID: 12773674]
68. **Medicare Payment Advisory Commission.** Report to the Congress: Improving Incentives in the Medicare Program. Washington, DC: Medicare Payment Advisory Commission; 2009. Accessed at www.medpac.gov/documents/Jun09_EntireReport.pdf on 30 November 2010.
69. **Swedlow A, Johnson G, Smithline N, Milstein A.** Increased costs and rates of use in the California workers' compensation system as a result of self-referral by physicians. N Engl J Med. 1992;327:1502-6. [PMID: 1406882]
70. **Studdert DM, Mello MM, Sage WM, DesRoches CM, Peugh J, Zapert K, et al.** Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. JAMA. 2005;293:2609-17. [PMID: 15928282]
71. Is time management an important cause of excessive imaging? BackLetter. 2009;24:50.
72. **Henschke N, Maher CG, Refshauge KM.** Screening for malignancy in low back pain patients: a systematic review. Eur Spine J. 2007;16:1673-9. [PMID: 17566791]
73. **Henschke N, Maher CG, Refshauge KM, Herbert RD, Cumming RG, Bleasel J, et al.** Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. Arthritis Rheum. 2009;60:3072-80. [PMID: 19790051]
74. **Joines JD, McNutt RA, Carey TS, Deyo RA, Rouhani R.** Finding cancer in primary care outpatients with low back pain: a comparison of diagnostic strategies. J Gen Intern Med. 2001;16:14-23. [PMID: 11251746]
75. **Burton AK, Waddell G, Tillotson KM, Summerton N.** Information and advice to patients with back pain can have a positive effect. A randomized controlled trial of a novel educational booklet in primary care. Spine (Phila Pa 1976). 1999;24:2484-91. [PMID: 10626311]
76. Summaries for patients: Radiology tests for patients with low back pain: high-value health care advice from the American College of Physicians. Ann Intern Med. 2011;154:I-36.
77. **American College of Physicians Foundation.** Health TiPS: Low Back Pain. Philadelphia: American Coll Physicians; 2011. Accessed at www.acpfoundation.org/hl/ht_back_en.htm.
78. **Buchbinder R, Gross DP, Werner EL, Hayden JA.** Understanding the characteristics of effective mass media campaigns for back pain and methodological challenges in evaluating their effects. Spine (Phila Pa 1976). 2008;33:74-80. [PMID: 18091029]
79. **U.S. Government Accountability Office.** Medicare part B imaging services: Rapid spending growth and shift to physician offices indicate need for CMS to consider additional management practices. GAO-08-452. Washington, DC: U.S. Government Accountability Office; 2008. Accessed at www.gao.gov/new.items/d08452.pdf on 30 November 2010.
80. **French SD, Green S, Buchbinder R, Barnes H.** Interventions for improving the appropriate use of imaging in people with musculoskeletal conditions. Cochrane Database Syst Rev. 2010:CD006094. [PMID: 20091583]
81. **Grimshaw JM, Shirran L, Thomas R, Mowatt G, Fraser C, Bero L, et al.** Changing provider behavior: an overview of systematic reviews of interventions. Med Care. 2001;39:II2-45. [PMID: 11583120]
82. **Schectman JM, Schroth WS, Verme D, Voss JD.** Randomized controlled trial of education and feedback for implementation of guidelines for acute low back pain. J Gen Intern Med. 2003;18:773-80. [PMID: 14521638]

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Correction: Diagnostic Imaging for Low Back Pain

In the guideline by Chou and colleagues (1), the third statement in the section "Defer imagery after a trial of therapy" in Table 4 should read as follows: Risk factors for vertebral compression fracture (history of osteoporosis, use of corticosteroids, significant trauma, or older age [>65 y in women and >75 y in men]). This has been corrected in the online version.

Reference

1. Chou R, Qaseem A, Owens DK, Shekelle P, for the Clinical Guidelines Committee of the American College of Physicians. Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians. Ann Intern Med. 2011;154:181-189. [PMID: 21282698].

Actigraphy

Plain Language Summary:

Coverage question: Should OHP cover a device used to measure sleep patterns and movements? The device is worn overnight.

Should OHP cover this treatment? No, limited medical studies show that using the device does not help tell if a person has sleeping problems.

Changes to issue summary after public comment period:

No public comment was received on this topic. This document contains no changes from the version released with the early VBBS/HERC packet.

Coverage Question:

Should actigraphy be covered for the evaluation of sleep disorders?

Question source:

Holly Jo Hodges, CCO medical director

Background:

Actigraphy is a procedure that records and integrates the occurrence and degree of limb movement activity over time. Actigraphic devices can be worn on the wrist, ankle or waist. Actigraphy testing consists of a small portable device (actigraph) that senses physical motion and stores the resulting information. Actigraphy testing has been predominantly used in research studies to evaluate rest-activity cycles in patients with sleep disorders, to determine circadian rhythm activity cycles, and to determine the effect of a treatment on sleep.

Alternative ways to measure movement during sleep are sleep logs, which is used for evaluation of conditions like insomnia. Actigraphy is commonly included as one of the measurements in home sleep apnea testing (HSAT) and polysomnograms (PSG).

Previous HSC/HERC reviews:

Actigraphy was last reviewed in 2008. No studies were identified that evaluate the effects of actigraphy on clinical outcomes for patients with sleep disorders. The 2007 American Society of Sleep Medicine guideline was included in the review. The decision was to place on the never covered file, which became GN173.

Current Prioritized List/Coverage status:

CPT 95803 (Actigraphy testing, recording, analysis, interpretation and report (minimum of 72 hours to 14 consecutive days of recording) is on line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

Actigraphy

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA)

For adults over the age of 18 years:

A) For patients with clinical signs and symptoms consistent with obstructive sleep apnea (OSA), a home sleep study is the first-line diagnostic test for most patients, when available.
   1) For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type I-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line.

B) Polysomnography in a sleep lab is indicated as a first-line test for patients with significant cardiorespiratory disease,
   potential respiratory muscle weakness due to a neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia.

C) If a patient has had an inconclusive (or negative) home sleep apnea test and a clinical suspicion for OSA remains, then attended polysomnography is included on this line. Split night diagnostic protocols are required when a diagnosis of OSA is confirmed in the first portion of the night.

D) Repeat sleep studies are covered up to twice a year when one of the following has occurred since the most recent test:
   1) recurrence of OSA symptoms
   2) weight change of more than 10% of body weight
   3) new or worsening health conditions related to OSA
   4) upper airway surgical procedures or initial treatment with oral appliances

For children age of 18 or younger:

A) Obstructive sleep apnea (OSA) must be diagnosed by
   1) nocturnal polysomnography with an AHI >5 episodes/h or AHI >1 episodes/h with history and exam consistent with
      OSA, OR
   2) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or
      alternatives desaturation (>3%) index >3.5 episodes/h,OR
   3) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
   4) consultation with a sleep medicine specialist.

B) Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify
   perioperative risk is recommended for
   1) high-risk children (i.e., children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
   2) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical
      examination and the reported severity of sleep-disordered breathing), children younger than three years of age

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

Actigraphy

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 654
The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
95803	Actigraphy	No clinically important benefit	January, 2009

Evidence:

1) **Smith 2018**, Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment
    a. N=81 studies comparing actigraphy to sleep logs and/or PSG
        i. The quality of evidence for actigraphy for both assessment and the evaluation of treatment response for critical clinical outcomes for insomnia was moderate to high depending on the outcome. The reason for downgrading the quality of evidence for some comparisons or outcomes was imprecision. Thus, the overall quality of evidence was moderate
    b. Evaluation of insomnia in adults
        i. Initial assessment
            1. Meta-analsysis found clinically significant differences between actigraphy and sleep logs in measurement of total sleep time (TST), sleep latency, and sleep efficiency
        ii. Assessment of response to treatment
            1. Meta-analysis did not show a clinically significant differences in total sleep time (TST) wake after sleep onset, or sleep efficiency between actigraphy and sleep logs or PSG to assess treatment results
            2. Meta-analysis did not show a clinically significant differences in sleep latency (SL) between actigraphy and sleep logs with treatment. Meta-analysis was not done between actigraphy and PSG to assess treatment results
    c. Evaluation of insomnia in pediatric populations
        i. With respect to treatment response, meta-analysis of 3 studies demonstrated that actigraphy and sleep logs yielded similar estimates of posttreatment SL with a small mean difference in SL of 2.94 minutes higher (95% CI: 13.10 minutes lower to 7.21 minutes higher) compared to sleep logs. The quality of evidence was moderate due to the small sample size
        ii. With respect to treatment response, meta-analysis of 4 studies demonstrated a clinically significant mean difference in WASO of 45.72 minutes higher (95% CI: 18.46 to 72.94 minutes higher) with actigraphy compared to sleep logs,

suggesting that actigraphy and sleep logs provide distinct information when assessing posttreatment WASO. The quality of evidence was moderate due to imprecision and small sample size

iii. No studies reported on sleep efficiency

d. Evaluation of circadian rhythm sleep-wake disorders in adults
   i. N=3 studies. The quality of evidence for sleep onset was very low due to small sample size and imprecision.
e. Evaluation of circadian rhythm sleep-wake disorders in pediatric populations
   i. 3 studies met inclusion criteria. The overall quality of evidence was low due to the small sample sizes, and imprecision
   ii. With respect to treatment response, meta-analysis of three studies demonstrated that actigraphy TST met the clinical significance threshold of 25 minutes, indicating that actigraphy and sleep logs provide distinct information when assessing posttreatment TST. Meta-analysis demonstrated a large mean difference of 52.7 minutes lower TST (95% CI: 20.8 to 84.6 minutes lower) for actigraphy estimates compared to sleep logs.
   iii. When assessing response to treatment, the small mean difference for posttreatment SL of 1.1 minutes lower (95% CI: 11.1 minutes lower to 9.0 minute higher) for actigraphy compared to sleep logs, was not clinically significant
   iv. Sleep onset response to treatment was examined in one study that did not find a clinically significant difference
f. Evaluation of sleep disordered breathing with home sleep apnea tests in adults
   i. Actigraphy appeared to be less accurate in estimating TST as PSG-determined AHI increases, likely due to movements related to severe and frequent apneas
g. Use of Actigraphy in the Evaluation of Central Disorders of Hypersomnolence With the Multiple Sleep Latency Test
   i. Only 1 study identified
   ii. An in-center sleep study with EEG, EMG and EOG recording is recommended as standard procedure for the night prior to the MSLT to identify any underlying clinical conditions that could result in sleep fragmentation and to document that the patient had a sufficient amount of sleep the night prior to the study
h. Use of Actigraphy in the Evaluation of Periodic Limb Movement Disorder
   i. N=5 studies, meta-analysis was not possible
   ii. These studies demonstrate that actigraphy does not accurately identify periodic limb movements, compared to the gold standard EMG. The quality of evidence was moderate due to imprecision.

Submitted literature:

None submitted to date.

Expert guidelines:

1) **Smith 2018**, Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Clinical Practice Guideline

Actigraphy

a. Recommendation 1: We suggest that clinicians use actigraphy to estimate sleep parameters in adult patients with insomnia disorder. (Conditional)
    i. The overall quality of evidence was moderate due to imprecision.
b. Recommendation 2: We suggest that clinicians use actigraphy in the assessment of pediatric patients with insomnia disorder. (Conditional)
    i. The overall quality of evidence was moderate due to imprecision and the small sample size.
c. Recommendation 3: We suggest that clinicians use actigraphy in the assessment of adult patients with circadian rhythm sleep-wake disorder. (Conditional)
    i. The overall quality of the evidence was very low due to small sample size and imprecision
d. Recommendation 4: We suggest that clinicians use actigraphy in the assessment of pediatric patients with circadian rhythm sleep-wake disorder. (Conditional)
    i. The overall quality of evidence was low due to imprecision and small sample sizes
e. Recommendation 5: We suggest that clinicians use actigraphy integrated with home sleep apnea test devices to estimate total sleep time during recording (in the absence of alternative objective measurements of total sleep time) in adult patients suspected of sleep-disordered breathing. (Conditional)
    i. The overall quality of evidence was low, due to imprecision, small sample size and only indirect comparison of HSAT with actigraphy versus PSG (instead of directly comparing HSAT with and without integrated actigraphy)
f. Recommendation 6: We suggest that clinicians use actigraphy to monitor total sleep time prior to testing with the Multiple Sleep Latency Test in adult and pediatric patients with suspected central disorders of hypersomnolence. (Conditional)
    i. The overall quality of evidence was moderate, downgraded due to imprecision and indirectness of additional evidence from other recommendations
g. Recommendation 7: We suggest that clinicians use actigraphy to estimate total sleep time in adult patients with suspected insufficient sleep syndrome (Conditional)
    i. The overall quality of evidence was moderate due to imprecision, heterogeneity, and small sample sizes in the treatment response studies
h. Recommendation 8: We recommend that clinicians not use actigraphy in place of electromyography for the diagnosis of periodic limb movement disorder in adult and pediatric patients (Strong)
    i. The overall quality of evidence was moderate due to low sample size and imprecision

Other payer policies:

1) CMS LCD 2019, Noridian: Polysomnography and Other Sleep Studies
    a. Actigraphy (CPT 93803) is not covered for diagnosis of any sleep disorder
2) Aetna 2023: Actigraphy testing/measurement (e.g., the Actiwatch, AW-64, and Emfit; not an all-inclusive list) for the following indications (not an all-inclusive list) because there is insufficient scientific evidence in the medical literature to support its use in clinical practice
3) Regency BCBS 2023
    a. Actigraphy is considered investigational as a technique to record and analyze body movement, including but not limited to its use to evaluate sleep disorders.

Actigraphy

4) United Health care 2023
    a. The following studies are not medically necessary due to insufficient evidence of efficacy: Actigraphy for any sleep disorders

Expert input:

None submitted to date.

Actigraphy

HERC staff summary: Actigraphy has limited evidence that it affects diagnosis or evaluation of treatment for various sleep disorders. The American Academy of Sleep Medicine gives use of actigraphy only a conditional recommendation for any condition other than periodic limb movement disorder which has a strong recommendation against. Alternative measurements, such as sleep logs, are lower cost and readily available. Actigraphy can be one of the modalities included in a sleep study; if that is the case, then the actigraphy is not billed separately. No private payer policy identified covers actigraphy.

HERC staff recommend against adding covering for actigraphy.

HERC staff recommendation:

1) Update the actigraphy entry in GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 654
The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
95803	Actigraphy	No clinically important benefit	May 2024 ~~January, 2009~~

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REVIEW ARTICLES

Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment

Michael T. Smith, MA, PhD[1]; Christina S. McCrae, PhD[2]; Joseph Cheung, MD, MS[3]; Jennifer L. Martin, PhD[4,5]; Christopher G. Harrod, MS[6]; Jonathan L. Heald, MA[6]; Kelly A. Carden, MD[7]

[1]Johns Hopkins School of Medicine, Baltimore, Maryland; [2]University of Missouri, Columbia, Missouri; [3]Stanford Center for Sleep Sciences and Medicine, Stanford University, Palo Alto, California; [4]David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, California; [5]VA Greater Los Angeles Healthcare System, Geriatric Research, Education and Clinical Center, Los Angeles, California; [6]American Academy of Sleep Medicine, Darien, Illinois; [7]Saint Thomas Medical Partners-Sleep Specialists, Nashville, Tennessee

Introduction: The purpose of this systematic review is to provide supporting evidence for a clinical practice guideline on the use of actigraphy.
Methods: The American Academy of Sleep Medicine commissioned a task force of experts in sleep medicine. A systematic review was conducted to identify studies that compared the use of actigraphy, sleep logs, and/or polysomnography. Statistical analyses were performed to determine the clinical significance of using actigraphy as an objective measure of sleep and circadian parameters. Finally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process was used to assess the evidence for making recommendations.
Results: The literature search resulted in 81 studies that met inclusion criteria; all 81 studies provided data suitable for statistical analyses. These data demonstrate that actigraphy provides consistent objective data that is often unique from patient-reported sleep logs for some sleep parameters in adult and pediatric patients with suspected or diagnosed insomnia, circadian rhythm sleep-wake disorders, sleep-disordered breathing, central disorders of hypersomnolence, and adults with insufficient sleep syndrome. These data also demonstrate that actigraphy is not a reliable measure of periodic limb movements in adult and pediatric patients. The task force provided a detailed summary of the evidence along with the quality of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations.
Keywords: actigraphy, circadian rhythm, sleep disorders, systematic review
Citation: Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, Carden KA. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med.* 2018;14(7):1209–1230.

INTRODUCTION

This systematic review is intended to provide supporting evidence for a clinical practice guideline on the use of actigraphy in patients with suspected or diagnosed sleep disorders or circadian rhythm sleep-wake disorders,[1] and update the evidence review conducted for the previously published American Academy of Sleep Medicine (AASM) practice parameters on the use of actigraphy in these populations.[2] The scientific literature summarized in prior practice parameters established the validity of actigraphy to assess sleep in healthy individuals and select groups of patients. The objective of this systematic review is to examine the clinical value of actigraphy in the assessment and treatment of patients with suspected or diagnosed sleep disorders and circadian rhythm sleep-wake disorders (CRSWDs). The review focuses exclusively on clinical grade devices approved by the FDA as an actigraph or equivalent device that uses an accelerometer to measure limb activity associated with movement during sleep for physiologic applications. The review does not cover consumer wearable devices,[3] or other non-prescription devices directly marketed to consumers.

BACKGROUND

Actigraphy is a procedure that records and integrates the occurrence and degree of limb movement activity over time. Actigraphic devices can be worn on the wrist, ankle or waist, relatively unobtrusively over a period of days to weeks. For sleep applications, the devices are typically worn on the wrist or ankle. Mathematical algorithms are then applied to these data to estimate wakefulness and sleep. In addition to providing a graphical summary of wakefulness and sleep patterns over time (ie, temporal raster plots), actigraphy generates estimates of certain sleep parameters that are also commonly estimated by using sleep logs, or measured directly by polysomnography (PSG), the gold standard measure of sleep. The sleep parameters estimated by actigraphy, in common with standard sleep logs, include: sleep latency (SL); total sleep time (TST); wake after sleep onset (WASO); and sleep efficiency (SE; SE = TST / time in bed). Unlike PSG, actigraphy does not provide estimates of sleep architecture, as information related to the staging of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep is generally not available,

and requires electroencephalogram (EEG), electrooculography (EOG), and electromyography (EMG). Similarly, actigraphy does not provide information related to respiratory function.

Actigraphy devices available for clinical use generally include a piezoelectric or a microelectromechanical systems accelerometer. The devices have storage to enable transfer of the resulting values into an interface (usually via USB or serial port) and to program the timing mechanism. Many devices also have at least one event button that can be used by the wearer to document select events (eg, drowsiness, bed time). Some actigraphy devices also have light sensors for detecting white light or specific wavelengths of light.

Several factors have been identified as important for the reliable and valid use of actigraphy to measure certain sleep parameters.[4] These include: (1) technical features of the device (eg, tri-axial versus dual or single axis accelerometers); (2) software driven data acquisition settings (eg, sampling rates and sensitivity settings); (3) location of device placement[5]; (4) the mathematical algorithms used to estimate sleep/wake[6]; (5) clinical features of the population being studied, (6) utilization of a standardized scoring approach to setting rest activity intervals; and (7) training of patients in data collection procedures.[7] Standardized information on the technical aspects of actigraphy as well as analysis and interpretation procedures for clinical and research use have recently been published.[8] It is important to note that the basic technology in products sold "direct to consumers" may differ significantly from what is available for clinical application. At the present time, data are not adequate to suggest that consumer products can be used as a replacement for clinical devices using validated sleep scoring algorithms, technologies, and procedures.

In clinical practice, patients or caregivers are sometimes asked to estimate and record certain sleep parameters and related information manually through daily sleep logs. Sleep logs provide critically important clinical information about the patient's subjective experience. However, when used as a sole assessment tool, sleep logs have some inherent and significant limitations, including: (1) they are subject to bias; (2) sometimes they cannot be completed accurately by patients with cognitive limitations or by infants and children; and (3) they may not be completed because they are cumbersome for many patients and caregivers. In contrast, actigraphy is a relatively passive, objective procedure that involves the use of a nonobtrusive monitor with a low device failure rate. Actigraphy is relatively inexpensive, patient adherence is typically good, and it can provide useful diagnostic information and data regarding treatment response. Actigraphy scoring software typically provides graphical detail about certain sleep parameters and patterns that can be communicated to patients and referring providers in simple, understandable terms.

The role of actigraphy may vary based on the specific sleep disorder and sleep assessment procedure. With respect to insomnia disorder, for example, actigraphy may be more useful as an adjunct to sleep logs (the reference standard for insomnia) or as a standalone procedure in special instances where reliable self-report is not feasible, such as young children ranging to identify sleep disruption in psychiatric, neurodevelopmental, medical, and sleep disorders. The sleep patterns of patients with insomnia are characterized by high night-to-night variability.[9] Concurrent actigraphy and sleep log collection provides information about that variability as well as the degree and pattern of discrepancy between the 2 types of assessment (ie, objective versus subjective).[10,11] Such information is useful for both diagnosis and treatment planning, for example, with respect to identifying and treating paradoxical insomnia.

In patients with suspected or diagnosed CRSWD, characterizing sleep across multiple 24-hour periods is essential for both adult and pediatric populations. Actigraphy-generated temporal raster plots can be extremely useful in visually depicting changing periodicities associated with circadian dysrhythmia, which can facilitate accurate diagnosis. This is true for multiple, specific CRSWDs, and also for differential diagnosis when the type of CRSWD is not clear based on clinical history alone. This is particularly critical as the treatment itself must be tailored to the precise CRSWD. For example, the timing of light exposure or melatonin administration is dependent upon precise estimates of intrinsic circadian phase. Actigraphy may also be a viable method for documenting disturbed sleep/wake patterns in individuals with shift work sleep disorder. The ability of actigraphy software to show time-based relations and easily identify shifting trends in bedtimes and wake times make it an especially useful tool for the assessment of multiple CRSWDs.

Actigraphy may also play a role when administration of a home sleep apnea test (HSAT) is appropriate in adult populations.[12] For gold standard sleep apnea assessment, PSG is used to measure the apnea-hypopnea index (AHI) as determined by the number of respiratory events × 60 divided by the TST in minutes. HSAT refers to a study performed to diagnose sleep-related breathing disorders such as obstructive sleep apnea (OSA), generally without direct determination of sleep versus wake or of sleep stages. The use of the respiratory event index (REI) was introduced to be used for HSATs that do not record sleep by EEG, EOG and EMG. The REI describes the total number of respiratory events scored × 60 divided by monitoring time. HSAT devices that do not have any mechanism for removing the wake time from the denominator in the calculation use total recording time (TRT) in determining the REI. Devices that use TRT in the index calculation are likely to underestimate the severity of the sleep-disordered breathing (SDB) and may result in increased false negatives. HSAT devices that use built-in actigraphy with the ability to eliminate wake and artifact time in estimating sleep time, therefore, may improve the diagnostic accuracy of the REI.

Actigraphy may be especially useful in documenting insufficient sleep both for the purpose of improving the interpretation of the Multiple Sleep Latency Test (MSLT) in adult and pediatric patients with suspected central disorders of hypersomnolence and for assessing insufficient sleep syndrome (ISS). Objective measurement may be especially important in facilitating treatment of the sometimes complex medical and occupational risks associated with ISS.

Some studies have sought to evaluate whether actigraphy worn on the ankles might provide a reasonable estimate of periodic limb movements in adult and pediatric patients, although it is increasingly clear that additional measures of arousal may

Table 1—PICO questions.

1. In adult patients with suspected insomnia disorder, does actigraphy improve the assessment of sleep parameters and treatment response compared to sleep logs alone?
2. In adult patients with suspected circadian rhythm sleep-wake disorders, does actigraphy improve the assessment of sleep parameters and treatment response compared to sleep logs alone?
3. In adult patients with suspected sleep-related breathing disorder, does concurrent actigraphy improve the measurement of SDB severity during home sleep apnea testing by providing an estimate of total sleep time during recording?
4. In patients with suspected central disorders of hypersomnolence, does actigraphy estimation of TST prior to the MSLT improve the diagnostic accuracy of the MSLT compared to sleep logs alone?
5. In patients with suspected periodic limb movement disorder, is lower extremity actigraphy a clinically acceptable alternative to lower extremity EMG for estimating periodic limb movement disorder severity?
6. Among individuals at risk for insufficient sleep syndrome, is actigraphy useful in the assessment of total sleep time and measurement of intervention response?
7. In infants and young children and adolescents with suspected sleep or circadian rhythm sleep-wake disorders, does actigraphy improve assessment of sleep parameters and treatment response compared to sleep logs and/or caregiver report alone?*

* = the results of this PICO question are presented in the text, organized by insomnia and CRSWD. CRSWD = circadian rhythm sleep-wake disorder, EMG = electromyography, MSLT = Multiple Sleep Latency Test, PICO = Patient, Intervention, Comparison, and Outcomes, SDB = sleep-disordered breathing, TST = total sleep time.

Table 2—"Critical" outcomes by patient population.

	TST	SL	WASO	SE	Accuracy*	PLMSI	Sleep Onset	Sleep Offset
Adult Patients								
Insomnia	✓	✓	✓	✓				
CRSWD							✓	✓
HSAT	✓				✓			
MSLT	✓							
PLMD					✓	✓		
ISS	✓							
Pediatric Patients								
Insomnia	✓	✓	✓	✓				
CRSWD	✓	✓					✓	✓
MSLT	✓							
PLMD					✓	✓		

* = accuracy encompasses sensitivity, specificity, and accuracy. CRSWD = circadian rhythm sleep-wake disorders, HSAT = home sleep apnea test, ISS = insufficient sleep syndrome, MSLT = Multiple Sleep Latency Test, PLMD = periodic limb movement disorder, PLMSI = periodic limb movement of sleep index, SE = sleep efficiency, SL = sleep latency, TST = total sleep time, WASO = wake after sleep onset.

be important in evaluating the clinical significance of periodic limb movement during sleep.

METHODS

Expert Task Force

The AASM commissioned a task force (TF) of sleep medicine clinicians with expertise in the use of actigraphy in patients with suspected sleep disorders to develop this systematic review. The TF was required to disclose all potential conflicts of interest (COI) according to the AASM's COI policy prior to being appointed to the TF, and throughout the development of this document. In accordance with the AASM's conflicts of interest policy, TF members with a Level 1 conflict were not allowed to participate. TF members with a Level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures section.

PICO Questions

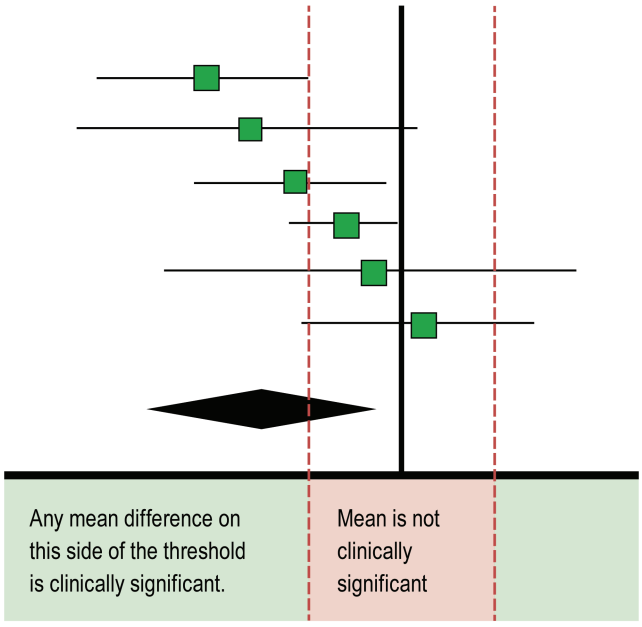
PICO (Patient, Intervention, Comparison, and Outcomes) questions were developed by the TF after a review of the existing AASM practice parameters on the use of actigraphy,[2] and a review of relevant systematic reviews, meta-analyses, and guidelines published since June 2005. To develop the PICO questions, the TF identified sleep disorders for which actigraphy may provide clinically useful information (summarized in **Table 1**), and the clinically relevant outcomes that actigraphy provides for each sleep disorder (summarized in **Table 2**). The

Table 3—Clinical significance thresholds for the minimum allowable mean difference between actigraphy versus sleep log or caregiver report.

	TST (minutes)	SL (minutes)	WASO (minutes)	SE (%)	Accuracy*	PLMSI (events/h)	Sleep Onset (minutes)	Sleep Offset (minutes)
Adult Patients								
Insomnia	20	15	15	2.5	–	–	–	–
CRSWD	–	–	–	–	–	–	20	20
HSAT	N/A	–	–	–	N/A	–	–	–
MSLT†	20	–	–	–	–	–	–	–
PLMD	–	–	–	–	N/A	N/A	–	–
ISS	20	–	–	–	–	–	–	–
Pediatric Patients								
Insomnia	25	20	20	5	–	–	–	–
CRSWD	25	20	–	–	–	–	25	25
MSLT†	20	–	–	–	–	–	–	–
PLMD	–	–	–	–	N/A	N/A	–	–

The thresholds in this table represent the minimum allowable mean difference; a mean difference greater than these thresholds indicates a need for objective reporting of sleep parameters. * = accuracy encompasses sensitivity, specificity, and accuracy. † = measurements prior to MSLT. CRSWD = circadian rhythm sleep-wake disorder, HSAT = home sleep apnea test, ISS = insufficient sleep syndrome, MSLT = Multiple Sleep Latency Test, PLMD = periodic limb movement disorder, PLMSI = periodic limb movement of sleep index, SE = sleep efficiency, SL = sleep latency, TST = total sleep time, WASO = wake after sleep onset.

Figure 1—Hypothetical mean difference of actigraphy versus sleep log measurements (clinically significant).



AASM Board of Directors approved the final list of questions before the literature searches were performed.

The TF compared actigraphy to both sleep logs and PSG to determine whether actigraphy provides information that is consistent with PSG and also distinct from patient-reported data. The TF set two different sets of clinical significance thresholds (CST) for each outcome and PICO to determine if the data provided by actigraphy was clinically significant. The first CSTs were set for comparisons of actigraphy to sleep logs and was defined as the minimum allowable mean difference between the measurements. When comparing actigraphy to sleep logs, a mean difference greater than these thresholds indicates a clinically meaningful difference and a need for objective reporting of sleep parameters. A summary of these CSTs is presented in **Table 3**; a graphical representation of these thresholds is presented in **Figure 1**. The second CSTs were set for comparisons of actigraphy to PSG and were defined as the maximum allowable 95% confidence interval (CI) for the mean difference (unless otherwise noted in **Table 4**). When comparing actigraphy to PSG, a 95% CI within these thresholds indicates that actigraphy provides a sufficiently narrow range of possible mean differences relative to PSG, and therefore provides consistent objective measurements for reporting of sleep parameters. A summary of these CSTs is presented in **Table 4**; a graphical representation of these thresholds is presented in **Figure 2**. The CSTs were established prior to analysis based on the clinical judgement and experience of the TF and informed by the literature. Larger CSTs were established for pediatric populations due to increased measurement error associated with caregiver report, and both PSG and self-report sleep diary alternatives pose additional challenges for some pediatric populations, such as those with developmental disabilities, which likely increase measurement error. In addition, there is more variability across pediatric patients based on age and other factors. The TF endeavored to balance the need for accuracy,

Table 4—Clinical Significance Thresholds for the maximum allowable 95% CI of the mean difference between actigraphy versus PSG.

	TST (minutes)	SL (minutes)	WASO (minutes)	SE (%)	Accuracy*	PLMSI (events/h)	Sleep Onset (minutes)	Sleep Offset (minutes)
Adult Patients								
Insomnia	40	30	30	5	–	–	–	–
CRSWD	–	–	–	–	–	–	40	40
HSAT	40‡	–	–	–	75§	–	–	–
MSLT†	40‡	–	–	–	–	–	–	–
PLMD	–	–	–	–	75§	5‡	–	–
ISS	30	–	–	–	–	–	–	–
Pediatric Patients								
Insomnia	50	40	40	10	–	–	–	–
CRSWD	50	40	–	–	–	–	50	50
MSLT†	40‡	–	–	–	–	–	–	–
PLMD	–	–	–	–	75§	1.75‡	–	–

The thresholds in this table represent the maximum allowable 95% CI for mean difference (unless otherwise noted); a 95% CI within these thresholds indicates that actigraphy provides consistent objective measurements relative to PSG. * = accuracy encompasses sensitivity, specificity, and accuracy. † = measurements prior to MSLT. ‡ = thresholds apply to both the maximum allowable mean difference and the maximum allowable 95% CI. § = thresholds for accuracy of % cutoffs, rather than maximum allowable 95% CI for mean difference. CI = confidence interval, CRSWD = circadian rhythm sleep-wake disorder, HSAT = home sleep apnea test, ISS = insufficient sleep syndrome, MSLT = Multiple Sleep Latency Test, PLMD = periodic limb movement disorder, PLMSI = periodic limb movement of sleep index, PSG = polysomnography, SE = sleep efficiency, SL = sleep latency, TST = total sleep time, WASO = wake after sleep onset.

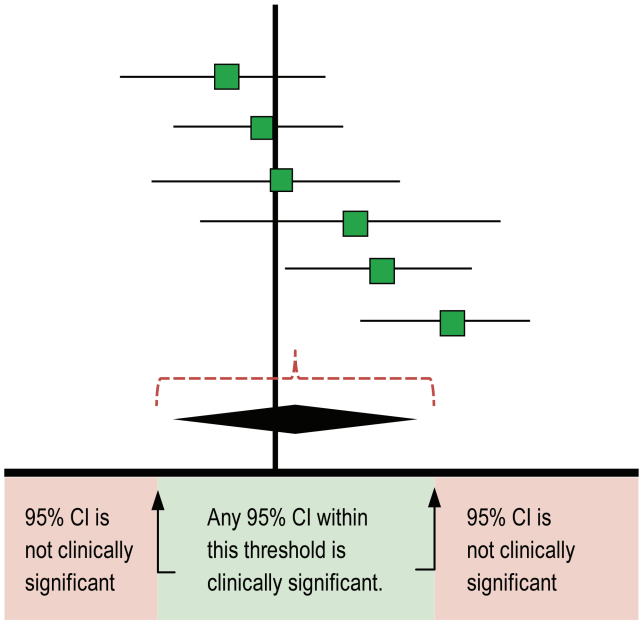
care giver burden, and the differential sleep needs of pediatric groups relative to adults.

Literature Searches, Evidence Review and Data Extraction

Literature searches were performed using the PubMed and Embase databases for individual questions. A combination of MeSH terms and keywords listed in the supplemental material were used. The databases were searched from June 1, 2005 through January 10, 2018 for any relevant literature published since the 2007 guideline literature search was performed. The articles that were cited in the 2007 AASM practice parameters were included if they met the study inclusion criteria. In addition, the task force reviewed all AASM guidelines published since 2006, to identify additional references that may be relevant to actigraphy. The limits of the searches (requiring all listed criteria to be met) were: humans, English, all adults (with the exception of questions 4, 5, and 7), and randomized controlled trial (RCT) or observational studies. A total of 3,073 citations were identified from both databases, and 37 studies were identified in the other AASM practice parameters.

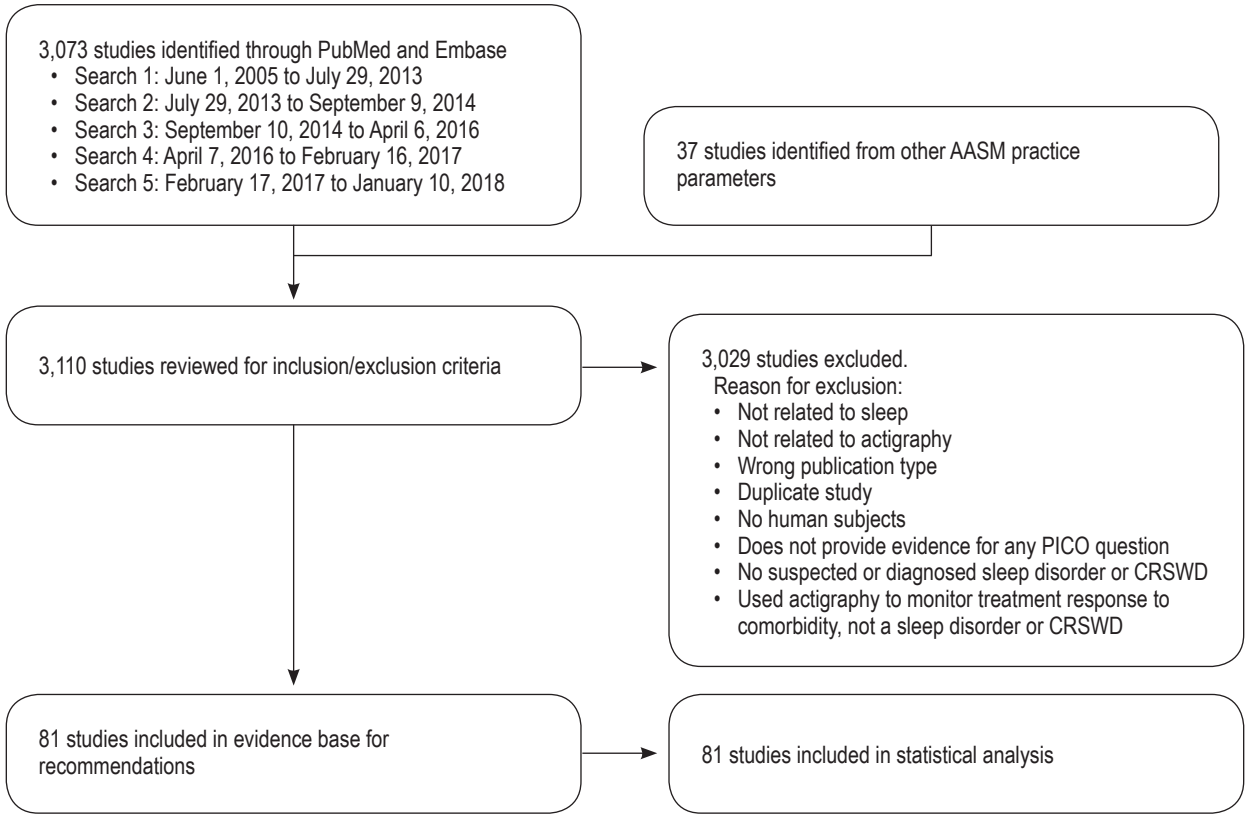
Articles were included for review and possible data extraction if they focused on patient assessment or monitoring of treatment response for a sleep disorder with actigraphy, sleep logs and/or PSG; addressed at least one of the PICO questions; and included one of the outcomes of interest. Articles were excluded if they focused on actigraphy not related to sleep; were not RCTs or observational studies; were duplicates; involved non-human subjects; involved subjects without a suspected or diagnosed sleep or circadian rhythm sleep-wake disorder; used actigraphy to monitor treatment response of a comorbid condition; or used actigraphy as a measurement tool, but did

Figure 2—Hypothetical range of mean differences of actigraphy versus PSG measurements (clinically significant).



CI = confidence interval, PSG = polysomnography.

Figure 3—Evidence base flow diagram.



AASM = American Academy of Sleep Medicine, CRSWD = circadian rhythm sleep-wake disorder, PICO = Patient, Intervention, Comparison, and Outcomes.

not provide evidence for any PICO questions. Studies were also excluded if they did not present data for any of the critical outcomes and/or did not present data in a format suitable for statistical analysis. A total of 81 articles from the literature searches were accepted and considered for meta-analysis and evidence grading. Specific data elements of all accepted studies were extracted into evidence tables (not published) to address each clinical question. Upon review of these articles, 81 studies were determined to be suitable for meta-analysis and/or the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. An evidence base flow diagram is presented in **Figure 3**.

Meta-Analysis and Interpretation of Clinical Significance

Meta-analyses were performed on outcomes of interest for each PICO question. Review Manager 5.3 software (The Cochrane Collaboration, London, United Kingdom) was used to compare the use of actigraphy versus sleep logs and actigraphy versus PSG for the assessment of sleep parameters and of treatment response in patients with various sleep disorders. All analyses were performed using the random effects model with results displayed as a forest plot. Meta-analyses were performed when at least 5 studies were available by pooling data across studies for each relevant outcome of interest for each PICO (studies for PICO 7 were grouped by patient population). When 3–4 studies were available, meta-analyses were performed at the discretion of the task force. For several questions, there was insufficient evidence to perform meta-analyses for certain comparisons and outcome measures. In these cases, studies are described individually.

For the assessment of sleep parameter estimates, the mean differences in baseline sleep parameter measurements from actigraphy, sleep logs and PSG were determined by pooling both intervention and non-intervention studies. (For simplicity, the term "baseline" is used in the text to describe all data extracted for the pre-intervention phase of interventional studies and the initial assessment time point for cross sectional studies.) For the assessment of treatment response, given the limited number of treatment outcome studies identified, the heterogeneity of intervention types and assessment time points, the task force was not able to evaluate whether actigraphy was sensitive to change relative to sleep logs or PSG. Instead, the TF analyzed the mean difference of posttreatment measurements from actigraphy, sleep logs and PSG. The pooled results for each continuous outcome measure are expressed as the mean difference between the intervention and comparator. The results of the meta-analyses are presented in the supplemental material.

Interpretation of clinical significance for the outcomes of interest was conducted in two different ways. First, by comparing the mean difference in measurements of actigraphy and sleep logs against their CSTs (**Table 3**). Next, by comparing the 95% CI of the mean difference of actigraphy versus PSG measurements to their CSTs (**Table 4**). For comparisons of actigraphy

to sleep logs, the CST was defined as the minimum allowable mean difference between the measurements; a mean difference greater than the threshold demonstrates that actigraphy provides unique information from sleep logs, and objective measurements are warranted (see **Figure 1**, which shows an example of a clinically significant mean difference). For comparisons of actigraphy to PSG, the CST was defined as the maximum allowable 95% CI for the mean difference between actigraphy and PSG (unless otherwise noted in **Table 4**); a 95% CI within the threshold demonstrates that actigraphy provides a sufficiently narrow range of possible mean differences relative to PSG (*regardless* of the mean difference, unless otherwise noted in **Table 4**). A sufficiently narrow range of mean differences indicates that actigraphy provides consistent objective measurements relative to PSG, and may be useful as an objective measurement of sleep parameters (see **Figure 2**, which shows an example of a sufficiently narrow range of mean differences).

Detailed reviews of the evidence and clinical significance of the findings for all critical outcomes are provided for each PICO question.

GRADE Assessment for Developing Recommendations

The evidence was assessed according to the GRADE process for the purposes of making clinical practice recommendations.[13,14] The TF considered the following four GRADE domains: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below:

1. **Quality of evidence:** based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% CI relative to the CST, sample size < 200), inconsistency and indirectness (study population), and risk of publication bias (funding sources), the TF determined their overall confidence that the estimated differences in measurements found in the body of evidence were representative of the true differences in measurements that patients would experience. The overall quality of the evidence was based on all outcomes that the TF deemed critical for decision making.
2. **Benefits versus harms:** based on any harms/side effects reported within the accepted literature, and the clinical expertise of the TF, the TF determined if the beneficial outcomes of using actigraphy outweighed any harms. Benefits versus harms compared to alternative measurement tools was also considered.
3. **Patient values and preferences:** based on the clinical expertise of the TF members and any data published on the topic relevant to patient preferences for actigraphy, the TF determined if patient values and preferences would be consistent across the majority of patients, and if patients would use actigraphy based on the body of evidence.
4. **Resource use:** based on the clinical expertise of the TF members, the TF determined if accessibility and costs associated with actigraphy compared favorably to alternative measurement tools. Information on both costs to patients and to the health care system were considered.

A summary of each GRADE domain is provided after the detailed evidence review for each PICO question.

Public Comment and Final Approval

Drafts of the systematic review and accompanying guideline were made available for public comment for a two-week period on the AASM website. AASM members, the general public and other relevant stakeholders were invited to provide feedback on the drafts. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the scope and feasibility of comments. The public comments and revised documents were submitted to the AASM Board of Directors who subsequently approved the final documents for publication.

The AASM expects this systematic review to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

THE USE OF ACTIGRAPHY

The aims of the current systematic reviews and data analyses were to address 7 PICO questions pertaining to the use of actigraphy relative to sleep logs and/or PSG across a wide range of clinical populations, and in conjunction with HSAT and MSLT. While sufficient data were available for meta-analyses for most PICO questions, there are caveats that should be considered with respect to interpreting the results. With regard to sleep parameters, the TF noted variability across studies with respect to definitions and technical details such as algorithms and sensitivity threshold settings used or reported. As is common practice, many studies utilized information noted by the patient in a sleep log for the analysis and interpretation of actigraphy-estimated sleep parameters. This is important particularly with respect to determining bedtime ("lights off") to calculate SL. Other studies relied completely on actigraphy algorithms to estimate SL, while some studies failed to report these details. The TF decided not to analyze the number of nightly awakenings as a sleep parameter of interest, since actigraphy typically identifies numerous isolated brief awakenings lasting less than a minute (eg, 30 seconds), which are common even in normal sleep and often not perceived, remembered or retrospectively reported by patients. Diary measures of awakenings likely reflect a distinct construct related to consolidated frank awakenings, which are not consistently defined or reported in standard software to date, making comparison across devices and sleep log estimates of questionable utility. The TF also cautions that generalizability of some of the meta-analytic findings may be limited due to a small number of studies meeting the inclusion/exclusion criteria and/or patients across studies. Generalizability to the broad spectrum of sleep disorder patients seen in clinical settings may also be limited by heterogeneity across sleep disorder severity and subpopulations with clinical comorbidities, both of which may influence validity.

Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed

by the task force. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the recommendations, which are provided in the accompanying clinical practice guideline.[1]

Use of Actigraphy in the Evaluation of Insomnia in Adults

Our review of the literature identified 46 studies[11,15–59] that used actigraphy concurrent with sleep logs and/or PSG in adults with suspected or diagnosed insomnia. Both non-intervention and intervention studies met the eligibility criteria and were included. The number of studies included in the analyses varied by sleep parameter and whether the comparison was to sleep logs or PSG. Overall, more studies were identified that provided comparisons of actigraphy to sleep logs than to PSG.

The data for examining the use of actigraphy for assessment were either based on a single night or drawn from the baseline periods of intervention trials with insomnia and represent sleep parameter values averaged over 1 to 2 weeks. Similarly, data for analyses examining the use of actigraphy to assess treatment response were either based on a single night or were drawn from sleep parameter values averaged over 1 to 2 weeks following treatment. The vast majority of the intervention studies reviewed involved 1 or more components of cognitive-behavioral treatment for insomnia. Due to the number of studies identified, they are not individually described here. A summary of the study characteristics can be found in the supplemental material.

The meta-analyses and figures are provided in the supplemental material, **Figure S1a** through **Figure S8b**. Summary of findings tables are provided in the supplemental material, **Table S1a** through **S2b**. A summary of the evidence for each outcome is provided below.

Total Sleep Time

A meta-analysis of 40 studies[11,15–50,56,57,59] compared actigraphy to sleep logs for the assessment of TST (**Figure S1a**). The meta-analysis showed a clinically significant mean difference of 37.40 minutes higher (95% CI: 22.14 to 52.67 minutes higher) TST as assessed by actigraphy compared to sleep logs. This difference indicates actigraphy and sleep logs provide distinct information when assessing TST. The quality of evidence was moderate due to imprecision.

A meta-analysis of 15 studies[15,16,18,20–22,24,27,33,39–41,43,46,56] compared actigraphy to PSG for the assessment of TST in patients with suspected or diagnosed insomnia. See supplemental material, **Figure S1b**. The meta-analysis showed a clinically significant range of possible mean differences of 35.12 minutes (95% CI: 8.07 minutes lower to 27.05 minutes higher) with an overall mean difference of 10.14 minutes. This range is narrow enough that actigraphy can be reliably used to provide an objective assessment of TST for the purpose of making clinical care decisions. The quality of evidence was high.

A meta-analysis of 30[11,25–50,57–59] studies compared actigraphy to sleep logs for the assessment of treatment response in TST (**Figure S5a**). The meta-analysis demonstrated a clinically insignificant mean difference in TST measured by actigraphy of 8.10 minutes higher (95% CI: 9.23 minutes lower to 25.42 minutes higher) as compared to logs. This small difference indicates actigraphy and sleep logs provide similar measurements of treatment-related changes in TST. The quality of evidence was moderate due to imprecision.

A meta-analysis of 7 studies[27,33,39–41,43,46] compared actigraphy to PSG for the assessment of treatment response in TST (**Figure S5b**). The meta-analysis demonstrated a clinically insignificant range of possible mean differences of 83.4 minutes (95% CI: 37.1 minutes lower to 46.3 minutes higher) with an overall mean difference of 4.6 minutes. This large range indicates actigraphy and PSG provide distinct information and should not be used interchangeably for the assessment of treatment-related changes in TST. The quality of evidence was moderate due to imprecision.

Sleep Latency

A meta-analysis of 36 studies[11,15–22,24,26,28–32,34–42,44–50,53,55,56,59] compared actigraphy to sleep logs for the assessment of SL (**Figure S2a**). The meta-analysis showed a clinically significant mean difference in SL measured by actigraphy of 23.99 minutes lower (95% CI: 27.29 to 20.69 minutes lower) as compared to sleep logs. This difference indicates actigraphy and sleep logs provide distinct information when assessing SL. The quality of evidence was high.

A meta-analysis of 12 studies[15,16,18,20–22,24,39–41,46,56] compared actigraphy to PSG for the assessment of SL (**Figure S2b**). The meta-analysis showed a clinically significant range of possible mean differences of 6.78 minutes (95% CI: 2.29 to 9.07 minutes lower) with a mean difference of 6.17 minutes. This range is narrow enough that actigraphy can be reliably used to provide an objective assessment of SL for the purpose of making clinical care decisions. The quality of evidence was high.

A meta-analysis of 27 studies[11,26,28–32,34–42,44–50,53,55,58,59] compared actigraphy to sleep logs for the assessment of treatment response in SL (**Figure S6a**). The meta-analysis demonstrated a clinically insignificant mean difference in SL measured by actigraphy of 10.55 minutes lower (95% CI: 8.20 to 12.90 minutes lower) as compared to sleep logs. This small difference indicates actigraphy and sleep logs provide similar measurements of treatment-related changes in SL. The quality of evidence was high.

Four studies[39–41,46] compared actigraphy to PSG for the assessment of treatment response in SL (**Figure S6b**). All studies reported a clinically significant range of possible mean differences, with the largest range of differences being 29.8 minutes (95% CI: 12.1 minutes lower to 17.7 minutes higher). This small range indicates actigraphy and PSG provide similar information for the assessment of treatment-related changes in SL. The quality of evidence was moderate due to imprecision due to small sample size.

Wake After Sleep Onset

A meta-analysis of 34 studies[11,15–23,25,27,28,30–32,34–43,46–50,53,55,59] compared actigraphy to sleep logs for the assessment of WASO (**Figure S3a**). The meta-analysis showed a clinically insignificant mean difference in WASO measured by actigraphy of 5.65

minutes lower (95% CI: 14.81 minutes lower to 3.51 minutes higher) as compared to sleep logs. This difference indicates actigraphy and sleep logs do not provide distinct information when assessing WASO. The quality of evidence was high.

A meta-analysis of 12 studies[15,16,18,20–22,27,39–41,43,46] compared actigraphy to PSG for the assessment of WASO (**Figure S3b**). The meta-analysis showed a clinically insignificant range of possible mean differences of 33.22 minutes (95% CI: 13.68 minutes lower to 19.54 minutes higher), with a mean difference of 1.5 minutes. This large range indicates actigraphy cannot be reliably used to provide an objective assessment of WASO that is comparable with PSG. The quality of evidence was downgraded to moderate due to imprecision.

A meta-analysis of 26 studies[11,25,27,28,30–32,34–43,46–50,53,55,58,59] compared actigraphy to sleep logs for the assessment of treatment response in WASO (**Figure S7a**). The meta-analysis demonstrated a clinically insignificant mean difference in WASO measured by actigraphy of 11.47 minutes higher (95% CI: 0.58 minutes lower to 23.51 minutes higher) as compared to sleep logs. This small difference indicates actigraphy and sleep logs provide similar measurements of treatment-related changes in WASO. The quality of evidence was moderate due to imprecision.

A meta-analysis of 6 studies[27,39–41,43,46] compared actigraphy to PSG for the assessment of treatment response in WASO (**Figure S7b**). The meta-analysis demonstrated a clinically insignificant range of possible mean difference in WASO measured by actigraphy as compared to PSG of 86.0 minutes (95% CI: 53.2 minutes lower to 32.8 minutes higher) with a mean difference of 10.2 minutes. This large range indicates actigraphy and PSG provide distinct information and cannot be used interchangeably for the assessment of treatment-related changes in WASO. The quality of evidence was moderate due to imprecision.

Sleep Efficiency

A meta-analysis of 34 studies[11,15,16,18–20,23,25,28–43,46–51,53,55,57,59] compared actigraphy to sleep logs for the assessment of SE (**Figure S4a**). The meta-analysis showed a clinically significant mean difference in SE measured by actigraphy of 7.5% higher (95% CI: 5.1% to 10.0% higher) as compared to sleep logs. This difference indicates actigraphy and sleep logs provide distinct information when assessing SE. The quality of evidence was high.

A meta-analysis of 9 studies[15,16,18,20,33,39–41,46] compared actigraphy to PSG for the assessment of SE (**Figure S4b**). The meta-analysis showed a clinically insignificant range of possible mean differences of 7.8% (95% CI: 4.9% lower to 3.0% higher), with a mean difference of 1%. This large range indicates actigraphy cannot be reliably used to provide an objective assessment of SE that is comparable with PSG. The quality of evidence was moderate due to imprecision.

A meta-analysis of 30 studies[11,25,28–43,46–51,53–55,57,59] compared actigraphy to sleep logs for the assessment of treatment response in SE (**Figure S8a**). The meta-analysis demonstrated a clinically insignificant mean difference in SE measured by actigraphy of 2.1% higher (95% CI: 0.6% lower to 4.8% higher) as compared to sleep logs. This small difference indicates actigraphy and sleep logs provide similar measurements of treatment-related changes in SE. The quality of evidence was moderate due to imprecision.

A meta-analysis of 5 studies[33,39–41,46] compared actigraphy to PSG for the assessment of treatment response in SE (**Figure S8b**). The meta-analysis demonstrated a clinically insignificant range of possible mean difference in SE measured by actigraphy as compared to PSG of 7.9% (95% CI: 0.2% to 8.1%), with a mean difference of 4.2%. This large range indicates actigraphy and PSG provide distinct information and cannot be used interchangeably for the assessment of treatment-related changes in SE. The quality of evidence was moderate due to imprecision.

Overall Quality of Evidence

The quality of evidence for actigraphy for both assessment and the evaluation of treatment response for critical clinical outcomes for insomnia was moderate to high depending on the outcome. The reason for downgrading the quality of evidence for some comparisons or outcomes was imprecision. Thus, the overall quality of evidence was moderate.

Benefits Versus Harms

Actigraphy may be useful to assess TST and SL in patients with suspected and diagnosed insomnia disorder and provides a consistent measure of SL, compared to PSG. Benefits include convenience and relatively low patient burden. Another convenience relative to PSG is that actigraphy requires considerably less time to prepare the patient and the patient can remove the actigraphy device as easily as taking off a watch. The ability of actigraphy to provide relatively low burden, and longitudinal assessment of sleep patterns and response to treatment is another benefit. Actigraphy-derived short sleep in patients with insomnia is associated with negative health outcomes (eg, cardiometabolic risk, hypertension, depression).[60–64] Thus, actigraphy may provide additional benefits for certain patient subgroups, including those with suspected paradoxical insomnia or at risk for cardiometabolic and other medical and psychiatric comorbidities impacted by short sleep duration. These benefits must be weighed against the potential for harm. The TF determined that there were no clinically significant and undesirable outcomes associated with actigraphy. Therefore, the TF determined that if actigraphy is used in the context described in the recommendation and remarks, the risk of harm is minimized and the probability of clinical benefits increased.

Patient Values and Preferences

Complaints of not getting enough sleep and difficulties falling and/or staying asleep are all primary reasons prompting seeking of medical care. Although SL, WASO, and SE are often the targets of treatment, TST is also a relevant outcome for some patients. One study[65] showed patients with objective short TST (< 6 h/night) based on two weeks of actigraphy prior to treatment did not respond as well to CBT-I as did patients with normal TST (≥ 6 hours). Specifically, patients with short TST on objective evaluation reported significantly less improvement in terms of insomnia remission, SE, WASO, and total wake time compared to patients with

normal sleep duration at six months after treatment. Thus, TST, SL, WASO, and SE are all sleep parameters that patients value. Patients may prefer actigraphy to completing daily sleep logs and/or undergoing overnight PSG, given the lower burden. Sleep logs require daily completion over multiple days. In contrast, PSG requires either an overnight stay in the sleep center or a home-based study. Although some individuals with insomnia often sleep better away from their home environment where conditioning often reinforces and perpetuates their insomnia, patients nonetheless may express concern and anxiety regarding their ability to sleep in the lab. For both sleep center and home-based studies, patients can experience burden and anxiety related to both the process of being prepared for the study and their ability to sleep while wearing testing-related equipment. PSG is not recommended for the routine assessment of insomnia, but may be indicated when other sleep disorders are suspected. The TF noted that the use of actigraphy (as reported in the studies evaluated) did not completely eliminate the need for patients to provide some daily self-report information, given that reported in and out of bed times were frequently used to set the sleep window used to score data from the actigraphy device. Some patients may prefer the combined approach of completing sleep logs and actigraphy. Some patients may object to actigraphy, because the wrist band has the potential to aggravate sensitive skin. Addressing the potential dermatological issues (different band, lining the band) may reduce or eliminate skin-related concerns for some patients. The TF determined that actigraphy provides outcomes that patients value with minimal undesired effects.

Resource Use

Actigraphy is more costly than sleep logs in terms of the technical and professional components of the service. However, these costs are relatively low and compare favorably to the technical and professional costs associated with PSG. Economic analyses comparing the cost-effectiveness of these devices for the assessment of insomnia or the evaluation of treatment response have not been conducted. The TF concluded actigraphy may be more cost effective *if* an objective measurement of sleep is needed.

Use of Actigraphy in the Evaluation of Insomnia in Pediatric Populations

Our review of the literature identified a total of 5 studies meeting inclusion criteria. Four studies[66–69] reported mean differences between actigraphy and sleep logs for TST (3 studies),[66,67,69] SL (3 studies),[66,67,69] and WASO (3 studies).[67–69] Data also included the review of one study[70] of non-specific sleep disorders (including participants with insomnia) in children with autism. We also identified 4 intervention studies[67–69,71] for meta-analysis that reported posttreatment actigraphy and sleep log estimates of TST (4 studies),[67–69,71] SL (3 studies)[67,69,71] and WASO (4 studies).[67–69,71] We also reviewed post intervention data from the study of non-specific sleep disorders in children with autism, reported posttreatment data on TST and SL.[70]

Regarding studies reporting baseline data on TST and SL, one was a case-control study comparing young children (mean age = 6.6 ± 1.1 years) with insomnia to healthy controls, and healthy snorers.[66] The other study reported data on TST, SL and WASO and was an RCT of group cognitive behavior therapy for insomnia in adolescents.[67] A single arm pilot study of CBT-I in adolescents also reported baseline data for WASO only (ages 11–18).[68] A second pilot study of modified CBT-I in adolescents with insomnia and depression reported data on TST, SL, and WASO.[69] The study of non-specific sleep disorders provided baseline data on TST and SL and was an RCT testing the effects of a weighted blanket in children with autism whose parents reported sleep problems (mean age = 9, range 5–16 years).[70]

The studies reporting posttreatment data included an RCT of CBT-I with behavioral treatment for anxiety in children (mean age = 9.3 ± 1.9)[71] two studies[67,68] of CBT-I in adolescents, and a pilot study of modified CBT-I in adolescents with insomnia and depression [69]. Posttreatment data was also reviewed for the RCT testing the effects of a weighted blanket in children and adolescents with autism (mean age = 9, range 5–16 years).[70] The meta-analyses and figures are provided in the supplemental material, **Figure S9** through **Figure S14**. Summary of findings tables are provided in the supplemental material, **Table S3** and **Table S4**. A summary of the evidence for each outcome is provided below.

Total Sleep Time

For baseline TST, all three studies[66,69,70] met our clinical significance threshold of 25 minutes, indicating that actigraphy and sleep logs provide distinct information when assessing TST. Actigraphy estimated lower TST compared to sleep logs by a large mean difference of 119.8 minutes (95% CI: 114.4 to 25.2 minutes lower) in one study[66], 27.0 minutes (95% CI: 4.1 to 49.9 minutes lower) in the second[67], and 32.0 minutes (95% CI: 78.79 minutes lower to 14.79 minutes higher) in the third[69]. One additional study of children with autism also met clinical threshold, demonstrating that actigraphy estimated lower TST compared to sleep logs by a large mean difference of 79.0 minutes (95% CI: 49.2 to 108.9 minutes lower)[70] (**Figure S9** and **Figure S28**). The quality of evidence was moderate due to imprecision.

Assessment of treatment response with meta-analysis of four studies[67–69,71] (n = 149) demonstrated that actigraphy TST did not meet the clinical significance threshold of 25 minutes. Actigraphy estimated lower TST compared to sleep logs by a mean difference of 19.14 minutes (95% CI: 46.41 minutes lower to 8.13 minutes higher). One additional study of children with autism[70] did meet the clinical threshold, finding that actigraphy estimated lower TST compared to sleep logs by a large mean difference of 74.5 minutes (95% CI: 40.5 to 108.50 minutes lower) (**Figure S12** and **Figure S29**). These studies indicate the actigraphy and sleep logs provide similar measurements. The quality of evidence was moderate due to the small sample size and imprecision.

Sleep Latency

For baseline SL, none of the three insomnia studies[66,67,69] demonstrated that actigraphy-based estimates of SL met the clinical significance threshold of 20 minutes, suggesting

they provide similar estimates. One study[67] demonstrated a mean difference in SL of 10.0 minutes lower (95% CI: 0.04 to 20.0 minutes lower) compared to sleep logs, the second[66] demonstrated a mean difference in SL of 2.9 minutes higher (95% CI: 1.4 to 4.4 minutes higher) compared to sleep logs, and the third[69] demonstrated a mean difference of 4.0 minutes lower (95% CI: 23.7 minutes lower to 15.7 minutes higher). Additionally, the study of children with autism[70] also failed to reach clinical significance, demonstrating a small mean difference of 6.60 minutes higher (95% CI: 9.7 minutes lower to 22.9 minutes higher) compared to sleep logs (**Figure S10** and **Figure S28**). The quality of evidence was moderate due to imprecision.

With respect to treatment response, meta-analysis of 3 studies[67,69,71] demonstrated that actigraphy and sleep logs yielded similar estimates of posttreatment SL with a small mean difference in SL of 2.94 minutes higher (95% CI: 13.10 minutes lower to 7.21 minutes higher) compared to sleep logs. Additionally, the study of children with autism[70] also failed to meet clinical significance with a small posttreatment mean difference of 18.70 minutes higher (95% CI: 3.3 to 34.1 minutes higher) (**Figure S13** and **Figure S30**). The quality of evidence was moderate due to the small sample size.

Wake After Sleep Onset

The baseline studies assessing WASO,[67–69] demonstrated that all three met the clinical significance threshold of 20 minutes, suggesting that actigraphy and sleep logs provide distinct information when assessing WASO. One study[67] demonstrated that actigraphy estimated a large mean difference in WASO of 23.0 minutes higher (95% CI: 12.8 to 33.2 minutes higher) compared to sleep logs, the second[68] demonstrated that actigraphy estimated a mean difference in WASO of 46.0 minutes higher (95% CI: 35.7 to 56.3 higher) compared to sleep logs, and the third[69] demonstrated a mean difference of 39.0 minutes higher (95% CI: 21.82 to 56.18 minutes higher) (**Figure S11**). The quality of evidence was moderate due to the small sample size.

With respect to treatment response, meta-analysis of 4 studies,[67–69,71] demonstrated a clinically significant mean difference in WASO of 45.72 minutes higher (95% CI: 18.46 to 72.94 minutes higher) with actigraphy compared to sleep logs, suggesting that actigraphy and sleep logs provide distinct information when assessing posttreatment WASO (**Figure S14**). The quality of evidence was moderate due to imprecision and small sample size.

Sleep Efficiency

None of the accepted studies provided data on SE.

Overall Quality of Evidence

The overall quality of evidence was moderate due to the small sample sizes and imprecision. Given the heterogeneous nature of pediatric populations in the included studies, which ranged in age from 3 to19, a span involving changing sleep needs, insomnia symptom presentations and potential distinct insomnia causes, the generalizability of the findings is significantly limited.

Benefits Versus Harms

Potential benefits of actigraphy include increased sensitivity over sleep logs in identifying short sleep and increased WASO, and the ability to obtain reliable sleep parameter estimates when many pediatric patients may be unable to reliably report sleep parameters or when caregiver burden and accuracy is an issue. Potential harms of actigraphy are mild and include skin irritation. When evaluating potential benefits versus harm, the task force considered the vulnerability of this population, the relatively high prevalence of insomnia in pediatric populations[72–74] and findings that sleep disturbance can impact growth and development, psychological and cognitive functions and may be an indicator of medical and psychiatric disorder.[72,75–79] Although studies with PSG data were not identified meeting our eligibility criteria, PSG validation studies have demonstrated acceptable validity of actigraphy in infants and children, particularly in healthy normal subjects.[80–83] Based on their clinical expertise, the task force determined that the potential benefits of actigraphy outweighed potential harms.

Patient Values and Preferences

Although minimal data exists related to patient values and preferences on the use of actigraphy versus sleep logs for assessing insomnia in pediatric populations, the task force's experience is that the use of actigraphy is favored by the majority of patients and caregivers with no significant uncertainty or variability due to: 1) the relatively unobtrusive nature and minor burden of this comparatively passive monitoring procedure; 2) the fact that monitoring sleep patterns over multiple days as required to assess insomnia, imposes a major burden to caregivers of young children unable to accurately report sleep parameters; 3) the utility of objective data monitoring to complement patient self-report and 4) the increased accuracy that actigraphy data adds to inform clinical diagnosis, decision making, and monitoring treatment response. However, families and caregivers sometimes express concern about out of pocket expenses related to inconsistent third-party reimbursements.

Resource Use

The cost of actigraphy is higher than paper sleep log monitoring, but much less expensive than PSG and other home sleep testing devices with multiple sensor technologies. Moreover, PSG and HSAT devices are not well tolerated over multiple consecutive monitoring periods. Minimal data exist evaluating the cost benefit, but potential savings to medical health care systems and third-party payers and employers is potentially high. Actigraphy has the potential to improve the accurate detection of insomnia and treatment. Policy interventions related to data obtained from actigraphy could result in a decrease in downstream health care expenses. At the present time, cost benefits of the use of actigraphy to assess pediatric insomnia and treatment response require systematic study.

Use of Actigraphy in the Evaluation of Circadian Rhythm Sleep-Wake Disorders in Adults

Our review of the literature identified 2 studies[84,85] meeting inclusion criteria. A cross-sectional study[84] compared craniopharyngioma patients, who are at risk for damage to the

sleep-wake and circadian rhythm systems, to matched healthy controls. The study included actigraphy and sleep log assessment of sleep onset and sleep offset, as well as melatonin secretion.[84] Another study[85] assessed sleep and circadian rhythms in hospitalized patients with decompensated cirrhosis. This patient population often exhibits poor sleep/wake, which may be linked to altered circadian rhythms. The figures are provided in the supplemental material, **Figure S15** through **Figure S18**. Summary of findings tables are provided in the supplemental material, **Table S5** and **Table S6**. A summary of the evidence for each outcome is provided below.

Sleep Onset

One study[84] measured sleep onset time in patients with suspected CRSWD due to craniopharyngioma or consequent surgery. In this study,[84] the mean difference in sleep onset time was 0.3 hours later (95% CI: 0.8 hours earlier to 1.4 hours later) with sleep logs compared to actigraphy (**Figure S15**). A second study[85] evaluated the effects of a circadian rhythm intervention (light therapy) on hospitalized patients with liver cirrhosis and found that the difference in measurement of a treatment effect for actigraphy compared to sleep logs was 0.60 hours later (95% CI: 0.1 to 1.1 hours later). These differences crossed the clinical significance thresholds established by the TF, indicating that actigraphy and sleep logs may provide distinct measurements in some patients (**Figure S17**). The quality of evidence for sleep onset was very low due to small sample size and imprecision.

Sleep Offset

The two studies described above[84,85] also assessed sleep offset time. One study[84] reported a mean difference between actigraphy and sleep logs of 0.2 hours later (95% CI: 1.0 hours earlier to 0.6 hours later) for sleep offset time (**Figure S16**). The other study[85] found a mean difference in the measured treatment effect between actigraphy and sleep logs of 0.4 hours earlier (95% CI: 0.9 hours earlier to 0.1 hours later) with actigraphy compared to sleep logs (**Figure S18**). These differences crossed the clinical significance thresholds established by the TF, indicating that actigraphy and sleep logs may provide distinct measurements in some patients. The quality of evidence for sleep onset was very low due to small sample size and imprecision.

Overall Quality of Evidence

The overall quality of evidence was very low due to small sample sizes and imprecision. The two available studies used concurrent measurement; however, the sample sizes in these studies were small. In addition, there was imprecision, with the 95% CI crossing the clinical significance threshold for assessment of treatment response as determined by the TF.

Benefits Versus Harms

The main benefit of actigraphy is that it can be worn in the home setting longitudinally and requires little or no effort for tracking sleep onset and sleep offset times by patients. There are minimal harms associated with the use of actigraphy. In some patient populations (eg, frail older adults in long-term care) where skin health is an issue, the risk of irritation under the device may be higher; however, this risk appears very low (< 1%) in studies recording actigraphy for up to 1 week. Based on their clinical expertise, the task force determined that the benefit of accurate assessment with minimal burden outweigh the potential harms associated with actigraphy devices. It should be noted, however, that the information provided by actigraphy, eg, sleep onset and offset patterns and sleep continuity parameters, is inherently limited with respect to assessing the underlying chronobiological complexity associated with CRSWDs.

Patient Values and Preferences

Indirect evidence suggests actigraphy is acceptable to patients with CRSWDs as shown by high patient acceptance of actigraphy in reviewed studies. Patients with CRSWDs may find it difficult to complete sleep logs for extended periods of time, and actigraphy may be a less cumbersome alternative. Also, given the useful information on sleep parameters that can be obtained with actigraphy, most patients are likely to use actigraphy in place of sleep logs alone. Laboratory PSG may also prevent assessment of "natural" sleep onset or sleep offset times in patients with very late or very sleep onset or sleep offset times. As a result, actigraphy is likely to provide more useful information to clinicians about sleep onset and sleep offset, and is likely to be more acceptable to patients than in-center assessment of these parameters with PSG.

Resource Use

Actigraphy is more expensive than sleep logs, and therefore may be more resource intensive. However, in the absence of a widely available objective method for assessment of circadian rhythms in the home environment, actigraphy is currently the most widely available tool for this purpose. Actigraphy is not routinely paid for by insurers for evaluation of sleep patterns in patients with suspected CRSWDs, and as a result, the cost to patients may be higher. The cost to the health care system with actigraphy monitoring may also be higher than sleep logs alone; however, some of the higher costs of diagnosis may be offset by reduced costs associated with fewer delays in identifying appropriate interventions (eg, light therapy) and avoiding inappropriate ones (eg, hypnotic medications) for patients with CRSWDs.

Melatonin Levels and Profiles

In addition to the above outcomes, the use of actigraphy is supported by multiple studies conducted to evaluate actigraphy-based estimates of sleep that included biological markers of circadian phase such as dim light melatonin onset (DLMO) and melatonin secretion profiles in patients with suspected or confirmed CRSWDs. The physiologic markers of circadian phase are considered gold standards. Studies with actigraphy and melatonin assessments included patients with advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD); the results of these studies informed the recent AASM clinical practice guidelines for the treatment of CRSWDs.[86] Studies show that actigraphy can reflect changes

in endogenous melatonin in patients with DSWPD,[87–89] and after circadian interventions for patients with DSWPD, ASWPD and shift work sleep/wake phase disorder.[87,90–93]

Use of Actigraphy in the Evaluation of Circadian Rhythm Sleep-Wake Disorders in Pediatric Populations

Our literature review identified 3 studies[94–96] meeting eligibility criteria for pediatric populations with CRSWD. TST actigraphy and sleep log data were available from baseline and posttreatment assessments and are included in the meta-analyses. The TF also reviewed TST data from a heterogenous study that included participants with suspected CRSWD, phase delay and/or insomnia.[97] For SL, data were available from three studies[94–96] for baseline and posttreatment assessment. Only 1 study[96] reported baseline and posttreatment data on sleep onset and sleep offset. All of the studies were RCTs testing melatonin and/or light therapy for delayed sleep phase syndrome in children with a wide age range (2–21 years old). Most of the studies included both male and female participants who were largely school age children. One study[94] included children primarily in their late adolescents/early adulthood. Two studies[95,97] involved children with neurodevelopmental disorders. No studies meeting our inclusion criteria included PSG assessments. PSG validation studies[81–83] have however, demonstrated acceptable validity of actigraphy in infants and children, particularly in healthy normal subjects. The meta-analyses and figures are provided in the supplemental material, **Figure S19** through **Figure S26**. Summary of findings tables are provided in the supplemental material, **Table S7** and **Table S8**. A summary of the evidence for each outcome is provided below.

Total Sleep Time

For baseline sleep parameters, meta-analysis of 3 studies[94–96] demonstrated that the clinical significance criteria of 25 minutes was met, indicating that actigraphy and sleep logs provide distinct information when assessing TST. Meta-analysis demonstrated a large mean difference in TST of 47.4 minutes lower (95% CI: 99.4 minutes lower to 4.5 minutes higher) for actigraphy compared to sleep logs. This was not statistically significant, however (P = .07). One additional study[97] of non-specific sleep disorders in children with developmental disorders, also met the clinical significance threshold for TST. This study demonstrated a large mean difference in TST of 96.6 minutes lower (95% CI: 65.2 to 128.0 minutes lower) for actigraphy compared to sleep logs[97] (**Figure S19** and **Figure S27**). The quality of evidence was low due to imprecision and the small sample size.

With respect to treatment response, meta-analysis of three studies[94–96] demonstrated that actigraphy TST met the clinical significance threshold of 25 minutes, indicating that actigraphy and sleep logs provide distinct information when assessing posttreatment TST. Meta-analysis demonstrated a large mean difference of 52.7 minutes lower TST (95% CI: 20.8 to 84.6 minutes lower) for actigraphy estimates compared to sleep logs. The study of non-specific sleep disorders in children with developmental disorders,[97] also met the clinical significance threshold for TST. This study demonstrated a large mean difference in posttreatment TST of 121.4 minutes lower (95% CI: 88.4 to 154.4 minutes lower) for actigraphy estimates compared to sleep logs (**Figure S23** and **Figure S29**). Interventions included melatonin supplementation and/or bright light therapy. Taken together, these data indicate that actigraphy measures of TST yield lower estimates compared to sleep logs at baseline and posttreatment, suggesting that actigraphy may be more sensitive at detecting sleep loss in pediatric populations with CRSWD. The quality of evidence was low due to imprecision and small sample size.

Sleep Latency

Three studies[94–96] reported baseline and posttreatment SL estimates. Meta-analyses for both baseline and posttreatment estimates of SL demonstrated that the small mean differences did not meet the clinical significance threshold of 20 minutes, indicating that actigraphy and sleep logs provide similar estimates. The mean difference for baseline SL was 3.0 minutes lower (95% CI: 14.9 minutes higher to 20.9 minutes lower) for actigraphy compared to sleep logs. Only one baseline study[94] met the clinical significance criteria, demonstrating a mean difference in SL of 20 minutes lower (95% CI: 6.8 minutes lower to 33.12 minutes higher) for actigraphy estimates compared to sleep logs. The other two studies[95,96] suggested actigraphy estimated slightly longer SL relative to sleep logs. One additional study of non-specific sleep disorders in children with developmental disorders[97] met the clinical threshold reporting a large mean difference in SL of 24.8 minutes higher (95% CI: 9.71 minutes lower to 59.3 minutes higher) for actigraphy estimates compared to sleep logs (**Figure S20** and **Figure S28**). The quality of evidence was low due to imprecision and small sample sizes.

When assessing response to treatment, the small mean difference for posttreatment SL of 1.1 minutes lower (95% CI: 11.1 minutes lower to 9.0 minute higher) for actigraphy compared to sleep logs, was not clinically significant, suggesting that actigraphy and sleep logs provide similar estimates. Only one arm of one study testing light therapy[94] met the clinical significance threshold, reporting a mean difference in posttreatment SL of 24.0 minutes lower (95% CI: 37.9 minutes lower to 10.1 to higher) for actigraphy estimates compared to sleep logs (**Figure S24**). The quality of evidence was low due to imprecision and small sample size.

Sleep Onset

Only one study[96] reported baseline sleep onset and the small mean difference between actigraphy and sleep logs estimates did not meet the clinical significance threshold of 25 minutes, suggesting that actigraphy and sleep logs provide similar estimates. This study[96] found a mean difference in sleep onset of 0 minutes (95% CI: 0.24 minutes lower to 0.24 minutes higher) between actigraphy and sleep logs. This study[96] also reported a mean difference in posttreatment sleep onset of 0 minutes (95% CI: 0.20 minutes lower to 0.20 minutes higher) between actigraphy and sleep logs (**Figure S21** and **Figure S25** respectively). The quality of evidence was very low due to imprecision and very small sample size.

Sleep Offset

Only one study[96] was identified that reported baseline sleep offset. The mean difference between actigraphy and sleep log

estimates met the clinical significance threshold of 25 minutes, suggesting actigraphy and sleep provide distinct estimates. This clinical trial of melatonin and light therapy in school aged children with likely delayed sleep phase syndrome demonstrated a large mean difference in baseline sleep offset of 1.4 hours lower (95% CI: 1.2 to 1.6 hours lower) for actigraphy estimates compared to sleep logs.[96] With respect to treatment response, a large mean difference of 1.7 hours lower (95% CI: 1.5 to 1.9 hours lower) for actigraphy estimates compared to sleep logs was found (**Figure S22** and **Figure S26**). The quality of evidence was very low due to imprecision and very small sample size.

Overall Quality of Evidence

The overall quality of evidence was low due to the small sample sizes, and imprecision. Given the heterogenous nature of pediatric populations included in the studies, which ranged in age from 2 to 21 years, a developmental span involving changing sleep and circadian rhythm patterns, the generalizability of the findings is significantly limited.

Benefits Versus Harms

As many pediatric patients are unable to accurately monitor and record their sleep and caregiver sleep logs are burdensome for caregivers and prone to error, actigraphy may be the only feasible means to assess certain sleep parameters over multiple nights. Based on their clinical expertise and the above reviewed data, the task force determined that the benefits that actigraphy provides outweigh potential minor harms. Benefits of actigraphy include a relatively unobtrusive, passive, and objective measure of sleep in pediatric populations. Alternative, more intensive home sleep testing devices, which also provide objective sleep parameter estimates using multiple and more obtrusive sensor technologies, may not be as well tolerated over multiple consecutive monitoring periods. The evidence reviewed above suggests that actigraphy, compared to sleep logs, provides distinct estimates for some key sleep parameters, notably TST. The finding that actigraphy may be more sensitive than sleep logs in detecting reduced sleep time in pediatric populations is an important potential benefit. The primary adverse effects associated with actigraphy monitoring are skin irritation, which is typically mild. When evaluating the benefits versus harms, the task force considered the vulnerability of this population and the relatively high prevalence of CRSWD in pediatric populations.[73,75–78]

Patient Values and Preferences

Although minimal data exists related to patient values and preferences on the use of actigraphy versus sleep logs for assessing CRSWD in pediatric populations, the task force's experience and opinion is that the use of actigraphy is favored by the majority of patients and caregivers. This is due to: (1) the relatively unobtrusive nature and minor burden of the monitoring procedure; (2) the fact that monitoring sleep patterns over multiple days is required to assess CRSWD, which imposes a major burden on caregivers of young children who may be unable to accurately report sleep parameters; (3) the utility of objective data monitoring to complement patient self-report and (4) the increased accuracy that actigraphy data provides to inform clinical diagnosis, decision making, and monitoring treatment response. Patients and caregivers sometimes express concern about out of pocket expenses related to inconsistent third-party reimbursements.

Resource Use

The cost of actigraphy is higher than paper sleep log monitoring, but much less expensive than PSG and other home sleep testing devices with multiple sensor technologies. Minimal data exist evaluating the cost benefit, but savings to medical health care systems and third-party payers and employers are potentially high. Actigraphy has the potential to improve the accurate detection of CRSWD: treatment and policy interventions related to these data could reduce downstream health care expenses. At the present time, however, cost benefits of the use of actigraphy to assess pediatric CRSWD and treatment response are unclear and require systematic study.

Use of Actigraphy in the Evaluation of Sleep-Disordered Breathing With Home Sleep Apnea Tests in Adults

Our review of the literature identified 6 studies[56,98–102] which examined the concomitant use of actigraphy with HSAT in the evaluation of SDB. It is important to note that the TF was unable to identify a single study which directly addresses the PICO question, which ideally should include data on comparing the accuracies of REI determination with and without actigraphy accompanying HSAT use, and simultaneously compared that to AHI determined by PSG as gold standard. Five of the studies contained data on comparing estimated TST by actigraphy against measured TST by PSG in patient population with SDB. Only one study used a HSAT device with integrated actigraphy.[101]

The meta-analyses are provided in the supplemental material, **Figure S31**. A summary of findings table is provided in the supplemental material, **Table S9**. A summary of the evidence for each outcome is provided below.

Total Sleep Time

In order to determine the utility of adding actigraphy to HSAT, the first critical outcome examined the accuracy of TST estimation by actigraphy compared to PSG in patients with suspected or diagnosed SDB. Five studies[56,98–100,102] were included in the meta-analysis. Of note, three of the studies[56,98,102] did not study the use of HSAT but instead presented data on the comparison of TST between actigraphy and PSG in the setting of OSA and were therefore included in the meta-analysis. Actigraphy appeared to be less accurate in estimating TST as PSG-determined AHI increases, likely due to movements related to severe and frequent apneas. The overall results showed a mean difference in TST measured by actigraphy as compared to PSG of 14.54 minutes higher (95% CI: 49.77 minutes higher to 20.70 minutes lower) which indicated a sufficiently small mean difference, however, variability was significant, with a range of possible mean differences of 70 minutes. These results are consistent with other studies[103–105] which have demonstrated the validity of actigraphy in estimating TST in the setting of

SDB (**Figure S31**). The quality of evidence was moderate due to imprecision.

Accuracy

One study[99] compared AHI values obtained by PSG versus AHI values calculated by simplified polygraphy (akin to a HSAT setup) with or without actigraphy-estimated TST in 20 subjects with SDB. Using actigraphy-estimated TST to calculate AHI improved both sensitivity (88% AHI-act versus 50% AHI-tib) and negative predictive value (92.5% AHI-act versus 75% AHI-tib) in the subset of patients with severe OSA (AHI > 30 events/h). However, for the diagnosis of moderate OSA (defined as AHI > 10 to 29 in this study) by simplified polygraphy, sensitivity and specificity were the same (at 100%) with or without actigraphy-estimated TST data.

Another study[100] compared a biomotion sensor and actigraphy-estimated TST with standard PSG. In a post hoc analysis, the use of actigraphy-estimated TST resulted in a reduced number of misclassifications of SDB severity categorizations compared to using TRT (~7% misclassifications with actigraphy versus ~10% misclassifications using TRT).

In one other study,[101] AHI/RDI thresholds of 10, 15, and 30 events/h were used to compare the accuracy of PSG versus an HSAT device with built-in actigraphy. Based on the manual analysis of two "observers," the sensitivity ranged between 83.8% and 95.8%, and the specificity between 92% and 100% for the different AHI thresholds studied. This study showed increased sensitivity with the addition of actigraphy TST, compared to using recording time in HSAT, with the increased sensitivity primarily observed in patients with severe OSA (RDI ≥ 30 events/h).

Another study[106] examined Taiwanese bus drivers who were studied for SDB. They used AHI thresholds of 5 and 15 events/h and showed an increase in AHI when measured with actigraphy-estimated TST as compared with recording time, but this was not statistically significant.[106] The quality of evidence was low due to indirectness and small sample size.

Overall Quality of Evidence

The overall quality of evidence on the use of actigraphy with HSAT to estimate TST (monitoring time) during recording, in the absence of alternative objective measurements of TST, in adult patients suspected of SDB was low due to imprecision, indirectness and small samples size. The overall quality of evidence was also downgraded based on the indirectness of additional evidence from other sleep disorders supporting that TST estimated by actigraphy is reliably accurate when compared to PSG. The quality of evidence in assessing the accuracy of REI by the addition of actigraphy with HSAT was also downgraded due to small sample size.

Benefits Versus Harms

By providing an improved TST estimation (monitoring time) over total time in bed (TIB) or TRT, actigraphy may improve the diagnostic accuracy of HSAT in calculating respiratory event indices and thus the diagnostic accuracy of HSAT in detecting SDB in the evaluation of patients suspected or diagnosed with SDB. In addition, the TF considered the empirical concern that in patients with short sleep duration or chronic insomnia (TST < 6 hours), simply using TIB or TRT may increase the denominator in calculating the AHI, thereby underestimating the severity of OSA or missing the diagnosis completely. Hence, actigraphy may be particularly useful in such patients with short sleep duration or chronic insomnia to help improve the diagnostic accuracy of HSAT. The TF determined that only actigraphy integrated within HSAT devices should be used in the clinical settings as adding actigraphy separately to a HSAT study will be impractical to do so. The TF cautions the limitation in actigraphy use in cases with limited upper extremity mobility (eg, stroke patients). Based on their clinical expertise and the above reviewed data, the TF determined that there were no clinically significant and undesirable outcomes associated with actigraphy (integrated within HSAT devices).

Patient Values and Preferences

In adult patients with suspected sleep-related breathing disorder, currently there are no available studies to draw from in assessing patients' values and preferences on actigraphy incorporated within HSAT devices. However, patients will likely value the potentially more accurate assessment of SDB severity that could be obtained with the addition of actigraphy (integrated within HSAT devices) which can impact access to treatment (eg, based on REI cut-off requirements of third-party payers, job requirements, disability benefits, etc.). Actigraphy should carry minimal burden for the patients.

Resource Use

From a resource use perspective, it would be most appropriate to compare the use of actigraphy integrated within HSAT device versus HSAT without actigraphy. It is neither practical to separately collect actigraphy data and synchronize with the HSAT recording, nor feasible to obtain actigraphy testing separately during a HSAT study for billing purposes. Several HSAT systems already have integrated actigraphy. However, economic analyses comparing the cost-effectiveness on HSAT with integrated actigraphy for the assessment of SDB have not been conducted. The TF concluded using HSAT with integrated actigraphy function may be more cost effective by potentially improving the diagnostic accuracy of SDB by HSAT when compared with only using TIB or TRT.

Use of Actigraphy in the Evaluation of Central Disorders of Hypersomnolence With the Multiple Sleep Latency Test

The MSLT measures the physiologic sleep tendency of an individual during the habitual wake period,[80] and is recommended in the diagnostic evaluation of narcolepsy and other central disorders of hypersomnolence.[107] The MSLT can be influenced by a number of factors, including sleep duration leading up to the testing.[108] An in-center sleep study with EEG, EMG and EOG recording is recommended as standard procedure for the night prior to the MSLT to identify any underlying clinical conditions that could result in sleep fragmentation and to document that the patient had a sufficient amount of sleep the night prior to the study.[80] Although the overnight PSG will rule out acute insufficient sleep that might influence interpretation

of the findings for diagnosing disorders of hypersomnolence, chronic insufficient sleep time may also negatively influence the MSLT study, and should be ruled out prior to the MSLT as well. Sleep-wake patterns over a period of time are most commonly assessed using sleep logs rather than actigraphy. Sleep logs, however may be subject to bias (eg, motivational factors) resulting in patients overestimating, or in some cases, underestimating their TST.

The figures are provided in the supplemental material, **Figure S32a** and **Figure S32b**. Summary of findings tables are provided in the supplemental material, **Table S10a** and **Table S10b**. A summary of the evidence for each outcome is provided below.

Total Sleep Time

In this review, we identified only one study[108] that examined the nightly sleep duration by both actigraphy as well as sleep logs in the 2-week period prior to a MSLT in patients with excessive daytime sleepiness. It found that actigraphy compared to sleep logs estimated a large mean difference that was clinically significant of 86 minutes lower (95% CI: 58.4 to 113.6 minutes lower).[108] See supplemental material, **Figure S32a**. These data demonstrate that actigraphy provides unique measurements compared to sleep logs, and may be helpful to ascertain nightly sleep duration prior to MSLT. When comparing the TST recorded by actigraphy and PSG on the night before the MSLT, the study reported a mean difference of 15.60 minutes, which is within the clinical significance threshold, however the 95% CI of 49.40 minutes (−40.30, 9.10) exceeded the clinical significance threshold.[108] See supplemental material, **Figure S32b**. The quality of evidence was moderate due to imprecision and small sample size.

In addition, in their subgroup analysis, patients who had a mean sleep latency (MSL) of less than 8 minutes in the MSLT were found to have a mean nightly sleep duration of only 4.53 ± 1.37 hours by actigraphy, while patients who had a MSL of more than or equal to 8 minutes were found to have a mean nightly sleep duration of 6.10 ± 1.37 hours by actigraphy.[108] This difference in mean nightly sleep duration between the two groups of patients was reported to be statistically significant.[108] However, in terms of sleep logs-recorded mean nightly sleep duration, no significant difference was found between these two groups of patients (7.08 ± 0.70 hours for patients with MSL < 8 minutes versus 6.94 ± 0.93 hours for patients with MSL ≥ 8 minutes).[108] Results from this study suggests that patients with a MSL < 8 minutes on the MSLT were more likely to overestimate their nightly sleep duration on sleep logs compared to actigraphy, suggesting that sleep logs may be unreliable in patients with a reduced SL on the MSLT.[108] It is likely that some patients who were referred for an MSLT in the evaluation for hypersomnia disorders had unrecognized insufficient sleep syndrome. The task force noted that this study was limited by a military sleep center setting, a relatively small sample size, and patients consisted of mostly men (87%).

Overall Quality of Evidence

The overall quality of evidence on the use of actigraphy to monitor TST prior to MSLT testing in adult and pediatric patients with suspected central disorders of hypersomnolence was moderate. The quality of evidence was downgraded due to imprecision due to small sample size from one single study. The overall quality of evidence was also downgraded due to indirectness of evidence; that is, some evidence supporting this recommendation was based on studies evaluating the accuracy of TST versus sleep logs in patients with a variety of sleep disorders or complaints. Despite looking broadly at available literature, no pediatric data were currently available. However, the TF determined that the findings and recommendation reported here could be extended to the pediatric population, particularly in adolescents, where differentiating CRSWDs from hypersomnia conditions can be clinically challenging.

Benefits Versus Harms

The ability for actigraphy to provide longitudinal assessment of TST and sleep patterns in patients with suspected hypersomnia disorder may improve the diagnostic accuracy of the subsequent MSLT and potentially reveal other sleep disorders or circadian rhythm sleep-wake disorders. Actigraphy is a noninvasive test that can be conducted over multiple nights, which is not feasible with PSG. The TF determined that there were no clinically significant and undesirable outcomes associated with actigraphy. Given the ICSD-3 diagnostic criteria on hypersomnia disorders recommending that insufficient sleep should be ruled out, the TF determined that there is evidence to suggest that actigraphy be used in combination with sleep logs prior to MSLT in adults suspected of central disorders of hypersomnolence to improve the diagnostic accuracy of the MSLT.

Patient Values and Preferences

Actigraphy is able to provide objective sleep duration data prior to MSLT which could improve the diagnostic accuracy of the MSLT compared to sleep logs alone. Patients with suspected hypersomnia condition will benefit from a more accurate diagnosis by use of actigraphy prior to MSLT. The TF determined that the vast majority of patients would want to receive a correct clinical diagnosis in the evaluation for hypersomnia disorders. However, minimal evidence exists to indicate how much patients value the main outcome. The use of actigraphy under consideration here requires patients to wear a wrist watch device continuously for up to two weeks prior to MSLT.

Resource Use

Actigraphy device is reusable and data can be collected from patient over a period of time prior to MSLT. In practical terms, actigraphy studies can be obtained over a period of 7–14 days, though currently there is no available data to determine the optimal length of study prior to MSLT. It is a relatively low cost medical diagnostic test.

Use of Actigraphy in the Evaluation of Insufficient Sleep Syndrome in Adults

Our review of the literature identified 11 studies[109–119] permitting the comparison of actigraphy and sleep log estimates of TST for routine assessment in participants at risk for insufficient sleep syndrome. These studies included data from male and female participants, ranging in age between 18–57.9 years.

The majority of the studies were within-subject, case control or quasi experimental designs evaluating workers with occupations involving extended shifts/duty hour schedules curtailing sleep opportunity relative to off duty hours. Occupations included pilots/astronauts (4 studies),[109,113,116,117] medical interns/residents (3 studies),[111,114,118] oil rig workers (1 study),[112] tunnel workers (1 study),[115] and ballet dancers (1 study) [110]. Three intervention studies[113,116,119] meeting eligibility criteria were identified, which assessed post intervention TST. Due to the small number of intervention studies and heterogeneity in the sample characteristics, as well as the varying interventions deployed, we did not conduct meta-analyses evaluating treatment response. The meta-analyses and figures are provided in the supplemental material, **Figure S33** and **Figure S34**. Summary of findings tables are provided in the supplemental material, **Table S11** and **Table S12**. A summary of the evidence for each outcome is provided below.

Total Sleep Time

Meta-analysis of the 10 baseline assessment studies[109–118] demonstrated that actigraphy estimated lower baseline TST relative to sleep logs by a large mean difference of 38.5 minutes (95% CI: 27.0 to 49.2 minutes lower), which exceeded the clinical significance threshold of 20 minutes. This finding suggests that actigraphy may be more sensitive than sleep logs in detecting short sleep in individuals at risk for ISS (**Figure S33**). The quality of evidence was high.

With respect to treatment response, only three studies[113,116,119] were identified. Similar to the baseline assessment studies, two studies, one in pilots[113] and the other astronauts,[116] demonstrated that actigraphy estimated lower posttreatment TST compared to sleep logs by large mean differences of 57.00 minutes (95% CI: 26.6 to 87.4 minutes lower) and 26 minutes (95% CI: 12.0 to 40.0 minutes lower), respectively. The mean differences in both studies were clinically significant. Interventions included a behavioral counter fatigue intervention in airline pilots[113] conducted in within subjects experimental study and sedative medications for on duty astronauts[116] in an observational study. A study[112] of offshore oil platform workers with difficulty adjusting to shiftwork, however, found that sleep logs tended to yield lower estimates of TST relative to actigraphy in this randomized cross-over experiment comparing light therapy and melatonin against placebo. The light therapy intervention arm demonstrated that posttreatment actigraphy estimated greater TST compared to sleep logs by a large mean difference of 38 minutes (95% CI: 76.7 minutes higher to .70 minutes lower), which was clinically significant.[112] This mean difference, however, was not statistically significant. The melatonin intervention arm actigraphy estimated higher TST compared to sleep logs by a small mean difference of 5.5 minutes (95% CI: 37.11 minutes higher to 26.11 minutes lower), which was neither clinically nor statistically significant[112] (**Figure S34**). These posttreatment data suggest that actigraphy estimates of posttreatment TST generally yield lower estimates of TST compared to sleep logs, though the direction of the differences may not be uniformly consistent and may be specific to a particular intervention types or subpopulations. The quality of posttreatment evidence was low due small sample size, imprecision, and heterogeneity of the studies.

Overall Quality of Evidence

The overall quality of the evidence was judged to be moderate due primarily to the three treatment response studies. Treatment response studies were downgraded because of heterogeneity, and imprecision, ie, one study had 95% CI crossing the clinically significance threshold. The evidence pertaining to the 10 assessment studies of baseline data was judged to be of high quality.

Benefits Versus Harms

The potential benefits of actigraphy assessment of TST in patients at risk for ISS are strong relative to the minor undesirable effects, which include as small risk of skin irritation. The majority of the studies demonstrate that actigraphy estimates of TST yield evidence of greater sleep loss compared to sleep log estimates. This indicates that actigraphy may be more sensitive in detecting insufficient sleep disorders compared to sleep logs. This is important because insufficient sleep is highly prevalent,[120–123] associated with motor vehicle accidents, diminished work-related productivity and medical and psychiatric morbidity.[60–64,122–127] The discrepancy of −38 minutes between actigraphy and sleep logs is clinically significant in that this differential degree of chronic sleep loss would be expected to impact sleep debt and be expected to be more robustly associated with physiologic and neurobehavioral risk factors of medical and psychiatric morbidity. Based on their clinical expertise, and the meta-analyses, the task force determined that the potential benefits of actigraphy outweighed its potential harms.

Patient Values and Preferences

Although minimal data exists related to patient values and preferences on the use of actigraphy versus sleep logs for assessing insufficient sleep, the task force's experience is that the use of actigraphy is favored by the majority of patients with no important uncertainty or variability due to: (1) the relatively unobtrusive nature and minor burden of this relatively passive monitoring procedure; (2) the utility of objective data monitoring to complement patient self-report; and (3) the increased accuracy that actigraphy data provides to inform clinical diagnosis, decision making, and monitoring treatment response. Patients sometimes express concern about out of pocket expenses related to inconsistent third-party reimbursements and variable co-pays.

Resource Use

The cost of actigraphy is higher than paper sleep log monitoring, but much less expensive than PSG and other home sleep testing devices with multiple sensor technologies. Minimal data exist evaluating the cost benefit, but potential savings to medical health care systems and third-party payers and employers are high. Actigraphy is expected to improve the accurate detection of insufficient sleep; treatment and policy interventions related to these data could reduce downstream health care expenses, lost productivity, reduced accidents and

other deleterious effects of insufficient sleep. At the present time cost benefits of the use of actigraphy to assess treatment response are less certain due to limitations in the small number of well-designed outcome studies and mixed findings related to clinical significance.

Use of Actigraphy in the Evaluation of Periodic Limb Movement Disorder

A review of the literature to identify studies including both actigraphy and EMG and EEG during in-center PSG to estimate periodic limb movement frequency yielded 3 studies in adults[128–130] and 2 in pediatric patients[131,132] meeting our inclusion/exclusion criteria. One study[128] compared two different actigraphy devices to EMG. A second study[130] examined the reliability of actigraphy to measure limb movements in a population with suspected insomnia, SRBD, or daytime sleepiness; only patients with a pre-PSG diagnosis of RLS were used in our analyses. The small number of studies precluded meta-analysis. However, summary information for each study are shown in the supplemental material, **Figure S35**. A summary of findings tables is provided in the supplemental material, **Table S13**. A summary of the evidence for each outcome is provided below.

Accuracy

None of the included studies in adults provided information on the accuracy of PLMD diagnosis using current diagnostic criteria. One study[129] of adults provided sensitivity/specificity using a PLMSI cutoff of 15 events/h on PSG and a PLMSI cutoff of 16 events/h on the actigraphy device, and reported sensitivity of 82.4% and specificity of 70.8%, a false-positive rate of 31.8 and a false-negative rate of 26.3. The PLMSI threshold of 16 events/h is not routinely used for diagnostic purposes in clinical practice. A study of children with sickle cell disease provided sensitivity/specificity data using a PLMSI cutoff of 5 events/h on PSG and a PLMSI cutoff of 5 events/h on actigraphy.[132] They reported sensitivity of 100%, and specificity of 8% for raw actigraphy, and 25% after correcting the PLMSI for sleep time. The false-positive rate was 58% (53% after correcting for sleep time), and the false negative rate was 0% (with or without sleep time correction). These studies indicate the accuracy of actigraphy for the diagnosis of PLMD is inadequate. The quality of evidence was moderate due to small sample size.

Periodic Limb Movement Index

The correspondence between the PLMSI derived from actigraphy varied widely. One study[128] compared EMG to two different actigraphy devices to EMG in patients with PLMSI > 5 events/h at baseline. They found that the average PLMSI using one device was 34.4 events/h (standard deviation [SD] = 30.7) measured on both legs with one device, and 63.6 events/h (SD = 39.3) measured on both legs with the second device, while the PLMSI based on EMG during laboratory PSG was 37.0 events/h (SD = 30.7). In a second study[129] patients with suspected PLMD were studied, and EMG derived PLMSI was compared to one actigraphy device worn for 5 consecutive nights (4 nights at home). The mean PLMSI was 30.4 events/h (SD = 34.3) on actigraphy, compared to 21.0 events/h (SD = 28.9) as measured by EMG during laboratory PSG. In a third study of patients suspected of RLS,[130] the mean PLMSI based on EMP during laboratory PSG was 51.2 events/h (SD = 34.1) while the mean PLMSI based on actigraphy was 47.71 events/h (SD = 35.42). However, the range of possible mean differences between EMG-derived and actigraphy-derived PMLSI was 58.14 events/h. In a study of pediatric patients,[131] the mean PLMSI based on EMG was 4.0 events/h (SD = 1.3) for the left leg and 4.0 events/h (SD = 1.5) for the right leg, while the PLMSI based on actigraphy was 6.4 events/h (SD = 4.1) on the left leg and 7.9 events/h (SD = 3.9) on the right leg (**Figure S35**). In a second study[132] of pediatric patients, Bland Altman analyses demonstrated that actigraphy overestimated the mean PLMSI, compared to EMG, by 8.1 events/h (SD = 10.7). These studies demonstrate that actigraphy does not accurately identify periodic limb movements, compared to the gold standard EMG. The quality of evidence was moderate due to imprecision.

Overall Quality of Evidence

The overall quality of evidence was moderate. The available studies used concurrent measurement; however, the evidence was drawn from only five studies with small sample sizes, and only two devices were studied. In addition, there was imprecision, with the 95% CI crossing the clinical significance threshold as determined by the TF for both adult and pediatric studies.

Benefits Versus Harms

The main benefit of actigraphy is that it can potentially be worn outside of the sleep center and may provide a simpler alternative for patients; however, the potential harms of misclassification of patients with and without PLMD outweighs the benefit of increased convenience. Given that actigraphy both over and under-estimated PLMSI compared to EMG during PSG, it cannot be viewed as a substitute for EMG during in-center PSG in the diagnosis of PLMD.

Patient Values and Preferences

While patients may prefer a simpler diagnostic tool, diagnostic accuracy is also important to patients. The TF concluded that most patients would prefer EMG during PSG over actigraphy.

Resource Use

Actigraphy may be less expensive than in-center PSG; however, actigraphy is not routinely covered by insurers for diagnosis of PLMD. As a result, the cost to patients may be higher for actigraphy compared to in-center PSG with EMG. Although data are limited, given the low diagnostic utility, there could also be added cost to the health care system from repeat diagnostic testing or use of inappropriate treatments, even if the cost was covered by insurers.

DISCUSSION AND FUTURE DIRECTIONS

Our review and analyses support the utility of actigraphy as a relatively low cost, objective measure of sleep patterns and certain estimated sleep parameters in both children and adults,

across a wide range of sleep disorders, when conducted using validated algorithms with attention to sensitivity settings and standardized scoring procedures.

Overall, our meta-analyses indicated that actigraphy yields significantly distinct estimates of sleep patterns when compared to sleep logs, suggesting that, although the two measures are often correlated, they provide unique information contributing to the clinical understanding of patients with sleep disorders. With respect to specific sleep and CRSWDs, the utility of actigraphy in objective estimation of sleep and wake parameters across multiple consecutive 24-hour periods renders it a very useful tool for assessing circadian dysrhythmia. With respect to insomnia disorder, there is ample evidence of its validity and utility in assessing sleep continuity in conjunction with sleep logs both in terms of general diagnostic assessment as well as posttreatment assessment. Actigraphy is also especially useful to assess sleep continuity in patients who are typically unable to complete sleep logs reliably, including children and individuals with cognitive impairment. Finally, actigraphy may be especially useful in assessing TST in individuals at risk for ISS. The data in populations at risk for insufficient sleep suggest that actigraphy estimated shorter sleep duration compared to sleep log estimates and therefore may be especially useful in identifying short sleep, which contributes to increased medical and psychiatric morbidity, injuries and workplace accidents.[60–64,122–127]

Future scientific reports using actigraphy should uniformly publish detailed technical and scoring procedures including sensitivity settings, scoring algorithms, and scoring procedures so that future research can more fully establish validity, particularly in special patient populations. A major finding across disorders is that actigraphy generally yields distinct information from sleep log estimates, and in some cases, actigraphy estimates in comparison to those from sleep logs correspond more closely with PSG measures. More research that compares all 3 approaches across patients with different types of sleep and circadian rhythm sleep-wake disorders is warranted. Given that actigraphy and sleep logs often generate distinct parameter estimates for the same variables, there is an important research imperative to establish normative data that account for demographic and developmental factors such as age, sex, ethnicity, as well as disease type (eg, sleep disorders, healthy individuals, medical and psychiatric disorders).

A key strength of actigraphy is that it provides relatively unobtrusive monitoring of sleep patterns over long periods of time. In addition, the use of these devices to measure sleep behavior is becoming broadly applied, and the experience of the task force is that actigraphy is largely acceptable to patients with sleep disorders; however, data are needed to understand patient preferences based on sleep disorder, age, and other factors. Future research should also explore statistical models that capitalize on these micro-longitudinal data, evaluating day-to-day variation in sleep parameters and trajectories over time rather than relying exclusively on aggregated, mean level data. Sleep disorders such as chronic insomnia disorder and CRSWDs often involve considerable variability in symptoms and sleep parameters, which may be readily captured via actigraphy and analyzed using time series data analytic approaches. In addition, this information can be displayed graphically to patients, enabling them to understand diagnostic decisions and evaluate their own response to treatment. The review and meta-analyses that the TF performed highlighted some important gaps that would benefit from future investigation. In particular, the TF identified very few studies that have evaluated the relative benefit of actigraphy-based TST estimates used in conjunction with HSAT devices that do not determine actual sleep time by EEG, EOG and EMG. Similarly, more studies are needed to evaluate the use of actigraphy prior to MSLT in assessment for narcolepsy and other central disorders of hypersomnolence. In pediatric patients, more research is needed to establish whether actigraphy can reliably detect response to well-established treatments. A similar need exists to determine the sensitivity of actigraphy to behavioral interventions that target extension of habitual sleep duration and quality in individuals with ISS.

REFERENCES

1. Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, Carden KA. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2018;14(7):1231–1237.
2. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep.* 2007;30(4):519–529.
3. Khosla S, Deak MC, Gault D, et al. Consumer sleep technology: an American Academy of Sleep Medicine position statement. *J Clin Sleep Med.* 2018;14(5):877–880.
4. Blackwell T, Ancoli-Israel S, Redline S, Stone KL; Osteoporotic Fractures in Men (MrOS) Study Group. Factors that may influence the classification of sleep-wake by wrist actigraphy: the MrOS Sleep Study. *J Clin Sleep Med.* 2011;7(4):357–367.
5. Zinkhan M, Berger K, Hense S, et al. Agreement of different methods for assessing sleep characteristics: a comparison of two actigraphs, wrist and hip placement, and self-report with polysomnography. *Sleep Med.* 2014;15(9):1107–1114.
6. Sadeh A. Iii. Sleep assessment methods. *Monogr Soc Res Child Dev.* 2015;80(1):33–48.
7. Patel SR, Weng J, Rueschman M, et al. Reproducibility of a standardized actigraphy scoring algorithm for sleep in a US Hispanic/Latino population. *Sleep.* 2015;38(9):1497–1503.
8. Ancoli-Israel S, Martin JL, Blackwell T, et al. The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med.* 2015;13(Suppl 1):S4–S38.
9. Buysse DJ, Cheng Y, Germain A, et al. Night-to-night sleep variability in older adults with and without chronic insomnia. *Sleep Med.* 2010;11(1):56–64.
10. Williams JM, Kay DB, Rowe M, McCrae CS. Sleep discrepancy, sleep complaint, and poor sleep among older adults. *J Gerontol B Psychol Sci Soc Sci.* 2013;68(5):712–720.
11. Kay DB, Buysse DJ, Germain A, Hall M, Monk TH. Subjective-objective sleep discrepancy among older adults: associations with insomnia diagnosis and insomnia treatment. *J Sleep Res.* 2015;24(1):32–39.
12. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017;13(3):479–504.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924–926.

14. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep.* 2007;30(11):1445–1459.
15. Creti L, Libman E, Baltzan M, Rizzo D, Bailes S, Fichten CS. Impaired sleep in chronic fatigue syndrome: how is it best measured? *J Health Psychol.* 2010;15(4):596–607.
16. Campbell CM, Buenaver LF, Finan P, et al. Sleep, pain catastrophizing, and central sensitization in knee osteoarthritis patients with and without insomnia. *Arthritis Care Res.* 2015;67(10):1387–1396.
17. Floam S, Simpson N, Nemeth E, Scott-Sutherland J, Gautam S, Haack M. Sleep characteristics as predictor variables of stress systems markers in insomnia disorder. *J Sleep Res.* 2015;24(3):296–304.
18. Lichstein KL, Stone KC, Donaldson J, et al. Actigraphy validation with insomnia. *Sleep.* 2006;29(2):232–239.
19. Levenson JC, Troxel WM, Begley A, et al. A quantitative approach to distinguishing older adults with insomnia from good sleeper controls. *J Clin Sleep Med.* 2013;9(2):125–131.
20. Vallieres A, Morin CM. Actigraphy in the assessment of insomnia. *Sleep.* 2003;26(7):902–906.
21. McCall C, McCall WV. Objective vs. subjective measurements of sleep in depressed insomniacs: first night effect or reverse first night effect? *J Clin Sleep Med.* 2012;8(1):59–65.
22. McCall C, McCall WV. Comparison of actigraphy with polysomnography and sleep logs in depressed insomniacs. *J Sleep Res.* 2012;21(1):122–127.
23. Straus LD, Drummond SP, Nappi CM, Jenkins MM, Norman SB. Sleep variability in military-related PTSD: a comparison to primary insomnia and healthy controls. *J Trauma Stress.* 2015;28(1):8–16.
24. Winkelman JW, Benson KL, Buxton OM, et al. Lack of hippocampal volume differences in primary insomnia and good sleeper controls: an MRI volumetric study at 3 Tesla. *Sleep Med.* 2010;11(6):576–582.
25. Lovato N, Lack L, Wright H, Kennaway DJ. Evaluation of a brief treatment program of cognitive behavior therapy for insomnia in older adults. *Sleep.* 2014;37(1):117–126.
26. Lengacher CA, Reich RR, Paterson CL, et al. The effects of mindfulness-based stress reduction on objective and subjective sleep parameters in women with breast cancer: a randomized controlled trial. *Psychooncology.* 2015;24(4):424–432.
27. Talbot LS, Maguen S, Metzler TJ, et al. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. *Sleep.* 2014;37(2):327–341.
28. Jarnefelt H, Lagerstedt R, Kajaste S, Sallinen M, Savolainen A, Hublin C. Cognitive behavioral therapy for shift workers with chronic insomnia. *Sleep Med.* 2012;13(10):1238–1246.
29. Edinger JD, Wohlgemuth WK, Radtke RA, Coffman CJ, Carney CE. Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial. *Sleep.* 2007;30(2):203–212.
30. Taylor DJ, Zimmerman MR, Gardner CE, et al. A pilot randomized controlled trial of the effects of cognitive-behavioral therapy for insomnia on sleep and daytime functioning in college students. *Behav Ther.* 2014;45(3):376–389.
31. Gross CR, Kreitzer MJ, Reilly-Spong M, et al. Mindfulness-based stress reduction versus pharmacotherapy for chronic primary insomnia: a randomized controlled clinical trial. *Explore.* 2011;7(2):76–87.
32. Edinger JD, Olsen MK, Stechuchak KM, et al. Cognitive behavioral therapy for patients with primary insomnia or insomnia associated predominantly with mixed psychiatric disorders: a randomized clinical trial. *Sleep.* 2009;32(4):499–510.
33. Ong JC, Manber R, Segal Z, Xia Y, Shapiro S, Wyatt JK. A randomized controlled trial of mindfulness meditation for chronic insomnia. *Sleep.* 2014;37(9):1553–1563.
34. Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. *Arch Intern Med.* 2005;165(21):2527–2535.
35. Taibi DM, Vitiello MV. A pilot study of gentle yoga for sleep disturbance in women with osteoarthritis. *Sleep Med.* 2011;12(5):512–517.
36. Garland SN, Carlson LE, Stephens AJ, Antle MC, Samuels C, Campbell TS. Mindfulness-based stress reduction compared with cognitive behavioral therapy for the treatment of insomnia comorbid with cancer: a randomized, partially blinded, noninferiority trial. *J Clin Oncol.* 2014;32(5):449–457.
37. Espie CA, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. *J Clin Oncol.* 2008;26(28):4651–4658.
38. Harris J, Lack L, Kemp K, Wright H, Bootzin R. A randomized controlled trial of intensive sleep retraining (ISR): a brief conditioning treatment for chronic insomnia. *Sleep.* 2012;35(1):49–60.
39. Tyagi S, Resnick NM, Perera S, Monk TH, Hall MH, Buysse DJ. Behavioral treatment of chronic insomnia in older adults: does nocturia matter? *Sleep.* 2014;37(4):681–687.
40. Buysse DJ, Germain A, Moul DE, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med.* 2011;171(10):887–895.
41. Mundt JM, Crew EC, Krietsch K, et al. Measuring treatment outcomes in comorbid insomnia and fibromyalgia: concordance of subjective and objective assessments. *J Clin Sleep Med.* 2016;12(2):215–223.
42. Falloon K, Elley CR, Fernando A 3rd, Lee AC, Arroll B. Simplified sleep restriction for insomnia in general practice: a randomised controlled trial. *Br J Gen Pract.* 2015;65(637):e508–e515.
43. Friedman L, Zeitzer JM, Kushida C, et al. Scheduled bright light for treatment of insomnia in older adults. *J Am Geriatr Soc.* 2009;57(3):441–452.
44. Yamadera W, Sato M, Harada D, et al. Comparisons of short-term efficacy between individual and group cognitive behavioral therapy for primary insomnia. *Sleep Biol Rhythms.* 2013;11(3):176–184.
45. Sato M, Yamadera W, Matsushima M, Itoh H, Nakayama K. Clinical efficacy of individual cognitive behavior therapy for psychophysiological insomnia in 20 outpatients. *Psychiatry Clin Neurosci.* 2010;64(2):187–195.
46. Friedman L, Benson K, Noda A, et al. An actigraphic comparison of sleep restriction and sleep hygiene treatments for insomnia in older adults. *J Geriatr Psychiatry Neurol.* 2000;13(1):17–27.
47. Yeung WF, Chung KF, Tso KC, Zhang SP, Zhang ZJ, Ho LM. Electroacupuncture for residual insomnia associated with major depressive disorder: a randomized controlled trial. *Sleep.* 2011;34(6):807–815.
48. Lovato N, Lack L, Kennaway DJ. Comparing and contrasting therapeutic effects of cognitive-behavior therapy for older adults suffering from insomnia with short and long objective sleep duration. *Sleep Med.* 2016;22:4–12.
49. Tang NK, Goodchild CE, Salkovskis PM. Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: a pilot randomised controlled trial. *Behav Res Ther.* 2012;50(12):814–821.
50. Yeung WF, Chung KF, Zhang SP, Yap TG, Law AC. Electroacupuncture for primary insomnia: a randomized controlled trial. *Sleep.* 2009;32(8):1039–1047.
51. Alessi C, Martin JL, Fiorentino L, et al. Cognitive behavioral therapy for insomnia in older veterans using nonclinician sleep coaches: randomized controlled trial. *J Am Geriatr Soc.* 2016;64(9):1830–1838.
52. Epstein DR, Sidani S, Bootzin RR, Belyea MJ. Dismantling multicomponent behavioral treatment for insomnia in older adults: a randomized controlled trial. *Sleep.* 2012;35(6):797–805.
53. Espie CA, MacMahon KM, Kelly HL, et al. Randomized clinical effectiveness trial of nurse-administered small-group cognitive behavior therapy for persistent insomnia in general practice. *Sleep.* 2007;30(5):574–584.
54. Kang SG, Kang JM, Cho SJ, et al. Cognitive behavioral therapy using a mobile application synchronizable with wearable devices for insomnia treatment: a pilot study. *J Clin Sleep Med.* 2017;13(4):633–640.
55. Chung KF, Yeung WF, Yu YM, et al. Acupuncture for residual insomnia associated with major depressive disorder: a placebo- and sham-controlled, subject- and assessor-blind, randomized trial. *J Clin Psychiatry.* 2015;76(6):e752–e760.
56. Choi SJ, Kang M, Sung MJ, Joo EY. Discordant sleep parameters among actigraphy, polysomnography, and perceived sleep in patients with sleep-disordered breathing in comparison with patients with chronic insomnia disorder. *Sleep Breath.* 2017;21(4):837–843.
57. Chung KF, Yeung WF, Yu BY, et al. Acupuncture with or without combined auricular acupuncture for insomnia: a randomised, waitlist-controlled trial. *Acupunct Med.* 2018;36(1):2–13.

58. Shechter A, Kim EW, St-Onge MP, Westwood AJ. Blocking nocturnal blue light for insomnia: a randomized controlled trial. *J Psychiatr Res.* 2018;96:196–202.
59. Taylor DJ, Peterson AL, Pruiksma KE, Young-McCaughan S, Nicholson K, Mintz J. Internet and in-person cognitive behavioral therapy for insomnia in military personnel: a randomized clinical trial. *Sleep.* 2017;40(6).
60. Covassin N, Singh P. Sleep duration and cardiovascular disease risk: epidemiologic and experimental evidence. *Sleep Med Clin.* 2016;11(1):81–89.
61. Diem SJ, Blackwell TL, Stone KL, et al. Measures of sleep-wake patterns and risk of mild cognitive impairment or dementia in older women. *Am J Geriatr Psychiatry.* 2016;24(3):248–258.
62. Gangwisch JE. A review of evidence for the link between sleep duration and hypertension. *Am J Hypertens.* 2014;27(10):1235–1242.
63. Song Y, Dzierzewski JM, Fung CH, et al. Association between sleep and physical function in older veterans in an adult day healthcare program. *J Am Geriatr Soc.* 2015;63(8):1622–1627.
64. Xi B, He D, Zhang M, Xue J, Zhou D. Short sleep duration predicts risk of metabolic syndrome: a systematic review and meta-analysis. *Sleep Med Rev.* 2014;18(4):293–297.
65. Bathgate CJ, Edinger JD, Krystal AD. Insomnia patients with objective short sleep duration have a blunted response to cognitive behavioral therapy for insomnia. *Sleep.* 2017;40(1).
66. Dayyat EA, Spruyt K, Molfese DL, Gozal D. Sleep estimates in children: parental versus actigraphic assessments. *Nat Sci Sleep.* 2011;3:115–123.
67. de Bruin EJ, Bogels SM, Oort FJ, Meijer AM. Efficacy of cognitive behavioral therapy for insomnia in adolescents: a randomized controlled trial with internet therapy, group therapy and a waiting list condition. *Sleep.* 2015;38(12):1913–1926.
68. Palermo TM, Beals-Erickson S, Bromberg M, Law E, Chen M. A single arm pilot trial of brief cognitive behavioral therapy for insomnia in adolescents with physical and psychiatric comorbidities. *J Clin Sleep Med.* 2017;13(3):401–410.
69. Conroy DA, Czopp AM, Dore-Stites DM, et al. Modified cognitive behavioral therapy for insomnia in depressed adolescents: a pilot study. *Behav Sleep Med.* 2017 Mar 23. doi:10.1080/15402002.2017.1299737. [Epub ahead of print].
70. Gringras P, Green D, Wright B et al. Weighted blankets and sleep in autistic children--a randomized controlled trial. *Pediatrics.* 2014;134(2):298–306.
71. Paine S, Gradisar M. A randomised controlled trial of cognitive-behaviour therapy for behavioural insomnia of childhood in school-aged children. *Behav Res Ther.* 2011;49(6–7):379–388.
72. Badin E, Haddad C, Shatkin JP. Insomnia: the sleeping giant of pediatric public health. *Curr Psychiatry Rep.* 2016;18(5):47.
73. Owens J. Classification and epidemiology of childhood sleep disorders. *Prim Care.* 2008;35(3):533–546, vii.
74. Owens JA, Mindell JA. Pediatric insomnia. *Pediatr Clin North Am.* 2011;58(3):555–569.
75. Tham EK, Schneider N, Broekman BF. Infant sleep and its relation with cognition and growth: a narrative review. *Nat Sci Sleep.* 2017;9:135–149.
76. Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. *Pediatr Clin North Am.* 2011;58(3):649–665.
77. Coogan AN, McGowan NM. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. *Atten Defic Hyperact Disord.* 2017;9(3):129–147.
78. Lunsford-Avery JR, Krystal AD, Kollins SH. Sleep disturbances in adolescents with ADHD: A systematic review and framework for future research. *Clin Psychol Rev.* 2016;50:159–174.
79. Meltzer LJ, Mindell JA. Systematic review and meta-analysis of behavioral interventions for pediatric insomnia. *J Pediatr Psychol.* 2014;39(8):932–948.
80. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep.* 2005;28(1):113–121.
81. Sadeh A, Lavie P, Scher A, Tirosh E, Epstein R. Actigraphic home-monitoring sleep-disturbed and control infants and young children: a new method for pediatric assessment of sleep-wake patterns. *Pediatrics.* 1991;87(4):494–499.
82. Meltzer LJ, Montgomery-Downs HE, Insana SP, Walsh CM. Use of actigraphy for assessment in pediatric sleep research. *Sleep Med Rev.* 2012;16(5):463–475.
83. Hyde M, O'Driscoll DM, Binette S, et al. Validation of actigraphy for determining sleep and wake in children with sleep disordered breathing. *J Sleep Res.* 2007;16(2):213–216.
84. Pickering L, Jennum P, Gammeltoft S, Poulsgaard L, Feldt-Rasmussen U, Klose M. Sleep-wake and melatonin pattern in craniopharyngioma patients. *Eur J Endocrinol.* 2014;170(6):873–884.
85. De Rui M, Middleton B, Sticca A, et al. Sleep and circadian rhythms in hospitalized patients with decompensated cirrhosis: effect of light therapy. *Neurochem Res.* 2015;40(2):284–292.
86. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2015;11(10):1199–1236.
87. Cole RJ, Smith JS, Alcala YC, Elliott JA, Kripke DF. Bright-light mask treatment of delayed sleep phase syndrome. *J Biol Rhythms.* 2002;17(1):89–101.
88. Mundey K, Benloucif S, Harsanyi K, Dubocovich ML, Zee PC. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. *Sleep.* 2005;28(10):1271–1278.
89. Serfaty M, Kennell-Webb S, Warner J, Blizard R, Raven P. Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. *Int J Geriatr Psychiatry.* 2002;17(12):1120–1127.
90. Palmer CR, Kripke DF, Savage HC Jr, Cindrich LA, Loving RT, Elliott JA. Efficacy of enhanced evening light for advanced sleep phase syndrome. *Behav Sleep Med.* 2003;1(4):213–226.
91. Mishima K, Okawa M, Hishikawa Y, Hozumi S, Hori H, Takahashi K. Morning bright light therapy for sleep and behavior disorders in elderly patients with dementia. *Acta Psychiatr Scand.* 1994;89(1):1–7.
92. Dorrian J, Darwent D, Dawson D, Roach GD. Predicting pilot's sleep during layovers using their own behaviour or data from colleagues: implications for biomathematical models. *Accid Anal Prev.* 2012;45 Suppl:17–21.
93. Arendt J, Middleton B, Williams P, Francis G, Luke C. Sleep and circadian phase in a ship's crew. *J Biol Rhythms.* 2006;21(3):214–221.
94. Saxvig IW, Wilhelmsen-Langeland A, Pallesen S, Vedaa O, Nordhus IH, Bjorvatn B. A randomized controlled trial with bright light and melatonin for delayed sleep phase disorder: effects on subjective and objective sleep. *Chronobiol Int.* 2014;31(1):72–86.
95. Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *J Pineal Res.* 2008;44(1):57–64.
96. van Maanen A, Meijer AM, van der Heijden KB, Oort FJ. The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Med Rev.* 2016;29:52–62.
97. Appleton RE, Jones AP, Gamble C, et al. The use of melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). *Health Technol Assess.* 2012;16(40):i–239.
98. Kim MJ, Lee GH, Kim CS, et al. Comparison of three actigraphic algorithms used to evaluate sleep in patients with obstructive sleep apnea. *Sleep Breath.* 2013;17(1):297–304.
99. Elbaz M, Roue GM, Lofaso F, Quera Salva MA. Utility of actigraphy in the diagnosis of obstructive sleep apnea. *Sleep.* 2002;25(5):527–531.
100. Pallin M, O'Hare E, Zaffaroni A, et al. Comparison of a novel non-contact biomotion sensor with wrist actigraphy in estimating sleep quality in patients with obstructive sleep apnoea. *J Sleep Res.* 2014;23(4):475–484.
101. Garcia-Diaz E, Quintana-Gallego E, Ruiz A, et al. Respiratory polygraphy with actigraphy in the diagnosis of sleep apnea-hypopnea syndrome. *Chest.* 2007;131(3):725–732.
102. Sharif MM, Bahammam AS. Sleep estimation using BodyMedia's SenseWear armband in patients with obstructive sleep apnea. *Ann Thorac Med.* 2013;8(1):53–57.
103. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med.* 2001;2(5):389–396.

104. Gagnadoux F, Nguyen XL, Rakotonanahary D, Vidal S, Fleury B. Wrist-actigraphic estimation of sleep time under nCPAP treatment in sleep apnoea patients. *Eur Respir J.* 2004;23(6):891–895.
105. Hedner J, Pillar G, Pittman SD, Zou D, Grote L, White DP. A novel adaptive wrist actigraphy algorithm for sleep-wake assessment in sleep apnea patients. *Sleep.* 2004;27(8):1560–1566.
106. Ting H, Huang RJ, Lai CH, et al. Evaluation of candidate measures for home-based screening of sleep disordered breathing in Taiwanese bus drivers. *Sensors.* 2014;14(5):8126–8149.
107. American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
108. Bradshaw DA, Yanagi MA, Pak ES, Peery TS, Ruff GA. Nightly sleep duration in the 2-week period preceding multiple sleep latency testing. *J Clin Sleep Med.* 2007;3(6):613–619.
109. Simons R, Wilschut ES, Valk PJ. Sleep and alertness in North Sea helicopter operations. *Aviat Space Environ Med.* 2011;82(7):704–710.
110. Fietze I, Strauch J, Holzhausen M, et al. Sleep quality in professional ballet dancers. *Chronobiol Int.* 2009;26(6):1249–1262.
111. Kim HJ, Kim JH, Park KD, Choi KG, Lee HW. A survey of sleep deprivation patterns and their effects on cognitive functions of residents and interns in Korea. *Sleep Med.* 2011;12(4):390–396.
112. Thorne H, Hampton S, Morgan L, Skene DJ, Arendt J. Differences in sleep, light, and circadian phase in offshore 18:00-06:00 h and 19:00-07:00 h shift workers. *Chronobiol Int.* 2008;25(2):225–235.
113. Rosekind MR, Gregory KB, Mallis MM. Alertness management in aviation operations: enhancing performance and sleep. *Aviat Space Environ Med.* 2006;77(12):1256–1265.
114. Gohar A, Adams A, Gertner E, et al. Working memory capacity is decreased in sleep-deprived internal medicine residents. *J Clin Sleep Med.* 2009;5(3):191–197.
115. Forberg K, Waage S, Moen B, Bjorvatn B. Subjective and objective sleep and sleepiness among tunnel workers in an extreme and isolated environment: 10-h shifts, 21-day working period, at 78 degrees north. *Sleep Med.* 2010;11(2):185–190.
116. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *Lancet Neurol.* 2014;13(9):904–912.
117. Signal TL, Gale J, Gander PH. Sleep measurement in flight crew: comparing actigraphic and subjective estimates to polysomnography. *Aviat Space Environ Med.* 2005;76(11):1058–1063.
118. Rose M, Manser T, Ware JC. Effects of call on sleep and mood in internal medicine residents. *Behav Sleep Med.* 2008;6(2):75–88.
119. Bjorvatn B, Stangenes K, Oyane N, et al. Randomized placebo-controlled field study of the effects of bright light and melatonin in adaptation to night work. *Scand J Work Environ Health.* 2007;33(3):204–214.
120. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev.* 2002;6(2):97–111.
121. Centers for Disease Control and Prevention (CDC). Short sleep duration among workers--United States, 2010. *MMWR Morb Mortal Wkly Rep.* 2012;61(16):281–285.
122. Morita Y, Sasai-Sakuma T, Asaoka S, Inoue Y. Prevalence and correlates of insufficient sleep syndrome in Japanese young adults: a web-based cross-sectional study. *J Clin Sleep Med.* 2015;11(10):1163–1169.
123. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of healthy sleep duration among adults--United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2016;65(6):137–141.
124. Centers for Disease Control and Prevention (CDC). Drowsy driving - 19 states and the District of Columbia, 2009-2010. *MMWR Morb Mortal Wkly Rep.* 2013;61(51–52):1033–1037.
125. Geiger-Brown J, Rogers VE, Trinkoff AM, Kane RL, Bausell RB, Scharf SM. Sleep, sleepiness, fatigue, and performance of 12-hour-shift nurses. *Chronobiol Int.* 2012;29(2):211–219.
126. Hartzler BM. Fatigue on the flight deck: the consequences of sleep loss and the benefits of napping. *Accid Anal Prev.* 2014;62:309–318.
127. Dashti HS, Scheer FA, Jacques PF, Lamon-Fava S, Ordovas JM. Short sleep duration and dietary intake: epidemiologic evidence, mechanisms, and health implications. *Adv Nutr.* 2015;6(6):648–659.
128. Gschliesser V, Frauscher B, Brandauer E, et al. PLM detection by actigraphy compared to polysomnography: a validation and comparison of two actigraphs. *Sleep Med.* 2009;10(3):306–311.
129. Kobayashi M, Namba K, Ito E, et al. The validity of the PAM-RL device for evaluating periodic limb movements in sleep and an investigation on night-to-night variability of periodic limb movements during sleep in patients with restless legs syndrome or periodic limb movement disorder using this system. *Sleep Med.* 2014;15(1):138–143.
130. Sforza E, Johannes M, Claudio B. The PAM-RL ambulatory device for detection of periodic leg movements: a validation study. *Sleep Med.* 2005;6(5):407–413.
131. Montgomery-Downs HE, Crabtree VM, Gozal D. Actigraphic recordings in quantification of periodic leg movements during sleep in children. *Sleep Med.* 2005;6(4):325–332.
132. Rogers VE, Gallagher PR, Marcus CL, Ohene-Frempong K, Traylor JT, Mason TB. Capturing PLMS and their variability in children with sickle cell disease: does ankle activity monitoring measure up to polysomnography? *Sleep Med.* 2012;13(8):1013–1020.

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SPECIAL ARTICLES

Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Clinical Practice Guideline

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Introduction: The purpose of this guideline is to establish clinical practice recommendations for the use of actigraphy in adult and pediatric patients with suspected or diagnosed sleep disorders or circadian rhythm sleep-wake disorders.

Methods: The American Academy of Sleep Medicine (AASM) commissioned a task force of experts in sleep medicine to develop recommendations and assigned strengths based on a systematic review of the literature and an assessment of the evidence using the GRADE process. The task force provided a summary of the relevant literature and the quality of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations that support the recommendations. The AASM Board of Directors approved the final recommendations.

Recommendations: The following recommendations are intended as a guide for clinicians using actigraphy in evaluating patients with sleep disorders and circadian rhythm sleep-wake disorders, and only apply to the use of FDA-approved devices. Each recommendation statement is assigned a strength ("Strong" or "Conditional"). A "Strong" recommendation (ie, "We recommend…") is one that clinicians should follow under most circumstances. A "Conditional" recommendation (ie, "We suggest…") reflects a lower degree of certainty regarding the outcome and appropriateness of the patient-care strategy for all patients. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources.

1. We suggest that clinicians use actigraphy to estimate sleep parameters in adult patients with insomnia disorder. (Conditional)
2. We suggest that clinicians use actigraphy in the assessment of pediatric patients with insomnia disorder. (Conditional)
3. We suggest that clinicians use actigraphy in the assessment of adult patients with circadian rhythm sleep-wake disorder. (Conditional)
4. We suggest that clinicians use actigraphy in the assessment of pediatric patients with circadian rhythm sleep-wake disorder. (Conditional)
5. We suggest that clinicians use actigraphy integrated with home sleep apnea test devices to estimate total sleep time during recording (in the absence of alternative objective measurements of total sleep time) in adult patients suspected of sleep-disordered breathing. (Conditional)
6. We suggest that clinicians use actigraphy to monitor total sleep time prior to testing with the Multiple Sleep Latency Test in adult and pediatric patients with suspected central disorders of hypersomnolence. (Conditional)
7. We suggest that clinicians use actigraphy to estimate total sleep time in adult patients with suspected insufficient sleep syndrome. (Conditional)
8. We recommend that clinicians *not* use actigraphy in place of electromyography for the diagnosis of periodic limb movement disorder in adult and pediatric patients. (Strong)

Keywords: actigraphy, circadian rhythm, clinical practice guideline, sleep disorder

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INTRODUCTION

This clinical practice guideline is intended to update the previously published American Academy of Sleep Medicine (AASM) practice parameters on the use of actigraphy[1] in patients with suspected or diagnosed sleep disorders or circadian rhythm sleep-wake disorders (CRSWDs) and reflects the current recommendations of the AASM. The prior practice parameters established the validity of actigraphy to assess sleep in normal, healthy adult populations, and therefore, this guideline does not address the use of actigraphy to assess normal sleep.

Actigraphy is a procedure that records and integrates the occurrence and degree of limb movement activity over time. Actigraphic devices can be worn on the wrist, ankle or waist, relatively unobtrusively over a period of days to weeks. For sleep applications, the devices are typically worn on the wrist or ankle. Mathematical algorithms are then applied to these data to estimate wakefulness and sleep. In addition to providing a graphical summary of wakefulness and sleep patterns

over time, actigraphy generates estimates of certain sleep parameters that are also commonly estimated by using sleep logs, or measured directly by polysomnography (PSG), the gold standard measure of sleep.

This guideline, in conjunction with the accompanying systematic review,[2] provides a comprehensive update of the recent available evidence and a synthesis of clinical practice recommendations for the assessment and treatment of patients with suspected or diagnosed sleep disorders and CRSWDs. It is intended to optimize patient-centric care by broadly informing clinicians who care for adult and pediatric patients with sleep disorders and CSRWDs.

METHODS

The AASM commissioned a task force (TF) of sleep medicine clinicians with expertise in the use of actigraphy. The TF was required to disclose all potential conflicts of interest (COI), per the AASM's COI policy, prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's conflicts of interest policy, TF members with a Level 1 conflict were not allowed to participate. TF members with a Level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures section.

The TF conducted a systematic review[2] of the published scientific literature, focusing on patient-oriented, clinically relevant outcomes. The review focused exclusively on clinical grade devices approved by the FDA as an actigraphy device or equivalent device that uses an accelerometer to measure limb activity associated with movement during sleep for physiologic applications. The review did not cover consumer wearable devices,[3] or other non-prescription devices directly marketed to consumers, which are beyond the scope of this clinical practice guideline. The purpose of the review was to compare actigraphy to both sleep logs and PSG to determine whether actigraphy provides information that is distinct from patient-reported data and consistent enough with results of PSG to use as an objective measure. The clinical practice recommendations were then developed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.[4,5] The TF assessed the following four components to determine the direction and strength of a recommendation: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use. Details of these assessments can be found in the accompanying systematic review.[2] Taking these major factors into consideration, each recommendation statement was assigned a strength ("Strong" or "Conditional"). Additional information is provided in the form of "Remarks" immediately following the recommendation statements, when deemed necessary by the TF. Remarks are based on the evidence evaluated during the systematic review and are intended to provide context for the recommendations and to guide clinicians in the implementation of the recommendations in daily practice.

The recommendations in this guideline define principles of practice that should meet the needs of most patients in most situations. A "Strong" recommendation is one that clinicians should follow for almost all patients (ie, something that might qualify as a Quality Measure). A "Conditional" recommendation reflects a lower degree of certainty in the appropriateness of the patient-care strategy for *all* patients. It requires that the clinician use clinical knowledge and experience, and strongly considers the individual patient's values and preferences to determine the best course of action. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources.

The AASM expects this guideline to have an impact on professional behavior, patient outcomes, and—possibly—health care costs. This clinical practice guideline reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

CLINICAL PRACTICE RECOMMENDATIONS

The following clinical practice recommendations are based on a systematic review and evaluation of evidence using the GRADE process. The implications of the strength of recommendations for guideline users are summarized in **Table 1.** Remarks are provided to guide clinicians in the implementation of these recommendations. The recommended duration of actigraphy recording is a minimum of 72 hours to 14 consecutive days, in accordance with the Current Procedural Terminology (CPT) coding requirements.[6]

Use of Actigraphy in the Evaluation of Insomnia in Adults

Recommendation 1: We suggest that clinicians use actigraphy to estimate sleep parameters in adult patients with insomnia disorder. (Conditional)

Remarks: Objective monitoring is not required for the routine diagnosis of insomnia; however, it is useful in differential diagnosis and when objective estimates of sleep parameters are important to clinical decision making (eg, nonresponse to cognitive behavioral therapy for insomnia, patient requests increased hypnotic dose, patient reporting is of questionable validity).

The TF compared actigraphy to sleep logs and PSG for the assessment and evaluation of treatment response in total sleep time (TST), sleep latency (SL), wake after sleep onset (WASO), and sleep efficiency (SE) in adult patients with suspected or diagnosed insomnia. The TF identified 46 studies that provided data suitable for meta-analyses. For assessment, meta-analyses comparing actigraphy and sleep logs demonstrated clinically significant large mean differences for TST, SL, and SE. Meta-analyses comparing actigraphy to PSG demonstrated clinically significant narrow ranges of mean differences for TST and SL. For the evaluation of treatment

Table 1—Implications of "Strong" and "Conditional" recommendations for users of AASM clinical practice guidelines.

User	Strong Recommendations "We Recommend…"	Conditional Recommendations "We Suggest…"
Clinicians	Almost all patients should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.	Most patients should receive the suggested course of action, however, different choices may be appropriate for different patients. The clinician must help each patient determine if the suggested course of action is clinically appropriate and consistent with his or her values and preferences.
Patients	Almost all patients should receive the recommended course of action, although a small proportion of patients would not.	Most patients should receive the suggested course of action, though some would not. Different choices may be appropriate for different patients. The patient should work with their clinician to determine if the suggested course of action is clinically appropriate and consistent with his or her values and preferences.
Insurance Providers	The recommended course of action can be adapted as policy for most situations. Adherence to the recommended course of action could be used as a quality criterion or performance indicator.	The ultimate judgment regarding the suitability of the suggested course of action must be made by the clinician and patient together, based on what is best for the patient. This decision-making flexibility should be accounted for when establishing policies.

AASM = American Academy of Sleep Medicine.

response, meta-analyses comparing actigraphy to PSG demonstrated clinically significant narrow ranges of mean differences for SL. Together these findings indicate that actigraphy provides objective data that is both consistent with PSG and unique from patient-reported data.

The overall quality of evidence was moderate due to imprecision. Potential benefits of actigraphy include convenience, relatively low patient burden, longitudinal assessment capability, and relatively low cost. Actigraphy may provide additional benefits for certain patient subgroups, including those with suspected paradoxical insomnia or those at risk for cardiometabolic, other medical, and psychiatric comorbidities impacted by short sleep duration. Based on their clinical experience, the TF concluded actigraphy may be more feasible and cost effective than PSG in obtaining objective measurement of sleep parameters, particularly if longitudinal objective measurement of sleep is needed. Additionally, patients with insomnia may have difficulty sleeping in a center setting and may prefer to remain at home for evaluation. Potential harms include minor skin irritation in some patients. Insomnia patients can be impacted by a host of environmental factors. Some complain of difficulty sleeping because of having the testing device in place. Nonetheless, the actigraphy device is easier to tolerate than the multiple PSG leads. The TF also determined that if actigraphy is used in the context described in the recommendation and remarks, the risk of harm is minimized and the probability of clinical benefits increased. Finally, based on their clinical experience, the TF determined that actigraphy provides outcomes that patients value with minimal undesired effects and that the vast majority of patients would elect to use actigraphy.

Use of Actigraphy in the Evaluation of Insomnia in Pediatric Populations

Recommendation 2: We suggest that clinicians use actigraphy in the assessment of pediatric patients with insomnia disorder. (Conditional)

Remarks: Though pertaining to the general pediatric population, this recommendation also includes pediatric patients with developmental disorders, based on one study that included patients with autism and suspected insomnia. Studies reviewed included young children and adolescents ranging in age from 3–19 years old.

The TF compared actigraphy to sleep logs for the assessment and evaluation of treatment response in TST, SL, WASO and SE in pediatric patients with suspected or diagnosed insomnia. The TF identified a total of 6 studies, including one study of non-specific sleep disorders (some with suspected insomnia) in children with autism. Because of the small number of studies reporting baseline data and heterogeneity of the studies, meta-analyses were not conducted for baseline data. For assessment, 3 studies comparing actigraphy to sleep logs demonstrated clinically significant large mean differences for TST and WASO. The study of non-specific sleep disorders (including patients with insomnia) in children with autism, also demonstrated a clinically significant large mean difference for TST. For the evaluation of treatment response, meta-analysis of 4 studies comparing actigraphy and sleep logs demonstrated large clinically significant mean differences for WASO. Overall, these findings indicate that actigraphy provides objective data that is consistent and also unique from patient-reported data, suggesting that actigraphy may be more sensitive in identifying sleep maintenance problems and reduced sleep duration in pediatric patients with insomnia. The overall quality of evidence was moderate due to imprecision and the small sample size. Potential benefits of actigraphy include reduced caregiver burden, increased feasibility of prolonged monitoring, increased sensitivity over sleep logs in identifying short sleep duration and increased WASO. Additional benefits supporting the use of actigraphy include: the consideration that children and some adolescents are unable to accurately or reliably keep sleep logs (especially outside of controlled research settings) and that sole reliance on caregiver data yields estimates that are variable in quality. The TF determined that the benefits of

using actigraphy outweigh the harms. Based on their clinical experience, the TF determined that the vast majority of patients/guardians would use actigraphy. The prevalence of multiple sleep disorders in young children and adolescents, and their association with many important developmental, medical and psychiatric outcomes[7] favors use of actigraphy.

Use of Actigraphy in the Evaluation of Circadian Rhythm Sleep-Wake Disorders in Adults

Recommendation 3: We suggest that clinicians use actigraphy in the assessment of adult patients with circadian rhythm sleep-wake disorder. (Conditional)

Since actigraphy can be used to assess patterns of sleep and wakefulness over multiple days, it is appealing for the evaluation of sleep patterns in adult patients with suspected CRSWD. The TF compared actigraphy to sleep logs and PSG for the assessment and evaluation of treatment response in sleep onset and sleep offset times in patients with suspected or confirmed CRSWDs. The TF identified two studies in patients at risk for circadian rhythm sleep-wake phase disorders. The small number of studies precluded meta-analysis. Results show that actigraphy is useful in the assessment of sleep onset and offset times and in the evaluation of treatment outcomes in some patients with CRSWD. The overall quality of the evidence was very low due to small sample size and imprecision. The potential benefit of objective measurement with actigraphy includes lower patient burden relative to sleep logs. PSG is not typically used in the assessment of CRSWDs. Based on clinical experience, the TF determined that the potential benefits of objective measurement of sleep onset and offset and the limited patient burden outweigh the potential harms, which are minimal. The TF also determined that the majority of patients would use actigraphy for the evaluation and treatment of CRSWDs.

Use of Actigraphy in the Evaluation of Circadian Rhythm Sleep-Wake Disorders in Pediatric Populations

Recommendation 4: We suggest that clinicians use actigraphy in the assessment of pediatric patients with circadian rhythm sleep-wake disorder. (Conditional)

Remarks: Though pertaining to the general pediatric population, this recommendation also includes patients with developmental delays, based on two studies that included participants with autism and other developmental disorders. Studies reviewed included patients ranging in age from 2–21 years old.

The TF compared actigraphy to sleep logs for the assessment and evaluation of treatment response in TST, SL, sleep onset, and sleep offset in pediatric patients with suspected or diagnosed CRSWD. The TF identified 4 studies of children and adolescents with delayed sleep phase syndrome, including one study of non-specific sleep disorders in children with autism (we use the term "delayed sleep phase syndrome" describing literature that used this nosology, which is similar to the newer ICSD-3 nosology, delayed sleep-wake phase disorder). All the studies reviewed were of suspected or diagnosed delayed sleep phase syndrome. For assessment, meta-analysis of 3 studies comparing actigraphy to sleep logs demonstrated a clinically significant large mean difference for TST. One additional study of non-specific sleep disorders (including patients with suspected delayed sleep phase syndrome) in children with developmental disorders, also demonstrated a large clinically significant mean difference for TST. One study demonstrated a large clinically significant mean difference for sleep offset time. For the evaluation of treatment response, meta-analysis of 3 studies demonstrated a clinically significant large mean difference for TST. Additionally, the study of non-specific sleep disorders in children with developmental disorders also demonstrated a large clinically significant mean difference for TST. One study of CRSWD demonstrated a clinically significant large mean difference for sleep offset. Overall, these findings indicate that actigraphy can provide objective data that is consistent and unique from patient-reported data.

The overall quality of evidence was low due to imprecision and small sample sizes. Potential benefits of actigraphy include reduced caregiver burden, increased feasibility of prolonged monitoring, increased sensitivity over logs in assessing reduced sleep duration and earlier sleep offset, and improved reliability compared to self-reported sleep parameters. Potential harms of actigraphy are minor, and include skin irritation. Although overall costs are relatively low, actigraphy is higher cost relative to paper logs. Based on their clinical expertise, the TF determined that the benefits of using actigraphy outweighs the harms. The TF also determined that the vast majority of patients would use actigraphy. The prevalence of multiple sleep disorders in infants, children and adolescents, and their association with many important developmental, medical and psychiatric outcomes[7] favors use of actigraphy.

Use of Actigraphy in the Evaluation of Sleep-Disordered Breathing with Home Sleep Apnea Tests in Adults

Recommendation 5: We suggest that clinicians use actigraphy integrated with home sleep apnea test devices to estimate total sleep time during recording (in the absence of alternative objective measurements of total sleep time) in adult patients suspected of sleep-disordered breathing. (Conditional)

Remarks: This recommendation only applies to patients who are appropriate candidates for a home sleep apnea test (HSAT).[8]

It has been well established that testing with an HSAT, in comparison to PSG, typically underestimates the severity of sleep-disordered breathing (SDB).[8] A component of this underestimation arises from the event-per-hour indices used for the diagnosis and severity determination of obstructive sleep apnea (OSA). Specifically, whether the denominator of hours reflects sleep as determined by sleep staging from electroencephalogram (EEG), electrooculography (EOG), and electromyography (EMG) during PSG; estimated sleep time as reflected by actigraphy or another method; or by simply

recording time or time in bed, both of which include at least some wake time. In the current analysis, the TF evaluated the accuracy of TST estimation by actigraphy compared to PSG in adult patients with SDB. The TF also sought to evaluate accuracy in the assessment of SDB severity when actigraphy was integrated with HSAT devices. The TF identified 6 studies, none of which directly compared the accuracy of the respiratory event index (REI) with and without actigraphy integrated into HSAT units, and simultaneously compared those REIs to apnea-hypopnea index (AHI) as determined by PSG as a gold standard. For the estimation of TST measured by actigraphy as compared to PSG, meta-analyses of 5 studies demonstrated a clinically significant small mean difference, but the range of possible differences exceeded the clinical significance threshold. In 3 studies that reported accuracy of AHI detected by HSAT (or similar set up) calculated with actigraphy-estimated TST, sensitivity ranged from 84% to 100% and specificity ranged from 88% to 100% in identifying cases of moderate to severe OSA when compared to PSG measurements. These data demonstrated slight improvement in the diagnostic accuracy of OSA with the use of integrated actigraphy to estimate TST during HSAT when compared with only using total time in bed or total recording time with HSAT, particularly in cases of severe OSA.

The overall quality of evidence was low, due to imprecision, small sample size and only indirect comparison of HSAT with actigraphy versus PSG (instead of directly comparing HSAT with and without integrated actigraphy). The TF determined that there are potential benefits to achieving a more accurate assessment of SDB by integrated actigraphy in the setting of HSAT, while there is negligible harm. The TF also determined that this recommendation should only apply to the use of HSAT devices with integrated actigraphy that are commercially available, as opposed to the use of HSAT devices with separate non-integrated actigraphy, for three reasons. First, it is improper coding for actigraphy testing (95803) to be coded concurrently with an HSAT (95800, 95801 and 95806). Secondly, as a separate service using a stand-alone actigraphy device, the code for actigraphy (CPT 95803) specifically requires a minimum of 72 hours of testing.[6] Third, it is impractical to separately collect and analyze actigraphy data and subsequently synchronize it with the HSAT recording to generate a combined study report.

Based on clinical experience, the TF determined patients will likely value the potentially more accurate assessment of SDB severity that could be obtained from use of actigraphy integrated with an HSAT, which in turn can impact access to treatment. There is an inherent risk of false negative results when using an HSAT, thus use in patients with an increased pretest probability of moderate-to-severe OSA has been recommended.[8] If the patient has comorbid insomnia or suspected comorbid sleep disorders, the risk of underestimating the severity of OSA is greater, and PSG is preferred.[8] It should be noted that in the 2007 Practice Parameters,[1] the use of actigraphy with an HSAT was a "Standard" recommendation based on the Oxford methodology used and the evidence available at that time.[1] In this guideline, which uses the GRADE methodology, the TF determined that based on existing evidence, the use of actigraphy technology integrated with HSAT devices is a "Conditional" recommendation.

Use of Actigraphy in the Evaluation of Central Disorders of Hypersomnolence With the Multiple Sleep Latency Test in Adult and Pediatric Populations

Recommendation 6: We suggest that clinicians use actigraphy to monitor total sleep time prior to testing with the Multiple Sleep Latency Test in adult and pediatric patients with suspected central disorders of hypersomnolence. (Conditional)

Remarks: Actigraphy can be used for 7–14 days prior to the PSG/Multiple Sleep Latency Test (MSLT) to assure adequate sleep time leading up to the testing.[6] Actigraphy can also be used to establish habitual sleep-wake timing. Actigraphy does not replace PSG prior to the MSLT.

Actigraphy is a diagnostic procedure that can be used in the evaluation of central disorders of hypersomnolence.[9] The TF compared actigraphy to sleep logs and PSG for the assessment of TST prior to MSLT in adult and pediatric patients with suspected central disorders of hypersomnolence. The TF identified one study that directly addressed this comparison in adults. When comparing TST estimated by actigraphy to sleep logs in the 2-week period prior to the MSLT, the study demonstrated a clinically significant large mean difference. When comparing TST recorded by actigraphy to PSG on the night before the MSLT, the study demonstrated a clinically significant small mean difference; however, the range of possible differences exceeded the clinical significance threshold. These data, in conjunction with supporting evidence from other sleep disorders described in this clinical practice guideline demonstrate that actigraphy provides objective data that are unique from patient-reported data. Data collected from actigraphy may be useful in the clinical assessment of patients with suspected hypersomnia (see accompanying systematic review[2]). The overall quality of evidence was moderate, downgraded due to imprecision and indirectness of additional evidence from other recommendations. The TF determined that the potential benefits of using actigraphy are large, based on the value of using actigraphy to assess TST and confirm that the patient has sufficient sleep prior to an MSLT. This would result in improved diagnostic accuracy and clinical utility of the resulting MSLT, and reducing the likelihood of misdiagnosis as well as unnecessary or inappropriate treatment. Additionally, actigraphy may be useful to establish habitual sleep-wake timing in the evaluation of patients with complaints of hypersomnia, which may reveal other sleep disorders such as insufficient sleep syndrome and CRSWDs, and may impact the interpretation of the MSLT. While data used in the included study came from an adult population only, and no pediatric studies were identified, the TF determined that the recommendation may also be relevant to the pediatric population, particularly in the adolescent population. The TF determined that the vast majority of patients would want to receive a correct clinical diagnosis in the evaluation for hypersomnia disorders and would therefore choose actigraphy as part of the evaluation. Of note,

actigraphy is obtained *prior to* the PSG/MSLT and is therefore billed separately from the PSG/MSLT.

Use of Actigraphy in the Evaluation of Insufficient Sleep Syndrome in Adults

Recommendation 7: We suggest that clinicians use actigraphy to estimate total sleep time in adult patients with suspected insufficient sleep syndrome. (Conditional)

Remarks: The duration of recording is recommended to be 2–3 weeks or more depending on the specific needs of the patient and the clinical issues[6,9]

The TF compared actigraphy to sleep log estimates of TST for the assessment and evaluation of treatment response for adult patients at risk for insufficient sleep syndrome. The TF identified 11 studies. For assessment, meta-analysis of 10 studies found a large mean difference in estimates of TST that was clinically significant. These data indicate that actigraphy yielded lower estimates of TST compared to sleep logs. For the assessment of treatment response, 2 of 3 studies demonstrated large mean differences that were clinically significant. These data indicate that actigraphy provides objective data that is unique from patient-reported data and may be useful in the assessment of insufficient sleep. The overall quality of evidence was moderate due to imprecision, heterogeneity, and small sample sizes in the treatment response studies. The potential benefit of actigraphy to assess insufficient sleep includes increased sensitivity over sleep logs in identifying short sleep duration. This is important due to the high prevalence of insufficient sleep and its association with medical and psychiatric morbidity and deleterious societal effects such as motor vehicle accidents and poor work performance. Additional benefits include the objective nature of the data. Potential harms of actigraphy are negligible and rare and include skin irritation. Although overall costs are low relative to more sophisticated, multiple sensor home sleep testing devices that can be worn over multiple days, actigraphy is higher in cost relative to paper logs. The TF determined that the benefits of using actigraphy outweigh the harms. Based on their clinical experience, the TF determined that the vast majority of patients would use actigraphy.

Use of Actigraphy in the Evaluation of Periodic Limb Movement Disorder in Adult and Pediatric Populations

Recommendation 8: We recommend that clinicians *not* use actigraphy in place of electromyography for the diagnosis of periodic limb movement disorder in adult and pediatric patients. (Strong)

Assessment of periodic limb movement disorder (PLMD) was not addressed in previous clinical practice guidelines; however, there is a growing interest in tests conducted out of the sleep center, and studies have explored whether actigraphy devices placed on the ankle or foot are a viable alternative to in-laboratory EMG in conjunction with PSG (as required by current diagnostic criteria[9]). The TF compared actigraphy to EMG for the assessment of periodic limb movements in adult and pediatric patients, to evaluate whether actigraphy could be used in place of EMG during PSG to assess the periodic limb movements of sleep index (PLMSI) and diagnose PLMD. The TF identified 5 studies (4 adult, 1 pediatric), one of which did not provide mean and standard deviation values and one of which used two actigraphy comparators. The small number of studies and sample heterogeneity precluded meta-analysis. Across the studies, the PLMSI as measured by actigraphy differed significantly from EMG measures in both adult and pediatric populations, demonstrating that actigraphy does not produce reliable estimates of periodic limb movements. The overall quality of evidence was moderate due to low sample size and imprecision. The TF determined that the potential for overestimating or underestimating PLMSI could lead to potentially unnecessary treatment or to missed cases of PLMD. In addition, without evaluation of simultaneous EEG, the evaluation of arousals from sleep is not possible with actigraphy alone. Thus, the TF concluded that the potential harms of misclassification outweighed the benefits of ease of monitoring with actigraphy versus EMG during PSG. Based on clinical expertise, the TF determined that the vast majority of patients would not use actigraphy in place of EMG, given the poor correspondence between the PLMSI as measured with actigraphy versus gold-standard EMG during PSG. The recommendation against using actigraphy in place of EMG for the diagnosis of PLMD is primarily a result of the unreliable estimates of periodic limb movement and the potential for misdiagnosis.

DISCUSSION

Wrist actigraphy was originally developed as a research-based method for estimating sleep parameters across multiple nights in the home sleep environment rather than measuring sleep during a single night in the sleep laboratory environment. In the last 15 years, actigraphy has been viewed as a useful clinical tool, particularly in the evaluation of patients with suspected or confirmed sleep disorders for whom understanding sleep/wake habits across multiple nights can inform clinical decision-making. Importantly, actigraphy can be used in both pediatric and adult patient populations. It is important to recognize that actigraphy is not a substitute for in-laboratory PSG when there is an indication for in-laboratory testing, however it can provide useful objective metrics across a variety of sleep-wake disorders to assist in the assessment and monitoring of treatment response. In general, we found that for many sleep parameters, actigraphy yields significantly distinct information from sleep logs and in some instances provides parameters estimates that are sufficiently similar to PSG. The parameters differ somewhat by disorder and application. With the exception PLMD, this general pattern of findings supports the utility of actigraphy to provide useful information in the diagnosis and monitoring or treatment as indicated in each of the 8 recommendations.

In February of 2008, actigraphy transitioned from a Current Procedural Terminology (CPT) Category III (emerging technology) to a Category I code (95803), which is a stand-alone code. These clinical practice guidelines are intended to

inform use of actigraphy as described under this code. When implementing the above recommendations, clinicians should be aware that, as noted by the descriptor for actigraphy, a minimum of 72 hours (with a maximum of 14 days) of consecutive recording is required, and the code cannot be used concurrently with HSAT or PSG codes.[6] In particular, HSAT devices that incorporate actigraphy should be coded only as HSAT, and actigraphy should not be coded separately.[6]

It should be noted that cost issues can influence patient preferences regarding use of actigraphy and must be considered when implementing these recommendations. At present, although many third-party payers reimburse for actigraphy procedures, there is significant variability from region to region and payer to payer as a clinical assessment tool, thereby impacting its use. However, if this procedure were reimbursed by payers and patient costs were reduced, this may change patient preferences regarding the use of actigraphy in clinical practice.

REFERENCES

1. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep*. 2007;30(4):519–529.
2. Smith MT, McCrae CS, Cheung J, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2018;14(7):1209–1230.
3. Khosla S, Deak MC, Gault D, et al. Consumer sleep technology: an American Academy of Sleep Medicine position statement. *J Clin Sleep Med*. 2018;14(5):877–880.
4. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926.
5. Morgenthaler TI, Deriy L, Heald JL, Thomas SM. The evolution of the AASM clinical practice guidelines: another step forward. *J Clin Sleep Med*. 2016;12(1):129–135.
6. American Medical Association. *CPT 2018 Professional Edition*. Chicago, IL: American Medical Association; 2017.
7. Owens J. Classification and epidemiology of childhood sleep disorders. *Prim Care*. 2008;35(3):533–546, vii.
8. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(3):479–504.
9. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

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SUBMISSION & CORRESPONDENCE INFORMATION

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Next Generation Sequencing of Malignancies with Liquid Biopsy

Plain Language Summary:

Coverage question: Should OHP cover a blood test to check for DNA changes from a person's cancer?

Should OHP cover this treatment? Yes, in certain cases:
1) When the patient is not well enough to give tumor samples OR
2) When the tumor sample taken isn't big enough to study closely

Changes to issue summary after public comment period:

No public comment was received on this topic. This document contains no changes from the version released with the early VBBS/HERC packet.

Coverage Question: Should the diagnostic guideline for next generation sequencing of malignancies be clarified regarding when liquid biopsies are covered?

Question source: Max Kaiser, CCO medical director, HERC member

Background: Liquid biopsy refers to serum testing for DNA fragments that are shed by cancer cells and released into the bloodstream. This method is purportedly used for screening, diagnosis and/or monitoring of cancer cells that may otherwise require a tissue sample. Dr. Kaiser has been seeing requests for both solid and liquid biopsies for next generation sequencing of malignancies.

Previous HSC/HERC reviews:

Next generation sequencing (NGS) of malignancies was reviewed in 2022 and 2023 with the Cancer Genetic Workgroup and at VBBS/HERC. A new diagnostic guideline for NGS was adopted in 2023 that includes the following wording: "for example CPT 81479, 81455, 0037U."

Current Prioritized List/Coverage status:

The following codes may represent PLA codes for liquid biopsy; these were pulled from multiple sources, including payer policies; some may represent liquid biopsy OR solid tumor in at least some cases. This is not an exhaustive list:

- 0091U Circulating Tumor DNA and Circulating Tumor Cells for Management of Solid Cancers (Liquid Biopsy)
- 0129U Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency)
- 0037U DNA gene analysis of 324 genes in solid organ tumor tissue
- 0111U KRAS, NRAS and BRAF variant analysis in metastatic colorectal cancer (including liquid biopsy)

Next Generation Sequencing of Malignancies with Liquid Biopsy

- 0172U Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for 7 Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency)
- 0179U Circulating Tumor DNA for Management of NSC Lung Ca (Liquid Biopsy)
- 0239U Circulating Tumor DNA for Management of NonSmall-Cell Lung Cancer (Liquid Biopsy)
- 0242U Circulating Tumor DNA for Management of NonSmall-Cell Lung Cancer (Liquid Biopsy)
- 0244U Gene analysis of 257 genes associated with solid organ cancer in tumor tissue sample, comprehensive genomic profiling
  0250U Gene analysis of 505 genes associated with solid organ cancer in tumor tissue sample, targeted genomic sequence interrogation for somatic alterations, microsatellite instability and tumor-mutation burden
- 0326U Circulating Tumor DNA and Circulating Tumor Cells for Management of Solid Cancers (Liquid Biopsy)
- 0338U Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
- 0329U Exome and transcriptome sequence analysis of DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutations with therapy associations
- 0334U Targeted genomic sequence analysis of 84 or more genes for detection of abnormalities associated with cancer of body organ
- 0338U Evaluation of circulating solid tumor cells in peripheral blood
- 0379U Genomic testing for solid organ cancer
- 0388U InVisionFirst®-Lung Liquid Biopsy
- 81445 Genomic sequence analysis panel of DNA or combined DNA and RNA of 5-50 genes associated with solid organ abnormal growth of tissue
- 81449 Genomic sequence analysis panel of RNA of 5-50 genes associated with solid organ abnormal growth of tissue
- 81479 Molecular pathology procedure
- 81455 Genomic sequence analysis panel of DNA or combined DNA and RNA of 51 or more genes associated with blood and lymphatic system disorders
- 81457 Genomic sequence analysis panel of DNA for microsatellite instability in solid organ abnormal growth of tissue
- 81458 Genomic sequence analysis panel of DNA for microsatellite instability and copy number of variants in solid organ abnormal growth of tissue
- 81459 Genomic sequence analysis panel of DNA or combined DNA and RNA for copy number variants, microsatellite instability, tumor mutation burden, and rearrangements in solid organ abnormal growth of tissue

DIAGNOSTIC GUIDELINE D13, NEXT GENERATION SEQUENCING OF MALIGNANCIES

Next Generation Sequencing (NGS, for example CPT 81479, 81455, 0037U) is covered when all of the following requirements are met:

A) The patient has
   1) A tissue diagnosis confirming cancer and has been evaluated by an oncologist or oncologic surgeon; AND
   2) Has not been previously tested using the same NGS test for the same primary diagnosis of cancer, unless the criteria in D) below are met; AND

3) Decided to seek further cancer treatment (for example, therapeutic chemotherapy) and has adequate performance status (ECOG 0-2) to undergo such treatment; AND

B) The diagnostic laboratory test using NGS must have:
   1) Clinical Laboratory Improvement Amendments (CLIA)-certification; AND
   2) The test is being used as a companion diagnostic test in accordance with Food & Drug Administration (FDA)-approved therapeutic labeling; AND
   3) Results provided to the treating physician for management of the patient using a report template to specify treatment options; AND

C) A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408 are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.

D) Repeat NGS testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

Expert guidelines:

1) NCCN 2.2024 Non small cell lung cancer
   a. Information about biomarker testing and plasma circulating tumor DNA (ctDNA) testing (so-called “liquid biopsy”) for actionable mutations is included in the algorithm (see Principles of Molecular and Biomarker Analysis in the NCCN Guidelines for NSCLC). Briefly, the panel feels that plasma ctDNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC. Standards and guidelines for plasma ctDNA testing for somatic variants/mutations have not been published, there is up to a 30% false-negative rate, and variants can be detected that are not related to the tumor (eg, clonal hematopoiesis of indeterminate potential [CHIP]).195,196 For example, an IDH1 mutation identified by plasma ctDNA testing is likely unrelated to NSCLC, given exceptionally low incidence, and is more likely to represent CHIP
   b. However, plasma ctDNA testing can be used in specific circumstances if 1) the patient is not medically fit for invasive tissue sampling; or 2) there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified. Data suggest that plasma ctDNA testing is a useful minimally invasive test that can be used to identify ALK, BRAF, EGFR, HER2, MET exon 14 skipping, RET, ROS1, and other oncogenic biomarkers that would not otherwise be identified in patients with metastatic NSCLC. Molecular testing of plasma ctDNA should be done using clinically validated tests
2) NCCN 1.2024 colon
   a. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (NTRK) and rearranged during transfection (RET) fusions and may be carried out using either a tissue or blood-based (eg, liquid) biopsy
3) NCCN 1.2024 breast cancer
   a. Testing can be done with either liquid biopsy or tumor tissue testing

Next Generation Sequencing of Malignancies with Liquid Biopsy

Other payer policies:

1) Aetna 2024
    a. Does not cover liquid biopsies for cancer of any type
2) Cigna 2023
    a. Liquid biopsy by cell-free DNA laboratory testing methods (e.g., cDNA, ctDNA) is considered medically necessary when tissue testing is not available or contraindicated for EITHER of the following:
        i. advanced or metastatic solid tumors
        ii. biomarker confirmation is required by an FDA-approved or cleared test as described within the section heading “Indications and Usage” of the US FDA-approved prescribing label prior to initiating therapy
    b. At present there are no standards for analytical performance and no guidelines exist for regarding the recommended performance characteristics. Cell-free DNA testing has a high specificity rate but limitations include a compromised sensitivity with up to a 30% false-negative rate. Such testing may also identify alterations that are unrelated to a lesion of interest. Nonetheless, the use of cell-free DNA testing may be considered appropriate when a patient is medically unfit for invasive tissue sampling or there is insufficient material for analysis in advanced (III or IV), metastatic, recurrent or refractory solid cancers.

Expert input:

None submitted to date.

Next Generation Sequencing of Malignancies with Liquid Biopsy

HERC staff summary:

Cell free tumor DNA testing is less accurate than testing directly on tumor tissue (traditional solid tissue biopsy). NCCN recommends cell free tumor DNA testing when either 1) the patient is not medically fit for invasive tissue sampling or 2) the invasive tissue sample produces insufficient tissue for molecular analysis.

HERC staff recommend modifying the Next Generation Sequencing of Malignancies guideline to clarify when liquid biopsy is covered.

HERC staff recommendation:

1) Modify Diagnostic Guideline D13 as shown below

DIAGNOSTIC GUIDELINE D13, NEXT GENERATION SEQUENCING OF MALIGNANCIES

Next Generation Sequencing (NGS, for example CPT 81479, 81455, 0037U) is covered when all of the following requirements are met:

A) The patient has
   1) A tissue diagnosis confirming cancer and has been evaluated by an oncologist or oncologic surgeon; AND
   2) Has not been previously tested using the same NGS test for the same primary diagnosis of cancer, unless the criteria in D) below are met; AND
   3) Decided to seek further cancer treatment (for example, therapeutic chemotherapy) and has adequate performance status (ECOG 0-2) to undergo such treatment; AND

B) The diagnostic laboratory test using NGS must have:
   1) Clinical Laboratory Improvement Amendments (CLIA)-certification; AND
   2) The test is being used as a companion diagnostic test in accordance with Food & Drug Administration (FDA)-approved therapeutic labeling; AND
   3) Results provided to the treating physician for management of the patient using a report template to specify treatment options; AND

C) A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408 are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.

D) Repeat NGS testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

In addition to the above requirements for NGS, NGS of circulating tumor DNA ("liquid biopsy") is covered only when one of the following requirements are met:

1) The patient is not medically fit for invasive tissue sampling; OR
2) The invasive tissue sample produces insufficient tissue for molecular analysis.

Leadless Pacemaker Review 2024

Plain Language Summary:

Coverage question: Should OHP cover a specific pacemaker, implanted directly into the heart? This type is called "leadless" because it doesn't have wires, called leads, that connect to the heart like traditional pacemakers do.

Should OHP cover this treatment? No, it's not clear if the benefits outweigh the harms.

Changes to issue summary after public comment period:

One public comment received on this topic from the device manufacturer. This comment supported the option staff had presented for adding coverage for leadless pacemakers in patients who have a contraindication to conventional pacemakers or who are at high risk of infection. The commentor provided additional literature on this topic, including a European guideline that recommended considering use of leadless pacemakers only on a case-by-case basis. Based on this guideline, further review of the literature, and lack of other payer coverage, HERC staff have modified their recommendations to continue non-coverage. Coverage of this technology can be done on an exception basis.

In addition to public comment, HERC staff were notified that a HCPCS code was released by CMS that is effective July 2024 which involves leadless pacemakers. The staff recommendation was modified to include this new code.

Coverage Question: Should leadless pacemakers be reconsidered for coverage?

Question source: Holly Jo Hodges, CCO medical director

Background: Pacemakers are standard treatments for bradyarrhythmia's and heart block. Standard pacemakers are surgically inserted into the chest wall with leads in the heart chambers. Leadless pacemakers, also known as intracardiac or transcatheter pacemakers, are pacemakers in which the components are combined into a single device implanted directly within the heart, without any subcutaneous pocket or tunneling. This is in contrast to traditional transvenous pacemakers that require a subcutaneous generator plus transvenous/epicardial lead(s). There are two leadless pacemaker systems that have been on the market which are the Micra transcatheter pacing system (Medtronic, Minneapolis, MN, USA) and the Nanostim (St Jude Medical Inc, Saint Paul, MN USA; now Abbott Medical Inc, IL, USA). However, the Micra is currently the only commercially available leadless pacemaker in the US.

Leadless pacemakers were last reviewed as new codes in November 2018. At that time, a 2018 NICE review found high risk of complications and CMS was only covering with evidence development. The new codes for leadless pacemakers were placed on what is now line 654/GN173.

Leadless Pacemaker Review 2024

Previous HSC/HERC reviews:

The only previous review of this technology was the 2018 review described above.

Current Prioritized List/Coverage status:

CPT 33206-33208 (Insertion of pacemaker) are on lines 69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION, 110 CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART, 188 CHRONIC ISCHEMIC HEART DISEASE, 279 LIFE-THREATENING CARDIAC ARRHYTHMIAS, 283 OMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT, 344 CARDIAC ARRHYTHMIAS

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 654

The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
33274 33275	Leadless cardiac pacemakers	Insufficient evidence of effectiveness; evidence of harm	November 2018

July 2024 HCPCS:
C1605 Pacemaker, leadless, dual chamber (right atrial and right ventricular implantable components), rate-responsive, including all necessary components for implantation

Evidence:

1) **Darlington 2022**, systematic review and meta-analysis of efficacy and safety of the leadless pacemaker
    a. N=18 studies (N=2496 patients)
        i. 14 prospective cohort studies, 4 retrospective cohort studies
        ii. Average age 80 years
    b. While all-cause mortality was occurred in 6.11% of patients, only 0.29% of patients had procedure or device related deaths. Any complication, high threshold or unsuccessful implant each occurred in approximately 3% of patients. Pericardial effusions and cardiac tamponade occurred in 0.96% and 1.47% of patients, respectively. Other complications such as device dislodgement, device revision, device malfunction, access site complications and infection occurred in less than 1% of patients.
    c. A total of 4 studies included both a leadless pacemaker group as well as a transvenous group, with a total of 400 patients in the leadless pacemaker group and 344 patients with transvenous systems. Meta-analysis of these studies suggests that there was no difference in hematoma (RR 0.67 95%CI 0.21-2.18, 3 studies), pericardial effusion (RR

0.59 95%CI 0.15-2.25, 3 studies), device dislocation (RR 0.33 95%CI 0.06-1.74, 3 studies), any complication (RR 0.44 95%CI 0.17-1.09, 4 studies) and death (RR 0.45 95%CI 0.15-1.35, 2 studies) between the two groups

d. In conclusion, this systematic review affirms high levels of safety and efficacy of leadless pacemakers in patients who have an indication for single chamber ventricular pacing, at levels that appear to be comparable to transvenous pacemakers. However, due to the fact that leadless pacemaker technology and widespread usage is relatively recent, randomized trials are lacking, evidentiary value of the current review is diminished.
e. Limitations: small sample sizes in included studies, significant heterogeneity between studies

2) **Crossley 2023**, 3 year follow up of Micra CED study
   a. Medicare claims database cohort study
   b. N=6219 leadless pacemakers patients; N=10,212 standard pacemaker patients
      i. Compared with transvenous, patients implanted with a leadless VVI pacemaker were more likely to have ESRD (12.0% vs. 2.3%, p < .001), renal dysfunction (48.8% vs. 42.1%, p < .001), and a higher mean Charlson Comorbidity Index (CCI) score (5.1 ± 3.4 vs. 4.6 ± 3.0, p < .001).
   c. The acute (30-day), 6-month, and 2-year outcomes have been previously reported, with leadless VVI associated with higher rates of acute pericardial effusion (0.8% vs. 0.4%), but lower rates of chronic complications and reinterventions at both 6 months and 2 years of follow-up (31% lower rate of chronic complications [3.6% vs. 6.5%] and 38% lower rate of device reintervention [3.1% vs. 4.9%] at 2 years).
   d. In the time-to-event model, patients implanted with a leadless pacemaker had significantly fewer overall chronic complications at 3 years compared with patients implanted with a transvenous pacemaker (unadjusted hazard ratio (HR) 0.73; 95% CI 0.64–0.84, p = < .0001; adjusted HR 0.68; 95% confidence interval (CI) 0.59–0.78, p < .0001).
   e. Reintervention rates were also significantly lower in the patients implanted with a leadless VVI pacemaker compared with the transvenous (adjusted, 3.6%, vs. 6.0%, p = .0002). System revisions, removals, and upgrades to both dual chamber and CRT devices were significantly lower in the patients implanted with a leadless VVI pacemaker compared with the transvenous, while system replacements were significantly higher. For the composite endpoint of reinterventions requiring a new device (inclusive of system removal, system replacement, system switch or upgrade to dual chamber or CRT), patients implanted with a leadless VVI pacemaker had significantly fewer reinterventions requiring a new device (adjusted, 3.6% vs. 5.0%, p = .02). In the time-to-event model, patients implanted with a leadless pacemaker had a lower rate of reintervention compared with patients implanted with a transvenous pacemaker (unadjusted HR 0.60; 95% CI 0.45–0.80, p = .0006; adjusted HR 0.59; 95% CI 0.44–0.78, p = .0002).
   f. Heart failure hospitalization rates were slightly lower among patients implanted with a leadless VVI pacemaker compared to transvenous in the overall patient cohort (adjusted, 19.9% vs. 22.0%, p = .005) as well as among patients without prior history of heart failure (adjusted, 11.2% vs. 13.6%), p = .003)
   g. The unadjusted 3-year all-cause mortality rate was significantly greater in the patients implanted with a leadless VVI pacemaker compared with the transvenous (HR, 1.09; 95% CI, 1.03−1.15, p = .003); however, there was no difference in the adjusted 3-year

all- cause mortality rate between leadless and transvenous (HR, 0.97; 95% CI, 0.92−1.03, p = .32) after accounting for differences in baseline characteristics

h. For the composite endpoint of time to heart failure hospitalization or death, there was no difference in the unadjusted rates for either the full cohort or those patients without history of heart failure (full cohort: unadjusted HR 1.03; 95% CI 0.98−0.1.08, p = .28; sub-cohort: unadjusted HR 1.00, 95% CI 0.93−1.08, p = .98). After statistical adjustment, there were small differences, with patients implanted with a leadless VVI pacemaker having slightly lower rates than transvenous (full cohort: adjusted HR 0.94; 95% CI 0.89–0.99, p = .01; sub-cohort: adjusted HR 0.92, 95% CI 0.85−0.99, p = .03)

i. Conclusion: In a real-world study of the United States Medicare patients, the leadless VVI pacemaker was associated with a 32% lower rate of chronic complications (4.9% vs. 7.1%) and a 41% lower rate of device reinterventions (3.6% vs. 6.0%) at 3 years. Rates of heart failure hospitalization were slightly lower among leadless VVI patients, and all-cause mortality rates were similar among leadless VVI and transvenous VVI patients at 3 years, suggesting no trade-off between lower rates of device reintervention and chronic right ventricular-only pacing outcomes for patients. Infections rates were remarkably lower in the leadless group

j. Limitations: some complications may not have ICD-10 codes or be otherwise reported to the database

3) **NICE 2018**, Interventional procedure overview of leadless cardiac pacemaker implantation for bradyarrhythmias

a. Studies included

i. Case series of 33 patients

1. the measures of pacing performance (sensing, impedance and pacing threshold) either improved or were stably within accepted range at 3, 6, 12 and 36 months follow-up

ii. Case series of 526 patients

1. the measures of pacing performance improved statistically significantly from pacemaker implantation to 12 months (mean pacing threshold (at a 0.4-ms pulse width) from 0.82±0.69 V to 0.58±0.31V, p< 0.01; mean R-wave amplitude from 7.8±2.9 mV to 9.2±2.9 mV, p< 0.01). The intention to treat primary efficacy point (acceptable pacing performance at 6 months) was achieved in 90% [270/300] of the primary cohort (95% confidence interval [CI] 86% to 93.2%, p=0.007)

iii. Case series of 725 patients

1. acceptable pacing performance was achieved in 93% (292/297) of the patients with paired 6-month data (95% CI, 96.1% to 99.5%; p< .001) compared with the efficacy performance goal of 80% (based on historical transvenous control data). 4 The measures of pacing performance improved statistically significantly from pacemaker implantation (n=725) to 24 months (n=58) (mean pacing threshold (at a 0.24-ms pulse width) from 0.63 V to 0.53±0.23 V; mean R-wave amplitude from11.2 mV to 15.5 mV; mean pacing impedance from 724 ohms to 596 ohms).

iv. Retrospective matched case control study comparing pacing thresholds at implant and subsequent follow-up (0 to 6 months) between 711 patients with TPS with threshold data at 0.24 ms and 538 patients with transvenous leads at 0.4 ms, pacing thresholds in patients with elevated thresholds at implant (high

more than 1.0 V or very high thresholds more than 1.5 V) decreased statistically significantly in both groups (TPS group: more than 1.0 V (n=45) : pacing threshold 87% decrease [1.28 to 0.78], p< 001; more than 1.5 (n=27) pacing threshold 85% decrease [2.22 to 1.38], p< 0.001; transvenous group more than 1.0 V (n=26) pacing threshold 80% decrease [1.31 to 0.85], p< 0.001; more than 1.5V (n=19) pacing threshold 100% decrease [2.23 to 0.84], p<0.001)

v. Case series of 795 patients
    1. the measures of electrical performance were low and stable
vi. Case series 127 patients
    1. acceptable sensing (R wave >5.0 mV) and pacing thresholds (<2.0 V at 0.4 ms) were reported in 95% (57/60) of patients in the LCP group and 97% (65/67) of patients in the CTP group (p=0.66)
vii. Complication rates overall 90% in one study, 4% in a second study
viii. Serious adverse device effects (SADEs) included cardiac perforation, cardiac perforations or effusion, bleeding, arteriovenous fistula, pseudoaneurysm, puncture site complications, DVT, PE, device dislodgement, device migration, battery failure, cardiopulmonary arrest, arrhythmia during implantation, hemothorax, stroke
ix. Deaths were reported in 3-11% of patients

Submitted literature:

1) Lancellotti 2019: article only available in French
2) El-Chami 2018: Micra study summarized above
3) El-Chami 2024: Micra study summarized above
4) Piccini 2021: Micra study summarized above
5) El-Chami 2022: Micra study summarized above
6) Crossley 2024: already included in staff evidence review above
7) Boveda 2024: Micra study summarized above
8) Garg 2020: Micra study summarized above
9) Wilkoff 2020: study on infections in conventional pacemaker placements
10) El-Chami 2019: Micra study summarized above
11) Glikson 2021: added to guidelines section below
12) Iwasaki 2024: unable to locate. Only identified published JCS guideline was from 2021
13) Kusumoto 2019: older ACC/AHA guideline that already included in guideline section
14) Haute Autorite de Sante 2023: not available at link provided
15) Australian Government Department of Health and Aged Care Medical Services Advisory Committee (MSAC), 2022: not available at link provided
16) NICE 2018: evidence summary added to evidence review above. Coverage policy added to coverage policies outlined below

Expert guidelines:

1) **American Heart Association/American Stroke Association 2024,** statement on leadless cardiac pacemaker devices
    a. Unlike traditional single- or double-chamber pacemakers, leadless cardiac pacemakers do not contain an intravascular lead. This eliminates the risk of complications such as lead failure, lead fracture, insulation defect, or pneumothorax. The known risks of

extraction such as a torn subclavian vein or tricuspid valve can be avoided because there is no lead to replace or extract. In addition, since there is no lead in the vascular system, the risk of venous thrombosis and occlusion of the subclavian system is eliminated, and the patient has vascular access preserved for other medical conditions (e.g., dialysis or chemotherapy). A leadless device may also decrease the risk of infectious complications since there is less surface area exposed to the bloodstream. And, there could be a decreased risk of tricuspid regurgitation depending on the placement of the device in the right ventricle, the number of devices planted, and the size of the right ventricle.

b. These benefits may make leadless cardiac pacemakers a viable option for patients who need a single chamber pacer, such as those with atrial fibrillation with heart block, patients with slow heart rates, those who need rare and intermittent pacing, or patients with many comorbidities who might not have enough benefit from atrioventricular synchrony that ventricular paced/ventricular sensed (VVI) pacing is sufficient. Leadless devices may also be a better option than a surgical endocardial pacemaker for patients with no vascular access due to renal failure or congenital heart disease.
c. Risks include cardiac tamponade, persistent arryhythmias, complications from groin vascular access, thrombus formation leading to PE or stroke, pacemaker migration, erosion
d. Leadless pacemakers may be difficult to monitor
e. Questions remain open: how to extract the leadless pacemaker? What happens when the battery runs out?

2) **Roberts 2022**, UK expert consensus statement of use of leadless pacing systems
    a. Leadless pacing appears to be a safe and effective alternative to conventional transvenous pacing.
    b. Leadless devices should be considered in certain patient populations
        i. High risk of infection
        ii. ESRD
        iii. Previous device infection
        iv. Anatomical constraints complicating/precluding transvenous pacing
        v. Immunocompromised
        vi. Undergoing radiotherapy
        vii. Congenital heart disease
        viii. Under age 40
        ix. Have or at high probability of needing indwelling vascular catheters
    c. The choice to use a leadless pacemaker should be clinically driven to ensure the best outcome for the patient.
3) **Glikson 2021**, European Society of Cardiology guidelines on cardiac pacing
    a. The first-generation leadless pacemakers have been proven to provide effective single-chamber pacing therapy. Albeit a promising technology, potential difficulty with leadless pacemaker retrieval at the end of service is a limitation. Thus far, there are no randomized controlled data available to compare clinical outcomes between leadless pacing and single-chamber transvenous pacing.
    b. A number of prospective registries have reported that implantation success rates are high, with adequate electrical results both at implant and at follow-up. ‘Real-world’ results of one leadless pacemaker system, including 1817 patients, reported serious adverse events in 2.7% of patients. The prevalence of leadless device infections is low as the principal sources of infection (i.e. the subdermal surgical pocket and pacemaker leads) are absent. However, during the initial operator experience, there was a higher

incidence of peri-operative major complications (6.5%), including perforation and tamponade, vascular complications, ventricular arrhythmias, and death

c. Indications for leadless pacemakers include obstruction of the venous route used for standard pacemaker implantation (e.g. bilateral venous thoracic outlet syndrome or chronic obstruction of the superior vena cava), pocket issues (e.g. in the case of cachexia or dementia), or particularly increased infection risk [e.g. in the case of dialysis or previous cardiovascular implantable electronic device (CIED) infection]. Observational data showed that a leadless pacemaker was a safe pacing alternative in patients with previous device infection and explant, and in patients on chronic hemodialysis. Whereas observational data indicate high efficacy and low complication rates with leadless pacemakers, there are currently no data from RCTs documenting the long-term safety and efficacy of leadless vs. standard transvenous pacemakers, and therefore the indication for a leadless pacemaker should be carefully considered on a case by case basis. The absence of long-term data on leadless pacemaker performance and limited data on retrievability and end-of-life strategy require careful consideration before selecting leadless pacemaker therapy, especially for younger patients (e.g. with a life expectancy >20 years).
d. In patients with an indication for VVI pacing, the long-term efficacy and safety of choosing leadless pacing need to be documented in RCT
e. Recommendations:
    i. Leadless pacemakers should be considered as an alternative to transvenous pacemakers when no upper extremity venous access exists or when risk of device pocket infection is particularly high, such as previous infection and patients on hemodialysis (Class IIa, level of evidence B)
    ii. Leadless pacemakers may be considered as an alternative to standard single-lead ventricular pacing, taking into consideration life expectancy and using shared decision-making (Class IIb, level of evidence C)

Other payer policies:

1) NICE 2018: Evidence on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well-recognized complications. The evidence on efficacy is inadequate in quantity and quality…leadless pacemakers should only be used in the context of research
2) CMS still only covers leadless pacing with evidence development
3) Aetna 2023: considers leadless pacemakers to be experimental
4) Cigna 2024: considers leadless pacemakers to be experimental
5) Anthem BCBS 2023: Use of the leadless pacemaker is considered **investigational and not medically necessary** for all applications.
6) Regence BCBS 2024
    a. A single-chamber transcatheter leadless cardiac pacing system may be considered medically necessary in patients when all the Criteria (A. – C.) . below are met:
    1) A. The device is approved by the Food and Drug Administration (FDA).
    2) B. The patient has one or more of the following:
        1. 1. Symptomatic paroxysmal or permanent high-grade atrioventricular (AV) block; or
        2. 2. Symptomatic bradycardia-tachycardia syndrome; or

3. 3. Sinus node dysfunction (sinus bradycardia or sinus pauses).

3) C. The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads, including but not limited to a history or high risk of infection, limited venous access, or presence of a bioprosthetic tricuspid valve.

b. A single-chamber transcatheter leadless pacing system is considered investigational for all other indications when Criterion I. is not met.

c. The initial insertion or replacement of a dual chamber leadless pacemaker is considered investigational.

d. There is enough research to show that Micra™ single-chamber transcatheter pacing system may improve health outcomes for patients with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system. Although evidence is limited and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks, in the context of the life-saving potential of this pacing system for patients who are ineligible for conventional pacing systems. Therefore, this pacemaker system may be considered medically necessary for patients who meet the policy criteria

Expert input:

Dr. Eric Stecker, OHSU cardiology

Yes I think it is very doubtful there will be RCT's.

That said, I think they have important roles in two contexts, and would recommend coverage for those

1. Patients without adequate vascular access or for whom access should be preserved (for instance for future hemodialysis fistulas)
2. Patients at high risk of infection

While an evidence review would not show robust support for #2, the theoretical basis + how the patients were selected or the cohort supports it in my mind. The advantage for infection was touted when the device was released, and as a result we and others selected the highest infection risk patients for leadless pacemaker and registry inclusion. That likely bias coupled with the low observed infection risk substantiates #2 pretty well for me.

Leadless Pacemaker Review 2024

HERC staff summary: Leadless pacemakers have only been studied in cohort studies. Recent systematic reviews have found evidence that these pacemakers, while initially having a higher rate of complications that traditional pacemakers, have lower rates of long-term complications and are similarly effective compared to traditional pacemakers. Leadless pacemakers tend to be placed in older patients and patients with more comorbidities that traditional pacemakers, which might skew data to show more complications.

Experts in the UK support use of leadless pacemakers in certain patient groups. The American Heart Association has not come out with a guideline recommending use outside of clinical trials. Local experts recommend coverage for certain clinical scenarios. One additional guideline was provided though public comment of a European guideline, which recommends consideration for use of this technology only on a case-by-case basis.

Currently, only one private payer was identified that is covering leadless pacemakers other than under Medicare evidence development criteria. One trusted evidence-based coverage guideline (NICE) does not recommend use of leadless pacemakers outside of the research setting.

One public comment was received on this topic from the manufacturer, which recommended coverage for patients who are poor candidates for transvenous pacers.

HERC staff recommend continuing non-coverage of this technology. The exceptions process provides a method for patients to have coverage reviewed on a case by case basis. Coverage should be re-evaluated when more studies are published and when other payers adopt coverage of this technology outside of the research setting.

HERC staff recommendation:

1) **C**ontinue non-coverage until evidence is further developed
    a. Consistent with almost all other payers
    b. Patients can be considered for this technology on a case by case basis as part of the exceptions process
    c. Update the GN173 entry as shown below
        i. Includes the newly released HCPCS code for dual chamber leadless pacemakers

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 654

The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
33274 33275 C1605	Leadless cardiac pacemakers	Insufficient evidence of effectiveness; evidence of harm	~~November 2018~~ May 2024

Posterior Tibial Nerve Stimulation

Disposition of Public Comments

Table of Contents

Discussion Table

IDs/#s	Summary of Issue	HERC Staff Response
A	Leadless pacemakers are safe and effective for treatment of bradyarrythmias.	Based on the submitted literature, specifically the European guideline for use, HERC staff have revised their recommendation to only included non-coverage. This guideline highlighted the need for case by case consideration of use of this technology, which can be done through the exceptions process.

Commenters

Identification	Stakeholder
A	Ania Ritter, Medtronic *[Submitted April 16, 2024]*

Public Comments

ID/#	Comment	Disposition
A	Leadless pacing has been widely used for more than 10 years, providing an alternative to traditional transvenous pacing for patients with bradyarrythmias. Two single-chamber leadless pacing devices (Micra™ VR and AV) have been studied extensively in controlled trials and in general clinical	Thank you for your comments. The submitted articles give information on the use of leadless pacemakers. The majority of the articles

Disposition of Public Comments

ID/#	Comment	Disposition
	practice since approval by the FDA in 2016. The safety and effectiveness of Micra leadless pacemakers have been robustly documented, with over 300 manuscripts published in peer-reviewed literature [1]. Below is a summary of the evidence establishing the patient benefit, safety, and efficacy persistent through 5 years of follow-up. •Micra leadless pacemakers reduce complications compared to transvenous pacemakers: The Micra Post-Approval Registry found lower major complications at 12 months (63% reduction) and at 5 years (53% reduction) with Micra VR compared to transvenous devices.[2,3] This is corroborated in real-world clinical use by both the Micra VR and Micra AV Coverage with Evidence Development (CED) Studies at multiple time points extending to 3 years.[4,5,6] •Micra leadless pacemakers demonstrate long-term patient outcome benefits: Compared to transvenous pacemakers, those with Micra leadless pacemakers show significant improvements in clinical outcomes consistently through 5 years, including reductions in reinterventions, therapeutic upgrades, and HF hospitalizations. [3,6,7] Additionally, Micra leadless pacemakers enable patients who are poor candidates for transvenous pacemakers to obtain the benefits of pacing therapy: •Patients with specific comorbid conditions: Among patients with high-risk comorbid conditions, Micra leadless pacemaker patients had significantly fewer chronic complications and device-related reinterventions compared to transvenous patients through 2 years.[8] •Patients clinically ineligible for transvenous pacing: Despite higher comorbidity burden/all-cause mortality, patients precluded from transvenous pacing (24% of patients), experienced similar safety and efficacy with no	(El-Chami 2018, El-Chami 2024, Piccine 2021, El-Chami 2022, Boveda 2024, Garg 2020, El-Chami 2019) all reported on the MICRA study, that was already included in the staff evidence review. Several additional articles could not be located by staff or did not relate to the question under study. The European guideline for cardiac pacing was added to the guidelines included in the evidence review. This guideline gave low level recommendations for use of leadless pacemakers for patients with no upper extremity venous access or at high risk of infection. However, it highlighted the risks of these devices and recommended further study in RCTs. Based on the submitted European guideline, staff have revised their recommendation to not provide coverage outside of the exceptions process.

Disposition of Public Comments

ID/#	Comment	Disposition
	difference in procedure-related death, acute complications, or major complications through 3 years.[9] •Patients with a previous transvenous device infection: Device infection is associated with serious risk of mortality and other clinical/economic outcomes.[10] Patients with a prior transvenous device infection receiving a Micra leadless pacemaker experienced no subsequent infections requiring device removal.[11] Clinical guidelines recommend leadless pacemaker therapy for patients at high risk of infection or who are poor candidates for transvenous devices, including the European ESC/EHRA 2021 Guidelines (Class IIA Level B)[12] and the Japanese JCS/JHRS 2024 Guidelines (Class I Level B)[13]. The U.S. guidelines[14] have not been updated since 2018 and are thus not reflective of current clinical literature or practice. Recently, global health technology assessments have also recognized the need for leadless pacing, including the 2023 French Haute Autorité de Santé[15] and the 2022 Australian Medical Services Advisory Committee[16] recommendations. The UK National Institute for Health and Care Excellence guidance[17] has not been updated since 2018 , however review is anticipated in the near future as the awaited 5-year outcomes have now been published. In summary, as recognized by clinical guidelines and health technology assessment bodies globally, the evidence establishes the relevance of leadless pacemakers to clinical practice decisions in support of patients needing pacemaker therapy, including those who are not good candidates for transvenous pacing. Micra leadless pacemaker therapy thus warrants medical	

Disposition of Public Comments

ID/#	Comment	Disposition
	plan coverage because it is well-established, supported by evidence, is not investigational, and positively contributes to patient health outcomes.	

References Provided by Commenters

ID	References
A	1. PubMed 2023. Available from: https://pubmed.ncbi.nlm.nih.gov/?term=micra+leadless+pacemaker. Accessed March 21, 2024. 2. El-Chami MF, Al-Samadi F, Clementy N, et al. Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous historical control. Heart Rhythm. 2018; 15(12):1800-1807. doi:10.1016/j.hrthm.2018.08.005 3. El-Chami M, Garweg C, Clementy N, et al. Performance of Leadless Pacemakers in Extended Follow-up: 5 Year Results from the Micra Transcatheter Pacing System Post-Approval Registry. Eur Heart J. 2024; 00:1-11. doi:10.1093/eurheartj/ehae101 4. Piccini JP, El-Chami M, Wherry K, et al. Contemporaneous Comparison of Outcomes Among Patients Implanted With a Leadless vs Transvenous Single-Chamber Ventricular Pacemaker. JAMA Cardiol. 2021; 6(10):1187-1195. doi:10.1001/jamacardio.2021.2621 5. El-Chami MF, Bockstedt L, Longacre C, et al. Leadless vs. transvenous single-chamber ventricular pacing in the Micra CED study: 2-year follow-up. Eur Heart J. 2022; 43(12):1207-1215. doi:10.1093/eurheartj/ehab767 6. Crossley G, Longacre C, Higuera L, et al. Outcomes of Patients Implanted with an Atrioventricular Synchronous Leadless Ventricular Pacemaker in the Medicare Population. Heart Rhythm. 2023; 21(1):66-73. doi:10.1016/j.hrthm.2023.09.017 7. Crossley GH, Piccini JP, Longacre C, Higuera L, Stromberg K, El-Chami MF. Leadless versus transvenous single-chamber ventricular pacemakers: 3 year follow-up of the Micra CED study. J Cardiovasc Electrophysiol. 2023; 34(4):1015-1023. doi:10.1111/jce.15863 8. Boveda S, Higuera L, Longacre C, et al. Two-year outcomes of leadless vs. transvenous single-chamber ventricular pacemaker in high-risk subgroups. Europace. 2023; 25(3):1041-1050. doi:10.1093/europace/euad016 9. Garg A, Koneru JN, Fagan DH, et al. Morbidity and mortality in patients precluded for transvenous pacemaker implantation: Experience with a leadless pacemaker. Heart Rhythm. 2020; 17(12):2056-2063. doi:10.1016/j.hrthm.2020.07.035 10. Wilkoff BL, Boriani G, Mittal S, et al. Impact of Cardiac Implantable Electronic Device Infection: A Clinical and Economic Analysis of the WRAP-IT Trial. Circ Arrhythm Electrophysiol. 2020; 13(5):e008280. doi:10.1161/CIRCEP.119.008280

Disposition of Public Comments

ID	References
	11. El-Chami MF, Johansen JB, Zaidi A, et al. Leadless pacemaker implant in patients with pre-existing infections: Results from the Micra postapproval registry. J Cardiovasc Electrophysiol. 2019; 30(4):569-574. doi:10.1111/jce.13851 12. Glikson M, Nielsen JC, Kronborg MB, et al. ESC 2021 Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA). European Heart Journal 2021; 42(35): 3427-3520. 13. Iwasaki Y, Noda T, et al. JCS/JHRS 2024 Guideline Focused Update on Management of Cardiac Arrhythmias. Circ J 2024; 3(8). 14. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2019; 140(8): e382-e482. 15. Haute Autorité de Santé, 2023. Notices on Medical Devices: MICRA VR Single-chamber implantable cardiac pacemaker, implanted via transcatheter route Renewal and modification of registration conditions. Available from: https://www.hassante.fr/upload/docs/evamed/ CNEDIMTS-7064_MICRA_VR_16%20mai%202023_7064_avis.pdf 16. Australian Government Department of Health and Aged Care Medical Services Advisory Committee (MSAC), 2022. Public Summary Document: Procedures for the insertion or removal of a leadless permanent pacemaker for the treatment of bradyarrhythmia. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/8BBF010B95DAC4F6CA2586D20009B97D/$File/1672%20Final%20PSD_Jul2022%20-%20redacted.pdf 17. National Institute for Health and Care Excellence, 2018. Leadless cardiac pacemaker implantation for bradyarrhythmias (IPG626). Available from: https://www.nice.org.uk/guidance/ipg626

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Efficacy and safety of leadless pacemaker: A systematic review, pooled analysis and meta-analysis

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ABSTRACT

Background: Leadless pacemakers have been designed as an alternative to transvenous systems which avoid some of the complications associated with transvenous devices. We aim to perform a systematic review of the literature to report the safety and efficacy findings of leadless pacemakers.
Methods: We searched MEDLINE and EMBASE to identify studies reporting the safety, efficacy and outcomes of patients implanted with a leadless pacemaker. The pooled rate of adverse events was determined and random-effects meta-analysis was performed to compare rates of adverse outcomes for leadless compared to transvenous pacemakers.
Results: A total of 18 studies were included with 2496 patients implanted with a leadless pacemaker and success rates range between 95.5 and 100%. The device or procedure related death rate was 0.3% while any complication and pericardial tamponade occurred in 3.1% and 1.4% of patients, respectively. Other complications such as pericardial effusion, device dislodgement, device revision, device malfunction, access site complications and infection occurred in less than 1% of patients. Meta-analysis of four studies suggests that there was no difference in hematoma (RR 0.67 95%CI 0.21–2.18, 3 studies), pericardial effusion (RR 0.59 95%CI 0.15–2.25, 3 studies), device dislocation (RR 0.33 95%CI 0.06–1.74, 3 studies), any complication (RR 0.44 95%CI 0.17–1.09, 4 studies) and death (RR 0.45 95%CI 0.15–1.35, 2 studies) comparing patients who received leadless and transvenous pacemakers.
Conclusion: Leadless pacemakers are safe and effective for patients who have an indication for single chamber ventricular pacing and the findings appear to be comparable to transvenous pacemakers.

1. Introduction

Permanent pacemakers (PPMs) are an established therapy for bradyarrhythmias and heart block. Benefits of pacemaker therapy include symptomatic relief and improved prognosis in certain high-risk groups [1]. A pacemaker system typically consists of a pulse generator situated in a subcutaneous or submuscular pocket connected to one or more leads positioned in the heart via transvenous access [2]. Despite the clear benefit of PPM therapy, previous literature reports significant complications associated with implantation and the long-term use of transvenous devices. Procedure related complications including pneumothorax, cardiac perforation and pericardial effusion have previously been reported in 2.77% of patients within two months of first PPM insertion [3]. Furthermore, lead related complications within two months of implant have been reported in 5.54% of cases, predominantly a result of early lead dislodgement [3]. Long-term follow-up of transvenous leads is associated with an increased incidence of lead insolation break down and lead conductor fracture, resulting in unwanted reintervention and the potential need for lead extraction [4]. Infection is another concern and meta-analysis of prospective studies has found 1.6% infection rate associated with transvenous lead implantation [5]. Transvenous lead-associated endocarditis is a major complication that usually requires extraction, resulting in a mortality rate of 26.9% after 20.1 months of follow up [6]. Pocket

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ORIGINAL ARTICLES

WILEY

Leadless versus transvenous single-chamber ventricular pacemakers: 3 year follow-up of the Micra CED study

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Abstract

Introduction: The Micra Coverage with Evidence Development (CED) Study is a novel comparative analysis of Micra (leadless VVI) and transvenous single-chamber ventricular pacemakers (transvenous VVI) using administrative claims data. To compare chronic complications, device reinterventions, heart failure hospitalizations, and all-cause mortality after 3 years of follow-up.

Methods: US Medicare claims data linked to manufacturer device registration information were used to identify Medicare beneficiaries with a de novo implant of either a Micra VR leadless VVI or transvenous VVI pacemaker from March 9, 2017 to December 31, 2018. Unadjusted and propensity score overlap-weight adjusted Fine-Gray competing risk models were used to compare outcomes at 3 years.

Results: Leadless VVI patients ($N = 6219$) had a 32% lower rate of chronic complications and a 41% lower rate of reintervention compared with transvenous VVI patients ($N = 10\,212$) (chronic complication hazard ratio [HR] 0.68; 95% confidence interval [CI], 0.59–0.78; reintervention HR 0.59; 95% CI 0.44–0.78). Infections rates were significantly lower among patients with a leadless VVI (<0.2% vs. 0.7%, $p < .0001$). Patients with a leadless VVI also had slightly lower rates of heart failure hospitalization (HR 0.90; 95% CI 0.84–0.97). There was no difference in the adjusted 3-year all-cause mortality rate (HR 0.97; 95% CI, 0.92–1.03).

Conclusion: This nationwide comparative evaluation of leadless VVI versus transvenous VVI de novo pacemaker implants demonstrated that the leadless group had significantly fewer complications, reinterventions, heart failure hospitalizations, and infections than the transvenous group at 3 years, confirming that the previously reported shorter-term advantages associated with leadless pacing persist and continue to accrue in the medium-to-long-term.

KEYWORDS
complications, leadless pacemakers, system reintervention, transvenous pacemakers

American Heart Association | American Stroke Association
life is why™

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Statement of the American Heart Association to the
Food and Drug Administration
Circulatory System Devices Panel
February 18, 2016

Leadless Cardiac Pacemaker Devices

The American Heart Association appreciates the opportunity to respond to the Food and Drug Administration's request for public comment on clinical trial study design, adverse event reporting and physician training requirements for leadless cardiac pacemaker technology.

Since 1924, AHA has dedicated itself to building healthier lives free of heart disease and stroke – the #1 and #5 leading causes of death in the United States – through research, public and provider education, healthcare provider quality improvement programs, and advocacy. We are joined in our efforts by more than 30 million volunteers and supporters, making AHA the nation's oldest and largest voluntary health organization devoted to fighting cardiovascular disease and stroke.

AHA supports the Agency's decision to convene this meeting and examine new developments in pacing technology. Leadless cardiac pacemakers may provide patients and providers with an important new option in treating or preventing abnormal heart rhythms. However, as with any new medical device, the FDA must carefully examine the potential benefits and risks before approving one of these devices for commercial use in the United States.

Potential Benefits and Risks

When evaluating leadless cardiac pacemakers, we encourage the Agency to consider how the risks and benefits compare to currently available pacer technology. The benefits are categorized into three major areas: avoidance of risks associated with intravascular leads, no pocket required for device placement, and an additional option for patients who require a single chamber pacer.

Unlike traditional single- or double-chamber pacemakers, leadless cardiac pacemakers do not contain an intravascular lead. This eliminates the risk of complications such as lead failure, lead fracture, insulation defect, or pneumothorax. The known risks of extraction

such as a torn subclavian vein or tricuspid valve can be avoided because there is no lead to replace or extract. In addition, since there is no lead in the vascular system, the risk of venous thrombosis and occlusion of the subclavian system is eliminated, and the patient has vascular access preserved for other medical conditions (e.g., dialysis or chemotherapy). A leadless device may also decrease the risk of infectious complications since there is less surface area exposed to the bloodstream. And, there could be a decreased risk of tricuspid regurgitation depending on the placement of the device in the right ventricle, the number of devices planted, and the size of the right ventricle.

Because leadless cardiac pacemakers are implanted directly inside the heart, there is no need for a subcutaneous pocket. This eliminates the risk of pocket infections, erosions and pain. A leadless cardiac pacemaker may also be more comfortable and appealing to patients since they are unable to see or feel the device on the chest wall.

These benefits may make leadless cardiac pacemakers a viable option for patients who need a single chamber pacer, such as those with atrial fibrillation with heart block, patients with slow heart rates, those who need rare and intermittent pacing, or patients with many comorbidities who might not have enough benefit from atrioventricular synchrony that ventricular paced/ventricular sensed (VVI) pacing is sufficient. Leadless devices may also be a better option than a surgical endocardial pacemaker for patients with no vascular access due to renal failure or congenital heart disease.

Leadless cardiac pacemakers, however, are not without risk. In the LEADLESS trial, three major adverse events were seen. One reported patient death was due to complications from cardiac tamponade with hemodynamic collapse secondary to repositioning of the leadless cardiac pacemaker. A second patient had the device inadvertently implanted into the left ventricle after the delivery sheath transited an unknown patent foramen ovale (PFO). A third patient required a conventional single chamber pacemaker due to persistent arrhythmias.

There are some additional risks to leadless cardiac pacemakers that must be considered. During implantation, for example, groin access and a larger sheath is required; this can result in increased bleeding, pseudoaneurysm, arterial perforation, or hematoma. Other potential risks include thrombus formation leading to pulmonary embolus or stroke, hemodynamic effects on the right ventricle, and leadless cardiac pacemaker infection. There is also a risk of pacemaker migration, perforation of ventricle during placement leading to cardiac tamponade, as well as long-term erosion through the right ventricular free wall or septum. Like a conventional pacemaker, a leadless cardiac pacemaker can fail to function if it is dislodged.

Monitoring a leadless pacemaker may also be difficult if it is not equipped for remote monitoring. Remote monitoring has been shown to improve outcomes in patients with conventional cardiovascular implantable electronic devices.

Finally, there are questions that remain to be answered. It is unclear how readily leadless cardiac pacemakers can be extracted, especially over the long-term. If there is a problem with the device, can it be removed? Patients and providers will also need a clear

understanding of what happens when the battery on a leadless cardiac pacemaker runs out or the patient needs to upgrade to a double-chamber pacemaker. Is the original device extracted or turned off and abandoned in place? If the original pacemaker remains, can a new device be implanted even if it results in the patient having multiple pacemakers? If a patient has multiple pacemakers, are there concerns related to mechanical interaction or noise?

Clinical Trials and Postapproval Study Design

Another area the FDA has asked the Panel to discuss is clinical trial design and the necessary elements for postapproval study collection. We offer our thoughts on the design of an equivalence trial versus a postapproval trial and/or surveillance as there are different needs for each type of study design. We feel it is very important that the FDA provides guidance for appropriate patient selection in clinical studies.

For the equivalence study, a non-randomized study may be reasonable. We recognize, however, that the patient population included in that study may not reflect the patient population at large. Therefore, product sponsors should be encouraged, if not required, to track comparable patient populations with conventional single-chamber pacemakers to facilitate device comparison over a period of time. For example, product sponsors could use a registry to compare patients enrolled in the study with consecutive patients who decline to participate. The Agency will have to determine the appropriate length of time to follow these patients and whether product sponsors should be required to provide these comparison data and show equivalency in order to obtain FDA-approval.

In the postapproval and/or surveillance setting, product sponsors should be required to follow long-term outcomes. The duration of follow-up may be dependent on the expected battery longevity. We recommend requiring product sponsors to collect data past the pacemaker's expected end-of-life in order to capture information related to device extraction and replacement options. This information can be captured in a patient registry or recorded directly by the manufacturer; the Agency should consult with product sponsors and providers to determine which is preferable.

Postapproval and/or surveillance studies can also be used to answer questions such as:

- Is the use of the device generalizable to all patients or should the device only be used for select populations?
- What are the consequences of shocks administered to patients with a leadless cardiac pacemaker?
- How often will patients need an upgraded or new device?
- When and how should leadless cardiac pacemakers be extracted? (We recommend that product sponsors work with a third party to develop an extraction system).

Finally, postapproval and/or surveillance studies should track patient-centered outcomes, including the patient experience during implantation (e.g., was the patient required to stay in the hospital), and patient quality-of-life after placement. For example, since remote monitoring of these devices is not currently available, patients will be required to regularly

visit their provider, which may impact the patient experience. These types of patient-focused questions must be incorporated into the study design.

Adverse Event Profile and Rates

As noted in the discussion of potential risks, leadless cardiac pacemakers can be associated with a number of adverse events including:

- Bleeding and vascular complications due to the larger sheath size
- Perforation and cardiac tamponade
- Hemodynamic consequences, such as tricuspid regurgitation or heart failure
- Infection
- Migration
- Device failure
- The need for surgery and/or extraction related to the device
- Mortality

There may also be other adverse events that will not be identified until the devices are used in a larger patient population and outcomes are followed for a longer period of time. For example, adverse events resulting from the placement of multiple pacemakers, as discussed above, may not be evident until leadless cardiac pacemakers have been in use for an extended period of time.

In terms of acceptable adverse event rates, we recommend that the Agency examine three different time intervals:

- Acute procedural complication rates
- Shorter-term complications (30 day, 90 day)
- Longer-term complications (1 year, 5 year, and 10 year or specific time period past the expected battery life)

The adverse event rate associated with each time frame may vary, but the acceptable adverse event rate should <u>not</u> be any higher than with conventional pacemakers in comparable patient populations. We recognize, however, that providers will have to familiarize themselves with this new technology and a learning curve will be required. Therefore, the FDA may wish to allow for a slightly higher adverse event rate until a reasonable training period has occurred.

Physician Training Requirements

Leadless cardiac pacemakers represent a new form of pacing technology. The indications for use, patient selection criteria, adverse event profiles, and implant and extraction procedures may differ from the conventional pacemakers providers are familiar with. As such, adequate provider training will be critical to maximizing patient outcomes. Therefore, we strongly support including a physician training requirement as a condition for securing FDA-approval or securing coverage by payors.

Ideally, the required training would not be provided by the product sponsor. We would prefer to see a train-the-trainer model, if possible, in which the product sponsor trains a small cadre of providers who could then take on the role of training providers in other

settings. However, we recognize that each leadless cardiac pacemaker may differ and there will be nuances of each device's implantation and extraction procedures that will likely require some manufacturer participation in the training program, at least in the first few years. A train-the-trainer model may also depend on the patient volume. If these devices are used in settings where the volume is high, a train-the-trainer model might be feasible.

In terms of the specific training requirements, providers will have to learn how to:

- Appropriately select patients
- Correctly place the device, including whether there are additional locations within the right ventricle that the pacemaker (or multiple pacemakers) can be placed
- Address vascular complications associated with the larger sheath size
- Turn off the pacemaker
- Extract the device
- Replace a leadless cardiac pacemaker at the end of its battery life or upgrade the patient to a double-chamber pacemaker

The training program should also address the informed consent process. The informed consent process must include a discussion about the extraction process (including whether or not that is an option); device abandonment (patients should be aware that the device may remain in their body indefinitely); and the possibility that multiple pacemakers will be inserted over the course of the patient's lifetime. Patients should also be educated about what it means to live with a cardiac device long-term, and advised that they will have to visit their provider on a regular basis since remote monitoring of leadless cardiac pacemakers is not currently available.

Lastly, as providers get more experience with these devices, the FDA should examine whether there is a correlation between higher volume providers and patient outcomes. If so, it may be reasonable to limit these devices to providers that perform a minimum number of implantations per year. In addition, as providers learn how to implant these devices, it may be helpful to have just-in-time consultative services available to providers to troubleshoot during a procedure, or a learning laboratory to help educate providers on common problems that could occur when implanting this type of device.

Closing

In summary, AHA appreciates the FDA's efforts to examine leadless cardiac pacemakers and their role as a new form of pacing technology. When evaluating these devices, we encourage the Agency to consider how their risk and benefit profile compares to the conventional single-chamber pacemakers currently on the market. In order to obtain FDA-approval, leadless cardiac pacemakers should have a safety profile that is as good, if not better, than currently available devices. Product sponsors should also be required to initiate a training program with the goal of eventually creating a train-the-trainer model that is not affiliated with the manufacturer. The training program must address patient selection, implantation, extraction, and abandonment, and the risk associated with each, as well as the informed consent process and real-time troubleshooting during device placement.

We hope the Agency will find our perspective and recommendations useful.

UK Expert Consensus Statement for the Optimal Use and Clinical Utility of Leadless Pacing Systems on Behalf of the British Heart Rhythm Society

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Abstract

Pacemakers are a key technology in the treatment of bradyarrhythmias. Leadless pacemakers (LP) were introduced to address limitations of transvenous devices. However, guidelines and other restrictions have led to LPs becoming niche products. The aim of this consensus statement was to determine the strength of opinion of UK implantation experts as to how LPs can be more optimally used. Using a modified Delphi approach, a panel of LP experts developed 36 statements that were used to form a survey that was distributed to LP implanters in the UK. Stopping criteria included a 3-month window for response, a minimum 25% response rate and at least 75% of statements achieving the threshold for consensus (agreed at 66%). In all, 31 of 36 statements reached consensus, and 23 of these achieved ≥90% agreement. Five statements did not achieve consensus. On the basis of these results, seven recommendations were proposed. The implementation of these recommendations may increase the use of LPs, with the aim of improving patient outcomes.

Keywords

Leadless pacing, cardiac pacing, consensus, expert opinion

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The implantation of permanent transvenous pacemakers has long been established as the first line treatment for patients with bradyarrhythmias. Continuous device improvements and an ageing population have led to a corresponding increase in implantations, with approximately 1,000 units per million people implanted annually in Europe.[1]

However, transvenous pacing still has several limitations, leading to significant complications in 9–12% of patients.[2,3] Complications may be acute (<30 days after implantation) and can include bleeding/haematoma, pneumothorax, pericardial effusion/perforation, infection and lead displacement. Chronic complications include lead fractures and infections, with rates particularly high at the time of generator change.

The development of leadless pacemakers was intended to address some of the limitations seen with transvenous pacemakers. The first leadless pacemaker was implanted in 2012. In all, 1,423 Nanostim devices (Nanostim Inc./St Jude Medical/Abbott Medical) were implanted before the device was withdrawn due to several cases of premature battery depletion.[4]

The first Micra transcatheter pacing system was implanted in 2013 (Micra transcatheter pacing system; Medtronic) and, to date, almost 150,000 devices have been implanted worldwide. The safety and efficacy of this device have been studied extensively. During trials, the utility of this device was demonstrated, with a 99% successful implantation rate (719 patients of 725 recruited) and a 96% primary safety end point (patients should be free of system- or procedure-related major complications).[5] Registry data following the investigational device exemption study continue to demonstrate 99% procedural success rates and low complication rates (2.7% at 12 months).[6] The second-generation Micra transcatheter pacing system uses the signal generated by the device's accelerometer to sense atrial activity and then sequentially pace the right ventricle, providing a

VDD pacing mode. Initial studies demonstrated a mean atrioventricular rate of synchrony of 87%.[7]

A key advantage of using leadless pacemakers over transvenous devices is the marked reduction in pacemaker-related infection. Pacemaker-related infections occur in 7–12% of cases of transvenous pacemakers, and the risk triples in replacement procedures.[3,8] During clinical trials of leadless pacemakers, there was an absence of pacemaker-related infections, even in bacteraemia settings.[3,2] It is likely that this is the result of encapsulation of the device within the right ventricle and the absence of leads in the vasculature and generator on the chest wall.

Although there is currently no head-to-head randomised controlled trial for leadless devices again transvenous pacemakers, the currently available evidence base suggests that leadless pacemakers have favourable complication rates, with a 63% lower rate of complications than transvenous devices.[6] As the number of devices implanted increases, the literature identifies certain patient populations where leadless pacing is considered advantageous. This includes patients with prior cardiac device infection, patients on haemodialysis and patients in whom there is an expectation of low levels of pacing in a young population (e.g. cardioinhibitory vasovagal syncope).[8–11]

Despite these advantages, current guidance within the UK limits the use of leadless devices only for the purposes of research or when conventional pacemakers are contraindicated.[12] Although the 2021 guidelines from the European Society of Cardiology (ESC) state that leadless devices can be used when the risk of infection is high, incorporating shared decision-making and taking into account life expectancy considerations, leadless pacing remains a relatively niche procedure.[13]

Recent efforts have been made by groups of Austrian and Polish healthcare professionals (HCPs) to identify the indications and contraindications for the wider use of leadless pacemakers, developing a set of criteria through which this could be achieved within their healthcare settings.[3,14] Given the state of leadless pacemaker implantation and the positions taken by the Austrian and Polish researchers, the intent of this study was to determine how leadless pacing could be more optimally used within the UK NHS.

A comprehensive literature review on leadless pacemakers was compiled and presented to a panel of experts in leadless pacing device implantation from across the UK. The panel convened in January 2022 to discuss current challenges around the optimal clinical use of leadless pacing. Using a modified Delphi methodology guided by an independent facilitator, the panellists identified five main topics of focus:

- problems that are experienced with transvenous pacing and need to be appreciated/acknowledged;
- the relative risk of leadless systems;
- patient types suitable for leadless pacemakers who may be at risk from transvenous devices;
- the role of a national register; and
- logistical requirements for the safe delivery of leadless pacemakers in the UK.

These topics were discussed further, with 36 statements developed and used to create an online questionnaire using Microsoft Forms. The questionnaire was distributed to 72 leadless implanters identified as working within the UK by PRR. Stopping criteria were agreed as a 3-month time period to collect responses (February–April 2022), a minimum 25% response rate, and at least 75% of statements achieving the agreement threshold for consensus. These criteria were set to allow for the greatest number of HCPs to respond given the pressures currently being experienced by the health service in relation to the COVID-19 pandemic. Given the speciality of the field, the threshold for consensus agreement was set at 66%. Consensus agreement was further defined as 'high' at ≥66% and 'very high' at ≥90%.

Respondents used a 4-point Likert scale (strongly disagree, tend to disagree, tend to agree and strongly agree) to indicate their corresponding level of agreement with each statement. The questionnaire also captured some demographic data for further analysis, including years of experience in implanting cardiac pacing devices, years of experience in implanting leadless devices and the number of leadless devices implanted per year.

Completed anonymised surveys were collated and analysed by an independent facilitator to produce an arithmetic agreement score for each statement. This information was then reviewed by the panel of experts to determine what recommendations could be made based on the responses received.

Because this study only sought the anonymous opinions of healthcare professionals, ethics approval was not sought. However, a statement of consent was provided at the start of the survey, and all completing participants provided consent in line with this statement.

Outcome of the Delphi Process

Of the 72 implanters identified, four could not be contacted for inclusion in the study; thus, 68 invitations sent out. Of these, 27 responses were received (40% response rate) and analysed.

From the first round of consensus, 23 of 36 statements attained very high (≥90%) agreement, eight attained high (<90% and ≥66%) agreement and five did not reach the threshold for consensus (<66%; *Figure 1*; *Table 1*). Given the high level of agreement attained for the statements and that the stopping criteria had been met, it was decided not to undertake a second round of testing.

The results demonstrate a strong degree of support for most statements, with more experienced clinicians showing a lower degree of support overall than more junior colleagues (*Supplementary Figure 1*). However, this association was less clear when examining the experience of respondents with implanting leadless devices (*Supplementary Figure 2*).

Discussion

Perception of the Safety of Leadless Pacemakers

It is clear from the level of agreement with Statements 6 and 7 (*Table 1*; 56% and 44%, respectively) that respondents are unclear as to the perceptions of the wider healthcare community around the safety of leadless pacemakers.

During discussion of the results, the panellists agreed that it is a challenge to know what other HCPs, especially those who refer patients on for pacemaker implantation, think about the safety and use of a leadless device over a more traditional transvenous pacemaker. It was also noted that, to date, patients offered leadless devices are those who are at greater risk of a complication to begin with, which therefore may inversely affect the perception of the safety of the device.

The panellists suggested that this is an area where improvements could be made by expanding the education around leadless pacemakers so that clinicians and referring colleagues are more aware of the advantages of the systems and how they can be used to improve patient outcomes.

Which Patients Benefit Most From a Leadless Pacemaker

Part of the intent of this study was to define suitable patient types who would benefit from leadless pacemaker implantation. This would build on the findings of previous studies to help establish the position of UK implanters. Based on the agreement from Statements 15–19 and 21–26 (*Table 1*), the panellists offered patient criteria for considering leadless pacemaker implantation, as presented in *Table 2*.

It is possible that the sub-threshold agreement level for Statement 19 (48%) indicates that the responders considered that single-chamber transvenous pacemakers were entirely reasonable in an uncomplicated population with AF and bradycardia. AF with bradycardia is supported as a basic criterion for leadless pacemaker implantation in both the ESC 2021 guidelines and within the study examining the position of Austrian HCPs conducted by Steinwender et al.[3,13]

Most of the recommended patient populations relate specifically to complications associated with transvenous systems that are mitigated by a leadless pacemaker. Infection has been recognised as a very remote complication of leadless pacemakers, with no devices having to be removed as a consequence of infection in either the investigational device exemption study or the postapproval registry.[1,6] Consequently, this device is attractive for patients who are at a high risk of infection, including those on haemodialysis, those with a previous cardiac device infection, those who are immunocompromised, those undergoing steroid therapy or receiving biological drugs and those with indwelling vascular catheters. Other recommendations are largely justified by the anatomical advantage of not having leads in blood vessels or a generator (i.e. patients undergoing thoracic radiotherapy, younger patients and patients with congenital heart disease who may be younger and not have appropriate venous access for transvenous pacing).

Further to this list, the cost of the device should be taken into consideration because there is variation across the UK. Therefore, the panellists recommended that leadless devices should be used in a targeted approach that takes into account patient experience and quality of life factors.

National Register Needs

The strength of the response to Statements 27–29 suggests that implanters recognise the need for a specific register to capture information around the use of leadless devices, including their risks and complication rates. The panellists suggested that these data should be input by implanters to ensure accuracy. Furthermore, the panellists agreed that the National Institute for Cardiovascular Outcomes Research (NICOR) database is not currently able to manage the information needs of leadless pacemakers, but that it could be expanded to provide the appropriate fields. However, it is beyond the scope of the present study to provide recommendations as to how this should be achieved.

Logistical Requirements for Delivering Leadless Systems

There was consensus that ultrasound should be used when implanting leadless pacemakers. It has been demonstrated that complication rates for femoral access for electrophysiology procedures are lower if ultrasound is used.[15] In that meta-analysis of 7,858 patients, the incidence of vascular complications in the ultrasound group was 1.2%, compared with 3.2% in the anatomic landmark guided group (p<0.00001).[15] Because the introducer sheaths for leadless devices are large (e.g. 23 Fr), it would seem logical that safety would be enhanced if ultrasound was used. The low complication rate and high success rates associated with leadless pacemaker implantation may be attributed, in part, to the extensive training available for this procedure and the experience of operators. Consequently, maintaining this high level of training and ensuring ongoing experience with recommended minimal annual numbers would seem appropriate, and was reflected by consensus on these points.

The evidence base on the Micra device indicates that the incidence of pericardial perforation requiring surgical intervention is low. In the postapproval registry, two of the 1,817 patients recruited (0.1%) required surgical intervention[6]. Despite this low number, there was no consensus about undertaking leadless pacing in non-cardiac surgical centres. However, there was consensus that centres should have a defined pathway in place to access cardiac surgical support. This would include procedures performed in a cardiac surgical centre and a non-cardiac surgical centre. In the latter situation, the process would be similar to that for the rare occasions when percutaneous coronary intervention or AF ablation require surgical input. This would need to be a predefined process of urgent transfer, recognising that any delay may adversely affect outcome. Similarly, it was recognised that centres implanting leadless pacemakers should have robust pathways in place to address any complications associated with the device or the procedure.

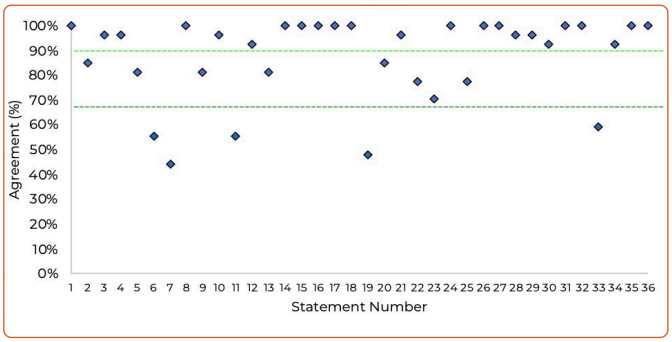
The use of shared decision-making is widely acknowledged as an important part of patient care and features highly within the NHS Long Term Plan, as well as General Medical Council guidance on consent.[16,17] Not surprisingly, the use of shared decision-making in deciding on leadless pacing reached 100% consensus.

Recommendations

Based on the levels of agreement from 27 responses, the authors offer the following set of recommendations:

- Education for implanters and referrers regarding the benefits and safety of leadless pacing systems should be improved.
- Awareness and training on the use of leadless devices should be improved for non-leadless implanters.
- A registry should be developed to track the complications and risks associated with the use of leadless devices.

Figure 1: Combined Consensus Agreement Scores



The dark green line represents the consensus threshold of 66% and the light green line represents the threshold for very high consensus (90%).

- Leadless devices should be more widely used so that implanters can better understand and mitigate the risks involved with the device.
- Leadless pacemakers should be considered in certain patient populations (*Table 2*).
- The choice to use a leadless pacemaker should be clinically driven to ensure the best outcome for the patient.
- A robust and defined pathway for timely cardiac surgical support for leadless pacing should be developed.

Table 1: Defined Consensus Statements and Corresponding Levels of Agreement from 27 Responses

No.	Statement	Score (%)
Topic A: Problems that are experienced with transvenous pacing and need to be appreciated/acknowledged		
1	There is a clear need for leadless pacing in NHS clinical practice	100
2	There is a perception that leadless pacing is underutilised in NHS clinical practice	85
3	There is an existing evidence base that demonstrates clinical limitations with transvenous pacing	96
4	Leadless pacing has a lower rate of infection compared with transvenous pacing	96
5	Leadless pacing has lower rates of complications versus transvenous pacing	81
6	Leadless pacing is perceived as a safer alternative by NHS implanters than transvenous pacing	56
7	Leadless pacing is perceived as a safer alternative by NHS referrers than transvenous pacing	44
8	It is acceptable to implant more than one leadless pacemaker over the patient's lifetime	100
9	Leadless pacing should be considered in order to preserve vascular access	81
10	It is reasonable to consider leadless pacing in order to reduce lead-related complications	96
Topic B: Relative risk of leadless systems		
11	The consequence of a complication with a leadless pacemaker is no more severe than with a transvenous pacer	56
12	The relative risk of a leadless pacemaker is dependent on the profile of the patient	93
13	An evidence base exists for patients at greater risk of cardiac perforation	81
Topic C: Suitable patient types for leadless pacemakers that may be at risk from transvenous devices		
14	Patient choice should always be considered when selecting a pacing option	100
15	Patients requiring a pacemaker who are considered to be at high risk of infection should be eligible for leadless pacing	100
16	Patients requiring a pacemaker who have end-stage renal disease should be eligible for leadless pacing	100
17	Patients requiring a pacemaker who have experienced previous device infections should be eligible for leadless pacing	100
18	Patients requiring a pacemaker who have anatomical constraints complicating or precluding a transvenous pacemaker should be eligible for leadless pacing	100
19	Any patient with AF and bradycardia should be eligible for leadless pacing	48
20	Patients requiring a pacemaker who are unwilling to consider a conventional transvenous device should be eligible for leadless pacing	85
21	Patients eligible for a pacemaker that should be considered for leadless pacing include those who are immunocompromised	96
22	Patients eligible for a pacemaker that should be considered for leadless pacing include those taking biological medicines	78
23	Patients eligible for a pacemaker that should be considered for leadless pacing include those undergoing radiotherapy	70
24	Leadless pacing should be an option for selected appropriate patients with congenital heart disease	100
25	Patients under the age of 40 years can be considered for leadless pacing	78
26	Patients who have, or are at, a high probability of needing indwelling catheters as part of the disease management plan should be considered for leadless pacing	100
Topic D: The role for a national register		
27	The usage and outcomes of leadless pacing should be measured in a national registry	100
28	A national registry would help appropriate patient access to leadless pacing	96
29	A national registry would help appropriate NHS funding decisions for leadless pacing	96
Topic E: Logistical requirements for safe delivery of leadless pacemakers in the UK		
30	Ultrasound should be used to guide vascular access for leadless pacing	93
31	Formal training and proctoring help improve the outcome of leadless pacing	100
32	Implanters should perform a requisite annual number of leadless pacing implants to maintain competence	100
33	Leadless pacing should not be limited to cardiac surgical support centres only	59
34	There should be a robust and defined pathway to access timely cardiac surgical support support when leadless pacing is used	93
35	There should be a robust pathway to deal with potential complications where leadless pacing is used	100
36	Shared decision-making with the patient is always required when deciding the appropriate pacing option	100

The results of this study are a representative sample of the opinions of implanters currently operating within the field. This provides a useful basis for the panel to propose recommendations to improve the use of leadless devices on a patient-centred basis.

As with all consensus studies, the wording of statements may have affected the levels of agreement attained. Future work could refine the statements found less agreeable in the present study to determine what elements are driving the agreement shown.

Conclusion

This consensus document is based on the expert opinion of 27 leadless pacemaker implanters currently operating within the UK, representing a response rate of 40%. The results provide a strong indication of the opinions of these specialists.

This study highlights that there are elements within the current approach to the use of leadless pacemakers that should be modified to improve the clinical utility of the device with a patient-centric focus, including patient types suitable for implantation, the role of a national register and the logistical requirements for delivering the system.

The implementation of the seven recommendations listed above may increase the use of leadless pacemakers, with the aim of improving patient outcomes. ❑

Table 2: Recommended Patient Criteria for Considering Leadless Pacemaker Implantation

• High risk of infection
• End-stage renal disease
• Previous device infection
• Anatomical constraints complicating/precluding transvenous pacing
• Immunocompromised
• Biological medicines (including immunosuppressants and steroids)
• Undergoing radiotherapy
• Congenital heart disease
• Under 40 years of age
• Have, or at high probability of needing, indwelling vascular catheters

Clinical Perspective

- Leadless pacing appears to be a safe and effective alternative to conventional transvenous pacing.
- A Delphi model was used to evaluate opinions on aspects of leadless pacing in the UK, including problems associated with transvenous pacing, risks of leadless pacing, patient types for leadless pacing, the role of a national register and the logistics of delivering leadless pacing.
- The results of the Delphi process and expert opinion resulted in seven recommendations, including the need for a national register.

1. Sideris S, Archontakis S, Dilaveris P, et al. Leadless cardiac pacemakers: current status of a modern approach in pacing. *Hellenic J Cardiol* 2017;58:403–10. https://doi.org/10.1016/j.hjc.2017.05.004; PMID: 28529181.
2. El-Chami MF, Bonner M, Holbrook R, et al. Leadless pacemakers reduce risk of device-related infection: review of the potential mechanisms. *Heart Rhythm* 2020;17:1393–7. https://doi.org/10.1016/j.hrthm.2020.03.019; PMID: 32247833.
3. Steinwender C, Lercher P, Schukro C, et al. State of the art: leadless ventricular pacing: a national expert consensus of the Austrian Society of Cardiology. *J Interv Card Electrophysiol* 2020;57:27–37. https://doi.org/10.1007/s10840-019-00680-2; PMID: 31863250.
4. Sperzel J, Hamm C, Hain A. Nanostim-leadless pacemaker. *Herzschr Elektophys* 2018;29:327–33. https://doi.org/10.1007/s00399-018-0598-3; PMID: 30341551.
5. Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. *N Engl J Med* 2016;374:533–41. https://doi.org/10.1056/NEJMoa1511643; PMID: 26551877.
6. El-Chami MF, Al-Samadi F, Clementy N, et al. Updated performance of the Micra transcatheter pacemaker in the real-world setting: a comparison to the investigational study and a transvenous historical control. *Heart Rhythm* 2018;15:1800–7. https://doi.org/10.1016/j.hrthm.2018.08.005; PMID: 30103071.
7. Chintz L, Ritter P, Khelae SK, et al. Accelerometer-based atrioventricular synchronous pacing with a ventricular leadless pacemaker: results from the Micra atrioventricular feasibility studies. *Heart Rhythm* 2018;15:1363–71. https://doi.org/10.1016/j.hrthm.2018.05.004; PMID: 29758405.
8. El-Chami MF, Clementy N, Garweg C, et al. Leadless pacemaker implantation in haemodialysis patients: experience with the Micra transcatheter pacemaker. *JACC Clin Electrophysiol* 2019;5:162–70. https://doi.org/10.1016/j.jacep.2018.12.008; PMID: 30784685.
9. El-Chami MF, Johanse JB, Zaidi A, et al. Leadless pacemaker implants in patients with pre-existing infections: results from the Mircra postapproval registry. *J Cardiovasc Electrophysiol* 2019;30:569–74. https://doi.org/10.1111/jce.13851; PMID: 30661279.
10. Roberts PR, Pepper C, Rinaldi CA, et al. The use of a single chamber leadless pacemaker for the treatment of cardioinhibitory vasovagal syncope. *Int J Cardiol Heart Vasc* 2019;23:100349. https://doi.org/10.1016/j.ijcha.2019.100349; PMID: 30976654.
11. Turagam MK, Gopinathannair R, Park PH, et al. Safety and efficacy of leadless pacemaker for cardioinhibitory vasovagal syncope. *Heart Rhythm* 2020;17:1575–81. https://doi.org/10.1016/j.hrthm.2020.05.006; PMID: 32389681.
12. Nice Institute for Health and Care Excellence (NICE). *Leadless Cardiac Pacemaker Implantation for Bradyarrhythmias.* London: NICE, 2018. https://www.nice.org.uk/guidance/ipg626/resources/leadless-cardiac-pacemaker-implantation-for-bradyarrhythmias-pdf-1899873986002117 (accessed 1 December 2021).
13. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;42:3427–520. https://doi.org/10.1093/eurheartj/ehab364; PMID: 34455430.
14. Kempa M, Mitkowski P, Kowalski O, et al. Expert opinion of a Working Group on Leadless Pacing appointed by the National Consultant in Cardiology and the Board of the Heart Rhythm Section of the Polish Cardiac Society. *Kardiol Pol* 2021;79:604–8. https://doi.org/10.33963/KP.15982; PMID: 34125944.
15. Triantafyllou K, Karkos CD, Fragakis N, et al. Ultrasound-guided versus anatomic landmark-guided vascular access in cardiac electrophysiology procedures: a systemic review and meta-analysis. *Indian Pacing Electrophysiol J* 2022;22:145–53. https://doi.org/10.1016/j.ipej.2022.01.005; PMID: 35143989.
16. National Health Service (NHS). *NHS Long Term Plan*. NHS, 2019. www.longtermplan.nhs.uk (accessed 1 December 2021).
17. General Medical Council (GMC). *Guidance on Professional Standards and Ethics for Doctors: Decision Making and Consent*. Manchester: GMC, 2020. https://www.gmc-uk.org/-/media/documents/gmc-guidance-for-doctors---decision-making-and-consent-english_pdf-84191055.pdf (accessed 1 December 2021).

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2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC)

With the special contribution of the European Heart Rhythm Association (EHRA)

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All experts involved in the development of these guidelines have submitted declarations of interest. These have been compiled in a report and published in a supplementary document simultaneously to the guidelines. The report is also available on the ESC website www.escardio.org/guidelines

For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the guidelines see *European Heart Journal* online

Keywords Guidelines • cardiac pacing • cardiac resynchronization therapy • pacemaker • heart failure • syncope • atrial fibrillation • conduction system pacing • pacing indications • alternate site pacing • complications • pacing in TAVI • bradycardia • temporary pacing

Table of contents

Absorbable Perirectal Spacer for Prostate Cancer Radiation Therapy

Plain Language Summary:

Coverage question: Should OHP cover a dissolvable spacer for prostate radiation therapy?

Should OHP cover this treatment? No, medical studies found the risks did not outweigh the harms.

Changes to issue summary after public comment period:

No public comment was received on this topic. This document contains no changes from the version released with the early VBBS/HERC packet.

Coverage Question: Should absorbable perirectal spacers be covered for prostate cancer radiation therapy?

Question source: Holly Jo Hodges, CCO medical director

Background: Radiotherapy (RT) is a primary management strategy for men who received a diagnosis of localized or locally advanced prostate cancer. The anterior rectal wall is particularly vulnerable to radiation-induced toxic effects given its anatomical proximity to the prostate, with 2 to 3 mm of distance typically separating the organs. Thus, the rectum is the dose-limiting structure with prostate RT. Greater rectal irradiation during RT increases the risk of both early and late gastrointestinal complications.

An absorbable perirectal spacer is composed of biodegradable material that temporarily positions the anterior rectal wall away from the prostate during radiotherapy for prostate cancer with the intent to reduce the radiation dose delivered to the anterior rectum. The absorbable spacer maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

Perirectal spacers were reviewed as a new CPT code in November 2017 and placed on GN173 as experimental due to a CMS NCD that found it to be experimental. CMS has changed the NCD to now allow coverage. Dr. Hodges is requesting an updated review on this technology.

Previous HSC/HERC reviews:

Perirectal spacers were reviewed as a new CPT code in November 2017. At that time, CMS had a national coverage determination that these spacers were "not reasonable for treatment"; therefore HERC placed the CPT code for these spacers on GN173.

Absorbable Perirectal Spacer for Prostate Cancer Radiation Therapy

Current Prioritized List/Coverage status:

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 654

The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
55874	Absorbable perirectal spacer for use during prostate cancer radiation therapy	Unproven treatment	November, 2017

ICD-10-CM C61 (Malignant neoplasm of the prostate) is on line 326 CANCER OF PROSTATE GLAND along with radiation therapy CPT codes

Evidence:

1) **NICE 2022**, evidence review for biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer
    a. Miller 2020 systematic review as summarized below
    b. Armstrong 2021 systematic review
        i. 19 studies (1 RCT, 18 nRCTs; with 3,622 patients) comparing patients who had a perirectal hydrogel spacer with patients who did not have a spacer (controls) across all types of radiotherapy for prostate cancer reported that rectal dose decreased significantly across 13 nRCTs in the hydrogel spacer group regardless of the type of radiotherapy used (all 5 EBRT studies, 1 HDR BT alone, 7 BT plus EBRT studies) and for all dosimetry outcomes (for example, V40 average difference -6.1% in high dose-rate brachytherapy plus IG-IMRT [Chao 2019] to -9.1% in IG-IMRT [Whalley 2016]).
        ii. GI and GU toxicities reduced but were not statistically significantly different in the hydrogel spacer plus radiotherapy group across 7 included nRCTs regardless of the type of radiotherapy used (5 EBRT studies, 1 HDR BT plus IG-IMRT study [Chao 2019], and 1 LDR BT alone or in combination with EBRT [Taggar 2018])
        iii. improvements were seen after perirectal spacer implantation in most EPIC QoL domains across 4 nRCTs but not statistically significant (in 3 EBRT studies with up to 60 months follow up). For example, in 1 study with EBRT plus LDR BT, bowel function score decreased at 3 and 6 months: average change of 0 versus -6.25 and -3.57, respectively. Another included study reported clinically meaningful differences in EPIC–bowel bother scores at 18 and 60 months (6

point and 5 points, respectively, p>0.05). The RCT also showed that hydrogel spacer significantly improves urinary, bowel and sexual QoL (MID declines in all 3 QoL domains, p=0.002)

c. Vaggers 2021 systematic review
    i. 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel spacers (controls) before brachytherapy for prostate cancer, the rectal D2 cc was reduced in the spacer group by between 22% and 53% and the median rectal V75% cc was reduced by between 92% to 100%
    ii. acute GI complications were mainly limited to grade 1 or 2 toxicity. One study (Chao 2019) on HDR BT with EBRT found a significantly lower rate of grade 1 acute GI complications in the spacer group compared with control group (13% versus 31%, p=0.05) but no statistically significant difference in grade 2 acute GI complications (0% versus 2%, p=0.48). Late grade 1 GI toxicity was less in the spacer group compared to control group (0% versus 8%, p=0.11). No late grade 2 or 3 GI toxicities were seen. In another case-control study (Taggar 2018), at a median follow up of 3 months, grade 1 or 2 rectal or GI toxicity was seen in 20% (n=15) patients in the spacer cohort and 24% (n=33) patients in the non-spacer cohort (p=0.95) (Vaggers 2021)

d. A review of complications of hydrogel spacer injections in the Manufacturer and User Facility Device Experience (MAUDE) database reported 22 unique reports discussing 25 patient cases (from January 2015 to March 2019), with an increasing number of reports each year up to 2019. The reported complications included:
    i. venous injection in 3 (no sequelae)
    ii. tenesmus with air in rectal wall in 1 (no sequelae), • rectal wall erosion in 1 (no sequelae)
    iii. purulent drainage from perineum in 1 (needing antibiotics)
    iv. acute pulmonary embolism in 4 (needing anticoagulant)
    v. perineal abscess in 3 (needing drainage)
    vi. proctitis in 1 (needing colostomy)
    vii. rectal ulcer and haemorrhage in 1 (needing surgery)
    viii. recto-urethral fistula in 4 (needing diverting colostomy)
    ix. perirectal fistula in 1 (needing surgical intervention)
    x. urinary tract infection and prostatic abscess in 1 (needing drainage)
    xi. perineal abscess and subsequent death from alcoholic cardiomyopathy in
    xii. severe urosepsis in 1 (needing ICU admission)
    xiii. severe anaphylaxis in
    xiv. dizziness and nausea post-procedure leading to unresponsiveness
    xv. death in 1 (the cause of death was unclear)

e. Another recent review of complications of hydrogel spacers in the MAUDE database reported 85 unique reports (from 2015 to 2020). Of these 69% (59/85) events were grade 3, 4, or 5. 24 per cent were grade 4 events, including colostomy (n=7) anaphylactic shock (n=2), rectal wall injection, pulmonary embolism requiring hospital admission (n=5), and recto-urethral fistula (n=8). One death was reported

f. An equity assessment was done on the NICE evidence review and found no significant equity issues

2) **Miller 2020**, systematic review and meta-analysis of perirectal hydrogel spacer for men receiving radiotherapy for prostate cancer

Absorbable Perirectal Spacer for Prostate Cancer Radiation Therapy

a. N=7 studies
    i. 1 RCT (Mariados 2015), 1 prospective cohort study (Wolf 2015), 1 cohort study with prospective enrollment in the hydrogel spacer group and retrospective enrollment for patients who received no spacer (Whalley 2016), and 4 retrospective cohort studies (Chao 2019, Pinkawa 2017, Tagger 2018, te Velde 2019)
    ii. N=1011 patients (N=486 with hydrogel spacer injection compared to 525 controls)
    iii. Radiotherapy protocols included external-beam RT with a total therapeutic dose ranging from 76 to 81 Gy (5 studies), brachytherapy with or without external-beam RT (1 study), or combination therapy (1 study)
b. In 5 studies, the hydrogel spacer was placed in 97.0% (95% CI, 94.4%-98.8%) of attempted cases.
c. Procedural complications were uncommon but reported inconsistently. In the hydrogel spacer pivotal trial (Mariados 2015) 10% of patients experienced mild and transient complications that did not delay RT. Whalley et al reported a single case (3%) of inadvertent injection into the rectal lumen without adverse sequelae. Pinkawa et al and Taggar et al reported no procedural complications among treated patients. The frequency of procedural complications was not reported in 3 studies
d. Compared with controls, men who received the hydrogel spacer prior to external-beam RT received 66% less v70 rectal irradiation (3.5% vs 10.4%; mean difference, −6.5%; 95% CI, –10.5% to –2.5%; P = .001 [6 studies]). There was no difference between the hydrogel spacer and control groups in the risk of early grade 2 or higher rectal toxic effects (4.5% vs 4.1%; risk ratio, 0.82; 95% CI, 0.52-1.28; P = .38 [6 studies]). However, in late follow-up (median, 38 months; range, 28-60 months), risk of grade 2 or higher rectal toxic effects was associated with a 77% reduction in the hydrogel spacer group relative to controls (1.5% vs 5.7%; risk ratio, 0.23; 95% CI, 0.06-0.99; P = .05 [4 studies]
e. Changes in bowel-related QoL were not different between the groups at 3-month follow-up (mean difference, 0.2; 95% CI, –3.1 to 3.4; P = .92 [2 studies]) but were greater in the hydrogel spacer group in late follow-up (median, 48 months; range, 36-60 months) and exceeded the threshold for a minimal clinically importance difference (mean difference, 5.4; 95% CI, 2.8-8.0; P < .001 [2 studies]
f. Among men planning to receive RT for localized or locally advanced prostate cancer, injection of a hydrogel spacer was safe, provided prostate-rectum separation sufficient to reduce v70 rectal irradiation, and was associated with lower rectal toxic effects and higher bowel-related QoL in late follow-up. The limitations of this review that may confound interpretation were a small number of eligible studies, the predominance of nonrandomized study designs with associated risks of bias, and follow-up durations that may be inadequate to detect long-term clinical manifestations of rectal irradiation.

Submitted literature:

No literature submitted to date

Expert guidelines:

1) **NCCN 3.2024** Prostate cancer

Absorbable Perirectal Spacer for Prostate Cancer Radiation Therapy

a. Biocompatible and biodegradable perirectal spacer materials may be implanted between the prostate and rectum in patients undergoing external radiotherapy with organ-confined prostate cancer in order to displace the rectum from high radiation dose regions for the purpose of toxicity reduction
    i. Biomaterials have been developed, tested, and FDA approved to serve as spacer materials when inserted between the rectum and prostate. In a randomized phase 3 multicenter clinical trial of patients undergoing image-guided IMRT (IG-IMRT), where the risk of late (3-year) common terminology criteria for adverse events (CTCAE) was grade 2 or higher, physician-recorded rectal complications declined from 5.7% to 0% in the control versus hydrogel spacer group. The hydrogel spacer group had a significant reduction in bowel QOL decline. No significant differences in adverse events were noted in those receiving hydrogel placement versus controls. Results of a secondary analysis of this trial suggest that use of a perirectal spacer may decrease the sexual side effects of radiation. Spacer implantation, however, is quite expensive and may be associated with rare complications such as rectum perforation and urethral damage. Retrospective data also support its use in similar patients undergoing brachytherapy. Overall, the panel believes that biocompatible and biodegradable perirectal spacer materials may be implanted between the prostate and rectum in patients undergoing external radiotherapy with organ-confined prostate cancer in order to displace the rectum from high radiation dose regions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.

2) **AUA/ASTRO 2022** guideline for clinically localized prostate cancer: principles of radiation
    a. Clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of external beam radiation therapy (EBRT) delivered for prostate cancer. (Clinical Principle)
        i. use of rectal spacers was evaluated in a trial that randomized 222 patients 2:1 to either a rectal spacer or control group prior to 79.2 Gy in 1.8 Gy fractions to the prostate seminal vesicles. With a median follow-up of three years, improvements in low-grade (one and two) rectal toxicity, no difference in urinary toxicity, and improvements in bowel health-related quality of life (QOL) were identified. Device-related toxicity events were not detected in this trial. Of note, the utility of this technology in conjunction with hypofractionated or ultra hypofractionated radiation therapy has not been reported in prospective randomized clinical trials to date

Other payer policies:

1) NICE 2023
    a. Evidence on the safety and efficacy of biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.
2) CMS 2021

Absorbable Perirectal Spacer for Prostate Cancer Radiation Therapy

a. Polyethylene-glycol (PEG) hydrogel is covered ONCE in patients with clinically localized prostate cancer with BOTH the following:
    i. Inclusion criteria including ALL of the following:
        1. Low* or Favorable Intermediate Prostate Cancer Risk Group (AUA or NCCN criteria)
            a. *Life expectancy ≥ 20 y (very low risk); ≥ 10 y (low risk)
        2. Dose escalated (≥ 76 Gy) conventional fractionation (1.8-2 Gy fractions) or moderate hypofractionation (HFX) (2.4-3.4 Gy fractions) IG-IMRT planned (7,8,9,25-27)
        3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (4) Modern localization techniques insufficient to improve oncologic cure rates and/or reduce side effects due to AT LEAST ONE of the following:
            a. Anatomic geometry precluding ideal rectal constraints
            b. Conventional fractionation (V70 <10%, V65 <20%, V40<40%)
            c. Moderate HPX (dose constraints not yet standardized; employ those used in the supporting phase III trials)
            d. Medication usage (e.g., anticoagulants)
            e. Comorbid conditions (e.g., increased age, Hx MI or CHF)
    ii. No Exclusion criteria including ALL of the following:
        1. Less than 5 year life-expectancy and asymptomatic
        2. Prior prostate cancer treatment (surgery or RT)
        3. Active bleeding disorder or clinically significant coagulopathy
        4. Active inflammatory or infectious disease in the perineum or injection area (e.g., prostatitis, anorectal IBD)
        5. Prostate volume > 80 CC

3) Aetna 2023
    a. Aetna considers transperineal periprostatic placement of biodegradable material (Barrigel, SpaceOAR) medically necessary for reducing rectal toxicity in men undergoing radiotherapy for prostate cancer.
4) UHC 2023
    a. The transperineal placement of biodegradable material, peri-prostatic (via needle) is proven and medically necessary for use with radiotherapy for treating prostate cancer.

Expert input:

No expert input received to date

HERC staff summary:

There are several recent systematic reviews of absorbable perirectal spacers for use in prostate cancer radiation, but they generally all included the same studies. The literature consists of one RCT and multiple prospective and retrospective cohort studies. The systematic reviews found a reduction in the total radiation dose to the rectum with no significant change in short term rectal toxic effects. However, there was a clinically significant reduction in longer term rectal toxic effects and improvement in GI quality of life. The NICE review found an overall small rate of adverse events, but some were serious and required surgery, ICU level care or death.

Absorbable Perirectal Spacer for Prostate Cancer Radiation Therapy

NICE did not find sufficient evidence that the effectiveness of this technology outweighed the risks. NCCN includes only a "may be used" comment regarding perirectal spacers. The AUA recommends perirectal spacer use based on the one available RCT results. Private payers surveyed are all covering this technology.

HERC staff recommend continued non-coverage of absorbable perirectal spacers for prostate cancer radiation therapy based on highly trusted evidence based source (NICE) not finding evidence that its effectiveness outweighs the harms and only a "may be used" recommendation by NCCN.

HERC staff recommendation:

1) Update the date of last review in the GN173 entry for perirectal spacers

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 654

The following Interventions are prioritized on Line 654 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
55874	Absorbable perirectal spacer for use during prostate cancer radiation therapy	Unproven treatment	~~November, 2017~~ May 2024

Interventional procedure overview of biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Description

Radiotherapy to treat prostate cancer can damage the rectum (the end part of the bowel). This can cause side effects such as bleeding, diarrhoea and faecal incontinence. The aim of this procedure is to reduce the amount of radiation reaching the rectum during radiotherapy, which may reduce the damage. It is usually done using general anaesthetic about 1 week before radiotherapy starts. The rectum is pushed slightly away from the prostate by inserting a balloon or injecting a gel (spacer) between them. This stays in place during radiotherapy. It is biodegradable, which means it breaks down and is absorbed by the body slowly over several months.

Contents

Abbreviations

Word or phrase	Abbreviation
Anterior posterior	AP
Brachytherapy	BT
Confidence Interval	CI
3-dimensional conformal radiation therapy	3D-CRT
External beam radiotherapy	EBRT
Expanded Prostate Cancer Index Composite	EPIC
Endorectal balloon	ERB
Fraction	fx
Gastrointestinal	GI
Genitourinary	GU
Grading of Recommendations, Assessment, Development and Evaluation	GRADE
Hazard Ratio	HR
High dose rate brachytherapy	HDR BT
Health technology assessment	HTA
Image-guided intensity modulated radiotherapy	IG-IMRT
Intensity modulated proton therapy	IMPT
Interventional procedure	IP
Low dose rate brachytherapy	LDR BT
Manufacturer and User Facility Device Experience	MAUDE
Mean difference	MD
Minimally Important Difference	MID
Non-randomised Control Trial	nRCT
National Cancer Institute Common Terminology Criteria for Adverse Events	NCI CTCAE
National Comprehensive Cancer Network	NCCN
Not significant	NS

Odds ratio	OR
Planning target volume	PTV
polyethylene glycol	PEG
Proton beam therapy	PBT
Preferred Reporting Items for Systematic reviews and Meta-Analyses	PRISMA
Prostate-specific antigen	PSA
Quality of life	QoL
Randomised Control Trial	RCT
Radiotherapy	RT
Radiation Therapy Oncology Group	RTOG
Risk difference	RD
Relative Risk	RR
Radiotherapy	RT
Reduction in rectal volume of dose of, for example 50Gy	rV
Stereotactic body radiation therapy	SBRT
Standard deviation	SD
Superior-inferior	SI
Volumetric modulated arc radiotherapy	VMAT
Vienna Rectoscopy scores	VRS

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2021 and updated in September 2022.

Procedure name

- Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Professional societies

- British Uro-Oncology Group (BUG; Predominantly formed by radiation/medical oncologists)
- British Association of Urological Surgeons (BAUS)
- Royal College of Radiologists (RCR)
- The Association of Coloproctology of Great Britain and Ireland.

Description of the procedure

Indications and current treatment

Prostate cancer is the most common cancer in men, and the second most common cancer in the UK. Most prostate cancers are either localised or locally advanced at diagnosis. Localised prostate cancer often does not cause any symptoms, but some people might have urinary problems or erectile dysfunction. Some people may not identify as men but may have a prostate.

Current treatment options for localised or locally advanced prostate cancer include 'watchful waiting', active surveillance, radiotherapy, radical prostatectomy, transurethral resection of the prostate, cryotherapy, high-intensity focused ultrasound, androgen deprivation therapy and chemotherapy (as recommended in NICE's clinical guideline on prostate cancer: diagnosis and treatment).

Radiation therapy is an established curative treatment and can either be external-beam radiotherapy or brachytherapy (also called interstitial radiotherapy). Brachytherapy can be given at low- or high-dose rates. Low-dose-rate brachytherapy may be used alone or with external-beam radiotherapy.

What the procedure involves

Radiotherapy for prostate cancer can cause rectal damage because of the close proximity of the prostate and the rectum. Symptoms of rectal damage can include diarrhoea, incontinence, proctitis and ulceration of the rectal mucosa. Injecting a biodegradable substance (examples include polyethylene glycol hydrogel,

hyaluronic acid, and human collagen), or inserting and inflating a biodegradable balloon spacer, in the space between the rectum and prostate is done to temporarily increase the distance between them. The aim is to reduce the amount of radiation delivered to the rectum and reduce the toxicity profile during prostate radiotherapy.

The procedure is usually done with the patient under general or local anaesthesia using transrectal ultrasound guidance, but it may also be done using spinal anaesthesia. The patient is placed in the dorsal lithotomy position. For gel injection, a needle is advanced percutaneously via a transperineal approach into the space between the prostate and the rectum. Hydrodissection with saline may be used to separate the prostate and the rectum for some gels but is always not necessary. After confirming the correct positioning of the needle, the gel is injected, filling the perirectal space; Some of the gels may polymerise to form a soft mass and some do not. The biodegradable hydrogel absorbs slowly over several months. Some gels are reversible and can be dissolved using enzymes. For balloon spacer insertion, a small perineal incision is typically used to insert a dilator and introducer sheath. The dilator is advanced towards the prostate base over the needle, which is then removed. A biodegradable balloon is introduced through the introducer sheath and is filled with saline and sealed with a biodegradable plug. The balloon spacer degrades over several months.

Efficacy summary

Placement success

In a prospective multicentre RCT of 222 patients with prostate cancer comparing hydrogel spacer injection (hydrogel, n=148) with no spacer injection as control (n=72) during IG-IMRT, spacer placement success in the spacer group (defined as hydrogel present in the perirectal space) was reported as 99%. Urologists and oncologists rated spacer application as ‘easy’ and ‘very easy’ 99% of the time (Mariados 2015, Karsh 2018).

In a systematic review and meta-analysis of 7 studies (1 RCT [Mariados 2015] and 6 cohort studies) comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a spacer (controls) before radiotherapy (EBRT, BT with or without EBRT, or combination therapy) for prostate cancer, the hydrogel spacer was successfully placed in 97% (95% CI, 95% to 99%) of patients and procedure failure was reported in 3% of patients (data from 5 studies). The reasons for procedure failure include unsuccessful hydrodissection (in 5), inadvertent needle entry into the rectal lumen with no clinical sequelae (in 3), and an unspecified cause (in 1) (Miller 2020).

In a systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel

spacers (controls) before brachytherapy for prostate cancer, most studies reported 100% success with hydrogel spacer placement. Procedure failure rate ranged between 4 to 27% (in 12 patients) across 3 studies and was most commonly because of failure of hydrodissection in 9 patients having salvage brachytherapy, unsuccessful hydrodissection of an unknown cause in 1 patient and because of operator inexperience and premature coagulation of the solution during injection in 1 patient. Both these procedures were aborted. There is some slight overlap of studies between the systematic reviews included (Vaggers 2021).

Perirectal separation distance

In the prospective multicentre RCT of 222 patients, perirectal space (defined as the distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs) after hydrogel insertion was 12.6±3.9 mm in the spacer group (post application) and 1.6±2.0 mm in the control group, respectively (Mariados 2015).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a hydrogel spacer (controls), the pooled results from 5 studies showed that the weighted mean perirectal separation distance was 11.2 mm (95% CI, 10.1 to 12.3 mm) (Miller 2020).

In a HTA report by EUnetHTA on using biodegradable rectal spacers for patients with prostate cancer having curative radiotherapy, they summarise the findings from the RCT (Mariados 2015 with several related studies from the same trial) which reported that the mean perirectal distance (defined as the distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs) in the hydrogel spacer plus radiotherapy group (n=149) increased by 1.1 cm (from baseline 0.16±0.22 cm to 1.26±0.39 cm after hydrogel insertion and 0.9±0.59 cm at 3 months). Perirectal space in the control group was 1.6±2.0 mm (NIPHNO 2021).

In the systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel spacers (controls) before brachytherapy for prostate cancer, the mean prostate-rectum space achieved varied between 7.7 mm to 16 mm in 6 studies that used a variety of techniques to measure the spacing distance (Vaggers 2021).

A systematic review of 11 studies on the use of different rectal spacers during different radiotherapy techniques for prostate cancer reported increased prostate-rectum space (ranging from 7 mm to 15 mm with hydrogel spacers in 4 studies, 19.2 mm with biodegradable balloon spacer in 1 study, 13 mm with collagen implant in 1 study, between 9.8 mm to 20 mm with hyaluronic acid in 5 studies) (Mok 2014).

Rectal dose volume

In the prospective multicentre RCT of 222 patients, there was a statistically significant reduction in mean rectal dose volume within the 70 Gy isodose in patients in the spacer group (from baseline, 12.4% to 3.3% after spacer injection, p<0.001) compared with patients in the control group (from baseline, 12.4% to 11.7%) (Mariados 2015).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a hydrogel spacer (controls), at a median follow up of 26 months (range, 3 months to 63 months), the pooled results from 6 studies showed that patients who had the hydrogel spacer before EBRT had 66% less v70 rectal irradiation compared with controls (3.5% versus 10.4%; MD, -6.5%; 95% CI, -10.5% to -2.5%; p=0.001) (Miller 2020).

In the HTA report by EUnetHTA on using biodegradable rectal spacers for patients with prostate cancer having curative radiotherapy, an RCT (n=220, with 5 companion studies from the same trial) reported that the proportion of patients in the hydrogel spacer plus radiotherapy group who had more than 25% reduction in rectal volume having an isodose of 70 Gy (rV70) was 97%. There was a statistically significant reduction in mean rectal dose volume within the 70 Gy isodose in patients in the spacer group (from 13% at baseline to 3% after spacer injection, p<0.001) compared with patients in the control group (from 13% at baseline to 12%). An nRCT included in the HTA also reported that hydrogel plus radiotherapy (n=29) and balloon spacer plus radiotherapy (n=30) may be effective in reducing the dose to the rectum when compared with radiotherapy alone (n=19), but the evidence is uncertain (p<0.001). Balloon spacer was superior in reducing rectum dose (-28%, p=0.034) but exhibited an average volume loss of more than 50% during the full course of treatment of 37 to 40 fractions, while the volume of gel spacers remained fairly constant (NIPHNO 2020).

A systematic review of 19 studies (1 RCT, 18 nRCTs; with 3,622 patients) comparing patients who had a perirectal hydrogel spacer with patients who did not have a spacer (controls) across all types of radiotherapy for prostate cancer reported that rectal dose decreased significantly across 13 nRCTs in the hydrogel spacer group regardless of the type of radiotherapy used (all 5 EBRT studies, 1 HDR BT alone, 7 BT plus EBRT studies) and for all dosimetry outcomes (for example, V40 average difference -6.1% in high dose-rate brachytherapy plus IG-IMRT [Chao 2019] to -9.1% in IG-IMRT [Whalley 2016]). The RCT (Mariados 2015) also showed that hydrogel spacer reduces rectal radiation dose (Armstrong 2021).

In the systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel

spacers (controls) before brachytherapy for prostate cancer, the rectal D2 cc was reduced in the spacer group by between 22% and 53% and the median rectal V75% cc was reduced by between 92% to 100% (Vaggers 2021).

A systematic review of 11 studies on using different rectal spacers during different radiotherapy techniques for prostate cancer reported that the mean rectal dose reduced in spacer group when compared with no spacer regardless of dose (with hydrogel spacers, hyaluronic acid) and when comparing preimplantation plans with postimplantation plans (with collagen implants, biodegradable balloons) (Mok 2014).

Rectal and urinary tract toxicity

In the prospective multicentre RCT of 222 patients, acute rectal toxicity was similar between the spacer and control groups (p=0.525), as was urinary tract toxicity (p=0.488). There was statistically significantly less rectal toxicity at 3 to 15 months in patients with a spacer (2% of patients: grade 1 events rectal bleeding, rectal urgency and proctitis, each in 1 patient) compared with patients in the control group (7% of patients: grade 1 events rectal bleeding in 3, rectal urgency in 1 and grade 3 proctitis in 1; p=0.04). There was no late rectal toxicity greater than grade 1 in patients in the spacer group. The 3-year incidence of rectal toxicity greater than grade 1 (2.0% versus 9.0%; p=0.28) and greater than grade 2 (0% versus 5.7%; p=0.012) was lower in the spacer group than control group. Urinary toxicity greater than grade 1 was also lower in the spacer arm (4% versus 15%; p=0.046), with no difference in greater than grade 2 urinary toxicity (7% versus 7%; p=0.7) (Mariados 2015, Hamstra 2017).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a rectal spacer (controls), pooled results from 6 studies showed that the risk of early grade 2 or higher rectal toxic effects (at 3 months follow up) was comparable and not statistically significantly different between the hydrogel spacer and control groups (5% versus 4%; RR, 0.82; 95% CI, 0.52 to 1.28; p=0.38). However, in a pooled analysis of 4 studies, at late follow up (median, 38 months; range, 28 to 60 months) the risk of grade 2 or higher rectal toxic effects was lower in the hydrogel spacer group compared to controls (2% versus 6%; RR, 0.23; 95% CI, 0.06 to 0.99; p=0.05). Another pooled analysis showed that the risk of grade 1 or higher rectal toxic effects was lower in patients treated with the hydrogel spacer compared to controls at early follow up (21% versus 30%; RR, 0.72; 95% CI, 0.58 to 0.91; p=0.005; 7 studies); and at late follow up (median, 40 months; range, 28 to 60 months) (5% versus 16%; RR, 0.38; 95% CI, 0.22 to 0.65; p<0.001; 5 studies); (Miller 2020).

The HTA report by EUnetHTA on the use of biodegradable rectal spacers for patients with prostate cancer receiving curative radiotherapy included 2 prospective comparative studies (1 RCT [Mariados 2015] with 5 related studies, a

registry record from the same trial and 1 nRCT) that assessed rectal and urinary or genitourinary toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE). In the RCT (220 patients) the risk of early grade 1 rectal toxicity (at 3 months follow up) was not statistically significantly different (RR 0.77, 95% CI 0.50 to 1.19) and the risk of grade 2 or greater rectal toxicity was also not statistically significantly different (RR 0.91, 95% CI 0.23 to 3.5) in the hydrogel spacer group compared with control group. No grade 3 or 4 toxicities were reported in the spacer group but 1 grade 3 toxicity was reported in the radiotherapy alone group. The risk of grade 1 urinary toxicity and the risk of developing grade ≥2 urinary toxicity were also not statistically significantly different (RR 1.03, 95% CI 0.87 to 1.21, p=0.74 and RR 0.97, 95% CI 0.81 to 1.18, p=0.79, respectively). No grades 3 or 4 were reported.

The risk of late grade 1 rectal toxicity (at 15 months follow up) was not statistically significantly different (RR 0.34, 95% CI 0.08 to 1.48). There was 1 grade 3 case in the radiotherapy alone group and no grades 2 or 4 were reported. At 15 months, the risk of late grade 1 urinary toxicity and the risk of late grade 2 or greater urinary toxicity were also not statistically significantly different (RR 0.65, 95% CI 0.15 to 2.85, p=0.57 and RR 1.57, 95% CI 0.44 to 5.53, p=0.47, respectively). No grade 3 or 4 urinary toxicities were reported.

The cumulative evidence (acute and late rectal toxicity, at a median follow up of 3 years, n=140), suggests that patients in the hydrogel spacer plus radiotherapy group were less likely to present grade 1 rectal toxicity than the radiotherapy alone group (HR 0.24, 95% CI 0.06 to 0.97, p<0.03). The HR was not presented for grades ≥2. There was 1 case of grade 3 toxicity in the radiotherapy alone group, and no cases of grade 4 reported. The difference between the groups for grade 1 urinary toxicity was HR 0.36, 95% CI 0.12 to 1.1, p=0.046 and for grade ≥2 urinary toxicity was HR 1.22, 95% CI 0.40 to 3.72, p=0.7.

In the nRCT at 3 months follow up, the risk of developing grade 1 rectal toxicity was not statistically significantly different in the radiotherapy alone group when compared with hydrogel spacer plus radiotherapy group (RR 1.58, 95% CI 0.34 to 7.60, p=0.55) or balloon plus radiotherapy group (RR 1.64, 95% CI 0.35 to 7.60, p=0.52). The risk of developing grade 2 GU toxicity was not statistically significantly different in the radiotherapy alone group (RR 1.39, 95% CI 0.57 to 3.38, p=0.46) or in the balloon plus radiotherapy group (RR 0.78, 95% CI 0.28 to 2.22, p=0.64). compared to hydrogel spacer plus radiotherapy group. No grades 3 or 4 were recorded (NIPHNO 2020).

The systematic review of 19 studies (1 RCT, 18 comparative nRCTs, with 3,622 patients) comparing patients who had a perirectal hydrogel spacer with patients who did not have a spacer (controls) across all types of radiotherapy for prostate cancer reported that GI and GU toxicities reduced but were not statistically significantly different in the hydrogel spacer plus radiotherapy group across 7 included nRCTs regardless of the type of radiotherapy used (5 EBRT studies, 1

HDR BT plus IG-IMRT study [Chao 2019], and 1 LDR BT alone or in combination with EBRT [Taggar 2018]). The RCT (Mariados 2015) included also showed that hydrogel spacer plus radiotherapy significantly reduced late GI and GU toxicities (Armstrong 2021).

In the systematic review of 9 studies comparing 671 patients who had hydrogel spacers (of 2 different types) with 537 patients who did not have hydrogel spacers (controls) before brachytherapy for prostate cancer, acute GI complications were mainly limited to grade 1 or 2 toxicity. One study (Chao 2019) on HDR BT with EBRT found a significantly lower rate of grade 1 acute GI complications in the spacer group compared with control group (13% versus 31%, p=0.05) but no statistically significant difference in grade 2 acute GI complications (0% versus 2%, p=0.48). Late grade 1 GI toxicity was less in the spacer group compared to control group (0% versus 8%, p=0.11). No late grade 2 or 3 GI toxicities were seen. In another case-control study (Taggar 2018), at a median follow up of 3 months, grade 1 or 2 rectal or GI toxicity was seen in 20% (n=15) patients in the spacer cohort and 24% (n=33) patients in the non-spacer cohort (p=0.95) (Vaggers 2021).

Quality of life

In the prospective multicentre RCT of 222 patients, at 15 months follow up, 12% of patients in the spacer group and 21% of patients in the control group reported a 10-point decline (p=0.087) in bowel QoL scores (assessed using the Expanded Prostate Cancer Index Composite self-assessment questionnaire). Bowel QoL consistently favoured the spacer group from 6 months (p=0.002), with the difference at 3 years (5.8 points; p<0.05) meeting the threshold for a minimally important difference (MID, 5 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in bowel QoL (5-point decline: 41% versus 14%; p=0.002; OR 0.28, 95% CI 0.13 to 0.63) and even large declines at twice the MID (10-point decline: 21% versus 5%, p=0.02, OR 0.30, 95% CI 0.11 to 0.83) (Mariados 2015, Hamstra 2017).

At 6 months follow up, 9% of patients in the spacer group and 22% of patients in the control group reported 10-point decline in urinary QoL scores (p=0.003). At 12 and 15 months follow up, the declines in urinary QoL scores were similar for both groups. At 3 years follow up, the control group had a 3.9-point greater decline in urinary QoL compared with the spacer group (p<0.05), but the difference did not meet the MID threshold (6 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in urinary QoL (6-point decline: 30% versus 17%; p=0.04; OR 0.41, 95% CI 0.18 to 0.95) and even large declines at twice the MID (12-point decline: 23% versus 8%; p=0.02; OR 0.31, 95% CI 0.11 to 0.85) (Mariados 2015, Hamstra 2017).

In the systematic review and meta-analysis of 7 studies comparing 486 patients who had a hydrogel spacer with 525 patients who did not have a spacer

(controls), pooled analysis of 2 studies showed that changes in bowel-related QoL were similar between the 2 groups at 3 months follow up (MD, 0.2; 95% CI, -3.1 to 3.4; p=0.92). At late follow up (median, 48 months; range, 36 to 60 months), the changes showed an improvement in QoL in the hydrogel spacer group and exceeded the threshold for a minimal clinically importance difference (MD, 5.4; 95% CI, 2.8 to 8.0; p<0.001) (Miller 2020).

In the HTA report by EUnetHTA, an RCT (Mariados 2015) that assessed QoL according to the EPIC 50 item scale (in which higher values indicate better QoL) and summarised on 3 domains (bowel, urinary, and sexual QoL) reported that the proportions of patients experiencing minimally important differences (declines) in all 3 QoL summary domains at 36 months were 2.5% with hydrogel spacer plus radiotherapy group compared with 20% in radiotherapy group (p=0.002). Results also indicate that hydrogel spacer plus radiotherapy group may improve bowel QoL (p=0.002), may have little to no effect on urinary QoL (p=0.13) over the entire follow-up period (n=140), but the evidence is uncertain (NIPHNO 2021).

The systematic review of 19 studies (1 RCT, 18 comparative nRCTs, with 3,622 patients) comparing patients who had a perirectal hydrogel spacer with patients who did not have a spacer (controls) across all types of radiotherapy for prostate cancer reported that improvements were seen after perirectal spacer implantation in most EPIC QoL domains across 4 nRCTs but not statistically significant (in 3 EBRT studies with up to 60 months follow up). For example, in 1 study with EBRT plus LDR BT, bowel function score decreased at 3 and 6 months: average change of 0 versus -6.25 and -3.57, respectively. Another included study reported clinically meaningful differences in EPIC–bowel bother scores at 18 and 60 months (6 point and 5 points, respectively, p>0.05). The RCT also showed that hydrogel spacer significantly improves urinary, bowel and sexual QoL (MID declines in all 3 QoL domains, p=0.002) (Armstrong 2021).

Spacer absorption

In the prospective multicentre RCT of 222 patients, hydrogel absorption was confirmed at 12 months (on MRI scans) in all the patients in the spacer group, with 2% (3/148) of them having small water density remnant cysts in unremarkable perirectal tissues (Mariados 2015, Hamstra 2017).

The systematic review of 11 studies on using different rectal spacers during different radiotherapy techniques for prostate cancer reported that time to complete absorption is variable among the spacers (with PEG hydrogels and biodegradable balloons reporting complete absorption after 6 months, collagen implants and hyaluronic acid at 12 months) (Mok 2014).

Prostate motion or displacement

In a systematic review of 21 studies evaluating the role of the biodegradable rectal spacers on prostate motion, hydrogel spacer placement (in 4 studies) was not associated with statistically significant changes in prostate motion, compared with no spacer or endorectal balloons but significantly reduces rectal wall doses and GI toxicities. Endorectal balloon (ERB) placement (in 12 studies) significantly decreases intra-fractional prostate motion. This reduces PTV margins and additional rectal dose sparing. Even with an ERB, inter-fractional prostate displacements are seen (Ardekani 2021).

Safety summary

Procedure-related complications

In the systematic review and meta-analysis of 7 studies, authors state that procedural complications (defined as inability to inject the hydrogel spacer into the perirectal space or any complication, regardless of severity, occurring during the procedure) were infrequent and reported inconsistently (Miller 2020).

The RCT included within several reviews reported mild and transient procedural adverse events (perineal discomfort and others, grade 1 to 2) in 10% of patients in the hydrogel spacer group. Grade 2 events (treated with medication) included mild lower urinary tract symptoms and hypotension, and moderate perineal pain. Fewer patients with a spacer had rectal pain (3% compared with 11% in control group, p=0.02). Hydrogel rectal infiltration during the procedure was reported in 6% (n=9) patients. Inadvertent needle penetration of the rectal wall (needing termination of the procedure) and hydrogel injected beyond the prostate were reported in 1 patient each. There were no grade 3 to 4 related adverse events or deaths (Mariados 2015).

In the systematic review of 13 studies (n=671 patients with hydrogel spacer versus 537 patients without a spacer before prostate cancer brachytherapy), some procedure-related complications were reported in the hydrogel spacer groups (in 8 of the studies). These included:

- rectal ulcer 2 months after hydrogel injection (causing frequent rectal bleeding, mucus discharge and bowel movements that resolved without intervention by 3 months) in a case report of 1 patient (Teh 2014),
- perineal pain (that resolved without intervention within 1 week) in 3 patients,
- sensation of pressure or fullness in the rectum (that resolved by 3 months with medication) in 1 patient,

- sudden need for defecation (that resolved by 3 months with medication) in 1 patient,
- infection (bacterial prostatitis after biopsies in 2 patients and epididymitis in 1 patient, which resolved after adjusting antibiotic prophylaxis),
- rectal perineal abscess (in 1 patient after 1 month, needed incision, drainage and antibiotics),
- severe proctitis (in 1 patient), and fistulas needing diverting colostomy (in 2 patients),
- other complications such as rectal discomfort (n=7), bleeding (n=2), and diarrhoea were reported in 1 study of 74 patients with hydrogel (Taggar 2018) (Vaggers 2021).

A review of complications of hydrogel spacer injections in the Manufacturer and User Facility Device Experience (MAUDE) database reported 22 unique reports discussing 25 patient cases (from January 2015 to March 2019), with an increasing number of reports each year up to 2019. The reported complications included:

- venous injection in 3 (no sequelae),
- tenesmus with air in rectal wall in 1 (no sequelae),
- rectal wall erosion in 1 (no sequelae),
- purulent drainage from perineum in 1 (needing antibiotics),
- acute pulmonary embolism in 4 (needing anticoagulant),
- perineal abscess in 3 (needing drainage), proctitis in 1 (needing colostomy), rectal ulcer and haemorrhage in 1 (needing surgery),
- recto-urethral fistula in 4 (needing diverting colostomy),
- perirectal fistula in 1 (needing surgical intervention),
- urinary tract infection and prostatic abscess in 1 (needing drainage),
- perineal abscess and subsequent death from alcoholic cardiomyopathy in 1, severe urosepsis in 1 (needing ICU admission),
- severe anaphylaxis in 1, dizziness and nausea post-procedure leading to unresponsiveness and

- death in 1 (the cause of death was unclear) (Aminsharif 2019).

Another recent review of complications of hydrogel spacers in the MAUDE database reported 85 unique reports (from 2015 to 2020). Of these 69% (59/85) events were grade 3, 4, or 5. 24 per cent were grade 4 events, including colostomy (n=7) anaphylactic shock (n=2), rectal wall injection, pulmonary embolism requiring hospital admission (n=5), and recto-urethral fistula (n=8). One death was reported (Hall 2021).

Inadvertent injection of hydrogel into the rectal lumen resulting in focal rectal mucosal necrosis and bladder perforation was reported after the procedure in 1 patient in a case series of 52 patients. This resolved with no sequelae (Uhl 2014, Song 2013). The same study included in the meta-analysis reported 1 case of inadvertent injection into the rectal lumen without adverse sequelae (Miller 2020).

A case series of 27 patients with ERB (Gez 2013) included in the HTA report by EUnetHTA reported:

- Acute urinary retention (needed catheterisation, which resolved within a few hours) in 12% (3/26) of patients during balloon insertion and in 1 patient during radiotherapy.
- Dysuria and nocturia (grade 1 to 2) in 12% (3/26) of patients during balloon insertion and in 65% (15/23) of patients during radiotherapy.
- Penile bleeding in 1 patient during balloon insertion. Further details were not reported.
- Other events during radiotherapy in the same study, including diarrhoea in 17% (4/23) of patients, mild proctitis in 8% (2/23) of patients, and , blood in the faeces, constipation, erectile dysfunction, itching, fatigue and decreased urine flow in 1 patient each (NIPHNO 2021).

Haematoma developed behind the bladder in 1 patient with a moderate platelet count (within hours after injection) in a case series of 36 patients injected with a hyaluronic acid spacer. This was removed by laparotomy (Chapet 2015).

In the systematic review of 11 studies, a case series of 11 patients injected with collagen implant during IMRT reported that 3 patients had self-limiting light rectal pressure. One patient needed temporary catheterisation for acute urinary retention (presumed to be secondary to pudendal nerve blocking) (Mok 2014).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: intraprostatic infiltration of gel, urinary retention, hydrogel not solidifying, loss of implant (user preparation error when the implant deployed while being prepared for insertion). They described that “there is a theoretical possibility that spacer insertion could cause displacement of extracapsular prostate cancer leading to reduced efficacy of radiotherapy”.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer. The following databases were searched, covering the period from their start to 30.09.2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with prostate cancer.
Intervention/test	Insertion of biodegradable spacer for prostate rectum separation during radiotherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the interventional procedures (IP) overview

This IP overview is based on 7,920 patients from 1 RCT, 2 meta-analysis, 1 HTA, 4 systematic reviews,1 review, 1 commentary and 1 case series. There is likely to be an overlap of primary studies between systematic reviews 2 to 7 and data between studies 9 and 10.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Study 1 Mariados N 2015, Hamstra DA 2017, 2018, Karsh 2018

Study details

Study type	**Randomised Controlled Trial**
Country	US (multicentre)
Recruitment period	2012 to 2013
Study population and number	n=**222 (149 with spacer versus 73 without spacer [control])** patients with clinical stage T1 or T2 prostate cancer (NCCN low or intermediate risk).
Age and sex	Mean age: spacer group 66.4 years; control group: 67.7% years; 100% male
Patient selection criteria	Men with stage T1 and T2 prostate cancer, a Gleason score of <7, PSA concentration of 20 nanograms/ml, and a Zubrod performance status of 0–1, planning to have image guided intensity modulated radiotherapy (IG-IMRT) were included. Patients with a prostate volume of >80 cm^3, extracapsular extension of disease or >50% positivity biopsy scores, metastatic disease, indicated for or had recent androgen deprivation therapy and prior prostate surgery or radiotherapy were excluded.
Technique	**Intervention: Injection of a prostate-rectum spacer (polyethylene glycol hydrogel-SpaceOAR system) during IG-IMRT** (total dose of 79.2Gy in 1.8 Gy fractions to the prostate with or without the seminal vesicles delivered 5 days weekly) A planning target volume of 5-10mm was used. **Control – IG-IMRT alone** (total dose of 79.2Gy in 1.8 Gy in 44 fractions to the prostate with or without the seminal vesicles delivered 5 days weekly) **with no injection.** Patients had CT and MRI scans for treatment planning, followed with fiducial marker placement using transperineal approach. Antibiotic prophylaxis was administered before procedure 95% of time. General anaesthesia in 36%, local in 31%, monitored anaesthesia in 26%, conscious sedation in 6%, other in 10%.
Follow-up	**Median 37 months (15 months, Mariados N, 2015; 3 years Hamstra DA 2017, 2018, Karsh 2018)**
Conflict of interest/source of funding	The study was supported by research funding from Augmenix. Two authors are shareholders and 1 author received speaking honoraria from the manufacturer. 2 authors have provided consulting services.

Analysis

Follow-up issues: short follow-up period. Patients evaluated at baseline, weekly during IG-IMRT, and at 3, 6, 12 and 15 months. Three patients were lost to follow up during the study period (15 months). Extended follow up at 3 years was voluntary, with each institute choosing whether to participate. 63% of both control and

spacer patients were available at extended follow up and no differences were found in the median follow-up period between the 2 treatment groups (control median 37 months, spacer median 37.1 months, p>0.05).

Study design issues: prospective single-blind phase III trial in 20 centres evaluating safety and effectiveness of hydrogel spacer, Patients were randomised 2:1 (by opening envelopes) to have either spacer injection or no injection (control). Patients were blinded to randomisation, allocation concealed. The planning methodology from baseline and post procedural treatment plans was same. The primary effectiveness endpoint was the proportion of patients achieving >25% reduction in rectal volume having at least 70Gy (V70) because of spacer placement. The primary safety endpoint was the proportion of patients having grade 1 or greater rectal or procedural adverse events in the first 6 months. All IG-IMRT planning documentation and CT and MRI scans were assessed by a blinded independent laboratory. All adverse events were recorded and attributed by an independent clinical events committee blinded to treatment randomisation. Rectal and urinary adverse events attributed to radiation were included for toxicity analysis according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4 grading system. Quality of life (QoL) assessed using the Expanded Prostate Cancer Index Composite (EPIC) health related QoL questionnaire at different follow-up visits. Declines in QoL assessed using predetermined 5- and 10-point thresholds for minimal clinically detectable QoL changes.

Study population issues: There were no differences between the groups with regard to baseline tumour characteristics, demographics and medical morbidities.

Key efficacy findings

Number of patients analysed: 220 (148 with spacer versus 72 without spacer [control])

Spacer placement success in spacer group (defined as hydrogel present in perirectal space): 98.7% (146/148)

Ease of spacer application:

Urologists and oncologists rated spacer application as 'easy' and 'very easy' 98.7% of time.

Perirectal space (distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs) (Mariados 2015).

	Spacer group	**Control group**
Baseline	1.6±2.2 mm	NR
Post spacer application	12.6±3.9 mm	1.6±2.0 mm
3 months	9.0±5.9 mm	NR

Rectal dose volume in spacer group (Mean±SD)[1]

Spacer group (n=148)					Control group (n=72)	p value
Parameter	**rV50**	**rV60**	**rV70**	**rV80**	**rV70**	
% before spacer	25.7±11.1	18.4±7.7	12.4±5.4	4.6±3.1	12.4	0.95
% after spacer	12.2±8.7	6.8±5.5	3.3±3.2	0.6±0.9	11.7	<0.0001
% of absolute reduction	13.442	11.56	9.078	3.933		
% of relative reduction	52.3	62.9	73.3	86.3		
p value	<0.0001	<0.0001	<0.0001	<0.0001		

Overall 97.3% of spacer patients had a 25% reduction in rV70. Additionally, 100% and 92% of all spacer and control patient plans met all rectal dose constraints respectively.

Spacer application did not increase the dose in neighbouring tissues (mean pre and post application bladder V70 being 11.3% and 11.0%). No differences were found in the values for bladder or bladder wall (p>0.001 for all).

The mean penile bulb dose was significantly reduced in spacer group than in the control group (18.0 Gy versus 22.8 Gy, p=0.036) and doses from V10 to V30.

Acute and late rectal and urinary tract toxicity

Acute toxicity (from procedure to 3-month visit)[Mariados 2015]						
Rectal toxicity scores (%)				**Urinary tract toxicity scores (%)**		
Grade	**Spacer % (n=148)**	**Control % (n=72)**	**p value**	**Spacer % (n=148)**	**Control % (n=72)**	**p value**
0	73 (108)	68 (49)	0.525	9.5 (14)	9.7 (7)	0.488
1	23 (34)	27.8 (20)		52.7 (78)	45.8 (33)	
>2	4.1 (6)*	4.2 (3)*		37.8 (56)*	44.4 (32)*	
Late toxicity (between 3 and 15 month visits)[Mariados 2015]						
Grade	**Spacer % (n=148)**	**Control % (n=71)**	**p value**	**Spacer % (n=148)**	**Control % (n=71)**	**p value**
0	98 (145)	93 966)	0.044	90.5 (134)	91.5 (65)	0.622
1	2 (3)+	5.6 (4)+		2.7 (4)	4.2 (3)	
>2	0	1.4 (1)+		6.8 (10)	4.2 (3)	
Late toxicity (between 15 months and 3 year visits)[Hamstra 2017]						
Rectal toxicity scores (%)				**Urinary tract toxicity scores (%)**		
Grade	**Spacer % (n=94)**	**Control % (n=46)**	**p value**	**Spacer % (n=94)**	**Control % (n=46)**	**p value**
>1	2.0 (95% CI 4-20%)	9.0 (95% CI 1-6%)	0.28	4 (95% CI 2-10%)	15 (95% CI 8-29%)	0.046

			HR 0.24 (95% CI 0.06-0.97)			HR 0.36 (95% CI 0.12 -1.1)
>2	0	5.7++ (95% CI 2-17%)	0.012	7	7	0.7

*No grade 3 or 4 toxicity reported within 3 months.

+ late rectal toxicity was seen in 2% of spacer patients (3 grade 1 events: 1 rectal bleeding, 1 rectal urgency, and 1 proctitis) and 7% of control patients (grade 1–3 rectal bleeding, 1 rectal urgency and 1 grade 3 proctitis). There was no rectal toxicity greater than grade 1 in spacer group[1]. ++ 1 case of grade 2 rectal toxicity in control arm (Hamstra 2017).

Bowel QoL (assessed using EPIC questionnaire)

At 15 months, 11.6% and 21.4% of spacer and control group patients had 10-point declines in bowel QoL (p=0.087)[1]. From 6 months onward, bowel QoL consistently favoured the spacer group (p=0.002), with the difference at 3 years (5.8 points; p<0.05) meeting the threshold for a MID (5-7 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in bowel QoL (5-point decline: 41% versus 14%; p=0.002; OR 0.28, 95% CI 0.13-0.63) and even large declines (twice the MID) (10 decline: 21% versus 5%, p=0.02, OR 0.30, 95% CI 0.11-0.83) (Hamstra 2017).

Urinary QoL (assessed using EPIC questionnaire)

At 6 months, 8.8% and 22.2% of spacer and control group patients had 10-point urinary declines (p=0.003). At 12 and 15 months the declines were similar for both groups (Mariados 2015).

The control group had a 3.9-point greater decline in urinary QoL compared with the spacer group at 3 years (p<.05), but the difference did not meet the MID threshold (5-7 points). At 3 years, more patients in the control group than in the spacer group had experienced a MID decline in urinary QoL (6-point decline: 30% vs 17%; p=0.04; OR 0.41, 95% CI 0.18-0.95) and even large declines (twice the MID) (12-point decline: 23% vs 8%; p=0.02; OR 0.31, 95% CI 0.11-0.85) (Hamstra 2017).

Sexual QoL: 41% (88/222) of patients with adequate baseline sexual QoL (EPIC mean, 77 ± 8.3) at 3 years had better sexual function (p=0.03) with a spacer with a smaller difference in sexual bother score (p=0.1), which resulted in a higher EPIC score on the spacer arm (58 ±24.1 versus control 45 ± 24.4) meeting threshold for MID without statistical significance (p=0.07). There were statistically nonsignificant differences favouring spacer for the proportion of patients with MID and 2× MID declines in sexual QoL (with 53% versus 75% having an 11-point decline, p=0.064 and 41% versus 60% with a 22-point decline, p=0.11). At 3 years, more patients potent at baseline and treated with spacer had “erections sufficient for intercourse" (control 37.5% versus spacer 66.7%, p=0.046) as well as statistically higher scores on 7 of 13 items in the sexual domain (all p<0.05) (Hamstra 2018, Karsh 2018).

Multi-domain changes (urinary, sexual and bowel): 46% of patients in the spacer group and 35% in the control group had no clinically detectable changes in any QoL domain at 3 years. 20% of patients in the control group had changes meeting the threshold for MID in all 3 domains compared with only 2.5% in the spacer group. Also, 12.5% of the control group had large changes (2xMID) in all 3 domains at 3 years compared with no patients in the spacer group (Hamstra 2017, 2018).

Spacer absorption (using MRI) at 12 months: confirmed in all, except 2% (3/148) patients exhibiting small water density remnant cysts in unremarkable perirectal tissues (Mariados 2015).

Safety

Primary safety endpoint

	Spacer group %	Control group %	p value
Rates of grade 1 or greater rectal or procedural adverse events at first 6 months	34.2	31.5	0.7
Acute rectal pain	2.7	11.1	0.022

No differences in acute rectal or urinary tract toxicities were seen in the first 3 months.

Overall adverse and serious adverse events

	Spacer group %	Control group %	p value
Adverse events	96.6	100	NS
Serious adverse events	13.4	15.1	NS

Spacer safety: there were no device related adverse events, rectal perorations, serious bleeding or infections in either group.

Study 2 Miller 2020

Study details

Study type	Systematic review and meta-analysis
Country	USA, UK, Switzerland and Germany
Study search details	Inception to September 2019; Databases searched: Cochrane Central Register of Controlled Trials, MEDLINE, and Embase; no language or date restrictions applied. Supplemental searches were done in the directory of open access journals, Google scholar, and reference lists of included articles and relevant meta-analyses searched. If outcomes were unclear in studies, authors were contacted.
Study population and number	n=7 studies with 1,011 patients (486 patients who had a perirectal hydrogel spacer injection versus 525 patients who did not receive a spacer [controls] before prostate cancer radiotherapy). (1 randomised clinical trial [RCT] and 6 cohort studies [1 prospective, 4 retrospective and 1 with prospective enrolment in spacer group and retrospective enrolment in no spacer group]) Clinical stages: localised or locally advanced prostate cancer (T1-T3) prostate-specific antigen levels ranged from 5.6 to 10.2 nanograms/ml
Age and sex	Mean age of 66 to 77 years.
Study selection criteria	Inclusion criteria: randomised clinical trials or cohort studies of patients who had the perirectal hydrogel spacer versus patients who had no spacer before radiotherapy for localised or locally advanced prostate cancer. Studies using external-beam RT that reported the percentage volume of the rectum receiving at least 70 Gy radiation (v70). Exclusion criteria: review articles, commentaries, letters, studies with no control or active control group, studies with fewer than 10 patients, pre-post dosimetric studies, studies that did not report a pre-specified outcome of this review, duplicate publications and unpublished or grey literature.
Technique	**Intervention:** Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel-SpaceOAR system) between the Denonvilliers fascia and anterior rectal wall before radiotherapy. Radiotherapy protocols: EBRT with a total therapeutic dose ranging from 76 to 81 Gy (5 studies), BT with or without EBRT (1 study), or combination therapy (1 study).
Follow up	Median 26 months (range, 3 to 63 months).
Conflict of interest/source of funding	The study was funded by Boston Scientific and they were involved in design and interpretation of data, review and approval of manuscript. Authors served as consultants, and either received personal fees, grants, honoraria, travel expenses, and non-financial support from Boston scientific and other companies.

Analysis

Follow-up issues: follow up varied across studies and data was analysed as reported by individual studies. Some attrition bias was reported at late follow up in included studies.

Study design issues: systematic review protocol was registered and was done according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. Comprehensive literature search was done, studies were screened and data extracted into a predesigned form, any disagreements were resolved by discussion. Multiple studies with overlapping patients were carefully assessed and included. Small numbers of nRCTs were included and were associated with risks of bias. A random-effects meta-analysis model was used for analysis of outcomes (rectal irradiation, rectal toxic effects, and bowel-related QoL). Heterogeneity was noted among study designs, patient characteristics, and radiotherapy protocols.
Study population issues: patient characteristics and risk categories varied between studies.
Other issues: One included study compared outcomes with the hydrogel spacer, biodegradable balloon, and no spacer treatment, but results of the balloon group were excluded from the analysis by the authors. Authors state that no studies of hydrogel spacer placement in patients receiving SBRT were eligible for inclusion in this review.

Key efficacy findings

Number of patients analysed: 1,011 patients (486 patients who had a perirectal hydrogel spacer injection versus 525 patients who did not receive a spacer [controls])

Procedural outcomes

Spacer placement success in spacer group (5 studies): the hydrogel spacer was successfully placed in 97.0% (95% CI, 94.4%-98.8%) of cases and failure reported in 3% cases. Causes of delivery failure were unsuccessful hydrodissection (n=5), inadvertent needle entry into the rectal lumen with no clinical sequelae (n=3), and unspecified cause (n=1).

Perirectal separation distance (distance between the posterior prostate capsule and anterior rectal wall on axial mid-gland T2 weighted MRIs): the weighted mean perirectal separation distance after hydrogel spacer placement was 11.2 mm (95% CI, 10.1-12.3 mm [5 studies]).

Rectal irradiation with perirectal hydrogel spacer versus without spacer (control)

In a pooled analysis of 6 studies, patients who had the perirectal hydrogel spacer before EBRT had 66% less v70 rectal irradiation compared with controls- patients who did not receive perirectal hydrogel spacer (3,5% versus 10.4%; MD -6.5%; 95% CI -10.5% to 2.5%; I^2=97%; p=0.001).

Rectal toxicity

Grade 2 or higher rectal toxic effects with versus without rectal hydrogel spacer

Early grade ≥2: In a pooled analysis of 6 studies, the risk of early (≤3 months) grade 2 or higher rectal toxic effects was comparable and not statistically different between the hydrogel spacer group and control groups (4.5% versus 4.1%; RR, 0.82; 95% CI, 0.52-1.28; I^2=0%; p=0.38).

Late grade ≥2: In a pooled analysis of 4 studies, at late follow up (median, 38 months; range, 28-60 months), the risk of grade 2 or higher rectal toxic effects was 77% lower in the hydrogel spacer group compared to controls (1.5% versus 5.7%; RR, 0.23; 95% CI, 0.06-0.99; I^2=24%; p=0.05).

Grade ≥1 rectal toxicity with versus without perirectal hydrogel spacer

Early grade ≥1: In a pooled analysis of 7 studies, the risk of early (≤3 months) grade 1 or higher rectal toxicity in patients treated with the hydrogel spacer was significantly lower (20.5% versus 29.5%; RR, 0.72; 95% CI, 0.58-0.91; I^2= 0%; p=0.005).

Late grade ≥1: In a pooled analysis of 5 studies, late grade ≥1 rectal toxicity (median, 40 months; range, 28-60 months) was significantly lower in the hydrogel spacer group (4.8% versus 16.2%; RR, 0.38; 95% CI, 0.22-0.65; I^2= 0%; p < 0.001).

Bowel quality of life (QoL) with versus without perirectal hydrogel spacer

Changes in early bowel-related QoL: in a pooled analysis of 2 studies, change in early bowel quality of life (≤3 months) (on EPIC questionnaire reported on a 0 to 100 scale where higher values indicate better QoL) was not statistically different between the groups (MD, 0.2; 95% CI, –3.1 to 3.4; I^2=21%; p=0.92).

Change in late bowel-related QoL: in a pooled analysis of 2 studies, change in bowel-related QoL was greater in the hydrogel spacer group in late follow up (median, 48 months; range, 36-60 months) and exceeded the threshold for a minimal clinically importance difference (MD, 5.4; 95% CI, 2.8-8.0; I^2=0%; p< 0.001). A 4-point change from baseline was considered a minimal clinically important difference.

Key safety findings

Procedural complications (defined as inability to inject the hydrogel spacer into the perirectal space or any complication, regardless of severity, occurring during the procedure).

Mariados 2015	mild and transient complications (did not delay radiotherapy)	10%
Whalley 2016	Inadvertent injection into the rectal lumen (without adverse sequalae)	3% (1/30)
Pinkawa 2017, Taggar 2018	None	0

The frequency of procedural complications was uncommon but reported inconsistently; it was not reported in 3 studies (Chao 2019, te Velde 2019, Wolf 2015).

Study 3 Norwegian Institute of Public Health (NIPHNO) EUnetHTA 2020

Study details

Study type	HTA
Country	Europe
Study search details	2010 to 2019; Databases searched for existing evidence syntheses (systematic reviews, HTAs) and primary studies include MEDLINE, AMED, Embase, Epistemonikos, and Cochrane Central Register of Controlled Trials. Also searched trial registry records at ClinicalTrials.gov and WHO ICTRP, Devices@FDA, the American Society of Clinical Oncology conference abstracts, and the Radiation Therapy Oncology Group clinical trials protocols. Considered information from clinical practice guidelines, information from a general literature search and input from clinical experts, and manufacturers. No language, design, publication restrictions applied.
Study population and number	n=2 prospective comparative studies including 298 patients with T1 and T2 stage localised prostate cancer) (1 RCT [SpaceOAR plus radiotherapy versus radiotherapy alone]) including 3 companion studies from the same clinical trial (NCT01538628) and 1 non-randomised control trial (nRCT; hydrogel plus radiotherapy, balloon plus radiotherapy and radiotherapy alone)
Age	RCT: spacer group 66.4 years; control group: 67.7 years nRCT: not reported
Study selection criteria	Inclusion criteria: adults (>18yrs) who had prostate cancer (both localised and metastatic undergoing curative treatment); studies on biodegradable rectal spacers for prostate cancer radiotherapy compared with current pathway of care (radiotherapy); RCTs and prospective nRCTs or observational studies with a control group, prospective studies or registry studies, (for effectiveness), including prospective registry-based data (for safety); reporting effectiveness and safety outcomes, in all languages. Exclusion criteria: study designs other than those specified in inclusion criteria, studies with no outcome of interest, wrong population, no data on patients with spacers, or no full text.
Technique	**Intervention:** biodegradable rectal spacers for prostate cancer radiotherapy. 2 different spacers used: t**ransperineal hydrogel (SpaceOAR) or balloon (BioProtect) plus radiotherapy versus radiotherapy alone (EBRT)** Radiotherapy protocols: RCT (n=222) IG-IMRT dose of 79.2 Gy at 1.8 Gy fractions, delivered to ≥98% of the planning target volume (PTV) and 100% of the clinical target volume, with the clinical target volume maximum of ≤110% of the prescription dose. nRCT: IMRT total dose of 75.85 Gy in daily fractional doses of 1.85 Gy prescribed to the 95% isodose using multi-segmental 7-field and shoot IMRT.
Follow up	RCT: 3,6,12,15 (Mariados 2015) and 36 months (Hamstra 2017). nRCT: up to 6 months (Wolf 2015)

Conflict of interest/source of funding	All authors, and stakeholders involved in the production of this assessment have declared they have no conflicts of interest according to the EUnetHTA declaration of interest (DOI) form.

Analysis

Follow-up issues: follow up varied across both studies and data was analysed as reported by individual studies. High attrition (>20%) was reported during long term follow up in the RCT.

Study design issues: Comprehensive systematic literature search was done, 2 reviewers screened studies and data extracted into a predesigned form, any disagreements were resolved by discussion. Quality of studies was assessed using the Cochrane risk of bias tool for RCT and the ROBINS-I tool (risk of bias in nRCTs– of Interventions) for nRCTs. Studies included were considered to be at high risk of bias (in the RCT methods were not well described, patients unblinded, selective reporting, and high attrition and in the nRCT selection bias, confounding, short follow up were reported). Same radiotherapy protocol was used in both studies.
GRADE approach was used to rate the evidence for each outcome through a structured process.
MID for the EPIC Short Form was used to identify MID standards for the outcomes and interpret the magnitude of effect sizes. Effect sizes were calculated for urinary and rectal toxicity (early and late) and QoL and for other outcomes, data was presented as reported in the individual studies. Multiple studies with overlapping patients were carefully assessed and included the study with final results. The 2 studies used the CTCAE grading system for grading adverse events.

Study population issues: patient characteristics were not well defined in both studies. RCT included patients at clinical stage T1 and T2, individuals in the control group had severe co-morbidities and compulsory anticoagulation.
Other issues: 15 trial registry records including biodegradable rectum spacers at different stages (completed, ongoing, recruiting) were identified by the authors but not were considered in this analysis. There were no comparative studies on hyaluronic acid.

Key efficacy findings

Number of patients analysed: 298 patients

Rectal and urinary toxicity (n=2 studies assessed according to the CTCAE)

Outcomes	No of patients		Relative effect (95% CI)	Absolute effect (95% CI)	GRADE Certainty of evidence	Comments
	Spacer+ radiotherapy	Radiotherapy alone				
RCT (Mariados 2015, Hamstra 2017)						
Rectal toxicity	**N=148 Spacer**	**N=71 no spacer**				
Acute (grade 1)-3 months	34	20	RR 0.77 (0.50 to 1.19), p=0.42	94 fewer per 1000 (from 204 fewer to 78 more)	Low [2-3]	

Acute (grade ≥2) – 3 months	6*	3**	RR 0.91 (0.23 to 3.5), p=0.89	6 fewer per 1000 (from 47 fewer to 152 more)		*no grade 3 or 4 toxicity reported **1 grade 3 case, no grade 4 reported
Late (grade 1) – 15 months	3	4	RR 0.34 (0.08 to 1.48), p=0.16	40 fewer per 1000 (from 56 fewer to 29 more)		
Late (grade≥2)[4] – 15 months	0	2*	RR 0.15 (0.01 to 3.71), p=0.25	13 fewer per 1000 (from 15 fewer to 41 more)		1 grade 3 case, no grade 4 reported
Cumulative (acute and late, grade 1) – median 3 years	2	4	HR 0.24, 95% CI 0.06 to 0.97, p<0.03	Not able to calculate	Very low [2,3,5]	Loss to follow up 37% (spacer+RT n=54 and RT alone n=25)
Cumulative (acute and late, grade ≥2) – median 3 years	0	3	HR not available	Not able to calculate		
nRCT (Wolf 2015)						
Acute rectal toxicity (grade 1) – 3 months	5	2	RR 1.58 (0.34 to 7.60), p=0.55	61 more per 1000 (from 69 fewer to 695 more)	Very low	hydrogel versus RT – no grade 2-3 toxicity
	5		RR 1.64 (0.35 to 7.60), p=0.52	67 more per 1000 (from 68 fewer to 695 more)	Very Low[3,6]	Balloon versus RT – no grade 2-3 toxicity

Outcomes	**No of patients**		**Relative effect (95% CI)**	**Absolute effect (95% CI)**	**GRADE**	**Comments**
	Spacer+ radiotherapy	**Radiotherapy alone**				
RCT (Mariados 2015, Hamstra 2017)						
Urinary toxicity	**N=148**	**N=71**				
Acute (grade 1)-3 months	78	33	RR 1.03 (0.87 to 1.21), p=0.74	25 more per 1000 (from 107 fewer to 173 more)	Low [2-3]	

Acute (grade ≥2) – 3 months	56	32	RR 0.97 (0.81 to 1.18), p=0.79	25 fewer per 1000 (from 156 fewer to 148 more)		*no grade 3 or 4 toxicity reported
Late (grade 1) – 15 months	4	3	RR 0.65 (0.15 to 2.85), p=0.57	15 fewer per 1000 (from 36 fewer to 75 more)		
Late (grade ≥2) – 15 months	10*	3*	RR 1.57 (0.44 to 5.53), p=0.47	25 more per 1000 (from 23 fewer to 196 more)		*no grade 3 or 4 toxicity reported
Cumulative (acute and late, grade 1) – median 3 years	4	7	HR 0.36 (0.12 to 1.1), p=0.046	Not able to calculate	Very low [2,3,5]	Loss to follow up 37% (spacer+RT n=54 and RT alone n=25)
Cumulative (acute and late, grade ≥2) – median 3 years	NR	NR	HR 1.22 (0.40 to 3.72), p=0.7	Not able to calculate		
Genitourinary toxicity (Wolf 2015)						
	n=30 hydrogel, n=29 balloon spacer)	**n=19 radiotherapy alone**				
Acute – grade 2	11	5	RR 1.39 (0.57 to 3.38), p=0.46	103 more per 1000 (from 113 fewer to 626 more)	Very Low [3,6]	hydrogel or Balloon versus RT – no grade 3 toxicity
		6	6 RR 0.78 (0.27 to 2.12), p=0.64	58 fewer per 1000 (from 192 to 295 more)		

QoL

Outcomes	No of patients		Relative effect (95% CI)	Absolute effect (95% CI)	GRADE	Comments
	Spacer+ radiotherapy	Radiotherapy				

RCT (Mariados 2015, Hamstra 2017)						
Bowel QoL assessed with EPIC 0-100 – greater values are better						
Summary Score: results suggest SpaceOAR +RT may improve bowel QoL (p=0.002) over the entire follow-up period (1 study, 220 participants; very low certainty of evidence) but the evidence is uncertain.						
Minimal Clinical Difference – 5-point decline						
Bowel QoL 3 months	49% (73/148)	46%(32/71)	RD 0.05, 95% CI -0.09 to 0.19	5 more people in intervention reported 5-point decline	Low [2,3]	
Bowel QoL 15 months	24%(36/148)	34% (24/71)	RD -0.09, 95% CI -0.22 to 0.04	9 less people in intervention reported 5-point decline		
Bowel QoL 36 months	14% (13/94)	41% (19/46)	OR 0.28, 95% CI 0.13 to 0.63*	27% less patients in the intervention experiencing 5-point decline	Very low [2, 3, 5]	
Minimal Clinical Difference X2 – 10 point decline						
Bowel QoL 3 months	34% (50/148)	32% (23/71)	RD 0.02, 95% CI -0.11 to 0.15	2 more people in the intervention reported 10-point decline	Low	
Bowel QoL 15 months	11%(17/148)	21% (15/71)	RD -0.09, 95% CI -0.20 to 0.01	10 fewer people in the intervention reported a 10-point decline	Low [2,3]	
Bowel QoL 36 months	5% (5/94)	16% (7/46)	OR 0.30, 95% CI 0.11 to 0.83	16% fewer patients in the intervention reported 10-point decline	Very low [2,3,5]	
Urinary QoL - assessed with EPIC 0-100 – greater values are better						
Summary Score: Results suggest SpaceOAR may have little to no effect on urinary QoL (p=.13) over the study follow-up period (1 study, 220 participants; very low certainty of evidence); the evidence is very uncertain.						
Minimal Clinical Difference – 6-point decline						
Urinary QoL 3 months	65%(97/148)	60% (42/71)	RD 0.07, 95% CI -0.07 to 0.21	7 more people in the intervention reported 6 point decline	Low [2,3]	

Urinary QoL 15 months	22% (32/148)	21% (15/71)	RD 0.01, 95% CI -0.11 to 0.12	There was no difference in the number of patients reporting 6 point decline		
Urinary QoL 36 months	30% (28/94)	17% (8/46)	OR 0.41, 95% CI 0.18 to 0.95	13% fewer participants in the intervention reported 6 point decline	Very low [2,3,5]	
Minimal Clinical Difference X2 – 10-point decline						
Urinary QoL 3 months	47% (70/148)	49% (34/71)	RD 0.00, 95% CI -0.14 to 0.14*	There was no difference in the number of patients reporting 12-point decline		
Urinary QoL 15 months	9% (14/148)	12% (9/71)	RD -0.03, 95% CI -0.12 to 0.06	3 fewer patients in the intervention reported 12-point decline		
Urinary QoL 36 months	23% (22/94)	8% (4/46)	OR 0.31, 95% CI 0.11 to 0.85*	15% fewer participants in the intervention reported 12-point decline		
Sexual QoL – assessed with EPIC 0-100 – greater values are better						
Summary Score: results suggest SpaceOAR may have little to no effect on sexual QoL (p=0.6) over the entire study period (1 study, 140 participants; very low certainty of evidence), but the evidence is very uncertain.						
36 months	94	46	Not estimable	Sexual composite over time p=0.59	Very low [2,3,5]	

Rectal dose

outcomes	No of patients		Relative effect (95% CI)	Absolute effect (95% CI)	GRADE	Comments
	Spacer+ radiotherapy	Radiotherapy				
RCT (Mariados 2015, Hamstra 2017)						
rV70 Mean ± SD	N=148	N=71	-	-	Low [2,3]	97%intervention patients reached ≧25%

						reduction in rV70
nRCT (Wolf 2015)						
Isodose	Hydrogel 30 Balloon 29	radiotherapy alone 19	95% isodose	38% and 63% less		g-gel, b-balloon c control
			10.9 cm^2-g 17.6 cm^2-c 6.6 cm^2-b	24% and 42% less 10% and 22% less	Very low [2,3,5]	
			85% isodose 18.3 cm^2-g 24.1 cm^2-c 13.2 cm^2-b 60% isodose 34.4 cm^2-g 38.3 cm^2-c 29.7 cm^2-b			
Distance between rectum and prostate – baseline, post-insertion, 3 months **RCT (Mariados 2015, Hamstra 2017)**						
Mean perirectal distance (mm)	149	-	Not estimable	Not estimable	Low [2,3]	1.6±2.2 mm, baseline 12.6±3.9 mm, after insertion 9±5.9 mm at 3 months
PSA relapse – baseline, 12 and 15 months						
Nanograms/ml – 12 months and 15 months	148	71	Not estimable	Not estimable	Low [2,3]	Values only presented as means (no SD available), no data for 36 months available.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Assessed according to CTCAE v4

2 Downgraded one level due to limitations in design (high risk of bias) (e.g. blinding, selective reporting)

3 Downgraded one level due to imprecision (one or 2 small studies)

4 Grade 2 is presented in Mariados' publication as '>2' and in Hamstra's as '≥2'; we have assumed this is ≥2 and reported as such

5 Downgraded one level due to limitations in design (large loss to follow up without imputations) 6 Downgraded one level due to limitations in design (high risk of bias) (e.g. bias due to confounding, selection of participants, bias of measurement of outcome)

Key safety findings

Outcomes	No of patients		Relative effect (95% CI)	Absolute effect (95% CI)	GRADE	Comments
	Spacer+ radiotherapy	Radiotherapy alone				
1 RCT (Mariados 2015 and 5 companion studies) and 1 nRCT (Wolf 2015)						
Deaths related to adverse events, grade 5	207	91	There was no (device) death related to adverse events reported in these studies		1 RCT and 1 nRCT	
Adverse events, grades 3-4	207	91	There was no (device) grade 3-4 related to adverse events reported in these studies			
Adverse events grades 1-2 [1]	148	71	Procedural adverse events • no unanticipated SpaceOAR related adverse events. • 10% of the spacer patients had mild transient procedural adverse events (perineal discomfort and others) • n=10 events requiring no medication* • grade 2 events treated with medication included mild lower urinary tract symptoms and hypotension, and moderate perineal pain.		Low [2,3]	The information reported in the RCT and companions studies: Mariados 2015, Pieczonka 2015, Karsh and Fisher Valuck 2017

			• no implant infections, rectal wall ulcerations or other more serious complications. • SpaceOAR Hydrogel procedural rectal wall infiltration in 6% (n=9). • 2/149 spacer patients had no SpaceOAR Hydrogel present after application: hydrogel injected beyond the prostate in 1 patient, no hydrogel injected in the other due to inadvertent needle penetration of the rectal wall requiring study-mandated termination of the procedure.		

*Haematospermia, anorectal pressure, haematuria, tight pain, discomfort while sitting, perineal pain, rectal pain, rectal bleeding (attributed to preoperative enema), constipation and flatulence (1 each).

Safety from other previous papers found by authors

Hydrogel spacer related adverse events:
A review of procedure related adverse events in the MAUDE database from January 2015 to March 2019 suggests that there were 22 unique reports discussing 25 patient cases, with an increasing number of reports each year up to 2018. Authors mentioned reported complications include acute pulmonary embolism, severe anaphylaxis, prostatic abscess and sepsis, purulent perineal drainage, rectal wall erosion, and recto-urethral fistula (see study 5 for further details). Authors state that a recent letter in response to this study suggests that 'the increase in the number of medical device reports in MAUDE over time is normal and proportionate to device usage and the rate of reports has remained relatively constant over time, ranging from 0.3 to 0.6 per 1000 SpaceOAR cases performed' (Babayan 2020).

A rectal ulcer, 1 cm in diameter (causing frequent rectal bleeding, mucus discharge and bowel movements) was reported in a case report of 1 patient 2 months after hydrogel injection. This had resolved without further intervention by 3 months. Digital rectal examination at 6 months revealed a healed ulcer, with only a non-tender slit in the anterior rectal wall. At subsequent examinations over 3 years, there was no recurrence of bowel symptoms (Teh 2014).

Inadvertent rectal wall injection (with hydrogel) resulting in focal rectal mucosal necrosis and bladder perforation was reported after the procedure in 1 patient in a case series of 52 patients. This resolved with no sequelae (Uhl 2014).

Infections (bacterial peritonitis in 2 patients and bacterial epididymitis in 1 patient) were reported in 3% (3/100) of patients injected with a hydrogel spacer in a retrospective comparative case series of 200 patients. The bacterial peritonitis occurred after prostate biopsies. All 3 infections resolved with antibiotic therapy. No infections were reported in the 100 patients treated with high dose rate brachytherapy without hydrogel (Storm 2014).

Balloon spacer related adverse events: a case series of 27 patients (Gez 2013) reported the following adverse events during balloon insertion and radiotherapy: penile bleeding and acute urinary retention (needed

catheterisation, which resolved within a few hours) during balloon insertion, dysuria and nocturia (grade 1-2). Other events reported during radiotherapy in the same case series included diarrhoea, mild proctitis, and blood in the faeces, constipation, erectile dysfunction, itching, fatigue and decreased urine flow.

Study 4 Armstrong N 2021

Study details

Study type	Systematic review
Country	UK, USA and Germany
Study search details	Search period: inception to May 2020; databases searched: MEDLINE, Embase, PubMed, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), KSR Evidence, Econlit (EBSCO), and NHS EED (CRD). HTA agency websites, clinical trials registers, conference abstracts databases and reference lists of included articles were also searched. No restrictions on language or publication status were applied.
Study population and number	19 studies (3,622 patients who had a perirectal hydrogel spacer versus patients who did not receive a spacer [controls] before prostate cancer radiotherapy). 1 RCT (10 references), 18 comparative nRCTs.
Age	patients between 65 to 75 years
Study selection criteria	Inclusion criteria: RCTs and nRCTs with patients receiving radiotherapy (all types) for localised or locally advanced prostate cancer with or without rectal hydrogel spacer; reporting a number of outcomes including radiation dose, toxicity and QoL.
Technique	Intervention: Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel-SpaceOAR system) between the Denonvilliers fascia and anterior rectal wall before RT. Comparator (control): no spacer Radiotherapy protocols: different RT modalities used. 1. EBRT- IG-IMRT- 1 RCT 2. EBRT, BT and combinations thereof (in 18 comparative nRCTs): • non-hypofractionated IMRT-7 studies, • ultra-hypofractionation - SBRT-2 studies, • PBT 1 study, • HDR BT monotherapy (1 study), • BT plus EBRT combination-7 studies (HDR BT +EBRT 3 studies, LDR BT +EBRT 4 studies)
Follow up	Varied across studies
Conflict of interest/source of funding	4 authors worked for a company which received funding for the project from Boston Scientific, few authors are employed by Boston Scientific, some received honoraria for advisory boards, travel expenses to medical meetings and 1 served as a consultant for different companies.

Analysis

Follow-up issues: adequate follow up in most studies.

Study design issues: systematic review protocol was registered and was done according to the PRISMA reporting guidelines, the Cochrane Handbook and the Centre for Reviews and Dissemination. Comprehensive literature search was done, 2 reviewers selected studies, extracted data and quality assessed the studies using Cochrane Risk of Bias Tool for RCT and Joanna Briggs Institute Critical Appraisal Checklist for cohort studies. The included studies were mainly non-RCT of low quality and in many studies patients were recruited to either the intervention or comparator at the same time. Treatment in nRCTs is usually allocated based on clinician or patient preference but 3 studies used historical matched controls. Studies with a range of radiotherapy modalities used in clinical practice are included. Dosing is measured in different ways. Because of the heterogeneity of studies a narrative synthesis was done.

Study population issues: patient characteristics and risk categories varied between studies.

Other issues: authors did not find any hypofractionated radiotherapy studies.

Key efficacy findings

- Number of patients analysed: 19 studies (3,622 patients)

Rectal dosimetry

1 RCT Mariados 2015 (hydrogel spacer versus no spacer)

	Measures of dosimetry	With spacer	Without spacer	Absolute reduction	Relative reduction
Rectum	V50	9.6	20.8	11.2	53.9
	V60	5.3	15.4	10.1	65.6
	V70	2.3	10.5	8.2	78.0
	V80	0.1	4.0	3.9	97.3

Pre and post hydrogel spacer

	Measures of dosimetry	Baseline dose Gy (mean±SD)	Post spacer dose Gy (mean±SD)	% Change in dose from baseline, p value
Bladder	V70	11.3	11	NR
Rectum	V50	25.7±11.1	12.2±8.7	52.3, p=<0.0001
	V60	18.4±7.7	6.8±5.5	62.9, p<0.0001
	V70	12.4±5.4	3.3±3.2	73.3, p<0.0001
	V80	4.6±3.1	0.6±0.9	86.3, p<0.0001

(13 nRCTs hydrogel spacer versus no spacer)

EBRT

Study, n	Clinical stage, risk status	Measures of dosimetry	With spacer Mean/median	Without spacer Mean/median	P value
Pinkawa 2017 IMRT (n=167)	T1-T3 Low to high risk	V70 %	20	32	<0.01
		V90 %	4	13	<0.01
Te Velde 2019 IMRT (n=125)	T1-T3 Low to high risk	V40 %	25.9	33.3	<0.0001
		V75%	2.1	7.4	<0.0001
		V65%	5.2	12.6	<0.0001
Whalley 2016 IMRT (n=140)	T1-T3 Intermediate/ high risk	V40 %	22.9	32	<0.01
		V65%	5.3	13.5	<0.01
Navaratnam 2020 PBT (n=72)	T-1-T3	V70 %	NR	NR	-
		V75 %	NR	NR	-
Fried 2017 SBRT (n=94)	Low/intermediate risk	D10 Gy	26.66	30.44	0.000
		D50 Gy	10.9	11.4	0.47
BT					
Baghwala 2019 HDR BT (n=36)	Low/intermediate risk	V75 cc	0.02	0.7	<0.05
		V90 cc	>92	NR	<0.05
HDR BT in combination with EBRT					
Chao 2019 HDR BT+IG-IMRT (n=97)	T1-T3 Intermediate/ high risk	V40%	4.6	10.7	<0.001
		V75%	0	0.55	<0.001
		V80%	0	0.21	<0.001
Wu 2018 HDR BT +/- EBRT (n=54)	T-T3	V40 cc	8.11	9.38	0.16
		V75	<0.005	0.12	<0.0005
		V80	<0.005	0.01	0.007
		V90	NR	<0.005	0.1
Saigal 2019 HDR BT + EBRT (n=117)	NR	D1 Gy	35.3	54.6	<0.05
		D90	100.1	101.3	0.354
LDR BT in combination with EBRT					
Morita 2020 LDR BT+IMRT (n=300)	T1-T4 Very low to very high	V100 cc	0.026	0.318	<0.001
		V150	0.001	0.025	<0.001
Patel 2018 LDR BT + EBRT (n=57)	NR	V50	0.53	.21	<0.001
		V100	0.0001	0.25	<0.001

Taggar 2018 LDR BT+EBRT (n=210)	T1-T3	V100	0.01	0.07	0
Liu 2020 LDR BT +/- EBRT (n=81)	Low/intermediate risk	D2 Gy	-25.1	5	<0.0001
		D0.1	-65.7	-1	<0.0001

Toxicity outcomes

1 RCT Mariados 2015 (hydrogel spacer versus no spacer)

Type of adverse event	Follow up	With spacer	Without spacer	P value	OR (95% CI)
Rectal or procedure related adverse events	6 months	34.2%	31.5%	0.7	
Rectal toxicity late	3 to 15 months				
Grade 1+		2.03 (3/148)	6.94 (5/71)	0.044	0.28 (0.06,1.19)
Grade 2+		0	1.39 (1/71)		NE
1		2.03 (3/148)	5.63 (4/71)		0.35 90.08, 1.59)
2		0	0		NE
3		0	1.41 (1/71)		
4		0	0		
Grade>1	36 months	2.0%	9.2%	0.028	
Grade>2	36 months	0	5.7%	0.012	
Rectal toxicity acute	3 months				
Grade 1+		27.03 (40/148)	31.94 (23/72)	0.525	0.79 (0.43,1.46)
Grade 2+		4.05 (6/148)	4.17 (3/72)		0.97 (0.24,4)
1		22.97 (34/148)	27.78 (20/72)		0.78 (0.41,1.47)
2		4.05 (6/148)	2.78 (2/72)		1.48 (0.29, 7.52)
3		0	1.39 (1/72)		NE
4		0	0		

Urinary toxicity late	3 to 15 months				
Grade 1+		9.46 (14/148)	8.33 (6/71)	0.622	1.15 (0.42, 3.13)
Grade 2+		6.76 (10/148)	4.17 (3/71)		1.67 (0.44, 6.25)
1		2.70 94/148)	4.23 (3/71)		0.63 (0.14, 2.89)
2		6.76 (10/148)	4.23 (3/71)		1.64 90.44, 6.16)
3		0	0		NE
4		0	0		
Urinary toxicity acute	3 months				
Grade 1+		90.54 (134/148)	90.28 (65/72)	0.488	1.03 (0.4, 2.68)
Grade 2+		37.84 (56/148)	44.44 (32/72)		0.76 (0.43, 1.35)
1		52.70 (78/148)	45.83 (33/72)		1.32 (0.75, 2.32)
2		37.84 (56/148)	44.44 (32/72)		0.76 (0.43, 1.35)
3		0	0		NE
4		0	0		

nRCTs (hydrogel spacer versus no spacer, 7 studies)

Study	**Adverse event (Grade)**	**Follow up (months)**	**With spacer % (n)**	**Without spacer % (n)**	**P value**	**OR (95% CI)**
EBRT						
Te Velde 2019 IMRT (n=125)	Diarrhoea (grade 1)	During radiotherapy	13.8% (9/65)	31.7 (19/60)	0.02	0.34 (0.14,0.84)
		3 months	4.6%	5%	1	0.92 (0.18,4.72)
		36 months	1.7%	7.3%	0.192	0.22 (0.03,1.86)
	Proctitis (grade 1)	During radiotherapy	9.2	13.3	0.6	0.66 (0.22,2.03)
		3 months	1.5	5	0.3	0.29 (0.03,2.86)

		36 months	1.7	3.6	0.606	0.46 (0.04,4.88)
	Proctitis Grade (2)	During radiotherapy	4.6	1.7	0.6	2.79 (0.28,27.56)
		3 months	0	0	1	
		36 months	0	3.6	0.227	
	Faecal incontinence (grade 1)	During radiotherapy	3.1	3.3	1	0.94 (0.13,6.87)
		3 months	0	1.7	0.5	
		36 months	0	0		
	Haemorrhoids (grade 1)	During radiotherapy	23.1	20	0.8	1.2 (0.51,2.83)
		3 months	3.1	11.7	0.09	0.24 (0.05,1.21)
		36 months	5	7.3	0.708	0.67 (0.15,2.98)
	Haemorrhoids (grade 2)	During radiotherapy	4.6	3.3	1	
		3 months	0	0		
		36 months	1.7	1.8	1	0.94 (0.06,14.5)
Whalley 2016 IMRT (n=140)	Rectal toxicity late -grade 1	Median 26-28 months	16.6 (5/30)	41.8 (46/110)	0.04	0.28 (0.1,0.78)
	Grade 2		3.3 (1/30)	3.6 (4/110)	NR	0.91 (0.1,8.49)
	Rectal toxicity acute -grade 1		43 (13/30)	50.6 (56/110)		0.74 (0.33,1.66)
	Grade 2		0	4.5 (5/110)		
Wolf 2015 IMRT (n=78)	Rectal toxicity acute-grade 1	NR	16.6	9	NR	
	Genitourinary toxicity- grade 1		12.5	21		
	Grade 2		36.6	28.5		
	Any toxicity acute -grade 3		0	0		
Navaratnam 2020 PBT (n=72)	Rectal toxicity-any -grade 1	During radiotherapy	35.3 (18/51)	9.5 (2/21)	0.061	5.2 (1.09,24.89)
		Median 8.7 to 10.3 months	7.7 (3/39)	0 (0/14)	NR	

	Grade 2	During radiotherapy	2 (1/51)	0 (0/21)	NR	
		Median 8.7 to 10.3 months	0 (0/39)	7.1 (1/14)		
Zelefsky 2019 SBRT (n=551)	GI toxicity acute (grade 2+)	NR	1 (269)	2 (282)	0.09	0.33 (0.07,1.55)
	GI toxicity late (grade 2+)		1	6	0.01	0.16 (0.05,0.48)
	GU toxicity acute (grade 2+)		9	12	0.19	0.73 (0.42,1.26)
	GU toxicity late (grade 2+)		15	32	<0.001	0.38 (0.25,0.57)
HDR BT in combination with EBRT						
Chao 2019 BT+IG-IMRT (n=97)	GI toxicity acute (grade 2)	3 months	0 (0/32)	1.5 (1/65)	0.48	
	Grade1+		13.3	30.8	0.05	0.34 (0.11,1.11)
	GI toxicity late (grade 1)		0	7.7	0.11	
	GU toxicity acute (grade 2)		0	1.5	0.48	
	Grade 1+		83.3	92.3	0.22	0.42 (0.11,1.56)
	GU toxicity late (grade 3)		3.3	6.2	0.57	0.52 (0.06,4.82)
	Grade 1+		46.7	43.1	0.74	1.16 (0.49,2.71)
	Grade 2+		3.3	7.7	0.4	0.41 (0.05,3.66)
LDR BT alone or in combination with EBRT						
Taggar 2018 LDR BT/LDR BT+/- EBRT (n=210)	Any rectal GI toxicity	NR	20.3 (15/74)	24.3 (33/136)	0.95	0.79 (0.4,1.58)
Taggar 2018 LDR BT monotherapy	Diarrhoea		7.7 (2/26)	15.9 (7/44)	NR	0.44 (0.08,2.31)
	Proctitis		0 (/26)	0 (/44)	NR	
	Rectal bleeding		0 (/26)	6.8 (/44)	NR	
	Rectal discomfort		15.7 (/26)	0 (/44)	NR	

Taggar 2018 LDR BT monotherapy (salvage for recurrent PC)	Diarrhoea	NR	12.5 (1/11)	5.3 (1/19)	NR	2.55 (0.14,45.36)
	Proctitis		0	0	NR	
	Rectal bleeding		0	5.3	NR	
	Rectal discomfort		0	0	NR	
Taggar 2018 LDR BT+EBRT combination therapy	Diarrhoea	NR	12.5 (5/42)	4.1 (3/73)	NR	3.34 (0.76,14.76)
	Proctitis		0	5.5		
	Rectal bleeding		5	19.2		0.22 (0.05,1.03)
	Rectal discomfort		5	0		

Health related QoL outcomes

1 RCT Mariados 2015 (hydrogel spacer versus no spacer)

EPIC dimension	**Follow up (months)**	**With spacer**	**Without spacer**	**Mean difference P value**
Bowel domain	3	-7.5	-6.2	NR
	36	0.5	-5.3	5.8, p<0.05
Urinary domain	3	-11.5	-11.2	NR
	36	0.6	-3.3	3.9, p=0.04
Authors definition				**OR (95% CI), p value**
10-point decline in bowel QoL	15	11.6	21.6	0.49 (0.21, 1.11) P=0.087
	36	5	21	0.3 (0.11, 0.83) P=0.02
10-point decline in urinary QoL	6	8.8	22.2	0.27 (0.11, 0.64) P=0.003
12-point decline in urinary QoL	36	8	23	0.31 (0.11, 0.85) P<0.03
5-point decline in bowel QoL		14	41	0.28 90.13, 0.63) P=0.002
6-point decline in urinary QoL		17	30	0.41 (0.18, 0.95) P<0.05
Patients experiencing MID	36	2.5	20	NR

declines in all 3 QoL domains (bowel, urinary, sexual)				P=0.002
Decline of all 11 or more points in EPIC sexual score		53	75	NR, P=0.064
Potent patients at baseline retaining erections sufficient for intercourse		66.7	37.5	NR, =0.046

MID = minimally important differences in the EPIC summary scores were evaluated according to previously published thresholds: bowel (5 points), urinary (6 points), sexual (11 points), and vitality/hormonal (5 points).

nRCTs (hydrogel spacer versus no spacer, 4 studies)

Study	EPIC outcome	Follow up (months)	With spacer, Mean change from baseline	Without spacer, mean change from baseline	p value
Patel 2018 EBRT + LDR BT (n=57)	Bowel function score	3 months	Median: 0.00, IQR: -8.93 to 0.89	Median: -6.25, IQR: -12.95 to 0	0.312
		6 months	Median: 0.00, IQR: -8.92 to 0	Median: -3.57, IQR: -9.82 to 0	0.650
Pinkawa 2012 IMRT (n=72)	Urinary function	Last day radiotherapy	-10	-10	NR
		2-3 months	-1	-5	
	Urinary bother score	Last day radiotherapy	-17	-18	
		2-3 months	-4	-6	
	Bowel function	Last day radiotherapy	-15	-14	
		2-3 months	-3	-3	
	Bowel bother score	Last day radiotherapy	-16	-17	
		2-3 months	-2	-6	
	Sexual function	Last day radiotherapy	-15	-10	
		2-3 months	-5	-9	
	Sexual bother score	Last day radiotherapy	-20	-18	
		2-3 months	-11	-15	
	Hormonal function	Last day radiotherapy	-3	-6	

		2-3 months	-1	-2	
	Hormonal bother score	Last day radiotherapy	-3	-2	
		2-3 months	-2	-1	
Pinkawa 2016 IMRT (n=202)	Bowel bother score	Last day radiotherapy	-14	-18	NR
		2 months	-3	-6	
		17 months	0	-7	
	Sexual bother score	Last day radiotherapy	-6	-9	
		2 months	-12	-19	
		17 months	-12	-17	
	Urinary bother score	Last day radiotherapy	-18	-21	
		2 months	-14	-17	
		17 months	1	2	
Pinkawa 2017 IMRT (n=167)	Urinary function	End of radiotherapy	-10	-13	NR
		2 months	-2	-4	
		>12 months	1	-	
	Bowel function	End of radiotherapy	-11	-14	NR
		2 months	-4	-5	
		>12 months	0	-5	<0.01
	Sexual function	End of radiotherapy	-12	-10	NR
		2 months	-6	-8	
		>12 months	-6	-	
	Hormone function	End of radiotherapy	-5	-7	NR
		2 months	-3	-4	
		>12 months	2	-	
	Bowel bother score	18 months	-1	-7	0.13
		60 months	-1	-6	0.99
	Sexual bother score	18 months	-13	-18	0.28
		60 months	-21	-28	0.77
	Urinary bother score	18 months	2	3	0.49
		60 months	0	3	0.22

There were no studies reporting QoL in EBRT+ HDR BT, BT monotherapy or hypofractionated EBRT.

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Study details

Study type	Systematic review
Country	UK
Study search details	Search period: January 2013 to December 2019; databases searched: MEDLINE, Embase, PubMed, CINAHL, and Cochrane library Google scholar, and reference lists of included articles were also searched.
Study population and number	13 studies: (9 retrospective case series and 4 case reports of less than 10 patients) n=1208 patients (671 patients who had a perirectal hydrogel spacer injection versus 537 patients who did not receive a spacer [controls] before prostate cancer brachytherapy).
Age	Not reported
Study selection criteria	Inclusion criteria: English-language articles, randomised and non-randomised studies of patients with localised or locally advanced prostate cancer receiving brachytherapy with or without PEG hydrogel spacer (salvage and primary treatment); reporting a number of outcomes including radiation dose, prostate-rectum separation, toxicity and technique for hydrogel insertion. Studies of more than 10 patients evaluated for efficacy and less than 10 patients reviewed for only procedure related complications. Exclusion criteria: case reports, review articles and editorials, non-English-language studies, animal and laboratory studies.
Technique	Intervention: under ultrasound guidance a needle is inserted into perineum. Hydrodissection of the potential space is done first and then a prostate-rectum spacer (absorbable polyethylene glycol hydrogel) is injected posterior to the Denonvilliers fascia and anterior to the rectal wall at the level between mid-gland and apex of the prostate (4 studies used DuraSeal off label and 5 used SpaceOAR since 2017). Comparator (control): no hydrogel spacer (in 6 studies) Radiotherapy protocols: LDR or HDR BT alone or in combination with EBRT • LDR BT monotherapy (in 2 studies), • BT plus EBRT combination (in 7 studies: HDR BT +EBRT in 5, LDR BT +EBRT in 2) All LDR or HDR BT start with seed insertion followed by spacer insertion and subsequent IMRT.
Follow up	Varied across studies (range 6 to 60 months)
Conflict of interest/source of funding	Authors state that there is no potential conflict of interest.

Analysis

Follow-up issues: adequate follow up in some studies, 3 studies did not report follow up period.

Study design issues: systematic review protocol was registered and was done according to the PRISMA reporting guidelines and the Cochrane methodology. Comprehensive literature search was done, 2 reviewers selected studies, extracted data but quality assessment of studies was not done. The included studies were mainly retrospective nRCTs of low quality and only 4 studies compared with controls. Studies were heterogenous both in treatment method and type of spacer used therefore a narrative synthesis was done. Genitourinary complications were not analysed by authors. 2 papers included in this study reported on the same patient group (Chao 2019).

Study population issues: patient characteristics and risk categories varied between studies.

Key efficacy findings

- Number of patients analysed: 13 studies (9 case series and 4 case reports or case series of less than 10 patients)

Mean prostate-rectum separation, acute and late GI complications

Study details	Mean follow up/scoring system	Mean prostate-rectum separation (mm)	Rectal dosimetric reduction/percentage dose reduction^	Acute GI toxicity (spacer versus no spacer)	Late GI toxicity (spacer versus no spacer)	Failure rate
Mahal 2014 Salvage LDR BT; prior pelvic irradiation (n=11) DuraSeal spacer	15.7 months/ EPIC questionnaire	10.9 in patients with prior BT 7.7 in patients with prior EBRT	Median V75% (cc): 0.07	Grade 1: 0% Grade 2: 9% (n=1 fistula) Grade >3: 0	Grade 1 or 2: 36% (4/11) Grade 3 or 4: 9% (n=1 patient developed prostatorectal fistula requiring a diverting colostomy and an interposition rotational gracilis muscle flap) 16 months: 26% (3/11) bowel QoL change	27.2%
Heikkila 2014 LDR BT (n=10) DuraSeal spacer	-	10	Rectal D2 cc 64±13 Gy with gel versus 95±13 Gy without gel	1 patient reported a sensation of pressure in the rectum. 1 patient felt a sudden need for defecation.	-	0%

			(p=0.005)/ (32.6%)			
Wu 2017 HDR BT: HDR BT+EBRT Salvage HDR BT (n=18 with spacer and 36 without spacer) (SpaceOAR)	-	-	Median V75% (cc): <0.005 versus 0.12 (p≤0.0005)/ (100%)	1 patient developed a rectal abscess.	-	0%
Chao 2019 HDR BT+IMRT (n=32 with spacer and 65 without spacer) (SpaceOAR)	60 months NCICTCAE v4.0	10	Median V75% (cc) 0.0 versus 0.45 (p≤0.001)/ (100%)	Grade 1 12.5% versus 30.8% (p=0.05)	Grade 1: 0% versus 7.7% (p=0.11)	-
Chao 2019 HDR BT+IMRT or VMAT (n=30 with spacer and 65 without spacer) (SpaceOAR)	58 months NCICTCAE v4.0	-	Median V75% (cc) 0.0 versus 0.45 (p≤0.001)/ (100%)	Grade 1 13.3% versus 30.8% (p=0.05) Grade 2 0% versus 1.5% (p=0.48)	Grade 1: 0% versus 7.7% (p=0.11)	-

Storm 2014 HDR BT +IMRT (n=100 with spacer and 100 without spacer) (DuraSeal)	8.7 months	12	Rectal D2 cc 47±9% versus 60±8% (p<0.001)/ (21.6%)	-	-	0%
Yeh 2016 HDR BT +IMRT (n=326) (DuraSeal)	16 months NCICTCAE v4.0	16	maximum dose to rectum 78% versus 95% (SD=11.9%)/ (17.3%)	Grade 1: 37.4% Grade 2: 2.8% Most commonly diarrhoea	Grade 1:12.7% Grade 2: 1.4% Grade 3: 0.7% 1 case of severe proctitis 1 case of fistula and necrotising fasciitis requiring a diverting colostomy.	-
Taggar 2017 LDR BT. LDR BT+EBRT Salvage LDR BT (74 with spacer 136 without spacer) (SpaceOAR)	6 months RTOG	11.2	Rectal D2 cc 20.47% versus 43.16% (p=0.000)/ (52.6%)	**Grade 1 or 2** 20.3% (n=15) versus 24.3% (n=33) (p= 0.95) **Diarrhoea:** LDR BT alone 7.7% versus 15.9% LDR BT +EBRT 12.5% versus 4.1% Salvage 12.5% versus 5.3% **Proctitis:** LDR BT alone 0% versus 0%, LDR BT+EBRT 0% versus 5.5% Salvage 0% versus 0% **Rectal discomfort** -	-	6.8% (2 aborted due to unsuccessful hydro dissections)

				8% (n=7) versus 0 **Rectal bleeding** 5% (n=2) versus 21.3% (n=18). No grade 3 or 4 complications		
Morita 2019 LDR BT; LDR BT+EBRT (100 with spacer 200 without spacer) (SpaceOAR)	-	11.6	Median V100% 0.026±0.14 versus 0.318+/1 0.34 (p≤0.001)/ (91.8%)	-	-	4% (1 aborted due to operator inexperience and premature coagulation of the solution during injection)

^spacer versus non-spacer.

Key safety findings

Study	N	Complications	n
Procedure related complications			
Teh 2014	1 spaceOAR	Rectal ulcer (1 month after hydrogel spacer insertion, resolved without further intervention)	1
Beydoun 2013 (BT)	5 spaceOAR	Perineal pain or rectal discomfort (resolved without intervention within 1 week)	3
Heikkila 2014 (LDR BT)	10 DuraSeal	Sensation of pressure/fullness in the rectum (self-limiting symptoms, resolved by 3 months with medication)	1

Heikkila 2014 (LDR BT)	10 DuraSeal	Sudden need for defecation (self-limiting, symptoms resolved by 3 months with medication)	1
Storm 2014 (HDR BT with IMRT)	100 with DuraSeal versus 100 without	Infection (bacterial prostatitis and epididymitis), adjusted antibiotic prophylaxis before procedure	6% (n=3)
Wu 2018 (HDR BT boost to EBRT)	18 with spaceOAR versus 36 without spacer)	Rectal perineal abscess (1 month after SpaceOAR insertion. required incision, drainage and antibiotics)	1
Mahal 2014 (salvage LDR BT) Yeh 2016 (HDR BT +IMRT)	11 DuraSeal 326 (SpaceOAR)	Prostatorectal fistula requiring diverting colostomy and an interposition rotational gracilis muscle flap Fistula and necrotising fasciitis requiring a diverting colostomy.	1 1
Yeh 2016 (HDR BT +IMRT)	326 (SpaceOAR)	Severe proctitis	1
Other complications at follow up			
Taggar 2018 LDR BT LDR BT+EBRT Salvage LDR BT	(74 with spacer 136 without spacer) (SpaceOAR)	Diarrhoea	LDR BT alone 7.7% versus 15.9% LDR BT +EBRT 12.5% versus 4.1% Salvage 12.5% versus 5.3%
		Rectal discomfort	8% (n=7) versus 0
		Rectal bleeding	5% (n=2) versus 21.3 (n=18)

Study 6 Payne 2021

Study details

Study type	Systematic review and meta-analysis
Country	USA, UK, Switzerland and Germany
Study search details	Inception to August 2020; Databases searched: Cochrane Central Register of Controlled Trials, MEDLINE, and Embase; no language or date restrictions applied. Supplemental searches were done in the directory of open access journals, Google scholar, and reference lists of included articles and relevant meta-analyses searched. Unpublished or grey literature was also included.
Study population and number	n=11 studies (14 papers) with 780 people having SpaceOAR hydrogel spacer before SBRT for localised prostate cancer. (5 prospective and 6 retrospective studies) Clinical stages: localised or locally advanced prostate cancer (T1-T3), Risk category: varied but intermediate risk PSA levels median 8.2 (range 6.3 to 9.8 nanograms/ml)
Age and sex	Median age 70 years (range 69 to 73 years).
Study selection criteria	Inclusion criteria: randomised clinical trials or observational studies of people who had the perirectal hydrogel spacer versus patients who had no spacer before SBRT for localised or locally advanced prostate cancer. Exclusion criteria: review articles, commentaries, letters, studies with fewer than 5 patients, studies of other rectal spacers such as hyaluronic acid and rectal balloons, studies that did not report an outcome specified in this review and duplicate publications.
Technique	**Intervention:** Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel-SpaceOAR system) between the Denonvilliers fascia and anterior rectal wall before radiotherapy. Radiotherapy protocols: SBRT (≥5.0 Gy fractions) protocols varied and ranged from 7 Gy to 10 Gy per fraction with total dose ranging from 19 to 45 Gy. 561/780 had dose-escalated SBRT regimens (37.5 GY to 45Gy in 5 fractions).
Follow up	Median 20 months (range, 9 to 24 months).
Conflict of interest/source of funding	The study was funded by Boston Scientific and they were involved in design and interpretation of data, review and approval of manuscript. Authors served as consultants, and either received personal fees, grants, honoraria, travel expenses, and non-financial support from Boston scientific and other companies.

Analysis

- Follow-up issues: follow up varied across studies and was limited to only mid-term.
- Study design issues: systematic review protocol was registered prospectively and was done according to the PRISMA reporting guidelines. Comprehensive literature search was done, studies were screened and data extracted into a predesigned form by 2 reviewers, any disagreements were resolved by discussion. Multiple studies with overlapping patients were carefully assessed and included. Observational studies included were

associated with risks of bias. A random-effects meta-analysis was done for analysis of rectal irradiation only. Heterogeneity was noted among study designs, patient characteristics, and SBRT protocols.

- Study population issues: patient characteristics inconsistently reported and risk categories varied between studies. Androgen deprivation therapy usage also varied.
- Other issues: quality of life not reported in any studies. Toxicities in other organs not assessed in this review.

Key efficacy findings

- Number of patients analysed: 780 patients

Perirectal separation distance: the perirectal distance achieved with SpaceOAR implant ranged from 9.6mm to 14.5mm (median 10.8mm).

Rectal irradiation with perirectal hydrogel spacer versus without spacer (the percentage reduction with spacer versus without spacer in the percentage of rectum having 50% (A), 70% (B), and (C) 90% of the maximum prescribed radiation dosage)

In a pooled analysis of 5 studies, patients who had the perirectal hydrogel spacer before SBRT had 29% to 56% lower rectal irradiation compared with control patients who did not have perirectal hydrogel spacer.

Gastrointestinal [GI] toxicity (risk of a grade 2 or 3+ bowel complication in early [<3months] and late [>3months] follow up)

In early follow up, grade 2 GI complications were reported in 7%- 18% patients and no early grade 3 complications were reported. In late follow up, rates were 4% for grade 2 and 1% for grade 3 GI toxicity. Over a median follow up of 16 months (range 11 to 36 months), freedom from biochemical failure ranged from 96.4% to 100%.

Study	Early grade 2	Early grade 3	Late grade 2	Late grade 3	Freedom from biochemical failure
Alongi (2013) (n=8)	-	0	0	0	8/8 (100%)
Chen (2020) (n=250)	18/250 (7.2%)	0	10/250 (4%)	1/250 (0.4%)	241/250 (96%)
Cuccia (2020) (n=10)	0	0	-	-	-
Hwang (2019, 2018) (n=50)	2/50 (4%)	0	0	0	50/50 (100%)

Jones 2017 (Folkert 2017) (n=44)	1/44	0	-	0	44/44 (100%)
King 2018 (n=6)	0	0	-	-	-
Ogita 2019 (n=40)	7/40 (18%)	0	-	-	-
Pryor 2019 Wilton 2017 (n=80)	-	0/80	-	-	-
Ruggeri 2014 (n=11)	-	-	-	-	-
Saito 2020 (n=20)	-	-	-	-	-
Zelefsky 2019 (n=269)	-	-	-	3/269 (1.1%)	-

Study 7 Mok G 2014

Study details

Study type	Systematic review
Country	UK
Study search details	Search period: not reported; databases searched: MEDLINE
Study population and number	11 studies (reported within 12 articles), n=346 patients
Age	Not reported
Study selection criteria	Inclusion criteria: published articles and conference abstracts from preclinical and clinical studies; prostate cancer patients in whom PR spaces were implanted Exclusion criteria: not provided.
Technique	Intervention: Prostate-rectum spacers compared to each other: PEG spacers (4 studies), hyaluronic acid spacers (5 studies), biodegradable balloons (1 study), and collagen implants (1 study). An additional 3 preclinical studies were included (2 used PEG spacers and 1 used a biodegradable balloon spacer). Radiotherapy protocols: different treatment techniques used (IMRT, VMAT, IMPT, 3D-CRT, and HDR monotherapy) in the primary studies. EBRT (6 studies) and BT (5 studies).
Follow up	3 to 72 months
Conflict of interest/source of funding	None; Review funded by an institute for a health technology assessment report.

Analysis

Follow-up issues: varied across studies.

Study design issues: review compared different spacers; comprehensive literature search was done but the review did not describe the included primary studies in detail including study designs and also did not assess the risk of bias. Dosimetric effects and clinical benefits were assessed. A narrative synthesis was done but risk of bias not considered while interpreting results.

Study population issues: patient characteristics of the included studies not described in the overview.

Key efficacy findings

Number of patients analysed: 346

Mean prostate-rectum distance, dosimetric outcomes (EBRT 6 studies)

Study	Spacer type (ml injected)	Radiation technique	Mean prostate-rectum distance (mm)	Mean rectal Vxx Gy/% without spacer/ with spacer	Relative reduction of rectal Vxx Gy/%	Acute or late toxicity
Weber 2012 N=8	PEG hydrogel (10)	IMRT (78 Gy) VMAT (78 Gy) IMPT (78 Gy)	7-10 7-10 7-10	V70Gy: 9.8%/5.3% V70Gy: 10.1%/3.9% V70Gy: 9.7%/5.0%	V70Gy: 46% V70Gy: 61% V70Gy: 49%	-
Pinkawa 2011 N=18	PEG hydrogel (10)	IMRT (78 Gy) 3D-CRT (78 Gy)	10 10	V70Gy:17.2%/7.5% V70Gy:14.4%/6.1%	V70Gy: 56% V70Gy: 58%	-
Song 2013 N=48	PEG hydrogel (10)	IMRT (78 Gy)	9.7	V70Gy:13.0%/5.1%	V70Gy: 60%	Focal rectal mucosal necrosis and bladder perforation (n=3, self-limiting) (Uhl 2014) Acute GI toxicity grade 1 39.6% grade 2 toxicity 12.5%. No grade 3 or 4 toxicities. Acute GU toxicity grade 1 41.7% grade 2 35.4% grade 3 2.1%. No grade 4 toxicities Late grade 1 GI toxicity 4.3% (2) no grade 2 or worse toxicity. Late GU toxicity grade 1 in 17.0% grade 2 toxicity 2.1%. No grade 3 or worse GU toxicity.

Chapet 2013 n-16	Hyaluronic acid (10)	IMRT (62 Gy, 3.1 Gy/fx)	11.5	V90%: 7.7 cc/2.1 cc V70%: 13.3 cc/7.6 cc	V90%: 74% V70%: 43%	Rectal toxicity 0% versus 30% in historical controls
Chapet 2014 N=10	Hyaluronic acid (10)	SBRT (32.5 Gy, 6.5 Gy/fx) (42.5 Gy, 8.5 Gy/fx)	10.1	V90% 3.2 cc/0.3 cc V90% 3.5 cc/0.3 cc	V90%: 90% V90%: 91%	-
Noyes 2012 N=11	Collagen (20)	IMRT (75.6 Gy)	12.7	V40Gy: 7%-15% in collagen group 20 to 25% without collagen	V40Gy: 40%-65%	No GI toxicities
Melchert 2013 N=22	Balloon (16)	IMRT/3D-CRT (74 Gy)	19.2	V60Gy: 30% pre-implant /15% post implant	V60Gy: 50% (Gez 2013) V90%: 72%	Acute dysuria grade 1 or 2 (58%) Urinary retention needing catheter (n=1) Diarrhoea (grade 1 17%) Proctitis (grade 1 8%)

Spacer absorption: reported in 2 studies:

Melchert 2013 (n=22, balloon implantation): complete deflation and absorption at 6 months in all except 2.

Noyes 2011 (n=11, collagen): 50% at 6 months; 100% at 12 months.

BT (5 studies)

Study	**Spacer type (ml injected)**	**Radiation technique**	**Mean prostate-rectum distance (mm)**	**Mean rectal Vxx Gy/% without spacer/ with spacer**	**Acute and late toxicity**
Storm 2014 (n=100 hydrogel versus no hydrogel)	PEG hydrogel (15)	HDR BT monotherapy (13.5-14.0 Gy x 2 fx) IMRT (45 Gy) + HDR BT boost (9.5-11.5 Gy x 2 fx)	12	D2cc = 60%/47%	Bacterial peritonitis 2 (had prophylactic treatment).
Prada 2007 (n=27)	Hyaluronic acid (3-7)	3D-CRT (46 Gy) + HDR BT boost (11.5 Gy x 2 fx)	20	Dmax = 7.1Gy/5.1Gy	None related to HA implant

				Dmean = 6.1 Gy/4.4 Gy	
Prada 2009 (n=36)	Hyaluronic acid (6-8)	LDR BT ^{125}I 145 Gy	20	NA	Rectal mucosal damage 5%
Prada 2012 (n=40)	Hyaluronic acid (NA)	HDR BT ^{192}Ir 19 Gy x 1 fx	20	NA	None related to HA implant GI toxicity: asymptomatic anal mucositis (grade 1) 12.5% GU toxicity -urinary obstruction grade 1 requiring catheterisation in 1 (2.5%). At 6 months 27.5% had mild grade 1 urinary obstruction.
Wilder 2010 (n=10)	Hyaluronic acid (9)	IMRT (50.4 Gy) + HDR BT boost (5.4 Gy x 4 fx)	13	V70Gy = 4% in HA group 25% in controls	None related to HA implant Grade 1-3 diarrhoea 0% versus 29.7%

Key safety findings

Study	**Complications**	**% (n)**
Noyes 2012 n=11 Collagen	Acute urinary obstruction	5/11
	Self-limiting light rectal pressure	3/11
	Temporary catheterisation for acute urinary retention (presumed to be secondary to pudendal nerve blocking)	1/11
Gez 2013 n=2013 ERB	**During balloon insertion**	**n=26**
	Pain at the perineal skin/scar (ranging 1–7, VAS score)	27 (7/26)
	Acute pain in the anus (ranging 2–9, VAS score)	15 (4/26)
	Acute urinary retention (needed catheterisation, resolved within few hours)	12 (3/26)
	Dysuria and nocturia (grade 1–2)	12 (3/26)
	Penile bleeding	4 (1/26)
	Balloon failure after implantation (needing removal)	4 (1/26)
	Premature balloon deflation	3
	During radiotherapy	**n=23**
	Proctitis	8 (2/23)
	Diarrhoea (grade 1)	17 (4/23)
	Signs of blood in faeces (grade 1)	4 (1/23)
	Constipation (grade1)	4 (1/23)

	Erectile dysfunction	4 (1/23)
	Fatigue	4 (1/23)
	Decreased urine flow	4 (1/23)

Study 8 Ardekani 2021

Study details

Study type	Systematic review
Country	USA, Netherlands, UK, Germany,
Study search details	Search period: January 2000 to December 2019; databases searched: PubMed; Additionally, a further search was done from January 2010 to December 2019 for abstracts. Reference lists of articles were also reviewed for relevant articles.
Study population and number	21 studies of patients with prostate cancer who had a rectal spacer during radiation therapy (n=287).
Age and sex	Age not reported
Study selection criteria	Inclusion criteria: studies in English, in humans, full text articles specifically investigating the impact of rectal displacement devices on prostate motion. Exclusion criteria: review articles, case reports, animal studies, lack of relevant outcome data, non-English articles, editorials and commentaries.
Technique	Rectal spacers used during EBRT for prostate cancer. Different radiotherapy techniques (IMRT, 3DCRT, VMAT, PT) were used. 12 studies evaluated role of ERBs, 4 evaluated polyethylene glycol hydrogel spacers (SpaceOAR) 4 studies assessed rectal retractors (RR), and 1 study assessed ProSpare.
Follow up	Not reported
Conflict of interest/source of funding	None reported

Analysis

Study design issues: systematic review protocol was done according to the PRISMA reporting guidelines. There were no prospective randomised controlled trials. All studies included were either non-randomised two-arm studies or single-arm studies, relatively small (less than 20 patients in each arm) and were heterogenous in terms of population and outcomes reported. There are conflicting findings reported by different studies, which may be due to case mix or other contextual factors.
Other issues: only data on ERBs and hydrogel spacers is considered within this review. data on alternative rectal spacers (Prospare and RR) are out of the scope of this review as they are not biodegradable spacers.

Key efficacy findings

No of patients analysed: 287 (ERB in 180 and hydrogel in 107)

Effect of ERB on prostate motion (8 studies, n=180 patients)

Study	No of patients	Radiotherapy technique	Results

Wacher 2002	10 with 40ml air filled ERB and 10 without	3DCRT	AP displacement: >5mm in 20% of ERB patients. >5mm in 80% of non-ERB patients. ERB significantly reduces maximum AP displacement of prostate (p=0.008).
Hung 2011	14 with 120ml water filled balloon and 15 without	IMRT	AP displacement: mean 5.4±3.4 mm in ERB. mean 7.3± 4.8 mm in non-ERB ERB reduces inter-fractional prostate motion but not statistically significant (p=0.22–0.38)
Van lin 2005	22 with an 80ml air filled ERB and 30 without	IMRT	AP displacement: mean 0.4±4.7mm ERB. 0.6±4.3mm in non-ERB ERB does not decrease the inter-fractional prostate motion (p=NR)
Smeenk 2012	15 with an 100ml air filled ERB and 15 without	IMRT	AP displacement: 3.9 mm ERB, 3.8 mm non-ERB ERB does not significantly reduce the inter-fractional variation (p=0.06–0.92).
Takayama 2011	7 with a double ERB and 7 without	3DCRT or IMRT	AP displacement: 1.3 ± 0.9mm ERB; 2.8 ± 1.8mm non-ERB. ERB only reduces inter-fractional prostate motion in the AP direction (p=0.014)
Teh 2002	10 with an 100ml air filled ERB	Combined radioactive seed implant and IMRT	AP displacement: 1mm ERB can reduce inter-fractional prostate motion.
Mc Gary 2002	10 with an 100ml air filled ERB	IMRT	AP displacement: 0.42 ± 0.35mm Most improvements observe in AP displacement.
El-Bassiouni 2006	15 with a 60ml air filled ERB	3DCRT	AP displacement: 3.8±4.0mm; ERB does not eliminate prostate motion in anterior rectal wall.

5 studies (3 two-arm and 2 single-arm studies; 113 patients) reported that using an ERB reduces intra-fractional prostate motion

5 two-arm studies (115 patients) have reported that using an ERB does not result in a significant reduction of inter-fractional prostate motion.

3 single-arm studies (35 patients) have reported that use of an ERB may reduce inter-fractional prostate motion.

Effect of SpaceOAR hydrogel spacer on prostate motion (4 studies, n=107 patients)

Study	No of patients	Radiotherapy technique	Results
Juneja 2015	12 with hydrogel spacer versus 14 without spacer	VMAT	Mean prostate motion was 1.5 ± 0.8mm with spacer and 1.1 ± 0.9mm without spacer (p< 0.05). No significant difference in the average time of motion >3mm between group with and without hydrogel, which were 7.7 ± 1.1% and 4.5 ± 0.9% (p> 0.05), respectively. Therefore, hydrogel spacer has no effect on intra-fractional prostate motion.
Hedrick 2017	10 with ERB versus 16 with hydrogel spacer	IGRT-PBT	The mean vector shift was 0.9mm with hydrogel and 0.6mm with ERB (p< 0.001). These results were not clinically significant because the minimum robust evaluation tolerance was 3mm. Prostate vector shifts were similar between ERB and hydrogel for shifts >3mm (p=0.13) and >5mm (p=0.36). Prostate displacements were clinically comparable for both ERB and hydrogel spacer groups.
Picardi 2016	10 with hydrogel spacer and 10 without	IGRT-VMAT	Overall mean inter-fraction prostate displacements >5mm in AP and SI direction were similar between with and without spacer (AP direction p=0.78; SI direction p=0.47). Prostate displacements 45mm in the AP and SI directions were similar for both groups. Systematic and random setup errors were similar for both groups.
Pinkawa 2013	15 with hydrogel spacer and 30 without	IMRT	Prostate position displacement >5mm were similar for both groups (no statistically significant difference p>0.05), but posterior prostate displacement could be decreased in group with hydrogel spacer (p=0.03).

4 two-arm studies (117 patients) reported that prostate displacements were clinically comparable with or without hydrogel spacer. One of those studies compared hydrogel spacer against ERB and found no significant differences in prostate motion.

Toxicity results

ERB (5 studies, 3 prospective and 2 retrospective; follow up to 62 months)

Study	No of patients	Radiotherapy technique	Toxicity results
Van lin 2017 Prospective randomised study	24 with an 80ml air filled ERB versus 24 non-ERB	3D-CRT	Acute rectal toxicity ERB versus non-ERB Grade 1: 46% versus 50%, NS Grade 2: 29.2% versus 29.2%, NS Late rectal toxicity ERB versus non-ERB Grade ≥1: 21% versus 58.3%, p=0.003 No grade 2–3 in ERB
Goldner 2007 Prospective study	166 with a 40ml air filled ERB	3D-CRT	Late rectal toxicity Grade 0: 57%; Grade 1: 11% Grade 2: 28%; Grade 3: 3% VRS Grade 0: 32%; Grade 1: 22% Grade 2: 32%; Grade 3: 14%
Deville 2012 Retrospective study	100 with a 100ml water filled ERB	IMRT	Acute GI toxicity Grade 0: 69% 1: 23% Grade 2: 8% Grade 3–4: 0%
Wortel 2017 Prospective phase III trial	85 with an 80–100ml air filled ERB versus 242 without ERB	IMRT	Acute mucous loss: 28.4% in non-ERB versus 16.8% in ERB, p< 0.001. Acute rectal discomfort: 59.9% in non-ERB versus 41.0% in ERB, p=0.003. Late rectal complaints in the ERB group were statistically significantly lower than in the non-ERB group.
Teh 2018 Retrospective study	596 with a 100ml air filled ERB	IMRT	Late GI toxicity Grade ≥2: 8.5% Grade ≥3: 1.2%

Hydrogel SpaceOAR (7 studies, 3 prospective [including 1 RCT], 4 retrospective; follow up to 36 months)

Study	No of patients	Radiotherapy technique	Toxicity results
Uhl 2013 Prospective study	52	IMRT	Presented under study 3, 6
Mariados 2015, Hamstra 2017	149 with hydrogel spacer	IMRT	Presented under study 1, 2, 3,4

Prospective RCT	versus 79 without		
Pinkawa 2017 Retrospective study	101 with spacer versus 66 without	IMRT/VMAT	Presented under study 2, 4
Te Velde 2017 Retrospective study	65 with spacer versus 56 without	IMRT	Presented under study 2, 4
Hwang 2019 Retrospective study	50	SBRT	GI toxicity 1 month after RT Grade 1: 8% Grade 2: 4% No acute or late rectal toxicity was reported.
Dinha 2020 Retrospective study	92 with a 90ml water filled ERB versus 75 with hydrogel spacer	PBT	At 2 years actuarial rate of grade ≥2 late rectal bleeding was 19% in ERB arm and 3% in spacer arm; p=0.003. EPIC-bowel QoL composite scores were less diminished in spacer arm (absolute mean difference 5.5; p=0.030).

Study 9 Aminsharif A 2019

Study details

Study type	Review
Country	USA
Study search details	Search period: January 2015 to March 2019, in the MAUDE database.
Study population and number	N=25 patients
Age	Not reported
Study selection criteria	Not reported
Technique	Injection of a prostate-rectum spacer (absorbable polyethylene glycol hydrogel SpaceOAR) posterior to the Denonvilliers fascia and anterior to the rectal wall at the level between mid-gland and apex of the prostate before radiotherapy.
Follow up	Varied across studies (range 6 to 60 months)
Conflict of interest/source of funding	Authors state that there is no potential conflict of interest and no funding was received.

Analysis

Study design issues: authors reviewed the manufacturer website for the safety profile and complications associated with the SpaceOAR hydrogel and compared with voluntary reports submitted to the Manufacturer and User Facility Device Experience (MAUDE) database. The reports were examined for potential device malfunction, post-malfunction manufacturer assessment, and potential changes to patient management. All included reports and adverse events were classified and stratified according to the previously established MAUDE complication classification system.

Study population issues: limited data about the patient and disease characteristics, physician experience, case volume reported on the database.

Other issues: authors state that the cause of these complications is unclear and may be potentially related to the disease process or patient co-morbidities, injection or radiotherapy rather than the hydrogel spacer.

Key safety findings

- Number of patients analysed: 22 reports of 25 cases.

Complications reported on MAUDE database

Study	Year of report	Reported adverse event	N=25
Level I*	2015, 2017	Venous injection—No sequelae	2
	2017	Tenesmus with air in rectal wall—No sequelae	1
	2018	Venous injection—No sequelae	1
	2018	Rectal wall erosion—No sequelae	1
Level II*	2018	Purulent drainage from perineum requiring antibiotics	1
	2018	Pulmonary embolism requiring anticoagulant	4
Level III*	2016,2018, 2019	Perineal abscess requiring drainage^	3
	2016	Proctitis requiring colostomy^	1
	2017, 2018, 2019	Recto-urethral fistula requiring diverting colostomy^	4
	2018	Rectal ulcer and haemorrhage requiring surgery^	1
	2018	Perirectal fistula requiring surgical intervention^	1
	2019	Urinary tract infection and prostatic abscess requiring drainage^	1
Level IV*	2018	Perineal abscess^—subsequent death from alcoholic cardiomyopathy	1
	2018	Severe urosepsis—ICU admission	1
	2018	Severe anaphylactic reaction	1
	2019	Dizziness/nausea post-procedure leading to unresponsiveness and death (cause of death unclear)	1

*Classified according to MAUDE classification system: Level I (none/mild)—no harm, Level II (moderate)—minimal harm requiring minor intervention, Level III (severe)—significant harm requiring major/procedural intervention(s), Level IV (life threatening)—ICU admission/death.

Surgical intervention was needed in 11 patients with infectious complications (proctitis and abscesses, perirectal fistulae and significant bleeding from the procedure).

Study 10 Hall WA 2021

Study details

Study type	Commentary
Country	USA, UK
Study search period	Search period: May 1, 2015, to May 1, 2020, MAUDE database.
Study population and number	N=85 patients
Age	Not reported
Study selection criteria	Not reported
Technique	Commentary including data from MAUDE database, not primary data.
Follow up	
Conflict of interest/source of funding	The project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK. Authors received some research and travel funding from companies, outside of this work. One author reports personal fees from The Institute of Cancer Research, during the conduct of the study and a patent for a prostate location and stabilisation device.

Analysis

Study design issues: data was accessed online. The description of each event was reviewed and scored by 2 independent radiation oncologists. Event descriptions were characterised using the Common Terminology Criteria for Adverse Events (version 5). The results were then compared collectively, and a final adjudication of scored toxicity events was created. Reporting of adverse events on the database is voluntary and is not comprehensive so it is difficult to calculate actual rates of adverse events. They are also limited in terms of accuracy, verifiability, and scope.

Key safety findings

- Number of patients analysed: 85 events related to hydrogel SpaceOAR

69% (59/85) events were grade 3, 4, or 5.

24% (20/85) were grade 4 events, including multiple independent descriptions of colostomy (n=7) anaphylactic shock (n=2), rectal wall injection, pulmonary embolism requiring hospital admission (n=5), recto-urethral fistula (n=8)

One death was reported.

Study 11 Chapet PJ [2015]

Study details

Study type	**Case series**
Country	France
Recruitment period	2010–12
Study population and number	n=**36** patients with low-risk to intermediate-risk localised prostate cancer Mean prostate volume: 45.9 cc Tumour classification: 1c (n=18), 2a (n=10), 2b (n=8). Gleason score: 6 (n=22), 7 (n=14) PSA: mean 9.46 nanograms/ml
Age and sex	Mean age: 71 years; 100% male
Patient selection criteria	patients aged between 18-80 years, adenocarcinoma of the prostate histologically proven, low- to intermediate-risk cancer according to the D'Amico classification (T1c to T2b, Gleason score <7, and PSA <20 nanograms/ml) and Karnofsky performance score >60 were included. Patients with metastases, regional lymph nodes1.5 cm on CT scan or MRI, inflammatory disease of the digestive tract, previous pelvic irradiation, and previous malignant disease other than basal cell carcinoma were excluded.
Technique	**Injection of 10 ml hyaluronic acid during hypofractionated intensity modulated radiation therapy (IMRT)** (with 20 fractions of 3.1 Gy, up to 62 Gy total dose over 4 weeks) Injection was done under local anaesthesia (10 ml lidocaine 1%). All patients had daily prostate repositioning on the 3 gold markers implanted. Antibiotics were given before and after injection.
Follow up	**3 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 1 patient who developed an adverse event (grade 3 toxicity) was excluded from the analysis because no radiotherapy was administered.

Study design issues: prospective study in 2 centres designed to assess acute toxicity and tolerance of the injection. Acute toxicity was defined as occurring during radiotherapy or within 3 months after radiotherapy and graded according to the CTCAE version 4.0. Tolerance of hyaluronic acid (pain) was assessed on a 10-point

visual analogue scale during the injection, 30 minutes after injection and then by the use of CTC at each visit. Patients who had at least 1 week of radiotherapy were included in the tolerance analysis

Key efficacy findings

Number of patients analysed: **36**

Acute toxicity during and at 3-month follow up (n=35)

Overall toxicity	**% (n)**
Grade 0 (no toxicity)	6 (2/35)
Grade 1	40 (14/35)
Grade 2	54 (19/35)
Grade 3 or 4 toxicity	0
During radiotherapy	
Acute GU toxicity^ (at least 1)	94.3 (33/35)
Grade 2 toxicity (at least 1): urinary obstruction, frequency*	54.2 (19/35)
Acute GI toxicity^^	57.1 (20/35)
Grade 1 (at least 1)	54.2 (19/35)
Grade 2	2.8 (1/35): proctitis
3-month follow up (n=34)	
GU toxicity	41.2 (14/34) 4 patients had grade 2 obstruction or frequency
GI toxicity: grade 1	2.9 (1/34)

*The toxicity was present at baseline in 7 patients.

^GU toxicities included obstruction, frequency, incontinence, haematuria, infection, spasms or stenosis.

^^ GU toxicities included diarrhoea, haemorrhoids, proctitis and rectal mucositis.

Key safety findings

Haematoma developed behind the bladder in 1 patient (within hours after injection) with a moderate platelet count. This was removed by laparotomy.

Tolerance of injection (measured on a VAS) (n=28)

At the time of injection the mean pain score was 4.6±2.3. Thirty minutes after the injection 2 patients reported pain scores as 2 and 3/10. 3 patients had other symptoms such as lower abdominal pain, haematuria and asthenia

Validity and generalisability of the studies

- Evidence assessments on different biodegradable perirectal spacers (including synthetic hydrogel, and biodegradable balloons) used during different radiotherapy techniques (EBRT or BT alone or in combination) for patients with low to intermediate prostate cancer were included within this overview.

- Systematic reviews included different types of studies but were predominantly based on 1 RCT done in the USA (Mariados 2015 and related publications) and non-randomised studies (nRCTs). There is overlap of primary studies between included systematic reviews.

- Hydrogel spacers were compared to no spacers in 3 systematic reviews (Miller 2020, Armstrong 2021, Vaggers 2021), and the RCT which was limited to T1 and T2 tumours (Mariados 2015). Hydrogel spacers were compared to balloons in a HTA (NIPHNO, EUnetHTA 2020) and 1 systematic review (Ardekani 2021). Biodegradable rectal spacers, including hydrogel spacers, balloons, and hyaluronic acid spacers, were compared to each other in one systematic review (Mok 2014).

- Outcomes assessed were mainly reduction in toxicity, reduction in radiation doses, increase in the distance between the prostate and rectum, quality of life and prostate motion or displacement. Outcomes such as survival, patient satisfaction were not reported in studies.

- Variations were noted in patient characteristics (tumour stages), radiotherapy techniques and protocols used (either on its own or in combination with other techniques), and follow-up periods across primary studies included within the systematic reviews. These variations might have influenced the performance of spacers and clinical outcomes.

- Follow-up varied across studies and ranged from 6 to 60 months.

- Most of the related case series with small sample sizes that assessed biodegradable rectal spacers have been included in the appendix. 3 of these small case series used a substance (DuraSeal) ‘off-label’ for this procedure.

Existing assessments of this procedure

The Institut national d'excellence en santé et en services sociaux (INESSS, in 2021) evaluated the use of a biodegradable spacer (SpaceOAR™ Hydrogel System) in patients with localized or locally advanced prostate cancer treated with external beam radiotherapy or brachytherapy combined or not with external beam radiotherapy. Avis - Utilisation de l’hydrogel SpaceOARMD comme espaceur rectal lors de la radiothérapie de la prostate (inesss.qc.ca)

Summary of deliberations

Authors concluded that based on best available data and given the significant uncertainty regarding the product’s therapeutic value that public coverage for the use of a biodegradable spacer is not supported. Additional evidence is necessary to support the adoption of this technology. Reasons for the unanimous position include:

- The limitations in the evidence, including the absence of data for groups considered to be at higher risk for rectal toxicity;
- The risk-benefit ratio, which does not appear to support the use of this technology;
- The possibility of major complications for patients;
- The possibility of an increased risk of complications for patients at increased risk for rectal toxicity;
- The observed dosimetric benefit (sometimes significant) in the evidence presented, which appears to offer only a small clinical benefit;
- The contradiction between the positions taken by other organizations;
- The potential difficulty of access to MRI.

Recommendation

The authors concluded that more evidence on safety and efficacy is needed to recommend this technology and that it should be available only within further research.

Cancer Care Ontario guideline (Chung 2019) provides clinical practice recommendations for the use of biodegradable spacers for prostate cancer treatment.

Recommendation 1 states that *'biodegradable spacer insertion is a technology that may be used to decrease toxicity and maintain quality of life (QOL) in appropriately selected prostate cancer patients receiving radiotherapy (RT)'*.

- *Spacer insertion should be performed by individuals trained in the use of transperineal interventional procedures and where there is institutional support.*

- *Selection of appropriate patients remains to be fully defined but may include those in whom standard rectal dose-volume criteria are not met; those treated with ultrahypofractionated RT; and those at higher baseline risk of rectal toxicity.*

Interpretation of evidence for recommendation 1

- Key evidence for this recommendation was from a multicentre RCT, (Mariados 2015), a follow-up report for this RCT (Hamstra 2017), and 3 non-randomised studies (Pinkawa 2017, Prada 2009, Te Velde 2017).

- The authors state that *'evidence is adequate to support the use of biodegradable rectal spacers for RT in patients with localized prostate cancer. However, given the low rates of toxicity observed overall in both arms of the RCT, there may be limited benefit to routine application of this technology. Further evidence to direct the appropriate selection of patients and to evaluate the efficacy of this technology beyond conventionally fractionated RT is warranted'*.

A CADTH rapid response report of clinical and cost effectiveness on hydrogel spacers for patients with prostate cancer in 2019 included 3 systematic reviews, 1 RCT (described within 2 eligible reports), 7 cohort studies, 2 economic evaluations, and 3 guidelines. Authors concluded that *'hydrogel spacers were effective in increasing the distance between the prostate and the rectum, and in reducing the radiation dose to the rectum while delivering radiation to the prostate in patients with localized prostate cancer'. However, 2 systematic reviews reported that the clinical benefits were not significant and were therefore uncertain. One systematic review developed for a HTA did not recommend the routine use of hydrogel spacers for prostate cancer, in consideration of the high costs for their patients. In contrast, 3 year follow-up results of an RCT indicated that hydrogel spacers were associated with improvements in bowel, urinary and sexual quality of life outcomes…… 'The guidelines by Cancer Care Ontario, the National Comprehensive Cancer Network, and the National Institute for Health*

and Care Excellence recommended the use of hydrogel spacers to reduce rectal toxicity and improve quality of life'.

The National Comprehensive Cancer Network (2018), in the USA states that "*endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions".* It recommends that *"patients with obvious rectal invasion or visible T3 and posterior extensions should not undergo perirectal spacer implantation for prostate cancer"*.

A product brief from an ECRI Institute Health Technology Assessment information service (in 2017) on use of biodegradable spacers concluded that these devices are "*well tolerated and work as intended to reduce rectal irradiation, long-term (but not acute) rectal toxicity, and improve bowel quality of life (QOL), based on 1 RCT and 3 non-RCTs".* The brief also reported that:

- A comparative study included in the brief found that none of the used spacers resulted in a reduction in acute rectal toxicity (<3 months).
- Clinicians may need to perform at least 32 procedures before achieving optimal insertion of the spacer and patient outcomes, based on evidence from a retrospective, single-centre comparison study.
- Placement and hydrogel material appear to be well tolerated based on results from the RCT and case series.
- RCT evidence showed that no rectal perforation, haemorrhage, or infection were associated with use of the biodegradable spacer. Most events were mild, transient, and similar between groups. Case series (n=683) reported few adverse events: 4 rectal wall penetrations (with dose escalation), 1 Grade 3 telangiectasia, and 1 asymptomatic necrotic rectal lesion.
- Longer-term (>5 years) and comparative data are needed because late effects can occur many years after prostate irradiation. A single-arm post-marketing study is collecting 5-year data on 250 patients.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer. NICE interventional procedure guidance IPG590 (2017) (current guidance on same procedure under review).
- Irreversible electroporation for treating prostate cancer. NICE interventional procedure guidance IPG572 (2016) Available from http://www.nice.org.uk/guidance/IPG572
- Focal therapy using cryoablation for localised prostate cancer. NICE interventional procedure guidance IPG423 (2012) Available from http://www.nice.org.uk/guidance/IPG423
- Laparoscopic radical prostatectomy. NICE Interventional Procedures Guidance 193 (2006). Available from http://www.nice.org.uk/guidance/IPG193
- High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. NICE Interventional Procedures Guidance 174 (2006). Available from http://www.nice.org.uk/guidance/IPG174
- Cryotherapy as a primary treatment for prostate cancer. NICE Interventional Procedures Guidance 145 (2005). Available from http://www.nice.org.uk/guidance/IPG145
- Low dose rate brachytherapy for localised prostate cancer. NICE Interventional Procedures Guidance 132 (2005). Available from http://www.nice.org.uk/guidance/IPG132
- Cryotherapy for recurrent prostate cancer. NICE Interventional Procedures Guidance 119 (2005). Available from http://www.nice.org.uk/guidance/IPG119
- High-intensity focused ultrasound for prostate cancer. NICE Interventional Procedures Guidance 118 (2005). Available from http://www.nice.org.uk/guidance/IPG118

NICE guidelines

- Prostate cancer: diagnosis and treatment. NICE guideline 131 (2019)

  Available from http://www.nice.org.uk/guidance/NG131

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

9 professional expert questionnaires for biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer were submitted and can be found on the NICE website.

Patient organisation opinions

One patient organisation submission for biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer was received and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 22 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing studies:

- **NCT02353832** Stereotactic ablative radiotherapy (SABR) for low risk prostate cancer with injectable rectal spacer (phase 2 study); interventional single group; n=44; device: SpaceOAR, Duraseal or equivalent; primary outcome: percentage of participants with reduction in acute per-prostatic rectal ulcer events from 90%+ to <70%, effectiveness of space creation of >= 7.5 mm in protecting rectum from toxicity; location: USA; study completion date: January 2021; status: active.
- **NCT02361515** Moderate hypofractionated radiotherapy (62 Gy in 20 fractions of 3.1 Gy) versus stereotactic radiotherapy (37.5 Gy in 5 fractions of 7.5 Gy) with hyaluronic acid injection between the prostate and the rectum for prostate cancer of low- to intermediate risk; RPAH2. RCT, n=96, primary outcome - number of patients with late urinary toxicities of grade ≥ 2; location France; study completion date: September 2019.
- **NCT02165020**: Hypofractionated radiotherapy for prostate cancer (62 Gy in 20 fractions of 3.1 Gy) with hyaluronic acid injection; non-randomised single group study, n=36, primary outcome: number of patients with late rectal toxicities (> 3 months) of grade ≥ 2; location France; study completion May 2017; status active.
- **NCT03386045**: Optimal prostate fractionation study; RCT, n=214, moderate hypofractionation or standard radiotherapy plus SBRT (BOOSTER) with hydrogel versus moderate hypofractionation or SBRT; primary outcome: local control; location Australia; study completion date: March 2026, status recruiting.
- **NCT03400150:** clinical protocol for the investigation of the ProSpace™ balloon system pivotal study BP-007; RCT, n=222, ProSpace balloon in prostate cancer during IMRT versus only IMRT; primary outcomes: adverse

event rate, reduction in rectal radiation exposure at 6 months; international study; study completion date: April 2022; status active.

- **NCT03525262** A phase II randomized controlled trial of stereotactic ablative body radiotherapy (SABR) with or without neurovascular sparing for erectile function preservation in localized prostate cancer, hydrogel used in the intervention group. RCT, n=120, primary outcome: reduction in EPIC sexual function domain composite score; location USA, study completion date: June 2024; status recruiting.
- **ACTRN12612000524897:** A trial of polyethylene glycol (PEG) hydrogel to reduce rectal radiation dose during radiotherapy for prostate cancer. Nonrandomised single group study, n=40; primary outcomes: radiation dose, prostate-rectum separation, toxicity; location Australia, completion date and status unknown.

References

1. Mariados N, Sylvester J et al (2015). Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. International Journal of Radiation Oncology Biology Physics.92 (5) 971-977.

   Hamstra da, Mariados N, Sylvester J et al (2017). Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Radiation Oncology International Journal of biology physics. 9 (5) 67-985.

   Hamstra DA, Mariados N, Sylvester J, et al.(2018) Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: secondary analysis of a phase 3 trial. Pract Radiat Oncol. 8(1):e7-e15.

   Karsh LI, Gross ET, Pieczonka CM, et al. (2018) Absorbable hydrogel spacer use in prostate radiotherapy: a comprehensive review of phase 3 clinical trial published data. Urology.115:39-44.

2. Miller LE, Efstathiou JA, Bhattacharyya SK et al. (2020) Association of the Placement of a Perirectal Hydrogel Spacer with the Clinical Outcomes of Men Receiving Radiotherapy for Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Network Open. 3(6):e208221-e

3. Norwegian Institute of Public Health (NIPHNO), National School of Public Health, Management and Professional Development (NSPHMPDB); et al. Biodegradable rectum spacers to reduce toxicity for prostate cancer. Collaborative Assessment. Oslo, Norway: EUnetHTA; 2020. Report No.: OTCA23.

4. Armstrong N, Bahl A, Pinkawa M, et al. (2021) SpaceOAR Hydrogel spacer for reducing radiation toxicity during radiotherapy for prostate cancer. A systematic review, Urology, doi: https://doi.org/10.1016/j.urology.2021.05.013

5. Vaggers S, Rai BP, Chedgy ECP et al. (2021) Polyethylene glycol-based hydrogel rectal spacers for prostate brachytherapy: a systematic review with a focus on technique. World Journal of Urology 39:1769–1780.

6. Payne HA, Pinkawa M, Peedell C et al. (2021) SpaceOAR hydrogel spacer injection prior to stereotactic body radiation therapy for men with localized prostate cancer: A systematic review. Medicine. 100 (49); e28111.

7. Mok G, Benz E, Vallee JP et al. (2014) Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. Int J Radiat Oncol Biol Phys. 90(2):278-288.

8. Ardekani MA, Ghaffari H, Navaser M et al. (2021) Effectiveness of rectal displacement devices in managing prostate motion: a systematic review. Strahlenther Onkol,197:97–115

9. Aminsharifi A, Kotamarti S, Silver D et al. (2019) Major complications and adverse events related to the injection of the SpaceOAR hydrogel system before radiotherapy for prostate cancer: Review of the manufacturer and user facility device experience database. J Endourol. 33(10):868-871.

10. Hall WA, Tree AC, Dearnaley D et al. (2021). Considering benefit and risk before routinely recommending SpaceOAR. The lancet oncology. 22 (1), 11-13.

11. Chapet O, Decullier E et al (2015). Prostate hypofractionated radiation therapy with injection of hyaluronic acid: Acute toxicities in a phase 2 study. International Journal of Radiation Oncology Biology Physics.91 (4) 730-736.

12. Institut national d'excellence en santé et en services sociaux (INESSS). Utilisation de l'hydrogel SpaceOARMD comme espace rectal lors de la radiothérapie de la prostate. Avis rédigé par Cathy Gosselin, Andréa Senay, Amélie Rousseau et Vanessa Dufour. Québec, Qc : INESSS; 2021. 200 p

13. Chao YS, MacDougall D, de Nanassy A. (2019) Hydrogel spacers for patients with prostate cancer: a review of clinical effectiveness and cost-effectiveness. Ottawa: CADTH; Feb. (CADTH rapid response report: summary with critical appraisal).

14. Chung P, Brown J, D'Souza D, Koll W, Morgan S, SPACER RRG. Cancer Care Ontario: biodegradable rectal spacers for prostate cancer radiotherapy. (Program in Evidence-based Care recommendation report no.: 21-5). Toronto (ON): Cancer Care Ontario; 2019 Jan 16: https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/pebc21-5f.pdf . Accessed 2021 September 29.

15. National Comprehensive Cancer Network. NCCN Guidelines: prostate cancer v. 4.2018. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2018. Accessed 2021 September 29.

16. SpaceOAR System (Augmenix, Inc.) Hydrogel Spacer for Reducing Exposure during Prostate Cancer Radiation Therapy. Product brief. ECRI Institute Health Technology Assessment Information Service, May 2017. Accessed 2021 September 29.

17. Babayan RK, Steinberg ML, Miller LE. Re: Aminsharifi et al. (2020) Major complications and adverse events related to the injection of the SpaceOAR hydrogel system before radiotherapy for prostate cancer: review of the manufacturer and user facility device experience database. J Endourol; 34: 240–41.

Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	14/09/2022	1946 to September 13, 2022
MEDLINE In-Process (Ovid)	14/09/2022	1946 to September 13, 2022
MEDLINE Epubs ahead of print (Ovid)	14/09/2022	September 13, 2022
EMBASE (Ovid)	14/09/2022	1974 to 2022 September 13
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	14/09/2022	Issue 8 of 12, August 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	14/09/2022	Issue 8 of 12, August 2022
International HTA database (INAHTA)	14/09/2022	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

Number	Search term
1	exp Prostatic Neoplasms/
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenes* or leiomyosarcoma* or lump*)).tw.
3	1 or 2
4	Hydrogels/
5	Hydrogel, Polyethylene Glycol Dimethacrylate/
6	(hydrogel* or hydrodissect*).tw.
7	(spacer* or spacing).tw.
8	((perirect* or rect* or prostate-rectum or denonvillier* or transperineal*) adj4 space*).tw.
9	or/4-8
10	3 and 9
11	spaceOAR*.tw.
12	Augmenix*.tw.
13	11 or 12

14	10 or 13
15	animals/ not humans/
16	14 not 15
17	limit 16 to ed=20200622--20220930
18	limit 17 to english language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Inert liquid-to-solid gels for prostate-rectum separation during prostate radiation therapy November (2010, 2013). Horizon scanning technology prioritising summary and Technology brief update: Prepared by Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S). Accessed 2021 September 29.	Horizon scanning summary report for Australia and New Zealand	A Horizon Scanning prioritising summary report concluded that *'some form of injected liquid-to-solid inert substance (mostly recently cross-linked hyaluronan gel) for prostate-rectum separation appears to be safe. It also appears to have the potential to lower rates of rectal toxicity and improve QOL for men having radiotherapy for prostate cancer. However, the technology is very early in its lifecycle and is not yet in clinical use'*. A 2013 technology update '*provides continued support for the safety and effectiveness of this modality. Although the evidence base remains small, injection of hyaluronic acid or the SpaceOAR™ System gel appears to successfully increase the distance between the posterior prostatic capsule and the anterior rectal wall which resulted in reduced gastrointestinal toxicity. Based on this, and the claim that inert liquid-to-solid gels have the potential to reduce the incidence of severe proctitis, necrosis, fistula or rectal bleeding by 50%, this technology will be monitored for a further 24 months*'	More recent assessments included.
Afkhami Ardekani M, Ghaffari H. Optimization of prostate brachytherapy techniques with	Systematic review 12 studies, involving 615 patients with PEG hydrogel injection, were included.	overall, patients well tolerated the implantation of PEG hydrogel spacers with an excellent safety profile. However, although there were	More comprehensive and recent reviews added.

polyethylene glycol-based hydrogel spacers: a systematic review. Brachytherapy. 2019:S1538-4721(19)30574-4.		some procedure-related complications, rates of these complications were very rare. Toxicities related to the spacer were limited to Grade 1 rectal discomfort and pain (9/615 patients), Grade 2 rectal ulceration (1 in 615 patients), perineal abscess (1 in 615 patients), and bacterial prostatitis (2/615 patients) according to Common Terminology Criteria for Adverse Events v4.0 grading scheme. The application of PEG hydrogel spacers significantly reduced radiation doses to the rectum during prostate brachytherapy in the different setting. Although there was no prospective randomized clinical trial, retrospective studies showed that reducing rectal doses by the implantation of PEG hydrogel may result in an improvement in rectal toxicity	
Aditama, E (2015). Evaluation of Hydrogel Spacer (SpaceOAR) to reduce rectal toxicity in dose-escalated intensity modulated radiotherapy (IMRT) 82Gy for prostate cancer. Journal of Medical Radiation Sciences (62) 89.	Case report A 54-year-old man was diagnosed with T1c prostate adenocarcinoma and treated with dose-escalated IMRT 82 Gy with injection of hydrogel spacer. Follow-up: 6 months	The injection of spacer results in reduction of rectal dose with V70 = 0% for post injection of spacer plan compared with V70Gy = 15% for pre injection of spacer plan. The distance created due to spacer is 7-10 mm.	Larger studies are included.
Alongi F, Cozzi L, Arcangeli S, Iftode C, Comito T, Villa E, et al. Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: Preliminary report of a phase II study. Radiation Oncology. 2013;8 (1) (no pagination)(171)	Case series N=40 patients prostate adenocarcinoma (T1-T2). hypo-fractionated SBRT programme with Volumetric Modulated Arc Therapy (VMAT) and Flattening Filter Free (FFF) beams. SpaceOAR™ gel was optionally implanted (in 8 patients). Median follow-up was 11 months (range: 5-16)	No acute G3 or greater toxicity was found. Median treatment time was 126 sec (120-136). Early findings suggest that SBRT with RapidArc and FFF beams for prostate cancer in 5 fractions is feasible and tolerated in acute setting.	Larger studies are included.

Alongi F, Riog M, Figlia V et al. (2020) Rectal spacer hydrogel in 1.5T MR-guided and daily adapted SBRT for prostate cancer: dosimetric analysis and preliminary patient-reported outcomes. Br J Radiol; 94: 20200848.	Case series N=20 patients with prostate cancer (cT1-T2 stage) treated using 1.5T MR-guided adaptive stereotactic body radiotherapy [SBRT - 35 Gy schedule delivered in 5 fractions] (10 patients in spacer group and 10 patients in no-spacer group).	Statistically significant dosimetric advantages were observed in favour of the spacer insertion, improving the planning target volume coverage in terms of V33.2Gy >95% and planning target volume 37.5 Gy <2% mainly during daily-adapted SBRT. Also, rectum V32, V28 and V18Gy and bladder V35Gy <1 ccs were significantly reduced in the spacer cohort. PROMS, showed no difference between the pre- and post-SBRT evaluation in both arms, excepting the physical functioning item of EORTC QLQ-C30 questionnaire that was declined in the no-spacer group.	Larger studies are included.
Ahmad Khalil D, Jazmati D, Geismar,D et al. (2022) Dosimetric feasibility of moderately hypofractionated/dose escalated radiation therapy for localised prostate cancer with intensity-modulated proton beam therapy using simultaneous integrated boost (SIB-IMPT) and impact of hydrogel prostate-rectum spacer. Radiation oncology. 17 (1); 64	N=23 patients with intermediate- and high-risk prostate cancer treated using IMPT -SIB technique prescribing 60 GyRBE and 72GyRBE in 30 fractions to PTV1 (prostate and seminal vesicle) and PTV2 boost (prostate and proximal seminal vesicle), respectively (15 had spacer, 8 were non spacer).	Hypofractionated/dose escalated radiotherapy with SIB-IMPT is dosimetrically feasible. Further reduction of the rectal volumes receiving high and medium dose levels (73-50 Gy) and rectal NTCP could be achieved through injection of spacers between rectum and prostate.	Dosimetry study. Larger studies with longer follow-up included.
Alshak MN, Eidelberg A, Diaz SM et al. (2022) Natural history of lower urinary tract symptoms among men undergoing stereotactic body radiation therapy for prostate cancer with and without a Rectal Hydrogel Spacer. World journal of urology. 40,1143–1150	Retrospective analysis n= 87 men (50 had SBRT+ SpaceOAR and 37 had SBRT with no SpaceOAR). Follow-up 6 months	Post-SBRT urinary frequency was more common in the non-SpaceOAR group versus the SpaceOAR group (68% versus 38%, $p = 0.006$), as was nocturia (35% vs. 8%, $p = 0.002$). Acute gastrointestinal symptoms did not differ. 58.8% of men were on α-inhibitors at 6-months of follow-up post-SBRT, an increase from 27.6% baseline usage ($p < 0.001$). Importantly, there was a difference of α-inhibitor use between non-SpaceOAR and SpaceOAR groups at the end of SBRT and at 1.5-, 3-, and 6-months follow up (86% vs. 53% [$p = 0.002$], 83% vs. 53%	Larger studies with longer follow-up included.

		[p = 0.005], 72% vs. 49% [p = 0.038], respectively).	
Babar M, Katz A, Ciatto M et al. (2021) Dosimetric and clinical outcomes of SpaceOAR in men undergoing external beam radiation therapy for localized prostate cancer: A systematic review. Journal of Medical Imaging and Radiation Oncology 65 (2021) 384–397	systematic review on controlled studies on the dosimetric and clinical outcomes of SpaceOAR in men undergoing external beam radiation therapy for localized prostate cancer. 8 studies were included.	All of the studies showed SpaceOAR to reduce the radiation dose volume to the rectum over numerous dosimetry levels. Of the four studies that assessed toxicity, one reported SpaceOAR to significantly decrease acute Grade 1 diarrhoea and two reported SpaceOAR to significantly decrease late Grade 1 and Grade ≥2 rectal toxicities. Two studies assessed cumulative incidence of toxicity at 3 years in which one reported SpaceOAR to significantly decrease urinary incontinence and Grade ≥1 and Grade ≥2 rectal toxicities, and the other reported SpaceOAR to significantly decrease Grade 1 diarrhoea and Grade 2 proctitis. Moreover, one study reported that fewer SpaceOAR patients experienced 10-point declines in bowel quality of life at 3 years, but another study reported no significant difference in 10-point declines in bowel quality of life between the SpaceOAR and control groups at 5 years. With the current research available, SpaceOAR may be beneficial to those who did not meet the standard rectal dose-volume criteria, have higher risk factors of developing rectal toxicities post-radiation, or wish to decrease the length and costs of radiotherapy by increasing the dose of radiation per fraction.	Similar comprehensive review on hydrogel spacers included.
Bahl A, Challapalli A, Jain S et al. (2021) Rectal spacers in patients with prostate cancer undergoing radiotherapy: A survey of UK uro-oncologists. Int J Clin Pract. 2021;75:e14338	Survey online questionnaire was completed by members of the British Uro-oncology Group (BUG).	63 specialists completed the survey (50% of BUG members at that point in time). Only 37% had used rectal spacers, mostly for private patients or those with pre-existing bowel conditions. However, many (68%) would like to use these devices in future. More than 70% of the uro-oncologists felt that bowel toxicity was under-reported, but 60% believed that the use of radiotherapy without bowel toxicity was	Survey

		achievable with the use of rectal spacers. The current use of rectal spacers by UK uro-oncologists for patients with localised or locally advanced prostate cancer receiving radiotherapy is low and largely restricted by resourcing issues.	
Beydoun N, Bucci JA et al (2013). First report of transperineal polyethylene glycol hydrogel spacer use to curtail rectal radiation dose after permanent iodine-125 prostate brachytherapy. Brachytherapy 12 (4) 368-374.	Case series n=5 prostate cancer patients with suboptimal rectal dosimetry after iodine 125 seed brachytherapy implant (low dose rate) and had hydrogel PEG spacer Follow-up: 6 weeks	All patients had a clinically significant reduction in the volume of rectum having greater than or equal to the prescription dose (RV100) on the post spacer postimplant dosimetry, compared with the pre-spacer postimplant dosimetry. Mean prostate-rectum separation that was achieved with the insertion of the spacer was 15.1 mm (+/-3.4). The mean difference in separation from before to after spacer insertion was 12.5 mm (+/-4.5). This was associated with a reduction in mean RV100 from 3.04 (+/-1.2) to 0.06 (+/-0.1) cc. Toxicities were limited to grade 1 perineal pain and rectal discomfort (3/5 patients). There were no grade 2 or greater toxicities reported after insertion of the spacer.	Larger and longer follow-up studies included.
Berlin A, Tomasso AD, Ballantyne H et al. (2017) Use of hydrogel spacer for improved rectal dose-sparing in patients undergoing radical radiotherapy for localized prostate cancer: First Canadian experience. : Can Urol Assoc J;11(12):373-5. http://dx.doi.org/10.5489/cuaj.4681	Case series N=5 patients with localised prostate cancer planned to undergo radical hypofractionated, image-guided, intensity-modulated radiotherapy (IG-IMRT using a hydrogel spacer SpaceOAR)	Authors discuss the impact of SpaceOAR in the context of hypofractionated IG-IMRT, and the particular considerations for its applications in the Canadian setting.	Larger studies included.
Boissier R, Udrescu C, Rebillard X et al (2017). Technique of Injection of Hyaluronic Acid as a Prostatic Spacer and Fiducials Before Hypofractionated External Beam Radiotherapy for Prostate Cancer. Urology (99) 265-269.	Case series n=30 patients with prostate cancer at low or intermediate risk. Implantation of fiducials and a prostatic spacer (hyaluronic acid [HA]) during image-guided external beam radiotherapy (EBRT) of 62 GY in 20 fractions of	The quality score increased from patients 1-10, 11-20, to 21-30 with respective median scores: 7 [2-10], 5 [4-7], and 8 [3-10]. The average thicknesses of HA between the base, middle part, and apex of the prostate and the rectum were the following: 15.1mm [6.4-29], 9.8mm [5-21.2], and 9.9mm [3.2-21.5]. The injection of the HA induced a median pain score of 4 [1-8]	Larger studies included.

	3.1 GY with intensity-modulated radiotherapy.	and no residual pain at mid-long term.	
Brooks E, Hu J, Yu J, et al. Cost effectiveness of the insertion of hydrogel spacer in men treated with radiation therapy for prostate cancer. Managed Care 2020;	Cost effectiveness		Costs not in remit.
Butler WM, Kurko BS, Scholl WJ et al. (2021) Effect of the timing of hydrogel spacer placement on prostate and rectal dosimetry of low-dose-rate brachytherapy implants. J Contemp Brachytherapy; 13, 2: 145–151	Retrospective study N=174 intermediate- and high-risk patients with hydrogel compared with 174 patients without hydrogel for prostate brachytherapy. Of the SpaceOAR™ patients, 91 had hydrogel upon completion of after brachytherapy implant, while 83 had hydrogel prior to EBRT, followed 2-10 weeks later by brachytherapy.	There was a significant rectal dose sparing in the cohort with hydrogel spacer compared to a reference group without spacer injection. The rectal dose sparing effect was similar in the sub-group of patients injected with hydrogel prior to EBRT and the sub-group injected with hydrogel at the conclusion of brachytherapy.	Larger studies included in table 2.
Chao M, Ho H, Chan Y et al. (2018) Prospective analysis of hydrogel spacer for patients with prostate cancer undergoing radiotherapy. BJU international, 122, 427-433.	Case series N=76 patients with prostate cancer Clinical stage T1-T3a Fiducial marker insertion plus injection of the hydrogel spacer into the perirectal space before intensity-modulated RT (IMRT) or volumetric-modulated arc RT (VMAT) 78 Gy in 2 Gy Follow-up Median 14 (IQR 12-29) months	16 patients (21%) developed acute Grade 1 GI toxicity, with all symptoms resolved within 3 months after completion of treatment. 1 patient (1%) developed a late Grade 1 rectal haemorrhage at 9 months after treatment; however, this was due to rectal haemorrhoids. 1 patient (1%) developed late Grade 1 proctitis at 8 months after treatment. No patients developed late GI toxicity of Grade ≥2.	Larger studies with controls included.
Chao, M. 2018. The use of hydrogel spacers in prostate radiation therapy. *BJU International,* 122**,** 10.	Case series N=31 patients with stage T1-T3a prostate cancer IMRT 78 Gy in 2 Gy fractions Follow-up median 12 (range 6-18) months		Larger studies included.
Chao M, Lim Joon D, Khoo V et al. (2019) The use of hydrogel spacer in men undergoing high-dose prostate cancer radiotherapy: results of a prospective phase 2 clinical trial. World J	Case series N=31 patients with cT1-3aN0M0 prostate adenocarcinoma receiving radical radiotherapy to 78 G and hydrogel spacer (SpaceOAR) implantation.	All patients had successful insertion of spacer with no peri-operative toxicity. The mean prostate-rectal separation achieved was 10.5 mm. 29 (93.5%) patients achieved a reduction in rV70 of at least 25%. Acute grade 1 GI toxicity was reported in 3 patients. All symptoms had	Larger studies with controls included.

Urol. 2019;37(6):1111-6.	Follow-up 12 months.	resolved by 3 months post RT. Late grade 1 GI toxicity was reported in one patient (3.2%) with bowel frequency occurring at 6 months and resolving by 12 months post RT.	
Chao M, Ow D, Ho H, et al. (2019) Improving rectal dosimetry for patients with intermediate and high-risk prostate cancer undergoing combined high-dose-rate brachytherapy and external beam radiotherapy with hydrogel space. Journal of Contemporary Brachytherapy. 11(1):8-13	Comparative study (retrospective) N=97 patients with prostate cancer 32 patients (33%) who had hydrogel spacer insertion compared with 65 patients (67%) without hydrogel spacer receiving combined HDR and EBRT. Median follow-up 60 months (12-125 months).	The median prostate-rectal separation achieved with hydrogel spacer (HS) was 10 mm (range, 5-14 mm). There were no post-operative complications following HS insertion. Patients with HS had significantly lower radiation dose to the rectum across all rectal dose volumes from rV30 to rV80, ($p < 0.001$). There was also significantly less acute > grade 1 GI toxicity (12.5% vs. 30.8%, $p = 0.05$) and a trend towards less late grade 1 GI toxicity (0% vs. 7.7%; $p = 0.11$) in the HS group compared to the non-HS group.	Larger studies included. Included in systematic review added.
Chao M, Bolton D, Joon DL et al. (2019) High dose rate brachytherapy boost for prostate cancer: Biochemical control and the impact of transurethral resection of the prostate and hydrogel spacer insertion on toxicity outcomes. Journal of Medical Imaging and Radiation Oncology 63, 415–421.	Retrospective case series N=95 patients with intermediate and high risk prostate cancer treated with high dose rate brachytherapy boost (HDR-BT, 50.4 Gy) combined with external beam radiotherapy (EBRT) Hydrogel spacers (HS) were used in 30 patients. Median follow-up was 58 months.	The 5-year biochemical progression free survival, local recurrence free survival (LRFS), metastatic free survival (MFS) and overall survival were 92%, 100%, 92% and 88%. Late > grade 2 genitourinary (GU) toxicity was 6.3%. The use of HS or prior TURP had no impact on late GU toxicity. Late Grade 1 gastrointestinal (GI) toxicity was 5.3%.	Larger studies included.
Chapet O, Udrescu C, Devonec M, et al (2013). Prostate hypofractionated radiation therapy: Injection of hyaluronic acid to better preserve the rectal wall. Int J Radiat Oncol Biol Phys; 86:72-76.	Case series n=16 patients with prostate cancer. Hyaluronic acid injection combined with hypofractionated radiotherapy (62Gy in 20 fractions) delivered via IMRT.	The mean rectal V90% 955.8Gy) for pre-implantation plans was 7.65cc compared with 2,1cc on plans generated in scans of patients who have implants. The mean rectal V90%, V705 AND v50% were reduced by 73.8% ($p<0.001$), 43% ($p=0.007$) and 25% ($p=0.036$) respectively.	Larger and longer follow-up studies.
Chapet O, Udrescu C, Tanguy R, et al (2014). Dosimetric implications of an injection of hyaluronic acid for preserving the rectal wall in prostate stereotactic body radiation therapy. Int J	Case series n=10 patients with prostate cancer Hyaluronic acid injection combined with hypofractionated radiotherapy (62Gy in 20 fractions) delivered via IMRT.	The mean rectal V90% and V80% were reduced by at least 90% ($p=0.002$) and 77% ($p=0.002$) respectively, regardless of the prescription dose.	Larger and longer follow-up studies.

Radiat Oncol Biol Phys; 88:425-432.			
Chapet O, Decullier E et al (2015). Prostate hypofractionated radiation therapy with injection of hyaluronic acid: Acute toxicities in a phase 2 study. International Journal of Radiation Oncology Biology Physics.91 (4) 730-736	Case series N=36 patients with low-risk to intermediate-risk localised prostate cancer. Injection of 10 ml hyaluronic acid (HA) during hypofractionated intensity modulated radiation therapy (IMRT) (with 20 fractions of 3.1 Gy, up to 62 Gy total dose over 4 weeks) Follow-up 3 months	The HA injection induced a mean pain score of 4.6/10 ± 2.3. 33 patients had at least 1 acute genitourinary toxicity and 20 patients at least 1 acute gastrointestinal toxicity. Grade 2 toxicities were reported for 19 patients with urinary obstruction, frequency, or both and for 1 patient with proctitis. No grade 3 or 4 toxicities were reported. At the 3-month visit, 4 patients described grade 2 obstruction or frequency, and no patients had any grade 2 gastrointestinal toxicities.	Larger studies included.
Chung H, Polf J, Badiyan S, Biagioli M, Fernandez D, Latifi K, et al. Rectal dose to prostate cancer patients treated with proton therapy with or without rectal spacer. J Appl Clin Med Phys. 2017;18(1):32-9.	Comparative study N=20 patients with prostate cancer treated with in silico with pencil beam scanning (PBS) photon therapy (12 with rectal spacer (DuraSealTM gel and 8 without).	Rectal spacers can significantly decrease rectal dose and predicted ≥grade 2 rectal toxicity in prostate cancer patients treated in silico with PBS. A minimum of 9 mm separation between the prostate and anterior rectal wall yields the largest benefit.	Larger studies included.
Cousins MM, Heckman P, Short E et al. (2022) Rectal sparing in prostate radiotherapy with combination-brachytherapy and hydrogel spacer. Brachytherapy.	Retrospective review N=60 patients (30 who had brachytherapy followed by EBRT with hydrogel spacer compared with 30 patients without spacer).	Through effective use of CBT and HS, extreme rectal dose restriction is possible. The goal for HS placement should be thickness >=1 cm from base to apex.	Dosimetry outcomes. Larger studies with longer follow-up included.
Cuccia F, Mazzola R, Nicosia L et al. (2020) Impact of hydrogel peri-rectal spacer insertion on prostate gland intra-fraction motion during 1.5 T MR-guided stereotactic body radiotherapy. Radiation Oncology 15:178.	Case series N= 20 patients who underwent MRI-guided prostate SBRT for low-to-intermediate risk prostate cancer with or without spacer.	A significant difference between spacer and no-spacer patients in terms of rotational shifts in the antero-posterior direction ($p = 0.033$) was observed; also for translational shifts a positive trend was detected in antero-posterior direction ($p = 0.07$), although with no statistical significance. We observed statistically significant differences in the pre-treatment planning phase in favor of the spacer cohort for several rectum dose constraints: rectum V32Gy < 5% ($p = 0.001$), V28 Gy < 10% ($p = 0.001$) and V18Gy < 35% ($p = 0.039$). Also for bladder V35 Gy < 1 cc, the use of spacer provided a dosimetric	Rectal spacer impact on intrafraction prostate motion was assessed.

		advantage compared to the no-spacer subpopulation (p = 0.04). Furthermore, PTV V33.2Gy > 95% was higher in the spacer cohort compared to the no-spacer one (p = 0.036).	
Dihn TK T, Lee HJ, Macomber MW et al. (2020) Rectal hydrogel spacer improves late gastrointestinal toxicity compared to rectal balloon immobilization after proton beam radiation therapy for localized prostate cancer: A retrospective observational study. Int J Radiation Oncol Biol Phys,108 (3), 635-643.	Retrospective review N=267 patients with localized, clinical stage T1-4 prostate adenocarcinoma treated with PBT (with rectal balloon, n=192 versus a hydrogel rectal spacer, n=75). Median follow-up 19-22 months	The 2- year actuarial rate of grade 2+ late rectal bleeding was 19% and 3% in the rectal balloon and hydrogel spacer groups, respectively (P =0.003). In univariable analysis, the probability of grade 2+ rectal bleeding was significantly correlated with increasing rectal dose. In multivariable analysis, only receipt of spacer hydrogel and anticoagulation use were significantly associated with grade 2+ bleeding. At 2-year follow-up, patient-reported EPIC bowel quality of life composite scores were less diminished in the hydrogel spacer group.	Larger studies included.
Drabble J, Drury-Smith H. What is the quality of hydrogel spacer insertions and which patients will benefit. A literature review. J Radiother Pract. 2019;Epub ahead of print doi: http://dx.doi.org/10.1017/S1460396919000979	Systematic review N=26 studies	HS showed a clinically significant relative reduction in rectal planning dose volumes for both high- and low-risk prostate cancer patients in a range of radiotherapy treatment modalities including volumetric modulated arc therapy, intensity-modulated radiotherapy, intensity-modulated proton therapy, stereotactic ablative body radiotherapy and brachytherapy. Spacer placements were successfully inserted in 99% of patients. However, rectal wall infiltration occurrence was 6% and ≥2 cm unsymmetrical placements in 2%. A spacer scoring system based on the HS symmetry has provided evidence of the quality of the position inserted, which was visually aided by T2-wieghted MRIs. Despite optimal HS placements ranging from 62 to 72%, HS had a clinically significant reduction of ≥25% in planned rectal V70 dose in 97% of patients	More comprehensive reviews on hydrogel spacers included.
Eckert F, Alloussi S et al (2013). Prospective evaluation of a	Case series	In 1 patient hydrodissection of the Denonvillier space was not possible. Radiation treatment	Larger and longer follow-up

hydrogel spacer for rectal separation in dose-escalated intensity-modulated radiotherapy for clinically localized prostate cancer. BMC Cancer.13 (no pagination).	n=11 patients with T1-2 N0 M0 localised prostate cancer having dose-escalated IMRT after injection of a hydrogel spacer. 78 Gy in 2 Gy fractions. Follow-up; 12 weeks	planning showed low rectal doses despite dose-escalation to the target. Acute rectal toxicity was mild without grade 2 events and there was complete resolution within 4 to 12 weeks.	studies included.
Forero D, Dendukuri N, Almeida N. Hydrogel spacer to reduce rectal toxicity in prostate cancer radiotherapy: a health technology assessment. (Report No. 82). Montreal (QC): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2018: https://muhc.ca/sites/default/files/users/user192/SpaceOAR%20Final%20May%2010%202018%20updated%20Dec13.pdf . Accessed 2021 September 21.	Systematic review informing an HTA N=10 studies (852 patients treated with EBRT) Included 1 RCT and 5 non-randomised studies, 1 HTA and 3 economic evaluations. Space OAR versus no spacer prostate cancer treatment: EBRT Follow-up: 3 to 72 months	Spacer OAR, a type of hydrogel spacer, was reported to be significantly associated with lower rectal radiation exposure; nonetheless, authors concluded that it may not contribute to an important reduction in rectal toxicity based on the review of one RCT and three observational studies. Quality of life within the first year of follow-up was not found to be significantly different between Spacer OAR and no spacer and the results of the four primary studies reporting on long-term quality of life were not consistent. Due to the high costs and limited benefits in long-term quality of life, routine use of Spacer OAR at the MUHC for patients with prostate cancer receiving radiotherapy was not recommended by the authors of the systematic review.	More comprehensive and recent reviews added.
Fagundes M, Rodrigues MA, Olszewski S et al. (2021) Expanding the Utilization of Rectal Spacer Hydrogel for Larger Prostate Glands (>80 cc): Feasibility and Dosimetric Outcomes. Advances in Radiation Oncology, 6, 100651	N=33 patients with localised prostate cancer with larger glands (>80 cm3) treated with intensity modulated radiation therapy (in 15) and proton therapy (PT in 18 patients). Conventional fractionation (CF) to 78 Gy in 39 fractions was used in 16 and moderate hypofractionation EBRT (HF) to 70 Gy in 28 fractions in 17 patients. Rectal hydrogel spacers inserted in all. Median follow-up was 10 months (range, 3-26)	In the CF group, mean rectum (r) V75, 70, 60, 50 was 0.87%, 2.25%, 5.61%, and 10.5%, respectively. For glands >80 to 100 cm3 and >100 cm3 , rV70 was 2.55% and 2%, respectively. In HF patients, mean rV65, 63, 60, and 50 was 1.67%, 2.3%, 3.4%, and 8.6%. For glands >80 to 100 cm3 and >100 cm3 , rV63 was 2% and 2.56%, respectively. Overall, the mean mid gland rectoprostatic hydrogel separation was 9.3 mm (range, 4.7-19.4 mm). All patients tolerated treatment well; no acute grade 2 or higher adverse gastrointestinal events were observed	Larger and more relevant studies included.
Farjam R Mahase, SS, Chen SL et al. (2021) Quantifying the impact of SpaceOAR hydrogel	Comparative case series N=20 prostate cancer patients (10 with and 10 without rectal spacer)	Inter-fractional changes in rectal and bladder dose were quantified in patients who underwent SBRT with/without	Dosimetry study. Larger and longer follow-up

on inter-fractional rectal and bladder dose during 0.35 T MR-guided prostate adaptive radiotherapy. Journal of applied clinical medical physics. 22 (9); 49-58	who had SBRT. Compared SBRT plans.	rectal SpaceOAR hydrogel. Rectal spacer does not eliminate the need for adaptive planning but reduces its necessity.	studies included in table 2.
Fischer-Valuck BW, Chundury A et al (2016). Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: Impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall. Practical Radiation Oncology no pagination.	Secondary analysis of a randomised controlled trial. 149 patients in a prospective randomised trial who had transperineal hydrogel spacer (SpaceOAR system) injection were assessed for hydrogel spacer symmetry with rectal dose reduction and rectal wall infiltration using a semi-qualitative scoring system. All patients had control treatment plans created before spacer injection.	Hydrogel spacer was symmetrically placed at midline for 71 (47.7%) patients at the prostate mid-gland as well as 1 cm superior and inferior to mid-gland. The remaining 78 (50.9%) patients had some level of asymmetry, with only 2 (1.3%) having far lateral distribution (i.e., >2 cm) of hydrogel spacer. All but the most asymmetrical 1.3% had significant rectal dose reduction ($P < .05$). Rectal wall hydrogel spacer infiltration was seen in 9 (6.0%) patients. RWI does not correlate with patient complications.	Spacer distribution and impact of spacer symmetry assessed. Included in HTA, systematic review added.
Folkert MR, Zelefsky MJ, Hannan R et al. (2021) A multi-institutional phase 2 trial of high-dose SAbR for prostate cancer using rectal spacer. Int J Radiation Oncol Biol Phys, Vol. 000, No. 00, pp. 1−9.	Prospective study N=44 men with stage ≤T2c localized grade group 1 to 3 prostate cancer underwent perirectal hydrogel spacer placement, followed by SABR of 45 Gy in 5 fractions. Median follow up 48 months.	Temporary hydrogel spacer placement before high-dose SABR treatment for localized prostate cancer and use of strict dose constraints are associated with a significant reduction in the incidence of rectal ulcer events compared with prior phase 1/2 trial results.	Larger studies included.
Fukumitsu N, Mima M, Demizu Y et al. (2022) Separation Effect and Development of Implantation Technique of Hydrogel Spacer for Prostate Cancers. Practical Radiation Oncology. 12 (3), 226-235.	N=160 patients with prostate cancer No spacer (group 1; n = 30), spacer placed using conventional technique-at the middle of the prostate gland (group 2; n = 100), and spacer placed using new technique-cranial:caudal ratio of 6:4 and close to the prostate gland (group 3; n = 30)	The separation, spacer thickness, and rectal exclusion from the middle to the apex of the prostate and the laterality of the hydrogel spacer affected the reduction in the rectal dose. The rectal dose can be further reduced by implanting a spacer on the caudal and prostate side.	Implantation technique and separation effect.
Gez E, Cytron S et al (2013). Application of an interstitial and biodegradable balloon system for prostate-rectum separation during prostate cancer radiotherapy: a prospective multi-	Case series N=27 patients with localised prostate cancer treated with biodegradable balloon implantation during external beam radiotherapy (EBRT). Follow-up 6 months.	The distance between the prostate and rectum increased 10-fold, from a mean 0.22 ± 0.2 cm to 2.47 ± 0.47 cm. Adverse events included mild pain at the perineal skin and in the anus and acute urinary retention. The implantation of the biodegradable balloon was	Larger studies included.

center study. Radiation Oncology 2013, 8:96.		safe and achieved a significant and constant gap between the prostate and rectum. This separation resulted in an important reduction in the rectal radiation dose.	
Gross A, Yuan J, Spratt D et al (2021) Case Report: Role of an Iodinated Rectal Hydrogel Spacer, SpaceOAR Vu eTM, in the Context of Low-Dose-Rate Prostate Brachytherapy, for Enhanced Post-Operative Contouring to Aid in Accurate Implant Evaluation and Dosimetry Frontiers in Oncology; 11; 810955.	Case series. N=13 patients with prostate cancer (low/ intermediate/high risk) treated with LDR brachytherapy/boost and iodinated hydrogel spacer (SpaceOAR VueTM). Follow-up 3 months.	The mean separation between the prostate and the rectum was 12.2 ± 2.1 mm. A favourable dose coverage was achieved in all. At 1-month follow-up, 54% of the patients experienced grade 2 urinary toxicity, and 46% had grade 0–1 urinary toxicity (urgency and frequency). There was a mean increase of 4.3 points on the International Prostate Symptom Score (IPSS) from baseline. At 3 months, 38.5% maintained grade 2 urinary toxicity, and reported a mean decrease of 4 points in IPSS compared to baseline. At 1-month follow-up, 92% reported no rectal toxicities, with only one patient experiencing grade 1 mild diarrhoea. No rectal toxicities were reported at 3 months.	Larger and longer follow-up studies included.
Giuliani J Fiorica, F (2021) Cost-effectiveness of SpaceOAR system during prostate cancer radiation therapy: Really helpful or excess of expectations?. Brachytherapy. 20 (6); 1341-1342.			Costs not in remit.
Jones S White N, Holt, T et al. (2021) Cost-effectiveness analysis of hydrogel spacer for rectal toxicity reduction in prostate external beam radiotherapy. Journal of medical imaging and radiation oncology. 65 (7); 931-939		The influence of parameter uncertainty currently limits the cost-effectiveness of this intervention in the Australian public health setting. However, a cost variation solution has been demonstrated to improve cost-effectiveness estimates for selected patients and should be examined further.	Costs not in remit.
Guimas V, Quivrin M, Bertaut A et al (2016). Focal or whole-gland salvage prostate brachytherapy with iodine seeds with or without a rectal spacer for postradiotherapy local failure: How best	Retrospective non-randomised comparative study n=18 Intervention: salvage prostate permanent implant (sPPI) with (125) I seed for local failure	The median cumulative dose after EBRT + sPPI was higher in patients treated with whole-gland sPPI than in patients treated with focal sPPI (313.5 Gy2 vs. 174.4 Gy2; p = 0.06 and 258.1 Gy3 vs. 172.6 Gy3; p < 0.01, respectively). The median D0.1cc was	Larger studies included.

to spare the rectum? Brachytherapy 15 (4) 406-411.	after external beam radiation therapy. (10 patients had whole-prostate sPPI, and 8 patients had focal sPPI). In 8 patients, hyaluronic acid (HA) gel was injected into the prostate-rectum space.	significantly lower in patients who had HA gel: 63.3 Gy (29.0-78.3) vs. 83.9 Gy (34.9-180.0) (p = 0.04).Cumulative prostate and rectum biological effective doses were lower with focal sPPI.	
Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. Int J Radiat Oncol Biol Phys. 2017;97(5):976-85.	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73). Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Follow-up 3 years	The 3-year incidence of grade >1 (9.2% vs 2.0%; P=.028) and grade >2 (5.7% vs 0%; P=.012) rectal toxicity favoured the spacer arm. Grade >1 urinary incontinence was also lower in the spacer arm (15% vs 4%; P=.046), with no difference in grade >2 urinary toxicity (7% vs 7%; P=0.7). From 6 months onward, bowel QOL consistently favoured the spacer group (P=.002), with the difference at 3 years (5.8 points; P<0.05) meeting the threshold for a MID. The control group had a 3.9-point greater decline in urinary QOL compared with the spacer group at 3 years (P<0.05) but the difference did not meet the MID threshold. At 3 years, more men in the control group than in the spacer group had experienced a MID decline in bowel QOL (41% vs 14%; P=.002) and urinary QOL (30% vs 17%; P=.04). Furthermore, the control group were also more likely to have experienced large declines (twice the MID) in bowel QOL (21% vs 5%; P=.02) and urinary QOL (23% vs 8%; P=.02).	Included in HTAs, systematic reviews added.
Hamstra DA, Mariados N, Sylvester J, et al. Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: secondary analysis of a phase 3 trial. Pract Radiat Oncol. 2018;8(1):e7-e15.	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73). Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Sexual quality of life measured by the	Hydrogel reduced penile bulb mean dose, maximum dose, and percentage of penile bulb receiving 10 to 30 Gy (all P < .05) with mean dose indirectly correlated with erections sufficient for intercourse at 15 months (= 0.03). Statistically nonsignificant differences favouring spacer for the proportion of men with MID and 2× MID declines in sexual QoL with 53% vs 75% having an 11-point decline (p=0.064) and 41% vs 60% with a 22-point decline (p=0.11). At 3	Included in HTAs, systematic reviews added.

	Expanded Prostate Cancer Index Composite (EPIC). Median follow-up of 37 months.	years, more men potent at baseline and treated with spacer had “erections sufficient for intercourse" (control 37.5% vs spacer 66.7%, p=0.046) as well as statistically higher scores on 7 of 13 items in the sexual domain (all p<0.05). The use of a hydrogel spacer decreased dose to the penile bulb, which was associated with improved erectile function compared with the control group based on patient-reported sexual QoL.	
Hatiboglu G, Pinkawa M et al (2012). Application technique: Placement of a prostate-rectum spacer in men undergoing prostate radiation therapy. BJU International 110:E647-E652.	Case series n=29 patients with prostate cancer Hydrogel injected during radiotherapy	Hydrogel injection resulted in mean (SD) additional prostate – rectum space relative to baseline of 9.87 (5.92) mm. The mean (SD) procedure time was 6.3 (3.2) min. The relative reduction in rectal V70 Gy was 60.6%. There were no unanticipated adverse events.	Larger and longer follow-up studies included.
Hayes, Inc. Absorbable perirectal spacer (SpaceOAR System; Augmenix Inc.) during radiation therapy for prostate cancer. Heath Technology Assessment. HAYES, Inc. 2018.	Heath Technology Assessment		More recent HTAs added.
Fagundes MA, Robison B, Price SG et al. (2015) High-dose rectal sparing with transperineal injection of hydrogel spacer in intensity modulated proton therapy for localized prostate cancer. International Journal of Radiation Oncology Biology Physics.1: E230.	N=10 patients with localized prostate cancer treated with intensity modulated proton therapy and transperineal rectal hydrogel spacer. pre- and post-spacer scans were assessed.	The use of a rectal spacer significantly reduced the amount of rectal volume exposed to high doses of radiation in patients planned with intensity modulated proton therapy. The rectal dose-sparing benefit was achieved without compromising target coverage or bladder dose sparing.	Larger and longer follow-up studies included. Dosimetry study.
Harvey M, Ong WL, Chao M et al. (2022) Comprehensive review of the use of **hydrogel spacer**s prior to radiation therapy for prostate cancer. BJU International.	Review	Hydrogel spacers provide a low-morbidity method to potential reduce rectal toxicity after radiation therapy in men with prostate cancer. Data outlining sexual function and oncological outcomes are limited to date. Future studies, currently being conducted, may provide further clarification of the role of	Review

		hydrogel spacers in prostate cancer management.	
Hedrick SG, Fagundes M, Case S et al. (2017) Validation of rectal sparing throughout the course of proton therapy treatment in prostate cancer patients treated with SpaceOAR((R)). J Appl Clin Med Phys, 18, 82-89.	Case series N=41 patients with low/intermediate prostate cancer Image-guided proton therapy Conventional fractionation (n=27) Hypofractionation (n=14) Follow-up 5 weeks	By extrapolating patient anatomy from 3-4 QACT scans, we have shown that the use of hydrogel in conjunction with our patient diet program and use of stool softeners is effective in achieving consistent rectal sparing in patients undergoing proton therapy. Toxicity not reported.	Larger studies included.
Hedrick SG, Fagundes M, Robison B, et al. A comparison between hydrogel spacer and endorectal balloon: an analysis of intrafraction prostate motion during proton therapy. J Appl Clin Med Phys. 2017;18(2):106-112.	Prospective cohort study N=26 patients with prostate cancer treated with proton therapy and an endorectal balloon (n=10) or a hydrogel spacer (n=16) using orthogonal x-rays acquired before and after each treatment field. Patients from 2 different trials included. Follow-up time not reported.	There was a statistically significant difference in the mean vector shift between ERB (0.06 cm) and GEL (0.09 cm), ($p<0.001$). There was no statistical difference between ERB and GEL for shifts greater than 0.3 cm ($p=0.13$) or greater than 0.5 cm ($p=0.36$). Prostate motion is clinically comparable between an ERB and a hydrogel spacer, and the time dependencies are similar.	Included in HTA report.
Hojjat F, Fritsche-Polanz S et al (2016). Goldmarker and spacer balloon implantation for prostate radiation therapy (RT). European Urology, Supplements (15) 11 e1353-e1355.	Case series n=40 patients with localized prostate cancer. Gold marker and bio-protect-balloon-implanted transperineally during image-guided volumetric arc therapy (VMAT).	Median distance of 1.6 cm between the prostate and the anterior wall of the rectum was obtained. Localisation of the balloon was achieved in 33/40 patients. Implantation well tolerated, no intestinal bleeding, no mucosal injury and no postoperative infection have been observed. Mild perineal foreign body sensation was present, only 2/40 patients reported on moderate symptoms. Acute GI and GU toxicity were very favourable and assessed using the RTOG scale system. In 66% of patients no GI-side effect was seen, while 28% and 6% had grade 1 and 2 toxicity, respectively. GU-symptoms grade 1 were about 66% and 3% grade 2, whereas 31% had no adverse effect. For both, GI and GU, grade 3-5 toxicity was not observed.	Larger studies included.
Hoe V, Yao HH, Huang JG et al. Abscess formation following hydrogel spacer for prostate cancer	Case report Patient with hydrogel spacer during prostate cancer radiotherapy.	Periprostatic abscess is a rare complication of hydrogel spacers in radiotherapy for prostate cancer. We present the case of a 61-year-old man	Adverse event already reported in included studies.

radiotherapy: a rare complication. BMJ Case Rep. 2019 Oct 5;12(10). pii: e229143. doi: 10.1136/bcr-2018-229143		who developed this condition. Abdominopelvis CT scan revealed a 54×35×75 mm collection in the location of the SpaceOAR, for which ultrasound-guided transperineal percutaneous drainage of the periprostatic abscess was performed. The patient remains well with serial CT scans showing near resolution of the collection.	
Hong A, Ischia J, Chao M. (2022) Case Report: Reversal of Hyaluronic Acid Rectal Wall Infiltration with Hyaluronidase. Frontiers in Oncology; 12; 870388	Case report patient with prostate cancer undergoing radiation therapy and rectal spacer insertion (hyaluronic acid gel injected).	The patient was asymptomatic, and a sigmoidoscopy confirmed healthy bowel mucosa. The misinjected hyaluronic acid was successfully treated with targeted injection of hyaluronidase into the rectal wall portion. Follow-up imaging demonstrated rapid dissolution of the hyaluronic acid. no side effects noted.	Larger studies with longer follow-up included.
Hwang ME, Black PJ, Elliston CD, Wolthuis BA, Smith DR, Wu CC, et al. A novel model to correlate hydrogel spacer placement, perirectal space creation, and rectum dosimetry in prostate stereotactic body radiotherapy. Radiation Oncology. 2018;13 (1) (no pagination)(192).	Case series (retrospective) N=20 men with low- and intermediate-risk prostate cancer treated with stereotactic body radiotherapy to 36.25 Gy in 5 fractions underwent hydrogel (SpaceOAR) placement. Median follow up of 14 months	no rectal toxicity >grade 2 was observed. Low grade rectal toxicity was observed in a third of men and resolved. Optimal hydrogel placement occurs at prostate midgland, midline. The novel parameter θ*hydrogel volume describes a large proportion of rectum dosimetric benefit derived from hydrogel placement and can be used to assess the learning curve phenomenon for hydrogel placement.	Larger studies included. analysed the symmetry of hydrogel placement, developed new metric to correlate the effect of hydrogel placement on rectum dosimetry.
Hwang ME, Mayeda M, Liz M, Goode-Marshall B, Gonzalez L, Elliston CD, et al. Stereotactic body radiotherapy with periprostatic hydrogel spacer for localized prostate cancer: Toxicity profile and early oncologic outcomes. Radiation Oncology. 2019;14 (1) (no pagination)(136).	Case series N=50 men with low- or intermediate-risk prostate cancer treated with SBRT (3625 cGy in 5 fractions) with or without androgen deprivation therapy (ADT) also had periprostatic hydrogel spacer (SpaceOAR). Median follow up 20 (range 4–44) months.	Mean prostate-rectum separation achieved with SpaceOAR was 9.6±4 mm at the prostate midgland. No grade ≥ 3 GU or GI toxicity was recorded. During treatment, 30% of men developed new grade 2 GU toxicity (urgency or dysuria). GI toxicity was limited to grade 1 symptoms (16%), 4% of men developed grade 2 symptoms during the first 4 weeks after SBRT. No acute or late rectal toxicity was reported > 1 month after treatment. Periprostatic hydrogel placement followed by prostate SBRT resulted in minimal GI toxicity, and	Larger studies included.

		favourable early oncologic outcomes.	
Hwang ME, Mayeda M, Shaish H, et al. (2021) Dosimetric feasibility of neurovascular bundle-sparing stereotactic body radiotherapy with periprostatic hydrogel spacer for localized prostate cancer to preserve erectile function. Br J Radiol; 94: 20200433.	Case series N= 35 men with low- and intermediate risk prostate cancer underwent rectal hydrogel spacer placement and treated with prostate SBRT (36.25 Gy in 5 fractions).	Neurovascular bundle (NVB) sparing SBRT with rectal hydrogel spacer significantly reduces the volume of NVB treated with high-dose radiation. Rectal spacer contributes to this effect through a dosimetrically meaningful displacement of the NVB.	Nerve sparing treatment planning.
Hutchinson RC, Sundaram V, Folkert M, and Lotan Y (2016). Decision analysis model evaluating the cost of a temporary hydrogel rectal spacer before prostate radiation therapy to reduce the incidence of rectal complications. Urologic Oncology 34 (7) 291-26.	Decision analysis to evaluate the cost effectiveness of a rectal spacer gel (SpaceOAR) for the reduction of rectal toxicity of prostate radiation therapy (RT).	The overall standard management cost for RT was $3,428 vs. $3,946 with rectal spacer for an incremental cost of $518 over 10 years. A 1-way sensitivity analyses showed the breakeven cost of spacer at $2,332 or a breakeven overall risk reduction of 86% at a cost of $2,850. For high-dose SBRT, spacer was immediately cost effective with a savings of $2,640 and breakeven risk reduction at 36%. The use of a rectal spacer for conformal RT results in a marginal cost increase with a significant reduction in rectal toxicity assuming recently published 15 month rectal toxicity reduction is maintained over 10 years. For high-dose SBRT it was cost effective.	Costs not in remit of interventional procedures programme.
Jones RT, Hassan Rezaeian N, Desai NB, et al. (2017) Dosimetric comparison of rectal-sparing capabilities of rectal balloon vs injectable spacer gel in stereotactic body radiation therapy for prostate cancer: lessons learned from prospective trials. Med Dosim. 42(4):341-347.	Prospective cohort study N=72 patients with low- to intermediate risk prostate cancer treated with stereotactic body radiation therapy in combination with rectal balloons (n=36) or absorbable injectable spacer gel (n=36). Patients from 2 different trials included. Follow-up time not reported.	injectable spacer gel was superior based on the maximum dose to the rectum (42.3 vs 46.2 Gy, p<0.001), dose delivered to 33% of the rectal circumference (28 vs 35.1 Gy, p<0.001), and absolute volume of rectum receiving 45 Gy (V45Gy), V40Gy, and V30Gy (0.3 vs 1.7 cc, 1 vs 5.4 cc, and 4.1 vs 9.6 cc, respectively; p<0.001 in all cases). There was no difference between the 2 groups with respect to the V50Gy of the rectum or the dose to 50% of the rectal circumference (p=0.29 and 0.06, respectively). The V18.3Gy of the bladder was significantly larger with the rectal balloon (19.9 vs 14.5 cc,	Included in HTA report added. Dosimetric and volumetric outcomes, comparative costs of balloons and gel out of remit.

		p=0.003). Injectable spacer gel outperformed the rectal balloon in the majority of the examined and relevant dosimetric rectal-sparing parameters.	
Karsh LI, Gross ET, Pieczonka CM, et al. Absorbable hydrogel spacer use in prostate radiotherapy: a comprehensive review of phase 3 clinical trial published data. Urology. 2018;115:39-44.	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73). Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Rectal and urinary adverse events and quality of life measured with the EPIC questionnaire. Median follow-up of 37 months	Spacer application was well tolerated with a 99% technical success rate. The mean additional space created between the prostate and the rectum was just over 1 cm, which allowed significant rectum and penile bulb radiation dose reduction, resulting in less acute pain, lower rates of late rectal toxicity, and improved bowel and urinary QoL scores from 6 months onward. Improvements in sexual QoL were also observed at 37 months in baseline-potent men, with 37.5% of control and 66.7% of spacer men capable of "erections sufficient for intercourse."	Study included in HTAs added.
Kamran SC; McClatchy DM, Pursley J et al. (2022) Characterization of an Iodinated Rectal Spacer for Prostate Photon and Proton Radiation Therapy. Practical radiation oncology; 12 (2); 135-144	Retrospective study N=100 patients with intact prostate cancer treated with photon and proton radiation therapy (n = 50 with iodine spacers and 50 with conventional spacers)	Iodine spacers provide a manifest CT contrast, allowing for delineation on planning CT alone with no MRI necessary. Iodine spacers radiopacity, size, and relative position remained stable over courses of treatment from 28 to 44 fractions. No changes in plan quality or robustness were seen comparing iodine spacers and conventional spacers.	Description of spacers, no clinical outcomes reported.
Khan J, Dahman B, McLaughlin C et al. (2020) Rectal spacing, prostate coverage, and periprocedural outcomes after hydrogel spacer injection during low-dose-rate brachytherapy implantation. Brachytherapy 19 228e233	Case series N= 80 patients with prostate cancer treated with low-dose-rate (LDR) prostate brachytherapy. 40 had bioabsorbable hydrogel rectal spacer injected. Follow-up 1 month.	There were no acute genitourinary or rectal toxicities attributed to the hydrogel spacer. Comparing patients with and without hydrogel, the mean separation between the prostate and rectum was 13.9±5.2 mm vs. 6.5±5.0 mm ($p<0.0001$), respectively. The adjusted mean dose to 1 cc, 2 cc, and 5 cc of the rectum relative to prescription dose was decreased by 32% ($p<0.01$), 26% ($p<0.01$), and 17% ($p< 0.01$), respectively. There were no statistically significant differences in prostate coverage: mean V100 (92% vs. 91%), V150 (45% vs.	Larger studies included.

		48%), and D90 (106% vs. 106%), respectively. At 1 month follow-up, grade 1 rectal toxicity was 12.5% vs. 17.5% (p 5 0.35). No patients developed Grade 2 rectal toxicity with hydrogel, although one did without.	
King RB, Osman SO, Fairmichael C, Irvine DM, Lyons CA, Ravi A, et al. Efficacy of a rectal spacer with prostate SABR-first UK experience. Br J Radiol. 2018;91(1083):20170672	Case series N=6 patients with prostate cancer treated with SABR -VMAT and rectal hydrogel spacer (SpaceOAR)	Substantial improvements in rectal dose metrics were observed in post-spacer plans, e.g. rectal volume receiving 36 Gy reduced by ≥42% for all patients. Median NTCP for Grade 2 + rectal bleeding significantly decreased from 4.9 to 0.8% with the use of a rectal spacer (p=0.031). The spacer resulted in clinically and statistically significant reduction in rectal doses for all patients.	Larger studies included.
Kouloulias V, Kalogeropoulos T et al (2013). Feasibility and radiation induced toxicity regarding the first application of transperineal implementation of biocompatible balloon for high dose radiotherapy in patients with prostate carcinoma. Radiation Oncology.8 (1) (no pagination).	Case series n=15 patients with prostate carcinoma treated with high dose external 3DCRT (76-78 Gy in 38-39 daily fractions) combined with injection of biodegradable balloon (ProSpace) Follow-up: 3 months	The acute toxicities were as follows: grade 1 GI toxicity in 2 patients and GU toxicity -3 patients with grade 1 nocturia, 4 patients with grade 1 frequency, 2 patients with grade 1 and 2 patients with grade 2 dysuria. The mean score of rectal toxicity according to S-RS score was 1.8 ±0.6. The mean VAS score related to ProSpace was 1.4±0.5. Erectile dysfunction was unchanged. The ProSpace was found stable in sequential CT scans during irradiation.	Larger and longer follow-up studies included.
Kobayashi H, Eriguchi T, Tanaka T et al. (2021) Distribution analysis of hydrogel spacer and evaluation of rectal dose reduction in Japanese prostate cancer patients undergoing stereotactic body radiation therapy. International Journal of Clinical Oncology. 26:736–743.	Retrospective analysis 70 patients with low and intermediate-risk prostate cancer treated with SBRT. Hydrogel spacers were inserted in 53 patients. Follow-up 6 months.	Hydrogel spacers could contribute to rectal dose reduction, especially in high dose regions, by creating a prostate–rectum distance. There was no grade≥3 toxicity observed, but grade 2 toxicity of GU and GI occurred in 17.1% and 1.4% of the patients, respectively.	Larger studies included.
Kundu P, Lin EY, Yoon SM (2022) Rectal Radiation Dose and Clinical Outcomes in Prostate Cancer Patients Treated With Stereotactic Body	Retrospective case series 92 patients with prostate cancer treated with SBRT (51 hydrogel and 41 without hydrogel)	Hydrogel reduces rectal radiation dose in patients receiving prostate SBRT and is associated with a decreased rate of acute GI toxicity. hydrogel group experienced significantly less acute overall	Larger studies with longer follow-up included.

Radiation Therapy With and Without Hydrogel. Frontiers in Oncology. 12; 853246	Median follow-up of 14.8 months.	GI toxicity (16% hydrogel vs. 28% non-hydrogel, p=0.006), while the difference in late GI toxicity trended lower with hydrogel but was not statistically significant (4% hydrogel vs. 10% non-hydrogel, p=0.219).	
Juneja P, Kneebone A (2015). Prostate motion during radiotherapy of prostate cancer patients with and without application of a hydrogel spacer: a comparative study. Radiation Oncology 10: 215.	Prospective cohort study (data from 2 clinical trials) n=26 patients with prostate cancer treated with radiotherapy (12 with hydrogel and 14 without hydrogel). Type of radiotherapy not specified. Follow-up time not reported.	The average of the mean motion during the treatment for patients with and without hydrogel was 1.5 (+/-0.8 mm) and 1.1 (+/-0.9 mm) respectively ($p<0.05$). The average time of motion >3 mm for patients with and without hydrogel was 7.7 % (+/-1.1 %) and 4.5 % (+/-0.9 %) respectively ($p>0.05$). The hydrogel age, fraction number and treatment time were found to have no effect (R (2) <0.05) on the prostate motion. This result confirms that the addition of a spacer does not negate the need for intrafraction motion management if clinically indicated.	Study evaluating prostate position. Included in HTA added.
Lawrie TA, Green JT, Beresford M, Wedlake L, Burden S, Davidson SE, Lal S, Henson CC, Andreyev HJN. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD012529. DOI: 10.1002/14651858.CD012529.pub2.	Cochrane review N=92 studies (RCTs) included. (0nly 2 studies were related to this overview). n= 229 and 69 men undergoing RT for prostate cancer. transperitoneal hydrogel spacer/injection versus no spacer Prostate cancer treatment: all types of pelvic radiation therapy eligible; IG-IMRT (79.2 Gy in 1.8-Gy fractions) in Mariados 2015 and brachytherapy in Prada 2009. Follow-up: up to 15 months in Mariados 2015 and a median of 26 months in Prada 2009.	“IMRT may be better than 3DCRT in terms of GI toxicity, but the evidence to support this is uncertain”. “Low-certainty evidence on balloon and hydrogel spacers suggests that these interventions for prostate cancer RT may make little or no difference to GI outcomes”.	Only 2 of these studies were eligible for analysis within this review. More comprehensive reviews added.
Haute Autorite de Sante. SpaceOAR, espaceur synthétique résorbable en hydrogel.: HAS; 2020.			French article
Kong VC, Dang J, Li W et al. (2022) Dosimetric	Retrospective comparative study N=25	Despite the presence of large interfraction organ volumes	Dosimetric study.

comparison of MR-guided adaptive IMRT versus 3DOF-VMAT for prostate stereotactic radiotherapy. Technical Innovations and Patient Support in Radiation Oncology; 21; 64-70.	patients with prostate cancer treated with High Dose Rate (HDR) brachytherapy followed by SBRT (15 with hydrogel spacer).	changes, clinically acceptable dose was delivered to the prostate by both systems. A-IMRT facilitated a greater rectal sparing from the high dose region than 3DOF-VMAT. Further reduction in rectal dose could be achieved by hydrogel spacer to displace the rectum, or by adaptation delivered by VMAT.	
Lehrich BM, Moyses HM, Ravera J et al. (2019) Five-year results of post-prostatectomy patients administered a hydrogel rectal spacer implant in conjunction with dose escalated external beam radiation therapy. Journal of Radiation Oncology (2019) 8:31–38.	Case series N= 21 patients who underwent radical prostatectomy and received high dose (> 72 Gy) radiation therapy with an absorbable polyethylene glycol (PEG) rectal spacer implant. Mean follow-up time was 59 months (SD 12, range 40–97).	Gastrointestinal [GI] toxicities for acute, 3 months, and after 6 months are as follows: grade 0 (57%, 86%, 86%), grade 1 (43%, 14%, 14%), and grade 2 (0%, 0%, 5%). Our genitourinary [GU] toxicities for acute, 3 months, and after 6 months are as follows: grade 0 (43%, 48%, 62%), grade 1 (48%, 43%, 24%), and grade 2 (10%, 5%, 14%). There were no late grade 3 GI/GU toxicities. The 5-year overall biochemical-relapse free survival rate was 62.2% (95% CI 42.6–90.9%, SE 12.0%).	Large studies included.
Lin YH, Loon W, Tacey M et al. (2021) Impact of hydrogel and hyaluronic acid rectal spacer on rectal dosimetry and toxicity in low-dose-rate prostate brachytherapy: a multi-institutional analysis of patients' outcomes. Journal of Contemporary Brachytherapy. 13 (6); 605-614	Retrospective comparative case series N=70 men with prostate cancer treated with iodine-125 LDR brachytherapy (28 with or 42 without hydrogel spacer or hyaluronic acid spacer). Median follow-up was 23.5 months.	The median prostate-rectal separation with spacer at mid prostate was 10 mm (IQR, 8-11.5 mm). There were no post-operative complications. There was significantly reduced rectal dosimetry in spacer-group versus non-spacer group; the median RV100 was 0.0 cc (IQR, 0.0-0.0 cc) vs. 0.4 cc (IQR, 0.1-1.1 cc) ($p < 0.001$), respectively. There were significantly less grade 1 acute and late GI toxicities in spacer-group when compared to non-spacer group (0% vs. 24%, p=0.004 for acute GI toxicity; 4% vs. 33%, p=0.003 for late GI toxicity). There were no reported acute or late grade 2 or above GI toxicities.	Similar studies included.
Latorzeff I, Bruguiere E, Bogart E et al. (2021) Use of a Biodegradable, Contrast-Filled Rectal Spacer Balloon in Intensity-Modulated Radiotherapy for Intermediate-Risk Prostate Cancer Patients: Dosimetric	Prospective case series n=24 patients with intermediate-risk prostate cancer had mage-guided, IMRT(in 20) or VMAT (in 3) with a biodegradable rectal spacer balloon. Follow-up 24 months.	86% of the implantation procedures were easy. Dosimetric gains associated with spacer implantation were highly significant ($p<0.001$). For the rectum, the median relative gain was 15.4% for D20cc to 91.4% for V70 Gy (%). 15 patients (62%) experienced an acute grade 1 adverse event (AE), 8 (33%)	Similar studies on balloon spacers included.

Gains in the BioPro-RCMI-1505 Study Frontiers in Oncology; 11; 701998		experienced a late grade 1 AE, 1 (4.2%) experienced an acute grade 2 AE, and 3 experienced a late grade 2 AE. No grade 3 AEs were reported. Quality of life was good at baseline) and did not worsen during RT and up to 24 months.	
Levy Y, Paz A et al (2009). Biodegradable inflatable balloon for reducing radiation adverse effects in prostate cancer. J Biomed Mater Res B Appl Biomater 91: 855-867.		The proper functionality of the insertion-mounting device as well as the balloon capability to retain its inflated form during patients' radiation session was demonstrated both in vitro and in vivo.	Preclinical study with in-vitro and in-vivo data.
Levy JF, Khairnar R, Louie AV et al. (2019) Evaluating the Cost-Effectiveness of Hydrogel Rectal Spacer in Prostate Cancer Radiation Therapy. Practical Radiation Oncology (2019) 9, e172-e179	Cost effectiveness analysis patients with prostate cancer undergoing external beam RT (EBRT alone versus EBRT + hydrogel rectal spacer [HRS]).	The per-patient 5-year incremental cost for spacers administered in a hospital outpatient setting was $3578, and the incremental effectiveness was 0.0371 QALYs. The incremental cost-effectiveness ratio was $96,440/QALY for patients undergoing HRS insertion in a hospital and $39,286/QALY for patients undergoing HRS insertion in an ambulatory facility. Based on the current Medicare Physician Fee Schedule, HRS is cost-effective at a willingness to pay threshold of $100,000. These results contain uncertainty, suggesting more evidence is needed.	Costs not in remit of interventional procedures programme.
Liu H, Borden L, Wiant D, Sintay B, Hayes L, Manning M. Proposed hydrogel-implant quality score and a matched-pair study for prostate radiation therapy. Pract Radiat Oncol. 2020;10(3):202-208. doi: http://dx.doi.org/10.1016/j.prro.2020.02.006	Matched paired study (retrospective) LDR BT +/- EBRT N= 81 patients with prostate cancer had SpaceOAR implantation 21 had EBRT only, 7 had combined EBRT and Iodine-125 LDR, and 53 had Iodine-125 LDR only.	The average HIQS was 77 ± 10.8 (range, 49-97). Rectal anatomic distortions were seen in 17 cases. Significant rectal dose reductions between intraoperative and postoperative plans were found for SpaceOAR patients compared with non-SpaceOAR patients (25.1 Gy vs -5.0 Gy for D2cc and 65.7 Gy vs 13.0 for D0.1cc). Additional rectal dose reductions (8.4 Gy for D2cc and 12.7 Gy for D0.1cc) were found for patients without rectal distortion when SpaceOAR was used.	Included in systematic review.

Mahal BA, Ziehr DR, Hyatt AS et al. (2014) Use of a rectal spacer with low-dose-rate brachytherapy for treatment of prostate cancer in previously irradiated patients: Initial experience and short-term results. Brachytherapy, 13, 442-9.	Case series N=11 patients with prostate cancer and prior radiotherapy received (125)I brachytherapy after placement of 10cc of a diluted hydrogel spacer between the prostate and rectum. Follow-up median 15.7 months	Spacing was achieved in 8 of the 11 (73%) patients but was not possible in 3 owing to fibrosis and adhesions. The median space between the prostate and rectum was 10.9mm (prior EBRT) vs. 7.7mm (prior brachytherapy), p=0.048. One patient developed a prostato-rectal fistula requiring a diverting colostomy. The 16-month estimate of late Grade 3 or 4 gastrointestinal or genitourinary toxicity was 26%. One patient developed lymph node-positive recurrence. The 16-month prostate-specific antigen failure-free survival rate was 89%.	Included in systematic review added.
Mazzola R, Sicignano G, Cuccia F et al. (2021) Impact of hydrogel peri-rectal spacer insertion on seminal vesicles intrafraction motion during 1.5 T-MRI-guided adaptive stereotactic body radiotherapy for localized prostate cancer. The British journal of radiology; 94 (1126); 20210521	Comparative case series n=10 patients with prostate cancer had MRI guided SBRT (5 had hydrogel spacer and 5 did not).	A favourable impact of the hydrogel-spacer on seminal vesicles motion was observed only in cranio-caudal translational shifts, although not clinically significant. Further studies are required to fully investigate the potential contribution of this device on vesicles motion.	Intrafraction motion assessed.
Mark EH, Paul JB, Carl DE et al. (2018) A novel model to correlate hydrogel spacer placement, perirectal space creation, and rectum dosimetry in prostate stereotactic body radiotherapy. Radiation oncology (London, England), 13, 192.	Case series N= 20 men with low- and intermediate-risk prostate cancer underwent hydrogel placement. Median follow up of 14 months	no rectal toxicity >grade 2 was observed. Low grade rectal toxicity was observed in a third of men and resolved within 1 month of SBRT. Men who had these symptoms had higher rD_{max} 1 cc and smaller θ*hydrogel volume measurements	Larger studies included.
Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity	Randomised controlled trial N=222 men with low-risk or intermediate-risk prostate cancer Randomised 2:1 to spacer hydrogel (n=149) or control (n=73).	Spacer application was rated as “easy” or “very easy” 98.7% of the time, with a 99% hydrogel placement success rate. Perirectal spaces were 12.6 ± 3.9 mm and 1.6 ± 2.0 mm in the spacer and control groups, respectively. There were no device-related adverse events, rectal perforations, serious bleeding, or infections within either	Included in HTAs and systematic reviews added.

modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2015;92(5):971-7.	Radiation treatment received: G-IMRT 79.2 Gy in 1.8-Gy fractions Follow-up 15 months.	group. Pre-to postspacer plans had a significant reduction in mean rectal V70 (12.4% to 3.3%, p<0.001). Overall acute rectal adverse event rates were similar between groups, with fewer spacer patients experiencing rectal pain (PZ.02). A significant reduction in late (3-15 months) rectal toxicity severity in the spacer group was observed (PZ.04), with a 2.0% and 7.0% late rectal toxicity incidence in the spacer and control groups, respectively. There was no late rectal toxicity greater than grade 1 in the spacer group. At 15 months 11.6% and 21.4% of spacer and control patients, respectively, experienced 10-point declines in bowel quality of life. MRI scans at 12 months verified spacer absorption.	
Manabe Y, Hashimoto S, Mukouyama H et al. (2021) Stereotactic body radiotherapy using a hydrogel spacer for localized prostate cancer: A dosimetric comparison between tomotherapy with the newly-developed tumor-tracking system and cyberknife. Journal of applied clinical medical physics. 22 (10); 66-72	Comparative case series N=20 patients with localised prostate cancer using a hydrogel spacer and had SBRT. 10 tomotherapy and 10 cyberknife SBRT plans were compared.	The tomotherapy plans were superior to the cyberknife plans for the rectum (V80% = 0.4 vs. 1.0 ml, p<0.001; D1ml = 26.4 vs. 29.0 Gy, p=0.013). Results suggested that tomotherapy with the tumour-tracking system has reasonable potential for SBRT for localized prostate cancer using a hydrogel spacer.	Dosimetry study. Larger and longer follow-up studies included in table 2.
Mathur M, Asch D & Israel G (2022). Polyethylene glycol-based gels for treatment of prostate cancer: pictorial review of normal placement and complications. *Abdom Radiol*.	Review	Polyethylene Glycol-based gels are the commonly used rectal spacers. Given their widespread use and the relative paucity of radiology literature, radiologist should recognize both the normal and abnormal placement of these polyethylene glycol-based rectal spacers, particularly they may be associated with suboptimal therapy and/or complications.	Review
Morita M, Fukagai T, Hirayama K, Yamatoya J, Noguchi T, Igarashi A, et al. (2019) Placement of SpaceOAR hydrogel spacer for prostate cancer patients treated	Case series N=100 patients with prostate cancer undergoing iodine-125 low-dose-rate brachytherapy and,	No complications were found during either the intraoperative or perioperative periods. The mean displacement distance of 11.64 mm was created, the mean value before spacer placement was 0.28 mm (P < 0.0001). The change of the	Included in systematic review added.

with iodine-125 low-dose-rate brachytherapy. International Journal of Urology. 27, 1, 60-66.	SpaceOAR hydrogel spacer was placed. Post-plan dosimetric data were compared with 200 patients treated without a spacer. Follow-up not reported.	prostate diameters showed a positive increase in all directions, with no significant negative change in any one direction. Regarding the change in distance between pubic symphysis and the prostate, no significant shortening trend was observed between the two groups (p=0.14). Whereas the dosimetric parameters showed means of 0.001 and 0.026 cc for RV150 and RV100 in the spacer group, they were 0.025 and 0.318 cc, respectively, in the non-spacer group, showing a significant decrease in both parameters (p<0.001).	
Melchert C, Gez E et al (2013). Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: results of a virtual planning investigation based on the pre and post-implant imaging data of an international multicenter study. Radiother Oncolo 106:210-214.	Case series n=26 patients with localized prostate cancer Interstitial inflatable and biodegradable balloon with radiotherapy (3D conformal external beam radiation treatment or IMRT). Follow-up; post implant CT imaging.	The dorsal prostate–ventral rectal wall separation resulted in an average reduction of the rectal V70% by 55.3% (±16.8%), V80% by 64.0% (±17.7%), V90% by 72.0% (±17.1%), and V100% by 82.3% (±24.1%). In parallel, rectal D2 ml and D0.1 ml were reduced by 15.8% (±11.4%) and 3.9% (±6.4%) respectively.	Study by same group reporting clinical and dosimetric outcomes included I systematic review added.
Muller AC, Mischinger J et al (2016). Interdisciplinary consensus statement on indication and application of a hydrogel spacer for prostate radiotherapy based on experience in more than 250 patients. Radiology and Oncology (50) 3 329-336.	Interdisciplinary meeting to develop consensus statement on hydrogel injections (SpaceOAR) in prostate cancer patients before dose-escalated radiotherapy.	A consensus was reached on the application of a hydrogel spacer. Current experience demonstrated feasibility, which could promote initiation of this method in more centres to reduce radiation-related gastrointestinal toxicity of dose-escalated IGRT. However, a very low rate of a potential serious adverse event could not be excluded. Therefore, the application should carefully be discussed with the patient and be balanced against potential benefits.	Interdisciplinary meeting to develop consensus statement.
Navaratnam A, Cumsky J, Abdul-Muhsin H et al. Assessment of polyethylene glycol hydrogel spacer and its effect on rectal radiation dose in prostate cancer patients receiving proton beam radiation	Retrospective cohort study N= 72 patients with prostate cancer (T1, T2, T3) EBRT-PBT-total dose 79.2 1.8 Gy per fraction	There was a 42.2% reduction in rectal dosing (mL3 rectum) in hydrogel patients (p<0.001). Increasing midline sagittal lift resulted in a greater mitigation of total rectal dose (p=0.031). The degree of prostate surface area coverage on coronal plane did not correlate with further reductions in rectal	Included in systematic review added.

therapy. Adv Radiat Oncol 2019; 5: 92–100.	51 with hydrogel spacers versus 21 without spacer Dose volume V70, , V75 Follow-up 9.5 months.	radiation dose (p=0.673). Patients who had PEG hydrogels placed reported more rectal side effects during treatment compared with those patients who did not (35.3% vs 9.5%, p =0.061). At median 9.5-month follow-up, there was no difference in reporting of grade >2 rectal toxicity between the 2 groups (7.7% vs 7.1%, p=0.145).	
Nehlsen AD, Sindhu KK, Moshier E et al. (2021). The impact of a rectal hydrogel spacer on dosimetric and toxicity outcomes among patients undergoing combination therapy with external beam radiotherapy and low-dose-rate. brachytherapy. Brachytherapy 20, 296-301.	Retrospective analysis N=168 patients with intermediate or high risk prostate cancer with a hydrogel spacer (n=22) or without a hydrogel spacer (n=146) prior external beam radiotherapy and low-dose-rate brachytherapy. Spacer group follow-up 9 months.	LDR brachytherapy appears feasible after the placement of a rectal hydrogel spacer. While there was a significantly reduced $V100_{rectum}$ among patients who had received a hydrogel spacer, there was no statistically significant difference in patients achieving a $D90_{prostate}$ of >100 Gy. Although there was no difference appreciated in QOL scores, the length of follow-up was limited in the rectal-spacer group.	Larger studies included.
Newman NB, Rajkumar, A, Cleary RK et al. (2021) Patient Reported Quality of Life Outcomes After Definitive Radiation Therapy With Absorbable Spacer Hydrogel for Prostate Cancer. Advances in Radiation Oncology; 6 (6); 100755	Prospective case series N=59 patients with low risk or favourable-intermediate risk localized prostate cancer had SBRT/ LDR brachytherapy, conventionally fractionated RT, or moderately hypofractionated RT with hydrogel spacer. Median follow-up 366 days.	There were no grade 3 toxicities. There were no significant changes in the American urology association symptom index (AUA-SI) score (p=0.69) compared with baseline, nor was there any change in Expanded Prostate Cancer Index Composite (EPIC-26) domain scores (p=0.19). There were no significant associations between AUA scores and EPIC-26 scores and the dose to the rectum, bladder, or urethra with the exception being dose to the 2 mL rectum correlated with decline in EPIC-26 rectal score (beta, -0.002; p=0.006). Patient-reported declines in bowel domains were less than previously reported data.	Larger and longer follow-up studies included.
SpaceOAR® perirectal spacing system for prostate cancer radiation. (December 2014) Technology Alert. National Institute for Health Research (NIHR) Horizon Scanning Centre.	Technology alert	This technology is predicted to have an impact on the following domains of the NHS Outcomes Framework: enhancing quality of life for people with long-term conditions; ensuring that people have a positive experience of care, treating and caring for people in a safe	More comprehensive and recent assessments added.

		environment; and protecting them from avoidable harm. If clinical and cost-effectiveness can be demonstrated, the SpaceOAR® system may offer an additional option for patients requiring prostate cancer radiation therapy.	
Nguyen PL, Devlin PM et al (2013). High-dose-rate brachytherapy for prostate cancer in a previously radiated patient with polyethylene glycol hydrogel spacing to reduce rectal dose: Case report and review of the literature. Brachytherapy.12 (1) 77-83.	Case report n=1 high risk prostate cancer patient previously irradiated. Hydrogel spacer during high dose rate brachytherapy.	The spacer allowed the rectal dose constraint goals to be easily met. Injecting an absorbable polyethylene glycol hydrogel to separate the prostate and rectum appears to be associated with decreased maximum and mean rectal doses and may have particular utility in previously irradiated patients.	Larger and longer follow-up studies included.
Noyes WR, Hosford CC et al (2012). Human collagen injections to reduce rectal dose during radiotherapy. International Journal of Radiation Oncology Biology Physics. 82: 1918-1922.	Case series N=11 patients with localised prostate cancer Injection of human collagen during IMRT (dose of 75.6 Gy in 42 fractions) Follow-up 12 months	The injection of human collagen in the outpatient setting was well tolerated. The mean separation between the prostate and anterior rectum was 12.7 mm. The mean reduction in dose to the anterior rectal wall was 50%. All men denied any rectal symptoms during the study.	Included in systematic review added.
Ogita M, Yamashita H, Nozawa Y et al. (2021) Phase II study of stereotactic body radiotherapy with hydrogel spacer for prostate cancer: acute toxicity and propensity score-matched comparison. Radiat Oncol.16:107, pp 1-11 Trial registration: UMIN-CTR, UMIN000026213	Case series N=40 patients with prostate cancer treated with SBRT (36.25 Gy in 5 fractions with volumetric modulated arc therapy) in combination with a hydrogel spacer.	Grade 2 acute GI and GU toxicity occurred in 7 (18%) and 17 (44%) patients. The EPIC bowel and urinary summary score declined from the baseline to the first month ($p<0.01$, $p=0.04$). For propensity score-matched analyses, no significant differences in acute GI and GU toxicity were observed between the two groups. The EPIC bowel summary score was significantly better in the spacer group at 1 month (82.2 in the spacer group and 68.5 in the control group). SBRT with a hydrogel spacer had the dosimetric benefits of reducing the rectal doses, did not reduce physician-assessed acute toxicity, but it improved patient-reported acute bowel toxicity.	Larger studies included.
Ogita M, Yamashita H, Sawayanagi S et al. (2020) Efficacy of a hydrogel spacer in	Case series N=39 patients who received stereotactic	Among 39 patients, 35 (90%), 19 (49%) and 13 (33%) and 38 (97%), 38 (97%) and 34 (87%) patients before and after the	Larger studies included.

three-dimensional conformal radiation therapy for prostate cancer. Japanese Journal of Clinical Oncology, 50(3)303–309.	body radiotherapy for prostate cancer inserted with a hydrogel spacer and underwent computed tomography scans before and after spacer insertion. 3D-CRT plans according to NCCN classification, low-, intermediate- and high-risk, were made. Dose constraints for rectum and bladder were V70 Gy ≤ 15%, V65 Gy ≤ 30% and V40 Gy ≤ 60%.	spacer insertion fulfilled rectum dose constraints for low-, intermediate- and high-risk plans, respectively. A hydrogel spacer significantly reduced rectum dose and improved the rectum dose constraints fulfilment rate in intermediate ($p<0.01$) and high ($p<0.01$), but no difference was found in low-risk 3D-CRT plan ($P = 0.25$). Although IMRT is the standard treatment, 3D-CRT using a hydrogel spacer may be a treatment option.	
Osman SOS; Fairmichael C, Whitten G et al. (2022) Simultaneous integrated boost (SIB) to dominant intra-prostatic lesions during extreme hypofractionation for prostate cancer: the impact of rectal spacers. Radiation oncology. 17 (1); 38	Case series N=12 patients with unfavourable intermediate or high risk prostate cancer treated with 5-fraction stereotactic ablative radiotherapy (SABR) volumetric modulated arc therapy (VMAT) 40 Gy or boosting up to 50 Gy in dominant intraprostatic lesions. Pre and post insertion plans assessed.	Compared to plans before spacer insertion, higher dose were achieved with spacer in situ for 25% of the patients. Moreover, significant reduction in rectal dose and better target coverage were also achieved for all patients with spacers in situ.	Dosimetry study. Larger studies with longer follow up included.
Padmanabhan R, Pinkawa M, Song DY. Hydrogel spacers in prostate radiotherapy: a promising approach to decrease rectal toxicity. Future Oncol. (2017) 13(29), 2697–2708	Review	Strategies for reducing dose to rectum include endorectal balloons as well as injection of rectal spacers like hydrogels. Early clinical studies with hydrogels have shown favourable outcomes. A low incidence of major procedural adverse effects with hydrogel use has been reported and it is well tolerated by patients. Hydrogel holds promise in establishing itself as an adjunct to standard of care in prostate radiation.	Review
Payne HA, Jain S. Peedell C et al. (2022) Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK. BMJ Open; 12 (7); e060506	Delphi study 6 clinical oncologists and 1 urologist from across the UK participated.	There is agreement that patients with prostate cancer undergoing radical radiation therapy have the potential to benefit from **hydrogel spacer**s. Currently, patients who could potentially benefit can access **hydrogel spacer**s. Implementation of the consensus recommendations would help prioritise access to rectal spacers for patients in the UK.	Consensus on patient prioritisation for hydrogel spacer use during radiotherapy.

Pepe P, Tamburo M, Pennisi M et al. (2021) Clinical Outcomes of Hydrogel Spacer Injection Space OAR in Men Submitted to Hypofractionated Radiotherapy for Prostate Cancer. In vivo (Athens, Greece); 35 (6); 3385-3389.	Case series N=32 patients with localized prostate cancer underwent hydrogel spacer (SpaceOAR) before hypofractionated radiotherapy. Median follow up 15 months	PSA levels was 0.52 nanograms/ml; 28.1% vs. 78.1% patients had GI vs. GU Grade 0 acute toxicity and 93.7% vs. 0% had GI vs. GU Grade 0 late toxicity. Furthermore, 88.1% of patients kept pretreatment sexual potency. The use of the hydrogel Spacer OAR before HRT is useful for reducing acute and late GU and GI toxicities.	Larger studies with longer follow-up included.
Patel AK, Houser C, Benoit R et al. (2020) Acute patient-reported bowel quality of life and rectal bleeding with the combination of prostate external beam radiation, low-dose-rate brachytherapy boost, and SpaceOAR. Brachytherapy 19, 477-483.	Retrospective review N=69 patients with prostate cancer treated with EBRT (45 Gy), cesium-131 LDR-BT (85 Gy), and SpaceOAR 3 months follow-up	With combination EBRT, LDR-BT, and SpaceOAR, bowel QOL returned to the baseline 3 months after LDR-BT. Clinically significant rectal bleeding was !5%. Further follow-up will confirm if low acute rectal toxicity translates to reduced late toxicity	Larger studies included.
Paetkau O, Gagne IM, Pai HH et al. (2019) Maximizing rectal dose sparing with hydrogel: A retrospective planning study. J Appl Clin Med Phys; 20:4: 91–98.	Retrospective study N= 13 prostate cancer patients implanted with 10 cc of SpaceOAR hydrogel.	Overall, treatment plans using the RW optimization structure offered the lowest rectal dose while VMAT treatment technique offered the lowest bladder and penile bulb dose.	Treatment planning study.
Pietro P, Maria T, Paolo P et al. (2022) Erectile dysfunction following hydrogel injection and hypofractionated radiotherapy for prostate cancer: Our experience in 56 cases. Archivio Italiano di Urologia e Andrologia 2022; 94, 2	N=56 patients with cT1c PCa were treated by HRT directed to the prostate and seminal vesicle. Follow-up 18 months	The use of hydrogel injection and intraprostatic fiducials followed by HRT allowed pre-treatment sexual potency in 62.5% of the cases.	Larger studies with longer follow-up included.
Pinkawa M, Bornemann C et al (2013). Treatment planning after hydrogel injection during radiotherapy of prostate cancer. Strahlentherapie und Onkologie.189 (9) 796-800.	Case study n=3 injection of 10 ml hydrogel in prostate cancer patients during IMRT.	Treatment planning based on imaging shortly after hydrogel injection overestimates the actual hydrogel volume during the treatment as a result of not-yet-absorbed saline solution and air bubbles.	Imaging for treatment planning study.
Pinkawa M, Piroth MD et al (2013). Spacer stability and prostate	Comparative case series n=15 prostate cancer patients with 10ml	Mean volume of the hydrogel increased slightly (17%; p< 0.01), in 4 of 15 patients >2	Study evaluating prostate position variability and

position variability during radiotherapy for prostate cancer applying a hydrogel to protect the rectal wall. Radiotherapy and Oncology.106 (2) 220-224.	hydrogen spacer injection (SpaceOAR) (G1) versus 30 patients without a spacer (g2) during radiotherapy Follow-up: 12 weeks	cm. The average displacement of the hydrogel centre of mass was 0.6 mm (87% < 2.2 mm), -0.6 mm (100% < 2.2 mm) and 1.4 mm (87% < 4.3 mm) in the x-, y- and z-axes (not significant). The average distance between prostate and anterior rectal wall before/at the end of radiotherapy was 1.6 cm/1.5 cm, 1.2 cm/1.3 cm and 1.0 cm/1.1 cm at the level of the base, middle and apex (G1). Prostate position variations were similar with or without hydrogel but significant systematic posterior displacements were only found in those without hydrogel.	spacer stability. Larger and longer follow-up studies.
Pinkawa, M (2015). Current role of spacers for prostate cancer radiotherapy. World Journal of Clinical Oncology 6 (6) 189-193.	General review.	Several studies have shown well tolerated injection procedures and treatments. Apart from considerable reduction of rectal irradiation, a prospective randomised trial demonstrated a reduction of rectal toxicity after hydrogel injection in men having prostate image-guided intensity-modulated radiation therapy.	General review.
Pinkawa M, Piroth MD et al (2012). Quality of life after intensity-modulated radiotherapy for prostate cancer with a hydrogel spacer Matched-pair analysis. Strahlentherapie und Onkologie.188 (10) 917-925.	Case –control study (matched pair analysis) n= 28 prostate cancer patients in each sub-group. Dose in spacer subgroup was 78 Gy in 2 Gy fractions compared with 2 matched-pair subgroups (treated without spacer): 3D conformal 70.2 Gy in 1.8 Gy fractions (3DCRT) and intensity-modulated radiotherapy (IMRT) 76 Gy in 2 Gy fractions.	Bowel bother scores were only significantly different in comparison to baseline levels in the spacer subgroup. The percentage of patients reporting moderate/big bother with specific symptoms did not increase for any item (urgency, frequency, diarrhoea, incontinence, bloody stools, pain). Moderate bowel quality-of-life changes can be expected during radiotherapy irrespective of spacer application or total dose.	Study evaluating quality of life. Larger and longer follow-up studies included.
Pinkawa M, Escobar Corral N et al (2011). Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. Radiotherapy and Oncology.100 (3) 436-441.	Case series n=18 patients with prostate cancer. Injection of a spacer gel (10 ml SpaceOAR™) done and 3D CRT and IMRT treatment plans used (78 Gy in 39 fractions). Follow-up: after injection	The injection of a spacer gel between the prostate and anterior rectal wall is associated with considerably lower doses to the rectum and consequentially lower NTCP values irrespective of the radiotherapy technique. Mean rectal V70 Gy of 14.4% on preimplantation scans compared with 6.1% on post implantation scans reported. A similar rectal V70Gy reduction	Dosimetric study. Larger and longer follow-up studies included.

		was reported in IMRT plans (pre-implantation 17.2%, post implant 7.2%). The spacer had no impact on the doses delivered to the PTV, bladder and femoral heads. 94% of IMRT plans met planning constraints compared with only 67% of 3D-CRT plans despite presence of spacers.	
Pinkawa M, Schubert C et al (2015). Application of a hydrogel spacer for postoperative salvage radiotherapy of prostate cancer. Strahlentherapie und Onkologie 191 (4) 375-379.	Case report n=1 prostate cancer patient presented 20 years after radical prostatectomy with a digitally palpable local recurrence at the urethrovesical anastomosis. hydrogel spacer application during salvage radiotherapy (IMRT total dose 76Gy in 2 Gy fractions)	Local recurrence was displaced more than 1 cm from the rectal wall. Patient reported rectal urgency during radiotherapy, resolved after treatment. PSA levels dropped after treatment. A hydrogel spacer was successfully applied for dose-escalated radiotherapy in a patient with macroscopic local prostate cancer recurrence at the urethrovesical anastomosis to decrease the dose at the rectal wall.	Larger and longer follow-up studies included.
Pinkawa M, Klotz J, Djukic V et al (2013). Learning curve in the application of a hydrogel spacer to protect the rectal wall during radiotherapy of localized prostate cancer. Urology; 82: 963-968	Case series n=64 patients with prostate cancer. PEG hydrogel with IMRT (78Gy in 38 fractions) Follow-up – until last day of radiotherapy.	A smaller mean perirectal separation of 1.1cm in the first 32 patients compared with 1.5 in the second 32 patients reported. Rectal V70 Gy in the first group was 6% compared with 2% in the second cohort. A greater relative reduction of 80% was reported in the second cohort compared with 62.5% in the first cohort. An increasingly symmetrical hydrogel distribution and significantly larger prostate-rectum distances with the same hydrogel volume was seen. An improved dosimetric rectum protection and smaller acute bowel quality-of-life changes resulted.	Learning curve, RT dosimetric study.
Pinkawa, M, Berneking, VK et al (2017). Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. Hydrogelinjektion vermindert die rektale Toxizitat nach Radiotherapie bei lokalisiertem Prostatakarzinom. (193) 1 22-28.	Prospective comparative study n=167 consecutive patients who received prostate RT with 2-Gy fractions up to 76 Gy (without hydrogel, n = 66) or 76-80 Gy (with hydrogel, n = 101) Follow-up: 17 months after RT.	Baseline patient characteristics were well balanced. Treatment for bowel symptoms (0 vs 11%; p<0.01) and endoscopic examinations (3 vs 19%; p<0.01) were performed less frequently with a spacer. Mean bowel function scores did not change for patients with a spacer in contrast to patients without a spacer (mean decrease of 5 points) >1 year after RT in comparison to baseline, with 0 vs. 12% reporting a new	Multiple publication of Pinkawa 2016 included in systematic review added.

		moderate/big problem with passing stools (p<0.01). Statistically significant differences were found for the items "loose stools", "bloody stools", "painful bowel movements" and "frequency of bowel movements".	
Pinkawa M, Berneking V, Schlenter M et al. (2017) Quality of Life After Radiation Therapy for Prostate Cancer with a Hydrogel Spacer: 5-Year Results. International Journal of Radiation Oncology Biology Physics. 99(2):374-7.	Case series N=114 prostate cancer patients (low/intermediate/high-risk) received external beam radiation therapy 76 -78Gy fractions (54 had hydrogel spacer and 60 had no spacer). QoL was measured by the EPIC-50 items scale. Follow-up 5 years	Mean bowel function and bother score changes of >5 points in comparison to baseline levels before treatment were found only at the end of RT (10-15 points; p < .01) for patients treated with a hydrogel spacer. No spacer patient reported moderate or big problems with his bowel habits overall. Mean bother score changes of 21 points at the end of RT, 8 points at 2 months, 7 points at 17 months, and 6 points at 63 months after RT were found for patients treated without a spacer. A bowel bother score change >10 points was found in 6% versus 32% (P<0.01) at 17 months and in 5% versus 14% (P=0.2) at 63 months with versus without a spacer.	Included in systematic review added.
Pinkawa M (2016). Rectal spacers to minimise morbidity in radiotherapy for prostate cancer. Radiotherapy and Oncology (119) S8.	Review	Biodegradable spacers, including hydrogel, hyaluronic acid, collagen or an implantable balloon can be injected or inserted in a short procedure under transrectal ultrasound guidance via a transperineal approach. A distance of about 1.0-1.5cm is usually achieved between the prostate and rectum, excluding the rectal wall from the high isodoses. Several studies have shown well tolerated injection procedures and treatments. Apart from considerable reduction of rectal dose compared to radiotherapy without a spacer, clinical toxicity results are favourable.	Review
Pinkawa M, Schubert C, Escobar-Corral N et al. (2018) Optimization of prostate cancer radiotherapy using of a spacer gel, volumetric modulated arc therapy and a single biological	Case series N=27 patients with localised prostate cancer: stage T1-T2c IMRT, VMAT 78 Gy in 2 Gy fractions VMAT versus IMRT plans	In addition to decreased rectal dose following spacer injection, VMAT with single biological organ at risk optimization resulted in further dose reduction to the organs at risk and improved dose homogeneity and conformity in	Larger studies included. Toxicity not reported.

organ at risk objective. International Journal of Radiation Research, 16, 169-176.	and plans before versus after spacer injection were compared.	comparison to the step-and-shoot IMRT technique with conventional objectives.	
Pinkawa M, Hermani H, Bischoff P et al. (2022) Focal injection of a radiopaque viscous spacer before focal brachytherapy as re-irradiation for locally recurrent prostate cancer Brachytherapy.	Case report N=2 patients with prostate cancer who had radiopaque viscous hydrogel spacer before brachytherapy. Follow-up 18 months.	The viscous hydrogel spacer can be injected focally at a specific prostate lobe or seminal vesicles. The spacer remains stable within fatty tissue in any areas that are accessible by an ultrasound guided needle injection to create a distance between the high brachytherapy dose within the target and the organ at risk.	Injection technique.
Pieczonka CM, veados N et al (2016). Hydrogel Spacer Application Technique, Patient Tolerance, and Impact on Prostate IMRT: Results from a Prospective Multicenter Pivotal Randomized Controlled Trial. Urology Practice 3 (2), 141–146.	RCT n=222 (149 spacer group versus 73 control group) men with stage T1 or T2 prostate cancer treated to 79.2 Gy with image guided intensity modulated radiation therapy in 44 fractions. Fiducial markers and perirectal spacer injection (spacer group) or fiducial markers alone (control group). Follow-up: 15 months Follow-up:15 months	Procedures were rated easy or very easy in 98.7% of cases with a 99.3% success rate. Mild transient rectal events were noted in 10% of patients in the spacer group (for example, pain, discomfort). Mean perirectal space was 12.6 mm after implant and 10.9 mm at 12.4 weeks with absorption at 12 months. A 25% or greater reduction in rectal V70 dose was produced in 97.3% of patients in the spacer group. The spacer group had a significant reduction in late rectal toxicity severity (p=0.044) as well as lower rates of decrease in bowel quality of life at 6, 12 and 15 months compared with the control group. There were no unanticipated adverse spacer effects or spacer related adverse events.	Multiple publication (of Mariados et al 2015) included in systematic review added.
Picardi C, Rouzaud M, Kountouri M et al. (2016) Impact of hydrogel spacer injections on interfraction prostate motion during prostate cancer radiotherapy. ACTA ONCOLOGICA, VOL. 55, NO. 7, 834–838	Prospective cohort study N=20 patients with prostate cancer had radiotherapy-IGRT (10 with or 10 without hydrogel spacers). Follow up time not reported.	In patients with or without HS, the overall mean interfraction prostate displacements were 0.4 versus -0.4 mm (p=0.0001), 0.6 versus 0.6 mm (p =0.85), and -0.6 mm versus -0.3 mm (p=0.48) for the left right, anterior-posterior (AP), superior-inferior (SI) axes, respectively. Prostate displacements 45 mm in the AP and SI directions were similar for both groups. No differences in setup errors were observed in the three axes between HS + or HS- patients. HS implantation does not significantly influence the	Included in HTA added.

		interfraction prostate motion in patients treated with RT for prostate cancer. The major expected benefit of HS is a reduction of the high-dose levels to the rectal wall without influence in prostate immobilization.	
Polamraju P, Bagley AF, Williamson T et al. (2019) Hydrogel Spacer Reduces Rectal Dose during Proton Therapy for Prostate Cancer: A Dosimetric Analysis. Int J Particle Therapy, 23-31	N=9 patients hydrogel spacer on rectal dose on plans for treating prostate cancer with intensity-modulated proton therapy (IMPT) or passive scattering proton therapy (PSPT)	Significant reductions in rectal dose occurred in both PSPT and IMPT plans, with the greatest reduction for IMPT-with-spacer relative to PSPT alone. Prospective studies are ongoing to assess the clinical impact of reducing rectal dose with hydrogel spacers.	Dosimetric analysis.
Porkhun K, Hagen G. "Hydrogel rectal spacer SpaceOAR™ in prostate cancer radiation therapy - Health economic evaluation" 2021. Oslo: Norwegian Institute of Public Health, 2021.	Health technology assessment.	Absolute shortfall for patients suffering from radiation-induced adverse events is 1.85 QALYs. • The cost-utility analysis indicated that SpaceOAR™ in combination with radiation therapy was more costly (incremental costs: 15,330 NOK) and slightly more effective (incremental effects: 0.008 QALYs) than radiation therapy alone. • The health benefit of the intervention is very uncertain. Our analysis indicates that the intervention only has a 59% likelihood of generating a net health benefit as measured in QALYs. • The incremental cost-effectiveness ratio (ICER) is NOK 2,006,985 per QALY. • The results of sensitivity analysis indicated that the price of the spacer, the quality of life weights and the efficacy of the treatment have the greatest impact on the results. • The budget impact analysis indicated that costs of the intervention would be approximately 15 million NOK per year. This report has assessed to what degree the technology meets the Norwegian priority setting criteria (health benefits, resource use and disease severity). The absolute shortfall is 1.85 QALY, placing	Economic evaluation. Not in remit.

		the disease in the lowest priority setting group following the approach suggested by the Magnussen group (https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/). The health benefit of the intervention is small (0.008 QALYs) and very uncertain.	
Prada PJ, Fernandez J et al (2007). Transperineal Injection of Hyaluronic Acid in Anterior Perirectal Fat to Decrease Rectal Toxicity from Radiation Delivered with Intensity Modulated Brachytherapy or EBRT for Prostate Cancer Patients. International Journal of Radiation Oncology Biology Physics.69 (1) 95-102.	Case series n=27 intermediate and high risk prostate cancer patients Injecting hyaluronic acid (HA) during external beam radiation therapy (EBRT TO 43 Gy in 23 fractions) with HDR brachytherapy (23 Gy in 2 HDR BT boosts) over 5 week period. HA was injected before the second HDR fraction. Follow-up: median 13 months.	No toxicity was produced from the HA or the injection. In follow-up CT and MRI the HA injection did not migrate or change in mass/shape for close to 1 year. The mean distance between rectum and prostate was 2.0 cm along the entire length of the prostate. The median measured rectal dose, when normalized to the median urethral dose, demonstrated a decrease in dose from 47.1% to 39.2% ($p < 0.001$) with or without injection. For an HDR boost dose of 1150 cGy, the rectum mean Dmax reduction was from 708 cGy to 507 cGy, $p < 0.001$, and the rectum mean Dmean drop was from 608 to 442 cGy, $p < 0.001$ post-HA injection.	Included in systematic review added.
Prada PJ, Gonzalez H, Menéndez C et al (2009) Transperineal injection of hyaluronic acid in the anterior perirectal fat to decrease rectal toxicity from radiation delivered with low-dose-rate brachytherapy for prostate cancer patients. Brachytherapy; 8(2):210-7.	Pseudo-RCT N=69 patients with low- and intermediate-risk prostate cancer had BT with I-125 seeds; dose of 145 Gy Transperineal injection of hyaluronic acid (n=36) versus no transperineal hyaluronic acid injection (n=33) Follow up median 26 months	No toxicity in fat or in rectal function. Mucosal damage post therapy 5% (2/36) versus. 36% (12/33), p=0.002. Macroscopic rectal bleeding 0 versus 12% (4/23), p=0.047. No side effects related to injection or hyaluronic acid.	Included in systematic review added.
Prada PJ, Jimenez I, Gonzalez-Suarez H et al. (2012) High-dose rate interstitial brachytherapy as monotherapy in one fraction and transperineal hyaluronic acid injection into the perirectal fat for the treatment of favorable stage prostate cancer:	Case series N=40 patients with prostate cancer treated with high-dose-rate (HDR) brachytherapy (20.5 Gy) plus transperineal hyaluronic acid injection into the perirectal fat to displace the rectal wall from radiation.	All patients tolerated the implantation procedure very well with minimal discomfort. No intraoperative or perioperative complications occurred. Acute toxicity Grade 2 or more was not observed in any patients. No chronic toxicity has been observed after treatment. Logistic regression showed that the late Grade 1 GU toxicity was associated with D(90)	Included in systematic review added.

Treatment description and preliminary results. Brachytherapy.11(2):105-10.	Median follow-up 19 months (range 8-32 months).	(p=0.050). The 32-month actuarial biochemical control was 100% and 88%, respectively (p=0.06) for low- and intermediate-risk groups.	
Prada PJ, Ferri M, Cardenal J et al. (2018) High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results. Brachytherapy. 17(6):845-51.	Case series N=60 patients with low- and intermediate-risk prostate cancer were treated with high-dose-rate monotherapy in one fraction (20.5 Gy) and transperineal hyaluronic acid injection into the perirectal space. Median follow-up was 51 months (range 30–79)	HDR brachytherapy is well-tolerated. No intraoperative or perioperative complications occurred. Grade 1 acute genitourinary toxicity occurred in 36% of patients, Grade 2 or more was not observed, only 1 patient requiring the use of a catheter for 7 days in the immediate postoperative period. No gastrointestinal toxicity or chronic toxicity has been observed after treatment. The actuarial biochemical control was better, 82% (±3%) at 6 years.	Large studies included.
Quinn TJ, Daignault-Newton S, Bosch W et al. (2020) Who Benefits from a Prostate Rectal Spacer? Secondary Analysis of a Phase III Trial. Practical Radiation Oncology 10, 186-194	RCT SpaceOAR phase III trial Clinical and dosimetric data for the 222 patients enrolled on the original trial were analysed in the present study 218 were assessed for bowel quality of life (QOL) at 15 months, and 140 with a minimum of 3 years of follow-up were assessed for more long-term changes in bowel QOL.	There was little heterogeneity in the likelihood of spacer reducing the risk of declines in bowel QOL across clinical and dosimetric variables. Even for the >95% of plans meeting QUANTEC rectal criteria, hydrogel spacer provided potentially meaningful Therefore, we were not able to identify a subgroup within this population that did not potentially benefit from spacer placement.	Data from the RCT included.
Rossi PJ, Marcus DM, Adrian Hall W et al. (2021) Hydrogel spacers and prostate brachytherapy. Brachyt herapy. 21 (1); 75-78.	Review	It is clear that spacing utilized in the setting of brachytherapy, may reduce early or late gastrointestinal side effects, and does not degrade the quality of the treatment. Although toxicities associated with spacers appear to be rare, clinicians should be aware of potential complications and should be trained on appropriate spacer placement. Further study with prospective evaluation is essential.	Review
Repka MC, Creswell M, Lischalk JW (2022). Rationale for Utilization of Hydrogel Rectal Spacers in Dose Escalated SBRT for the Treatment of	Review	Outlines a framework and rationale for the utilization of rectal spacers when treating unfavourable risk prostate cancer with dose escalated	Review

Unfavorable Risk Prostate Cancer. Frontiers in Oncology; 12; 860848		Stereotactic Body Radiation Therapy (SBRT).	
Ruggieri R, Naccarato S, Stavrev P et al. (2015) Volumetric-modulated arc stereotactic body radiotherapy for prostate cancer: dosimetric impact of an increased near-maximum target dose and of a rectal spacer. *The British journal of radiology,* 88**,** 20140736.	Prospective cohort study N=11 patients with low/intermediate risk prostate adenocarcinoma, had VMAT-SBRT 35 Gy in 5 fractions- IMRT (10 ml of hydrogel spacer versus no spacer) Patients selected from 2 different trials. Follow-up not reported.	The increased D2% was associated with improvements in target coverage, whereas spacer insertion was associated with improvements in both target coverage and rectal Vr X . By linear correlation analysis, spacer insertion was related to the reductions in rectal Vr X for X ≥ 28GyA slightly increased $D_{2\%}$ or the use of spacer insertion was each able to improve VPTV 33:2 . Their combined use assured VPTV 33:2 $ 98% to all our patients. Spacer insertion was further causative for improvements in rectal sparing.	Larger studies included.
Rucinski A, Brons S, Richter D, et al. (2015) Ion therapy of prostate cancer: daily rectal dose reduction by application of spacer gel. Radiat;10:56.	Retrospective cohort study N=19 patients with prostate cancer treated with photons and ions (10 with Hydrogel spacer versus 9 without spacer). Patients selected from 2 different trials.	The application of spacer gel did substantially diminish rectum dose. Dmax-1 ml on the treatment planning CT was on average reduced from 100.0 ± 1.0% to 90.2 ± 4.8%, when spacer gel was applied. Spacer gel results in a decrease of the daily V90Rectum index, which calculated over all patient cases and CT studies was 10.2 ± 10.4 [ml] and 1.1 ± 2.1 [ml] for patients without and with spacer gel, respectively.	Larger studies included.
Seymour ZA, Daignault S, Bosch W, Gay HA, Michalski JM, Hamstra DA, et al. Long-term follow-up after radiotherapy for prostate cancer with and without rectal hydrogel spacer: A pooled prospective evaluation of quality of life.. BJU Int 2020; 126: 367–372 doi:10.1111/bju.15097	Case series N=380 men treated with radiotherapy (RT) for prostate cancer (64% with rectal hydrogel spacer and 36% without) Pooled analysis of two series (a prospective Phase III multi-centred randomised trial and a prospective non-randomised single-institution analysis) Follow-up (median 39 months) QOL was examined using the Expanded Prostate Cancer Index Composite (EPIC) and mean changes from	Treatment with spacer was associated with less decline in average long-term bowel QOL (89.4 for control and 94.7 for spacer) with differences at >24 months meeting the threshold of a MID difference between cohorts (bowel score difference from baseline: control = -5.1, spacer = 0.3, difference = -5.4; P < 0.001). When evaluated over time men without spacer were more likely to have MIDx1 (5 points) declines in bowel QOL (P = 0.01). At long-term follow-up MIDx1 was 36% without spacer vs 14% with spacer (P In this pooled analysis of QOL after prostate RT with up to 5 years of follow-up, use of a rectal spacer was associated	Similar study included in HTA added.

	baseline in EPIC domains were evaluated.	with preservation of bowel QOL. This QOL benefit was preserved with long-term follow-up.	
Stavrev P, Ruggieri R, Stavreva N et al (2016). Applying radiobiological plan ranking methodology to VMAT prostate SBRT. Phys Med 32 (4) 636-641.	Case series n=11 patients (35Gy-in-five-fractions VMAT prostate SBRT) 4 plans were generated before and after spacer insertion.	The plans without rectal spacer were ranked worse compared to those with rectal spacer except for one set of Hom plans. The use of rectal spacer leads in general to lower risk of rectal complications, as expected, and even to better tumour control. Plans with increased near maximum target dose (D2%40.2Gy) are expected to perform much better in terms of tumour control than those with D2%37.5Gy.	Treatment planning study.
Strom TJ, Wilder RB et al (2014). A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy+/-intensity modulated radiation therapy. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology.111 (1) 126-131.	Retrospective comparative case series n=200 (100 gel versus 100 no gel) patients with clinically localised prostate cancer who had high dose rate (HDR) brachytherapy with or without intensity modulated radiation therapy (IMRT) and injection of a polyethylene glycol hydrogel spacer (10 ml Duraseal). Follow-up median 8.7 months.	There was a success rate of 100% (100/100) with PEG hydrogel implantation. PEG hydrogel significantly increased the prostate-rectal separation (mean±SD, 12±4mm with gel vs. 4±2mm without gel, p<0.001) and significantly decreased the mean rectal D2 ml (47±9% with gel vs. 60±8% without gel, p<0.001). Gel decreased rectal doses regardless of body mass index (BMI).	Study included in systematic review added.
Song DY, Herfarth KK et al (2013). A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: Analysis of dosimetric outcomes. International Journal of Radiation Oncology Biology Physics.87 (1) 81-87.	Case series N=52 patients with localised prostate cancer (T1-T2). Injection of a prostate-rectum spacer (polyethylene glycol hydrogel [SpaceOAR] during IMRT- 78 Gy in 2 Gy fractions Follow-up not reported	Injection of hydrogel into the prostate-rectal interface resulted in dose reductions to rectum for >90% of patients treated. Rectal sparing was statistically significant across a range of 10 to 75 Gy and was demonstrated within the presence of significant interinstitutional variability in plan conformity, target definitions, and injection results.	Included in systematic review added.
Sidhom M, Arumugam S et al (2016). Early results of Australian multicentre phase 2 trial of stereotactic "virtual HDR" radiation therapy for intermediate	Multicentre case series n=43 patients with intermediate and high risk prostate cancer who completed	Treatment was well tolerated. Genitourinary (GU) and gastrointestinal (GI) CTCAEv4 toxicities were minimal with no acute or late grade 3 GU or GI toxicity. At the end of treatment, any grade 1 GU	Injectable hydrogel spacer inserted in 10 patients only. Larger studies with longer

and high risk prostate cancer. Journal of Medical Imaging and Radiation Oncology (60) 48.	stereotactic body radiotherapy (SBRT) as a "virtual HDR" with stepwise dose escalation of 19 Gy in 2 fractions 1 week apart (in 28), followed by 46 Gy in 23 fractions (in 15). Median follow-up: 12 months	toxicity occurred in 54%, and grade 2 in 31%. Acute grade 1 GI toxicity occurred in 26%, while no patients experienced acute grade 2 GI toxicity. For the 31 patients with 6-month follow-up, at last follow-up the rate of late grade 2 GU toxicity was 10%, while no patients developed late grade 2 GI toxicity. Rectal displacement during SBRT was achieved with an injectable hydrogel spacer (SpaceOAR) in 10 patients, and an external rectal retraction system (Rectafix) in 33 patients. No SpaceOAR patients reported discomfort from rectal displacement, while 39% of Rectafix patients reported moderate discomfort and 11% severe discomfort during SBRT.	follow-up included.
Sato H, Kato T, Motoyanagi T et al. (2021) Preliminary analysis of prostate positional displacement using hydrogel spacer during the course of proton therapy for prostate cancer. Journal of Radiation Research. 62, 2, 294–299.	Case series N=22 patients with intermediate-risk prostate cancer (11 with hydrogel spacer [HS] insertion and 11 without HS insertion).	No significant difference was observed across the groups in the LR and SI directions. Conversely, a significant difference was observed in the AP direction ($P < 0.05$). The proportion of the 3D vector length ≤5 mm was 95% in the inserted group, but 55% in the non-inserted group. Therefore, HS is not only effective in reducing rectal dose, but may also contribute to the positional reproducibility of the prostate.	Effect of HS insertion on the inter-fraction prostate motion.
Saito M, Suziki T, Suguama Y et al. (2020) Comparison of rectal dose reduction by a hydrogel spacer among 3D conformal radiotherapy, volumetric-modulated arc therapy, helical tomotherapy, CyberKnife and proton therapy. Journal of Radiation Research, 61, 3, pp. 487–493.	Case series (retrospective) N=20 patients with hydrogel spacer for prostate radiotherapy (3D conformal radiotherapy (3DCRT), volumetric modulated arc therapy (VMAT), helical tomotherapy (HT), CyberKnife (CK) and proton therapy).	Significant rectal dose reduction ($P < 0.001$) between the treatment plans on pre- and post-CT images were achieved for all modalities for D50%, D20% and D2%. The dose reduction of high-dose (D2%) ranges were −40.61 ± 11.19, −32.44 ± 5.51, −25.90 ± 9.89, −13.63 ± 8.27 and −8.06 ± 4.19%, for proton therapy, CK, HT, VMAT and 3DCRT, respectively. The area under the rectum dose–volume histogram curves were 34.15 ± 3.67 and 34.36 ± 5.24% ($P = 0.7841$) for 3DCRT with hydrogel spacer and VMAT without hydrogel spacer, respectively. Results indicate that 3DCRT with hydrogel spacer would reduce the cost	Dosimetric outcomes.

		by replacing the conventional VMAT without spacer for prostate cancer treatment, from the point of view of the rectal dose. For the high-dose gradient region, proton therapy and SBRT with CK showed larger rectal dose reduction than other techniques.	
Schorghofer A, Drerup M, Kunit T et al. (2019) Rectum-spacer related acute toxicity – endoscopy results of 403 prostate cancer patients after implantation of gel or balloon spacers. Radiat Oncol J; 14 (47): 1–7.	Cohort study N=403 patients 139 with hydrogel spacer (SpaceOAR) versus 264 with endorectal balloon (prospace) using endoscopy. IMRT 276 patients were treated with normo-fractionated regimen (78 at 2Gy fraction), 125 treated with moderate hypofractionation (63 at 2 Gy fraction). 116 high risk patients additionally received 50 Gy in pelvic nodes. 12 months follow-up.	Overall rectal toxicity was very low with average VRS scores of 0.06 at the day after implantation, 0.10 at the end of RT, 0.31 at 6 months and 0.42 at 12 months follow up. Acute Grade 3 toxicity (rectum perforation and urethral damage) directly related to the implantation procedure occurred in 1.49% (n = 6) and was seen exclusively in patients who had received the spacer balloon. Analysis of post implant MR imaging did not identify abnormal or mal-rotated positions of this spacer to be a predictive factors for the occurrence of spacer related G3 toxicities.	Included in systematic review added.
Saito M, Suzuki T, Suzuki H et al. (2022) Minimum required interval between hydrogel spacer injection and treatment planning for stereotactic body radiation therapy for prostate cancer. Practical Radiation Oncology.	Retrospective study N=15 patients treated with SBRT + hydrogel spacer for prostate cancer. Pre and post MRI (within 3 days) with spacer were evaluated.	A single day is an acceptable interval between hydrogel spacer injection and treatment planning for SBRT for prostate cancer	Volume of spacer on MRI assessed.
Sturt P, Suh YE, Khoo V et al. (2022) The dosimetric advantages of perirectal hydrogel spacer in men with localized prostate cancer undergoing stereotactic ablative radiotherapy (SABR). Medical Dosimetry.	N=22 patients with hydrogel spacer (SpaceOAR) undergoing stereotactic ablative radiotherapy (SABR) for localized prostate cancer	The use of hydrogel spacer was able to significantly reduce planned dose to the rectum, bladder and penile bulb with SABR techniques associated with the CyberKnife VSI system.	Dosimetry outcome. Larger studies with longer follow-up included.
Sawayanagi S, Yamashita H, Ogita M et al. (2022) Injection of hydrogel spacer increased maximal intrafractional prostate motion in anterior and superior	Retrospective study. N= 38 patients who had definitive volumetric modulated arc therapy (VMAT)-stereotactic body radiation therapy (SBRT) for prostate cancer (8	Our findings suggest that maximum intrafractional prostate motion monitoring during VMAT-SBRT was larger in patients with hydrogel spacer injection in the superior and anterior directions. Since this difference seemed not to	Prostate motion outcome. Studies with similar outcomes reported in the overview.

directions during volumetric modulated arc therapy-stereotactic body radiation therapy for prostate cancer. Radiation oncology. 17 (1); 41	with spacer and 30 without spacer).	disturb the dosimetric advantage of the hydrogel spacer, we do not recommend routine avoidance of the hydrogel spacer use.	
See AW; Bowden P, Geoffrey W et al. (2022) Dose-escalated radiotherapy to 82 Gy for prostate cancer following insertion of a peri-rectal hydrogel spacer: 3-year outcomes from a phase II trial. Radiation oncology; 2022; vol. 17 (no. 1); 131	Prospective study N= 70 men with localised prostate cancer who had a IMRT 82 Gy in 2 Gy fractions after insertion of SpaceOAR. Median 37.4 months.	Dose-escalation to 82 Gy, and use of a hydrogel spacer, is safe and feasible, with minimal toxicity when compared to rates of rectal toxicity in previous dose-escalation trials up to 80 Gy.	Dosimetry outcomes. Larger studies with longer follow-up included.
Suziki T, Saito M, Onishi H et al. (2020) Effect of a hydrogel spacer on the intrafractional prostate motion during CyberKnife treatment for prostate cancer. J Appl Clin Med Phys; 21:10:63–68	Case series (retrospective) N=21 patients with prostate cancer (12 with and 12 without a hydrogel spacer during CyberKnife treatment) evaluated the effect of a hydrogel spacer on intrafractional prostate motion during CyberKnife treatment.	The offset values (mean ± SD) for the X-, Y-, and Z-axes were −0.04 ± 0.92 mm, −0.03 ± 0.97 mm (P = 0.66), 0.02 ± 0.51, −0.02 ± 0.49 mm (P = 0.50), and 0.56 ± 0.97 mm, 0.34 ± 1.07 mm (P = 0.14), in patients inserted without or with the hydrogel spacer, respectively. There was no effect of a hydrogel spacer on the intrafractional prostate motion in the three axes during CyberKnife treatment for prostate cancer.	Larger studies included.
Su Z, Henderson R, Nichols R et al. (2021) A comparative study of prostate PTV margins for patients using hydrogel spacer or rectal balloon in proton therapy. Physica Medica 81, 47–51.	Retrospective analysis N=190 prostate patients treated with proton therapy (96 had hydrogel spacer injection and 94 patients had only rectal balloons insertion).	Statistically significant differences were observed in the patient setup and prostate intrafraction motion errors of the two patient groups. However, under the current protocol of bladder preparation and daily marker-based x-ray image-guidance, population PTV margins were comparable between the two patient groups.	Retrospective planning study.
Taggar AS, Charas T, Cohen GN et al. (2018) Placement of an Absorbable Rectal Hydrogel Spacer in Patients Undergoing Low-dose-rate Brachytherapy with Palladium-103. Brachytherapy. 17(2): 251–258	Retrospective cohort study N=74 patients with prostate cancer had rectal hydrogel spacer inserted following LDR brachytherapy with Pd-103 seed-implant procedure. Brachytherapy was delivered a monotherapy to 26 (35%) patients; as part of planned	(SD 3.81), and112.4% (SD 12.0), respectively. Urethral D20, D5cc and D1cc were 122.0% (SD 17.27), 133.8% (SD 22.8), and 144.0% (SD 25.4), respectively. After completing all treatments, at the time of first the follow up, seven patients reported acute rectal toxicity –six experiencing grade 1 rectal discomfort and one (with pre-existing haemorrhoids)	Included in systematic review added.

	combination therapy with EBRT to 40 (54%) patients; or as a salvage monotherapy to 8 (11%) patients. Compared with 136 patients treated with seed implantation (from another cohort). Follow-up not reported.	experiencing grade 1 bleeding. (SD 3.81), and112.4% (SD 12.0), respectively. Urethral D20, D5cc and D1cc were 122.0% (SD 17.27), 133.8% (SD 22.8), and 144.0% (SD 25.4), respectively. After completing all treatments, at the time of first the follow up, seven patients reported acute rectal toxicity –six experiencing grade 1 rectal discomfort and one (with pre-existing haemorrhoids) experiencing grade 1 bleeding.	
Tang Q, Zhao F, Yu X, Wu L, Lu Z, Yan S. The role of radioprotective spacers in clinical practice: a review. Quant Imaging Med Surg. 2018;8(5):514-524. doi:10.21037/qims.2018.06.06	Review on different types of spacers and their application in various tumour sites.	Placement-related complications and the cost-effectiveness of the spacers are also discussed. With the increasing use of high-precision radiotherapy in clinical practice, especially the paradigm-changing stereotactic body radiotherapy (SBRT), more robust studies are warranted to further establish the role of radioprotective spacers through materials development and novel placement techniques.	Review
Taniguchi T, Iinuma K, Nakano M et al. (2022) Chronological changes of lower urinary tract symptoms after low-dose-rate brachytherapy for prostate cancer using SpaceOAR system. Prostate International; 2022	Retrospective study n=483 patients with prostate cancer who underwent low-dose-rate brachytherapy (LDR-BT) and SpaceOAR system (n=30) and (n=453) who had LDR BT alone. Follow-up 12 months	SpaceOAR use may temporally increase PVR; however, IPSS, OABSS, IPSS-QOL, Qmax, and voided volume were not significantly associated with LUTS before and after LDR-BT. The combination of LDR-BT and SpaceOAR may be acceptable for treating patients with prostate cancer regarding the chronological changes in LUTS after brachytherapy.	Larger studies with longer follow-up included.
Teyateeti A, Grossman C, Kollmeier, MA et al. (2022) Influence of hydrogel spacer placement with prostate brachytherapy on rectal and urinary toxicity. BJU international. 129 (3); 337-344	Retrospective comparative study. N= 224 patients with LDR brachytherapy +/-EBRT and hydrogel spacer compared with 139 without spacer. Follow-up 3 years.	Rectal doses of the spacer cohort were significantly lower compared to the non-spacer cohort. The incidence rates of overall and grade > 2 rectal toxicity were lower in patients with spacer compared non-spacer group: 12% and 1.8% vs 31% and 5.8%, respectively. The 3-year cumulative incidence of overall rectal toxicity was significantly lower with spacer than without (15% vs 33%; P < 0.001), (HR 0.45, 95% CI 0.28-0.73; P = 0.001). None of the urethral	Studies with similar outcomes included.

		dosimetric variables or the presence or absence of spacer was associated with late urinary toxicity.	
Trifiletti DM, Garda AE and Showalter TN (2016). Implanted spacer approaches for pelvic radiation therapy. Expert Review of Medical Devices 13 (7) 633-640.	Review describes the commercially available rectal spacers in pelvic radiation therapy, including prostate cancer and gynaecologic malignancies, and the application, dosimetric effects, and reports clinical outcomes to date.	Several groups have reported significantly reduced rectal doses and decreased rectal toxicity with prostate-rectal spacers, and additional evidence continues to emerge to support this promising approach	Review
te Velde BL, Westhuyzen J et al (2017). Can a peri-rectal hydrogel spaceOAR programme for prostate cancer intensity-modulated radiotherapy be successfully implemented in a regional setting? Journal of Medical Imaging and Radiation Oncology, 61, 528–533.	Retrospective case series n=125 patients with localised prostate cancer were treated with 81 Gy prostate intensity-modulated radiotherapy (IMRT). 65 with SpaceOAR 60 without SpaceOAR. Patients treated with 81 Gy in 45Fx of IMRT over 9 weeks. Follow-up: 12 weeks	Rectal volume parameters were all significantly lower in the SpaceOAR group, with an associated reduction in acute diarrhoea (13.8% vs 31.7%). There were no significant differences in the very low rates of acute and late faecal incontinence or proctitis, however, there was a trend towards increased haemorrhoid rate in the SpaceOAR group (11.7% vs 3.1%, P = 0.09).	Included in systematic review added.
te Velde BL, Westhuyzen J, Awad N et al (2019). Late toxicities of prostate cancer radiotherapy with and without hydrogel SpaceOAR insertion. Journal of Medical Imaging and Radiation Oncology. 2019.	Case series N=121 patients with localised prostate cancer (intermediate and high risk patients) treated with 81 Gy in 45 fx of IMRT over 9 weeks were retrospectively compared: 65 patients with SpaceOAR and 56 patients without SpaceOAR. Follow-up 3 years	The cumulative incidence of low-grade diarrhoea (G1) was significantly higher in the non-SpaceOAR group (21.4% vs 6.2%; P = 0.016). The cumulative incidence of proctitis (grades G1 and G2) was also higher in the non-SpaceOAR group (26.7% vs 9.2%; P = 0.015); the cumulative incidence of G2 proctitis was higher in the latter group (P = 0.043). There were no differences between the treatment groups for cumulative incidences of faecal incontinence and/or haemorrhoids. Three years after IMRT, diarrhoea and proctitis were higher in the non-SpaceOAR group, without reaching statistical significance. This finding was unchanged after correcting for baseline symptoms.	Included in systematic review added.
Teh AYM, Ko H-T et al (2014). Rectal ulcer associated with SpaceOAR hydrogel insertion during	Case report N=1 patient with intermediate risk prostate cancer.	Rectal ulcer associated with SpaceOAR hydrogel insertion during prostate brachytherapy.	Included in systematic review added.

prostate brachytherapy. BMJ Case Reports.2014 (no pagination).	Injection of hydrogel (SpaceOAR) spacer during low dose rate (LDR) prostate brachytherapy Follow-up 3 years		
Uhl M, Herfarth K et al (2014). Absorbable hydrogel spacer use in men undergoing prostate cancer radiotherapy: 12 month toxicity and proctoscopy results of a prospective multicenter phase II trial. Radiation oncology 9:96.	Case series N=52 patients with localised prostate cancer (T1-T2). Injection of a prostate-rectum spacer (polyethylene glycol hydrogel [SpaceOAR] during IMRT- 78 Gy in 2 Gy fractions Follow-up 12 months	19 (39.6%) and 6 (12.5%) patients experienced acute Grade 1 and Grade 2 GI toxicity, respectively. There was no Grade 3 or Grade 4 acute GI toxicity experienced in the study. 45 (95.7%) patients experienced no late GI toxicity (95.7%), with 2 (4.3%) patients experiencing late Grade 1 GI toxicity. There was no late Grade 2 or greater GI toxicity experienced in the study. 20 (41.7%), 17 (35.4%) and 1 (2.1%) patients experienced acute Grade 1, Grade 2 and Grade 3 GU toxicity, respectively (Table 1). There was no Grade 4 acute GU toxicity experienced in the study. 8 (17.0%) and 1 (2.1%) patients experienced late Grade 1 and Grade 2 GU toxicity, respectively. There was no late Grade 3 or greater GU toxicity experienced in the study.	Larger studies with longer follow-up included. Included in systematic review added.
Uhl M, van Triest B et al (2013). Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. Radiother Ocol 106:215-219.	Case series n=48 prostate cancer patients with hydrogel spacer injection then had intensity modulated radiotherapy (IMRT).	Hydrogel application was straight forward with minimal patient discomfort. Six patients (12%) had acute GI grade 2 toxicity, with no patients having grade 3 or 4 toxicity. In addition, no patients had early late GI toxicity $\geqslant$ grade 2 after 12 months. The gel was stable during the course of radiotherapy and was not detectable in MRI after 9–12 months because of absorption in 42/43 patients.4 failed implantations occurred before routine implantation under TRUS guidance. 3 reports of focal rectal mucosal necrosis and bladder perforation were reported but were self-limiting without further complications. After TRUS guidance implementation no instances	Initial clinical outcomes with acute toxicity results of first 48 patients and late toxicity of 27 patients. Included in systematic review added.

		of failed implantations, perforations were reported.	
Underwood TSA., Voog JC, Moteabbed M et al. (2017). Hydrogel rectum-prostate spacers mitigate the uncertainties in proton relative biological effectiveness associated with anterior-oblique beams. Acta oncologica (Stockholm, Sweden), 56, 575-581.	Case series N=10 patients with rectal spacers treated with AO proton beams, SB proton beams and IMRT 29.2 Gy in 1.8 Gy fractions 60 Gy in 3 Gy fractions 36.25 Gy in 7.25 Gy fractions	Rectal spacers enabled the generation of anterior beam proton plans that appeared robust to modelled variation in RBE. However, further analysis of day-to-day robustness would be required prior to a clinical implementation of AO proton beams. Such beams offer almost complete femoral head sparing, but their broader value relative to IMRT and SB protons remains unclear.	Larger and longer follow-up studies included. Toxicity profile not reported.
van Wijk Y, Vanneste BGL, Walsh S, et al. (2018) Development of a virtual spacer to support the decision for the placement of an implantable rectum spacer for prostate cancer SpaceOAR 30 April 16, Technology Assessment Unit, MUHC radiotherapy: Comparison of dose, toxicity and cost-effectiveness. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2017.	Cost effectiveness (using Markov model comparing gains in quality of life versus increases in cost). Prediction model to identify patients most likely to benefit from SpaceOAR. Model included real spacers implanted (8 patients with hydrogel spacer and 15 with rectal balloon implant), and a group with virtual spacers (8 hydrogel and 8 balloon spacers) created using computed tomography scans of patients with rectal balloon implants	For a defined threshold of €80,000, the hydrogel spacer resulted in a cost-effective intervention in 2 out of 8 patients. The authors conclude that these devices are not cost-effective for all patients, and that more individual-patient information is needed.	Economic evaluation. Not in remit.
van Gysen K, Kneebone A et al (2014). Feasibility of and rectal dosimetry improvement with the use of SpaceOAR hydrogel for dose-escalated prostate cancer radiotherapy. Journal of Medical Imaging and Radiation Oncology.58 (4) 511-516.	Case series n=10 patients had 10ml injection of hydrogel and radiotherapy. Follow-up: 3 months	In the first 24 h, 2 patients had increase in bowel movement frequency. The comparison plans had identical prescription doses. Rectal doses were significantly lower for all hydrogel patients for all dose endpoints ($P < 0.001$). Post-treatment MRI showed gel stability. grade 1 bowel toxicity was reported in 6 patients during radiotherapy and 2 patients at 3 months' follow-up. No grade 2 or grade 3 acute bowel toxicity was reported.	Larger and longer follow-up studies included.
Van Gysen K, Kneebone A, Alfieri F, et al. (2013) Feasibility and rectal dosimetry improvement with the use of spaceOAR hydrogel for dose	Case series n=10 patients had 10ml injection of hydrogel and radiotherapy. Follow-up: 3 months	In the first 24 h, 2 patients had increase in bowel movement frequency. The comparison plans had identical prescription doses. Rectal doses were significantly lower for all hydrogel patients for all dose	Larger and longer follow-up studies included.

escalated prostate cancer radiotherapy. J Med Imaging Radiat Oncol. 1:59.		endpoints (P < 0.001). Post-treatment MRI showed gel stability. grade 1 bowel toxicity was reported in 6 patients during radiotherapy and 2 patients at 3 months' follow-up. No grade 2 or grade 3 acute bowel toxicity was reported.	
Van Der Meer S, Vanneste BGL et al (2016). A novel decision support method to estimate the value of a rectum spacer: 'Virtual Rectum Spacer'. Radiotherapy and Oncology (119) S638-S639.	Case series n=16 prostate cancer patients with CT imaging prior and 3-5 days after a gel RS implantation (SpaceOARTM System, Augmenix Inc.) Decision support system to predict the CT images with a 'virtual rectal spacers (RS) through non-rigid deformations based on a CT scan without RS to be integrated into a decision support system.	We have developed a novel method to simulate a model based virtual RS that is a useful tool to identify patients with a potentially high benefit of a RS implantation. The volume of the virtual RS can be estimated through the use of different deformation fields. In future, a dose comparison study is necessary to extend into a full decision support system using the virtual RS approach.	Decision support method.
Vassilis K, George M, John G et al (2013). Transperineal implementation of biocompatible balloon in patients treated with radiotherapy for prostate carcinoma: Feasibility and quality assurance study in terms of anatomical stabilization using image registration techniques. Journal of Bioequivalence and Bioavailability.5 (3), 142-148.	Case series n=10 patients with localised low risk prostate cancer treated with external 3 dimensional radiation therapy (3DCRT with 76-78 Gy in 38-39 daily fractions) combined with biodegradable balloon (ProSpace) implantation Follow-up: 3 weeks after treatment.	By using registration techniques, the ProSpace device was found stable in sequential CTs with x,y,z-axis displacements up to 2.1 mm, 3 mm and 2.2 mm respectively. The mean VAS score related to ProSpace was 1.4(± 0.5) and the mean score of rectal toxicity according to S-RS score was 1.9(± 0.6). The implementation of PROSPACE is feasible. Implant's position is relative stable. The procedure is minimally invasive with no recorded side effects. The incidence of patient-reported acute Gastrointestinal (GI) and Genitourinary (GU) toxicity as well as findings from flexible rectosigmoidoscopy, following high dose of 3DCRT after the implantation, were low.	Larger and longer follow-up studies included.
Vanneste Ben GL, Hoffmann AL (2016). Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology	Case series n=26 patients with localized prostate cancer a hydrogel rectum spacer injected. Dose distributions with (IMRT+IRS) and without (IMRT-IRS) IRS were calculated.	IMRT+IRS revealed a significant reduction in V40Gy (p=0.0357) and V75Gy (p<0.0001) relative to IMRT-IRS. For G2-3 acute GI toxicity and G2-3 LRB, the predicted toxicity rates decreased in 17/26 (65%) and 20/26 (77%) patients, and decision rules were derived for 22/32 (69%) and 12/64 (19%) respectively. From the decision rules, it follows that diabetes status	Larger studies with longer follow-up included.

and Oncology (121) 1 118-123.		has no impact on G2-3 acute toxicity, and in absence of pre-RT abdominal surgery, the implantation of an IRS is predicted to show no clinically relevant benefit for G2-3 LRB.	
Vanneste BGL, Buettner F et al (2016). Localizing the benefit of a hydrogel rectum spacer for prostate IMRT within the ano-rectal wall. Radiotherapy and Oncology (119) S412.	Case series n=26 patients with localized prostate cancer a hydrogel rectum spacer injected. Study assessed spatio-dosimetric differences in Dose-surface maps (DSMs) obtained from planned ano-rectal wall (ARW) dose distributions in patients receiving IMRT with and without implanted rectum spacer (IRS) (IMRT+IRS; IMRT-IRS, respectively).	Significant spatio-dosimetric differences in ARW DSMs exist between prostate cancer patients undergoing IMRT with and without IRS. The IRS particularly reduces the lateral and longitudinal extent of high-dose areas (>50 Gy) in anterior and superior-inferior directions.	Larger studies with longer follow-up included.
Vanneste BG, Pijls-Johannesma M, Van De Voorde L, et al. (2015) Spacers in radiotherapy treatment of prostate cancer: is reduction of toxicity cost-effective? Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2015;114(2):276- 281	Cost-effectiveness study Patients with prostate cancer who had intensity-modulated radiation therapy and a spacer (IMRT+S) versus IMRT-only without a spacer (IMRT-O). decision-analytic Markov model constructed to examine late rectal toxicity, costs and quality of life.	IMRT+S revealed a lower toxicity than IMRT-O. Treatment follow-up and toxicity costs for IMRT-O and IMRT+S amounted to €1604 and €1444, respectively, thus saving €160 on the complication costs at an extra charge of €1700 for the spacer in IMRT+S. The QALYs yielded for IMRT-O and IMRT+S were 3.542 and 3.570, respectively. This results in an incremental cost-effectiveness ratio (ICER) of €55,880 per QALY gained. For a ceiling ratio of €80,000, IMRT+S had a 77% probability of being cost-effective.	Costs not in remit of Interventional procedures programme.
Vanneste BG, Buettner F, Pinkawa M et al. (2019) Ano-rectal wall dose-surface maps localize the dosimetric benefit of hydrogel rectum spacers in prostate cancer radiotherapy. Clinical and Translational Radiation Oncology, 14: 17-24.	Case series n=26 prostate cancer patients receiving intensity-modulated radiation therapy (IMRT) with and without implantable hydrogel rectum spacers (IRS-SpaceOAR). Spatial differences in dose distributions of the ano-rectal wall (ARW) evaluated using dose-surface maps (DSMs). Dose surface maps are generated for prostate radiotherapy using an IRS.	Local-dose effects are predicted to be significantly reduced by an IRS. The spatial NTCP model predicts a significant decrease in Gr 2 late rectal bleeding and subjective sphincter control. Dose constraints can be improved for current clinical treatment planning.	Comparative dosimetric study. Larger studies included.

Vanneste BGL, Van Limbergen EJ, van de Beek K et al. (2018) A biodegradable rectal balloon implant to protect the rectum during prostate cancer radiotherapy for a patient with active Crohn's disease. Technical Innovations and Patient Support in Radiation Oncology;6:1-4	Case report Patient with Crohn's disease was implanted with a biodegradable balloon to protect the rectum during prostate cancer radiotherapy	The patient was at high-risk for rectal toxicity and was successfully irradiated to his prostate with only a grade 1 urinary toxicity, no acute rectal toxicity or toxicity flare of the IBD.	Larger studies included.
Vanneste BGL, van Wijk Y, Lutgens LC, Van Limbergen EJ, van Lin EN, van de Beek K, et al. Dynamics of rectal balloon implant shrinkage in prostate VMAT: Influence on anorectal dose and late rectal complication risk. Strahlenther Onkol. 2018;194(1):31-40	Case series N=15 patients with localized prostate cancer had a rectal balloon implanted during moderately hypofractionated prostate radiotherapy.	Despite significant decrease in rectal balloon implant volume (average 70.4%), the high-dose rectal volume and the predicted late rectal bleeding risk were not significant due to a persistent spacing between the prostate and the anterior rectal wall.	Larger studies included.
Vanneste BGL, Van Limbergen EJ, Marcelissen T et al. (2021) Is prostate cancer radiotherapy using implantable rectum spacers safe and effective in inflammatory bowel disease patients? Clinical and Translational Radiation Oncology,, 27, 121125.	Case report N= 8 patients with all-risk prostate cancer with the comorbidity of an IBD. 5 patients were treated with external beam RT (70 Gray (Gy) in 28 fractions), and 3 patients were treated with 125I-implant (145 Gy) in combination with a biodegradable prostate-rectum spacer balloon implantation. Median follow-up was 13 months (range: 3–42 months).	Only one acute grade 2 gastrointestinal (GI) toxicity was observed: an increased diarrhoea (4–6 above baseline) during RT, which resolved completely 6 weeks after treatment. No late grade 3 or more GI toxicity was reported, and no acute and late grade 2 genitourinary toxicity events were observed.	Larger studies included.
Wilton L, Richardson M, Keats S et al. (2017) Rectal protection in prostate stereotactic radiotherapy: A retrospective exploratory analysis of two rectal displacement devices. J Med Radiat Sci 64, 266–273.	Prospective cohort study (retrospective analysis of data from PROMETHEUS trial ACTRN 126150002235380) N=45 patients with non-metastatic intermediate- or high-risk prostate cancer and treated with stereotactic body radiation therapy (total dose of 19 or 20 Gy in two fractions followed by 46 Gy in 23 fractions).	In comparison (1) Rectafix demonstrated lower mean doses at 9 out of 11 measured intervals (P = 0.0012). Comparison (2) demonstrated a moderate difference with centre 2 plans producing slightly lower rectal doses (P = 0.013). Comparison (3) further demonstrated that Rectafix returned lower mean doses than SpaceOAR (P < 0.001). Although all dose levels were in favour of Rectafix, in absolute terms differences were small (2.6–9.0%). In well-selected prostate SBRT	Included in HTA added to table 2. hydrogel spacers were compared to Rectafix, a plastic rod.

	Centre 1:16 Rectafix and 10 SpaceOAR patients. Centre 2: 19 Rectafix patients. dosimetric difference between two methods of rectal displacement compared: (1) centre 1 Rectafix versus centre 1 SpaceOAR; (2) centre 1 Rectafix versus centre 2 Rectafix and (3) centre 1+ centre 2 Rectafix versus centre 1 SpaceOAR follow up time not reported.	patients, Rectafix and SpaceOAR RDD's provide approximately equivalent rectal sparing.	
Whalley D, Hruby G, Alfieri F, Kneebone A, and Eade T (2016). SpaceOAR Hydrogel in Dose-escalated Prostate Cancer Radiotherapy: Rectal Dosimetry and Late Toxicity. Clin Oncol 28(10):e148-e54.	Case series n=30 patients with prostate cancer. Injection of a prostate-rectum spacer (polyethylene glycol hydrogel (SpaceOAR) during dose escalated intensity modulated radiotherapy (IMRT) median 28 months (range 24-38)	There were no perioperative complications. Rectal doses were significantly lower for the post-hydrogel plans, especially above 65 Gy (V82 = 0.2% versus 1.3%; V80 = 0.8% versus 5.3%; V75 = 2.2% versus 9.5%; V70 = 3.7% versus 12.3%; V65 = 5.4% versus 14.7%; V40 = 22.9% versus 32% and V30 = 42.7% versus 49.4%). There was no significant difference in acute grade 1 and 2 gastrointestinal toxicity, which was 43% versus 51% and 0% versus 4.5% in the hydrogel and control groups, respectively. Late grade 1 was significantly less frequent in the hydrogel group (16.6% versus 41.8%, P ¼ 0.04).	Included in systematic review added.
Weber DC, Zilli T, Vallee J et al (2012). Intensity modulated proton and photon therapy for early prostate cancer with or without transperineal injection of a polyethylene glycol spacer: A treatment planning comparison study. International Journal of Radiat Oncol Biol Phys. 84: e311-318	Comparative case series n=8 patients with localised prostate cancer PEG hydrogel + intensity modulated radiation therapy [IMRT] (78 Gy in 39 fractions), volumetric modulated arc therapy [VMAT] (78Gy) and intensity modulated proton therapy [IMPT] (78 Gy).	Spacer injection significantly decreased the rectal dose in the 60 - 70 Gy range. Mean V70 Gy and V60 Gy with IMRT, RA and IMPT planning were 5.3+/-3.3% / 13.9+/-10.0%, 3.9+/-3.2% / 9.7+/-5.7% and 5.0+/-3.5% / 9.5+/-4.7% after Spacer injection. Spacer injection usually improved the PTV coverage for IMRT. With this technique, mean V70.2 Gy and V74.1 Gy were 100+/-0% - 99.8+/-0.2% and 99.1+/-1.2% - 95.8+/-4.6% with (p = 0.07) and without (p Z0.03) Spacer respectively. As a result of Spacer injection, bladder doses were usually higher but not significantly so.	Comparative dosimetric study. Included in systematic review added.

Wilder RB, Barme GA et al (2010). Cross-linked hyaluronan gel reduces the acute rectal toxicity of radiotherapy for prostate cancer. International Journal of Radiat Oncol Biol Phys. 77(3): 824-830.	Comparative case series with historical controls n=10 patients with early stage prostate cancer. Hyaluronan gel injection combined with HDR brachytherapy (4 fractions of twice daily for a total dose of 22 Gy) followed by IMRT to 50.4 Gy in 28 daily fractions over 5.5 weeks. Dosimetric profiles of these patients were compared with 239 historical controls without gel. Follow-up: median 3 months	There was 0% incidence of rectal toxicity versus 30% in historical controls (p=0.04). In the HA spacer group, the mean rectal radiation dose V70 Gy was 4% (73Gy) compared with 25% (106 Gy) in the control group (p=0.005) without the spacer.	Included in systematic review added.
Wilder RB, Barme GA et al (2010). Cross-linked hyaluronan gel improves the quality of life of prostate cancer patients undergoing radiotherapy. Brachytherapy.	Case series with contemporary controls n=30 had cross-linked hyaluronan gel before brachytherapy and IMRT. controls n=5 without spacer Follow-up: median 5 months	Acute GI related quality of life: results showed that EPIC bowel bother scores did not change (0±3) pre versus post-treatment for the patients who had implanted pre-radiotherapy (n=30) but scores declined by 11±14 for those who did not have the intervention (p=0.03).	Larger studies with longer follow-up included.
Wei B, See A, El-Hage L et al (2016). Dosimetric and clinical effects of hydrogel insertion in patients receiving dose-escalated prostate radiotherapy: Interim analysis of a phase II trial. Journal of Medical Radiation Sciences (63) 37.	Case series N=42 men with histologically confirmed adenocarcinoma of the prostate. Insertion of a hydrogel into the retro prostatic space undergoing dose-escalated prostate radiotherapy.	Increased perirectal space in post hydrogel scans resulted in improvement in rectal dosimetry in all patients. Our early results demonstrated that dose escalation and rectal sparing can be achieved with the application of hydrogel.	Larger and longer follow-up studies included.
Wolf F, Gaisberger C et al (2015). Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. Radiotherapy & Oncology 116 (2) 221-225.	Comparative case series N=78 (30 spacer gel group versus 29 balloon spacer group versus 19 control group) patients with prostate cancer. Total dose was 75.85 Gy in daily fractional doses of 1.85 Gy prescribed to the 95% isodose using multisegmental 7-field and shoot IMRT. Follow-up 6 months.	Both spacer systems significantly reduced the rectum surface encompassed by the 95% isodose (gel: -35%, p<0.01; balloon -63.4%, p<0.001) compared to a control group. The balloon spacer was superior in reducing rectum dose (-27.7%, p=0.034), but exhibited an average volume loss of >50% during the full course of treatment of 37-40 fractions, while the volume of gel	Study included in systematic review added.

		spacers remained fairly constant.	
Wu SY, Boreta L, Wu A et al. (2018) Improved rectal dosimetry with the use of SpaceOAR during high-dose-rate brachytherapy. Brachytherapy. 17(2):259-64.	Cohort study N=18 patients with prostate cancer had HDR brachytherapy and underwent transperineal ultrasound-guided placement of 10 cc of SpaceOAR hydrogel. Then compared with 36 patients treated with HDR brachytherapy without SpaceOAR. Follow-up 13.3 months.	Patients who received SpaceOAR hydrogel had significantly lower dose to the rectum as measured by percent of contoured organ at risk (median, V80 ! 0.005% vs. 0.010%, p 5 0.003; V75 ! 0.005% vs. 0.14%, p ! 0.0005; V70 0.09% vs. 0.88%, p!0.0005; V60 5 1.16% vs. 3.08%, p!0.0005); similar results were seen for rectal volume in cubic centimetres. One patient who received SpaceOAR developed a perineal abscess 1 month after treatment.	Included in systematic review added.
Yang Y, Ford EC et al (2013).An overlap-volume-histogram based method for rectal dose prediction and automated treatment planning in the external beam prostate radiotherapy following hydrogel injection. Medical Physics.40 (1) (no pagination)	Case series n=21 prostate cancer patients Treatment planning both pre and post hydrogel injection with 5 field IMRT.	Application of the predicted rectum and bladder doses to automated planning produced acceptable treatment plans, with rectal dose reduced for eight of ten plans. The OVH metric can predict the rectal dose in the external beam prostate radiotherapy for patients with hydrogel injection. The predicted doses can be applied to the objectives of optimization in automated treatment planning to produce acceptable treatment plans.	Treatment planning study. Overlap volume histogram for rectal dose prediction evaluated.
Yang DX, Verma V, An Y et al (2020) Radiation dose to the rectum with definitive radiation therapy and hydrogel spacer versus postprostatectomy radiation therapy. Advances in Radiation Oncology, 5, 1225-1231	Retrospective analysis N=51 patients with prostate cancer who underwent RT with a hydrogel spacer (n=16) versus postoperative RT (n=35) Follow-up not reported.	Rectal dosimetry is more favourable for definitive RT (79.2 Gy) with a hydrogel spacer compared with postoperative RT (70.2 or 66.6 Gy).	Larger studies included.
Yeh J, Tokia K et al (2015). Rectal Spacer Injection in Postprostatectomy Patients Undergoing High-Dose Salvage External Beam. Oncology April (P141)	Case series n=32 patients who have had a prostatectomy and had high-dose (>72 Gy) salvage IRMT with the rectal spacer – Follow-up: 6 months	At the end of treatment, 23 patients (72%) had no change in rectal symptoms. Nine patients (28%) developed grade 1 gastrointestinal (GI) toxicity. No patients developed grade ≥ 2 GI toxicity. At 6 months after treatment, 29 patients (91%) were back to their baseline GI function, with only 3 patients (9%) with residual grade 1 GI toxicity. No	Poster presentation. Safety events reported.

		patients developed grade ≥ 2 GI toxicity.	
Yeh J, Lehrich B et al (2016). Polyethylene glycol hydrogel rectal spacer implantation in patients with prostate cancer undergoing combination high-dose-rate brachytherapy and external beam radiotherapy. Brachytherapy 15(3):283-287.	Case series N=326 prostate carcinoma patients had high-dose-rate brachytherapy 16 Gy and external beam radiotherapy of 59.4 Gy plus injected with 10 ml of a PEG hydrogel. Follow-up median 16 months	The mean anterior-posterior separation achieved was 1.6 cm (SD = 0.4 cm). Rates of acute Grade 1 and 2 rectal toxicity were 37.4% and 2.8%, respectively. There were no acute Grade 3/4 toxicities. Rates of late Grade 1, 2, and 3 rectal toxicity were 12.7%, 1.4%, and 0.7%, respectively. There were no late Grade 4 toxicities. PEG rectal spacer implantation is safe and well tolerated. Acute and chronic rectal toxicities are low despite aggressive dose escalation.	Included in systematic review added.
Zelefsky MJ, Pinitpatcharalert A, Kollmeier M, et al. Early tolerance and tumor control outcomes with high-dose ultrahypofractionated radiation therapy for prostate cancer. European Urology Oncology. 2019; doi: https://dx.doi.org/10.1016/j.euo.2019.09.006	Case series (retrospective) N=551 patients with low- or intermediate-risk prostate cancer were treated with 37.5–40 Gy SBRT in 5 fractions. 85% (471/551) received 40 Gy in 8 fractions. Follow-up 17 months SBRT	Acute grade 2 gastrointestinal (GI) toxicities occurred in 1.8% of patients, and late grade 2 and 3 GI toxicities were observed in 3.4% and 0.4% of patients, respectively. Acute grade 2 genitourinary (GU) toxicities occurred in 10% of patients, and grade 3 acute GU toxicities were observed in 0.7% of patients. Late grade 2 and 3 GU toxicities were observed in 21.1% and 2.5% of patients, respectively. The use of a hydrogel rectal spacer was significantly associated with reduced late GI toxicity and lower odds of developing late GU toxicity. The median follow-up was 17 months, and 53% of those with at least 2 years of follow up (103/193) had a biopsy performed. The 5-yr cumulative incidence of PSA failure was 2.1%, and the incidence of a positive 2-yr treatment biopsy was 12%. Limitations to this report include its retrospective nature and short follow-up time.	Included in systematic review added.
Zhang H, Wang L, Riegel AC et al. (2022) Biological effective dose in analysis of rectal dose in prostate cancer patients who underwent a combination therapy of VMAT and LDR with hydrogel spacer insertion. Journal of applied clinical	Retrospective analysis Prostate cancer patients who underwent a combination of volumetric modulated arc therapy (VMAT) and low-dose-rate (LDR) brachytherapy (35 with **hydrogel spacer** and 30 with no spacer)	Our result suggested a significant reduction of rectal doses in those patients who underwent a combination of VMAT and LDR with hydrogel spacer placement.	Dosimetry impact analysis. Larger studies with longer follow-up included.

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INTERVENTIONAL PROCEDURES PROGRAMME

Equality impact assessment

Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

The impact on equality has been assessed during guidance development according to the principles of the NICE Equality scheme.

Briefing

1. Have any potential equality issues been identified during the scoping process (development of the scope or discussion at the Committee meeting), and, if so, what are they?
Prostate cancer is the most common cancer in men, accounting for approximately 25% of new diagnoses of cancer in men and 12% of all cancers. Prostate cancer increases with age. Most cases develop in men aged 70 or older. In the UK, men of African-Caribbean or African descent have approximately two to three times the risk of being diagnosed or dying from prostate cancer than white men. Asian men generally have a lower risk than the national average. There is a higher incidence of prostate cancer in the less socio-economically deprived areas, which is assumed to be due to higher rates of prostate specific antigen (PSA) testing among affluent men All people with cancer are covered by the disability provision of the Equality Act 2010 from the point of diagnosis.

2. What is the preliminary view as to what extent these potential equality issues need addressing by the Committee? If there are exclusions listed in the scope (for example, populations, treatments or settings), are these justified?
This was not thought to have an impact on the assessment of the procedure. No exclusions were applied.

3. Has any change to the scope (such as additional issues raised during the Committee meeting) been agreed to highlight potential equality issues?

No

4.	Have any additional stakeholders related to potential equality issues been identified during the committee meeting, and, if so, have changes to the stakeholder list been made?’
No	

Kevin Harris

Approved by Programme Director and Clinical Advisor

Date: 30/11/2022

Consultation

1.	Have the potential equality issues identified during the scoping process been addressed by the Committee, and, if so, how?
No specific data relating to the potential equality issues were identified in the literature presented in the overview.	

2.	Have any other potential equality issues been raised in the overview, specialist adviser questionnaires or patient commentary, and, if so, how has the Committee addressed these?
No	

3.	Have any other potential equality issues been identified by the Committee, and, if so, how has the Committee addressed these?
No	

4.	Do the preliminary recommendations make it more difficult in practice for a specific group to access a technology or intervention compared with other groups? If so, what are the barriers to access for the specific group?
No	

5.	Are there any recommendations or explanations that the Committee could make to remove or alleviate barriers to access identified in question 4, or otherwise fulfil NICE's obligation to promote equality?
Not applicable	

6.	Have the Committee's considerations of equality issues been described in the consultation document, and, if so, where?
Not applicable	

Kevin Harris

Approved by Programme Director and Clinical Advisor

Date: 30/11/2022

Final interventional procedures document

1.	Have any additional potential equality issues been raised during the consultation, and, if so, how has the Committee addressed these?
No	

2.	If the recommendations have changed after consultation, are there any recommendations that make it more difficult in practice for a specific group to access a technology or intervention compared with other groups? If so, what are the barriers to access for the specific group?
Not applicable	

3.	If the recommendations have changed after consultation, is there potential for the preliminary recommendations to have an adverse impact on people with disabilities because of something that is a consequence of the disability?
Not applicable	

4.	If the recommendations have changed after consultation, are there any recommendations or explanations that the Committee could make to remove or alleviate barriers to access identified in question 2, or otherwise fulfil NICE's obligations to promote equality?
Not applicable	

5.	Have the Committee's considerations of equality issues been described in the final interventional procedures document, and, if so, where?
No	

Anastasia Chalkidou

Approved by Associate Director

Date: 02/12/2022

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Original Investigation | Oncology

Association of the Placement of a Perirectal Hydrogel Spacer With the Clinical Outcomes of Men Receiving Radiotherapy for Prostate Cancer

A Systematic Review and Meta-analysis

Larry E. Miller, PhD, PStat; Jason A. Efstathiou, MD, DPhil; Samir K. Bhattacharyya, PhD; Heather A. Payne, FRCR, FRCP; Emily Woodward, MSc; Michael Pinkawa, MD, PhD

Abstract

IMPORTANCE Perirectal spacers are intended to lower the risk of rectal toxic effects associated with prostate radiotherapy. A quantitative synthesis of typical clinical results with specific perirectal spacers is limited.

OBJECTIVE To evaluate the association between perirectal hydrogel spacer placement and clinical outcomes of men receiving radiotherapy for prostate cancer.

DATA SOURCES A systematic search was performed of the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase for articles published through September 2019.

STUDY SELECTION Studies comparing men who received a hydrogel spacer vs men who did not receive a spacer (controls) prior to prostate radiotherapy.

DATA EXTRACTION AND SYNTHESIS Via random-effects meta-analysis, group comparisons were reported using the weighted mean difference for continuous measures and the risk ratio for binary measures.

MAIN OUTCOMES AND MEASURES Procedural results, the percentage volume of rectum receiving at least 70 Gy radiation (v70), early (≤3 months) and late (>3 months) rectal toxic effects, and early and late changes in bowel-related quality of life on the Expanded Prostate Cancer Index Composite (minimal clinically important difference, 4 points).

RESULTS The review included 7 studies (1 randomized clinical trial and 6 cohort studies) involving 1011 men (486 who received a hydrogel spacer and 525 controls), with a median duration of patient follow-up of 26 months (range, 3-63 months). The success rate of hydrogel spacer placement was 97.0% (95% CI, 94.4%-98.8% [5 studies]), and the weighted mean perirectal separation distance was 11.2 mm (95% CI, 10.1-12.3 mm [5 studies]). Procedural complications were mild and transient, occurring in 0% to 10% of patients within the studies. The hydrogel spacer group received 66% less v70 rectal irradiation compared with controls (3.5% vs 10.4%; mean difference, −6.5%; 95% CI, −10.5% to −2.5%; $P = .001$ [6 studies]). The risk of grade 2 or higher rectal toxic effects was comparable between groups in early follow-up (4.5% in hydrogel spacer group vs 4.1% in control group; risk ratio, 0.82; 95% CI, 0.52-1.28; $P = .38$ [6 studies]) but was 77% lower in the hydrogel spacer group in late follow-up (1.5% vs 5.7%; risk ratio, 0.23; 95% CI, 0.06-0.99; $P = .05$ [4 studies]). Changes in bowel-related quality of life were comparable between groups in early follow-up (mean difference, 0.2; 95% CI, −3.1 to 3.4; $P = .92$ [2 studies]) but were greater in the hydrogel spacer group in late follow-up (mean difference, 5.4; 95% CI, 2.8-8.0; $P < .001$ [2 studies]).

(continued)

Key Points

Question What is the association between perirectal hydrogel spacer placement and clinical outcomes of men receiving radiotherapy for prostate cancer?

Findings This systematic review and meta-analysis, including results from 7 studies with 1011 patients receiving prostate cancer radiotherapy, found that perirectal hydrogel spacer placement was associated with less rectal irradiation, fewer rectal toxic effects, and higher bowel-related quality of life in long-term follow-up.

Meaning Perirectal hydrogel spacer placement prior to prostate radiotherapy may be a prudent preventive strategy for reduction of radiotherapy-induced rectal complications.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Clinically Localized Prostate Cancer: AUA/ASTRO Guideline. Part III: Principles of Radiation and Future Directions

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Abbreviations and Acronyms

3DCRT = 3-D conformal radiation therapy
ADT = Androgen deprivation therapy
ASCO = American Society of Clinical Oncology
ASTRO = American Society for Radiation Oncology
AUA = American Urological Association
CI = Confidence interval
CT = Computed tomography
DE-EBRT = Dose-escalated external beam radiation therapy
EBRT = External beam radiation therapy
GC = Genomic classifier
HDR = High-dose rate
HR = Hazard ratio
IMRT = Intensity-modulated radiation therapy
LDR = Low-dose rate
LHRH = Luteinizing hormone-releasing hormone
MRI = Magnetic resonance imaging
NCCN = National Comprehensive Cancer Network
NGI = Next generation imaging
PBRT = Proton beam radiation therapy
PET = Positron emission tomography
PFS = Progression-free survival
PSMA = Prostate-specific membrane antigen
QOL = Quality of life
RR = Relative risk
SBRT = Stereotactic body radiation therapy
VMAT = Volumetric modulated arc therapy

Purpose: The summary presented herein represents Part III of the three-part series dedicated to Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, discussing principles of radiation and offering several future directions of further relevant study in patients diagnosed with clinically localized prostate cancer. Please refer to Parts I and II for discussion of risk assessment, staging, and risk-based management (Part I), and principles of active surveillance and surgery and follow-up (Part II).

Materials and Methods: The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. A research librarian conducted searches in Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. The methodology team supplemented searches of electronic databases with the studies included in the prior AUA review and by reviewing reference lists of relevant articles.

Results: The Clinically Localized Prostate Cancer Panel created evidence- and consensus-based guideline statements to aid clinicians in the management of patients with clinically localized prostate cancer. Statements regarding management of patients using radiation therapy as well as important future directions of research are detailed herein.

Conclusions: This guideline aims to inform clinicians treating patients with clinically localized prostate cancer. Continued research and

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publication of high-quality evidence from future trials will be essential to further improve care for these men.

Key Words: Prostate cancer, Radical prostatectomy, Radiation therapy for prostate cancer, Active surveillance, Shared decision making

BACKGROUND

The selection of a management strategy for clinically localized prostate cancer is preference-sensitive and very often based on patients' interpretation of the balance between treatment-specific risks and benefits. The content summarized herein outlines principles of radiation therapy for patients electing this management strategy and provides a discussion of several relevant topics of continued investigation in localized prostate cancer.

As is common with other tumor systems in which radiation therapy is delivered for therapeutic benefit, an overarching paradigm in prostate cancer radiation therapy is the application of appropriate evidence-based dosages to the cancer target while simultaneously avoiding sensitive adjacent normal tissues. In this way, the therapeutic ratio between tumor control and normal tissue injury is established to maximize therapeutic benefit while minimizing toxicity, morbidity, and potentially treatment-related mortality. Over the past few decades, the specialty of radiation oncology has leveraged various technologies to achieve this goal of improved cancer outcomes with equal or improved toxicity profiles.

GUIDELINE STATEMENTS

Principles of Radiation

27. Clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of external beam radiation therapy (EBRT) delivered for prostate cancer. (Clinical Principle)

A variety of approaches exist to optimize the therapeutic ratio in radiation oncology. A non-exhaustive list of these approaches include the following:

- Simulation procedures: Bladder/rectum filling instructions, patient immobilization, placement of fiducial markers, and use of rectal spacers
- Imaging procedures: Computed tomography (CT) simulations, integrations of fusion imaging (eg, magnetic resonance imaging [MRI prostate), image-guided radiation therapy approaches (eg, cone-beam CT)
- Planning procedures: Use of highly conformal radiation therapy such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic body radiation therapy (SBRT), combined with published target and normal tissue dose objectives to optimize planning

Most of these approaches have not been subject to prospective randomized phase III trial testing. One exception is the use of rectal spacers, which was evaluated in a trial that randomized 222 patients 2:1 to either a rectal spacer or control group prior to 79.2 Gy in 1.8 Gy fractions to the prostate±seminal vesicles.[1,2] With a median follow-up of three years, improvements in low-grade (one and two) rectal toxicity, no difference in urinary toxicity, and improvements in bowel health-related quality of life (QOL) were identified.[2] Device-related toxicity events were not detected in this trial.[1] Of note, the utility of this technology in conjunction with hypofractionated or ultra hypofractionated radiation therapy has not been reported in prospective randomized clinical trials to date.

28. Clinicians should utilize dose escalation when EBRT is the primary treatment for patients with prostate cancer. (Strong Recommendation; Evidence Level: Grade A)

Since the 1990s, multiple phase III randomized prospective studies have compared dose-escalated EBRT (DE-EBRT) using both 3-D conformal radiation therapy (3DCRT) and IMRT with standard dose EBRT and have consistently demonstrated improved biochemical progression-free survival (PFS) with dose escalation. Multiple randomized trials have compared escalated versus conventional dose radiation therapy in patients with localized prostate cancer.[3–11] The trials enrolled a mix of low-, intermediate-, and high-risk patients. The trials consistently demonstrated that escalated dose radiation therapy was associated with decreased rates of biochemical failure or recurrence. Of note, the Panel acknowledges that estimates from these trials for the endpoints of metastatic-disease free survival, prostate cancer-specific survival, and overall survival were imprecise and did not indicate a benefit to dose escalation, with the exception of one trial[6–8] that did report reduced risks of distant metastatic failure (Hazard Ration [HR] 0.33, 95% Confidence Interval [CI] 0.13 to 0.82) and prostate cancer mortality (HR 0.52, 95% CI 0.27 to 0.98). The largest of the trials was NRG-RTOG 0126 (n=1,499) which looked at standard versus dose-escalated radiation therapy in patients with intermediate-risk prostate cancer.[11] This trial demonstrated improvements in biochemical failure and distant metastases; however, the dose-escalated radiation therapy arm

was not associated with improvements in overall survival. Furthermore, higher radiation doses were also associated with lower rates of post-radiation salvage at the expense of higher rates of late toxicity. Importantly, this trial has provided clinicians valuable information about radiation dose constraints for the safe planning of dose-escalated radiation therapy for intermediate-risk prostate cancer.[11]

29. Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (Conditional Recommendation; Evidence Level: Grade C)

To date, no prospective study has demonstrated improved disease control or side effects with proton beam radiation therapy (PBRT) compared to IMRT. Proponents of PBRT have offered that it has dosimetric advantages compared to IMRT. That is, while the target volume for both techniques includes the prostate and a margin of normal tissue (bladder and rectum) that is irradiated to the prescribed dose, proton beam delivers lower integral doses and mean doses to normal tissues than IMRT.[12] However, this dosimetric difference has not been shown to result in fewer side effects or better patient reported QOL. Indeed, the existing peer-reviewed literature suggests that clinical outcomes (eg, complications, patient reported QOL) are similar.[13] Randomized trials are ongoing comparing IMRT and PBRT using long-term side effects and QOL as the primary endpoints (eg, PARTIQoL, which has a primary endpoint of bowel function at 24 months).

30. Clinicians should offer moderate hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (Strong Recommendation; Evidence Level: Grade A)

31. Clinicians may offer ultra hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (Conditional Recommendation; Evidence Level: Grade B)

Using fewer (but larger dose) radiation treatments (ie, hypofractionation) may be more convenient for patients with prostate cancer electing radiation therapy.[14] A systematic review compared hypofractionated (>2 Gy per fraction, range 2.35 to 3.4 Gy) versus conventionally fractionated (1.8 to 2 Gy) EBRT in patients with localized prostate cancer.[14] This review included 10 randomized trials (N=8,278). In pooled analyses, no differences were noted between hypofractionation versus conventional fractionation with regard to biochemical recurrence-free survival (HR 0.88, 95% CI 0.68 to 1.13, 5 trials), metastasis-free survival (HR 1.07, 95% CI 0.65 to 1.76, 5 trials), prostate cancer-specific survival (HR 1.00, 95% CI 0.72 to 1.39, 8 trials), or overall survival (HR 0.94, 95% CI 0.83 to 1.07, 10 trials). There were also no differences identified with regard to acute genitourinary radiation therapy toxicity (Relative Risk [RR] 1.03, 95% CI 0.95 to 1.11), late genitourinary radiation therapy toxicity (RR 1.05, 95% CI 0.93 to 1.18), or late gastrointestinal radiation therapy toxicity (RR 1.10, 95% CI 0.68 to 1.78).

One randomized trial (HYPO-RT, n=1,200) compared ultra hypofractionation (42.7 Gy in 7 fractions, fraction size 6.1 Gy) versus conventional fractionation (78.0 Gy in 39 fractions, fraction size 2 Gy) in patients undergoing radiation therapy with image-guided 3DCRT, IMRT, or VMAT for intermediate- or high-risk localized prostate cancer.[15,16] Ultra fractionation was found to be non-inferior to conventional fractionation with regard to failure-free survival (HR 1.00, 95% CI 0.76 to 1.32), prostate cancer mortality (incidence at 5 years 2% versus 1%, p=0.46), and overall survival (HR 1.11, 95% CI 0.73 to 1.69). In addition, although ultra hypofractionation was associated with increased incidence of acute urinary and bowel symptoms, no differences were found in late symptoms or QOL.

Currently, data on long-term control with ultra hypofractionated compared to moderate hypofractionation is less well documented; however, data to date support the use of hypofractionated EBRT. Of note, the recommendations herein are consistent with existing guidance provided by American Society for Radiation Oncology (ASTRO)/American Society of Clinical Oncology (ASCO)/American Urological Association (AUA).[17]

32. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment. (Strong Recommendation; Evidence Level: Grade B)

Trial data support the use of dose-escalated hypofractionated EBRT or brachytherapy including temporary HDR or permanent LDR prostate implants as appropriate treatment options for patients with low- or favorable intermediate-risk prostate cancer.[18]

Importantly, the systematic review undertaken for guideline development identified no randomized trials comparing EBRT to brachytherapy. Of note, a recent retrospective analysis among patients with intermediate-risk prostate cancer (n=684) found no difference between EBRT (75.3 Gy) versus brachytherapy (radioactive iodine seeds at minimum peripheral dose of 145 Gy), with or without neoadjuvant

androgen deprivation therapy (ADT), in propensity score adjusted 10-year metastasis-free survival (91% versus 94%), prostate cancer-specific survival (96% versus 95%), or overall survival (76% versus 78%).[19] EBRT was associated with decreased likelihood of freedom from biochemical failure (57% versus 80%).

To note as well, in a Phase II trial of 170 patients randomized to receive HDR as either a single (19 Gy) fraction or as two fractions (13.5 Gy), the 5-year biochemical disease-free survival and cumulative incidence of local failure was 73.5% and 29% in the single fraction arm and 95% ($p=0.001$) and 3% ($p<0.001$) in the 2-fraction arm, respectively.[20] Toxicity results from this study were reported separately; in the single fraction arm, the 5-year cumulative incidence of Grade 2 or higher genitourinary and gastrointestinal toxicity was 62% and 12%, and was 47% and 9% in the two-fraction arm. Grade 3 genitourinary toxicity was only seen in the single fraction arm. No significant differences in mean urinary health related QOL were seen compared to baseline in the two-fraction arm, in contrast to the single-fraction arm, wherein a decline in urinary health-related QOL was seen at 4 and 5 years. The authors ultimately concluded that both single fraction and 2-fraction HDR monotherapy were well tolerated.[21]

33. In patients with low- or intermediate-risk prostate cancer electing radiation therapy, clinicians should not electively radiate pelvic lymph nodes. (Strong Recommendation; Evidence Level: Grade B)

A prior trial ($n=446$) that compared whole pelvis (46 Gy with cone-down to prostate) to prostate only (66 to 70 Gy) radiation therapy among low-, intermediate-, and high-risk patients with clinical stage T1b-T3 localized prostate cancer found no difference in PFS (adjusted HR 0.96, 95% CI 0.64 to 1.43) or overall survival between the treatment arms.[22,23] Similarly, the RTOG 9413 trial, which contained intermediate-risk patients and utilized a 2 x 2 factorial design, demonstrated no significant difference in biochemical failure when comparing whole pelvic radiation therapy to prostate only radiation.[24–26] As these are the only prospective trials with sub-groups of intermediate-risk patients, and no benefit was found with nodal radiation, the Panel recommends against the routine use of elective pelvic nodal irradiation for low- and intermediate-risk patients electing radiation therapy.

34. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should not routinely use ADT. (Moderate Recommendation; Evidence Level: Grade B)

ADT is associated with well-recognized side effects and may significantly impact patients' health-related QOL. These side effects commonly include (but are not limited to) decreased libido, erectile dysfunction, hot flashes, depression and other mood disturbances, fatigue, and weight gain. In addition, treatment with ADT may result in significant changes in metabolic function, including reduction in bone mineral density, increased insulin resistance, and changes in blood lipid profiles.[27]

Given the potential deleterious short- and long-term effects of ADT, its application in the treatment of localized prostate cancer must be based on an individualized risk-benefit balance. In a large trial ($n=2,028$) that included patients in all risk strata, the use of ADT was not associated with improved overall survival outcome for low-risk patients (HR 0.93, 95% CI 0.72 to 1.20).[28] Moreover, although trials have demonstrated a benefit to ADT with radiation for intermediate-risk patients, these trials have not consistently sub-stratified intermediate-risk patients into favorable and unfavorable risk for separate outcome reporting. The Panel believes that routine use of ADT in favorable intermediate-risk patients is not recommended given the observed positive cancer outcomes of radiotherapeutic monotherapy for this patient population (acknowledging the exception of unique circumstances such as planned prostate gland volume reduction prior to definitive radiation therapy, in which ADT may be useful). At the same time, the Panel recognizes that the utility of ADT for favorable intermediate-risk localized prostate cancer is currently under investigation (eg, NRG Oncology/RTOG 0815).

35. In patients with unfavorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer the addition of short-course (four to six months) ADT with radiation therapy. (Strong Recommendation; Evidence Level: Grade A)

Given the higher risk of local and distant relapse with unfavorable intermediate-risk disease, the use of ADT is recommended for this patient population. Multiple randomized trials have evaluated the role of ADT with radiation therapy versus radiation therapy alone.[29–32] These studies collectively demonstrated a consistent benefit with regard to oncologic outcomes among the patients who received ADT with radiation. The benefit of hormonal therapy was also demonstrated in the recently published MARCAP meta-analysis, which demonstrated that the addition of ADT to radiotherapy significantly improved metastasis-free survival (HR 0.83, 95% CI 0.77 to 0.89, $p<0.0001$).[33]

With regard to the duration of ADT with radiation in unfavorable intermediate-risk disease, multiple clinical trials have assessed very short course ADT (eight weeks to three months) versus standard short course ADT (six months) in intermediate-risk

disease, some of which have demonstrated that the six-month approach had superior cancer outcomes, including all-cause mortality and/or prostate cancer-specific mortality.[34–39] Nevertheless, the Panel acknowledges that a four-month course of ADT is also commonly given to patients with radiation therapy for intermediate-risk disease in an effort to mitigate the deleterious effects of ADT while maintaining the benefit of combination therapy for cancer control.

36. Clinicians should offer moderate hypofractionated EBRT for patients with high-risk prostate cancer who are candidates for EBRT. (Moderate Recommendation; Evidence Level: Grade C)

As noted above, moderate hypofractionation holds important advantages in terms of patient convenience and resource utilization. Moreover, large-scale randomized prospective clinical trials have been completed comparing moderately hypofractionated and conventionally fractionated EBRT.[4,40] These studies have demonstrated that moderate hypofractionation confers similar prostate-cancer-control outcomes and similar rates of late toxicity compared to conventional fractionation. In one study, men with intermediate-to high-risk prostate adenocarcinoma were randomized to receive C-IMRT (76 Gy in 38 fractions; n=152) or H-IMRT (70.2 Gy in 26 fractions; n=151).[40] High-risk patients were prescribed 24 months of ADT. Intermediate-risk patients were prescribed 4 months of ADT at the discretion of the treating physician. The primary end point was the cumulative incidence of biochemical and/or clinical disease failure. Median follow up was 130 months. Ten-year biochemical disease free survival was similar in both arms (25.9% in the C-IMRT arm and 30.6% in the H-IMRT arm; HR 1.31, 95% CI 0.82 to 2.11). The two treatment groups also had similar rates of 10-year freedom from metastatic disease, prostate cancer-specific, and overall survival. The authors concluded that H-IMRT demonstrated no difference in disease outcomes when compared to C-IMRT at 10 years.

Of note, ultra hypofractionation in high-risk patients receiving EBRT with elective nodal coverage is not currently recommended outside a clinical trial or multi-institutional registry due to insufficient comparative evidence.

37. In patients with unfavorable intermediate- or high-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT or combined EBRT+brachytherapy (LDR, HDR) along with a risk-appropriate course of ADT. (Strong Recommendation; Evidence Level: Grade A/B)

Trials have demonstrated a benefit in clinical control for unfavorable intermediate- or high-risk prostate cancer patients who receive either dose-escalated moderately hypofractionated IMRT or EBRT plus a brachytherapy boost (HDR temporary prostate implant or LDR permanent prostate implant).[41–46] Combining EBRT and brachytherapy has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials.[41–44]

Interestingly, the phase III randomized ASCENDE-RT trial compared two methods of dose escalation in 398 patients with intermediate- or high-risk prostate cancer: dose-escalated EBRT boost to 78 Gy or LDR brachytherapy boost.[44–46] All patients were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. The primary endpoint of control (biochemical, no evidence of disease) was 89% versus 84% at 5 years; 86% versus 75% at 7 years; and 83% versus 62% at 9 years for the LDR versus EBRT boost arms (log-rank $p < 0.001$). However, toxicity was higher in the brachytherapy arm, with a cumulative incidence of grade 3 genitourinary events at 5 years of 18.4% for brachytherapy boost and 5.2% for EBRT boost ($p < 0.001$). In addition, increased gastrointestinal toxicity among patients treated with a brachytherapy boost was also seen (cumulative incidence of grade 3 events at 5 years, 8.1% versus 3.2%; $p = 0.12$).

38. In patients with high-risk prostate cancer electing radiation therapy, clinicians may offer radiation to the pelvic lymph nodes. (Conditional Recommendation; Evidence Level: Grade B)

39. When treating the pelvic lymph nodes with radiation, clinicians should utilize IMRT with doses between 45 Gy to 52 Gy. (Strong Recommendation; Evidence Level: Grade B)

The recently published POP-RT trial randomized patients (n=224) with National Comprehensive Cancer Network (NCCN) high- (~50%) and very high-risk (~50%) prostate cancer[47] to IMRT to the whole pelvis (68 Gy in 25 fractions to prostate with 50 Gy to pelvic lymph nodes) versus prostate-only (68 Gy). This currently represents the only trial of elective pelvic nodal irradiation that delivered both modern standard-of-care radiotherapy doses and ADT duration while looking exclusively at high-risk patients.

All patients received ADT (surgical or medical) starting eight weeks prior to radiation therapy; medical ADT was via a luteinizing hormone-releasing hormone (LHRH) agonist and was administered for two years. The trial demonstrated improved 5-year biochemical failure-free survival (HR 0.23, 95% CI 0.10 to 0.52; trial's primary endpoint), distant metastasis-free survival (HR 0.35, 95% CI 0.15 to 0.82), and disease-free survival (HR 0.40, 95% CI 0.22 to 0.73) with whole pelvis IMRT, although no difference was detected in overall survival (HR 0.92, 95% CI 0.41 to 2.05).

Despite not showing an overall survival benefit, the Panel notes that elective nodal irradiation for high-risk patients may be offered given the reasonable morbidity (higher late grade II genitourinary toxicity with whole pelvis radiation but no difference in late gastrointestinal toxicity and no difference in grade III/IV genitourinary or gastrointestinal toxicity noted) as well as the reductions in biochemical failure and distant metastases.

40. In patients with high-risk prostate cancer electing radiation therapy, clinicians should recommend the addition of long-course (18 to 36 months) ADT with radiation therapy. (Strong Recommendation; Evidence Level: Grade A)

The primary evidence for the use of ADT with radiation in high-risk disease comes from EORTC 22863, a trial that randomized 415 patients with locally advanced prostate cancer to 3 years of ADT plus 70 Gy of prostate radiation therapy versus radiation therapy alone.[29,30,48,49] Benefits were noted in the combination treatment arm with regard to both prostate cancer-specific survival (HR 0.38, 95% CI 0.24 to 0.60) and overall survival (HR 0.60, 95% CI 0.45 to 0.80). From this study, three years of ADT was established as a reference standard ADT treatment for the duration of combined ADT with radiation therapy in the treatment of patients with high-risk prostate cancer. A subsequent RCT among high-risk patients tested 18 versus 36 months of ADT.[39] This trial did not demonstrate differences in disease-free survival, disease-specific survival, or overall survival between the treatment durations, and has thereby introduced a minimum threshold duration of ADT when combined with radiation therapy for the management of high-risk disease.

41. When combined ADT and radiation are used, ADT may be initiated neoadjuvantly, concurrently, or adjuvantly. (Conditional Recommendation; Evidence Level: Grade C)

42. When combining ADT with radiation therapy, clinicians may use combined androgen suppression (LHRH agonist with an anti-androgen), an LHRH agonist alone, or an LHRH antagonist alone. (Expert Opinion)

Various compositions of ADT have been used in combination with radiation in the randomized trials to date. The Panel believes that clinicians may use any one of these options in combination with radiation.

FUTURE DIRECTIONS

Clinically localized prostate cancer remains among the most active areas of investigation in urology. As such, patient care will likely continue to be refined—and enhanced—in the near future.

Treatment Intensification for High-Risk Disease

The STAMPEDE trial results showing a benefit to the addition of abiraterone to ADT in very high-risk localized and node positive disease has ignited interest in treatment intensification in this patient population.[50] Multiple trials evaluating next generation androgen signaling inhibitors in high-risk clinically localized disease have either fully accrued or are currently accruing.

Genomic Classifiers (GC)

The ability for commercially available GCs to improve the outcomes of patients with clinically localized prostate cancer has not been validated in prospective clinical trials to date. Prospective validation of the predictive capacity of GCs in localized disease will be important to support widespread use for treatment selection. Several ongoing clinical trials are indeed evaluating treatment intensification and de-intensification based on GC results in both intermediate- and high-risk patient populations.

Advanced Imaging

A number of novel imaging radiotracers utilizing positron emission tomography (PET)-based technology have emerged over the past several years and have been demonstrated to improve detection of disease over conventional imaging. Broadly, these imaging modalities have been referred to as next generation imaging (NGI), and among these, prostate-specific membrane antigen (PSMA)-based PET scanning has received the most attention. This interest has been bolstered by recent US FDA approval of two PSMA based tracers: Gallium 68 PSMA-11 (Ga 68 PSMA-11) and piflufolastat F-18 (18F-DCFPyL). Moreover, continued evaluation of novel PSMA PET agents remains ongoing. As such, PSMA PET may become an accepted standard in the staging evaluation of patients with localized high-risk prostate cancer. Nevertheless, future studies are needed to determine how the information from NGI should be incorporated into clinical decision-making due to both the limitations of these advanced imaging techniques and the fact that the data to date on outcomes following treatment upon which management recommendations are based stem from patients evaluated with conventional imaging. Prospective studies incorporating NGI as staging will be required to determine clinical utility. Until such data are available, clinicians should exercise caution when using PSMA PET results to justify substantial alterations in standard-of-care treatments the utility of which has been established among patients who were staged with conventional imaging.

REFERENCES

1. Mariados N, Sylvester J, Shah D et al: Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2015; **92:** 971.
2. Hamstra DA, Mariados N, Sylvester J et al: Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. Int J Radiat Oncol Biol Phys 2017; **97:** 976.
3. Beckendorf V, Guerif S, Le Prise E et al: 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011; **80:** 1056.
4. Dearnaley D, Syndikus I, Mossop H et al: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016; **17:** 1047.
5. Dearnaley DP, Jovic G, Syndikus I et al: Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol 2014; **15:** 464.
6. Kuban DA, Tucker SL, Dong L et al: Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008; **70:** 67.
7. Pasalic D, Kuban DA, Allen PK et al: Dose escalation for prostate adenocarcinoma: a long-term update on the outcomes of a phase 3, single institution randomized clinical trial. Int J Radiat Oncol Biol Phys 2019; **104:** 790.
8. Pollack A, Zagars GK, Starkschall G et al: Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002; **53:** 1097.
9. Zietman AL, Bae K, Slater JD et al: Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/American College of Radiology 95-09. J Clin Oncol 2010; **28:** 1106.
10. Zietman AL, DeSilvio ML, Slater JD et al: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005; **294:** 1233.
11. Michalski JM, Moughan J, Purdy J et al: Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer. JAMA Oncol 2018; **4:** e180039.
12. Cella L, Lomax A, Miralbell R et al: Potential role of intensity modulated proton beams in prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 2001; **49:** 217.
13. Coen JJ, Paly JJ, Niemierko A et al: Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2012; **82:** e201.
14. Hickey BE, James ML, Daly T et al: Hypofractionation for clinically localized prostate cancer. Cochrane Database Syst Rev 2019; **9:** CD011462.
15. Widmark A, Gunnlaugsson A, Beckman L et al: Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019; **394:** 385.
16. Fransson P, Nilsson P, Gunnlaugsson A et al: Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. Lancet Oncol 2021; **22:** 235.
17. Morgan SC, Hoffman K, Loblaw DA et al: Hypofractionated radiation therapy for localized prostate cancer: an ASTRO, ASCO, and AUA evidence-based guideline. J Clin Oncol 2018; **36:** JCO1801097.
18. Hathout L, Mahmoud O, Wang Y et al: A Phase 2 randomized pilot study comparing high-dose-rate brachytherapy and low-dose-rate brachytherapy as monotherapy in localized prostate cancer. Adv Radiat Oncol 2019; **4:** 631.
19. Goy BW, Burchette R, Soper MS et al: Ten-year treatment outcomes of radical prostatectomy vs external beam radiation therapy vs brachytherapy for 1503 patients with intermediate-risk prostate cancer. Urology 2020; **136:** 180.
20. Morton G, McGuffin M, Chung HT et al: Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol 2020; **146:** 90.
21. Corkum M, Loblaw A, Hasan Y et al: Prostate high dose-rate brachytherapy as monotherapy for prostate cancer: late toxicity and patient reported outcomes from a randomized phase II clinical trial. Radiother Oncol 2021; **156:** 160.
22. Pommier P, Chabaud S, Lagrange JL et al: Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 2007; **25:** 5366.
23. Pommier P, Chabaud S, Lagrange JL et al: Is there a role for pelvic irradiation in localized prostate adenocarcinoma? update of the long-term survival results of the GETUG-01 randomized study. Int J Radiat Oncol 2016; **96:** 759.
24. Roach M III, DeSilvio M, Lawton C et al: Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: radiation Therapy Oncology Group 9413. J Clin Oncol 2003; **21:** 1904.
25. Roach M, Moughan J, Lawton CAF et al: Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. Lancet Oncol 2018; **19:** 1504.
26. Lawton CA, DeSilvio M, Roach M III et al: An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys 2007; **69:** 646.
27. Nguyen PL, Alibhai SM, Basaria S et al: Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol 2015; **67:** 825.
28. Jones CU, Hunt D, McGowan DG et al: Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011; **365:** 107.
29. Ataman F, Zurlo A, Artignan X et al: Late toxicity following conventional radiotherapy for prostate cancer: analysis of the EORTC trial 22863. Eur J Cancer 2004; **40:** 167481.
30. Bolla M, Maingon P, Carrie C et al: Short androgen suppression and radiation dose escalation for intermediate- and high-risk localized prostate cancer: results of EORTC Trial 22991. J Clin Oncol 2016; **34:** 1748.
31. McPartlin AJ, Glicksman R, Pintilie M et al: PMH 9907: long-term outcomes of a randomized phase 3 study of short-term bicalutamide hormone therapy and dose-escalated external-beam radiation therapy for localized prostate cancer. Cancer 2016; **122:** 2595.
32. Vargas CE, Alam NB, Terk M et al: Initial results of a randomized phase III trial of high dose image guided radiation with or without androgen deprivation therapy for intermediate-risk prostate cancer. Cancer Treat Res Commun 2019; **19:** 100119.
33. Kishan AU, Sun Y, Hartman H et al: Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol 2022; **23:** 304.
34. Bolla M, de Reijke TM, Van Tienhoven G et al: Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009; **360:** 2516.
35. Denham JW, Joseph D, Lamb DS et al: Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate

cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. Lancet Oncol 2019; **20:** 267.

36. Hanks GE, Pajak TF, Porter A et al: Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol 2003; **21:** 3972.

37. Pisansky TM, Hunt D, Gomella LG et al: Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation Therapy Oncology Group randomized clinical trial 9910. J Clin Oncol 2015; **33:** 332.

38. Zapatero A, Guerrero A, Maldonado X et al: High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. Lancet Oncol 2015; **16:** 320.

39. Nabid A, Carrier N, Martin AG et al: Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. Eur Urol 2018; **74:** 432.

40. Avkshtol V, Ruth KJ, Ross EA et al: Ten-year update of a randomized, prospective trial of conventional fractionated versus moderate hypofractionated radiation therapy for localized prostate cancer. J Clin Oncol 2020; **38:** 1676.

41. Hoskin PJ, Rojas AM, Bownes PJ et al: Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol 2012; **103:** 217.

42. Hoskin PJ, Rojas AM, Ostler PJ et al: Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: mature 12-year results. Radiother Oncol 2021; **154:** 214.

43. Sathya JR, Davis IR, Julian JA et al: Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol 2005; **23:** 1192.

44. Morris WJ, Tyldesley S, Rodda S et al: Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017; **98:** 275.

45. Rodda S, Morris WJ, Hamm J et al: ASCENDE-RT: an analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017; **98:** 581.

46. Rodda S, Tyldesley S, Morris WJ et al: ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017; **98:** 286.

47. Murthy V, Maitre P, Kannan S et al: Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. J Clin Oncol 2021; **39:** 1234.

48. Bolla M, Collette L, Blank L et al: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002; **360:** 103.

49. Bolla M, Van Tienhoven G, Warde P et al: External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010; **11:** 1066.

50. Attard G, Murphy L, Clarke NW et al: Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022; **399:** 447.

Periurethral injection of bulking agents for urinary incontinence—2024 review

Plain Language Summary:

Coverage question: Should OHP cover a shot to control when urine is passed? The shot contains bulking agents (tiny balls, bone-like material, silicone bits) that help keep the urethra closed.

Should OHP cover this treatment? No, the medical studies that show this treatment does not work well.

Changes to issue summary after public comment period:

No public comment was received on this topic. This document contains no changes from the version released with the early VBBS/HERC packet.

Coverage Question: Should non-coverage periurethral injection of bulking agents for urinary incontinence be reconsidered?

Question source: Axionics Inc

Background: Periurethral or transurethral injection of bulking agents is a minimally invasive surgical procedure used as one the surgical treatments of stress urinary incontinence (SUI) in adult women. It involves the injection of carbon beads, hydroxyapatite, silicone particles, polymers, collagen or similar materials into the tissue around the urethra to help the urethra close. This is an office procedure done under local anesthetic. Other treatments for urinary incontinence include medications, pessaries, pelvic floor physical therapy, and bladder surgeries such as colposuspension, urethral slings, or colporrhaphy.

Bulking agents for urinary incontinence was last reviewed in 2019. At that time, injection of these agents was found to be significantly less effective at long term treatment of urinary incontinence that this procedure was placed on then line 500.

Previous HSC/HERC reviews:

Urethral bulking agents for urinary incontinence was last reviewed in 2019. At that time, a 2012 Cochrane review found insufficient evidence of effectiveness. Expert guidelines recommended these agents when other treatments have failed or the patient is not a candidate for surgery.

The staff summary for the 2019 review reads as follows: “There is very little evidence available regarding periurethral injection of bulking agents for treatment of urinary incontinence. The low-quality evidence that is available indicates that these agents have little long term effectiveness, but may provide some

short term benefits. There are adverse events associated with these injections. Other treatments for urinary incontinence that are currently covered on the Prioritized List are more effective than bulking agent therapy. However, bulking agents are recommended by expert groups and covered by other payers, due to the short term improvement in symptoms and the preference of some patients to avoid more invasive procedures."

Based on the 2019 review, the CPT code for insertion of urethral bulking agents was removed from 3 covered lines and placed on an uncovered line.

Current Prioritized List/Coverage status:

CPT 51715 (Injection of implant material beneath lining of bladder and/or urethra using an endoscope) is online 495 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 495

The following interventions are prioritized on Line 495 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck surgical; with thermally-induced capsulorrhaphy	More effective treatments are available	August 2019

GUIDELINE NOTE 47, URINARY INCONTINENCE

Line 454

Surgery for genuine stress urinary incontinence may be indicated when all of the following are documented (A-G):

A) Patient history of (1 or 2):
   1) Involuntary loss of urine with exertion (for example: laughing, coughing, or sneezing)
   2) Identification and treatment of transient causes of urinary incontinence, if present (e.g., delirium, infection, pharmaceutical causes, psychological causes, excessive urine production, restricted mobility, and stool impaction)

B) Patient's voiding habits

C) Physical or laboratory examination evidence of either (1 or 2):
   1) Intrinsic sphincter deficiency (closing pressure of <20 cm H2) documented on urodynamic studies)
   2) Involuntary loss of urine on examination during stress (provocative test with direct visualization of urine loss) and low or absent post void residual

D) Evaluation to rule out urgency incontinence
E) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized
F) Nonmalignant cervical cytology, if cervix is present and clinically appropriate
G) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training and/or pelvic floor exercises, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

GUIDELINE NOTE 193, ARTIFICIAL URINARY SPHINCTERS

Line 454

Artificial urinary sphincters are included on this line only for patients with intrinsic sphincter deficiency with any of the following indications:

A) Children with intractable urinary incontinence due to intrinsic sphincter deficiency who are refractory to behavioral or pharmacological therapies and are unsuitable candidates for other types of surgical procedures for correction of urinary incontinence; OR
B) Patients who are 6 or more months post-prostatectomy who have had no improvement in the severity of urinary incontinence despite trials of behavioral and pharmacological therapies; OR
C) Men with epispadias-exstrophy in whom bladder neck reconstruction has failed; OR
D) Women with intractable urinary incontinence who have failed behavioral, pharmacological, and other surgical treatments

GUIDELINE NOTE 219, CHEMODENERVATION

Lines 290,324,348,359,375,407,493,510,519

[excerpt]

Line 324 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION

Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least two urinary incontinence antimuscarinic or beta-3 adrenergic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium, mirabegron, vibegron). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.

Evidence:

1) **Kirchin 2017**, Cochrane review of urethral injection therapy for urinary incontinence in women
   a) N=14 trials (2004 women)
   b) The limited data available were not suitable for meta-analysis because they all came from separate trials. Trials were small and generally of moderate quality.

c) One trial of 45 women that compared injection therapy with conservative treatment showed early benefit for the injectable therapy with respect to continence grade (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.52 to 0.94) and quality of life (mean difference (MD) 0.54, 95% CI 0.16 to 0.92). Another trial, comparing Injection of autologous fat with placebo, terminated early because of safety concerns. Two trials that compared injection with surgical management found significantly better objective cure in the surgical group (RR 4.77, 95% CI 1.96 to 11.64; and RR 1.69, 95% CI 1.02 to 2.79), although the latter trial data did not reach statistical significance if an intention-to-treat analysis was used.

d) Conclusions: The available evidence base remains insufficient to guide practice. In addition, the finding that placebo saline injection was followed by a similar symptomatic improvement to bulking agent injection raises questions about the mechanism of any beneficial effects

2) **Pivazyan 2022**, systematic review and meta-analysis of effectiveness and safety of bulking agents vs surgical methods for stress urinary incontinence
   a) N=6 studies (710 patients; 288 in the urethral bulking agent group and 317 in the surgery group)
   b) Bulking agents are less effective than surgical procedures according to subjective improvement after treatment (RR = 0.70, 95% CI: 0.53 to 0.92, p = 0.01). There was no statistically significant difference between these two methods with regard to complications after the intervention (RR = 1.30, 95% CI: 0.30 to 5.66, p = 0.73)
   c) Reported complications: retention, transient difficultly voiding, transient hematuria, urinary tract infection, need for surgical treatment,
3) **Braga 2022**, systematic review and meta-analysis of urethral bulking agents for recurrent stress urinary incontinence
   a) N=11 studies (542 patients)
      i) 7 retrospective cohort studies, 4 prospective cohort studies
      ii) Evaluated bulking agent therapy after failed mid-urethral sling (MUS) procedure
   b) The overall cure and improvement rate ranged from 64% to 85% in the included studies with a pooled value of 75%. The related I 2 – test result was 88.9% (95%CI = 82.5% to 92.3%), demonstrating significant statistical heterogeneity among the studies
   c) The overall failure rate ranged from 22% to 43% with a pooled value of 32%. Here, the I 2 – test result was 85.6% (95%CI = 75.5% to 90.3%), which was representative of significant statistical heterogeneity among the studies
4) **Kocjancic 2019**, review on complications of urethral bulking therapy for female stress urinary incontinence
   a) Approximately, 1/3 of the patients experience some type of a complication after urethral bulking therapy. The majority of these complications are of low grade, transient, do not necessitate additional surgical intervention, and amenable to treatment with conservative measures such as clean intermittent catheterization and antibiotics. However, more serious complications such as abscess formation, delayed hypersensitivity reactions, and vaginal erosion have been reported. Some of the injectable bulking agents have been withdrawn from the market because of their unfavorable adverse effect profile
   b) Available evidence precludes objective comparison between them in terms of safety and efficacy and it is not possible to recommend of one injectable agent over another
   c) Overall, UBT provides a subjective improvement rate of 50-70% which lacks long-term durability.

Periurethral injection of bulking agents for urinary incontinence—2024 review

Submitted literature:

1) **Freitas 2019**, RCT on vaginal tape surgery vs polyacrylamide hydrogel injection for primary stress urinary incontinence
    a) N=224 women (111 vaginal tape surgery, 113 hydrogel injection)
        i) 1 year follow up
    b) At 1 year a satisfaction score of 80 or greater on a visual analogue scale of 0 to 100 was reached in 95.0% and 59.8% of patients treated with tension-free vaginal tape and polyacrylamide hydrogel, respectively. Thus, polyacrylamide hydrogel did not meet the noninferiority criteria set in our study
    c) most perioperative complications, including those in 19 tension-free vaginal tape cases vs 3 polyacrylamide hydrogel cases (difference 16.0%, 95% CI 7.8-24.9), and all 6 reoperations due to complications (difference 5.9%, 95% CI 1.2-12.4) were associated with tension-free vaginal tape
    d) Conclusions: Mid urethral tension-free vaginal tape slings were associated with better satisfaction and cure rates than polyacrylamide hydrogel in women with primary stress urinary incontinence.
2) **Brosche 2020**, 7 year efficacy and safety outcomes for Bulkamid
    a) Single center retrospective cohort study
    b) N=388 women (261 Bulkamid was primary procedure, 127 secondary procedure)
    c) A total of 67.1% of the patients reported feeling cured or improved if Bulkamid was a primary procedure, 11.1% reported no change, and 2.3% reported worsening of incontinence. A total of 19.5% of patients received a subsequent other incontinence procedure.
    d) The ICIQ-UI SF was reduced by 8.6 points.
        i) MCID=1.46 points
    e) VAS QoL improved by a mean of 4.3 points.
        i) MCID=2.5 points
    f) Postoperative complications were transient. Prolonged bladder emptying time was reported in 15.3% of patients and urinary tract infection in 3.5%
    g) Conclusions: Bulkamid injections are an effective and safe first-line treatment option for women with SUI or stress-predominant MUI providing durable outcomes at 7 years.

Expert guidelines:

1) **Kobashi 2023**, AUA/SUFU guideline for surgical treatments of female stress urinary incontinence
    a) AUA=American Urological Association; SUFU=Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction
    b) Because re-treatment is common for urethral bulking injection, outcomes assessment is challenging. Inadequate data exist to support recommendation of 1 injectable agent over another. Still, bulking agents may have a role in patients who wish to avoid more invasive surgical management, lengthier recovery time after surgery, or who experience insufficient improvement following an anti-incontinence procedure. Patients should be counseled on the expected need for repeat injections
    c) There are limited long-term data on bulking agents.

d) The Panel maintains the consensus from the 2017 guideline that the autologous pubovaginal sling (PVS) is a preferred approach over retropubic midurethral sling (RMUS) and bulking agents for treatment of SUI in the patient with a fixed immobile urethra. This position is based upon the lack of robust evidence for RMUS in these patients, the suboptimal outcomes with bulking injections, and the long track record of PVS.
e) Buking agents are listed as a surgical option in the treatment pathway diagram

2) **Sussman 2020**, review of guidelines for treatment of urinary incontinence in women
   a) Counsel women undergoing periurethral bulking about need for repeat injection
   b) Do not recommend periurethral bulking agents to women seeking a permanent cure for stress incontinence (SUI)
   c) Bulking agents are periurethral injections that allow for improvement in SUI that are recommended as an option by all guidelines, especially for poor surgical candidates. The European Association of Urology (EAU) determined that while improvement is often short term (12 months) (Level 1b), there are fewer adverse risks compared with open surgery (Level 2a). Similarly, the ACOG recommends the use of bulking agents for women with intrinsic sphincteric deficiency, recurrent SUI after surgical failure, and poor surgical candidates (Level B). The International Consultation on Incontinence (ICI) cites Level 4 data that there may be some benefit to bulking agents in women with SUI following pelvic radiation

Other payer policies:

1) Aetna 2024
   a) Aetna considers periurethral injections of bulking agents that are cleared by the Food and Drug Administration (FDA) for UI (e.g., Bulkamid (polyacrylamide hydrogel), Coaptite [calcium hydroxylapatite], Contigen [glutaraldehyde crossed-linked collagen], Durasphere [carbon-coated spheres/beads], Macroplastique [polydimethylsiloxane], Uryx [ethylene vinyl alcohol copolymer]) medically necessary for the management of members with UI resulting from intrinsic sphincter deficiency that is refractory to conservative management (e.g., Kegel exercises, biofeedback, electrical stimulation, and/or pharmacotherapies).
   b) Members whose incontinence does not improve after 3 treatments with bulking agents are considered treatment failures and are not likely to respond to this therapy. In such cases, further treatment with bulking agents is not considered medically necessary.
2) Anthem BCBS 2024
   a) Injection of periurethral bulking agents is considered **medically necessary** when the individual has stress urinary incontinence (SUI) meeting one the following two criteria (A or B):
      i) The incontinence is due to trauma or injury; **or**
      ii) Both of the following are true (1 and 2):
         (a) The incontinence persists despite conservative treatment for at least a sufficient duration to fully assess treatment effect*; **and**
         (b) One of the following is true:
            (i) The incontinence is caused by intrinsic sphincter deficiency (ISD), **or**
            (ii) The incontinence is due to urethral hypermobility in individuals with abdominal leak point less than 100 cm H_2O.

3) Providence Health Plan 2024
    a) FDA-approved injectable bulking agents (e.g. Coaptite, Durasphere, Macroplastique) may be considered medically necessary for patients with urinary stress incontinence who meet all of the following criteria:
        i) Patient's symptoms limit activities of daily living; and
        ii) Failure, intolerance, or contraindication to conservative medical management; and
        iii) Patient lacks the following contraindications (1. and 2.):
            (a) Acute urogenital tract inflammation or infection; and
            (b) Fragile urethral mucosal lining (e.g. post-radiation therapy, post-surgery to the bladder neck.

Expert input:

None received to date

Periurethral injection of bulking agents for urinary incontinence—2024 review

HERC staff summary:

Since the 2019 review, there has been an update to the Cochrane review which continues to find insufficient evidence of effectiveness, as well as concern for high rates of placebo response. there has been no change to the staff conclusion that low-quality evidence that is available indicates that these agents have little long term effectiveness, but may provide some short term benefits. There are adverse events associated with these injections. Other treatments for urinary incontinence that are currently covered on the Prioritized List, specifically surgical approaches such as bladder slings and vaginal tape, are more effective than bulking agent therapy. Bulking agents are included in expert guidelines for patients who are not surgical candidates, patients who prefer non-invasive therapies, or patients who fail surgical treatments. However, a recent systematic review found a high failure rate (22-43%) when used after failure of surgical treatment. All insurers surveyed are covering this therapy for patients who do not respond to conservative therapy or are not surgical candidates/prefer non-surgical treatment.

HERC staff recommend continued non-coverage of periurethral injection of bulking agents due to insufficient evidence of efficacy and inferior results compared to other covered treatments of urinary incontinence.

HERC staff recommendation:

1) Update the date of last review for the entry in GN172

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 495

The following interventions are prioritized on Line 495 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck surgical; with thermally-induced capsulorrhaphy	More effective treatments are available	~~August 2019~~ May 2024

[Intervention Review]

Urethral injection therapy for urinary incontinence in women

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Editorial group: Cochrane Incontinence Group.
Publication status and date: Edited (no change to conclusions), published in Issue 7, 2017.

Citation: Kirchin V, Page T, Keegan PE, Atiemo KOM, Cody JD, McClinton S, Aluko P. Urethral injection therapy for urinary incontinence in women. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD003881. DOI: 10.1002/14651858.CD003881.pub4.

ABSTRACT

Background

Urinary incontinence imposes a significant health and economic burden to society. Periurethral or transurethral injection of bulking agents is a minimally invasive surgical procedure used as one the surgical treatments of stress urinary incontinence (SUI) in adult women.

Objectives

To assess the effects of periurethral or transurethral injection therapy on the cure or improvement of urinary incontinence in women.

Search methods

We searched the Cochrane Incontinence Group Specialised Trials Register (searched 8 November 2010) and the reference lists of relevant articles.

Selection criteria

All randomised or quasi-randomised controlled trials of treatment for urinary incontinence in which at least one management arm involved periurethral or transurethral injection therapy.

Data collection and analysis

Two review authors independently assessed methodological quality of each study using explicit criteria. Data extraction was undertaken independently and clarification concerning possible unreported data sought directly from the investigators.

Main results

Excluding duplicate reports, we identified 14 trials (excluding one that was subsequently withdrawn from publication and not included in this analysis) including 2004 women that met the inclusion criteria. The limited data available were not suitable for meta-analysis because they all came from separate trials. Trials were small and generally of moderate quality.

One trial of 45 women that compared injection therapy with conservative treatment showed early benefit for the injectable therapy with respect to continence grade (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.52 to 0.94) and quality of life (mean difference (MD) 0.54, 95% CI 0.16 to 0.92). Another trial, comparing Injection of autologous fat with placebo, terminated early because of safety concerns. Two trials that compared injection with surgical management found significantly better objective cure in the surgical group (RR 4.77, 95% CI 1.96 to 11.64; and RR 1.69, 95% CI 1.02 to 2.79), although the latter trial data did not reach statistical significance if an intention-to-treat analysis was used.

Eight trials compared different agents and all results had wide confidence intervals. Silicone particles, calcium hydroxylapatite, ethylene vinyl alcohol, carbon spheres and dextranomer hyaluronic acid combination gave improvements which were not shown to be more or less efficacious than collagen. Dextranomer hyaluronic acid compound treated patients appeared to have significantly higher rates of injection site complications (16% with the hyaluronic acid compound versus none with collagen; RR 37.78, 95% CI 2.34 to 610.12) and this product has now been withdrawn from the market.

A comparison of periurethral and transurethral methods of injection found similar outcomes but a higher (though not statistically significant) rate of early complications in the periurethral group. One trial of 30 women showed a weak (but not clinically significant) advantage for patient satisfaction (data not suitable for analysis in RevMan) after mid-urethral injection in comparison to bladder neck injection but with no demonstrable difference in continence levels.

Authors' conclusions

The available evidence base remains insufficient to guide practice. In addition, the finding that placebo saline injection was followed by a similar symptomatic improvement to bulking agent injection raises questions about the mechanism of any beneficial effects. One small trial comparing silicone particles with pelvic floor muscle training was suggestive of benefit at three months but it is not known if this was sustained, and the treatment was associated with high levels of postoperative retention and dysuria. Greater symptomatic improvement was observed with surgical treatments, though the advantages need to be set against likely higher risks. No clear-cut conclusions could be drawn from trials comparing alternative agents, although dextranomer hyaluronic acid was associated with more local side effects and is no longer commercially available for this indication. There is insufficient evidence to show superiority of mid-urethral or bladder neck injection. The single trial of autologous fat provides a reminder that periurethral injections can occasionally cause serious side effects. Also, a Brief Economic Commentary (BEC) identified three studies suggesting that urethral bulking agent might be more cost-effective compared with retropubic mid-urethral slings, transobturator or traditional sling procedure when used as an initial treatment in women without hypermobility or as a follow-up to surgery failure provided injection is kept minimal. However, urethral bulking agent might not be cost-effective when compared with traditional sling as an initial treatment of SUI when a patient is followed up for a longer period (15 months post-surgery).

PLAIN LANGUAGE SUMMARY

Injections of bulking agents for urinary incontinence in women

Stress incontinence is losing urine when coughing, laughing, sneezing or exercising. A significant amount of a woman's and their family's income can be spent on managing the symptoms. Usually muscles and tissue form a cushion supporting the base of the bladder and closing the urethra (the passage through which urine leaves the body). If they do not, artificial cushioning can be created by injecting bulking agents into the area around the urethra. The review of 14 trials, which included 2004 women, found some limited evidence that this can relieve stress incontinence in women. Other treatments such as surgery might be better. Using the women's own fat tissue as the agent injected can cause serious complications. In terms of costs, a brief review of economic studies suggested that collagen injection was less costly than surgery when used as first treatment or after initial surgery failure.

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REVIEW ARTICLE

Effectiveness and safety of bulking agents versus surgical methods in women with stress urinary incontinence: a systematic review and meta-analysis

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Abstract

Introduction and hypothesis The objective was to evaluate the efficacy and safety of bulking agents compared with surgical methods for female stress urinary incontinence.

Methods Inclusion and exclusion criteria: women with stress urinary incontinence. Bulking agents versus any surgical treatment as a comparison. Patients with other types of incontinence and treatment were excluded. Electronic databases (PubMed, MEDLINE, and the Cochrane Library) were searched from 2000 until 2021 to identify articles evaluating the effectiveness and safety of urethral bulking agents versus surgical methods. Risk-of-bias assessment tools recommended by the Cochrane Society were used to evaluate the risk of bias in the studies included.

Results Six studies were included in the quantitative synthesis for a total of 710 patients. Our systematic review and meta-analysis showed that bulking agents are less effective than surgical procedures according to subjective improvement after treatment (RR = 0.70, 95% CI: 0.53 to 0.92, $p = 0.01$). There was no statistically significant difference between these two methods with regard to complications after the intervention (RR = 1.30, 95% CI: 0.30 to 5.66, $p = 0.73$).

Conclusion The main limitation of this systematic review and meta-analysis was the absence of a common objective outcome measure to evaluate effectiveness. However, it shows that bulking agents are less effective than surgical procedures in subjective improvement. Safety analysis showed no significant difference between these methods. Hence, we believe that the first and final surgery is considered to be the best.

Keywords Stress urinary incontinence · Bulking agents · Surgery · TVT

Introduction

According to recent publications, controversy has been raised regarding surgical procedures for stress urinary incontinence (SUI) in women worldwide. International debates about the safety of these methods have led to court actions in Canada, the USA, the UK, and some European countries against the use of vaginal approaches that employ slings and tapes [1, 2].

For this reason, it has become more prevalent to use a conservative and alternative approach to avoid complications and side effects after surgery. Conservative approaches to the treatment of SUI include pelvic floor muscle training and incontinence pessaries [3].

An alternative technique that avoids surgical treatment is, for instance, the injection of urethral bulking agents. Several types of bulking agents are available for the treatment of SUI; these include Bulkamid (a polyacrylamide hydrogel), Macroplastique (crosslinked polydimethylsiloxane), Urolastic (a crosslinked polydimethylsiloxane), Durasphere EXP, (carbon-coated zirconium oxide), and Coaptite, (calcium hydroxylapatite) [4]. The two commonly used modes for the injection of bulking agents are periurethral and transurethral, and the target is the submucosa or below the bladder neck [5]. Based on the latest adverse reporting on the sling and

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Review article

Urethral bulking agents for the treatment of recurrent stress urinary incontinence: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Urethral bulking agent
Recurrent stress urinary incontinence
Persistent stress urinary incontinence
Mid-urethral sling failure
Female urinary incontinence

ABSTRACT

Recurrent stress urinary incontinence (rSUI) represents a major challenge for most clinicians as there is little evidence in the literature on the best option after sling failure. The objective of this study is to summarise the findings on the use of urethral bulking agents (UBAs) in the management of rSUI after the failure of a mid-urethral sling (MUSs). We performed a systematic review and meta-analysis, according to PRISMA 2020 guidelines, and selected eleven publications for inclusion in the analysis. We found that the overall cure and improvement rate ranged from 64% to 85% in the included studies, with a pooled value of 75%, compared with pooled failure and re-operation rates of 32% (95% CI: 22%–43%) and 25% (95% CI: 17%–34%), respectively. The I^2 test indicated significant statistical heterogeneity among the studies in relation to all the outcome measures; however, no risk of publication bias was found. To explore this heterogeneity in more depth, we performed a sub-group analysis of the two most commonly used bulking agents (Bulkamid and Macroplastique). The pooled values of the cure and improvement rate were 84% (95% CI: 77.0%–90.0%) and 80% (95% CI: 74.0%–85.0%) for Macroplastique and Bulkamid, respectively. We did not find significant heterogeneity or significant differences in the outcome measures in either group.

For the first time in literature, our study provides an insight into the use of UBAs after failed MUSs. Although the results seem very promising, future studies with shared protocols are needed in order to recommend the use of UBAs in the treatment of recurrent cases.

1. Introduction

Over the past twenty years, Mid-Urethral Slings (MUSs) have become the most popular surgical procedure for female Stress Urinary Incontinence (SUI), with excellent subjective and objective cure rates in the medium to long term [1,2]. However, the failure rate after MUS, has been reported to be 5% - 20% of previously treated patients [3,4].

Recurrent Stress Urinary Incontinence (rSUI) represents a major challenge for most clinicians. Unfortunately, there is a lack of robust evidence in literature regarding the best option available after sling failure. In 2017, a Cochrane Collaboration Review was unable to find enough high-quality data to assess the effects of any of the management strategies for rSUI after failed MUS [5]. A global survey of experienced urogynaecological clinicians and members of the International Urogynaecological Association (IUGA) could not even fill this knowledge gap [6]. Consequently, to date, there is a significant variation in the use of second-line surgical treatments depending on the surgeon's experience.

Repeat MUS is still the most common option used in these

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REVIEW ARTICLE

WILEY Neurourology Urodynamics ICS SUFU

Complications of urethral bulking therapy for female stress urinary incontinence

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Aims: To review, report, and discuss the complications associated with urethral bulking therapy in female stress urinary incontinence.

Methods: An extensive nonsystematic literature review on complications associated with injectable bulking agents used in the clinical practice was conducted. We reviewed articles published in English and indexed in the PubMed, Embase, and Google Scholar databases. Original articles, case reports, and case series were taken into consideration. Data regarding the safety of injectable bulking agents and the complications associated with their utility within the context of urethral bulking therapy for female stress urinary incontinence were extracted and discussed.

Results: Approximately, 1/3 of the patients experience some type of a complication after urethral bulking therapy. The majority of these complications are of low grade, transient, do not necessitate additional surgical intervention, and amenable to treatment with conservative measures such as clean intermittent catheterization and antibiotics. However, more serious complications such as abscess formation, delayed hypersensitivity reactions, and vaginal erosion have been reported. Some of the injectable bulking agents have been withdrawn from the market because of their unfavorable adverse effect profile.

Conclusions: Urethral bulking therapy can be considered as a low-risk procedure. However, it is not without complications which can be severe in rare instances. The search for the ideal urethral bulking agent is ongoing and future comparative studies assessing the safety and efficacy of these compounds in randomized controlled settings are warranted.

KEYWORDS
complications, injectable agent, stress incontinence, urethral bulking

1 | INTRODUCTION

Stress urinary incontinence (SUI) is defined as involuntary urine loss during coughing, sneezing, physical exertion or any other activity which may lead to sudden rises in intraabdominal pressure and it is mainly caused by intrinsic sphincter deficiency (ISD) and/or urethral hypermobility.[1,2] It is a commonly encountered problem in females with an associated high socioeconomic burden and negative influences on quality of life (QoL) issues.[1,3]

David Ginsberg led the peer-review process as the Associate Editor responsible for the paper.

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ORIGINAL CLINICAL ARTICLE

Neurourology Urodynamics ICS SUFU WILEY

Seven-year efficacy and safety outcomes of Bulkamid for the treatment of stress urinary incontinence

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Abstract

Aims: Bulking agents are a minimally invasive treatment option for women with stress urinary incontinence (SUI) or stress-predominant mixed urinary incontinence (MUI). The aim of this study was to evaluate long-term efficacy and safety following treatment with Bulkamid as a primary procedure for SUI or stress-predominant MUI.

Methods: This was an Institutional Review Board-approved single-center retrospective study of female patients with SUI or stress-predominant MUI who had undergone injection with Bulkamid since 2005 and had completed 7 years of follow up. The primary endpoint was patient satisfaction measured on a four-point scale as cured, improved, unchanged, or worse. Secondary outcomes included the number of incontinence pads used, International Consultation on Incontinence Questionnaire-Short Form (ICIQ-UI SF) scores, Visual Analog Scale Quality of Life (VAS QoL), reinjection rates, and perioperative and postoperative complications.

Results: A total of 1,200 patients were treated with Bulkamid since 2005 and of these, 388 (32.3%) had completed 7 years of follow-up. A total of 67.1% of the patients reported feeling cured or improved if Bulkamid was a primary procedure, 11.1% reported no change, and 2.3% reported worsening of incontinence. A total of 19.5% of patients received a subsequent other incontinence procedure. The ICIQ-UI SF was reduced by 8.6 points. VAS QoL improved by a mean of 4.3 points. Postoperative complications were transient. Prolonged bladder emptying time was reported in 15.3% of patients and urinary tract infection in 3.5%.

Conclusions: Bulkamid injections are an effective and safe first-line treatment option for women with SUI or stress-predominant MUI providing durable outcomes at 7 years.

KEYWORDS

Bulkamid, bulking agents, long-term follow-up, mixed urinary incontinence, stress urinary incontinence

Tension-Free Vaginal Tape Surgery versus Polyacrylamide Hydrogel Injection for Primary Stress Urinary Incontinence: A Randomized Clinical Trial

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From the Department of Obstetrics and Gynecology, Helsinki University Hospital (AMIF, MM, PR-S, TSM) and Doctoral Programme in Clinical Research (ST), Helsinki University and Folkhälsan Research Center Biomedicum (TSM), Helsinki, Finland

Abbreviations and Acronyms

PAHG = polyacrylamide hydrogel
PVR = post-void residual urine
SUI = stress urinary incontinence
TVT = tension-free vaginal tape
VAS = visual analogue scale

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The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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The funders of the study had no influence in the study design, data collection, data analysis, data interpretation or writing of the report.

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No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.

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† Financial interest and/or other relationship with Contura.

Purpose: We evaluated whether polyacrylamide hydrogel is noninferior to tension-free vaginal tape to treat women with primary stress urinary incontinence.

Materials and Methods: In this controlled noninferiority clinical trial patients with primary stress urinary incontinence were randomized to tension-free vaginal tape or polyacrylamide hydrogel treatment. The primary outcome was patient satisfaction and secondary outcomes were effectiveness in reducing urinary leakage and complications at 1-year followup. For statistical power significance was considered at 5%, power was set at 80% and the noninferiority limit was 20% with a 10% expected dropout rate.

Results: A total of 224 women with primary stress urinary incontinence entered the study between September 28, 2015 and March 1, 2017. Of the women 111 were randomized to tension-free vaginal tape and 113 were randomized to polyacrylamide hydrogel. At 1 year a satisfaction score of 80 or greater on a visual analogue scale of 0 to 100 was reached in 95.0% and 59.8% of patients treated with tension-free vaginal tape and polyacrylamide hydrogel, respectively. Thus, polyacrylamide hydrogel did not meet the noninferiority criteria set in our study. As secondary outcomes, the cough stress test was negative in 95.0% of tension-free vaginal tape cases vs 66.4% of polyacrylamide hydrogel cases (difference 28.6%, 95% CI 18.4-38.5). However, most perioperative complications, including those in 19 tension-free vaginal tape cases vs 3 polyacrylamide hydrogel cases (difference 16.0%, 95% CI 7.8-24.9), and all 6 reoperations due to complications (difference 5.9%, 95% CI 1.2-12.4) were associated with tension-free vaginal tape.

Conclusions: Mid urethral tension-free vaginal tape slings were associated with better satisfaction and cure rates than polyacrylamide hydrogel in women with primary stress urinary incontinence. However, complications were mainly associated with tension-free vaginal tape. Thus, tension-free vaginal tape should be offered as first line treatment in women who expect to be completely cured by the initial treatment and are willing to accept the complication risks. Since polyacrylamide hydrogel treatment also provides high satisfaction and cure rates, women with primary stress urinary incontinence can be offered polyacrylamide hydrogel as an alternative treatment.

Key Words: urethra; urinary incontinence, stress; suburethral slings; hydrogels; risk

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Check for updates

Updates to Surgical Treatment of Female Stress Urinary Incontinence (SUI): AUA/SUFU Guideline (2023)

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Purpose: The purpose of this guideline is to provide a clinical structure with which to approach the diagnosis, counseling, and treatment of female patients with stress urinary incontinence (SUI).

Materials/Methods: The primary source of evidence for the 2017 version of the SUI guideline was the systematic literature review conducted by the ECRI Institute. The initial search spanned literature from January 2005 to December 2015, with an additional updated abstract search through September 2016. The current amendment represents the first update to the 2017 iteration and includes updated literature published through February 2022.

Results: This guideline has been amended to reflect changes in and additions to the literature since 2017. The Panel maintained that the differentiation between index and non-index patients remained important. The index patient is a healthy female with minimal or no prolapse who desires surgical therapy for treatment of pure SUI or stress-predominant mixed urinary incontinence. Non-index patients have factors that may affect their treatment options and outcomes, such as high grade prolapse (grade 3 or 4), urgency-predominant mixed incontinence, neurogenic lower urinary tract dysfunction, incomplete bladder emptying, dysfunctional voiding, SUI following anti-incontinence treatment, mesh complications, high body mass index, or advanced age.

Conclusion: While gains have been made in the field to support new methods for the diagnosis, treatment, and follow-up of patients with SUI, the field continues to expand. As such, future reviews of this guideline will take place to stay in keeping with the highest levels of patient care.

Key Words: stress urinary incontinence, counseling, diagnosis, education, complications, surgery, therapy, female

SUI is a prevalent condition characterized by loss of urine in the setting of increased abdominal pressure. The various treatment alternatives range from non-surgical to surgical, and the modalities have continued to evolve. As length of patient follow-up has increased and new therapeutic options have emerged, counseling of patients should inevitably progress as well. This

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Guideline of guidelines: urinary incontinence in women

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Keywords

urinary incontinence, overactive bladder, diagnosis, stress urinary incontinence, urgency urinary ncontinence

Key Points

- Guidelines are not exhaustive, but practical evidence-based reviews of 'index patients'.
- Evaluation should include detailed history and characterisation of urinary incontinence (UI).
- Guidelines suggest a stepwise approach to treat both urgency UI and stress UI, starting with conservative therapy, advancing to more invasive procedures as needed
- Urodynamics should be used when it will change management and if there is recurrent UI after failure of invasive treatments.
- When treating women with mixed UI, focus on treating the predominant symptom.

Introduction

Urinary incontinence (UI) is a common disease, with prevalence rates as high as 44–57% in middle-aged and post-menopausal women [1]. Those with UI may experience physical, functional, and psychological limitations and diminished quality of life (QoL) at home and at work [2]. The financial burden of UI care is significant, with an estimated direct cost of $19.5 billion (American dollars) in the USA alone [3].

UI can be classified into a number of different categories, with stress UI (SUI) and urgency UI (UUI) being the most common. Many professional organisations have created guidelines to help clinicians navigate the diagnosis and evaluation of UI, as well as the treatments including conservative, pharmacological, and surgical. The methodologies upon which most guidelines are based are similar, starting with systematic reviews and grading of available literature (Table A1). Organisations then make recommendations with different definitions and strengths (Table A2). Guidelines are not exhaustive, but rather serve as a practical review of evidence-based management of 'index patients'.

The present 'Guideline of guidelines,' updated from a 2016 publication [4], reviews various international guidelines that have been updated at different time intervals and provides an updated summary of the important similarities and differences on the management of UI in women.

Methodology

We performed a Medical Literature Analysis and Retrieval System Online (MEDLINE)/PubMed search for the period of January 2010 to May 2019, to identify relevant guidelines for addressing UI in women. We also manually searched the websites of the following national and international societies to identify relevant guidelines for inclusion in this review: the AUA, European Association of Urology (EAU), National Institute for Health and Care Excellence (NICE), American Urogynecologic Society (AUGS), American College of Obstetrics and Gynecology (ACOG), Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), Canadian Urological Association (CUA), and the ICS.

We used the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [5] to describe the guidelines reviewed. When provided, supplementary material was reviewed and included in our analysis. The present paper's authors found that all guidelines drew upon high-quality literature and thus had high values for the 'Rigour of Development', and generally had excellent description of scope, purpose, and applicability, with clear presentation of topics. However, several of the guidelines were limited in describing contributing authors' conflicts and competing interests, and at times the intended user of the guideline was not clearly articulated. Scores were assigned based on careful review of the guidelines and material provided.

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Ultrasound Guided Percutaneous Tenotomy

Plain Language Summary:

Coverage question: Tendinosis happens when a tendon gets damaged or worn out from over-use or injury and doesn't heal properly. Should a treatment using soundwaves to break down the injured area (ultrasound) be covered for any type of injury?

Should OHP cover this treatment? No, there is very little evidence that this treatment is helpful.

Changes to issue summary after public comment period:

No public comment was received on this topic. This document contains no changes from the version released with the early VBBS/HERC packet.

Coverage Question:

Should ultrasound guided percutaneous tenotomy be covered for treatment of tendonitis or other conditions?

Question source:

Doug Carr, CCO medical director

Background:

Tendinitis is described as an acutely inflamed and swollen tendon without microscopic tendon damage. In contrast, tendinosis is a clinically damaged tendon with disorganized fibers and a hard, thickened, scarred and rubbery appearance. The underlying cause of tendinosis is degeneration. Tendinosis is chronic and occurs in the Achilles tendon, extensor tendon of the elbow (tennis elbow), gluteal tendons on the outside of the hip, the patellar tendon, and the rotator cuff tendons of the shoulder. Standard treatment for tendinosis may include rest, non-steroidal anti-inflammatory drugs, braces, splints and straps, physical therapy, or injection therapy.

Ultrasound guided percutaneous tenotomy is a minimally invasive procedure to treat inflammation of the tendon (tendonitis) of the elbow, hip, knee, ankle and plantar fascia of the foot. The procedure involves ultrasound to determine the location of degenerative tissue, insertion of a probe under guidance, which produces ultrasonic energy, and that theoretically breaks down the damaged tissue. At the same time, a built-in inflow-outflow fluid system simultaneously irrigates and sucks up the broken down/emulsified tissue. Once the tissue is cleared away, the probe is removed. This procedure is also referred to as radiofrequency coblation.

Several devices have received U.S. Food and Drug Administration (FDA) 510(k) clearance for percutaneous ultrasonic ablation. Two examples are the Tenex system (Tenex Health, Inc., Lake Forest, CA) and the Sonopet iQ Ultrasonic Aspirator System (Stryker Instruments, Kalamazoo, MI). One device for radiofrequency coblation tenotomy is the TOPAZ EZ Microdebrider Coblation Wand (Arthrocare, Austin TX).

Ultrasound Guided Percutaneous Tenotomy

Dr. Carr has received requests for this procedure from several orthopedists for shoulder conditions and from podiatrists for treatment of Achilles tendonitis and plantar fasciitis

Previous HSC/HERC reviews:

No previous review of this technology was identified

Current Prioritized List/Coverage status:

This procedure has no specific CPT or HCPCS code on the Prioritized List

Tendinopathy and enesthopathies are on various covered and uncovered lines on the Prioritized List with various paired procedures.

Evidence:

1) **Zadeh 2023**, meta-analysis of percutaneous ultrasound-guided needle tenotomy (PUNT) for treatment of chronic tendinopathy and fasciopathy
    a. No apparent conflicts of interest
    b. N=38 studies (1674 participants with 1876 tendons treated)
        i. 29 studies included in meta-analysis
        ii. N=12 RCTs (369 patients) compared PUNT to surgical tenotomy or injections
        iii. N=26 case series
        iv. 5 articles only had abstracts available
    c. Pain
        i. N=26 studies (mix of RCTs and case series in the meta-analysis)
        ii. Most studies used the visual analogue scale (VAS) scores
            1. Minimal clinically important difference=1.4
        iii. The standard mean difference of the pain scoring systems improved 2.5 points (95% CI: 2.0–3.0; $p<0.05$), 2.2 points [95% CI: (1.8–2.7), $p<0.05$) and 3.6 points [95% CI (2.8–4.5), $p<0.05$) at short-term, intermediate-term and long-term follow up respectively
    d. Function improvement
        i. N=16 studies (mix of RCTs and case series in the meta-analysis)
        ii. Various tools used to measure function, appears to have only included Disabilities of the Arm, Shoulder and Hand (DASH) scores in meta-analysis
            1. minimal clinically important difference=13
        iii. The standard mean difference improved 1.4 points [95% CI (1.1–1.8), $p<0.05$), 1.8 points [95% CI (1.3–2.2), $p<0.05$), and 2.1 points [95% CI (1.6–2.6), $p<0.05$) at short-term, intermediate-term and long-term follow up respectively
    e. Complications
        i. Among 1876 procedures, only one ruptured patellar tendon occurred 6 weeks following needle tenotomy. One case of acute inflammatory reaction needing steroid injection, three cases of nonactivity-restricting pain, wound hypersensitivity superficial skin infection, and a few mild complaints of tenderness, stiffness, and soreness were also reported
    f. Conclusions

i. Our findings indicate that PUNT substantially improves pain intensity (as measured by VAS score) and function (as measured by DASH score) compared to pre-treatment baseline measures. This improvement continued after intermediate- long-term follow-ups; however, improvement was most significant at short-term follow-up. The clinical evidence supports that PUNT is an effective, minimally invasive treatment for chronic recalcitrant tendinopathy and fasciopathy with a low rate of complications and failures.

2) **Vajapey 2021**, systematic review of the utility of percutaneous ultrasonic tenotomy (PUT) for tendinopathies
   a. Most authors declared conflicts of interest
   b. N=7 studies
      i. 3 retrospective cohort studies, 4 prospective cohort studies
   c. Chronic epicondylosis of the elbow/ elbow tendinopathy
      i. N=5 studies (76 patients)
      ii. Overall, the VAS and DASH scores improved 1 year status post–PUT procedure as compared with baseline. Patients undergoing PUT for elbow tendinopathy observed a difference of more than 4 points in the visual analogue scale (VAS) score (minimal clinically important difference=1.4) and more than 20 points for each of the Disabilities of the Arm, Shoulder and Hand (DASH) subscores (minimal clinically important difference=13)
   d. Plantar fasciitis
      i. N=1 study (12 patients)
      ii. 11 experienced complete pain relief 3 months after Tenex and this improvement was sustained at 12 months postoperatively. There were no complications noted and the mean American Orthopaedic Foot & Ankle Score (AOFAS) score improved from 30.1 at baseline to 88.1 at 3 months postoperatively.
         1. Minimal clinically important difference of AOFAS score is reported to be between 7.9 to 30.2
   e. Achilles tendinopathy
      i. N=1 study (34 patients)
      ii. There was 1 complication reported: superficial surgical site infection treated with oral antibiotics alone. Of the 34 patients, 4 had no pain at long-term follow-up (11-36 months), 13 had mild pain, 2 had moderate pain, 1 had severe pain, and the rest were lost to follow-up. There was some improvement in the physical component of 12-Item Short Form Health Survey (SF-12), but no improvement in the mental component of SF-12 survey at short-term follow-up (6-12 weeks).
   f. Conclusion: PUT is a minimally invasive treatment technique that can be considered in patients with tendinopathy refractory to conservative treatment measures. Further, higher quality studies are necessary to accurately assess the comparative effectiveness of this treatment modality

Submitted literature:

None received to date

Ultrasound Guided Percutaneous Tenotomy

Expert guidelines:

1) **Finnoff 2015**, American Medical Society for Sports Medicine (AMSSM) Position Statement: Interventional Musculoskeletal Ultrasound in Sports Medicine
    a. Note: multiple authors reported financial conflicts with Tenex Healthcare
    b. Described as a new generation techniques: "tenotomy/ fasciotomy using specialized devices that not only cut but also debride damaged tissue". This type of procedure likely "will be adopted" In the near future. It was also noted that "research will be needed to determine the efficacy, safety profile, and cost-effectiveness of these new procedures."

Other payer policies:

1) Aetna 2023
    a. Experimental or investigational: the TENEX procedure (ultrasound-guided percutaneous fasciotomy/tenotomy)
    b. Notes that there is no specific code for this procedure
2) Cigna 2023
    a. Percutaneous ablation of soft tissue for treatment of any musculoskeletal condition (e.g., tendinosis, tendinopathy) is considered experimental, investigational or unproven.
3) Anthem Blue Cross Blue Shield 2023
    a. Percutaneous ultrasonic ablation of soft tissue is considered **investigational and not medically necessary** for the treatment of **any** condition, including, but not limited to **any** of the following musculoskeletal conditions:
        i. Achilles tendinosis; **or**
        ii. Lateral or medial elbow tendinosis; **or**
        iii. Patellar tendinosis; **or**
        iv. Recalcitrant plantar fasciitis; **or**
        v. Rotator cuff or shoulder tendinosis.
4) Providence Health Plan 2024
    a. Percutaneous ultrasonic ablation for the treatment of tendinopathy (e.g. Tenex Health TX® System) is considered not medically necessary

Expert input:

None received to date

HERC staff summary:

The evidence regarding ultrasound guided percutaneous tenotomy is limited to small RCTs and case series. Little evidence exists comparing ultrasound guided percutaneous tenotomy to standard therapies. No private payer surveyed is covering this procedure.

HERC staff recommends specifying that this procedure is not covered for treatment of any condition.

Ultrasound Guided Percutaneous Tenotomy

HERC staff recommendation:

1) Adopt a new guideline for ultrasound guided percutaneous tenotomy as shown below

GUIDELINE NOTE XXX ULTRASOUND GUIDED PERCUTANEOUS TENOTOMY
Lines 356, 373, 398, 413, 414, 481, 496, 498, 521, 533, 597, 601
Ultrasound guided percutaneous tenotomy is not included on any line on the Prioritized List for treatment of any condition due to lack of evidence of effectiveness. There is no specific CPT or HCPCS code for this procedure.

Line 356 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS
Line 373 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT
Line 398 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS
Line 413 PERIPHERAL NERVE ENTRAPMENT; PALMAR FASCIAL FIBROMATOSIS
Line 414 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6
Line 481 PERIPHERAL ENTHESOPATHIES Treatment MEDICAL THERAPY
LINE 496 OTHER DISORDERS OF SYNOVIUM, TENDON AND BURSA, COSTOCHONDRITIS, AND CHONDRODYSTROPHY
Line 498 PERIPHERAL ENTHESOPATHIES Treatment SURGICAL TREATMENT
LINE 521 DEFORMITIES OF UPPER BODY AND ALL LIMBS
LINE 533 LESION OF PLANTAR NERVE; PLANTAR FASCIAL FIBROMATOSIS
LINE 597 DISORDERS OF SOFT TISSUE
LINE 601 PRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR

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Percutaneous ultrasound-guided needle tenotomy for treatment of chronic tendinopathy and fasciopathy: a meta-analysis

Firoozeh Shomal Zadeh[1] · Mehrzad Shafiei[1] · Mostafa Shomalzadeh[1] · Jennifer Pierce[2] · Peter Christian Thurlow[1] · Majid Chalian[1]

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Abstract

Objectives To systematically assess the efficacy of percutaneous ultrasound-guided needle tenotomy (PUNT) in the treatment of chronic tendinopathy and fasciopathy.

Methods A comprehensive literature search was performed with the following search terms: tendinopathy, tenotomy, needling, Tenex, fasciotomy, ultrasound-guided, and percutaneous. Inclusion criteria consisted of original studies evaluating pain or function improvement after PUNT. Meta-analyses investigating standard mean differences were performed to assess the pain and function improvement.

Results Thirty-five studies with 1674 participants (1876 tendons) were enrolled in this article. Of which 29 articles were included in meta-analysis and the remaining 9 articles without enough numeric data were included in descriptive analysis. PUNT significantly alleviated pain with the standard mean difference of 2.5 (95% CI: 2.0–3.0; $p<0.05$), 2.2 (95% confidence interval (CI): 1.8–2.7; $p<0.05$), and 3.6 (95% CI: 2.8–4.5; $p<0.05$) points in short-term, intermediate-term, and long-term follow-up intervals, respectively. It was also associated with marked improvement in function with 1.4 (95% CI: 1.1–1.8; $p<0.05$), 1.8 (95% CI: 1.3–2.2; $p<0.05$), and 2.1 (95% CI: 1.6–2.6; $p<0.05$) points, respectively in short-term, intermediate-term, and long-term follow-ups.

Conclusion PUNT improved pain and function at short-term intervals with persistent results on intermediate- and long-term follow-ups. PUNT can be considered an appropriate minimally invasive treatment for chronic tendinopathy with a low rate of complications and failures.

Clinical relevance Tendinopathy and fasciopathy are two common musculoskeletal complaints that can cause prolonged pain and disability. PUNT as a treatment option could improve pain intensity and function.

Key Points

- *The best improvement in pain and function was achieved after the first 3 months following PUNT and was continued to the intermediate- and long-term follow-ups.*
- *No significant difference was found between different tenotomy methods in terms of pain and function improvement.*
- *PUNT is a minimally invasive procedure with promising results and low complication rates for treatments of chronic tendinopathy.*

Keywords Tenotomy · Tendinopathy · Tendon

Abbreviations

MCID	Minimal clinically important difference
PRP	Plasma-rich platelet
PUNT	Percutaneous ultrasound guided tenotomy
SI	Steroid injection

Introduction

Tendinopathy is an over-arching term describing a range of tendon diseases with multiple pathogeneses affecting various anatomical sites [1]. It is responsible for about

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Utility of Percutaneous Ultrasonic Tenotomy for Tendinopathies: A Systematic Review

Sravya Vajapey, MD, MBA,[†] Sennay Ghenbot, BS,[‡] Michael R. Baria, MD,[§] Robert A. Magnussen, MD,[†] and W. Kelton Vasileff, MD*[†]

Context: Chronic tendinopathy is a challenging problem that can lead to significant disability and limitation in not only athletics but also activities of daily living. While there are many treatment techniques described for this overuse injury, no single modality has been proven superior to all others. With recent advances in medical technology, percutaneous ultrasonic tenotomy (PUT) for tendinosis has gained traction with promising results.

Objective: To examine the data published on PUT for treatment of tendinopathy, analyze the outcomes of the procedure, including duration of pain relief and patient-reported outcomes, and assess the rate of complications associated with the procedure.

Data Sources: PubMed, MEDLINE, EMBASE, and Google Scholar.

Study Selection: The following combination of keywords was entered into the electronic search engines: *ultrasonic tenotomy, ultrasound tenotomy, Tenex*, and *ultrasonic percutaneous tenotomy*. The search results were screened for studies relevant to the topic. Only English-language studies were considered for inclusion. Studies consisting of level 4 evidence or higher and those involving human participants were included for more detailed evaluation.

Level of Evidence: Level 4.

Data Extraction: Articles meeting the inclusion criteria were sorted and reviewed. Type of tendinopathy studied, outcome measures, and complications were recorded. Both quantitative and qualitative analyses were performed on the data collected.

Results: There were a total of 7 studies that met the inclusion criteria and quality measures—5 studies involving the treatment of elbow tendinopathy and 1 study each involving the management of Achilles tendinopathy and plantar fasciitis. PUT resulted in decreased pain/disability scores and improved functional outcome scores for chronic elbow tendinopathy and plantar fasciitis. Results for Achilles tendinopathy showed modest improvement in the short term, but long-term data are lacking.

Conclusion: PUT is a minimally invasive treatment technique that can be considered in patients with tendinopathy refractory to conservative treatment measures. Further higher quality studies are necessary to accurately assess the comparative effectiveness of this treatment modality.

Keywords: ultrasonic tenotomy; tenex; tendinopathy; tendinosis; tendonitis; systematic review

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The following authors declared potential conflicts of interest: W.K.V. is a paid consultant for Zimmer Biomet. M.B., R.M., and W.K.V. received payments for development of educational presentations from CDC Medical, and R.M. also received payments from Zimmer Biomet.

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Special Feature

American Medical Society for Sports Medicine (AMSSM) Position Statement: Interventional Musculoskeletal Ultrasound in Sports Medicine

Jonathan T. Finnoff, DO, Mederic M. Hall, MD, Erik Adams, MD, PhD, David Berkoff, MD, Andrew L. Concoff, MD, William Dexter, MD, Jay Smith, MD

Abstract

The use of diagnostic and interventional ultrasound has significantly increased over the past decade. A majority of the increased utilization is by nonradiologists. In sports medicine, ultrasound is often used to guide interventions such as aspirations, diagnostic or therapeutic injections, tenotomies, releases, and hydrodissections. This American Medical Society for Sports Medicine (AMSSM) position statement critically reviews the literature and evaluates the accuracy, efficacy, and cost-effectiveness of ultrasound-guided injections in major, intermediate, and small joints, and soft tissues, all of which are commonly performed in sports medicine. New ultrasound-guided procedures and future trends are also briefly discussed. Based upon the evidence, the official AMSSM position relevant to each subject is made.

Introduction

The use of diagnostic and interventional musculoskeletal ultrasound (MSK US) in sports medicine has increased over the past several decades for a variety of reasons including decreased equipment costs, increased educational opportunities, expanded research, patient safety initiatives, and technological advances leading to higher resolution images [1]. Between 2000 and 2009, there was a 717% increase in the number of outpatient diagnostic MSK US studies, a majority of which were performed by nonradiologists [2]. Ultrasound can be used to diagnose disorders of bone, joints, tendons, muscles, ligaments, blood vessels, and nerves as well as to guide interventions such as aspirations, diagnostic or therapeutic injections, tenotomies, releases, hydrodissections, and biopsies [3].

As the utilization of MSK US within sports medicine increases, it is important to critically review the existing literature and, based upon the available evidence, make recommendations for its appropriate use. The purpose of this position statement is to evaluate the accuracy, efficacy, and cost-effectiveness of ultrasound-guided injections (USGIs) in major, intermediate, and small joints, and soft tissues, all of which are commonly performed in sports medicine. New procedures and future trends will also be briefly discussed.

Materials and Methods

Relevant English language articles through November 2013 were identified by searching Cochrane Database of Systematic Reviews and PubMed with the search terms injection, accuracy, efficacy, ultrasonography, fluoroscopy, joint, and arthrography. The references of the articles were subsequently reviewed to identify additional articles not found in the original literature search. Articles that studied the accuracy, efficacy, or cost-effectiveness of USGIs or landmark-guided injections (LMGIs) were included in the analysis for this position statement. Accuracy was defined as being able to place the injectate or needle tip in the intended structure. Studies that evaluated efficacy were defined as studies that evaluated a change in an outcome measure such as pain, range of motion, mobility, function, or patient satisfaction following the procedure. Cost-effectiveness studies were defined as studies that evaluated the health care cost of the procedure relative to another treatment.

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The literature search was performed by a single researcher (MMH). An initial review of each study was subsequently performed by a separate researcher (JTF) and the level of evidence for each article was ranked according to the scale published by the *Journal of Bone and Joint Surgery* [4]. For accuracy studies, the level of evidence was determined as follows: Level 1—injections performed on live subjects with accuracy confirmed using gold standard diagnostic imaging (ie: arthrogram for joints, magnetic resonance imaging [MRI] for soft tissues) or systematic review of level 1 studies; Level 2—injections performed on live subjects using non–gold standard imaging for accuracy confirmation, injections performed on cadaveric specimens with accuracy confirmed using gold standard diagnostic imaging or dissection, or systematic review of level 2 studies; Level 3— injections performed on cadaveric specimens with accuracy confirmed using non–gold standard diagnostic imaging; Level 4—injections performed on a small number ($\leq$10) of live subjects or cadaveric specimens, injections performed on live subjects with accuracy confirmed by clinical outcome, or retrospective case series; Level 5—case study or expert opinion. The literature was then distributed to the remaining authors for review and analysis. Disputes on classification were resolved via discussion and consensus. The literature was divided into the following categories for analysis: major joints, intermediate joints, small joints, multiple joints, and soft tissues.

Results

The initial literature search identified 216 potential articles. Of these, 124 met the inclusion criteria for the position statement.

Major Joints

Fifty-seven studies assessing injections in major joints were identified (see online supplementary Appendix 1) [5-61]. A majority of the studies (49/57 [86%]) [6,7,9,11-13,15,17-25,27-30,32-51,53-61] evaluated injections in a single joint, whereas 14% (8/57) [5,8,10,16,26,31,52,55] assessed injections in more than one joint. Thirty-five percent (20/57) of the studies evaluated knee injections [8-10,13,15,16,19-23,26,31,32,36,37,48,52,56,57], 46% (26/57) evaluated glenohumeral (GH) joint injections [5,7,8,10,11,15-17,24-26,28,29,31,38-40,42,43,46,47,49,52,54,60,61], 21% (12/57) evaluated hip injections [8,12,27,30,33,35,41,44,45,50,52,59,62], and 4% (2/57) evaluated sacroiliac (SI) joint injections [18,34]. Four studies (7%) assessed injections in the "shoulder" but didn't specify which shoulder structure or joint they were injecting [6,53,55,58].

The results of the studies investigating major joint injection accuracy are summarized in Table 1. The level of evidence for a majority of the studies evaluating major joint USGI accuracy (15/23 [65%]) [5,8,9,15,16,18,20,21,23,27,30,32,34,36-39,41,42,44-46,49] or LMGI accuracy (28/28 [100%]) [5,7,9-13,17,19,21-26,28,31,32,36-38,40,43,47,48,50,60,61] were level 1 or 2. The mean accuracy of GH, hip, and knee joint USGIs in studies with level 1 or 2 evidence ranged from 91%-100% [5,8,9,15,18,21,23,32,36-39,42,46,49], whereas the mean accuracy of LMGIs were between 64% and 81% [5,7,9-13,17,19,21-26,28,31,32,36-38,40,43,47,48,50,60,61]. These findings provide strong evidence that USGIs in the GH, hip, and knee joints are more accurate than LMGIs.

Only 2 studies investigated the accuracy of SI joint injections [18,34], and both studies only evaluated the accuracy of USGIs. While ultrasound-guided (USG) SI joint injections were 100% accurate in one of the studies [34], the other study reported an accuracy rate of only 40% [18]. The discrepancy between the 2 studies may be due to a number of factors such as differences in accuracy assessment (color Doppler–US versus MRI arthrogram), patient population, equipment variability, injector experience, and injection technique. No studies were identified that evaluated the accuracy of

Table 1
Major joint injection accuracy

	Level of Evidence				
	Level 1 Mean, % (Range, %)	Level 2 Mean, % (Range, %)	Level 3 Mean, %	Level 4 Mean, %	Level 5 Mean, %
GH joint					
USGI	100 (97-100) [8,15,39,42,46,49]	91 (89-93) [5,38]	—	100 [16]	—
LMGI	64 (27-100) [7,10,24,31,40,43,47]	73 (10-100) [5,11,17,25,26,28,38,60,61]	—	—	—
Hip joint					
USGI	99 (97-100) [8,27,41,44,45]	—	—	100 [30]	100 [44]
LMGI	—	73 (67-78) [12,50]	—	—	—
Knee joint					
USGI	95 (75-100) [8,21,23,32,36,37]	98 (96-100) [5,9]	—	100 [16]	100 [20]
LMGI	81 (62-100)[10,19,21-23,31,32,36,37,48]	74 (55-100) [5,9,10,13,26]	—	—	—
SI joint					
USGI	40 [18]	—	100 [34]	—	—
LMGI	—	—	—	—	—

GH = glenohumeral; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; SI = sacroiliac.

Table 2
Major joint injection efficacy

	Level of Evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
GH joint	—	3 studies: USGIs are more efficacious than LMGIs [29,51,54]	—	1 study: LMGIs are efficacious [31]	—
Hip joint	—	—	1 study: USGIs are more efficacious than no injection [33]	3 studies: USGIs are efficacious, [35,41] and pain reduction from injection predicts better surgical outcome [59]	—
Knee joint	1 study: accurate injections are more efficacious than inaccurate injections [48]	3 studies: USGIs are less painful and more efficacious than LMGIs [5,56,57]	—	1 study: LMGIs are efficacious [31]	—
SI joint	—	—	—	1 study: USGIs are efficacious [34] 1 study: USGIs are no better than LMGIs [18]	—
Shoulder*	2 studies: image-guided injections are more efficacious than LMGIs [55,58] 1 study: no significant difference between USGI and LMGI efficacy [6]	—	1 study: USGI no better than LMGI [53]	—	—

GH = glenohumeral; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; SI = sacroiliac.
* Shoulder refers to studies in which the "shoulder" was injected, but the location of the injection was not further specified.

landmark-guided (LMG) SI joint injections. Further studies are required to determine the accuracy of USG and LMG SI joint injections.

Nine studies with level 1 or 2 evidence investigated the efficacy of USGIs in major joints relative to LMGIs (see Table 2) [5,6,29,51,54-58]. The joints evaluated in the studies included the glenohumeral joint (3 studies) [29,51,54], shoulder (joint unspecified [3 studies]) [6,55,58], and knee joint (3 studies) [5,56,57]. Eighty-nine percent (8/9) of these studies found that USGIs were more efficacious than LMGIs [5,29,51,54-58], while the remaining study found no difference in efficacy between the 2 injection techniques [6]. A single study with level 1 evidence demonstrated no difference in efficacy between corticosteroid knee injections that were accurate versus those that were inaccurate [48]. Based upon the available research, in major joints, the majority of studies with level 1 or 2 evidence indicate that USGIs are more efficacious than LMGIs.

Only 2 studies compared the cost-effectiveness of USGIs versus LMGIs (see Table 3) [56,57]. Both of the studies were performed by the same group of researchers and evaluated the cost-effectiveness of USGIs and LMGIs in the knee. While both studies provided level 2 evidence suggesting that USGIs were more cost-effective than LMGIs, further research is required to corroborate their findings.

In summary, USGIs in major joints other than the SI joint are more accurate than LMGIs. Further research is required to determine the accuracy of USG and LMG SI joint injections. The majority of evidence indicates USGIs in major joints are more efficacious than LMGIs in major joints. While the preliminary research suggests that USGIs are more cost-effective than LMGIs, further research is required before making a final determination on the cost-effectiveness of USGIs.

Intermediate Joints

Twenty-three studies assessing injections into intermediate sized joints were identified (see online supplementary Appendix 2) [8,16,26,31,52,63-80]. Seventy-four percent (17/23) of the studies evaluated injections into a single joint [8,63-65,67-70,72-80] and 26% (6/23) assessed injections into multiple joints [16,26,31,52,66,71]. Injections into the following joints were evaluated: sternoclavicular (SC) (1/23 [4%]) [79], acromioclavicular (AC) (7/23 [30%]) [26,63,69,70,72,73,78], elbow (3/23 [13%]) [16,26,31], wrist (4/23 [17%])

Table 3
Major joint injection cost-effectiveness

	Level of Evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
Knee joint	—	2 studies: USGIs are more cost-effective than LMGIs [56,57]	—	—	—

USGI = ultrasound-guided injection; LMGI = landmark-guided injection.

[8,16,26,31], distal radioulnar (RU) (1/23 [4%]) [77], scapho-trapezio-trapezoidal (STT) (1/23 [4%]) [74], proximal tibiofibular (TF) (1/23 [4%]) [76] tibiotalar (TT) (7/23 [30%]) [16,26,31,65,66,71,80], subtalar (ST) (5/23 [22%]) [66-68,71,75], and midfoot (1/23 [4%]) [64].

Twenty-one of the 23 studies (91%) assessed intermediate joint injection accuracy (see Table 4) [8,16,26,31,52,63,65-72,74-80]. Their findings are summarized in Table 4. Similar to the injection accuracy studies in major joints, a majority (20/21 [95%]) of the intermediate joint injection accuracy studies provided either level 1 or level 2 evidence [8,26,31,52,63,65-72,74-80]. In the studies with level 1 or 2 evidence, the mean accuracy of USGIs into intermediate joints ranged from 95%-100% [8,52,63,66,70,71,74-77,80]. The mean accuracy of LMGIs into intermediate joints with level 1 or 2 evidence was between 0% and 92% [26,31,52,63,65-70,72,74,76,78-80]. The accuracy of LMGIs varied widely by joint and approach.

The only study that evaluated injection accuracy into the SC joint used an LMG approach, and reported a mean accuracy of 78% [79]. Since no USGI studies into the SC joint have been performed, a comparison of SC joint injection accuracy between the 2 techniques cannot be made.

Two level 2 studies evaluated USGI accuracy into the AC joint, and reported mean accuracy of 95% [63,70]. Five level 2 studies [63,69,70,72,78] evaluated the accuracy of LMG AC joint injections and reported a mean accuracy of 52%. In addition to accuracy, the results presented by Sabeti-Aschraf et al [72] looked at USGI and LMGI accuracy of 3 sub-groups: physician specialist, physician nonspecialist, and student. As expected, the student's LMGI accuracy was the lowest (60%) and the physician specialist's LMGI accuracy was the highest (80%). When the same providers used USGI, accuracy improved to 90%-100%, with the students being the highest of the three sub-groups. Based upon the available evidence, USGIs into the AC joint are significantly more accurate than LMGIs.

Two level 1 studies evaluated LMGI accuracy into the elbow joint [26,31]. The mean accuracy of these studies was 97%. The only study evaluating the accuracy of USGIs into the elbow joint provided level 4 evidence that elbow joint USGI accuracy was 100%. The current

Table 4
Intermediate joint injection accuracy

	Level of Evidence				
	Level 1 Mean, % (Range, %)	Level 2 Mean, % (Range, %)	Level 3 Mean, %	Level 4 Mean, %	Level 5 Mean, %
SC joint					
USGI	–	–	–	–	–
LMGI	–	78 (74-82) [79]	–	–	–
AC joint					
USGI	–	95 (90-100) [63,70]	–	–	–
LMGI	–	52% (33-72) [63,69,70,72,78]	–	–	0 [26]
Elbow joint					
USGI	–	–	–	100 [16]	–
LMGI	97 (83-100) [26,31]	–	–	–	–
Distal RU joint					
USGI	–	100 [77]	–	–	–
LMGI	–	–	–	–	–
Wrist joint					
USGI	100 [8]	–	–	100 [16]	–
LMGI	74 (50-97) [26,31]	–	–	–	–
STT joint					
USGI	–	100 [74]	–	–	–
LMGI	–	80 [74]	–	–	–
Proximal TF joint					
USGI	–	100 [76]	–	–	–
LMGI	–	58 [76]	–	–	–
TT joint					
USGI	–	100 (100) [66,71,80]	–	100 [16]	–
LMGI	64 (50-77) [26,31]	87 (78-100) [65,66,80]	–	–	–
ST joint					
USGI	–	97 (90-100) [66,71,75]	–	–	–
LMGI	–	89 (68-100) [66-68]	–	–	–
Elbow, wrist, TT joint					
USGI	–	100 [52]	–	–	–
LMGI	–	29 [52]	–	–	–

SC = sternoclavicular; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; AC = acromioclavicular; RU = radioulnar; STT = scaphotrapeziotrapezoidal; TF = tibiofibular; TT = tibiotalar; ST = subtalar.

research suggests that elbow joint LMGIs are quite accurate and, although preliminary findings imply that elbow joint USGIs are also accurate, further research is required to corroborate these data.

The accuracy of injections into 3 different sites about the wrist has been studied. The first is the distal radioulnar joint (DRUJ). A single level 2 study reported the accuracy of USGIs into the DRUJ to be 100% [77]. No DRUJ LMGI accuracy studies were identified. A single level 1 study demonstrated 100% accuracy of wrist joint USGIs [8]. The mean accuracy of wrist joint LMGIs reported by two level 2 studies was 74% [26,31]. A single level 2 study demonstrated the accuracy of USG scaphotrapeziotrapezoidal (STT) joint injections to be 100%, while LMGI accuracy was 80% [74]. Therefore, initial findings indicate USGI accuracy into the distal RU, wrist, and STT joints is 100% accurate, but further research is required to confirm these conclusions. The current evidence suggests LMGIs into the wrist and STT joints are less accurate than USGIs (74% and 80%, respectively, versus 100%), and no research is available regarding the accuracy of distal RU joint LMGIs. However, due to the paucity of research on injections in the wrist region, further research is required before definitive conclusions can be drawn.

The accuracy of injections into 3 intermediate sized, lower extremity joints (proximal tibiofibular [TF], tibiotalar [TT], and subtalar [ST] joints) has been studied. A level 2 study reported proximal TF joint USGIs to be 100% accurate, while LMGIs into the same joint were 58% accurate [76]. Tibiotalar joint USGIs were found to be 100% accurate in 3 level 2 studies [66,71,80]. The mean TT joint LMGI accuracy was 64% in 2 level 1 studies [26,31] and 87% in 3 level 2 studies [65,66,80]. The mean ST joint USGI accuracy of 3 level 2 studies was 97% [66,71,75], while 3 level 2 studies reported the accuracy of LMGI to be 89% [66-68]. These findings suggest that proximal TF, TT, and ST joint USGIs are highly accurate, while LMGIs into the same regions have variable accuracy, with the highest level of accuracy found in the ST joint (89%).

Finally, one level 2 study evaluated the accuracy of USGIs and LMGIs into multiple joints (elbow, wrist, and TT joints) [52]. Balint et al [52] reported 100% accuracy of USGIs into the elbow and TT joints, while the mean accuracy of LMGIs into the elbow, wrist, and TT joints was only 29%. However, the conclusions of this study are significantly limited based upon the small number of injections performed.

Four studies evaluated the efficacy of intermediate joint USGIs versus LMGIs (see Table 5) [16,26,64,73]. One was a level 2 study [73], another was a level 3 study [26], and the remaining two were level 4 studies [16,64]. Sabeti-Aschraf et al [73] found no difference in efficacy between AC joint USGIs and LMGIs. Jones et al [26] found no difference in efficacy between accurate and inaccurate injections into the AC, elbow, wrist, and ankle joints, but the conclusions of this study are limited due to the study design. Both level 4 studies demonstrated that USGIs were efficacious into intermediate joints [16,64].

No studies evaluated the cost-effectiveness of USG versus LMG intermediate joint injections.

In summary, USGIs into a majority of intermediate joints are more accurate than LMGIs, although LMGIs into the ST joint were relatively accurate (mean accuracy of 89%). However, most joints only had one or two studies evaluating injection accuracy. Therefore, further USG and LMG intermediate joint injection accuracy studies are necessary to make definitive conclusions regarding intermediate joint injection accuracy. Despite the difference in accuracy between USG and LMG intermediate joint injections, the only study that evaluated the difference in efficacy between the 2 injection techniques did not find a difference [73]. Interestingly, the joint evaluated in this study (AC joint) was one of the joints with a fairly large difference in accuracy between USG and LMG injections (95% versus 52%). Since they did not evaluate the accuracy of their injections, it is difficult to determine whether the lack of difference in efficacy between the 2 techniques is because they had similar accuracy rates between the 2 techniques, or because efficacy is not related to accuracy in this particular joint. Due to the paucity of research, a definite conclusion regarding whether or not USG improves the efficacy of intermediate joint injections cannot be made.

Table 5
Intermediate joint injection efficacy

	Level of Evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
AC joint	—	1 study: no difference in efficacy between USGI and LMGI [73]	—	—	—
Elbow joint	—	—	—	1 study: USGIs are efficacious [16]	—
Wrist joint	—	—	—	1 study: USGIs are efficacious [16]	—
TT joint	—	—	—	1 study: USGIs are efficacious [16]	—
Midfoot joint	—	—	—	1 study: USGIs are efficacious [64]	—
AC, wrist, elbow, and TT joints	—	—	1 study: no difference in efficacy between accurate and inaccurate injections [26]	—	—

AC = acromioclavicular; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; TT = tibiotalar.

Small Joints

Nine studies assessing injections in small joints were identified (see online supplementary Appendix 3) [16,26,31,52,66,71,81-83]. A small majority of these studies (5/9 [56%]) [31,66,71,82,83] evaluated injections into a single type of small joint (eg, metacarpophalangeal [MCP] joint), while the remainder (4/9 [44%]) [16,26,52,81] evaluated injections into multiple small joints. Sixty-seven percent (6/9) [16,26,31,52,81,82] of the studies assessed small joint injections in the hands and 56% (5/9) [16,52,66,71,83] evaluated small foot joint injections. Of those studies assessing hand procedures, 3 studies (50%) included the carpometacarpal (CMC) joint [26,52,82], two (33%) the proximal interphalangeal (PIP) joints [52,81], and one (17%) [26] the distal interphalangeal (DIP) joints. Among the studies of foot procedures, 4 (60%) [16,52,71,83] were directed at the metatarsophalangeal (MTP) joints and one (20%) [66] the tarsometatarsal (TMT) joints.

The results of the studies investigating small joint accuracy are summarized in Table 6. The majority (5/8 [63%]) of small joint injection accuracy studies provided level 1 or 2 evidence [31,66,71,82,83]. The remaining studies provided level 3 or 5 evidence [26,52,81]. In the hand, a single level 2 study reported the mean USGI accuracy of the CMC joint to be 94% [82]. There were no level 1 or 2 studies for LMGI accuracy of the CMC joint. A single level 3 study compared the accuracy of USG and LMG CMC joint injections and found the mean accuracy of USGI to be 100% and of LMGI to be 0% [52]. No study was identified that addressed the accuracy of USG MCP joint injections, but a single level 1 study reported the mean accuracy of LMGI to be 97% [31]. No level 1 or 2 studies evaluated the accuracy of interphalangeal (IP) joint injections. One level 3 study compared the accuracy of USG versus LMG IP joint injections and found the mean accuracy of USGI to be 100%, while the accuracy of LMGI was 0% [52]. Another level 3 study reported the accuracy of USG MCP and PIP joint injections to be 96% and LMGI to be 59% [81].

Regarding small joint injections in the feet, a single level 2 study compared the accuracy of USG and LMG TMT joint injections and found the USGIs to be more accurate (64% accurate) than LMGIs (25% accurate) [66]. Three studies (two with level 2 evidence [71,83] and one with level 3 evidence [52]) found 100% accuracy for USGI of the MTP joints, with 1 of the 3 [52] noting poor accuracy (0% accurate) with LMGI.

Only a single, level 4 study addressed the efficacy of USGI of the small joints (see Table 7) [16]. This case series demonstrated that USGIs of the MCP and MTP joints were efficacious, but the strength of the findings is limited by the study design [16]. No studies were identified that compared the cost-effectiveness of USGI versus LMGI of the small joints. Thus, it is unclear from the available literature whether the superior accuracy suggested by the available studies translates into improved outcomes or cost savings.

In summary, current research suggests that USGIs in small joints are more accurate than LMGIs. However, due to the paucity of high-quality research evaluating small joint injection accuracy, further research is required to confirm these initial findings prior to drawing final conclusions. There is insufficient evidence at this time to determine whether USG small joint injections are more efficacious or cost-effective than LMGIs.

Table 6
Small joint injection accuracy

	Level of Evidence				
	Level 1 Mean, %	Level 2 Mean, %	Level 3 Mean, %	Level 4 Mean, %	Level 5 Mean, %
CMC joint					
USGI	–	94 [82]	100 [52]	–	–
LMGI	–	–	0 [26,52]		
MCP joint					
USGI	–	–	–	–	–
LMGI	97 [31]	–	–	–	0 [26]
IP joint					
USGI	–	–	100 [52]	–	–
LMGI	–	–	0 [52]	–	0 [26]
TMT joint					
USGI	–	64 [66]	–	–	–
LMGI	–	25 [66]	–	–	–
MTP joint					
USGI	–	100 [71,83]	100 [52]	–	–
LMGI	–	–	0 [52]	–	–
MCP and PIP joints					
USGI	–	–	96 [81]	–	–
LMGI	–	–	59 [81]	–	–

CMC = carpometacarpal; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; MCP = metacarpophalangeal; IP = interphalangeal; TMT = tarsometatarsal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.

Table 7
Small joint injection efficacy

	Level of evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
MCP and MTP	—	—	—	1 study: USGIs are efficacious [16]	—

MCP = metacarpophalangeal; MTP = metatarsophalangeal; USGI = ultrasound-guided injection.

Soft Tissues

Forty-nine studies assessing injections into soft tissues were identified (see online supplementary Appendix 4) [17,51,52,54,69,71,80,84-125]. Most studies evaluated injections into a single structure (42/49 [86%]) [17,51,54,69,80,84-87,90-95,97-101,103-113,115-125], but 7 studies (14%) investigated injections into more than one structure [52,71,88,89,96,102,114]. In decreasing frequency, studies evaluated injections into bursae (19/49 [39%]) [17,51,52,54,69,87,91-93,95,97,100,101,103,105,110,115,121,123], tendon sheaths (9/49 [18%]) [71,89,102,106,108,111-113,116], tendons or fascia (8/49 [16%]) [96,102,107,112,119,120,124,125], perineural regions (6/49 [12%]) [85,88,94,104,109,122], muscles (5/49 [10%]) [86,97,114,117,118], cysts (2/49 [4%]) [84,90], peritendinous regions (2/49 [4%]) [71,102], wounds (1/49 [2%]) [52], and periarticular spaces (1/49 [2%]) [80].

Soft tissue injection accuracy studies are summarized in Table 8. Four level 1 or 2 studies evaluating the accuracy of tendon sheath or peritendinous injections were identified [71,99,113,116]. Multiple regions were evaluated including the Achilles peritendinous region [71] and the tendon sheaths of the long head biceps [99], first dorsal wrist compartment, flexor hallucis longus [71], tibialis posterior [71], popliteus [116], and peroneal (fibularis) tendons [113]. Although the criteria used to define "accurate injections" were different in the various studies, the mean reported accuracy of USGIs into tendon sheaths or peritendinous regions ranged from 87%-100%, while the mean accuracy of LMGIs ranged from 27%-60%. Thus, there is strong evidence that USG tendon sheath or peritendinous injections are more accurate than LMGIs.

Ten level 1 or 2 studies examined the accuracy of subacromial-subdeltoid (SA-SD) bursa injections [17,69,91,93,95,101,105,110,115,123]. As with peritendinous injections, the definition of an "accurate injection" was not uniform among the studies. Accuracy rates for LMG SA-SD bursa injections ranged from 24%-100%, while USGI accuracy ranged from 65%-100%. Although USG SA-SD bursa injections were more consistently accurate than LMGIs, due to the highly variable results reported across different studies, a definite conclusion regarding whether or not USG SA-SD bursa injections are more accurate than LMGIs cannot be made at this time. Further research is required to clarify this question.

A single level 2 study evaluated the accuracy of LMGI versus USGI into the pes anserinus bursa [98]. The accuracy rate for LMG pes anserinus bursa injections was 17%, while USGI accuracy was 92%. These preliminary findings suggest that USG pes anserinus bursa injections are more accurate than LMGIs.

One level 2 study compared the accuracy of USG piriformis injections to fluoroscopically guided injections [97]. Ultrasound guidance provided accurate injections in 95% of cases, while fluoroscopically guided injections were accurate only 30% of the time. Furthermore, one of the fluoroscopically guided injections placed the injectate into the sciatic nerve. Another level 2 study reported the accuracy of USG obturator internus injections to be 100% [118]. Although preliminary, these findings suggest US guidance enables accurate injections into the deep gluteal musculature, is more accurate than fluoroscopically guided injections into this region, and minimizes the potential for complications associated with inadvertent needle placement into adjacent neurologic structures.

A level 1 study evaluated the accuracy of placing the needle tip of a compartment pressure monitor into the deep and superficial posterior leg compartments using landmark or US guidance in cadavers [114]. The accuracy was similar between the 2 techniques. This was likely due to the relatively superficial location and large size of the 2 posterior leg compartments. Therefore, based on the current evidence, US guidance is not recommended for routine compartment pressure testing of the posterior leg compartments.

Two level 2 studies evaluated the accuracy of USGIs into Morton's neuromas [94,104]. Both reported 100% accuracy. No studies were identified that evaluated the accuracy of LMG Morton's neuroma injections. Based upon the available evidence, USG Morton's neuroma injections are highly accurate and the accuracy of LMG Morton's neuroma injections is unknown.

The final soft tissue injection accuracy study was a level 2 study that evaluated the accuracy of LMG sinus tarsi injections versus USGIs [80]. Wisniewski et al [80] reported the accuracy of USG sinus tarsi injections to be 90%. LMGIs were only 35% accurate. These findings suggest that USG sinus tarsi injections are more accurate than LMGIs.

Regarding efficacy, only one study was identified with level 1 or 2 evidence that directly compared LMGIs to USGIs for the treatment of a tendon disorder (see Table 9) [106]. Kume et al [106] demonstrated

Table 8
Soft tissue injection accuracy

	Level of Evidence				
	Level 1 Mean, % (Range, %)	Level 2 Mean, % (Range, %)	Level 3 Mean, %	Level 4 Mean, % (Range, %)	Level 5 Mean, %
SA-SD bursa					
USGI	100 [115]	65 [91]	—	—	—
LMGI	82 (69-100) [101,115]	78 (29-90) [17,69,91,93,95,105,110,123]	—	—	—
BT sheath					
USGI	87 [99]	—	—	—	—
LMGI	27 [99]	—	—	—	—
FFT sheath					
USGI	—	—	—	100 [89]	—
LMGI	—	—	—	—	—
FET sheath					
USGI	—	—	—	85 (70-0) [89,108]	—
LMGI	—	—	—	15 [108]	—
ECUT sheath					
USGI	—	—	—	100 [89]	—
LMGI	—	—	—	—	—
Obturator internus					
USGI	—	100 [118]	—	—	—
LMGI	—	—	—	—	—
Piriformis					
USGI	—	95 [97]	—	USGIs are accurate (rate not reported) [117]	USGIs with EMG assistance are 100% accurate [88]
LMGI	—	—	—	—	—
Pes anserinus bursa					
USGI	—	92 [98]	—	—	—
LMGI	—	17 [98]	—	—	—
Popliteus tendon sheath					
USGI	—	92 (83-100) [116]	—	—	—
LMGI	—	—	—	—	—
Achilles region					
USGI	—	100 [71]	—	—	—
LMGI	—	—	—	—	—
Peroneal tendon sheath					
USGI	—	100 [113]	—	100 [89]	—
LMGI	—	60 [113]	—	—	—
FHL tendon sheath					
USGI	—	100 [71]	—	—	—
LMGI	—	—	—	—	—
TP tendon sheath					
USGI	—	100 [71]	—	100 [89]	—
LMGI	—	—	—	—	—
SPC					
USGI	—	100 [114]	—	—	—
LMGI	—	100 [114]	—	—	—
DPC					
USGI	—	88 [114]	—	—	—
LMGI	—	90 [114]	—	—	—
Sinus tarsi					
USGI	—	90 [80]	—	—	—
LMGI	—	35 [80]	—	—	—
Morton's neuroma	USGI				
USGI	—	100 [94,104]	—	—	—
LMGI	—	—	—	—	—
Bursa, tendon sheath, cyst, wound					
USGI	—	—	—	USG aspirations are 100% accurate [52]	—
LMGI	—	—	—	—	—

SA-SD = subacromial-subdeltoid; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; BT = biceps tendon; FFT = finger flexor tendon; FET = finger extensor tendon; ECUT = extensor carpi ulnaris tendon; EMG = electromyographic; FHL = flexor hallucis longus; TP = tibialis posterior; SPC = superficial posterior compartment; DPC = deep posterior compartment.

Table 9
Soft tissue injection efficacy

	Level of Evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
SA-SD bursa	—	4 studies: USGIs are more efficacious than LMGIs [54,87,103,121] 1 study: USGI produces more pain relief with local anesthetic injection than LMGI [100] 1 study: USGI more efficacious than LMGI in some but not all outcome measures [51] 1 study: USGI more efficacious than oral steroids in some but not all outcome measures [92] 1 study: accurate injections are more efficacious than inaccurate injections [93] 2 studies: accurate injections no more efficacious than inaccurate injections [91,105]	—	—	—
Rotator cuff	—	—	—	1 study: USG lavage and aspiration of calcific tendinopathy is efficacious [124]	—
Lateral elbow common extensor tendon	—	—	—	1 study: USG needle tenotomy is efficacious [112]	—
de Quervain tenosynovitis	—	1 study: USGI more efficacious than LMGI [106]	—	1 study: USGIs are efficacious [111]	—
Carpal tunnel syndrome	—	3 studies: USGI more efficacious and less painful than LMGI [85,109,122]	—	—	—
Gluteus medius tendon	—	—	—	1 study: USGIs are efficacious [107]	—
Baker's cyst	—	1 study: USGI Baker's cyst aspiration and injection more efficacious than Baker's cyst aspiration and knee injection [84]	—	1 study: USG aspiration and injection are efficacious [90]	—
Plantar fascia	—	1 study: no difference in efficacy between USGI, LMGI, or SGI [125] 1 study: no difference in efficacy between USGI and LMGI, but less recurrence following USGI [119]	—	1 study: USGIs are efficacious [120]	—
Morton's neuroma	—	—	—	2 studies: USGI are efficacious [94,104]	—
FFT, FET, ECUT, TP tendon, and peroneal tendon sheath	—	—	—	1 study: USGIs are efficacious [89]	—
Patellar, Achilles, gluteus medius, ITB, hamstring, lateral elbow, rectus femoris	—	—	—	1 study: USG needle tenotomies are efficacious [102]	—
Multiple upper and lower extremity tendons	—	—	—	1 study: USG needle tenotomies with PRP injections are efficacious [96]	—
Post-upper extremity amputation neuromas	—	—	—	—	1 study: USGIs are efficacious [88]

SA-SD = subacromial-subdeltoid; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; USG = ultrasound guided; SGI = scintigraphy guided injection; FFT = finger flexor tendon; FET = finger extensor tendon; ECUT = extensor carpi ulnaris tendon; TP = tibialis posterior; ITB = iliotibial band; PRP = platelet-rich plasma.

significantly more pain reduction from USGIs than LMGIs in patients with septation between the extensor pollicis brevis (EPB) and abductor pollicis longus (APL) tendons in the first dorsal compartment. Septation is present in the first dorsal compartment in greater than 50% of patients [111]. Although further studies are needed, USGIs for the treatment of de Quervain tenosynovitis may be superior to LMGIs, particularly in the setting of a septated first dorsal compartment.

Two level 2 studies compared the efficacy of USG plantar fascia injections versus LMGIs [119,125]. Neither of the studies found any difference in efficacy between USG plantar fascia injections and LMGIs, although one of the studies reported less recurrent pain following USGIs [119]. In addition, one of the studies evaluated the efficacy of scintigraphically guided plantar fascia injections compared to USGIs and LMGIs [125]. No difference in outcomes was found between the 3 groups. Interestingly, "scintigraphic guidance" was actually an unguided injection since the injector performed an LMGI in the region where the scintigram was positive. There is currently insufficient evidence to support routine US guidance for plantar fascia injections. Further studies are needed to determine whether USG plantar fascia injections reduce recurrence rates, which may decrease the costs associated with treating this condition. Finally, research is also required to determine whether US guidance reduces complications associated with plantar fascia injections (eg, plantar fascia rupture, calcaneal fat pad atrophy).

Five level 2 studies evaluated the efficacy of USG SA-SD bursa injections versus LMGIs [51,54,87,103,121]. All 5 studies demonstrated better outcomes following USG SA-SD bursa injections compared to LMGIs. Three level 2 studies assessed the efficacy of accurate versus inaccurate SA-SD bursa injections [91,93,105]. Two of the studies concluded there was no difference in efficacy between accurate and inaccurate injections [91,105], and one reported that accurate injections are more efficacious than inaccurate injections [93]. A single level 2 study demonstrated more pain relief following USG SA-SD bursa local anesthetic injections than LMGI, suggesting USG SA-SD bursa injections may provide more diagnostic information regarding the etiology of shoulder pain than LMGIs [100]. A final level 2 study demonstrated more improvement in a majority of outcome measures following USG SA-SD bursa injections than oral steroids for shoulder pain [92]. Therefore, current studies indicate USG SA-SD bursa injections are more efficacious than LMGIs or oral steroids for shoulder pain. Furthermore, USGIs provide more diagnostic information regarding the etiology of shoulder pain than LMGIs.

Three level 2 studies compared the efficacy of USG carpal tunnel injections to LMGIs [85,109,122]. All 3 studies reported that USG carpal tunnel injections were less painful and more efficacious than LMGIs. Furthermore, one of the studies performed a cost analysis and concluded that USG carpal tunnel injections were also more cost-effective than LMGIs (see Table 10) [85]. However, the cost analysis only included those who responded to the injection. When all patients were included in the cost analysis (responders and non-responders), the cost was higher for USGIs than for LMGIs when the procedure was performed in a physician's office, and was equivalent when performed in a hospital-based setting. The findings of these studies provide strong evidence that USG carpal tunnel injections are more efficacious than LMGIs. However, further research is required to determine if USG carpal tunnel injections are more cost-effective than LMGIs.

In summary, USGIs into tendon sheaths, peritendinous regions, deep gluteal muscles (eg, piriformis and obturator internus), the pes anserinus bursa and sinus tarsi are all more accurate than LMGIs. USG Morton's neuroma injections are highly accurate, but the accuracy of LMGIs into Morton's neuromas is unknown at this time. Although USG SA-SD bursa injections appear to be more accurate than LMGIs, the wide range of reported accuracy limits the ability to draw a definitive conclusion at this time. USG SA-SD bursa, carpal tunnel, and first dorsal wrist compartment injections are more efficacious than LMGIs. USG plantar fascia injections appear to have equivalent outcomes to LMGIs. Finally, further research is required to determine if USGIs into soft tissues are more cost-effective than LMGIs.

Multiple Joints

Three studies were identified that evaluated joint injections in multiple locations (see online supplementary Appendix 5) [126-128]. None of the 3 studies specified which joints were assessed. The accuracy, efficacy, and cost-effectiveness data from these studies are summarized in Tables 11, 12 and 13. The first study evaluated the efficacy and cost-effectiveness of USG versus LMG

Table 10
Soft tissue injection cost-effectiveness

	Level of Evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
Carpal tunnel syndrome		1 study: USGIs are more cost-effective than LMGIs [85]			

USGI = ultrasound-guided injection; LMGI = landmark-guided injection.

Table 11
Multi-joint injection accuracy

	Level of Evidence				
	Level 1 Mean, %	Level 2 Mean, %	Level 3 Mean, %	Level 4 Mean, %	Level 5 Mean, %
Joints with inflammatory arthritis					
USGI	83 [126]	—	—	—	—
LMGI	—	—	—	—	—

USGI = ultrasound-guided injection; LMGI = landmark-guided injection.

injections into joints with inflammatory arthritis [127]. This level 2 study found that USGIs into joints with inflammatory arthritis produced less procedural pain, more pain relief, more responders and less nonresponders to the injection, and was less expensive than LMGIs. In a study with level 1 evidence, Cunnington et al [126] determined that USGIs into joints with inflammatory arthritis were 83% accurate, while LMGI injections were only 66% accurate. Their study also provided level 2 evidence that USGIs into joints with inflammatory arthritis resulted in more clinical improvement and pain reduction at 6 weeks follow-up than those who received an LMGI. The final multiple joint injection study performed by Sibbitt et al [128] provided level 2 evidence that subjects with painful joints who received USGIs experienced less procedural pain and more pain relief than those who received LMGIs. Moreover, when compared to LMGIs, USGIs resulted in a larger number of responders, less nonresponders, and an improved ability to detect and aspirate joint effusions.

In summary, these findings suggest that USGIs into inflamed or painful joints are more accurate, less painful, more efficacious, and less expensive than LMGIs. However, further research is required to confirm these findings due to the limited number of studies.

New Procedures and Future Trends

As the field of MSK US has continued to mature, practitioners from multiple disciplines have capitalized on US's powerful combination of high (sub-millimeter) resolution and real-time imaging capability to expand the applications of interventional MSK US in clinical practice. These applications can be considered in 3 broad categories, or generations.

First-generation techniques apply US guidance to improve the accuracy of established procedures such as joint injections, peritendinous injections, and perineural injections, and are the focus of the current position statement. The use of first-generation techniques has continued to expand as additional therapeutic and regenerative agents have been introduced into clinical practice, including but not limited to dextrose, autologous blood, and platelet-rich plasma [129-139]. This trend will continue as practitioners utilize US guidance as the primary deployment mechanism to deliver an increasing repertoire of drugs, cell-based therapeutic-regenerative agents, and tissue scaffolds to soft tissues and accessible joint regions [62,140-143].

Second-generation techniques have predominately emerged during the past decade and can be generally considered to be advanced procedures performed with commonly available needles. However, in contradistinction to first-generation techniques, most of the second-generation techniques were developed primarily as a result of the availability of US guidance. Common examples include needle tenotomy/fasciotomy for chronic tendinosis/fasciosis, fenestration of the transverse carpal ligament to treat carpal tunnel syndrome, neovessel ablation via sclerosing agent injection or mechanical disruption to treat chronic tendinosis, needle release of the A1 pulley for trigger finger, needle aponeurotomy for Dupuytren's contracture, and hydrodissection to treat peripheral neuritis due to mild compression or adhesions [62,140,141,143-154]. Prior to the widespread adoption of US guidance, these procedures either did not exist, or were performed relatively rarely due to the inability to directly visualize target tissues and subsequent safety concerns. Currently, many of these procedures are being increasingly utilized on a regular basis in diverse clinical practices. Percutaneous USG fenestration and aspiration (ie, barbotage) of calcific tendinosis can also be considered to be a second-generation procedure. Although originally described as a fluoroscopic procedure, the role of fluoroscopy has largely been supplanted by US guidance due to US's excellent safety profile and clinical efficacy [155-158].

Third-generation techniques are perhaps the most exciting for the field, and are characterized by the use of pre-existing, specialized surgical tools or specially designed devices to perform a specific USG procedure. Many of these techniques duplicate well-accepted surgical procedures using percutaneous US guidance to improve safety and reduce morbidity. Recently described techniques include A1 pulley release using hook knives, carpal tunnel release using hook knives, arthroscopic equipment, or specially designed devices, and tenotomy/fasciotomy using specialized devices that not only cut but also debride damaged tissue [159-167]. The integration of these techniques into clinical practice represents a major advancement in the field of musculoskeletal medicine. In

Table 12
Multi-joint injection efficacy

	Level of Evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
Joints with inflammatory arthritis	—	2 studies: USGIs are more efficacious than LMGIs [126,127]	—	—	—
Painful joints	—	1 study: USGIs are more efficacious than LMGIs [128]	—	—	—

USGI = ultrasound-guided injection; LMGI = landmark-guided injection.

the near future, it is likely that additional USG surgical procedures will be adopted with advanced US imaging techniques and/or specialized equipment.

In summary, the current trend toward expanded applications of interventional MSK US can be expected to continue for decades, driven by advances in US technology, practitioner expertise with US guidance, and the development of specialized tools. Many traditional surgical procedures will become office-based, lower cost procedures performed by skilled practitioners, and some will be combined with precise delivery of therapeutic-regenerative agents.

Discussion and Recommendations

The purpose of this position statement was to determine the accuracy, efficacy, and cost-effectiveness of USGIs in joints and soft tissues. A brief discussion of new USG procedures and future trends was also conducted. During the following discussion, the AMSSM position on each topic will be stated, and the strength of the evidence associated with the position will be graded using the following strength of recommendation taxonomy (SORT):

A. Consistent, good-quality evidence
B. Inconsistent or limited-quality evidence
C. Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Accuracy

AMSSM Position: USGIs are more accurate than LMGIs (SORT Evidence Rating = A).

A majority of the relevant research investigated USGI accuracy. There is evidence that USGIs into large, intermediate, and small joints, tendon sheaths, peritendinous regions, deep gluteal muscles, pes anserinus bursa, sinus tarsi, and inflamed joints are more accurate than LMGIs. The preponderance of studies evaluated the accuracy of large joint injections followed by intermediate joints with the minority of studies evaluating the accuracy of small joint injections. Due to the limited number of small and intermediate joint injection accuracy studies, further research in these areas is warranted.

Preliminary research suggests that USGIs into Morton's neuromas are highly accurate, but no LMGI accuracy studies have been performed, so a comparison between the 2 techniques cannot be made. Similarly, no LMGI accuracy studies have been performed in the SI joint, and the 2 USG SI joint injection studies that have been published reported conflicting accuracy rates. Therefore, further research is required to determine whether USG SI joint and Morton's neuroma injections are more accurate than LMGIs.

The soft tissue structure with the most injection accuracy studies was the SA-SD bursa. Although a majority of research suggested that USG SA-SD bursa injections are more accurate than LMGIs, the reported accuracy rates for both USGIs and LMGIs were highly variable. This may have been due to several factors. First, USGIs are only accurate if the injector can correctly identify the target and guide the needle into the target. Therefore, the variability of the USGI accuracy results suggests that the injectors in some USG SA-SD bursa injection studies were either unable to accurately identify the SA-SD bursa or correctly guide the needle into the target. Since the injector's ability to correctly identify the SA-SD bursa was not assessed, nor was their

Table 13
Multi-joint injection cost-effectiveness

	Level of Evidence				
	Level 1	Level 2	Level 3	Level 4	Level 5
Joints with inflammatory arthritis	—	1 study: USGIs are more cost-effective than LMGIs [127]	—	—	—

USGI = ultrasound-guided injection; LMGI = landmark-guided injection.

ability to guide a needle into a specific target, the influence of the injector's technical abilities on the study's outcome is unknown. The technique by which accuracy is confirmed may also have influenced the study outcomes. For instance, in the study by Mathews et al [110], 20 cadaveric shoulders were injected with radiocontrast into the subacromial bursa using 2 different approaches, and the accuracy of the injections was initially determined by fluoroscopy to be 90%. However, after dissecting the shoulders, the actual accuracy rate was determined to be 60%. This demonstrates that imaging modalities cannot always be relied upon to provide correct information regarding injection accuracy, particularly into soft tissues. The heterogeneity of accuracy confirmation techniques (computed tomography [CT], CT arthrography, MRI, MR arthrography, standard radiographic arthrography, intraoperative confirmation, cadaveric dissection) employed by different researchers contributes to the difficulty of interpreting the injection accuracy literature. Further research in which the injector's technical abilities are confirmed and the correct imaging technique is used to grade accuracy is required to definitively answer the question of whether or not USG SA-SD bursa injections are more accurate than LMGIs.

Efficacy

AMSSM Position: USGIs are more efficacious than LMGIs (SORT Evidence Rating = B).

There is evidence that USGIs are more efficacious than LMGIs in large joints, inflamed joints, SA-SD bursa, carpal tunnel, and first dorsal wrist compartment tendon sheath. Only one study evaluated the efficacy of USG intermediate joint injections (AC joint) relative to LMGIs and found no difference in efficacy between the 2 techniques, but the study's design limits the strength of the conclusions. No studies have been performed comparing the efficacy of USG small joint injections to LMGIs. Therefore, although a majority of studies suggest that USGIs are more efficacious than LMGIs, further research is required to fully answer this question.

There are some difficulties with performing efficacy research that warrant mention. The most commonly injected substance to treat musculoskeletal conditions is corticosteroids. There is limited evidence that the systemic effects of corticosteroids provide similar therapeutic benefits to localized injections [92]. In the study by Ekeberg et al [92], a corticosteroid injection in the gluteal region was compared to an USG SA-SD bursa injection for patients with rotator cuff disease. While their conclusions need to be interpreted with caution due to significant study limitations (eg, heterogeneity of shoulder pathology in the study subjects, lack of control group, soft tissue corticosteroid injections in both groups which may result in larger systemic effects than intra-articular injections, etc), both groups showed similar improvements in their primary outcome measures, although there were some secondary outcome measures that were better in the USGI group than in the gluteal (systemic) injection group. Therefore, it is possible that the systemic effects of corticosteroids may make it difficult to detect a difference in efficacy between an accurately and inaccurately placed corticosteroid injection. Despite this possibility, it is important to remember that several studies have been able to demonstrate greater efficacy with accurately placed corticosteroids than with inaccurately placed corticosteroids. This may be due to the type of pathology that is being treated. Specifically, although corticosteroids have been demonstrated to provide short-term therapeutic benefits for arthritis [168], it can be argued that corticosteroid injections may not be an effective treatment for some conditions such as rotator cuff tendinopathy [169]. So, the issue of injection accuracy and efficacy may be irrelevant if the injected agent (eg, corticosteroids) is inappropriate for the pathology being treated. Certainly one could postulate that injectable therapeutic agents that do not have demonstrable systemic therapeutic benefits (eg, viscosupplements, platelet-rich plasma) would be ineffective if placed in the wrong region. Therefore, therapeutic benefit would be dependent upon correct injectate placement for these compounds. However, further research is required to determine if this hypothesis is correct.

While the difference in efficacy between USGIs and LMGIs is important, since it has been established that LMGIs are less accurate than USGIs, it is also important to consider the nontherapeutic ramifications of inaccurate injectate placement. If an injectate is misplaced, it may lead to complications such as skin depigmentation, subcutaneous fat atrophy, tendon rupture, neurovascular injury, increased procedural and postprocedural pain, or intra-arterial injection [99,108]. In addition, correct injectate placement can provide useful diagnostic information regarding the location of a pain generator. All of these factors must be taken into consideration when choosing which injection technique to employ.

Cost-Effectiveness

AMSSM Position: USGIs are more cost-effective than LMGIs (SORT Evidence Rating = B).

The area with the least research is cost-effectiveness. Only 4 studies were identified that compared the cost-effectiveness of USGIs to LMGIs. The preliminary findings of these studies suggest that USGIs are more cost-effective than LMGIs for large joints, inflamed joints, and carpal tunnel syndrome since more people responded to the USGIs, their improvement was greater and lasted longer than those who received LMGIs, and they utilized health care services less often following USGIs than LMGIs. However, due to the limited

number of studies, additional well-designed studies are required to determine if USGIs are more cost-effective than LMGIs.

New Procedures and Future Trends

AMSSM Position: US guidance is required to perform many new procedures (SORT Evidence Rating = C).

Finally, the scope of USG procedures in sports medicine continues to evolve with the introduction of second-generation (eg, tenotomies, transverse carpal ligament fenestrations, peripheral nerve hydrodissections) and third-generation (eg, percutaneous A1 pulley releases with a surgical hook knife) procedures. Direct visualization of the target structure, relevant surrounding structures, and guidance of the procedural device is required for the performance of these procedures. Although the need for radiologic guidance (eg, US guidance) is inherent to the performance of these procedures, research will be needed to determine the efficacy, safety profile, and cost-effectiveness of these new procedures.

Conclusions

The use of diagnostic and interventional US has significantly increased over the past decade. A majority of the increased utilization is by nonradiologists. In sports medicine, ultrasound is often used to guide interventions such as aspirations, diagnostic or therapeutic injections, tenotomies, releases, and hydrodissections, and is rapidly becoming part of the standard practice of sports medicine. The findings of this position statement indicate there is strong evidence that USGIs are more accurate than LMGIs, moderate evidence that they are more efficacious, and preliminary evidence that they are more cost-effective. Furthermore, US guidance is required to perform many new, advanced procedures and will likely enable the development of innovative USG surgical techniques in the future.

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References

1. Smith J, Finnoff JT. Diagnostic and interventional musculoskeletal ultrasound: Part 1. Fundamentals. PM R 2009;1:64-75.
2. Sharpe R, Nazarian LN, Parker L, Rao VM, Levin DC. Utilization from 2000 to 2009, especially by podiatrists in private offices. J Am Coll Radiol 2012;9:141-146.
3. Smith J, Finnoff JT. Diagnostic and interventional musculoskeletal ultrasound: Part 2. Clinical applications. PM R 2009;1:162-177.
4. Wright J, Swiontkowski MF, Heckman JD. Editorial. Introducing levels of evidence to the journal. J Bone Joint Surg Am 2003;85:1-3.
5. Berkoff DJ, Miller LE, Block JE. Clinical utility of ultrasound guidance for intra-articular knee injections: A review. Clin Interv Aging 2012;7:89-95.
6. Bloom JE, Rischin A, Johnston RV, Buchbinder R. Image-guided versus blind glucocorticoid injection for shoulder pain. Cochrane Database Syst Rev 2012;8:CD009147.
7. Catalano OA, Manfredi R, Vanzulli A, et al. MR arthrography of the glenohumeral joint: Modified posterior approach without imaging guidance. Radiology 2007;242:550-554.
8. Choudur HN, Ellins ML. Ultrasound-guided gadolinium joint injections for magnetic resonance arthrography. J Clin Ultrasound 2011;39:6-11.
9. Curtiss HM, Finnoff JT, Peck E, Hollman J, Muir J, Smith J. Accuracy of ultrasound-guided and palpation-guided knee injections by an experienced and less-experienced injector using a superolateral approach: A cadaveric study. PM R 2011;3:507-515.
10. Daley EL, Bajaj S, Bisson LJ, Cole BJ. Improving injection accuracy of the elbow, knee, and shoulder: Does injection site and imaging make a difference? A systematic review. Am J Sports Med 2011;39:656-662.
11. DeMouy EH, Menendez CV Jr, Bodin CJ. Palpation-directed (non-fluoroscopically guided) saline-enhanced MR arthrography of the shoulder. AJR Am J Roentgenol 1997;169:229-231.
12. Diracoglu D, Alptekin K, Dikici F, Balci HI, Ozcakar L, Aksoy C. Evaluation of needle positioning during blind intra-articular hip injections for osteoarthritis: Fluoroscopy versus arthrography. Arch Phys Med Rehabil 2009;90:2112-2115.
13. Esenyel C, Demirhan M, Esenyel M, et al. Comparison of four different intra-articular injection sites in the knee: A cadaver study. Knee Surg Sports Traumatol Arthrosc 2007;15:573-577.
14. Esenyel CZ, Esenyel M, Yesiltepe R, et al. [The correlation between the accuracy of steroid injections and subsequent shoulder pain and function in subacromial impingement syndrome]. Acta Orthop Traumatol Turc 2003;37:41-45.
15. Gokalp G, Dusak A, Yazici Z. Efficacy of ultrasonography-guided shoulder MR arthrography using a posterior approach. Skel Radiol 2010;39:575-579.
16. Goncalves B, Ambrosio C, Serra S, Alves F, Gil-Agostinho A, Caseiro-Alves F. US-guided interventional joint procedures in patients with rheumatic diseases—when and how we do it? Eur J Radiol 2011;79:407-414.
17. Hanchard N, Shanahan D, Howe T, Thompson J, Goodchild L. Accuracy and dispersal of subacromial and glenohumeral injections in cadavers. J Rheumatol 2006;33:1143-1146.
18. Hartung W, Ross CJ, Straub R, et al. Ultrasound-guided sacroiliac joint injection in patients with established sacroiliitis: Precise IA injection verified by MRI scanning does not predict clinical outcome. Rheumatology 2010;49:1479-1482.
19. Hermans J, Bierma-Zeinstra SM, Bos PK, Verhaar JA, Reijman M. The most accurate approach for intra-articular needle placement in the knee joint: A systematic review. Semin Arthritis Rheum 2011;41:106-115.
20. Hurdle MF, Wisniewski SJ, Pingree MJ. Ultrasound-guided intra-articular knee injection in an obese patient. Am J Phys Med Rehabil 2012;91:275-276.
21. Im SH, Lee SC, Park YB, Cho SR, Kim JC. Feasibility of sonography for intra-articular injections in the knee through a medial patellar portal. J Ultrasound Med 2009;28:1465-1470.
22. Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. J Bone Joint Surg Am 2002;84-A:1522-1527.
23. Jang SH, Lee SC, Lee JH, Nam SH, Cho KR, Park Y. Comparison of ultrasound (US)-guided intra-articular injections by in-plain and out-of-plain on medial portal of the knee. Rheumatol Int 2013;33:1951-1959.
24. Jo CH, Shin YH, Shin JS. Accuracy of intra-articular injection of the glenohumeral joint: A modified anterior approach. Arthroscopy 2011;27:1329-1334.

25. Johnson TS, Mesfin A, Farmer KW, et al. Accuracy of intra-articular glenohumeral injections: The anterosuperior technique with arthroscopic documentation. Arthroscopy 2011;27:745-749.
26. Jones A, Regan M, Ledingham J, Pattrick M, Manhire A, Doherty M. Importance of placement of intra-articular steroid injections. BMJ 1993;307:1329-1330.
27. Kantarci F, Ozbayrak M, Gulsen F, Gencturk M, Botanlioglu H, Mihmanli I. Ultrasound-guided injection for MR arthrography of the hip: Comparison of two different techniques. Skeletal Radiol 2013;42:37-42.
28. Kim JS, Yun JS, Kim JM, et al. Accuracy of the glenohumeral injection using the superior approach: A cadaveric study of injection accuracy. Am J Phys Med Rehabil 2010;89:755-758.
29. Lee HJ, Lim KB, Kim DY, Lee KT. Randomized controlled trial for efficacy of intra-articular injection for adhesive capsulitis: Ultrasonography-guided versus blind technique. Arch Phys Med Rehabil 2009;90:1997-2002.
30. Levi DS. Intra-articular hip injections using ultrasound guidance: Accuracy using a linear array transducer. PM R 2013;5:129-134.
31. Lopes RV, Furtado RN, Parmigiani L, Rosenfeld A, Fernandes AR, Natour J. Accuracy of intra-articular injections in peripheral joints performed blindly in patients with rheumatoid arthritis. Rheumatology (Oxford) 2008;47:1792-1794.
32. Luc M, Pham T, Chagnaud C, Lafforgue P, Legre V. Placement of intra-articular injection verified by the backflow technique. Osteoarthritis Cartilage 2006;14:714-716.
33. Micu MC, Bogdan GD, Fodor D. Steroid injection for hip osteoarthritis: Efficacy under ultrasound guidance. Rheumatology (Oxford) 2010;49:1490-1494.
34. Migliore A, Bizzi E, Massafra U, et al. A new technical contribution for ultrasound-guided injections of sacro-iliac joints. Eur Rev Med Pharmacol Sci 2010;14:465-469.
35. Migliore A, Granata M, Tormenta S, et al. Hip viscosupplementation under ultra-sound guidance riduces NSAID consumption in symptomatic hip osteoarthritis patients in a long follow-up. Data from Italian registry. Eur Rev Med Pharmacol Sci 2011;15:25-34.
36. Park Y, Choi WA, Kim YK, Lee SC, Lee JH. Accuracy of blind versus ultrasound-guided suprapatellar bursal injection. J Clin Ultrasound 2012;40:20-25.
37. Park Y, Lee SC, Nam HS, Lee J, Nam SH. Comparison of sonographically guided intra-articular injections at 3 different sites of the knee. J Ultrasound Med 2011;30:1669-1676.
38. Patel DN, Nayyar S, Hasan S, Khatib O, Sidash S, Jazrawi LM. Comparison of ultrasound-guided versus blind glenohumeral injections: A cadaveric study. J Shoulder Elbow Surg 2012;21:1664-1668.
39. Perdikakis E, Drakonaki E, Maris T, Karantanas A. MR arthrography of the shoulder: Tolerance evaluation of four different injection techniques. Skeletal Radiol 2012;42:99-105.
40. Porat S, Leupold JA, Burnett KR, Nottage WM. Reliability of non-imaging-guided glenohumeral joint injection through rotator interval approach in patients undergoing diagnostic MR arthrography. AJR Am J Roentgenol 2008;191:W96-W99.
41. Pourbagher MA, Ozalay M, Pourbagher A. Accuracy and outcome of sonographically guided intra-articular sodium hyaluronate injections in patients with osteoarthritis of the hip. J Ultrasound Med 2005;24:1391-1395.
42. Rutten MJ, Collins JM, Maresch BJ, et al. Glenohumeral joint injection: A comparative study of ultrasound and fluoroscopically guided techniques before MR arthrography. Eur Radiol 2009;19:722-730.
43. Sethi PM, Kingston S, Elattrache N. Accuracy of anterior intra-articular injection of the glenohumeral joint. Arthroscopy 2005;21:77-80.
44. Smith J, Hurdle MFB. Office based ultrasound-guided intra-articular hip injection—technique for physiatric practice. Arch Phys Med Rehabil 2006;87:296-298.
45. Smith J, Hurdle MF, Weingarten TN. Accuracy of sonographically guided intra-articular injections in the native adult hip. J Ultrasound Med 2009;28:329-335.
46. Souza PM, Aguiar RO, Marchiori E, Bardoe SA. Arthrography of the shoulder: A modified ultrasound guided technique of joint injection at the rotator interval. Eur J Radiol 2010;74:e29-e32.
47. Tobola A, Cook C, Cassas KJ, et al. Accuracy of glenohumeral joint injections: Comparing approach and experience of provider. J Shoulder Elbow Surg 2011;20:1147-1154.
48. Toda Y, Tsukimura N. A comparison of intra-articular hyaluronan injection accuracy rates between three approaches based on radiographic severity of knee osteoarthritis. Osteoarthritis Cartilage 2008;16:980-985.
49. Valls R, Melloni P. Sonographic guidance of needle position for MR arthrography of the shoulder. AJR Am J Roentgenol 1997;169:845-847.
50. Ziv YB, Kardosh R, Debi R, Backstein D, Safir O, Kosashvili Y. An inexpensive and accurate method for hip injections without the use of imaging. J Clin Rheumatol 2009;15:103-105.
51. Zufferey P, Revaz S, Degailler X, Balague F, So A. A controlled trial of the benefits of ultrasound-guided steroid injection for shoulder pain. Joint Bone Spine 2012;79:166-169.
52. Balint PV, Kane D, Hunter J, McInnes IB, Field M, Sturrock RD. Ultrasound guided versus conventional joint and soft tissue fluid aspiration in rheumatology practice: A pilot study. J Rheumatol 2002;29:2209-2213.
53. Elkousy H, Gartsman GM, Drake G, Sola W Jr, O'Connor D, Edwards TB. Retrospective comparison of freehand and ultrasound-guided shoulder steroid injections. Orthopedics 2011;34(4).
54. Naredo E, Cabero F, Beneyto P, et al. A randomized comparative study of short term response to blind injection versus sonographic-guided injection of local corticosteroids in patients with painful shoulder. J Rheumatol 2004;31:308-314.
55. Sage W, Pickup L, Smith TO, Denton ER, Toms AP. The clinical and functional outcomes of ultrasound-guided vs landmark-guided injections for adults with shoulder pathology—a systematic review and meta-analysis. Rheumatology 2013;52:743-751.
56. Sibbitt WL Jr, Band PA, Kettwich LG, Chavez-Chiang NR, Delea SL, Bankhurst AD. A randomized controlled trial evaluating the cost-effectiveness of sonographic guidance for intra-articular injection of the osteoarthritic knee. J Clin Rheumatol 2011;17:409-415.
57. Sibbitt WL Jr, Kettwich LG, Band PA, et al. Does ultrasound guidance improve the outcomes of arthrocentesis and corticosteroid injection of the knee? Scand J Rheumatol 2012;41:66-72.
58. Soh E, Li W, Ong KO, Chen W, Bautista D. Image-guided versus blind corticosteroid injections in adults with shoulder pain: A systematic review. BMC Musculoskelet Disord 2011;12:137.
59. Yoong P, Guirguis R, Darrah R, Wijeratna M, Porteous MJ. Evaluation of ultrasound-guided diagnostic local anaesthetic hip joint injection for osteoarthritis. Skeletal Radiol 2012;41:981-985.
60. Esenyel CZ, Ozturk K, Demirhan M, et al. Accuracy of anterior glenohumeral injections: A cadaver study. Arch Orthop Trauma Surg 2010;130:297-300.
61. Sethi PM, El Attrache N. Accuracy of intra-articular injection of the glenohumeral joint: A cadaveric study. Orthopedics 2006;29:149-152.
62. Albano J, Alexander RW. Autologous fat grafting as a mesenchymal stem cell source and living bioscaffold in patellar tendon tear. Clin J Sport Med 2011;21:359-361.
63. Borbas P, Kraus T, Clement H, Grechenig S, Weinberg AM, Heidari N. The influence of ultrasound guidance in the rate of success of acromioclavicular joint injection: An experimental study on human cadavers. J Shoulder Elbow Surg 2012;21:1694-1697.
64. Drakonaki EE, Kho JS, Sharp RJ, Ostlere SJ. Efficacy of ultrasound-guided steroid injections for pain management of midfoot joint degenerative disease. Skeletal Radiol 2011;40:1001-1006.
65. Heidari N, Pichler W, Grechenig S, Grechenig W, Weinberg AM. Does the anteromedial or anterolateral approach alter the rate of joint puncture in injection of the ankle?: A cadaver study. J Bone Joint Surg Br 2010;92:176-178.

66. Khosla S, Thiele R, Baumhauer JF. Ultrasound guidance for intra-articular injections of the foot and ankle. Foot Ankle Int 2009;30:886-890.
67. Kirk KL, Campbell JT, Guyton GP, Schon LC. Accuracy of posterior subtalar joint injection without fluoroscopy. Clin Orthop Relat Res 2008;466:2856-2860.
68. Kraus T, Heidari N, Borbas P, Clement H, Grechenig W, Weinberg AM. Accuracy of anterolateral versus posterolateral subtalar injection. Arch Orthop Trauma Surg 2011;131:759-763.
69. Partington PF, Broome GH. Diagnostic injection around the shoulder: hit and miss? A cadaveric study of injection accuracy. J Shoulder Elbow Surg 1998;7:147-150.
70. Peck E, Lai JK, Pawlina W, Smith J. Accuracy of ultrasound-guided versus palpation-guided acromioclavicular joint injections: A cadaveric study. PM R 2010;2:817-821.
71. Reach JS, Easley ME, Chuckpaiwong B, Nunley JA 2nd. Accuracy of ultrasound guided injections in the foot and ankle. Foot Ankle Int 2009;30:239-242.
72. Sabeti-Aschraf M, Lemmerhofer B, Lang S, et al. Ultrasound guidance improves the accuracy of the acromioclavicular joint infiltration: A prospective randomized study. Knee Surg Sports Traumatol Arthrosc 2011;19:292-295.
73. Sabeti-Aschraf M, Ochsner A, Schueller-Weidekamm C, et al. The infiltration of the AC joint performed by one specialist: Ultrasound versus palpation a prospective randomized pilot study. Eur J Radiol 2010;75:e37-e40.
74. Smith J, Brault JS, Rizzo M, Sayeed YA, Finnoff JT. Accuracy of sonographically guided and palpation guided scaphotrapeziotrapezoid joint injections. J Ultrasound Med 2011;30:1509-1515.
75. Smith J, Finnoff JT, Henning PT, Turner NS. Accuracy of sonographically guided posterior subtalar joint injections: Comparison of 3 techniques. J Ultrasound Med 2009;28:1549-1557.
76. Smith J, Finnoff JT, Levy BA, Lai JK. Sonographically guided proximal tibiofibular joint injection: Technique and accuracy. J Ultrasound Med 2010;29:783-789.
77. Smith J, Rizzo M, Sayeed YA, Finnoff JT. Sonographically guided distal radioulnar joint injection: Technique and validation in a cadaveric model. J Ultrasound Med 2011;30:1587-1592.
78. Wasserman BR, Pettrone S, Jazrawi LM, Zuckerman JD, Rokito AS. Accuracy of acromioclavicular joint injections. Am J Sports Med 2013;41:149-152.
79. Weinberg AM, Pichler W, Grechenig S, Tesch NP, Heidari N, Grechenig W. Frequency of successful intra-articular puncture of the sternoclavicular joint: A cadaver study. Scand J Rheumatol 2009;38:396-398.
80. Wisniewski SJ, Smith J, Patterson DG, Carmichael SW, Pawlina W. Ultrasound-guided versus nonguided tibiotalar joint and sinus tarsi injections: A cadaveric study. PM R 2010;2:277-281.
81. Raza K, Lee CY, Pilling D, et al. Ultrasound guidance allows accurate needle placement and aspiration from small joints in patients with early inflammatory arthritis. Rheumatology (Oxford) 2003;42:976-979.
82. Umphrey GL, Brault JS, Hurdle MF, Smith J. Ultrasound-guided intra-articular injection of the trapeziometacarpal joint: Description of technique. Arch Phys Med Rehabil 2008;89:153-156.
83. Wempe MK, Sellon JL, Sayeed YA, Smith J. Feasibility of first metatarsophalangeal joint injections for sesamoid disorders: A cadaveric investigation. PM R 2012;4:556-560.
84. Bandinelli F, Fedi R, Generini S, et al. Longitudinal ultrasound and clinical follow-up of Baker's cysts injection with steroids in knee osteoarthritis. Clin Rheumatol 2012;31:727-731.
85. Chavez-Chiang NR, Sibbitt WL, Band PA, DeLea SL, Park KS, Bankhurst AD. The outcomes and cost-effectiveness of intra-articular injection of the rheumatoid knee. Rheumatol Int 2012;32:513-518.
86. Chen H, Takemoto R, Hata J. Ultrasound guided piriformis injection with confirmation of needle placement through electromyography. Pain Med 2012;13:978-979.
87. Chen MJ, Lew HL, Hsu TC, et al. Ultrasound-guided shoulder injections in the treatment of subacromial bursitis. Am J Phys Med Rehabil 2006;85:31-35.
88. Chen PJ, Liang HW, Chang KV, Wang TG. Ultrasound-guided injection of steroid in multiple postamputation neuromas. J Clin Ultrasound 2013;41:122-124.
89. Di Geso L, Filippucci E, Meenagh G, et al. CS injection of tenosynovitis in patients with chronic inflammatory arthritis: The role of US. Rheumatology 2012;51:1299-1303.
90. Di Sante L, Paoloni M, Ioppolo F, Dimaggio M, Di Renzo S, Santilli V. Ultrasound-guided aspiration and corticosteroid injection of Baker's cysts in knee osteoarthritis: A prospective observational study. Am J Phys Med Rehabil 2010;89:970-975.
91. Dogu B, Yucel SD, Sag SY, Bankaoglu M, Kuran B. Blind or ultrasound-guided corticosteroid injections and short-term response in subacromial impingement syndrome: A randomized, double-blind, prospective study. Am J Phys Med Rehabil 2012;91:658-665.
92. Ekeberg OM, Bautz-Holter E, Tveita EK, Juel NG, Kvalheim S, Brox JI. Subacromial ultrasound guided or systemic steroid injection for rotator cuff disease: Randomised double blind study. BMJ 2009;338:a3112.
93. Eustace JA, Brophy DP, Gibney RP, Bresnihan B, FitzGerald O. Comparison of the accuracy of steroid placement with clinical outcome in patients with shoulder symptoms. Ann Rheum Dis 1997;56:59-63.
94. Fanucci E, Masala S, Fabiano S, et al. Treatment of intermetatarsal Morton's neuroma with alcohol injection under US guide: 10-month follow-up. Eur Radiol 2004;14:514-518.
95. Farshad M, Jundt-Ecker M, Sutter R, Schubert M, Gerber C. Does subacromial injection of a local anesthetic influence strength in healthy shoulders?: A double-blinded, placebo-controlled study. J Bone Joint Surg Am 2012;94:1751-1755.
96. Finnoff JT, Fowler SP, Lai JK, et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. PM R 2011;3:900-911.
97. Finnoff JT, Hurdle MF, Smith J. Accuracy of ultrasound-guided versus fluoroscopically guided contrast-controlled piriformis injections: A cadaveric study. J Ultrasound Med 2008;27:1157-1163.
98. Finnoff JT, Nutz DJ, Henning PT, Hollman JH, Smith J. Accuracy of ultrasound-guided versus unguided pes anserinus bursa injections. PM R 2010;2:732-739.
99. Hashiuchi T, Sakurai G, Morimoto M, Komei T, Takakura Y, Tanaka Y. Accuracy of the biceps tendon sheath injection: Ultrasound-guided or unguided injection? A randomized controlled trial. J Shoulder Elbow Surg 2011;20:1069-1073.
100. Hashiuchi T, Sakurai G, Sakamoto Y, Takakura Y, Tanaka Y. Comparative survey of pain-alleviating effects between ultrasound-guided injection and blind injection of lidocaine alone in patients with painful shoulder. Arch Orthop Trauma Surg 2010;130:847-852.
101. Henkus HE, Cobben LP, Coerkamp EG, Nelissen RG, van Arkel ER. The accuracy of subacromial injections: A prospective randomized magnetic resonance imaging study. Arthroscopy 2006;22:277-282.
102. Housner JA, Jacobson JA, Misko R. Sonographically guided percutaneous needle tenotomy for the treatment of chronic tendinosis. J Ultrasound Med 2009;28:1187-1192.
103. Hsieh LF, Hsu WC, Lin YJ, Wu SH, Chang KC, Chang HL. Is ultrasound-guided injection more effective in chronic subacromial bursitis? Med Sci Sports Exerc 2013;45:2205-2213.
104. Hughes RJ, Ali K, Jones H, Kendall S, Connell DA. Treatment of Morton's neuroma with alcohol injection under sonographic guidance: Follow-up of 101 cases. AJR Am J Roentgenol 2007;188:1535-1539.
105. Kang MN, Rizio L, Prybicien M, Middlemas DA, Blacksin MF. The accuracy of subacromial corticosteroid injections: A comparison of multiple methods. J Shoulder Elbow Surg 2008;17(1 suppl):61S-66S.
106. Kume K, Amano K, Yamada S, Amano K, Kuwaba N, Ohta H. In de Quervain's with a separate EPB compartment, ultrasound-guided

steroid injection is more effective than a clinical injection technique: A prospective open-label study. J Hand Surg Eur Vol 2012;37:523-527.
107. Labrosse JM, Cardinal E, Leduc BE, et al. Effectiveness of ultrasound-guided corticosteroid injection for the treatment of gluteus medius tendinopathy. AJR Am J Roentgenol 2010;194:202-206.
108. Lee DH, Han SB, Park JW, Lee SH, Kim KW, Jeong WK. Sonographically guided tendon sheath injections are more accurate than blind injections: Implications for trigger finger treatment. J Ultrasound Med 2011;30:197-203.
109. Makhlouf T, Emil NS, Sibbitt WL Jr, Fields RA, Bankhurst AD. Outcomes and cost-effectiveness of carpal tunnel injections using sonographic needle guidance. Clin Rheumatol 2014;33:849-858.
110. Mathews PV, Glousman RE. Accuracy of subacromial injection: Anterolateral versus posterior approach. J Shoulder Elbow Surg 2005;14:145-148.
111. McDermott JD, Ilyas AM, Nazarian LN, Leinberry CF. Ultrasound-guided injections for de Quervain's tenosynovitis. Clin Orthop Relat Res 2012;470:1925-1931.
112. McShane JM, Shah VN, Nazarian LN. Sonographically guided percutaneous needle tenotomy for treatment of common extensor tendinosis in the elbow: Is a corticosteroid necessary? J Ultrasound Med 2008;27:1137-1144.
113. Muir JJ, Curtiss HM, Hollman J, Smith J, Finnoff JT. The accuracy of ultrasound-guided and palpation-guided peroneal tendon sheath injections. Am J Phys Med Rehabil 2011;90:564-571.
114. Peck E, Finnoff JT, Smith J, Curtiss H, Muir J, Hollman JH. Accuracy of palpation-guided and ultrasound-guided needle tip placement into the deep and superficial posterior leg compartments. Am J Sports Med 2011;39:1968-1974.
115. Rutten MJ, Maresch BJ, Jager GJ, de Waal Malefijt MC. Injection of the subacromial-subdeltoid bursa: Blind or ultrasound-guided? Acta Orthop 2007;78:254-257.
116. Smith J, Finnoff JT, Santaella-Sante B, Henning T, Levy BA, Lai JK. Sonographically guided popliteus tendon sheath injection: Techniques and accuracy. J Ultrasound Med 2010;29:775-782.
117. Smith J, Hurdle MF, Locketz AJ, Wisniewski SJ. Ultrasound-guided piriformis injection: Technique description and verification. Arch Phys Med Rehabil 2006;87:1664-1667.
118. Smith J, Wisniewski SJ, Wempe MK, Landry BW, Sellon JL. Sonographically guided obturator internus injections: Techniques and validation. J Ultrasound Med 2012;31:1597-1608.
119. Tsai WC, Hsu CC, Chen CP, Chen MJ, Yu TY, Chen YJ. Plantar fasciitis treated with local steroid injection: Comparison between sonographic and palpation guidance. J Clin Ultrasound 2006;34:12-16.
120. Tsai WC, Tang FT, Hsu TC, Hsu KH, Wong MK. Treatment of proximal plantar fasciitis with ultrasound-guided steroid injection. Arch Phys Med Rehabil 2000;81:1416-1421.
121. Ucuncu F, Capkin E, Karkucak M, et al. A comparison of the effectiveness of landmark-guided injections and ultrasonography guided injections for shoulder pain. Clin J Pain 2009;25:786-789.
122. Ustun N, Tok F, Yagz AE, et al. Ultrasound-guided vs. blind steroid injections in carpal tunnel syndrome: A single-blind randomized prospective study. Am J Phys Med Rehabil 2013;92:999-1004.
123. Yamakado K. The targeting accuracy of subacromial injection to the shoulder: An arthrographic evaluation. Arthroscopy 2002;18:887-891.
124. Yoo JC, Koh KH, Park WH, Park JC, Kim SM, Yoon YC. The outcome of ultrasound-guided needle decompression and steroid injection in calcific tendinitis. J Shoulder Elbow Surg 2010;19:596-600.
125. Yucel I, Yazici B, Degirmenci E, Erdogmus B, Dogan S. Comparison of ultrasound-, palpation-, and scintigraphy-guided steroid injections in the treatment of plantar fasciitis. Arch Orthop Trauma Surg 2009;129:695-701.
126. Cunnington J, Marshall N, Hide G, et al. A randomized, double-blind, controlled study of ultrasound-guided corticosteroid injection into the joint of patients with inflammatory arthritis. Arthritis Rheum 2010;62:1862-1869.
127. Sibbitt WL Jr, Band PA, Chavez-Chiang NR, Delea SL, Norton HE, Bankhurst AD. A randomized controlled trial of the cost-effectiveness of ultrasound-guided intraarticular injection of inflammatory arthritis. J Rheumatol 2011;38:252-263.
128. Sibbitt WL Jr, Peisajovich A, Michael AA, et al. Does sonographic needle guidance affect the clinical outcome of intraarticular injections? J Rheumatol 2009;36:1892-1902.
129. Connell D, Ali KE, Ahmad M, Lambert S, Corbett S, Curtis M. Ultrasound guided autologous blood injection for tennis elbow. Skeletal Radiol 2006;35:371-377.
130. Creaney L, Wallace A, Curtis M, Connell D. Growth factor based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: A prospective, single blind, randomized trial of autologous bloos injections versus platelet rich plasma injections. Br J Sports Med 2011;45:966-971.
131. Dragoo J, Wasterlain AS, Braun HJ, Nead KT. Platelet rich plasma as a treatment for patellar tendinopathy: A double-blind, randomized controlled trial. Am J Sports Med 2014;42:610-618.
132. Filardo G, Kon E, DiMatteo B, Pelotti P, DiMartino A, Marcacci M. Platelet-rich plasma for the treatment of patellar tendinopathy: Clinical and imaging findings at medium term follow-up. Int Orthop 2013;37:1583-1589.
133. Gaweda K, Tarczynska M, Krzyzanowski W. Treatment of Achilles tendinopathy with platelet rich plasma. Int J Sports Med 2010;31:577-583.
134. James S, Ali K, Pocock C, et al. Ultrasound guided dry needling and autologous blood injection for patellar tendinosis. Br J Sports Med 2007;41:518-521.
135. Kim E, Lee JH. Autologous platelet-rich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis. PM R 2013;6:152-158.
136. Podesta L, Crow SA, Volkmer D, Bert T, Yocum LA. Treatment of partial ulnar collateral ligament tears in the elbow with platelet-rich plasma. Am J Sports Med 2013;41:1689-1694.
137. Ryan M, Wong A, Taunton J. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional and midportion achilles tendinosis. AJR Am J Roentgenol 2010;194:1047-1053.
138. Suresh S, Ali KE, Jones H, Connell DA. Medial epicondylitis: Is ultrasound guided autologous blood injection an effective treatment. Br J Sports Med 2006;40:935-939.
139. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: A randomized controlled clinical trial. Am J Sports Med 2011;39:2130-2134.
140. Campbell K, Boykin RE, Wijdicks CA, Erik-Giphart J, LaPrade RF, Philippon MJ. Treatment of hip capsular injection in a professional soccer player with platelet rich plasma and bone marrow aspirate concentrate therapy. Knee Surg Sports Traumatol Arthrosc 2013;21:1684-1688.
141. Connell D, Datir A, Alyas F, Curtis M. Treatment of lateral epicondylitis using skin-derived tenocyte-like cells. Br J Sports Med 2009;43:293-298.
142. Obaid H, Clarke A, Rosenfeld P, Leach C, Connell D. Skin-derived fibroblasts for the treatment of refractory Achilles tendinosis: Preliminary short term results. J Bone Joint Surg Am 2012;94:193-200.
143. Wang A, Breidahl W, Mackie KE, et al. Autologous tenocyte injection for the treatment of severe chronic resistant lateral epicondylitis. A pilot study. Am J Sports Med 2013;41:2925-2932.
144. Alfredson H, Lorentzon R. Sclerosing polidocanol injections of small vessels to treat the chronic painful tendon. Cardiovasc Hematol Agents Med Chem 2007;5:97-100.
145. Alfredson H. Ultrasound and Doppler-guided mini-surgery to treat midportion Achilles tendinosis: Results of a large material and a randomised study comparing two scraping techniques. Br J Sports Med 2011;45:407-410.

146. Chiavaras M, Jacobson JA. Ultrasound guided tendon fenestration. Semin Muscuoloskelet Radiol 2013;17:85-90.
147. Finnoff J, Fowler SP, Lai JK, et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. PM R 2011;3:900-911.
148. Hoksrud A, Bahr R. Ultrasound guided sclerosing treatment in patients with patellar tendinopathy (Jumper's knee): 44 month follow-up. Am J Sports Med 2011;39:2377-2380.
149. Maffulli N, Oliva F, Testa V, Capasso G, DelBuono A. Multiple percutaneous longitudinal tenotomies for chronic Achilles tendinopathy in runners: A long-term study. Am J Sports Med 2013;41:2151-2157.
150. McShane J, Slaff S, Gold JE, Nazarian LN. Sonographically guided percutaneous needle release of the carpal tunnel for treatment of carpal tunnel syndrome. J Ultrasound Med 2012;31:1341-1349.
151. Mulvaney S. Ultrasound-guided percutaneous neuroplasty of the lateral femoral cutaneous nerve for the treatment of meralgia paresthetica: A case report and description of a new ultrasound-guided technique. Cur Sports Med Rep 2011;10:99-104.
152. Rajeswaran G, Lee JC, Eckersley R, Katsarma E, Healy JC. Ultrasound guided percutaneous release of the annular pulley in trigger digit. Eur Radiol 2009;19:2232-2237.
153. Sampson S, Meng M, Schulte A, Trainor D, Montenegro R, Aufiero D. Management of Dupytren contracture with ultrasound-guided lidocaine injection and needle aponeurotomy coupled with osteopathic manipulative treatment. J Am Osteopath Assoc 2011;111:113-116.
154. Willberg L, Sunding K, Forssblad M, Fahlstrom M, Alfredson H. Sclerosing polidocanol injections or arthroscopic shaving to treat patellar tendinopathy/jumper's knee. A randomized controlled study. Br J Sports Med 2011;45:411-415.
155. deWitte P, Selten JW, Navas A, et al. Calcific tendinitis of the rotator cuff: A randomized controlled trial of ultrasound-guided needling and lavage versus subacromial steroids. Am J Sports Med 2013;41:1665-1673.
156. DeZordo T, Ahmad N, Odegaard F, et al. US-Guided therapy of calcific tendinopathy: Clinical and radiological outcome assessment in shoulder and non-shoulder tendons. Ultraschall Med 2011;32(suppl 1):S117-S123.
157. Sconfienza L, Vigano S, Martini C, et al. Double-needle ultrasound-guided percutaneous treatment of rotator cuff calcific tendinitis: Tips & tricks. Skeletal Radiol 2013;42:19-24.
158. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F. Rotator cuff calcific tendonitis: Short-term and 10-year outcome after two-needle US-guided percutaneous treatment—nonrandomized controlled trial. Radiology 2010;252:157-164.
159. Buncke G, McCormack B, Bodor M. Ultrasound-guided carpal tunnel release using the Manos CTR system. Microsurgery 2013;33:362-366.
160. de-la-Fuenta J, Miguel-Perez MI, Balius R, Guerrero V, Michaud J, Bong D. Minimally invasive ultrasound guided carpal tunnel release: A cadaver study. J Clin Ultrasound 2013;41:101-107.
161. Koh J, Mohan PC, Howe TS, et al. Fasciotomy and surgical tenotomy for recalcitrant lateral elbow tendinopathy: Early clinical experience with a novel device for minimally invasive percutaneous microresection. Am J Sports Med 2013;41:636-644.
162. Lecoq B, Hanouz N, Vielpeau C, Marcelli C. Ultrasound-guided percutaneous surgery for carpal tunnel syndrome: A cadaver study. Joint Bone Spine 2011;78:516-518.
163. Nakamichi K, Tachibana S, Yamamoto S, Ida M. Percutaneous carpal tunnel release compared with mini-open release using ultrasonic guidance for both techniques. J Hand Surg Am 2010;35:437-445.
164. Rojo-Manaute J, Rodriguez-Maruri G, Capa-Grasa A, Chana-Rodriguez F, Soto-Mdel V, Martin JV. Sonographically guided intrasheath percutaneous release of the first annular pulley for trigger digits, part 1. Clinical efficacy and safety. J Ultrasound Med 2012;31:417-424.
165. Rojo-Manaute J, Capa-Grasa A, DelCerro-Gutierrez M, Martinez MV, Chana-Rodriguez F, Martin JV. Sonographically guided intrasheath percutaneous release of the first annular pulley for trigger digits, part 2. Randomized comparative study of the economic impact of 3 surgical models. J Ultrasound Med 2012;31:427-438.
166. Rojo-Manaute J, Capa-Grasa A, Rodriguez-Maruri GE, Moran LM, Martinez MV, Martin JV. Ultra-minimally invasive sonographically guided carpal tunnel release: Anatomic study of a new technique. J Ultrasound Med 2013;32:131-142.
167. Smith J, Rizzo M, Lai JK. Sonographically guided percutaneous first annular pulley release: Cadaveric safety study of needle and knife techniques. J Ultrasound Med 2010;29:1531-1542.
168. Stitik T, Kumar A, Foye PM. Corticosteroid injections for osteoarthritis. Am J Phys Med Rehabil 2006;85(suppl):S51-S65.
169. Koester M, Dunn WR, Kuhn JE, Spindler KP. The efficacy of subacromial corticosteroid injection in the treatment of rotator cuff disease: A systematic review. J Am Acad Orthop Surg 2007;15:3-11.

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Appendix 1
Summary of the literature evaluating major joint injections

First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Zufferey 2012 [51]	GH joint	Prospective, randomized, blinded comparison study of USGI vs LMGI efficacy	Level 2	67 live human subjects	None	More pain relief at rest and more good responders in USGI at 2 and 6 wk postinjection
Migliore 2010 [34]	SI joint	Case series, USGI accuracy and efficacy	Level 3 = accuracy, level 4 = efficacy	7 live human subjects	Color Doppler ultrasound	USGI = 100% accurate, all patients reported significant pain improvement at 6-mo follow-up
Naredo 2004 [54]	GH joint	Prospective, randomized, blinded comparison study of USGI vs LMGI efficacy	Level 2	41 live human subjects	None	USGI had greater pain relief than LMGI
Sibbitt 2011 [56]	Knee	Prospective, randomized comparison study of USGI vs LMGI efficacy	Level 2	94 live human subjects	None	USGIs were less painful, had more responders, provided more improvement and lasted longer than LMGIs
Hanchard 2006 [17]	GH joint	Cadaveric LMGI accuracy	Level 2	11 cadaveric specimens	Dissection	64%-86% accurate
Pourbagher 2005 [41]	Hip	Case series, USGI accuracy and efficacy	Level 1 = accuracy, level 4 = efficacy	10 live human subjects	CT arthrogram	100% accurate, 80% of patients had less pain and improved function 6 mo postinjection
Esenyel 2010 [60]	GH joint	Cadaveric LMGI accuracy	Level 2	25 cadaveric specimens	Dissection	96% accurate
Sethi 2005 [43]	GH joint	Human LMGI accuracy	Level 1	41 live human subjects	MRI arthrogram	26.8% accurate
Park 2012 [36]	Knee	Prospective comparison study of USGI vs LMGI accuracy	Level 1	99 live human subjects	Arthrogram	USGI = 96% accurate, LMGI = 83.7% accurate
Kim 2010 [28]	GH joint	Cadaveric LMGI accuracy	Level 2	23 cadaveric specimens	Dissection	95% accurate
Tobola 2011 [47]	GH joint	Human LMGI accuracy	Level 1	106 live human subjects	Athrogram	45.5%, 45.7%, and 64.7% accurate, depending on approach
Johnson 2011 [25]	GH joint	Human LMGI accuracy	Level 2	42 live human subjects under anesthesia	Arthroscopic confirmation	91% accurate
Sethi 2006 [61]	GH joint	Cadaveric LMGI accuracy	Level 2	40 cadaveric specimens	Arthrogram	50% and 80% accurate [61] depending on approach
Jo 2011 [24]	GH joint	Human LMGI accuracy	Level 1	256 live human subjects	Arthrogram	73.8% accurate
Lopes 2008 [31]	GH joint, knee	Case series, LMGI accuracy and efficacy	Level 1 = accuracy, level 4 = efficacy	71 live human subjects	Arthrogram	GH joint = 82% accurate, knee = 100% accurate, significant improvement in pain
Jackson 2002 [22]	Knee	Human LMGI accuracy	Level 1	240 live human subjects	Arthrogram	71%, 75%, and 93% accurate depending on approach
Smith 2009 [45]	Hip	Human USGI accuracy	Level 1	28 live human subjects	Arthrogram	97% accuracy
Curtiss 2011 [9]	Knee	Cadaveric USGI vs LMGI accuracy	Level 2	20 cadaveric specimens	Dissection	USGI = 100% accurate, LMGI = 55%-100% depending on injector
Ziv 2009 [50]	Hip	Human LMGI accuracy	Level 2	40 live human subjects under anesthesia	Intraoperative confirmation	77.5% accuracy
Souza 2010 [46]	GH joint	Human USGI accuracy	Level 1	180 live human subjects	MRI	92% accurate on 1 attempt, remaining 8% accurate on second attempt

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First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Berkoff 2012 [5]	GH joint, knee	Meta-analysis USGI vs LMGI accuracy and efficacy	Level 2	13 studies (5 knee, 7 shoulder, 1 both)	N/A	USGI knee = 95.8% accurate, LMGI knee = 77.8% accurate, USGI GH joint = 88.8% accurate, LMGI GH joint = 61.1% accurate; all 6 studies that evaluated efficacy showed better efficacy with USGI than LMGI
Esenyel 2007 [13]	Knee	Cadaveric LMGI accuracy	Level 2	39 cadaveric specimens	Dissection	56%, 73%, 76%, or 85% accurate depending on approach
Toda 2008 [48]	Knee	Human LMGI accuracy and efficacy	Level 1	50 live human subjects	Arthrogram	62%, 70%, and 86% accurate depending on approach; accurate injections = better efficacy than inaccurate injections
Park 2011 [37]	Knee	Human USGI accuracy	Level 1	126 live human subjects	Arthrogram	75%, 95%, and 100% accurate depending on approach
Jang 2013 [23]	Knee	Human USGI vs LMGI accuracy	Level 1	128 live human subjects	Arthrogram	USGI = 95% and 97% accurate depending on approach, LMGI = 78% accurate
Patel 2012 [38]	GH joint	Cadaveric USGI vs LMGI accuracy	Level 2	80 cadaveric specimens	Arthrogram	USGI = 92.5% accurate, LMGI = 72.5% accurate
Sibbitt 2012 [57]	Knee	Prospective, randomized comparison study of LMGI vs USGI injection efficacy and cost-effectiveness	Level 2	64 live human subjects	None	USGI had less procedural pain, aspirated more fluid, had better outcomes, and reduced health care costs
Gokalp 2010 [15]	GH joint	Human USGI accuracy	Level 1	29 live human subjects	MRI arthrogram	96.7% accurate
Diracoglu 2009 [12]	Hip	Human LMGI accuracy	Level 2	16 live human subjects	Arthrogram	66.7% accurate
Yoong 2012 [59]	Hip	Prospective human study of value of response to diagnostic USGI hip injection to predict good surgical outcomes for total hip arthroplasty	Level 4	138 live human subjects	None	93% of patients who had reduced pain from injection had a successful surgical outcome
Im 2009 [21]	Knee	Human USGI vs LMGI accuracy	Level 1	89 live human subjects	Arthrogram	USGI = 95.6% accurate, LMGI = 77.3% accurate
Rutten 2009 [42]	GH joint	Human USGI vs FSGI accuracy and procedural pain	Level 1	25 live human subjects	MRI arthrogram	USGI = 94% accurate first attempt, 100% accurate after second attempt, less painful than FSGI; FSGI = 72% accurate first attempt, 100% accurate after second attempt
Migliore 2011 [35]	Hip	Open, retrospective, study evaluating NSAID consumption following USGI with hyaluronic acid	Level 4	2343 live human subjects	None	48.2% decrease in NSAID consumption following USGI
Soh 2011 [58]	Shoulder (didn't specific GH joint vs subacromial, etc)	Meta-analysis of image-guided injections vs LMGI	Level 1	2 studies	N/A	Image-guided injections had better outcomes than LMGI, but only 2 studies met inclusion criteria

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First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Bloom 2012 [6]	Shoulder (didn't specific GH joint vs subacromial, etc)	Cochrane database review of efficacy of USGI vs LMGI or intramuscular steroid injection	Level 1	5 studies	N/A	Initial analysis revealed significant difference in pain reduction at 6 wk favoring USGI, but reanalysis after removing trials with inadequate blinding revealed no difference between LMGI and USGI
Jones 1993 [26]	Knee, GH joint	Prospective, blinded study of LMGI accuracy	Level 2	109 live human subjects	Arthrogram	LMGI GH joint = 10% accurate, LMGI knee = 64% accurate
Daley 2011 [10]	Knee, GH joint	Systematic literature of injection accuracy	Level 1	27 studies	N/A	LMGI GH joint = 27%, 40%, 42%, 85%, 100% accurate depending on approach; LMGI knee = 70%, 83%, 85% accurate depending on approach
Levi 2013 [30]	Hip	Retrospective Review of USGI accuracy	Level 4	11 live human subjects	Arthrogram	USGI = 100% accurate
Perdikakis 2012 [39]	GH joint	Prospective, randomized study comparing accuracy of USGI vs FSGI vs CT-guided injection	Level 1	125 live human subjects	MRI arthrogram	100% accurate for all techniques
Catalano 2007 [7]	GH joint	Human LMGI accuracy	Level 1	147 live human subjects	MRI arthrogram	LMGI 85% accurate
Smith 2006 [44]	Hip	Human USGI technique description	Level 5	1 live human subject	Arthrogram	100% accurate
DeMouy 1997 [11]	GH joint	Human LMGI accuracy	Level 2	8 live human subjects	MRI arthrogram	LMGI = 100% accurate
Luc 2006 [32]	Knee	Human LMGI accuracy	Level 1	33 live human subjects	Arthrogram	LMGI = 97% accurate
Lee 2009 [29]	GH joint	Prospective, randomized of LMGI vs USGI efficacy for adhesive capsulitis	Level 2	43 live human subjects	None	USGI resulted in significantly more pain reduction, increased range of motion, and improved function than the LMGI
Elkousy 2011 [53]	Shoulder (didn't specify location [eg, GH joint vs subacromial bursa, etc])	Retrospective comparison study of USGI vs LMGI efficacy	Level 3	272 live human subjects	None	No difference in efficacy between LMGI and USGI
Valls 1997 [49]	GH joint	Human USGI accuracy	Level 1	50 live human subjects	MRI arthrogram	USGI = 100% accurate
Micu 2010 [33]	Hip	Case control study comparing USGI efficacy vs no injection	Level 3	61 live human subjects	None	USGI = significant pain reduction at 1- and 3-mo follow-up, no pain relief in group that didn't receive injection
Sage 2013 [55]	Shoulder (didn't specify location [eg, GH joint vs subacromial bursa, etc])	Meta-analysis comparing LGMI vs USGI efficacy	Level 1	6 studies	None	USGI = significantly more reduction in pain and night pain at 6 wk and improved shoulder abduction range of motion compared to LMGI; no between-group difference was found in function
Hermans 2011 [19]	Knee	Systematic review of LMGI accuracy	Level 1	9 studies	N/A	LMGI = 67%, 72%, 85%, and 91% accurate depending on approach
Choudur 2011 [8]	GH joint, hip, knee	Human USGI accuracy	Level 1	100 live human subjects	Arthrogram	USGI = 100% accurate
Kantarci 2013 [27]	Hip	Human USGI accuracy comparing 2 techniques	Level 1	59 live human subjects	MRI arthrogram	USGI = 100% accurate

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First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Hurdle 2012 [20]	Knee	Case report of USGI accuracy in an obese patient	Level 5	1 patient	Joint fluid aspiration	USGI allowed accurate knee injection in an obese patient
Hartung 2010 [18]	SI joint	USGI accuracy and efficacy	Level 1 = accuracy, level 4 = efficacy	14 live human subjects (20 SI joints)	MRI arthrogram	USGI = 40% accurate, no difference in clinical outcomes between intra-articular and periarticular injections
Balint 2002 [52]	GH joint, hip, knee	Comparison study between ability to aspirate joints with LMG vs USG	Level 2	30 live human subjects (32 joints)	None	Ability to aspirate joints with USG = 97%, ability to aspirate joints with LMG = 32%
Goncalves 2011 [16]	GH joint, knee	Human USGI accuracy and efficacy	Level 4	31 live human subjects	None	USGI = 100% accurate by clinical evaluation, but not confirmed radiologically; all patients had improved clinically following the injection
Porat 2008 [40]	GH joint	Human LMGI accuracy	Level 1	100 live human subjects	MRI arthrogram	LMGI = 99% accurate

GH = glenohumeral; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; SI = sacroiliac; MRI = magnetic resonance imaging; FSGI = fluoroscopically guided injection; NSAID = nonsteroidal anti-inflammatory drug; CT = computed tomography; LMG = landmark guidance; USG = ultrasound guidance.

Appendix 2
Summary of the literature evaluating intermediate joint injections

First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Wasserman 2013 [78]	AC joint	Human LMGI accuracy	Level 2	30 live human subjects	Arthrogram	LMGI = 43.3% accurate
Kraus 2011 [68]	ST joint	Cadaveric LMGI accuracy	Level 2	68 cadaveric specimens	Dissection	LMGI = 67.6% and 91.2% accurate depending on approach
Lopes 2008 [31]	Elbow, wrist, TT joint	Prospective LMGI accuracy	Level 1	Live human subjects (31 elbows, 37 wrists, 54 TT joints)	Arthrogram	LMGI elbow = 100% accurate, LGMI wrist = 97% accurate, LMGI TT joint = 77% accurate
Kirk 2008 [67]	ST joint	Cadaveric LMGI accuracy	Level 2	20 cadaveric specimens	Arthrogram	LMGI = 96% accurate
Smith 2011 [74]	STT joint	Cadaveric USGI vs LMGI accuracy	Level 2	20 cadaveric specimens	Dissection	USGI = 100% accurate, LMGI = 80% accurate
Smith 2009 [75]	ST joint	Cadaveric USGI accuracy	Level 2	12 cadaveric specimens	Dissection	USGI = 100% accurate
Reach 2009 [71]	TT and ST joints	Cadaveric USGI accuracy	Level 2	10 cadaveric specimens	Dissection	USGI TT joint = 100% accurate, USGI ST joint = 90% accurate
Peck 2010 [70]	AC joint	Cadaveric USGI vs LMGI accuracy	Level 2	20 cadaveric specimens	Dissection	USGI = 100% accurate, LMGI = 40% accurate
Partington 1998 [69]	AC joint	Cadaveric LMGI accuracy	Level 2	12 cadaveric specimens	Dissection	LMGI = 33% accurate
Heidari 2010 [65]	TT joint	Cadaveric LMGI accuracy	Level 2	76 cadaveric specimens	Dissection	LMGI = 77.5% and 86.1% accurate depending on approach
Drakonaki 2011 [64]	Midfoot	Retrospective USGI efficacy	Level 4	59 live human subjects	None	78.4% had pain relief at 3-mo follow-up
Weinberg 2009 [79]	SC joint	Cadaveric LMGI accuracy	Level 2	38 cadaveric specimens	Dissection	LMGI = 74% to 82% accurate depending on injector experience
Jones 1993 [26]	AC joint, elbow, wrist, TT joint	Prospective LMGI accuracy and efficacy	Level 1 = accuracy, level 3 = efficacy	102 live human subjects	Arthrogram	Accuracy of LMGI of AC joint = 0%, elbow = 83%, wrist = 50%, TT = 50%; no difference in efficacy between accurate and inaccurate injections
Smith 2011 [77]	Distal RU joint	Cadaveric USGI accuracy	Level 2	10 cadaveric specimens	Dissection	USGI = 100% accurate
Smith 2010 [76]	Proximal TF joint	Cadaveric USGI vs LMGI accuracy	Level 2	12 cadaveric specimens	Dissection	USGI = 100% accurate, LMGI = 58% accurate
Sabeti-Aschraf 2010 [73]	AC joint	Prospective, randomized study comparing USGI vs LMGI efficacy	Level 2	20 live human subjects	None	No difference between groups immediately postinjection or 1 or 3 wk postinjection

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First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Borbas 2012 [63]	AC joint	Cadaveric USGI vs LMGI accuracy	Level 2	80 cadaveric specimens	Dissection	USGI = 90% accurate, LMGI = 70% accurate
Khosla 2009 [66]	ST joint, TT joint	Cadaveric USGI vs LMGI accuracy	Level 2	14 cadaveric specimens	Arthrogram and dissection	USGI and LMGI of ST and TT joints = 100% accurate
Sabeti-Aschraf 2011 [72]	AC joint	Cadaveric USGI vs LMGI accuracy	Level 2	60 cadaveric specimens	Not reported	USGI = 95% accurate, LMGI = 72% accurate
Choudur 2011 [8]	Wrist	Human USGI accuracy	Level 1	100 live human subjects	MRI arthrogram	USGI = 100% accurate
Balint 2002 [52]	Elbow, Wrist, TT joint	Comparison study between ability to aspirate joints with LMG vs USG	Level 2	30 live human subjects (32 joints)	None	Ability to aspirate joints with USG = 100%, ability to aspirate joints with LMG = 29%
Wisniewski 2010 [80]	TT Joint	Cadaveric USGI vs LMGI accuracy	Level 2	12 embalmed and 8 unembalmed cadaveric specimens	Dissection	USGI = 100% accurate, LMGI = 85% accurate
Goncalves 2011 [16]	Elbow, Wrist, TT joint	Human USGI accuracy and efficacy	Level 4	31 live human subjects	None	USGI = 100% accurate by clinical evaluation, but not confirmed radiologically; all patients had improved clinically following the injection

AC = acromioclavicular; LMGI = landmark-guided injection; ST = subtalar; TT = tibiotalar; STT = scaphotrapeziotrapezoidal; USGI = ultrasound-guided injection; SC = sternoclavicular; RU = radioulnar; TF = tibiofibular; USG = ultrasound guidance; LMG = landmark guidance.

Appendix 3
Summary of the literature evaluating small joint injections

First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Lopes 2008 [31]	MCP joint	Prospective LMGI accuracy	Level 1	39 live human subjects	Arthrogram	LMGI = 97% accurate
Reach 2009 [71]	MTP joint	Cadaveric USGI accuracy	Level 2	10 cadaveric specimens	Dissection	USGI = 100% accurate
Wempe 2012 [83]	MTP joint	Cadaveric USGI accuracy	Level 2	5 cadaveric specimens	Dissection	USGI = 100% accurate
Jones 1993 [26]	CMC, MCP, DIP joints	Human LMGI accuracy	Level 3 for CMC, level 5 for MCP and DIP	Live human subjects (CMC = 3, MCP = 1, DIP = 1)	Arthrogram	LMGI CMC, MCP, and DIP = 0% accurate
Khosla 2009 [66]	TMT joint	Cadaveric USGI vs LMGI accuracy	Level 2	14 cadaveric specimens	Arthrogram and dissection	USGI = 64% accurate, LMGI = 25% accurate
Umphrey 2008 [82]	CMC joint	Cadaveric USGI accuracy	Level 2	17 cadaveric specimens	Arthrogram	USGI = 94% accurate
Balint 2002 [52]	CMC, MTP, PIP joints	Prospective, nonrandomized comparison study between ability to aspirate fluid from joint using USG vs LMG	Level 3	30 live human subjects	None	Successful aspiration with USG = 100%, successful aspiration with LMG = 0%
Raza 2003 [81]	MCP, PIP joints	Prospective, nonrandomized comparison study of USGI vs LMGI accuracy	Level 3	70 live human subjects	Ultrasound imaging	USGI = 96% accurate, LMGI = 59% accurate
Gonclaves 2011 [16]	MCP, MTP joints	Human USGI efficacy	Level 4	27 live human subjects	None	Accuracy was not assessed; all subjects improved

MCP = metacarpophalangeal joint; LMGI = landmark-guided injections; MTP = metatarsophalangeal; USGI = ultrasound-guided injections; CMC = carpometacarpal; DIP = distal interphalangeal; TMT = tarsometatarsal; PIP = proximal interphalangeal; USG = ultrasound guidance; LMG = landmark guidance.

Appendix 4
Summary of the literature evaluating soft tissue injections

First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Ucuncu 2009 [121]	SA-SD bursa	Prospective, randomized comparison study of USGI vs LMGI efficacy	Level 2	60 live human subjects	None	USGI = more improvement and pain relief than LMGI
Zufferey 2012 [51]	SA-SD bursa	Prospective, randomized comparison study of USGI vs LMGI efficacy	Level 2	67 live human subjects	None	USGI = had less pain at rest and more responders than LMGI at 2- and 6-wk follow-up; no difference between groups in daytime and night pain or functional improvement
Naredo 2004 [54]	SA-SD bursa	Prospective, randomized comparison study of USGI vs LMGI efficacy	Level 2	41 live human subjects	None	USGI = significantly greater improvement in pain and function than LMGI group
Hanchard 2006 [17]	SA-SD bursa	Cadaveric LMGI accuracy	Level 2	5 cadaveric specimens	Dissection	LMGI = 72% accurate
Hashiuchi 2011 [99]	BT sheath	Prospective, randomized comparison study of USGI vs LMGI accuracy	Level 1	30 live human subjects	CT arthrogram	USGI = 87% accurate, LMGI = 26.7% accurate
Peck 2011 [114]	DPC, SPC	Cadaveric USGI vs LMGI accuracy	Level 2	20 cadaveric specimens	Dissection	USGI DPC = 88% accurate, LMGI DPC = 90% accurate, USGI and LMGI SPC = 100% accurate
Kang 2008 [105]	SA-SD bursa	Prospective study evaluating LMGI accuracy and efficacy of accurate vs inaccurate injections	Level 2	60 live human subjects	Bursogram	LMGI = 70% accurate; accurate injections had significantly more pain reduction on Neer's impingement test immediately postinjection, no difference in efficacy between accurate and inaccurate injections at 3-mo follow-up
Mathews 2005 [110]	SA-SD bursa	Cadaveric LMGI accuracy	Level 2	20 cadaveric specimens	Bursogram, dissection	LMGI anterolateral approach = 90% accurate when graded by bursogram, but after anatomic dissection, only 60% of injections were accurate; LMGI posterior approach = 80% accurate
Henkus 2006 [101]	SA-SD bursa	Prospective, randomized LMGI accuracy	Level 1	33 live human subjects	MRI arthrogram	LMGI = 69% and 76% accurate depending on approach
Reach 2009 [71]	Achilles peritendinous space, FHL tendon sheath, TP tendon sheath	Cadaveric USGI accuracy	Level 2	10 cadaveric specimens	Dissection	USGI = 100% accurate
Finnoff 2008 [97]	Piriformis	Cadaveric USGI vs FGI accuracy	Level 2	10 cadaveric specimens	Dissection	USGI = 95% accurate, FGI = 30% accurate
Finnoff 2010 [98]	Pes anserinus bursa	Cadaveric USGI vs LMGI accuracy	Level 2	24 cadaveric specimens	Dissection	USGI = 92% accurate, LMGI = 17% accurate

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Appendix 4 (*continued*)

First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Dogu 2012 [91]	SA-SD bursa	Prospective, randomized comparison study of USGI vs LMGI accuracy and efficacy	Level 2	46 live human subjects	MRI arthrogram	USGI = 65% accurate, LMGI = 70% accurate, no difference in efficacy between accurate and inaccurate injections
Hashiuchi 2010 [100]	SA-SD bursa	Prospective study comparing pain relief following local anesthetic injection with USG vs LMG	Level 2	16 live human subjects	None	USGI = more pain relief than LMGI
Eustace 1997 [93]	SA-SD bursa	Prospective study comparing efficacy of accurate vs inaccurate LMGI	Level 2	37 live human subjects	Arthrogram	LMGI = 29% accurate; accurate injections = more pain relief and functional improvement at 2-wk follow-up
Yucel 2009 [125]	Plantar fascia	Prospective, randomized comparison of USGI vs LMGI vs SGI efficacy	Level 2	27 live human subjects	None	No significant difference in efficacy between the 3 techniques
Di Geso 2012 [89]	Finger flexor, finger extensor, extensor carpi ulnaris, peroneal, and TP tendons	Prospective USGI accuracy and efficacy	Level 4	30 live human subjects	Ultrasound	USGI = 100% accurate, 100% had significant improvement in clinical measures and sonographic findings
Partington 1998 [69]	SA-SD bursa	Cadaveric LMGI accuracy	Level 2	12 cadaveric specimens	Dissection	LMGI = 83% accurate
Farshad 2012 [95]	SA-SD bursa	Human LMGI accuracy	Level 2	10 live human subjects	Ultrasound	LMGI = 90% accurate
Labrosse 2010 [107]	Gluteus medius tendon	Prospective USGI efficacy	Level 4	54 live human subjects	None	At 1-mo follow-up, 72% of patients = clinically significant pain reduction, 70% satisfied with treatment
Kume 2012 [106]	de Quervain tenosynovitis	Prospective, randomized comparison between USGI vs LMGI efficacy	Level 2	44 live human subjects	None	USGI = more significant pain relief at 4-wk follow-up than LMGI
Rutten 2007 [115]	SA-SD bursa	Prospective, randomized comparison between USGI vs LMGI accuracy	Level 1	20 live human subjects	MRI arthrogram	USGI and LMGI = 100% accurate
Hsieh 2013 [103]	SA-SD bursa	Prospective, randomized comparison between USGI vs LMGI efficacy	Level 2	92 live human subjects	None	USGI = significantly more improvement in shoulder range of motion and physical functioning and vitality scores on the SF-36 than LMGI
Bandinelli 2012 [84]	Baker's cyst	Prospective comparison of USG Baker's cyst aspiration followed by Baker's cyst injection or knee injection	Level 2	40 live human subjects	None	USGI Baker's cyst aspiration followed by Baker's cyst injection = greater reduction in Baker's cyst size and improvement in function than Baker's cyst aspiration followed by knee injection

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Appendix 4 (*continued*)

First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Makhlouf 2014 [109]	Carpal tunnel	Prospective, randomized comparison of USGI vs LMGI efficacy	Level 2	77 live human subjects	None	USGI = significantly less procedural pain and more pain reduction than LMGI
Chavez-Chiang 2012 [85]	Carpal tunnel	Prospective, randomized comparison of USGI vs LMGI efficacy	Level 2	76 live human subjects	None	USGI = significantly less procedural pain, more clinical improvement and less expense than LMGI
Tsai 2006 [119]	Plantar fascia	Prospective, randomized comparison of USGI vs LMGI efficacy	Level 2	25 live human subjects	None	USGI = significantly less recurrence than LMGI, but no differences in pain or structural improvement
Smith 2012 [118]	OI muscle and bursa	Cadaveric USGI accuracy	Level 2	5 cadaveric specimens	Dissection	USGI = 100% accurate
Housner 2009 [102]	Patellar, Achilles, gluteus medius, iliotibial tract, hamstring, common extensor (elbow), and rectus femoris tendons	Prospective USGI efficacy of needle tenotomy	Level 4	13 live human subjects (14 tendons)	None	USGI = significant reductions in pain at 4- and 12-wk follow-up
McShane 2008 [112]	Common extensor (elbow) tendon	Prospective USGI efficacy of needle tenotomy	Level 4	57 live human subjects	None	USGI = good to excellent outcomes in 92% of subjects, and 90% subjects were satisfied at average 22-mo follow-up
Smith 2010 [116]	Popliteus tendon sheath	Cadaveric USGI accuracy	Level 2	24 cadaveric specimens	Dissection	USGI = 83% or 100% accurate, depending on approach
Lee 2011 [108]	Finger flexor tendon sheath	Cadaveric USGI vs LMGI accuracy	Level 2	5 cadaveric specimens (40 fingers)	Dissection	USGI = 70% accurate, LMGI = 15% accurate
Ekeberg 2009 [92]	SA-SD bursa	Prospective, randomized comparison of USGI vs systemic steroid administration efficacy	Level 2	106 live human subjects	None	USGI = significantly more improvement in primary outcome measures at 6-wk follow-up than LMGI; no between group differences in secondary outcomes of range of motion or 2 pain assessments
Muir 2011 [113]	Peroneal tendon sheath	Cadaveric USGI vs LMGI accuracy	Level 2	20 cadaveric specimens	Dissection	USGI = 100% accurate, LMGI = 60% accurate
Yoo 2010 [124]	Rotator cuff calcific tendinopathy	Prospective USG calcific aspiration and SA-SD bursa injection efficacy	Level 4	30 live human subjects (35 shoulders)	None	USG calcific aspiration and SA-SD bursa injection = significant improvement in pain and function in 71.4% of subjects at 6-mo follow-up
Yamakado 2002 [123]	SA-SD bursa	Human LMGI accuracy	Level 2	53 live human subjects (56 shoulders)	Arthrogram	LMGI = 70% accurate

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First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Finnoff 2011 [96]	Multiple upper and lower extremity tendons	Retrospective case series of efficacy of USG tenotomy (part A) and prospective case series of structural changes following USG tenotomy (part B)	Level 4	41 live human subjects (part A) and 34 live human subjects (part B)	None	USG tenotomy = 68% pain improvement and 83% patient satisfaction; 84% had improvement in echotexture
Fanucci 2004 [94]	Morton's neuroma	Human USGI accuracy and efficacy	Level 2 = accuracy, level 4 = efficacy	40 live human subjects	Ultrasound	USGI = 100% accurate; 90% of patients had significant pain relief
Hughes 2007 [104]	Morton's neuroma	Human USGI accuracy and efficacy	Level 2 = accuracy, level 4 = efficacy	101 live human subjects	Ultrasound	USGI = 100% accurate; 94% of patients had significant pain relief
Tsai 2000 [120]	Plantar fascia	Human USGI efficacy	Level 4	14 live human subjects	None	USGI = significant improvement in pain and decreased plantar fascia thickness on ultrasound
Di Sante 2010 [90]	Baker's cyst	Human USG aspiration and injection efficacy	Level 4	26 live human subjects	Ultrasound	USG aspiration and injection = significant reduction in cyst volume and pain reduction
McDermott 2012 [111]	de Quervain tenosynovitis	Human USGI efficacy	Level 4	40 live human subjects	None	USGI = significant improvement in 97% of subjects
Smith 2006 [117]	Piriformis	Cadaveric USGI accuracy	Level 4	Cadaveric specimens (unknown number)	Dissection	USGI = accurate (accuracy rate not reported)
Chen 2012 [86]	Piriformis	Human study evaluating accuracy of USGI combined with EMG confirmation	Level 5	1 live human subject	EMG	USGI = 100% accurate
Chen 2006 [87]	SA-SD bursa	Human USGI vs LMGI efficacy	Level 2	40 live human subjects	None	USGI = significantly more shoulder range of motion 1 wk postinjection than LMGI
Balint 2002 [52]	Bursa, tendon sheath, cyst, wound	Comparison study between ability to aspirate joints with LMG vs USG	Level 2	4 live human subjects	None	Ability to aspirate joints with USG = 100%
Wisniewski 2010 [80]	Sinus tarsi	Cadaveric USGI vs LMGI accuracy	Level 2	20 cadaveric specimens (40 ankles)	Dissection	USGI = 90% accurate, LMGI = 35% accurate
Ustun 2013 [122]	Carpal tunnel	Prospective, randomized, single-blind comparison of USGI vs LMGI efficacy	Level 2	46 live human subjects	None	USGI = significantly more clinical improvement than the LMGI group at 12-wk follow-up
Chen 2013 [88]	Post—upper extremity amputation neuromas	Human USGI efficacy	Level 5	1 live human subject	None	USGI = significant pain reduction postinjection

SA-SD = subacromial-subdeltoid; USGI = ultrasound-guided injection; LMGI = landmark-guided injection; BT = biceps tendon; CT = computed tomography; DPC = deep posterior compartment; SPC = superficial posterior compartment; FHL = flexor hallucis longus; TP = tibialis posterior; FGI = fluoroscopically guided contrast controlled injection; MRI = magnetic resonance image; USG = ultrasound guided; LMG = landmark guided; SGI = scintigraphy-guided injection; SF-36 = Short Form—36; OI = obturator internus; EMG = electromyography.

Appendix 5
Summary of the literature evaluating multijoint injections

First Author/Year	Target	Study Design	Level of Evidence	Subject Type/ Number	Accuracy Confirmation	Outcome
Sibbitt 2011 [127]	Joints with inflammatory arthritis	Prospective, randomized comparison of USGI vs LMGI efficacy and cost-effectiveness	Level 2	244 live human subjects	None	USGI = less procedural pain, more pain relief, more responders, less nonresponders, and less expense than LMGI
Cunnington 2010 [126]	Joints with inflammatory arthritis	Prospective, randomized comparison of USGI vs LMGI accuracy and efficacy	Level 1 = accuracy, level 2 = efficacy	184 live human subjects	Arthrogram	USGI = 83% accurate, LMGI = 66% accurate, USGI = more clinical improvement and pain reduction at 6 wk compared to LMGI
Sibbitt 2009 [128]	Painful joints	Prospective, randomized comparison of USGI vs LMGI efficacy	Level 2	148 live human subjects	None	USGI = less procedural pain and more pain relief, ability to detect and aspirate effusions, more responders, and fewer nonresponders than LMGI

USGI = ultrasound-guided injection; LMGI = landmark-guided injection.

Section 8.0

Biennial Review

2026 Biennial Review: Neonatal Circumcision

Plain Language Summary:

Coverage question: Should OHP cover removing the loose skin covering the end of a boy's penis (foreskin)? If so, for what ages?

Should OHP cover this treatment? Unknown. The Commission is seeking written and verbal public comments. VbBS and HERC will discuss this topic at the May 16, 2024 meetings.

Coverage Questions:

1) Should routine neonatal circumcision be added as a covered benefit?
2) Should routine circumcision be added as a covered benefit for older boys?

Question sources:

1) Circumcision in infancy: Yahya Haqiqi, President and CEO of the Afghan Support Network; Dr. Abdul Rahim, family physician in the Portland area; Mark Buchholz, CCO medical director; Jeanne Savage, CCO medical director; Brenden Magee (Provider Clinical Support Unit Manager, OHA)
2) Circumcision in older boys: Yahya Haqiqi; Dr. Abdul Rahim

Background:

Historically, the OHP has never covered elective newborn circumcision. Newborn elective circumcision is currently prioritized to line 566 REDUNDANT PREPUCE Treatment ELECTIVE CIRCUMCISION. Medically indicated circumcision is found on several higher priority lines, 324 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION, 410 BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS, and 496 PHIMOSIS. Medical conditions of the foreskin are also on higher priority lines without pairing with circumcision, such as balanitis on line 412 BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS.

At the March 2024 HERC staff listening session, two speakers requested consideration of coverage of male circumcision as a culturally appropriate practice and as an effective procedure to reduce the risk of UTIs, STIs, penile cancer, and other conditions. These speakers requested consideration of both neonatal circumcision as well as circumcision of older boys as is practiced in the Afghan community.

Multiple stakeholders, including CCO medical directors and OHA Medicaid leadership have also requested a review of coverage of neonatal circumcision. Of note, CareOregon is covering neonatal circumcision, which is creating inconsistent coverage among patients in various CCOs in the state.

2026 Biennial Review: Neonatal Circumcision

Previous HSC/HERC reviews:

Neonatal circumcision was reviewed as a biennial review item in 2018. The HERC staff conclusion of that review was:

> "Neonatal circumcision remains a controversial topic. Studies have found that neonatal circumcision reduces the rate of HIV and other STI acquisition; however, this conclusion is based on data from high prevalence countries, is limited to heterosexual patients, and it is not clear how it translates to areas of lower HIV/STI prevalence. Neonatal circumcision reduces the risk of UTI in infants and young boys, with a NNT of between 4 and 111 (the literature is highly variable on this estimate). The reason for the variation in NNT for prevention of UTI may be in the study methods (higher NNT came from a review that specifically excluded high risk boys). Boys with vesicoureteral reflux appear to have greater benefit in UTI prevention with circumcision given their higher prevalence of UTI. The complications of circumcision are generally minor, but can include rare serious adverse events. The rate of complications is estimated to be 1.5% overall, with 0.23% rate of serious complications. The risks of circumcision are much higher when done outside of the neonatal period, due to need for general anesthesia, etc. There appears to be no impact on sexual satisfaction with circumcision. Coverage for routine neonatal circumcision is highly variable among Medicaid programs. Desire for circumcision varies widely among families, depending on religious and cultural norms and other factors."

Based on this review, the redundant prepuce line was reprioritized from then line 623 to then line 569 (now line 566).

Current Prioritized List/Coverage status:

CPT code	Code description	Current Placement
54000	Incision of newborn foreskin	410 BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS 566 REDUNDANT PREPUCE
54001	Incision of foreskin	410,566
54150	Removal of foreskin using clamp or device	21 VESICOURETERAL REFLUX 324 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION 410 BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS 491 PHIMOSIS 566 REDUNDANT PREPUCE
54160	Removal of foreskin (28 days or younger)	21,324,410,491,566
54161	Removal of foreskin (older than 28 days)	21,324,410,491,566
54162	Removal of scar tissue after foreskin removal	421 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT,566
54163	Repair of incomplete removal of foreskin	566

54164	Incision of membrane attaching foreskin and penis	566
54450	Repositioning of foreskin including scar tissue removal	410,566

GUIDELINE NOTE 73, PENILE ANOMALIES

Lines 421,431,566,650

Congenital anomalies of the penis (ICD-10-CM Q54.4, Q55.5 and Q55.6) are included on Line 431 only when they

A. Are associated with hypospadias, OR
B. Result in documented urinary retention, OR
C. Result in repeated urinary tract infections, OR
D. Result in recurrent infections such as meatitis or balanitis, OR
E. Involve 35 degrees of curvature or greater for conditions resulting in lateral or ventral curvature, OR
F. Involve 60 degrees of rotation or greater for conditions resulting in penile torsion, OR
G. Involve aplasia/congenital absence of the penis.

Otherwise, these diagnoses are included on Line 650.

Acquired anomalies of the penis (ICD-10-CM N48.82, N48.83, N48.89 or T81.9XXA) are included on Line 421 only when they are the result of a prior penile procedure AND either

A. Result in a skin bridge, OR
B. Result in a buried penis, OR
C. Are associated with hypospadias, OR
D. Result in documented urinary retention, OR
E. Result in repeated urinary tract infections, OR
F. Result in recurrent infections such as meatitis or balanitis, OR
G. Involve 35 degrees of curvature or greater for conditions resulting in lateral or ventral curvature, OR
H. Involve 60 degrees of rotation or greater for conditions resulting in penile torsion.

Otherwise, these diagnoses are included on Line 566 or Line 650.

Line 623 REDUNDANT PREPUCE
Category: 7
HL: 0
Suffering: 0
Population effects: 1
Vulnerable population: 0
Tertiary prevention: 2
Effectiveness: 5
Need for service: 0.1
Net cost: 4
Score: 30
Line placement: 566

2026 Biennial Review: Neonatal Circumcision

Evidence:

No new evidence was found on benefits of circumcision on reduction of HIV, STIs, or UTIs that was not included in the 2017 evidence review

Evidence on lack of Medicaid coverage for routine circumcision on downstream impacts

1) **Lin 2023,** Lack of Medicaid Coverage of Routine Newborn Circumcision Leads to Increased Operative Circumcisions, Chordee Procedures, and Balanitis
    a. Retrospective claims dataset study
        i. 20 states with Medicaid circumcision coverage, 8 states without coverage
    b. A total of 118,530 circumcisions were reviewed. Covered states had significantly higher proportions of circumcision overall (9.7% vs 7.1%, P < 0.0001). Noncovered states had significantly higher proportions of Medicaid-covered operative circumcisions (54.9% vs 47.7%, P < 0.0001). Compared to covered states, noncovered states had significantly higher median ages of all types of circumcisions. Noncovered states also had higher numbers of balanitis cases and double the incidence of balanitis compared with covered states. The median age of chordee (1.07 vs 0.79 years, P < 0.0001) and proportion of chordee repairs (15.2% vs 12.9%, P < 0.0001) were also significantly higher in noncovered states
        i. Incidence of balanitis overall was very low (0.0056% in non-covered states vs 0.0025% in covered states)
        ii. The was no significant difference in the proportion of phimosis cases seen in covered versus noncovered states (51.6% vs 55.6%, P = 0.21)
    c. Conclusions: The lack of Medicaid coverage of circumcision increases the number of foreskin procedures done in the operating room. In addition, in states without Medicaid coverage of circumcision, there is an increased burden of disease related to the foreskin. These findings represent a need to further investigate the costs of healthcare associated with Medicaid coverage of circumcision or the lack thereof.
2) **Navia 2020**, State-Level Public Insurance Coverage and Neonatal Circumcision Rates
    a. Retrospective cohort study
        i. N=1,149,576
        ii. The cohort was 52.8% white, 45.3% covered by Medicaid, and 47.6% covered by private insurance over all study years combined.
        iii. The State Inpatient Databases were used to determine rates of neonatal male circumcision in 4 states (CO, FL, MI, and NY) at 4 time points (2001, 2006, 2011, 2016). Neonatal circumcision was defunded by Medicaid in Florida (2003) and Colorado (2011)
    b. Overall, 54.5% of neonates underwent circumcision. States where Medicaid defunded neonatal circumcision revealed a decrease in circumcision rates in subsequent years (47.4% to 37.5% in FL; 61.9% to 52.0% in CO). Neonates with private insurance had higher odds of circumcision compared with those with public insurance (adjusted odds ratio [aOR] 2.23; 95% confidence interval [CI] 2.21–2.25). When Medicaid coverage was available, Black neonates had higher odds of circumcision compared with white neonates (aOR 1.44; 95% CI 1.42–1.46). When Medicaid coverage was not available, Black neonates had lower odds compared with white neonates (aOR 0.40; 95% CI 0.39–0.41).

c. Conclusions: State-specific data reveal trends in neonatal circumcision similar to previous national estimates. Colorado and Florida revealed 20.9% and 16.0% reductions in neonatal circumcision rates, respectively, after defunding. Black neonates appeared to be disproportionately affected by changes in Medicaid coverage.

Submitted literature:

No literature received to date

Expert guidelines:

1) **CDC 2022** Male Circumcision for HIV Prevention fact sheet
    a. Available at https://www.cdc.gov/nchhstp/newsroom/fact-sheets/hiv/male-circumcision-HIV-prevention-factsheet.html
    b. Health care providers should inform all uncircumcised adolescent and adult males that male circumcision reduces, but does not eliminate, the chance of acquiring HIV and other STIs during heterosexual contact. Additionally, the patients should be informed of the potential risks associated with the procedure.
    c. Parents and guardians of male newborns, children, and adolescents: Parents should be informed of the medical benefits – including a lower chance of getting HIV – and the risks of male circumcision and should make decisions in consultation with a health care provider. When providing information to parents about male circumcision for an adolescent minor, the adolescent should be included in the decision-making process.
    d. Health benefits: Male circumcision can reduce a male's chances of acquiring HIV by 50% to 60% during heterosexual contact with female partners with HIV, according to data from three clinical trials. Circumcised men compared with uncircumcised men have also been shown in clinical trials to be less likely to acquire new infections with syphilis (by 42%), genital ulcer disease (by 48%), genital herpes (by 28% to 45%), and high-risk strains of human papillomavirus associated with cancer (by 24% to 47% percent). While male circumcision has not been shown to reduce the chances of HIV transmission to female partners, it does reduce the chance that a female partner will acquire a new syphilis infection by 59%. In observational studies, circumcision has been shown to lower the risk of penile cancer, cervical cancer in female sexual partners, and infant urinary tract infections in male infants.
    e. Health risks: The overall risk of adverse events associated with male circumcision is low, with minor bleeding and inflammation cited as the most common complications. A CDC analysis found that the rate of adverse events for medically attended male circumcision is 0.4% for infants under 1 year, about 9% for children ages 1 to 9 years, and about 5% for males 10 years and older. More severe complications can occur but are exceedingly rare. Adult men who undergo circumcision generally report minimal or no change in sexual satisfaction or function.
    f. Stage of life: Circumcision is simpler, safer, and less expensive for newborns and infants than for adult males. Delaying circumcision until adolescence or adulthood enables the male to participate in – or make – the decision, but could diminish the potential benefits related to sexual health and increases the risks.

g. Informed Choice: Male circumcision is a voluntary procedure. The decision regarding circumcision should be made in consultation with a health care provider, and consider personal, cultural, religious, and ethical beliefs

2) **American Academy of Pediatrics 2012** www.pediatrics.org/cgi/doi/10.1542/peds.2012-1990
   a. Systematic evaluation of English-language peer-reviewed literature from 1995 through 2010 indicates that preventive health benefits of elective circumcision of male newborns outweigh the risks of the procedure. Benefits include significant reductions in the risk of urinary tract infection in the first year of life and, subsequently, in the risk of heterosexual acquisition of HIV and the transmission of other sexually transmitted infections.
   b. The procedure is well tolerated when performed by trained professionals under sterile conditions with appropriate pain management. Complications are infrequent; most are minor, and severe complications are rare. Male circumcision performed during the newborn period has considerably lower complication rates than when performed later in life.
   c. Although health benefits are not great enough to recommend routine circumcision for all male newborns, the benefits of circumcision are sufficient to justify access to this procedure for families choosing it and to warrant third-party payment for circumcision of male newborns. It is important that clinicians routinely inform parents of the health benefits and risks of male newborn circumcision in an unbiased and accurate manner. Parents ultimately should decide whether circumcision is in the best interests of their male child. They will need to weigh medical information in the context of their own religious, ethical, and cultural beliefs and practices. The medical benefits alone may not outweigh these other considerations for individual families.

Other payer policies:

There are several CCOs in Oregon that are currently covering newborn circumcision due to patient and provider demand.

The following states do NOT pay for routine Medicaid circumcision: Arizona, California, Colorado, Florida, Idaho, Louisiana, Maine, Minnesota, Mississippi, Montana, Nevada, North Dakota, Oregon, South Carolina, Utah, and Washington [Lin 2023].

Federal law does not permit federal match for services rendered for cultural reasons. However, states may determine that circumcision may be considered medically necessary.

Expert input:

No expert input received to date

2026 Biennial Review: Neonatal Circumcision

HERC staff summary:

Since the 2017 HERC review, there have been no additional studies identified regarding the impact of routine neonatal circumcision on HIV or other STI rates or on UTI rates. As identified in the 2017 review, studies have found a significant reduction in HIV acquisition in areas of high HIV endemicity, but it is unclear how these study findings translate to areas with low HIV endemicity like Oregon. Circumcision reduces the risk of UTI with a NNT of between 4 and 111. Complications rates are low and generally minor. Circumcision does not appear to affect sexual satisfaction. Both the CDC and AAP continue to recommend circumcision as a method to reduce STI and UTI rates. The majority of state Medicaid programs cover routine circumcision, with 16 states not currently covering the procedure.

A recent study comparing Medicaid populations found that states that did not cover routine circumcision compared to states that did cover this procedure routinely had an increase rate of balanitis (pain and swelling in the glans of the penis) although the overall rate of balanitis was very low; no difference in phimosis (inability to retract the foreskin) rates; and increase in the rates of circumcisions done in the operating room. Another recent study on Medicaid coverage policies found a greater reduction in neonatal circumcision in Black neonates compared to non-Black neonates in states who stopped covering routine circumcision.

HERC staff recommend discussion of reprioritization of the routine circumcision line for neonatal circumcision. Due to the higher risks of circumcision in boys over the age of 6 months (related mostly to general anesthesia) and lack of AAP recommendation for non-infant circumcision, HERC staff recommend continued non-coverage of non-medically necessary circumcision in older boys.

HERC staff recommendation:

1) Discuss possible reprioritization of routine neonatal circumcision

Lack of Medicaid Coverage of Routine Newborn Circumcision Leads to Increased Operative Circumcisions, Chordee Procedures, and Balanitis

Chung Y. Lin, Emilie K. Johnson, Carlos V. Del Rio, and Gwen M. Grimsby

OBJECTIVE To compare proportions of newborn circumcisions, operative circumcisions, chordee procedures, and cases of balanitis in states where Medicaid covers newborn circumcision (covered states) versus states that do not (noncovered states) using the pediatric health information system database.

METHODS A retrospective review of pediatric health information system data was conducted from 2011 to 2020. The proportions and median ages of newborn circumcision current procedural terminology (CPT 54,150, 54,160), operative circumcision (CPT 54,161), chordee (CPT 54,360), and balanitis (ICD-9 607.1, ICD-10 N48.1, N47.6) were compared in covered versus noncovered states.

RESULTS A total of 118,530 circumcisions were reviewed. Covered states had significantly higher proportions of circumcision overall (9.7% vs 7.1%, $P < 0.0001$). Noncovered states had significantly higher proportions of Medicaid-covered operative circumcisions (54.9% vs 47.7%, $P < 0.0001$). Compared to covered states, noncovered states had significantly higher median ages of all types of circumcisions. Noncovered states also had higher numbers of balanitis cases and double the incidence of balanitis compared with covered states. The median age of chordee (1.07 vs 0.79 years, $P < 0.0001$) and proportion of chordee repairs (15.2% vs 12.9%, $P < 0.0001$) were also significantly higher in noncovered states.

CONCLUSION The lack of Medicaid coverage of circumcision increases the number of foreskin procedures done in the operating room. In addition, in states without Medicaid coverage of circumcision, there is an increased burden of disease related to the foreskin. These findings represent a need to further investigate the costs of healthcare associated with Medicaid coverage of circumcision or the lack thereof. UROLOGY 179: 136–142, 2023. © 2023 Elsevier Inc. All rights reserved.

In 2012, the American Academy of Pediatrics (AAP) recognized that the benefits of male circumcision outweighed the potential risks associated with the procedure.[1] Furthermore, the AAP reported that the benefits of the prevention of urinary tract infections, penile cancer, and transmission of sexually transmitted infections such as HIV, justified access to circumcision.[1] Despite these recommendations, a study examining neonatal circumcision trends before and after the AAP statement found that boys with private insurance were significantly more likely to undergo circumcision compared with publicly insured boys even after controlling for demographics, region, hospital characteristics, and year.[2] Currently in the United States, Medicaid or state-level public health insurance in seventeen states still does not pay for routine elective male circumcision.

Prior analyses have found that circumcision is cost-effective for disease prevention.[3] Some families may consider circumcision for their child based on the fact that in their lifetime, many uncircumcised males will require treatment for a medical condition related to the foreskin.[3] Additional studies have observed a continual increase in the number of elective, operative circumcisions performed.[4–6] Also, it is possible that billing codes for penile abnormalities, such as penile torsion, hidden penis, or chordee may be used in states without Medicaid circumcision coverage to justify a foreskin procedure more so than in states that cover routine newborn circumcision.

Based on this information, we hypothesized that compared to states with public insurance coverage for newborn circumcision, states without public insurance

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State-Level Public Insurance Coverage and Neonatal Circumcision Rates

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abstract

OBJECTIVES: Seventeen states do not provide Medicaid coverage for neonatal male circumcision, despite American Academy of Pediatrics recommendations supporting access for families that choose it. Our study objectives were to (1) compare state-specific trends in neonatal circumcision to previously established estimates and (2) assess the impact of changes in Medicaid coverage of the procedure.

METHODS: The State Inpatient Databases were used to determine rates of neonatal male circumcision in 4 states (CO, FL, MI, and NY) at 4 time points (2001, 2006, 2011, 2016). Neonatal circumcision was defunded by Medicaid in Florida (2003) and Colorado (2011). A multivariable logistic regression model was created to assess associations between patient and state characteristics and odds of neonatal circumcision.

RESULTS: Overall, 54.5% of neonates underwent circumcision. States where Medicaid defunded neonatal circumcision revealed a decrease in circumcision rates in subsequent years (47.4% to 37.5% in FL; 61.9% to 52.0% in CO). Neonates with private insurance had higher odds of circumcision compared with those with public insurance (adjusted odds ratio [aOR] 2.23; 95% confidence interval [CI] 2.21–2.25). When Medicaid coverage was available, Black neonates had higher odds of circumcision compared with white neonates (aOR 1.44; 95% CI 1.42–1.46). When Medicaid coverage was not available, Black neonates had lower odds compared with white neonates (aOR 0.40; 95% CI 0.39–0.41).

CONCLUSIONS: State-specific data reveal trends in neonatal circumcision similar to previous national estimates. Colorado and Florida revealed 20.9% and 16.0% reductions in neonatal circumcision rates, respectively, after defunding. Black neonates appeared to be disproportionately affected by changes in Medicaid coverage.

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Mr Zambrano Navia conceptualized and designed the study, analyzed and interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Jacobson and Johnson and Ms Rosoklija conceptualized and designed the study and critically reviewed and revised the manuscript; Dr Balmert contributed to the analysis and interpretation of data and results and critically reviewed and revised the manuscript; Drs Davis and Holl contributed to the analysis of results and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The American Academy of Pediatrics supports access to neonatal circumcision, yet 17 states do not offer Medicaid coverage for the procedure. Neonatal circumcision rates have been decreasing modestly in the United States because of factors including cost and access.

WHAT THIS STUDY ADDS: In this study, we assess the impact of discontinuation of Medicaid funding for neonatal circumcision on rates of neonatal circumcision in different racial and/or ethnic groups. Black neonates are disproportionately impacted by these changes in Medicaid policy when compared with other racial and/or ethnic groups.

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