2024

OREGON HEALTH AUTHORITY

Northwest Regional Newborn Bloodspot Screening

Advisory Board Report to the Legislature

Acknowledgments

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For the full report or previous reports to the legislature, go to:
https://www.oregon.gov/oha/ERD/Pages/Government-Relations.aspx

For details about the work of the board, go to:
NWRNBS Advisory Board

Contents

Executive summary

Background

This is the fourth report to the Oregon legislature from the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board (the board), fulfilling reporting requirements outlined in HB 2563 (2019). In the 2019 report, the board adopted a protocol and criteria for recommending the addition of disorders to Oregon's newborn bloodspot screening panel. In the 2020 report, the board added two disorders to the newborn bloodspot screening panel using those criteria. Additionally, the board formulated criteria for removing disorders from the panel. In the 2022, the board applied the criteria to consider removal of two disorders from the screening panel, Gaucher disorder and Fabry disorder.

Work of the NWRNBS Advisory Board: 2022–2024

Summary of 2022 to 2024 board meetings

The board met seven times in this report period, between September 2022 and June 2024, to review topics that included:

- Two disorder additions to the testing panel
- Updated disorder review protocols with criteria
- Findings and recommendations from a third-party review of the NWRNBS Section
- Legislative allocation for out-of-pocket screens
- Long-term funding for the NWRNBS Section

Disorders considered for addition to the screening panel and updates to condition review process and criteria.

The board considered and determined that two disorders should be added to the screening panel: Mucopolysaccharidosis Type II (MPS II) and Guanidinoacetate Methyltransferase (GAMT) deficiency.

The board applied its criteria for each disorder and concluded, by strong consensus that both disorders meet all criteria for addition to the screening panel. See appendices A and B for independent executive summaries.

After reviewing the two conditions, the board reevaluated the process and criteria. An additional step that invites public input on the disorder review was added to be more transparent and responsive to the needs of families in Oregon. Additionally, minor updates to the criteria were made to represent current practices.

Onsite Section Review and Evaluation

In January of 2024, a team of expert reviewers comprised of public health professionals and the Association of Public Health Laboratories (APHL) staff conducted a comprehensive onsite review of the Oregon Newborn Screening (NBS) Section. The visit assessed various components of the OR NBS Section including the laboratory program, birth facilities, and the follow-up program for quality improvement purposes.

The outcome of the onsite review included an assessment of the different areas in which the NBS section operates, including the work of the board. The final report made a series of recommendations pertinent to the board in the areas of legislation and policy as well as NBS section funding.

Legislative Allocation for Out-of-Pocket Screens

The NBS fee increase was implemented in August of 2022 and ratified during the 2023 session. Community birth providers and small hospitals opposed the fee increase and highlighted the need to cover the cost for families who pay out of pocket, because insurance or the Oregon Health Plan did not include screening. The NBS section worked with Representative McLain to request general funds so that all families have access to this mandated public health resource.

Long-term Funding Subcommittee

The Advisory Board convened a Long-term Funding Subcommittee to explore what funding model may work well to sustain the NWRNBS Section long-term. The Subcommittee held two meetings in 2022 and determined additional information on funding models and other programs was needed for an informed discussion. The Subcommittee will reconvene in 2024 and continue its work.

Work within Legislative Sessions: 2023–2024

Legislative Session 2023

- SB5526 The fee change that occurred between legislative sessions was ratified by the legislature.
- HB2617 that sought to modify NBS advisory board membership and activities did not pass.
  - Re-establishes the membership requirements of the board.
  - Directs the advisory board to develop, evaluate, and modify criteria used in the review of new conditions for the NBS panel.
  - Directs the board to review MPSII, GAMT deficiency, and Krabbe disease using the established criteria.
  - Waives the fee for families who pay out-of-pocket (or cannot afford to pay) for newborn screening.
  - An accompanying bill (HB2608) that appropriates general funds to cover the fee waiver for families who pay out-of-pocket did not pass.
- HB2927 that sought to establish a statewide steering committee on sickle cell disease and trait did not pass.
  - Requires committee to:
    - Establish statewide network of stakeholders.
    - Provide education services.
    - Identify funding sources.
    - Make recommendations for best practices.
- Requires Oregon Health Authority to provide social support and other services for individuals with sickle cell disease, including testing services and genetic counseling.

Legislative Session 2024

- NWRNBS Section received one-time general funds ($250,000) to cover the costs of Oregon families who pay out of pocket for screening.

Introduction

This is the fourth report of the Northwest Regional Newborn Bloodspot Screening Program Advisory Board (the board). The board was formed under HB 2563 (2019). This report fulfills a requirement of that bill.

The board meets a minimum of every six months to assist the Northwest Regional Newborn Bloodspot Screening Program (also called the NBS Section of the Oregon State Public Health Laboratory and referred to here as the "section"). The board assists by providing the following:

- Advocacy
- Advice
- Recommendations
- Technical information

Newborn bloodspot screening is more than a test

Newborn Screening is a coordinated public health system. This system relies on providers, parents and the public health laboratory. The section sells test kits to medical providers. The provider takes a small blood sample from the newborn's heel and sends the specimen to the section. The laboratory conducts over 40 tests for heritable disorders that may not be clinically apparent in the first weeks after birth but may lead to disability or death if not detected early. The section sends the test results to providers who perform confirmatory testing, discuss any abnormal results with parents, and set up treatment plans, if needed. The section provides ongoing education and works with providers to continually improve the quality of screening.

By identifying infants early and referring them to care:

- Lifelong outcomes improve
- Children who would have been affected lead healthier and more productive lives
- Families receive critical support, and
- Health care costs go down.

Newborn bloodspot screening saves lives.

Board members assist based on their respective areas of expertise. The board's goal is to improve health outcomes for all infants and their families.

This report reflects the board's work at meetings on:

- September 8, 2022
- November 30, 2022
- May 31, 2023
- June 8, 2023
- September 6, 2023
- January 30, 2024
- May 29, 2024

Detailed summaries of those meetings are available at the OHA website at: NWRNBS Advisory Board

The report provides the Legislature with a summary of the board's activities related to the following topics:

- Information from experts about MPSII and GAMT Deficiency disorders. These disorders were evaluated for recommended for addition the NBS section's testing panel during this report period.
- A review and update to the process and criteria for adding disorders to the testing panel, and the board's decisions about adding the disorders.
- Findings and recommendations from an onsite section evaluation conducted by a team of NBS experts.
- The legislative allocation of general funds to cover the cost of families who pay out-of-pocket for screening.
- The initial work of a Long-term Funding Subcommittee.

MPS II Background, Criteria, and Consensus Check

Review to add MPS II to the screening panel

The board considered a proposal to add the MPSII disorder to the newborn bloodspot screening panel and reached a strong consensus that it should be added to the panel.

With the addition of MPSII to the Recommended Uniform Screening Panel (RUSP) HRSA Newborn screening Recommended Uniform Screening Panel (RUSP), the Board members reviewed, discussed, and evaluated the disorder based on Category One Criteria and determined MPSII met all the criteria. Subsequently, per protocol, the board reviewed and evaluated the disorder using the Category Two Criteria and agreed MPSII passed all the criteria. The board's evaluations were conducted using a consensus tool. The results of the evaluation informed the recommendations to the NWRNBS Section.

MPS II background

Mucopolysaccharidosis type II (MPS II, also called Hunter syndrome) is an X-linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (I2S) due to pathogenic variants in the iduronate-2-sulfatase (IDS) gene. As an X-linked disorder males are predominantly affected; few affected females have been reported in cases of skewed X-inactivation or X chromosome abnormalities. This enzymatic defect results in progressive accumulation of two glycosaminoglycans (GAGs, also known as mucopolysaccharides), dermatan and heparan sulfate, in various body tissues, causing a multisystem disorder with highly variable age of onset, rate of progression, and disease severity. Primary clinical features include progressive airway disease, cardiac disease, skeletal involvement, and central nervous system (CNS) involvement in the form of progressive cognitive decline. MPS II is characterized clinically as "severe" or "attenuated" (previously "neuronopathic" and "non-neuronopathic") depending on the degree of neurological involvement. Individuals with an attenuated phenotype can have similar somatic manifestations but no or minimal CNS involvement. Approximately two-thirds of affected individuals have the severe form of MPS II. From GeneReviews, "Additional findings in both forms of MPS II include: short stature; macrocephaly with or without communicating

hydrocephalus; macroglossia; hoarse voice; conductive and sensorineural hearing loss; hepatosplenomegaly; dysostosis multiplex; spinal stenosis; and carpal tunnel syndrome."1 Without treatment, individuals with the severe form typically live only into their second decade. Individuals with the attenuated form may live into their fifth or sixth decade.

Application of criteria for addition

Category one criteria: The following criteria were responded to by the Section:

1. The condition is well-defined in newborns. **Yes.**
2. Earlier intervention results in improved outcomes compared to later identification. **Yes.**
3. The population level incidence and prevalence are known. **Yes.**
4. There is a Federal Drug Administration (FDA) approved testing method available using dried blood spots or an accurate testing method is available that meets clinical laboratory requirements for validation and testing by the laboratory using dried blood spots. **Yes.** The laboratory can develop an assay for detecting this condition.
5. Diagnostic and specialty testing is available. **Yes.**
6. A treatment is available. **Yes.**
7. The contracted NWRNBS medical consultants have been consulted and appropriate specialized medical consultation is available or can be obtained by the Section. **Yes.**
8. The specific condition appears in the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission. **No longer a relevant criterion as written.**
9. The NWRNBS Section has sufficient information to perform a fiscal analysis. **Yes.**
10. The impact to the NWRNBS contracted partners has been assessed. No perceived challenges for New Mexico. Additional contracted partners not reached are Saipan, Guam, Navajo Nations and some military bases. Because contracts with partners can be amended to include this condition (or not), the relevance of this criteria for determination if Oregon should add the condition is no longer significant. **This criterion should be reconsidered.**

Category two criteria: The board had the following discussion on category two criteria as is applied to MPSII (Appendix A):

1. The population level public health benefits of screening outweigh the risks and harms.
2. There is adequate capacity and expertise in the NWRNBS section to implement and maintain testing and reporting.
3. The NWRNBS Section has adequate capacity for conducting follow-up and education for providers and parents.
4. The NWRNBS Section has received grant funding for MPSII screening, which should cover the first 2-3 years. Necessary fee increases overtime to cover the addition of new conditions is a concern, but this issue is not just linked to MPS II. It is a broader system issue.
5. The population level incidence, prevalence, and disease burden are significant enough to merit screening.
6. Diagnostic and specialty testing is available and accessible that allows a definitive diagnosis to be made.
7. An effective treatment that is proven to result in clinically significant benefits is available and accessible.
8. There is equitable care and treatment for the disorder.
9. The impact to the NWRNBS partners does not prohibit the addition or removal of the disorder.

Consensus check

The board conducted a consensus check (see Appendix A) to determine whether it would recommend adding MPSII to the screening panel.

There was a *strong consensus* to recommend adding MPSII to the Newborn Screening Panel.

GAMT deficiency Background, Criteria, Consensus Check and Next Steps

Review to add GAMT Deficiency to the screening panel

The board considered a proposal to add the GAMT Deficiency disorder to the newborn bloodspot screening panel and reached a strong consensus that it should be added to the panel.

With the addition of GAMT to the RUSP, the Board members reviewed, discussed, and evaluated the disorder based on Category One Criteria and determined GAMT met all the criteria. Subsequently, per protocol, the board reviewed and evaluated the disorder using the Category Two Criteria and agreed GMAT passed all of the criteria. The board's evaluations were conducted using a consensus tool. The results of the evaluation informed the recommendations to the NWRNBS Section.

GAMT Deficiency background

Board members reviewed an evidence report regarding GAMT deficiency prepared by a consultant and Jessica Scott Schwoerer, an expert in GAMT deficiency, shared her expertise at a board meeting.

Guanidinoacetate methyltransferase (GAMT) deficiency is one of three metabolic disorders related to cerebral creatine deficiency. It is an autosomal recessive disorder due to variants in the gene, GAMT, which encodes for the enzyme guanidinoacetate methyltransferase (OMIM #601240). This enzyme converts Guanidinoacetate (GUAC) to creatine and a deficiency in this enzyme leads to a build-up of GUAC and low creatine levels. This disorder presents neurologic signs and symptoms including developmental delays particularly in speech, intellectual disability, behavioral issues including autism, seizures, and movement disorders like ataxia. Pre-symptomatic treatment with dietary interventions and supplements has shown significantly improved outcomes with most individuals being neurologically typical.

Application of criteria for addition

Using the established review protocol, the Board deliberated on the considerations for whether to recommend adding this disorder to the screening panel.

Category one criteria: The following criteria were responded to by the Section:

1. The condition is well-defined in newborns. **Yes.**
2. Earlier intervention results in improved outcomes compared to later identification. **Yes.**
3. The population level incidence and prevalence are known. **Yes.**
4. There is a Federal Drug Administration (FDA) approved testing method available using dried blood spots or an accurate testing method is available that meets clinical laboratory requirements for validation and testing by the laboratory using dried blood spots. **Yes.** The laboratory can develop as assay for detecting this condition.
5. Diagnostic and specialty testing is available. **Yes.**
6. A treatment is available. **Yes.**
7. The contracted NWRNBS medical consultants have been consulted and appropriate specialized medical consultation is available or can be obtained by the Section. **Yes.**
8. The specific condition appears in the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission. **No longer a relevant criterion as written.**
9. The NWRNBS Section has sufficient information to perform a fiscal analysis. **Yes.**
10. The impact to the NWRNBS contracted partners has been assessed. No perceived challenges for New Mexico. Additional contracted partners not reached are Saipan, Guam, Navajo Nations and some military bases. Because contracts with partners can be amended to include this condition (or not), the relevance of this criteria for determination if Oregon should add the condition is no longer significant. **This criterion should be reconsidered.**

Category two criteria: The board had the following discussion on category two criteria as is applied to the GAMT deficiency:

1. The population level public health benefits of screening outweigh the risks and harms.
2. There is adequate capacity and expertise in the NWRNBS Section to implement and maintain testing and reporting.
3. The NWRNBS Section has adequate capacity for conducting follow-up and education for providers and parents.
4. The NWRNBS Section has adequate fiscal resources for implementing screening (testing, follow-up, and education).
5. The population level incidence, prevalence, and disease burden are significant enough to merit screening.
6. Diagnostic and specialty testing is available and accessible that allows a definitive diagnosis to be made.
7. An effective treatment that is proven to result in clinically significant benefits is available and accessible.
8. There is equitable care and treatment for the disorder.
9. The impact to the NWRNBS partners does not prohibit the addition or removal of the disorder.

Consensus check

The board conducted a consensus check to determine whether it would recommend adding GAMT deficiency to the screening panel.

There was *strong consensus* for the board to make a recommendation to add GAMT deficiency to the Newborn Screening Panel.

Next steps for Addition of MPSII and GAMT Deficiency to Panel

The Section offered next steps upon approval of adding these two disorders to the screening panel. Historically, it's taken at minimum four years for Oregon to add a condition to its panel once the disorder has been added to the RUSP. These following steps are required before full implementation of the condition to the state's screening panel, after the disorder has been adopted by the board:

- Perform a fiscal analysis to determine whether there is adequate funds to screen for the condition.
- Approach the legislature with a fee increase or request for general funding, if needed.
- Initiate a rule change to add the disorder.
- Determine if there are enough staff and experts in the laboratory and follow-up unit.
- Seek position authority from the legislature, if necessary.
- Locate an effective test.
- Procure testing equipment.
- Validate that the testing method works and how the test results will appear on the report.
- Determine the follow-up flow process.
- Update the laboratory information system.
- Update the state's Oregon Newborn Bloodspot Screening Practitioner's Manual.
- Create and disseminate educational materials for parents and providers.
- Notify providers of the coming change.

Disorder Review Protocol

In late 2023 and early 2024, the Advisory Board reviewed the process for adding disorders to the NWRNBS Section testing panel in an effort to determine how the process could be more transparent, iterative, and inclusionary for all interested parties. They also wanted to make sure any evaluation criteria was based on sound data, viability of testing results, available treatment resources, equity, testing capacities, and responsive to Oregon's population.

Subsequently, the Advisory Board, developed a four-step procedure for disorder evaluations summarized below and updated criteria for step 2 and 4.

Proposed Procedure for Disorder Evaluation

Step 1: Addition to the RUSP

Determine if the disorder has been reviewed by the ACHDNC and added to the RUSP. Disorder recommended for addition to the RUSP by the ACHDNC will advance to Step 2 for consideration to the NWRNBS Section testing panel.

Step 2: NWRNBS Section Evaluation

The NWRNBS Section will work with an outside consultant to provide a review of the condition and address the NWRNBS Section Criteria and the Advisory Board Criteria. A report will be provided to the Advisory Board along with a presentation to assist in the deliberations.

Step 3: Public Input on Disorder Review

The Advisory Board will invite input from the public to inform deliberations and recommendation on the disorder to the Section. This public engagement process will be transparent and provide clear opportunities for participation with timely notices and using multiple communication venues. The Advisory Board will dedicate time during a meeting for public input on the disorder.

Step 4: NWRNBS Advisory Board Evaluation and Recommendation using Input from Steps 1–3

The NWRNBS Advisory Board will evaluate disorders using criteria and public input. A consensus tool (see below) will be used to gauge the Board's level of agreement or support for recommending the Section add a disorder to the panel.

Criteria for Disorder Evaluation

(Step 2) Section Review Criteria. *The following questions will be reviewed by the consultant and offered as a starting place to the Advisory Board to inform deliberations.*

1. Is the condition well-defined in newborns? Do patients present within the newborn period or are there late-onset, mild presentations of the condition?
2. Will earlier intervention result in improved outcomes?
3. Is the population incidence / prevalence known?
4. Is there a Federal Drug Administration (FDA) approved testing method available or a peer reviewed laboratory developed test for detecting the condition in dried blood spots? Does the method meet clinical laboratory requirements for validation?
5. Is diagnostic and specialty testing available?
6. Is a treatment available or expected to become available?
7. Is appropriate specialized medical consultation available or able to be obtained by the Section?
8. Does the NWRNBS Section have sufficient information to perform a fiscal analysis?
9. What capacity and expertise are available (or needed) in the NWRNBS Section to implement and maintain testing and reporting?
10. What capacity and expertise are available (or needed) to implement and maintain follow-up and education for providers and parents?

(Step 4) Advisory Board Criteria *(Evaluated using the Consensus Method).* *Considering the above feedback from the Section, the Board will deliberate on the following additional criteria:*

1. What is the population level incidence, prevalence, and burden for this disorder for the state/territory?
2. Does diagnostic and specialty testing provide a definitive diagnosis for the intended screened disorder?
3. What is the risk for the family with a false positive newborn screen?
4. What is the risk for the family with an unintended diagnosis, such as late-onset disease?

5. Is an effective treatment for those with a diagnosis, proven to result in clinically significant benefits, available to families in Oregon?
6. What are the significant risks associated with treatment, if any?
7. Is equitable long-term follow-up and management of the disorder available to families in Oregon?
8. Do the population level public health benefits of screening outweigh the risks and harms?

This procedure was approved by consensus at the Advisory Board's May 29, 2024, meeting. A copy of the full disorder review protocol, including criteria, is provided in Appendix C.

Onsite Section Review and Evaluation

In January 2024, a team of expert reviewers comprised of public health professionals and the Association of Public Health Laboratories (APHL) staff conducted a comprehensive onsite review of the Oregon (OR) Newborn Screening (NBS) Section. The visit assessed various components of the OR NBS system including the laboratory program, birth facilities, and follow-up program for quality improvement purposes.

During the onsite review, the reviewers met with Advisory Board members to solicit their perceptions. They also met with NBS staff, medical consultants, hospitals, and community birth providers.

The assessment found several strengths and opportunities for the NBS Section including an engaged leadership that is open to change, seamless communications between the laboratory and follow-up divisions, a committed Advisory Board, commendable relationships with NBS Section partners, and forward-thinking approaches.

At the same time, the review recognized the NBS Section's challenges, shared by NBS programs nationally, that included maintaining daily operations while pursuing quality improvement efforts, expanding screening panels, and modernizing information system infrastructures.

The review focused on 12 areas including:

- organizational structure
- state legislation and policy; ethics
- funding models
- laboratory system
- emergency preparedness
- short-term follow-up system
- long-term follow-up system
- regional considerations
- birth facilities
- education
- information systems

Recommendations relevant to the charge and work of the Advisory Board included:

State Legislation and Policy

1. Suggestions on amendments to Oregon statute and rules
2. Enhance transparency of condition review process by posting the process and any associated forms on the NWRNBS Advisory Board website
3. Ensure proper governance of the NWRNBS Advisory to include improved education, training, and onboarding of Board members.
4. Examine membership of committee and consider inclusion of bioethicist.
5. Consider participation in other jurisdictions' Advisory Boards or Committees.
6. Assess the utility of a two-screen program.
7. Investigate why approximately one percent of babies are not screened and consider if education and outreach could decrease the number of babies who miss being screened.

Funding

1. Explore pursuing equity-based funding (federal, state, non-profit) to pay for NBS quality improvement efforts.
2. Consider the possibility of invoicing for screening services rather than a pre-pay model.
3. Communicate with birth providers at least six months ahead of any future NBS fee increases.
4. Introduce legal protections/safeguards so that other parts of OHA cannot use funds collected for NBS for non-NBS work without prior approval or NBS Section discretion.

These recommendations were presented to the Advisory Board at their meeting on May 29, 2023.

Next Steps

The NBS Section plans to distribute the final site review report to all internal and external partners. The section will also begin conversations with leadership within OHA on how to prioritize and address the recommendations.

The advisory board will have opportunities to share their vision and work with the section on development of a strategic plans that integrates the site review recommendations.

Legislative Allocation for Out-of-Pocket Screens

The NBS fee increase was implemented in August of 2022 and ratified during the 2023 session. Community birth providers and small hospitals who opposed the fee increase highlighted impact to small business and also the need to cover the cost for families who pay out of pocket, because either their private insurance or the state plan (OHA) did not include screening.

The NBS Section worked with state representatives to address these needs so that all families have access to this mandated public health screening resource.

During the 2023 legislative session, HB2617 was introduce that sought to waives the fee for families who pay out-of-pocket (or cannot afford to pay) for newborn screening. An accompanying bill (HB2608) was drafted that appropriated general funds to cover the fee waiver for families who pay out-of-pocket. Neither bill passed.

During the 2024 legislative session state budget allocation, the NWRNBS Section received one-time general funds ($250,000) to cover the costs of Oregon families who pay out of pocket for screening.

The NBS Section has now implemented for one year a process in which community birth providers and hospitals can request subsidized screening cards for families who pay out-of-pocket for screening. Providers must demonstrate that the family's private insurance, nor OHP, would cover the costs.

Next steps for the advisory board is to reconvene a long-term funding subcommittee to address sustainable funding options for the section.

Long-term Funding Subcommittee

In 2022, the Advisory Board convened a Long-term Funding Subcommittee to explore what funding model may work well to sustain the NWRNBS Section long-term. The Subcommittee held two meetings in August and September of 2022.

These initial meetings helped to further define the long-term funding challenges for the NWRNBS Section which is funded through the NBS kit fee. These kits are purchased upfront by birthing providers and reimbursed by insurance plans, if available to the patients. As new disorders are added to the testing panel the cost per kit increases.

The Subcommittee discussed other section funding sources, potential criteria for funding models, and how other states funded their programs. It was determined that additional data and information was needed from other programs, organizations, and interests, to fully consider any alternative funding sources or models.

The Subcommittee meetings were paused during 2023 but will be reconvened in 2024.

Conclusion

Efficient review and recommendations to add MPSII and GAMT deficiency to the screening panel are signs of a high functioning board. The board acknowledged requests for greater transparency and adopted changes to the condition review process that include testimony from family and advocacy groups. The board supported the section in undergoing an external review by experts in the field of newborn screening, which will lead to the creation of a strategic plan. Recognizing the impact of the fee increase, the board formed a subcommittee to evaluate options for long-term funding of the section and advocated for general funding to cover the cost of screening for families who pay-out-of-pocket. In this report period, the board has demonstrated its maturity and its ability to move forward as the state's primary source of experts advising the NWRNBS Section.

Appendix A: Independent evidence report on MPSII Disorder

Evidence Report: Newborn Screening for Mucopolysaccharidosis type II (MPS II)

Prepared for the Northwest Regional Newborn Bloodspot Screening Program Advisory Board

May 2023

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Publication date: May 13, 2023
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Table of Contents

Introduction

Background and Purpose

HB 2563 required the formation of the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board (the board). HB 2563 tasked the board with reporting its findings and recommendations to the Legislature. In addition, the board's charter states that it is to assist with the modernization of the newborn bloodspot screening program (the program), including advising on changes to the newborn bloodspot screening panel.

The board has approved a process and criteria for evaluating additions to the newborn bloodspot screening panel whose stages are summarized below:

- Stage 1: Addition to the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) Recommended Uniform Screening Panel (RUSP)
- Stage 2: NWRNBS Program criteria
- Stage 3: NWRNBS Advisory Board criteria

Mucopolysaccharidosis type II (MPS II) has been added to the RUSP, but the program is not screening for it. This report is meant to provide information to assist with the board's evaluation of whether to recommend the addition of MPS II to the program's newborn screening panel.

Scope of Review

This report follows the evidence outline as presented by ACHDNC, beginning with a discussion of the natural history of the condition, followed by incidence and prevalence estimates and a discussion of screening, diagnosis, treatment, and finally context for the NWRNBS program and state of Oregon. The Executive Summary for MPS II presents evidence for each criterion as ordered by Stages 1-3 above.

This report documents, evaluates, and summarizes available scientific evidence and expert opinion for evaluation by the board. This report is not intended to make recommendations for or on behalf of the board.

Methods

This report summarizes findings from the ACHDNC review and more recent literature. The ACHDNC initial literature search was conducted for references published from January 1, 2001 to June 10, 2021, and a bridge search was conducted to update the references with publications from June 10, 2021 through January 1, 2022 (publications through December 31, 2021). To capture recent, relevant literature for this report an updated literature search was conducted using ACHDNC review search criteria for references published from January 1, 2022 to March 31, 2023.

Documentation of literature review is in Appendix A, a list of included articles is in Appendix B, and a list of excluded articles is in Appendix C.

Key Questions for Evidence Review: MPS II

Case Definition

Mucopolysaccharidosis type II (MPS II, also called Hunter syndrome) is an X-linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (I2S) due to pathogenic variants in the iduronate-2-sulfatase (*IDS)* gene. As an X-linked disorder males are predominantly affected; few affected

females have been reported in cases of skewed X-inactivation or X chromosome abnormalities. This enzymatic defect results in progressive accumulation of two glycosaminoglycans (GAGs, also known as mucopolysaccharides), dermatan and heparan sulfate, in various body tissues, causing a multisystem disorder with highly variable age of onset, rate of progression, and disease severity. Primary clinical features include progressive airway disease, cardiac disease, skeletal involvement, and central nervous system (CNS) involvement in the form of progressive cognitive decline. MPS II is characterized clinically as "severe" or "attenuated" (previously "neuronopathic" and "non-neuronopathic") depending on the presence or absence of neurological involvement. Individuals on the severe end of the disease spectrum manifest features between 2-4 years of age and experience rapid neurological decline resulting in severe cognitive impairment. Individuals with an attenuated phenotype can develop similar somatic manifestations at the same or later ages but with no or minimal CNS involvement. Approximately two-thirds of affected individuals have the severe form of MPS II. From GeneReviews, "Additional findings in both forms of MPS II include: short stature; macrocephaly with or without communicating hydrocephalus; macroglossia; hoarse voice; conductive and sensorineural hearing loss; hepatosplenomegaly; dysostosis multiplex; spinal stenosis; and carpal tunnel syndrome."[1] Without treatment, individuals with the severe form typically live only into their second decade. Individuals with the attenuated form may live into their fifth or sixth decade.[2]

For the purpose of this report and as used so far by labs performing newborn screening for MPS II, the case definition is demonstration of 1) low/absent iduronate-2-sulfatase activity with normal measurement of at least one other sulfatase to rule out multiple sulfatase deficiency and 2) elevated dermatan and heparan sulfate in urine to rule out I2S biochemical pseudodeficiency. Molecular testing of the *IDS* gene supports the diagnosis and may provide genotype-phenotype correlation but is not necessary.

Natural History of MPS II

What is the natural history of this condition with usual clinical detection?

Much of the data outlining the natural history of MPS II has come from the Hunter Outcome Survey (HOS), a voluntary registry including patients who are untreated, have been treated with enzyme replacement therapy (ERT) or hematopoietic stem cell transplant (HSCT), as well as retrospective data on patients who passed away prior to study entry. The ACHDNC review summarized the first publication which described the prevalence and age of onset of initial symptoms of MPS II for individuals enrolled in the HOS.[2] From the ACHDNC review:

> An initial report of the first 263 MPS II patients registered in the HOS describes the prevalence of initial symptom characteristics, with age of onset. Of these patients, 24% were receiving idursulfase (ERT) at the time of enrollment in the HOS and had a median age of 12.2 years. Table [1] summarizes those features reported by at least 30% of patients in this HOS report, in order of median age of onset. Over 80% of patients registered in the Hunter Outcome Survey (HOS) reported at least one neurological (84%) or cardiovascular (82%) symptom, as well as involvement in the abdomen, head and neck, skeletal, ear, mouth, and chest and lungs, and at least 60% of patients additionally reported throat, skin, nose and gastrointestinal symptoms.

Table 1. Features of individuals with MPS II registered in the HOS (n=263)

Clinical Finding	Prevalence (%)	Median age of onset in years
Otitis media	74	1.2
Abdominal hernia	78	1.3
Nasal obstruction	34	2.0
Facial dysmorphism	95	2.8
Enlarged liver or spleen	89	2.8
Enlarged tonsils or adenoids	68	2.9
Cognitive problems	37	3.2
Enlarged tongue	70	3.4
Hyperactivity	31	3.5
Joint stiffness/musculoskelotal	84	3.6
Behavior problems	36	3.7
Fine motor skill impairment	33	4.0
Gait problems	33	5.5
Heart murmur	62	5.8
Cardiac valve disease	57	6.1

How is the condition defined in newborns?

While the HOS data outlined above demonstrates that the earliest signs and symptoms of MPS II may be present in the first year or two of life, there will generally not be any clinical signs in the newborn period to distinguish an affected infant from an unaffected infant. For this reason, neonatal diagnosis relies on biochemical screening and molecular analysis (I2S enzyme, GAG analysis, *IDS* sequencing), underscoring the importance of newborn screening for presymptomatic diagnosis and timely initiation of treatment.

What are the ages of onset, diagnosis, and treatment without newborn screening?

An analysis of ERT-treated (n=800) and untreated (n=95) patients from the HOS provides data on ages of onset, diagnosis, and treatment. [3] Individuals who died prior to study entry, had received HSCT, or had participated in a clinical trial were excluded. The investigators reported that the median ages of symptom onset in the two groups (ERT-treated and untreated) were 1.6 years and 1.5 years, respectively, and the median ages at diagnosis were 3.3 years and 3.2 years, respectively. A similar proportion of treated and untreated patients were reported to have cognitive impairment (~58% in both groups). Among the ERT-treated patients, the median age of treatment initiation was 6.9 years (10th-90th percentile: 2.1-19.8 years).

How do clinical outcomes differ with early detection and treatment of MPS II through newborn screening?

Since Illinois implemented newborn screening for MPS II, eight newborns and four extended family members, all male, have been diagnosed. Three are predicted to have severe phenotypes based on genotype and/or family member assessment, four are predicted to have attenuated phenotypes, and one phenotype is unknown. Three affected infants were started on ERT in the first three months of life (two with predicted severe phenotype and one with an undetermined phenotype). The boys are now 2-4 years old and are reported to all have developmental delay but no somatic manifestations of MPS II, suggesting that early, pre-symptomatic ERT implementation may not prevent CNS manifestations. The four with predicted attenuated phenotypes remain asymptomatic.[4]

Missouri has not published clinical outcomes of their two individuals diagnosed with severe MPS II.

Taiwan has diagnosed 10 infants with MPS II since implementation of newborn screening, though they are not categorized as severe or attenuated in the 2022 publication by Lin et al. Four individuals started ERT by 6 months of age and three of the four later received HSCT. Two of the treated individuals are reported to have skeletal changes identified by X-ray, which had progressed at follow-up around 3 years of age. One of these two treated individuals is also reported to have mitral and atrial regurgitation and mild splenomegaly at follow-up that was not present at baseline. All other diagnosed individuals are reported to have normal/unremarkable skeletal, cardiac, and abdominal studies at baseline and follow-up. Developmental outcomes were not reported.[5]

As NBS-diagnosed individuals with MPS II are no older than 8 (in Taiwan) and 5 years old (in the US), we have limited observations so far on developmental and cognitive outcomes. With time, additional data will better define how the neurological and somatic presentation of NBS-diagnosed individuals differs from those clinically diagnosed as well as from previously diagnosed family members or members identified through cascade testing following the child's diagnosis through NBS.

Incidence and Prevalence of MPS II

How many people are diagnosed with this condition clinically?

The birth prevalence of MPS II, as assessed prior to newborn screening, is unclear. One study reported a birth prevalence of 0.26 per 100,000 in the United States based on 1995-2005 National MPS Society Membership, though as this a voluntary registry the number is likely an underestimate.[6] The ACHDNC review assumed an incidence of clinically detected MPS II (either attenuated or severe) of 0.67 per 100,000 births.

What is the estimated birth prevalence with newborn screening?

Updated birth prevalence data is emerging as states have implemented newborn screening for MPS II. Illinois described a birth prevalence of 1 in 73,290 or 1.4 per 100,000 based on screening 586,323 infants between December 12, 2017 and April 30, 2022.[4] Missouri reported summary data at a recent MPS conference[7] that described a birth prevalence of 1 in 96,297 or 1.0 per 100,000 based on screening 288,892 infants between November 1, 2018 and December 31, 2022. The ACHDNC review assumed an overall incidence after NBS of 1.6 per 100,000 births.

Screening

What is the screening method to detect MPS II among newborns?

Screening for MPS II is based on measurement of I2S enzyme activity as the primary target. Two different methods of enzyme analysis are used by states screening for MPS II.

Illinois performs I2S enzyme analysis in a multiplexed validated laboratory developed test (LDT) along with other lysosomal storage disorders. The method for MPS II requires a separate punch from the DBS card for the incubation step but can be combined with the other LSD enzyme for analysis. The incubation time is roughly 17 hours, followed by an approximate analysis time of 2 minutes per sample using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The Illinois program defines a positive screen as I2S activity less than or equal to 10% of the daily median and these reports recommend immediate referral to a medical consultant. Borderline screens are defined as those with I2S enzyme activity >10% but less than or equal to 13% of the daily median and reports request a second

sample. If the second specimen is again borderline or positive, the report recommends referral to a medical consultant. No second-tier testing is performed by the Illinois state newborn screen program.[8]

Missouri performs a multiplexed fluorometric enzymatic assay that is a validated laboratory developed test (LDT) using FDA-registered analyte specific reagents. The total assay time is approximately 3.5 hours, which includes incubation and analysis time. To validate the clinical performance of their assay, the Missouri program tested 5,301 deidentified newborn DBS samples (presumed to be normal/unaffected) and seven known diagnostic samples collected from MPS II patients with excellent separation of presumed normal and affected samples (greater than 25 standard deviations).[9] Their screening algorithm dictates that an I2S enzyme activity below their provisional cut-off will be retested (cut-off values not published) If the enzyme activity remains below their action cut-off on the average of three runs, the sample will progress to second-tier GAGS sent to Mayo Clinic Laboratories. If both or either heparan or dermatan sulfate are abnormal (or if GAGS are normal but I2S enzyme is below a failsafe cut-off), the case is reported as abnormal and the PCP and consultant are notified.

How well does it work?

Assay screen positive rate (calculated as the number of specimens sent for second-tier testing divided by the total number of specimens tested), callout rate (calculated as the number of cases referred divided by the total number of specimens tested), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for Illinois and Missouri NBS data are presented in Table 2. It should be noted that Missouri switched from second-tier *IDS* sequencing to second-tier GAG analysis on January 1, 2020. There is no published data differentiating their case outcomes with each second-tier test, so the data below combines both second-tier tests. Neither program is aware of any individuals diagnosed clinically with MPS II that were missed by newborn screening.

Table 2. Newborn Screen Performance Metrics

Statistical Measure	Missouri	Illinois
Assay screen positive rate	0.022%	0.013%
Referral rate	0.012%	0.013%
Sensitivity	100%	100%
Specificity	99.9%	99.9%
Positive predictive value (PPV)	8.8%	11.4%
Negative predictive value (NPV)	100%	100%

Missouri's assay screen positive rate (0.022%) is approximately twice that of Illinois (0.0013%), but referral rates become similar (0.012% in Missouri, 0.013% in Illinois) once second-tier testing is performed. As Missouri does not publish their algorithm's cut-off values it is difficult to examine why the difference in assay screen positive rates exists, though it is possible the methods themselves play a role (LC-MS/MS vs fluorometric enzyme assay).

Benefit of second-tier biochemical testing

Outcomes data from the states and countries doing MPS II newborn screening have shown that the incidence of pseudodeficiency is higher than predicted and represents the majority of abnormal newborn screen cases. Several studies have shown that performing second-tier GAG analysis on the DBS

reduces the false positive rate as it reliably distinguishes affected patients from those with pseudodeficiency.[10] GAG biomarker detection requires a mass spectrometer with higher detection sensitivity than is typically used in NBS labs so all states currently screening for MPS II with second-tier GAG analysis send their samples to a reference laboratory for that testing. All US reference labs use the internal disaccharide method, and Herbst et al conclude "the classic internal disaccharide method is comparably sensitive to the endogenous biomarker method" and strongly recommend that any program screening for MPS II include second-tier GAG analysis, regardless of methodology, to decrease the false positive rate.[11] Completing second-tier GAG analysis prior to calling out an abnormal NBS case will also greatly decrease referrals, thereby decreasing laboratory and consultant/clinician time and preventing families from experiencing undue stress and concern in cases that will ultimately be deemed false positive with normal GAG analysis.

The following high-level data summary was provided in email correspondence with Mayo Clinic Laboratories representatives for inclusion in this document (timeframe and origin of abnormal NBS cases not reported):

- 47 patients received GAG analysis in DBS for the indication of deficient I2S enzyme analysis in newborn screening
    - 46 males; 1 female
    - 4 males had markedly abnormal DBS GAGs (elevated DS and HS) with molecular results consistent with
        - 3 pathogenic/likely pathogenic variants
        - 1 variant of uncertain significance
    - 43 had normal DBS GAGS (normal DS and HS) - molecular was ordered concurrently on a subset and is not available for all patients
        - 26 of these had variants of uncertain significance identified (including 5 samples with the same variant later determined to be a pseudodeficiency allele)

What is the role of *IDS* sequencing in the NBS process?

A 2013 study from Greenwood Genetics Center's Biochemical Diagnostic Laboratory outlined variant categories in their MPS cohorts. *IDS* was found to have the most diverse variant spectrum; of the 218 patients, 85% had sequence variants, 7.3% had rearrangements with the *IDSP1* pseudogene, and 6.9% had multi-exon deletions or duplications. Using three methodologies as needed (sequencing analysis, allele-specific PCR for the common *IDS/IDSP1* inversion, and MLPA analysis), they suggest that the detection rate for *IDS* pathogenic variants in affected individuals is 97% (38 of 39 patients with I2S enzyme performed in house were found to have an *IDS* variant).[12] It is unclear whether newborn screening laboratories would be able to provide all necessary genetic testing technologies, which may limit the yield of genetic testing within the newborn screen pipeline. Additionally, as a pre-newborn screening cohort, these subjects are presumed to have had some clinical or biochemical reason to suspect an MPS or MPS II specifically, which may have contributed to the high yield of molecular testing. A newborn screen population may not be as enriched for pathogenic *IDS* variants.

Eight hundred and thirty-five variants in the *IDS* gene have been described in the Human Gene Mutation Database (HGMD), including 397 missense/nonsense, 75 splicing variants, 172 small deletions, 73 small insertions, 21 small indels, 67 gross deletions, seven gross insertions/duplications, and 22 complex rearrangements.[13] The *IDS* gene entry in ClinVar lists 946 variants, with a similarly broad variation type spectrum.[14] Both HGMD and ClinVar can be used to assess *IDS* variants, though HGMD trends toward

collection of pathogenic and likely pathogenic variants and has an 11-fold lower variant reclassification rate than ClinVar.[15] This suggests that while HGMD may be useful for confirming status of *IDS* variants reported to be pathogenic or likely pathogenic, ClinVar may be more useful in newborn screen scenarios for examining rare variants, variants of uncertain significance, or variants with changing classifications.

Data presented by Greenwood Genetic Center at a recent MPS conference showed that 64% of *IDS* genotypes were of uncertain significance following abnormal newborn screening for MPS II.[16] They reported that enzyme and urine GAG results reduced inconclusive cases with variants of uncertain significance (VUS) in *IDS* by 85% (from 27 to 5 cases). Mayo Clinic Laboratories reported similar data at the same conference, stating that 77% of variants identified in *IDS* in abnormal newborn screen cases were variants of uncertain significance.[17]

The Missouri newborn screening program used *IDS* sequencing as second-tier testing from November 1, 2018 to December 31, 2019, but switched to second-tier GAG analysis from January 1, 2020 onward due to challenges with many variants of uncertain significance being identified in infants who went on to have normal confirmatory GAG analyses, confusing the clinical determination for each case.[9] Indeed, the program has characterized these infants with *IDS* VUS and normal GAGs as having "phenotypes of uncertain significance" with ongoing monitoring recommended. This is likely why Missouri has a much higher unresolved case rate than Illinois (Table 3).

Given this, it seems that molecular testing for MPS II may have low enough diagnostic utility at present to make it difficult to justify as part of the newborn screen program pipeline. As additional states add MPS II to the NBS panel it is expected that the number of variants reported as VUS will go down (and likely at least some will be reassigned as pseudodeficiency variants). There may be a time in future when sequencing as part of the newborn screen pipeline will be of sufficiently high diagnostic or prognostic utility to consider its addition.

What is the genotype-phenotype relationship? Can the severity or type of MPS II be predicted at the time of screening?

As outlined in the previous section, current evidence suggests that while molecular testing can be useful when interpreted as part of the whole dataset collected on each individual patient (NBS enzyme and second-tier GAG analysis, clinical confirmatory biochemical testing with urine GAGs, *IDS* sequencing results), molecular testing has lower diagnostic or prognostic utility in isolation than biochemical testing for patients with abnormal NBS for MPS II. Multiple studies have been unable to establish firm molecular genotype-phenotype correlations for predicting severe vs attenuated status.[18] [19] Chkioua et al suggested that high urinary GAG levels were more strongly correlated with a severe phenotype, but even in their own cohort there were overlapping GAG levels in patients categorized as attenuated and severe. In cases with abnormal or equivocal GAGs and an *IDS* VUS, the presence and/or severity of the disease may not be able to be predicted. This may lead to significant challenges for clinicians to identify the most reasonable schedule for regular assessments and decide when to start treatment.

IDS variants causing pseudodeficiency are being identified and better characterized over time as a result of newborn screening. The Illinois NBS program reports that of the 76 infants referred for diagnostic testing in their publication timeframe, 53 were determined to be cases of pseudodeficiency. They list the 24 pseudodeficiency variants identified in their cohort, with two additional being listed for infants

with “probable pseudodeficiency.” The most common variant in their cohort was c.1499C>T (p.Thr500Ile), identified in 9 infants with a % daily median I2S activity of 7–13%.[4]

Novel variants are being identified routinely in infants following abnormal MPS II newborn screening. The Taiwan program reported that 76% of the 21 unique *IDS* variants reported in their August 2015 – April 2022 cohort were novel, necessitating testing adult male family members to better clarify possible phenotypes.[5] In the three cases where an adult male family member with the same variant was found to have normal urine GAG analysis and unremarkable clinical history and physical exam, the variant was deemed likely benign. Family members will not always be available or willing to undergo such evaluations, so assessment of novel variants will remain a challenge.

What are the findings from other regions that have implemented screening?

Illinois

Illinois has been screening for MPS II since December 12, 2017. Their newborn screening methods and algorithm are described elsewhere in this document (“What is the screening method to detect MPS II among newborns?”). Summary data is presented in Table 3, below.

Missouri

Missouri has been screening for MPS II since November 1, 2018. Their newborn screening methods and algorithm are described elsewhere in this document (“What is the screening method to detect MPS II among newborns?”). Summary data is presented in Table 3, below. Missouri is noted to have a much higher unresolved rate as they consider their 16 cases in which *IDS* variants of uncertain significance were identified “diagnostically uncertain.”

Table 3. U.S. Newborn Screen Metrics

	Missouri[7]		Illinois[4]		Combined	
Category	**n**	**Incidence per 100,000**	**n**	**Incidence per 100,000**	**n**	**Incidence per 100,000**
Total newborns screened	288,892	-	586,323	-	875,215	-
Timeframe	11/1/18-12/31/22	-	12/12/17-4/30/22	-	-	-
Positive screen	34	11.7 per 100,000	76	13.0 per 100,000	110	12.6 per 100,000
Confirmed MPS II	3	1.0 per 100,000	8	1.4 per 100,000	11	1.3 per 100,000
Unresolved case due to diagnostic uncertainty	16	5.5 per 100,000	3	0.5 per 100,000	19	2.2 per 100,000
False positive (including pseudodeficiency)	12	4.2 per 100,000	62	10.6 per 100,000	74	8.5 per 100,000

Unresolved case due to lost to follow-up/parental refusal/pending case	3	1.0 per 100,000	2	0.3 per 100,000	5	0.6 per 100,000

New York

New York has been screening for MPS II as part of the ScreenPlus pilot panel since May 2021. First tier testing is I2S enzyme analysis by LC-MSMS, second tier is DBS GAG analysis, and third tier is *IDS* sequencing. In email correspondence with a ScreenPlus research program manager, a total of 5,970 samples have been screened through February 28, 2023 and there were two samples that went to second and third tier testing for MPS II. One case was referred as an abnormal screen and ultimately determined to be a false positive. The other case had normal third tier testing and never reached call out. Further details were not provided.

Taiwan

Taiwan has been screening for MPS II since August 2015 using a tandem mass spectrometry-based enzyme assay with no second-tier analysis in the NBS pipeline. Summary data is presented in Table 4 below. Birth prevalence of MPS II in Taiwan is higher than what has been identified in US states through newborn screening, though this difference was more pronounced prior to US newborn screening-based birth prevalence numbers.

Table 4. Taiwan MPS II Newborn Screen Experience[5]

Category	n	Incidence per 100,000
Total newborns screened	548,624	-
Timeframe	8/2015 - 4/2022	-
Positive screen	202	36.8 per 100,000
Confirmed MPS II (Group 1)	10	1.8 per 100,000
"Suspected MPS II" or pseudodeficiency (Group 2)	151	27.5 per 100,000
False positive (Group 3)	41	7.5 per 100,000
Unresolved case due to lost to follow-up/parental refusal/pending case	0	1.0 per 100,000

Confirmatory Testing and Diagnosis

Is definitive diagnostic or specialty testing available to confirm or diagnose positive screens? How well does it work?

Clinical confirmatory testing must be performed following an abnormal newborn screen for MPS II. Infants with an abnormal screen should have a whole blood or DBS sample sent for iduronate-2-sulfatase (I2S) analysis by fluorometric assay as well as a random urine sample (early morning sample preferred) sent for glycosaminoglycan (GAG) analysis. There are several national reference laboratories who offer these tests.

To rule out multiple sulfatase deficiency, at least one other sulfatase should be analyzed and demonstrated to be normal. Several of these enzymes can also be performed on a whole blood or DBS sample and are available through several national reference laboratories, including arylsulfatase

A (metachromatic leukodystrophy), arylsulfatase B (MPS VI/Maroteaux-Lamy syndrome), galactosamine (N-acetyl)-6-sulfate sulfatase (MPS IVA/Morquio syndrome), heparin sulfate sulfatase (MPS IIIA/Sanfilippo A syndrome), and N-Acetylglucosamine-6-sulfatase (MPS IIID/Sanfilippo D syndrome).

IDS sequencing is indicated if enzyme analysis and urine GAGs are consistent with disease or to confirm pseudodeficiency status if I2S enzyme is deficient and urine GAGs are normal. Clinicians may choose to complete *IDS* sequencing in this tiered fashion or concurrent to the initial enzyme and GAG analyses; this approach will differ by clinician preference and access to genetic testing. If *IDS* sequencing is negative in an infant with biochemical evidence supporting a diagnosis of MPS II, the methodology of the sequencing test and need for additional genetic testing should be considered, given that 10-20% of MPS II patients have been shown to have variants other than point mutations and small insertions/deletions, including inversions, whole gene deletions, and complex genomic rearrangements.[20]

Treatment for MPS II

What are the standard treatments for MPS II and what is the evidence for their effectiveness?

Enzyme replacement therapy

The most commonly used available treatment for MPS II is an enzyme replacement therapy (ERT) called idursulfase (Elaprase; Takeda Pharmaceutical Company Limited) that was approved by the FDA in 2006. The recommended dosage regimen is 0.5 mg per kg of body weight, administered once weekly as an intravenous (IV) infusion. From the Elaprase website: "ELAPRASE has been shown to improve walking capacity in patients 5 years and older. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long-term clinical outcome; however, treatment with ELAPRASE has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age."[21] A significant limitation of idursulfase is that it does not cross the blood-brain barrier so it cannot impact GAG accumulation in the brain or progression of central nervous system disease.

The pivotal idursulfase trial enrolled 96 participants who were between 5-31 years of age at enrollment and diagnosed between the ages of less than 1 year and 23 years of age. The study demonstrated that weekly infusions of idursulfase produced significant clinical benefit based on improvements in the two-component composite endpoint (six-minute walk test (6MWT) distance and %-predicted forced vital capacity (%FVT)) compared to placebo, in addition to decreasing urinary GAG levels and reducing liver and spleen volume.[22] Participants also had increased elbow mobility and in a two-year open label follow-up study all participants had improvements in shoulder range of motion,[23] though no other joints were improved by treatment. Approximately 50% of participants had positive IgG anti-idursulfase antibodies and while this attenuated the reduction in urine GAG levels, it did not increase adverse infusion-related reactions or impact clinical outcomes. Based on the age at diagnosis and age at enrollment of the participants, this study cannot be used to consider the impact of treatment for a newborn screen population.

As summarized by the ACHDNC review, the following publications report outcomes for patients started on ERT before one year of age:

A multicenter international 52-week open-label study included 27 out of 28 initial subjects with a mean age of diagnosis of 3.5 years (range: 0.2-6.5 years).[24] More than half (57.1%) had at least one infusion-related adverse event that were managed clinically without the need to end ERT therapy. Nineteen subjects developed anti-idursulfase antibodies. Insufficient evidence was provided to evaluate safety or effectiveness by age of diagnosis or treatment.

Another 52-week open-label study in Korea enrolled 6 subjects diagnosed before 4 years of age, including one diagnosed < 1 year (around 2 months) who began treatment around 4 months, one diagnosed at 1.2 years who began treatment at 1.3 years, and one diagnosed at 1.7 years who began treatment at 2.4 years.[25] One subject had infusion-related reactions that were treated with antihistamines and four subjects had antidrug antibodies at least once. All subjects had lowered urine GAG levels throughout the treatment period. All subjects had an increase in height and weight, although the sample size is insufficient to evaluate differences. Four of the subjects had severe MPS II. The report states that there was no significant loss or gain of developmental milestones over the study period.

One retrospective study of cardiovascular outcomes evaluated 48 subjects in Taiwan with MPS II, including 7 subjects referred from newborn screening.[26] None of the subjects identified through newborn screening had abnormal echocardiographic findings at baseline compared to abnormal findings in the rest of the cohort. Insufficient evidence was provided in this report to directly compare echocardiographic findings at age-matched points for those identified through newborn screening.

One case series describes a convenience sample of 8 infants diagnosed with MPS II based on family history of MPS II (n=7) or MPS I (n=1) and who received ERT from 10 days to 6.5 months of age.[27] Two of the eight infants discontinued ERT after 6 and 10 weeks after receiving a HSCT. Post-treatment outcomes are described for the six infants who continued ERT, with follow-up ranging from 20 months to 5.5 years at the last visit, and all were noted to be continuing ERT at the time of the report. These cases are summarized in the following table:

Table 5. Summary of Eight Subjects Receiving ERT <1 year of age

Factor Leading to Diagnosis	Age at MPS II Diagnosis	Clinical assessment at TX baseline	Age at Treatment Treatment follow up
Family history	Prenatal	– Subtle lumbargibbus – Lumbar x-ray (L3-L5) abnormality – Echocardiogram - normal	**ERT Initiation at 10 days of age** ERT for 6 weeks, then HSCT at 70 days (no more ERT) – Development has progressed – Maternal report doing much better than older brother at same age.
Sibling diagnosed during pregnancy	1 week	– Ultrasound - Ventriculomegaly in the fetus – At 6 hours old, respiratory distress – Hepatomegaly – Lumbar kyphosis	**ERT initiation at 6 weeks** ERT duration at follow up– 2 years – Physical exam completely normal except somewhat broad forehead with mild frontal bossing – Development – normal, age appropriate

Family history	6 weeks	– Cognitive function (Bayley's scale) – normal – Echocardiogram –normal – Diastasis recti abdominis – Hepatosplenomegaly – Umbilical hernia	**ERT initiation at 8 weeks of age** ERT duration 10 weeks, then received HSCT Follow up at 18 weeks: – Liver palpable – No developmental delays – Mild left convex scoliosis but no dysostosis multiplex. – No hearing loss.
Family history	Birth	– Failed routine hearing test – Mild frontal bossing – Slightly coarse facial features at 2 weeks – Hepatosplenomegaly – Mild lumbar kyphosis at L2 (imaging only, not clinically)	**ERT initiated at 10 weeks** At 7 months of age: – hearing loss treated with tubes and aids At 18 months of age: – Mild coarse facial features – Mild joint stiffness – Exam otherwise unremarkable – Parents report development much better than affected brother – Bayley's scale – gross motor and expressive language age appropriate, self-help, fine motor, receptive language at 6-9-month delay.
Family history	4 weeks	– Hypotonic at birth – pneumonia in first 13 days – Exam at 11 weeks: – Mild coarse facies – Diastasis recti abdominis – Hepatomegaly – Umbilical hernia	**ERT initiated at 11 weeks** At 5.5 years: – Normal growth – Very minor joint range of motion restrictions – Echocardiogram – mild aortic valve stenosis, valve insufficiency, normal left ventricular function
Family History of MPS I (but not MPS II)	11 weeks	– Hydrocele – Inguinal hernia – Hepatomegaly – Congestive heart failure	**ERT initiation at 12 weeks of age** ERT duration at last follow up– 30 months – Cardiac symptoms worsening At 1 year: – Above average growth (height, weight, head) – Normal motor development – Absence of hepatosplenomegaly – Normal joint range of motion At 16 months: – Echocardiogram showed sustained dilated cardiomyopathy
Family history	1 week	– Mild frontal bossing – Chronic otitis media with effusion scapular flaring with shoulder abduction	**ERT initiated at 6 months of age** – Development average-above average on Mullen Scales at 6 months and 2 years At 4 years: – Growth parameters normal – Slightly coarse facies, with frontal bossing, receding anterior hairline, eyelid puffiness – Tapering fingers, reduced extension of the digits at the joint – No evidence of macroglossia, organomegaly, spine deformities, hearing loss, or hernias. – Reports he is developing normally and keeping up with peers.

Family history	5 months	– Mild coarse facies – Small, thickened ears hepatomegaly – Gibbus – Bilateral foot adduction – Frequent upper respiratory infections – Recurrent otitis media	**ERT initiated at 6.5 months of age** At 3.5 years: – Liver size normalized – Echocardiogram remains normal – Gibbus deformity progressed at age 2, stabilized since age 3 years. – Slight contractures of the joints in upper extremities by 3.5 years. Carpal tunnel surgery at 3.5 years. – Neurodevelopmental evaluation at 3 years 8 months – (Cognitive Adaptive Test) Age Equivalent 30 months, visual-motor skills and language quotient of 68 and 75.

The following retrospective studies identified by the ACHDNC review compare outcomes for sibships with earlier and later ERT initiation, as summarized in table format from the ACHDNC review:

Table 6. Sibling Case Reports with ERT Initiation < 7 Months of Age in the Younger Sibling

Reference	Older sibling (O)	Younger sibling (Y)
Publication: Tajima et al. (2013)[28]	O (M) MPS II diagnosis at 2 years 7 months **ERT initiation at 3 years** ERT duration 34 months Symptoms Pre- / Post-ERT (34 months) – Coarse facial features – yes / stable – Thick and coarse skin – yes / improved – Hepatosplenomegaly – yes/improved – Cardiac dysfunction – yes/stable – Problems in joints – yes/stable – Dysostosis multiplex -yes/slowly progressive – Exudative otitis media -yes/persistent – DQ 49/42	Y (M) MPS II diagnosis <1 month (just after O's diagnosis) No clinical symptoms **ERT initiation at 4 months** After 32 months of ERT – Course facial features – none – Thick, coarse skin – no/no – Hepatosplenomegaly -none – Cardiac dysfunction – none – Problems in joints – yes/stable – Dysostosis multiplex -yes/slowly progressive – Exudative otitis media – no/yes – DQ Baseline 89, Post ERT 74 – some decline
Publication: Tylki-Szymanska et al. (2012)[29]	O (F) MPS II Diagnosis at 5 years Clinical symptoms – Coarse facial features - mild – Joint range of motion – decreased (especially elbow, hip and ankle joints) – Slight hepatomegaly and a mild umbilical hernia – Cognitive retardation, IQ of 50 **ERT initiated at 7.5 years** Post 3 years ERT (10 years of age): – MPS II disease progression – Significant joint contractures – Cardiac disease – worsened – Hepatomegaly and short stature – Cognitive decline, IQ of 24	Y (M) MPS II diagnosis at 14 days (twin brother was healthy) No clinical symptoms **ERT initiated at 3 months** After 3 years ERT: – Coarse facial features - none – Echocardiography -normal – Liver and spleen size – normal – Cardiac function – normal – Joint range of motion – normal – Dysostosis multiplex - none – Intelligence – normal (IQ 98 vs. 118 for his twin brother).

Publication: Tomita et al. (2021)[30]	O (M) MPS II diagnosis at 2 years **ERT initiated at 2 years** – Post ERT follow up of 5 years: – Inguinal hernia and adenoid vegetation – Hepatomegaly – Joint stiffness – Skeletal deformity – Language acquisition – delayed, worsens – Mild ventriculomegaly and brain atrophy – Attention and behavioral problems – Cognitive and motor function - impaired – Ambulation impaired, worsens (Able to go up and down stairs with a handrail, later unable to use stairs) – Cognitive impairment, DQ 53 at 4 years	Y (M) MPS II diagnosed prenatally **ERT initiated at 1 month** (switched to pabinafusp alfa at 1 year 11 months) <u>After ERT follow up 5 years:</u> – Inguinal hernia – Slight hepatomegaly – Atrial septal defect detected on echocardiography – No somatic symptoms – Cognitive function – normal (DQ of 104 at 3 years, 11 months)
Abstract: Quadri et al. (2022)[31] (3 sibling pairs)	3Os – **ERT after diagnosis at 21-36 months** – Post ERT 2-3 years – Persistent coarse facial features – Persistent generalized stiffness – Cardiac involvement (aortic root dilatation, thickened mitral & aortic valves) in 2 of 3 Os – Hepatosplenomegaly, resolved post ERT – Persistent middle ear effusions or PE tubes – Persistent developmental or speech delays	3Ys- **ERT at 1-2 months** <u>After ERT 2-3 years</u> – Coarse facial features – none – Joint stiffness - none – Hepatosplenomegaly – none – Echocardiogram – normal – Physical exam - normal – Speech – mild delay in 2 of 3
Abstract: Vashakmadze et a l.(2021)[32]	O – Attenuated MPS II diagnosed at 2.9 years Presenting symptoms: – Coarse – facial features – Dysostosis multiplex – mild – Cardiac dysfunction (mitral and aortal incompetence) – Hepatomegaly and splenomegaly – Otitis adenoid hypertrophy **ERT initiated at 4 years** <u>After ERT at 11 years</u> – Claw-hand deformity – mild – Persistent multiplex dysostosis – Cardiac dysfunction (mitral and aortal incompetence) – Carpal tunnel syndrome – Cardiomyopathy – Cognitive function – normal	Y – Attenuated MPS II diagnosed at 1 month Presenting symptom: – Mild muscle dystony **ERT initiated at 5 months** <u>After ERT at 5 years:</u> – Slight coarsening face – Mild splenomegaly – Slight thickening of the mitral valve

Subsequent to the publication of the ACHDNC review, a retrospective chart review study was published examining the impact of the timing of enzyme replacement therapy initiation and cognitive impairment (CI) status on outcomes for patients with MPS II. It found that affected individuals who started ERT before age 3 had later documentation of somatic disease manifestations, lower symptom burden, and reduced health resource utilization (HRU) than those who started ERT after age 3.[33] They also found a higher symptom burden and HRU in individuals with CI than those without CI, consistent with individuals with central nervous system involvement having more severe disease. The study asserts their findings "support recommendations for ERT to be administered as early as possible in the disease course to maximize halting or slowing down the progression of MPS II disease manifestations." It should be noted

that four of the six authors were employees of Takeda Development Center Americas, Inc. at the time of the analysis.

ERT Takeaways:

- Idursulfase does not cross the blood-brain barrier
- Early initiation of ERT has a significant benefit in preventing somatic manifestations of MPS II
- Cognitive outcomes with early initiation of ERT are less well understood and at times conflicting; additional data is needed
- While development of anti-idursulfase antibodies is common, it does not impact clinical outcomes or increase infusion-related adverse events

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is shown to increase I2S enzyme activity and eliminates the need for enzyme replacement therapy but carries with it a risk of mortality. And unlike in MPS I, where HSCT is the preferred form of treatment for the most severe form of the disorder because it can preserve neurocognition when performed before the age of 2 and prior to cognitive involvement,[34] the benefit of HSCT in MPS II is under debate.

A 2018 study from Japan evaluated the efficacy of HSCT for MPS II prospectively in 27 new cases of HSCT, 51 new cases of ERT, and 15 untreated cases and retrospectively by comparing outcomes with 119 reported cases of HSCT from 19 published studies published between 1984 and 2016.[35] They did note that most HSCT cases received ERT before their transplant. They report that although three of 27 new cases of MPS II patients treated with HSCT had acute graft versus host disease (GvHD), all patients survived the treatment and showed clinical improvements. From their review of the previously published cases, nine died of transplant-associated complications, resulting in 8% mortality rate among the 119 published cases from 1984 to 2016. While ERT patients showed progressive brain deterioration with age, HSCT treated patients showed either stable or improved brain lesions over time (graded across four distinct categories: I, cystic or cribriform lesions; II, white matter signal changes; III, ventricular enlargement; IV, brain atrophy). The study suggests that several factors can improve the impact of HSCT, namely timing of transplantation (age, clinical severity, and stage), primary pathology, graft source (HLA matching, donor source), preparative regimen, and well-trained institutes.

The ACHDNC review summarizes several studies as follows:

> A recently published abstract describes 36 subjects in the HOS from 2018 who received HSCT, of whom 13 died.[36] One study in Japan described 26 subjects with MPS II who underwent HSCT, with a five-year survival rate from 1990-2003 of 12.5%.[37] Although there was a decrease in urinary GAGs, the heterogeneity of the study population, treatment, and timing of outcomes precludes further analysis. A subsequent report suggested that there was a delayed decrease in the ability of individuals to complete activities of daily life for subjects receiving early HSCT versus early ERT or later ERT.[38] However, there are many confounders that limit this analysis. Another report from Japan with overlapping subjects found that growth was similar for 18 subjects who received HSCT, 6 of whom also received ERT, compared to those who were treated with ERT alone.[39] Insufficient information is available to further explore the potential benefits of HSCT or HSCT and ERT by age.

A case series of three subjects describes a subject diagnosed at 16 months of age who received ERT and then HSCT at 22 months. At nearly 6 years of age, the report states, "His regular yearly check-ups···have shown unrefined and immature, nonetheless qualitatively normal motor skills. There is still a developmental cognitive and speech delay; he is hyperactive and has a short attention span."[40] The somatic manifestations were not described. Another case report describes a subject diagnosed prenatally and transplanted at 70 days of age who demonstrated normal growth, mild dysostosis multiplex, and hearing loss with an IQ of 47.[41]

HSCT Takeaways:

- Early HSCT is not the gold standard treatment for MPS II as it is for MPS I
- Several factors can improve the impact of and lower the risk of mortality from HSCT, namely timing of transplantation (age, clinical severity, and stage), primary pathology, graft source (HLA matching, donor source), preparative regimen, and well-trained institutes.
- Existing clinical outcomes data do not clearly delineate benefits of HSCT over ERT

What are the emerging treatments for MPS II?

No alternative treatments for MPS II are currently FDA-approved, though several modalities are in varying stages of development, outlined below.

Intracerebroventricular ERT

Idursulfase beta (Hunterase ICV; GC Pharma) is a recombinant form of I2S that is delivered via intracerebroventricular (ICV) administration, which allows it to access the central nervous system directly. Data from the phase I/II study of Hunterase ICV demonstrated a 70% reduction of heparan sulfate concentration in the CSF at week 100 of treatment and an increase in developmental age of 5.1 months in all but one patient compared to historical controls.[42] Hunterase ICV received regulatory approval in Japan and Europe in 2021 but is not currently FDA approved.

IV ERT

Pabinafusp alfa (JR-141/IZCARGO®; JCR Pharmaceuticals) is an investigational drug consisting of human iduronate-2-sulfatase fused to an anti-human transferrin receptor (hTfR) antibody, which allows for successful delivery across the blood-brain barrier. All patients in the phase II, III and extension studies showed decreased HS in CSF and improvement or at least stabilization in age-equivalent scores across several standardized neurocognitive assessments, as well as subjective improvements speech, motor functions, and behaviors. Liver and spleen volumes significantly decreased in ERT naïve patients and decreased by about 5% in patients who were switched from conventional ERT to pabinafusp alfa.[43] Pabinafusp Alfa received regulatory approval for use in Japan in March 2021 under the brand name IZCARGO®. A phase III clinical trial of JR-141 is currently underway in the US, Europe, and Brazil.[44] At this time, IZCARGO® is not FDA approved but the FDA granted it Rare Pediatric Disease Designation (RPDD) in December 2022, which means that the sponsor may be entitled to receive a pediatric priority review voucher if the drug is initially approved for that rare disease.

DNL310 (Denali Therapeutics) is an investigational ERT consisting of I2S linked to a proprietary enzyme transport vehicle (ETV) engineered to cross the blood-brain barrier via human transferrin receptor-mediated transcytosis in the brain. Phase 1/2 trial data was presented at the 2022 SSIEM conference on 27 participants, all but one of whom had severe MPS II. Data show "rapid and sustained normalization to healthy levels of CSF heparan sulfate and improvements in biomarkers of lysosomal function consistent

with durable central nervous system activity." Safety has been similar to standard of care (idursulfase). Standardized assessments of behaviors, cognitive skills, physical ability, and daily living skills are reported to show improvement or stabilization for most participants across all domains since entering the Phase 1/2 study.[45] A Phase 2/3 clinical trial, called COMPASS, is currently underway and will randomize children with neuronopathic and nonneuronopathic MPS II 2:1 to receive either DNL310 or idursulfase to assess efficacy and safety.[46] DNL310 received Fast Track designation from the FDA in March 2021, which is an FDA process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need.[47]

Gene Therapy

REGENXBIO Inc. is currently recruiting a phase I/II/III CAMPSIITE™ trial of RGX-121, an AAV9 vector gene therapy.[48] The company reported at the 2023 WORLDSymposium that 15 patients had been treated across three dose levels and the therapy was well-tolerated with no drug-related significant adverse events across all dose levels. All patients showed dose-dependent reduction of CSF GAGs and I2S protein concentration in the CSF went from undetectable to measurable in a majority of patients.

Homology medicines is currently recruiting a phase 1, open-label, sequential ascending dose-escalation study designed to evaluate the safety and efficacy of a single IV infusion of investigational gene therapy HMI-203.[49]

Sangamo Therapeutics has concluded recruitment for a phase 1/2, open-label, ascending dose study to assess safety and tolerability of SB-913, a rAAV2/6-based gene therapy[50] and rolled all nine subjects over to a non-interventional long-term follow-up study.[51] In their 2022 publication, the authors conclude, "These early results of first-generation ZFN *in vivo* genome editing studies demonstrated a favorable safety profile and evidence of low-level *in vivo* genome editing in the liver but no long-term sustained enzyme expression in blood."[52]

What are the current care and treatment guidelines for MPS II, and do they address pre-symptomatic detection?

No evidence-based formal guidelines have been published for MPS II. The ACMG commissioned a Delphi study, which published the clinical practice resource, "Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi-derived practice resource of the American College of Medical Genetics and Genomics (ACMG)" in 2020. While newborn screening was already taking place at the time that this review was commissioned, the newborn screening diagnostic scenario is not specifically considered in the report. The final recommendations of this Delphi review are:

1. All individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting ERT, prior to showing signs or symptoms.
2. Individuals with signs or symptoms with either attenuated or severe MPS II warrant ERT.
3. Individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant ERT.
4. Home infusions may be considered for those with early disease, easily managed ERT infusion reactions, and a stable home environment.
5. Individuals receiving ERT who have developed allergic reactions that cannot be controlled by standard therapies or immunomodulation should have ERT discontinued.
6. Pressure equalizing (PE) tubes and hearing aids are useful therapies.

7. Clinical evaluation of liver and spleen size are recommended for judging clinical effectiveness of treatment, with optional use of imaging modalities (ultrasound or MRI of the abdomen) to follow organ size. Pulmonary function tests (PFTs) are recommended if the individual can reliably perform them, but there are concerns on the utility of the 6 - minute walk test (6MWT). Lab studies of GAGs are recommended, as well as antibodies to ERT to assess infusion reactions. Finally, neuropsychology testing is recommended for following disease progress.[53]

The technical expert panel (TEP) convened for the ACHDNC review "recommended that all infants diagnosed with newborn screening should be offered ERT after diagnosis regardless of the expected phenotype." They based this recommendation on the following statements:

- There is greater accumulation of GAGs when MPS II is untreated. This accumulation leads to more significant and progressive somatic involvement regardless of phenotype.
- ERT will not reverse the damage caused by the accumulation of GAGs. Early initiation of ERT can decrease this accumulation and therefore prevent or at least slow irreversible damage.
- Although a significant amount of ERT does not cross the blood-brain barrier, all individuals, regardless of phenotype, benefit from preventing the somatic manifestations of MPS II. Preventing these somatic manifestations could also lead to better developmental outcomes, regardless of phenotype, by preventing sensory deficits (e.g., hearing impairment), preventing spine involvement, decreasing sleep apnea, and through improved mobility.

Potential Benefits and Harms of Newborn Screening for MPS II

What are the benefits and harms (not related to treatment) that could result from newborn screening and early diagnosis, both to the infant and to family members?

Biochemical pseudodeficiency

While parents may experience anxiety at any form of an abnormal result, significant anxiety or unknowns may be avoided by waiting to notify the PCP and medical consultant of an abnormal screen with low I2S enzyme until results of second-tier GAG analysis are available. In Missouri, NBS cases with normal GAG analysis are not being referred unless I2S enzyme is below a fail-safe cutoff. This likely means that not all cases of pseudodeficiency are being identified, but as a non-disease this seems reasonable. This reduces resource utilization and strain on the system, as well as spares parent anxiety at abnormal results when a call-out can be prevented. Without second-tier GAG analysis or in cases with equivocal results, *IDS* sequencing will often be necessary to determine affected vs pseudodeficiency. The longer timeframe needed to complete molecular testing may increase family uncertainty and stress as they wait to learn whether their child is affected or not.

Follow-up of cases with novel variants or indeterminate results

All programs currently performing MPS II newborn screening have cases they consider unresolved due to equivocal data. In fact, the ACHDNC review used decision analytic modeling to estimate population impact of newborn screening for MPS II and while they estimated that NBS would identify a greater number of cases compared to clinical identification, the number of cases estimated to be diagnosed with MPS II by NBS would be roughly equivalent to the number of unresolved cases.

Missouri considers 16 cases (47% of their screen positive cases) diagnostically uncertain due to finding an *IDS* VUS, though many cases had normal confirmatory urine GAGs. Illinois' three unresolved cases (4% of screen positive cases) have I2S enzyme activity in the same range as affected infants; two of the

three have elevated HS and a novel *IDS* variant and the third has had all normal biochemical screening and an *IDS* variant that has been observed in two other infants classified as having pseudodeficiency.

Each newborn screen program and clinical team may take a different approach but will need to consider what to do with cases like these. One argument would be to recommend regular follow-up (Taiwan suggests follow-up every 6-months for their uncertain cases) to closely monitor for emerging signs or symptoms and be able to institute treatment as soon as possible. Another argument may be to avoid overmedicalization and limit use of healthcare resources and dollars by minimizing potentially unnecessary medical care for cases not clearly proven to be affected.

Identification of carriers

Review of the literature did not find any cases of asymptomatic female carriers identified by newborn screening. Rarely affected female cases are identified, but these girls are found to have skewed X inactivation or chromosomal anomalies.

Family testing

As an X-linked disorder, identifying an affected individual may result in identification of additional at-risk males – either older siblings or extended relatives in the maternal lineage born before MPS II was added to the newborn screen or in a state not yet screening for MPS II. In a 2013 publication (prior to newborn screening for MPS II), approximately a quarter of affected individuals were found to have de novo variants.[12] If this holds true in the newborn screen population, it implies that the majority of affected infants will have a carrier mother, opening the door to cascade evaluation and testing in the family. Diagnosing at-risk individuals can give them access to treatments and maximize health outcomes. Additionally, diagnosis of asymptomatic or mildly affected family members may provide a reassuring prognosis for the individual diagnosed by newborn screening.

Lack of care and treatment guidelines

No formal evidence-based care and treatment guidelines exist for MPS II due to its rarity. With the natural history and presentation in neonatally-diagnosed individuals relatively unknown, providers may struggle to decide on a reasonable schedule of ongoing assessments, as well as when or whether to offer treatment, especially for those infants with unclear phenotypes or equivocal results (for instance due to *IDS* VUS).

NWRNBS Program Impact Assessment

Positive Screen Referral and Diagnosis based on IL and MO NBS Data

Assuming a birth rate of 40,000 per year in Oregon and extrapolating from the combined incidence data in Table 3, 5.04 positive screens would be expected to be called out per year with less than one true diagnosis per year.

Fiscal Analysis

The Oregon State Public Health Laboratory (OSPHL) newborn bloodspot screening program submitted a proposal titled, "Implementation of New Conditions to the Oregon Newborn Screening Panel", for the HRSA NBS Propel funding opportunity (HRSA-23-065). The proposal addresses two distinct goals: creation of a comprehensive implementation guide for new conditions and initiation of screening for mucopolysaccharidosis type II (MPS II). Relevant lab costs from the grant proposal budget are outlined in Table 7, below. Equipment reflects the cost to lease an additional mass spectrometer for MPS II screening. Each year's increase in costs is due to inflation. Supplies reflects the total cost of reagents and supplies needed for MPS II screening. Years one and two are lesser amounts because the assay will be under validation. Costs in years four and five increase due to inflation. Additional costs for second-tier GAG testing were not included at the time the budget analysis was performed. If the requested $1,000,000 grant funding for laboratory testing is received, it would cover approximately 70% of the cost of screening within the first five years. The remaining 30% will need to be covered by the program. After the funding ends (if awarded), the cost will be roughly $350,000 per year, although the mass spectrometer (equipment cost) could be used for other testing within the laboratory.

Table 7. NWRNBS Grant Proposal Budget, relevant portions

Budget Item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Equipment	$ 139,452	$ 143,636	$ 147,945	$ 152,383	$ 156,954	$ 740,370
Supplies	$ 19,207	$ 54,695	$ 192,066	$ 197,828	$ 203,763	$ 667,559

At the contractor's request in preparing this document, Mayo Clinic Laboratories (MCL) provided the following information and fees for relevant second-tier testing options (Table 8). Estimated annual volumes were calculated by MCL and not reexamined by the contractor.

Table 8. Second-tier costs from Mayo Clinic Laboratories

Test name - description (MCL test ID)	Estimated Annual Volume	Cost per test
Mucopolysaccharidosis, Blood Spot (MPSBS)	30	$62.00
Hunter Syndrome- MPS-II (IDS Gene), Full Gene Analysis - full gene sequencing of the *IDS* gene with a turnaround time of approximately 2 weeks (MPS2Z)	20	$1,000.00
G145 - Hereditary Custom Gene Panel Tier 1 (Bill Only) - full gene sequencing and copy number variant analysis of the *IDS* gene with a current turnaround time of approximately 4 weeks. (CGPH)	20	$1,350.00

Regarding clinical contract costs, the NWRNBS estimates 13.3 screened positive cases per 100,000 for MPS II. Estimated annual screen positive case count was not reexamined by the contractor. The OHSU clinical program provided the following cost assessment for that volume of cases (Table 9). The first year is higher to allow the program to update the clinical follow-up care algorithms as well as the long-term follow-up database.

Table 9. OHSU Clinical Contract Costs

Budget Item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Clinical Contract	$ 17,450	$ 12,726	$ 13,108	$ 13,501	$ 13,906	$ 70,691

Availability of medical consultants

The program has four medical geneticists and two nurse practitioners who serve as metabolic medical consultants. This is expected to be adequate for coordination of the first steps following notification of an abnormal newborn screen, namely providing guidance to the PCP on what confirmatory testing should be ordered or recommendation that infant should be referred to the medical genetics clinic. However, medical consultants are only located in Portland, so access may be an issue for those infants with severely abnormal lab values or concerning clinical status at the point of callout who will require urgent in-person assessment. Telemedicine is unlikely to be appropriate for urgent MPS II assessments but may be utilized for education and initial coordination of care for asymptomatic infants.

Capacity and expertise to implement and maintain testing and reporting

The state lab will need to lease an additional mass spectrometer for MPS II screening, but the cost for this is already written into the proposed 5- year grant budget. No additional staff will need to be hired for MPS II screening as it would be multiplexed with the current assay for lysosomal storage disorders.

Capacity and expertise to implement and maintain follow-up and education for providers and parents

The state lab has a document bank of recommendation letters by NBS indication that have been written/vetted by the medical consultants and approved by OHA. These letters are sent to the primary care provider or NICU provider by fax to provide information on the NBS indication and recommended next steps. The program has recently developed high-quality educational reference materials for medical professionals for other conditions on the panel and intends to develop similar materials for MPS II and all new conditions added to the panel.

Assessment of the impact of implementing screening for NWRNBS program partners (readiness, barriers, etc.)

New Mexico

On April 30, 2023 and May 8, 2023, the contractor reached out to a program partner in New Mexico to ask the following questions regarding implementation of MPS II screening:

1. What impact would implementation of newborn screening for MPS II have on your region?
2. What implementation activities would you need to complete before screening for MPS II could begin?

3. Are there any special considerations for infants identified to have severe or neuronopathic MPS II regarding the transition from OR newborn screen and diagnostic confirmation to NM clinical care?

At the time of submission of this document, no response has been received.

While a response was not received from the New Mexico program partner, Oregon clinical consultants shared that they feel an appropriate transition of care process already exists with conditions already screened by NWRNBS and do not anticipate significant differences or concerns using this process for MPS II. Additionally, a second medical geneticist will reportedly be joining the existing program partner in New Mexico which will be expected to increase capacity to manage NBS-diagnosed infants.

Access to Care and Equity of Treatment and Follow-Up

Is this condition on the Prioritized List as determined by the Oregon Health Evidence Review Commission?

Oregon's legislature approved funding for lines 1-472 of the Oregon Health Evidence Review Commission's (HERC) February 1, 2023 Prioritized List of Health Services. MPS II appears on Lines 60, 71, 292, 345 and 377 and is therefore on the funded region of the Prioritized List as an ancillary service. The Oregon Pharmacy and Therapeutic Committee does not have prior authorization criteria for approving idursulfase for treatment of MPS II. Medicaid fee-for-service, coordinated care organization (CCO), and private insurance criteria may differ from HERC.

Prioritized list locations:
Line: 60
Condition: METABOLIC DISORDERS
Treatment: MEDICAL THERAPY

Line: 71
Condition: NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES (See Guideline Notes 6,129,170 and 229)
Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., G-TUBES, J-TUBES, RESPIRATORS, TRACHEOSTOMY, UROLOGICAL PROCEDURES)

Line: 292
Condition: NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS (See Guideline Notes 6,170,178,205,219 and 226)
Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., DURABLE MEDICAL EQUIPMENT AND ORTHOPEDIC PROCEDURE)

Line: 345
Condition: NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS (See Guideline Notes 6 and 205)
Treatment: MEDICAL THERAPY

Line: 377

Condition: DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELFDIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION (See Guideline Notes 6,38 and 205)
Treatment: MEDICAL THERAPY (SHORT-TERM REHABILITATION WITH DEFINED GOALS)

ICD-10 code: E76.1 Mucopolysaccharidosis, type II
HCPCS: J1743 - Injection, idursulfase, 1 mg

Are experts available to provide treatment?

Yes, metabolic genetics experts are available. The primary metabolic clinic is at OHSU in Portland. OHSU also has outreach clinics twice a year in both Medford and Eugene.

What's the availability and accessibility of care and treatment?

According to the Office of Rural Health, 35% of Oregonians live in rural or frontier communities. Rural is defined as all geographic regions 10 or more miles from a population center of 40,000 people or more. Frontier counties are defined as those with six or fewer people per square mile[54]. For individuals along the north-south I-5 freeway corridor on the west side of the state, there is reasonable geographic access to metabolic genetics centers. However, there are no medical genetics clinics in the central and east side of the state, presenting patients and families with financial, geographic, and logistic barriers to care.

In consultation with two Oregon medical consultants and clinicians, access to ERT is reportedly manageable, but not ideal. The clinical team has long experience with other disorders coordinating orders and care at local infusion centers. Centers who have experience with the condition or drug are preferred, but the clinical program has adapted to providing guidance remotely for new drugs and would do so for initiation of a patient on idursulfase if needed following diagnosis by newborn screening. Transition to home infusion is supported if considered feasible/reasonable on a patient-by-patient basis, depending on clinical status, insurance, access to local home nursing staff, among other factors. The following excerpt from an interview with a medical consultant highlights additional considerations for ERT management (transcription minimally edited for accuracy and clarity):

> **Contractor:** "Are there barriers beyond the geography that you consistently identify for newborn screen follow up?"
>
> **Medical consultant:** "The other barrier that we've had, and I don't know if this is universal, but again, when it comes to infusions because we can't manage everybody ourselves, we have to use other sites. My sense is that the nursing shortage has absolutely decimated some of these infusion centers, so they have like one nurse who's doing everything [like] managing prior authorizations and managing billing, and they're overworked. They're exhausted. There's been a couple of situations where they weren't increasing a weight-based dose on a growing child. And so the child was under dosed chronically and that's hard for us to manage because we don't get the full records of what exactly is being administered. We just send our orders, but it's rife for miscommunication and patients falling through the cracks just in and of itself. When you're coordinating complex care like that which our system is just not built for and it's been really bad in the last two years. And when I talk to people on the ground at those infusion sites, they just say, "We're dying out here." And Oregon is the most medically underserved state. You know we have the fewest per capita hospital beds in America and that certainly doesn't help either, so the nursing shortage… and medical staffing burnout shortage has been really felt here."

Is care and treatment for this condition equitable?

Oregon's geography and high proportion of the population living in rural or frontier communities present barriers to accessible care. These barriers are not unique to consideration of adding MPS II to the newborn screen panel, but as a complex disorder requiring close, careful management (especially if symptomatic and/or on treatment) this will potentially be a more acute problem for this patient population than for another disorder with more straightforward care requirements.

There is concern that treatment for MPS II is not equitable if HSCT is recommended or is the family's preference. To the knowledge of an Oregon medical consultant, the family would be recommended to seek a second opinion from more experienced centers such as in Minnesota. Not all families will be able to travel for this.

Appendix A: Literature Review Technical Methods

Key Questions from ACHDNC Review

The updated literature search followed the same key questions and inclusion/exclusion criteria for published articles that the ACHDNC review used. From the ACHDNC review:

1. What is the natural history and epidemiology of MPS II?

Relevant studies could be cross-sectional, case-control, longitudinal (retrospective or prospective), or randomized. Outcomes could include the incidence or prevalence, timing of the development of signs or symptoms of MPS II, age of diagnosis, age at treatment initiation, quality of life, or mortality. Included studies must include at least 10 subjects with MPS II identified without screening.

The term "natural history" is complex. Traditionally it refers to disease outcomes in the absence of targeted interventions. However, with the availability of ERT, most affected individuals in the United States and many other countries will be offered therapy. Some consider the natural

history to reflect what happens following clinical identification, which now includes targeted treatment. Although the term "natural history" is used throughout this report, information is provided to clarify its use and the implications of the findings.

1. What is the analytic or clinical validity of newborn screening for MPS II?

Relevant studies could be cross-sectional, case-control, longitudinal (retrospective or prospective), or randomized. The studies should include at least 5,000 infants at average risk (e.g., not known to have MPS II), be screened for MPS II in the first month of life, and those with a positive screen should have diagnostic confirmation. Outcomes include sensitivity, specificity, positive predictive value, negative predictive value, reliability, diagnostic yield, or the cost of screening.

2. What are the harms associated with newborn screening for MPS II?

Relevant studies could be cross-sectional, case-control, longitudinal (retrospective or prospective), randomized, case reports, or case series. Studies should include at least one average-risk newborn screened in the first month of life for MPS II. Outcomes include any reported adverse event related to newborn screening for MPS II, including the harms related to false-positive or false-negative screening, or identification of biochemical pseudodeficiency.

3. What are the benefits and harms of MPS II presymptomatic or early treatment compared to when MPS II is usually identified?

Relevant studies had to be longitudinal (prospective or retrospective observational or interventional) with at least 6 months of follow-up after diagnosis or until death if that occurred before 6 months of follow-up after treatment. Studies should include at least one subject diagnosed with MPS II before 12 months of age. Such diagnosis could be based on newborn screening, prenatal diagnosis, or diagnosis based on having an affected family member.

Outcomes could include mortality, organ involvement (e.g., cardiac, liver, lung, spleen), development (e.g., cognitive, gross motor, fine motor), ability to ambulate, endurance, joint mobility, sleep apnea, growth (e.g., height, weight, head circumference), quality of life, physical features, urinary GAG level, or harms related to early treatment, including any adverse event or development of antibodies to I2S.

In addition to these key questions, we also considered contextual questions that provide important background information. These included:

1. What is the distribution of MPS II phenotypes and I2S biochemical pseudodeficiency? What is the relationship between *IDS* genotype and phenotypic expression? What other factors predict phenotypic expression?
2. What clinical practice guidelines are available for the diagnosis and treatment of MPS II? What is the availability of specialists to provide care for newborns identified with MPS II? How accessible is treatment for MPS II?
3. What is the impact of MPS II newborn screening on newborn screening programs, public health programs, or the population? How feasible is MPS II newborn screening in the United States? To what degree are newborn screening programs ready to screen for MPS II?

Literature Search

The following tables list the search terms and results for each of the three databases that were queried to identify articles for the updated literature review. The literature search was conducted for references published from January 1, 2022 to March 31, 2023.

PubMed

Set	Terms	1/1/22 - 3/31/23
#1	(((((((Mucopolysaccharidosis II[MeSH Terms]) OR (Mucopolysaccharidosis type II)) OR (MPS II)) OR (Hunter Syndrome)) OR (iduronate-2-sulfatase deficiency)) OR (I2S deficiency)) OR (idursulfase)) OR (idursulfase[Supplementary Concept])	
#2	English, Humans, 2001-present	
#3	#1 and #2	274

CINAHL

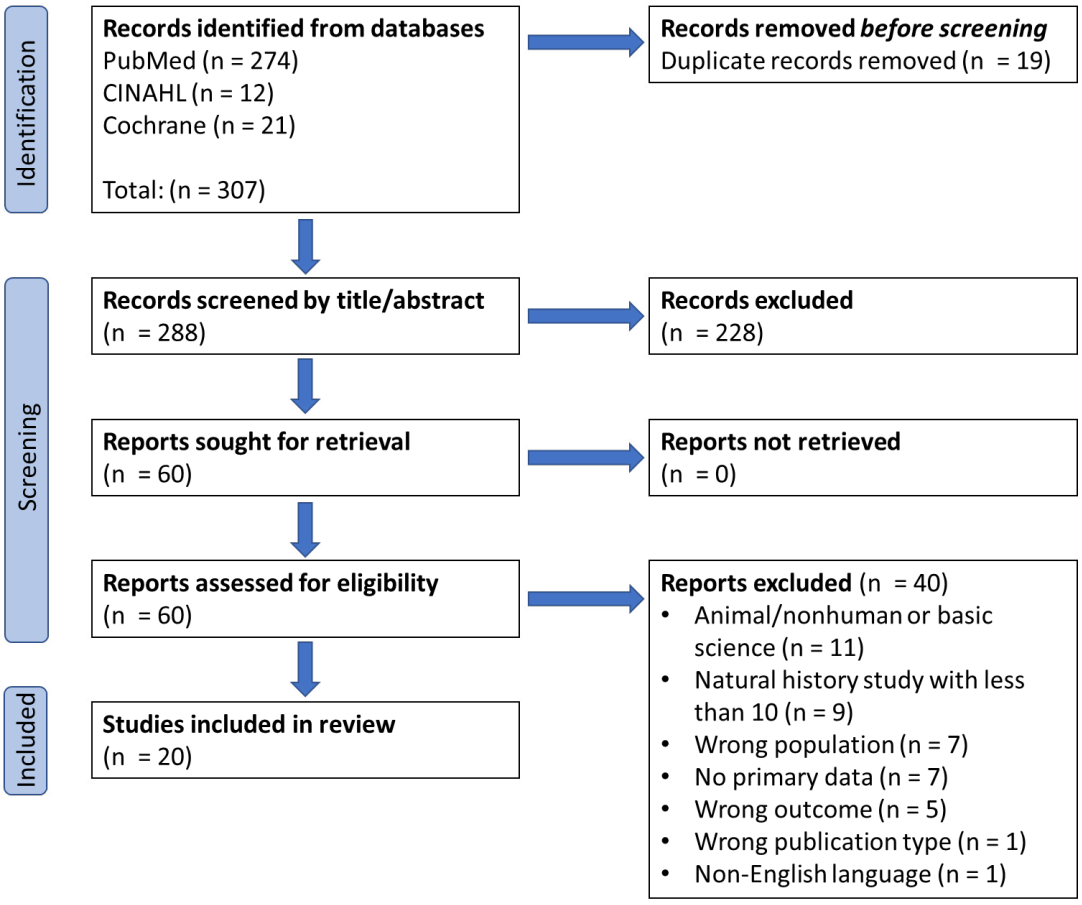
Set	Terms	1/1/22 - 3/31/23
#1	"mucopolysaccharidosis type ii" OR "mps ii" OR "hunter syndrome" OR "iduronate-2-sulfatase deficiency" OR "i2s deficiency" OR "idursulfase"	
#2	Limits: 2001-present, English	
#3	#1 and #2	21

Cochrane Library

Set	Terms	1/1/22 - 3/31/23
#1	"mucopolysaccharidosis type ii" OR "mps ii" OR "hunter syndrome" OR "iduronate-2-sulfatase deficiency" OR "i2s deficiency" OR "idursulfase" *(all additional word variations searched)*	12

PRISMA Diagram

Figure 1. Identification of Studies for Updated Literature Review



Appendix B: Included Articles

Agrawal, Neha, Gaurav Verma, Deepti Saxena, Madhulika Kabra, Neerja Gupta, Kausik Mandal, Amita Moirangthem, et al. “Genotype-Phenotype Spectrum of 130 Unrelated Indian Families with Mucopolysaccharidosis Type II.” *European Journal of Medical Genetics* 65, no. 3 (2022). https://doi.org/10.1016/j.ejmg.2022.104447.

Chuang, Chih Kuang, Yuan Rong Tu, Chung Lin Lee, Yun Ting Lo, Ya Hui Chang, Mei Ying Liu, Hsin Yun Liu, et al. “Updated Confirmatory Diagnosis for Mucopolysaccharidoses in Taiwanese Infants and the Application of Gene Variants.” *International Journal of Molecular Sciences* 23, no. 17 (2022). https://doi.org/10.3390/ijms23179979.

Dias, Bianca M. C., Fernanda C. Lanza, Jenifer Dos Santos, Carolina S. Aranda, Dirceu Solé, Ana Maria Martins, and Gustavo F. Wandalsen. “Mucopolysaccharidosis Patients Have Reduced Functional Capacity.” *Pediatric Pulmonology* 57, no. 2 (February 2022): 538–43. https://doi.org/10.1002/ppul.25750.

Fang, Xiaohua, Chaofeng Zhu, Xiaofan Zhu, Yin Feng, Zhihui Jiao, Huikun Duan, Xiangdong Kong, and Ning Liu. “Molecular Analysis and Novel Variation Identification of Chinese Pedigrees with Mucopolysaccharidosis Using Targeted Next-Generation Sequencing.” *Clinica Chimica Acta* 524 (2022): 194–200. https://doi.org/10.1016/j.cca.2021.11.019.

Herbst, Zackary M., Leslie Urdaneta, Terri Klein, Barbara K. Burton, Khaja Basheeruddin, Hsuan Chieh Liao, Maria Fuller, and Michael H. Gelb. “Evaluation of Two Methods for Quantification of Glycosaminoglycan Biomarkers in Newborn Dried Blood Spots from Patients with Severe and Attenuated Mucopolysaccharidosis Type II.” *International Journal of Neonatal Screening* 8, no. 1 (2022). https://doi.org/10.3390/IJNS8010009.

Kim, Hwa Young, Man Jin Kim, Moon Woo Seong, and Jung Min Ko. “Skewed X-Chromosome Inactivation in a Korean Girl with Severe Mucopolysaccharidosis Type II.” *Annals of Laboratory Medicine* 42, no. 3 (2022): 373–75. https://doi.org/10.3343/alm.2022.42.3.373.

Kor, Deniz, Fatma Derya Bulut, Sebile Kılavuz, Berna Şeker Yılmaz, Burcu Köşeci, Esra Kara, Ömer Kaya, Sibel Başaran, Gülşah Seydaoğlu, and Neslihan Önenli Mungan. “Evaluation of Bone Health in Patients with Mucopolysaccharidosis.” *Journal of Bone and Mineral Metabolism* 40, no. 3 (2022): 498–507. https://doi.org/10.1007/s00774-021-01304-4.

Marucha, Jolanta, Patryk Lipiński, and Anna Tylki-Szymańska. “Efficacy of Enzyme Replacement Therapy on the Range of Motion of the Upper and Lower Extremities in 16 Polish Patients with Mucopolysaccharidosis Type II: A Long-Term Follow-up Study.” *Acta Biochimica Polonica* 69, no. 1 (2022): 251–55. https://doi.org/10.18388/abp.2020_6071.

Muenzer, Joseph, Barbara K. Burton, Paul Harmatz, Luis González Gutiérrez-Solana, Matilde Ruiz-Garcia, Simon A. Jones, Nathalie Guffon, et al. “Intrathecal Idursulfase-IT in Patients with Neuronopathic Mucopolysaccharidosis II: Results from a Phase 2/3 Randomized Study.” *Molecular Genetics and Metabolism* 137, no. 1 (2022): 127–39. https://doi.org/10.1016/J.YMGME.2022.07.017.

“Long-Term Open-Label Extension Study of the Safety and Efficacy of Intrathecal Idursulfase-IT in Patients with Neuronopathic Mucopolysaccharidosis II.” *Molecular Genetics and Metabolism* 137, no. 1 (2022): 92–103. https://doi.org/10.1016/j.ymgme.2022.07.016.

Muenzer, Joseph, Suresh Vijayaraghavan, Margot Stein, Shauna Kearney, Yuna Wu, and David Alexanderian. “Long-Term Open-Label Phase I/II Extension Study of Intrathecal Idursulfase-IT in the Treatment of Neuronopathic Mucopolysaccharidosis II.” *Genetics in Medicine* 24, no. 7 (2022): 1437–48. https://doi.org/10.1016/j.gim.2022.04.002.

Pantel, Tobias, Mona Lindschau, Andreas M. Luebke, Philip Kunkel, Marc Dreimann, Nicole Muschol, and Sven O. Eicker. “Spinal Cord Compression in Patients with Mucopolysaccharidosis.” *European Spine Journal* 31, no. 7 (2022): 1693–99. https://doi.org/10.1007/s00586-022-07168-0.

Ramírez-Hernández, M. A., L. E. Figuera, L. C.Rizo De la Torre, M. T. Magaña-Torres, S. C. Mendoza-Ruvalcaba, L. Arnaud-López, J. E. García-Ortiz, et al. “Mutational Spectrum of the Iduronate-2-Sulfatase Gene in Mexican Patients with Hunter Syndrome.” *European Review for Medical and Pharmacological Sciences* 26, no. 14 (2022): 5115–27. https://doi.org/10.26355/eurrev_202207_29300.

Ream, Margie A, Wendy K K Lam, Scott D Grosse, Jelili Ojodu, Elizabeth Jones, Lisa A Prosser, Angela M Rosé, et al. “Evidence and Recommendation for Mucopolysaccharidosis Type II Newborn Screening in the United States.” *Genetics in Medicine : Official Journal of the American College of Medical Genetics* 25, no. 2 (2023): 100330. https://doi.org/10.1016/j.gim.2022.10.012.

Różdżyńska-Świątkowska, Agnieszka, Anna Zielińska, and Anna Tylki-Szymańska. “Comparison of Growth Dynamics in Different Types of MPS: An Attempt to Explain the Causes.” *Orphanet Journal of Rare Diseases* 17, no. 1 (2022). https://doi.org/10.1186/S13023-022-02486-4.

Sestito, Simona, Giada Rinninella, Angelica Rampazzo, Francesca D’Avanzo, Lucia Zampini, Lucia Santoro, Orazio Gabrielli, et al. “Cardiac Involvement in MPS Patients: Incidence and Response to Therapy in an Italian Multicentre Study.” *Orphanet Journal of Rare Diseases* 17, no. 1 (2022). https://doi.org/10.1186/s13023-022-02396-5.

Stephan, Bruno de Oliveira, Caio Robledo Quaio, Gustavo Marquezani Spolador, Ana Carolina de Paula, Marco Antônio Curiati, Ana Maria Martins, Gabriela Nunes Leal, et al. “Impact of ERT and Follow-up of 17 Patients from the Same Family with a Mild Form of MPS II.” *Clinics* 77 (2022). https://doi.org/10.1016/j.clinsp.2022.100082.

Vollebregt, Audrey A.M., Marianne Hoogeveen-Westerveld, George J. Ruijter, Hannerieke van den Hout, Esmee Oussoren, Ans T. van der Ploeg, and W. W.M.Pim Pijnappel. “Effect of Anti-Iduronate 2-Sulfatase Antibodies in Patients with Mucopolysaccharidosis Type II Treated with Enzyme Replacement Therapy.” *Journal of Pediatrics* 248 (2022): 100-107.e3. https://doi.org/10.1016/J.JPEDS.2022.05.008.

Yee, Karen, Costel Chirila, Eric Davenport, Deirdre Mladsi, Christine Barnett, and William Kronenberger. “Using Projected Retained Ability Score to Assess Cognitive Development in Patients with Neuronopathic Mucopolysaccharidosis II Receiving Intrathecal Idursulfase-IT.” *Molecular Genetics and Metabolism* 132 (2021): S105. https://doi.org/10.1016/S1096-7192(21)00243-2.

Yoldaş Çelik, Merve, Ebru Canda, Havva Yazıcı, Fehime Erdem, Sema Kalkan Uçar, and Mahmut Çöker. “Impact of the COVID-19 Pandemic on Inherited Metabolic Diseases: Evaluation of Enzyme Replacement Treatment Adherence with Telemedicine.” *The Journal of Pediatric Research* 9, no. 4 (2022): 391–96. https://doi.org/10.4274/JPR.GALENOS.2022.04206.

Appendix C: Excluded Articles

Article	Rayyan Exclusion Reason
"2022 ONS Congress® Poster Abstracts." Oncology Nursing Forum 49, no. 2 (March 2022): E2. https://doi.org/10.1188/22.ONF.E2.	Wrong publication type
Aboulnasr, Aly A., Amr Elnouri, Gamal Abdel Sameea, Amr S. Gouda, Mona M. Ibrahim, Taghreed A. Shalabi, and Khaled R. Gaber. "Prenatal Diagnosis of Mucopolysaccharidoses Type II by Two-Dimensional Electrophoresis and Mass Spectrometry in Amniotic Fluid." Journal of Obstetrics and Gynaecology Research 48, no. 3 (March 2022): 682–87. https://doi.org/10.1111/JOG.15135.	Wrong outcome
Altami, Basil, Hamza Alkelabi, and Mansour Mohammed Al-Qwaiee. "An Infant Presenting with Interstitial Lung Disease Diagnosed Later as Hunter Syndrome: A Case Report." American Journal of Case Reports 23 (2022). https://doi.org/10.12659/AJCR.937527.	Natural history study w/ < 10 subjects
Ayaz, Ercan, and Ayse Ergul Bozaci. "Radiographic Findings of Mucopolysaccharidosis and Comparison with Bone Mineral Density: A Study from Southeastern Turkey." Journal of Clinical Densitometry 25, no. 4 (October 2022): 475–84. https://doi.org/10.1016/j.jocd.2022.08.001.	Natural history study w/ < 10 subjects
Casamassa, Alessia, Alessandra Zanetti, Daniela Ferrari, Ivan Lombardi, Gaia Galluzzi, Francesca D'Avanzo, Gabriella Cipressa, et al. "Generation of an Induced Pluripotent Stem Cells Line, CSSi014-A 9407, Carrying the Variant c.479C>T in the Human Iduronate 2-Sulfatase (HIDS) Gene." Stem Cell Research 63 (August 2022). https://doi.org/10.1016/j.scr.2022.102846.	Animal/nonhuman or basic science
Corrêa, Thiago, Fabiano Poswar, and Cíntia B. Santos-Rebouças. "Convergent Molecular Mechanisms Underlying Cognitive Impairment in Mucopolysaccharidosis Type II." Metabolic Brain Disease 37, no. 6 (August 2022): 2089–2102. https://doi.org/10.1007/s11011-021-00872-8.	Animal/nonhuman or basic science
D'Avanzo, Francesca, Alessandra Zanetti, Andrea Dardis, Maurizio Scarpa, Nicola Volpi, Francesco Gatto, and Rosella Tomanin. "Mucopolysaccharidoses Differential Diagnosis by Mass Spectrometry-Based Analysis of Urine Free Glycosaminoglycans-A Diagnostic Prediction Model." Biomolecules 13, no. 3 (March 2023): 532. https://doi.org/10.3390/biom13030532.	Wrong outcome
Denamur, Sophie, Thibault Chazeirat, Martyna Maszota-Zieleniak, Romain R. Vivès, Ahlame Saidi, Fuming Zhang, Robert J. Linhardt, et al. "Binding of Heparan Sulfate to Human Cystatin C Modulates Inhibition of Cathepsin L: Putative Consequences in Mucopolysaccharidosis." Carbohydrate Polymers 293 (October 2022). https://doi.org/10.1016/j.carbpol.2022.119734.	Animal/nonhuman or basic science
Elkhatib, Amira Abdelhafeez. "Improving Oral Health-Related Quality of Life for a Child with Hunter's Syndrome: A Case Report and Review of Literature." Special Care in Dentistry : Official Publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry 43, no. 2 (March 2023): 250–57. https://doi.org/10.1111/scd.12753.	Natural history study w/ < 10 subjects

EUCTR2021-005200-35-NL. "Study to Determine Effectiveness and Safety of DNL310 vs Idursulfase in Pediatric Participants With Neuronopathic or Non-Neuronopathic Hunter Syndrome." Https://Trialsearch.Who.Int/Trial2.Aspx?TrialID=EUCTR2021-005200-35-NL, n.d. https://doi.org/10.1002/CENTRAL/CN-02410471.	No primary data
Guffon, Nathalie, Delphine Genevaz, Didier Lacombe, Eliane Le Peillet Feuillet, Pascale Bausson, Esther Noel, François Maillot, Nadia Belmatoug, and Roland Jaussaud. "Understanding the Challenges, Unmet Needs, and Expectations of Mucopolysaccharidoses I, II and VI Patients and Their Caregivers in France: A Survey Study." Orphanet Journal of Rare Diseases 17, no. 1 (December 2022). https://doi.org/10.1186/s13023-022-02593-2.	Natural history study w/ < 10 subjects
Hagemeijer, Marne C., Jeroen C. van den Bosch, Michiel Bongaerts, Edwin H. Jacobs, Johanna M.P. van den Hout, Esmee Oussoren, and George J.G. Ruijter. "Analysis of Urinary Oligosaccharide Excretion Patterns by UHPLC/HRAM Mass Spectrometry for Screening of Lysosomal Storage Disorders." Journal of Inherited Metabolic Disease, March 2023. https://doi.org/10.1002/jimd.12597.	Wrong outcome
Harmatz, Paul, Carlos E. Prada, Barbara K. Burton, Heather Lau, Craig M. Kessler, Liching Cao, Marina Falaleeva, et al. "First-in-Human in Vivo Genome Editing via AAV-Zinc-Finger Nucleases for Mucopolysaccharidosis I/II and Hemophilia B." Molecular Therapy 30, no. 12 (December 2022): 3587–3600. https://doi.org/10.1016/j.ymthe.2022.10.010.	Treatment study w/ no dx of MPS II by 12 mos
Haroldson, Jeffrey, Cj Witalisz, Cara Mayfield, N. Matthew Ellinwood, Leslie Urdaneta, Rick Martin, and Gabriel Cohn. "Patient and Physician Perspectives Inform Clinical Trial Design for a Single Intravenous Dose of HMI-203, a Gene Therapy Candidate for Adults with Mucopolysaccharidosis Type II (MPS II, Hunter Syndrome)." Molecular Genetics and Metabolism 135, no. 2 (February 2022): S54–55. https://doi.org/10.1016/J.YMGME.2021.11.133.	Wrong outcome
Harris, Jeffrey, Yuda Zhu, Judy Ho, Charlene Chen, Anna Bakardjiev, Fabian Model, Matthew Troyer, Carole Ho, and Peter Chin. "A Blinded Randomized Phase 2/3 Study of the Efficacy and Safety of Intravenous DNL310 (Brain-Penetrant Enzyme Replacement Therapy) in MPS II." Molecular Genetics and Metabolism 135, no. 2 (February 2022): S55. https://doi.org/10.1016/J.YMGME.2021.11.134.	No primary data
Hong, Junjie, Yu Shan Cheng, Shu Yang, Manju Swaroop, Miao Xu, Jeanette Beers, Jizhong Zou, et al. "IPS-Derived Neural Stem Cells for Disease Modeling and Evaluation of Therapeutics for Mucopolysaccharidosis Type II." Experimental Cell Research 412, no. 1 (March 2022). https://doi.org/10.1016/j.yexcr.2021.113007.	Animal/nonhuman or basic science
Horgan, Claire, Simon A. Jones, Brian W. Bigger, and Robert Wynn. "Current and Future Treatment of Mucopolysaccharidosis (MPS) Type II: Is Brain-Targeted Stem Cell Gene Therapy the Solution for This Devastating Disorder?" International Journal of Molecular Sciences 23, no. 9 (May 2022). https://doi.org/10.3390/ijms23094854.	No primary data
ISRCTN11652897. "Study to Determine the Effectiveness and Safety of DNL310 vs Idursulfase in Pediatric Participants with Neuronopathic or Non-Neuronopathic Hunter Syndrome." Https://Trialsearch.Who.Int/Trial2.Aspx?TrialID=ISRCTN11652897, n.d. https://doi.org/10.1002/CENTRAL/CN-02429815.	No primary data

Jacques, Carlos Eduardo Diaz, Franciele Fátima Lopes, Edina Poletto, Luisa Natalia Pimentel Vera, Priscila Vianna, Luiza Steffens Reinhardt, Guilherme Baldo, and Carmen Regla Vargas. "Evaluation of Oxidative Stress and Mitochondrial Function in a Type II Mucopolysaccharidosis Cellular Model: In Vitro Effects of Genistein and Coenzyme Q10." Metabolic Brain Disease 38, no. 2 (February 2023): 519–29. https://doi.org/10.1007/s11011-022-01062-w.	Animal/nonhuman or basic science
Kimura, Motoya, Yoshiteru Azuma, Soutarou Taguchi, Mizuki Takagi, Hiromitsu Mori, Yasuto Shimomura, Jun Ichi Niwa, Manabu Doyu, and Akihisa Okumura. "Subcortical Infarction in a Young Adult with Hunter Syndrome." Brain and Development 44, no. 5 (May 2022): 343–46. https://doi.org/10.1016/j.braindev.2022.01.003.	Natural history study w/ < 10 subjects
Kumar, Piyush, Pratap C. Das, and Anupam Das. "Hunter Syndrome." JAMA Dermatology 158, no. 12 (December 2022): 1438. https://doi.org/10.1001/JAMADERMATOL.2022.4049.	Natural history study w/ < 10 subjects
Li, Gaijie, Liping Tian, Yuanfang Guo, Yulin Li, Meng Sun, and Hui Zou. "Cut-off Values of Neonatal Lysosomal Storage Disease-Related Enzymes Detected by Tandem Mass Spectrometry." Zhejiang Da Xue Xue Bao. Yi Xue Ban = Journal of Zhejiang University. Medical Sciences 51, no. 3 (June 2022): 321–25. https://doi.org/10.3724/zdxbyxb-2022-0095.	Non-English
Martín-Juste, Pablo, Isabel Parada-Avendaño, Victoria E. Gómez-Palacio, and Jorge Gil-Albarova. "Bilateral Carpal Tunnel Syndrome in Mucopolysaccharidosis Type II: A Case Report." Child's Nervous System 38, no. 8 (August 2022): 1651–53. https://doi.org/10.1007/s00381-022-05492-w.	Natural history study w/ < 10 subjects
Millington, David S., and Can Ficicioglu. "Addition of MPS-II to the Recommended Uniform Screening Panel in the United States." International Journal of Neonatal Screening 8, no. 4 (December 2022). https://doi.org/10.3390/IJNS8040055.	No primary data
Minami, Kohtaro, Hideto Morimoto, Hiroki Morioka, Atsushi Imakiire, Masafumi Kinoshita, Ryuji Yamamoto, Tohru Hirato, and Hiroyuki Sonoda. "Pathogenic Roles of Heparan Sulfate and Its Use as a Biomarker in Mucopolysaccharidoses." International Journal of Molecular Sciences 23, no. 19 (October 2022). https://doi.org/10.3390/ijms231911724.	Animal/nonhuman or basic science
Molnár, Kinga, Julianna Kobolák, and András Dinnyés. "Golgi Requires a New Casting in the Screenplay of Mucopolysaccharidosis II Cytopathology." Biologia Futura 73, no. 1 (March 2022): 31–42. https://doi.org/10.1007/s42977-021-00107-y.	Animal/nonhuman or basic science
NCT05371613. "A Study to the Efficacy and Safety of DNL310 vs Idursulfase in Pediatric Participants With Neuronopathic (NMPS II) or Non-Neuronopathic Mucopolysaccharidosis Type II (NnMPS II)." Https://Clinicaltrials.Gov/Show/NCT05371613, n.d. https://doi.org/10.1002/CENTRAL/CN-02395859.	No primary data
Podetz-Pedersen, Kelly M., Kanut Laoharawee, Sajya Singh, Tam T. Nguyen, Miles C. Smith, Alexa Temme, Karen Kozarsky, R. Scott McIvor, and Lalitha R. Belur. "Neurologic Recovery in MPS i and MPS II Mice by AAV9-Mediated Gene Transfer to the CNS after the Development of Cognitive Dysfunction." Human Gene Therapy 34, no. 1 (January 2023): 8–18. https://doi.org/10.1089/hum.2022.162.	Animal/nonhuman or basic science

Pulock, Orindom Shing, Susmita Dey Pinky, and Syeda Humaida Hasan. "Limited Diagnostic Facilities Impeding the Therapeutic Approach of Mucopolysaccharidosis in Bangladesh: A Case Report." Journal of International Medical Research 50, no. 6 (June 2022). https://doi.org/10.1177/03000605221106412.	Natural history study w/ < 10 subjects
Rodriguez, Jose Alcantara, Jeff Harris, Peter Cygon, Yuda Zhu, Natalie Engmann, Simona Costanzo, Fabian Model, Wei Dong, Carole Ho, and Peter Chin. "COMPASS, a Double-Blinded Randomized Phase 2/3 Study of the Efficacy and Safety of Intravenous DNL310 (Brain-Penetrant Enzyme Replacement Therapy) in MPS II." Molecular Genetics and Metabolism 138, no. 2 (February 2023): 106996. https://doi.org/10.1016/J.YMGME.2022.106996.	No primary data
Rossi, Alessandro, and Giancarlo Parenti. "Cervical Spondylolisthesis in Mucopolysaccharidosis Type II." Neurological Sciences 44, no. 1 (January 2023): 409–10. https://doi.org/10.1007/S10072-022-06357-5.	Natural history study w/ < 10 subjects
Schwab, Marisa E., Julia E.H. Brown, Billie Lianoglou, Chengshi Jin, Patricia C. Conroy, Renata C. Gallagher, Paul Harmatz, and Tippi C. MacKenzie. "Fetal Therapies and Trials for Lysosomal Storage Diseases: A Survey of Attitudes of Parents and Patients." Orphanet Journal of Rare Diseases 17, no. 1 (December 2022). https://doi.org/10.1186/s13023-022-02178-z.	Wrong population
ŞENGÜL EMEKSIZ, Zeynep, Şule BÜYÜK YAYTOKGIL, Ilknur KÜLHAŞ ÇELIK, Çiğdem KASAPKARA, and Emine DIBEK MISIRLIOĞLU. "Successful Idursulfase Desensitization Experience in a Pediatric Patient." Asthma Allergy Immunology 20, no. 1 (April 2022): 68–70. https://doi.org/10.21911/AAI.667.	Treatment study w/ no dx of MPS II by 12 mos
Smith, Miles C., Lalitha R. Belur, Andrea D. Karlen, Olivia Erlanson, Kelly M. Podetz-Pedersen, Jessica McKenzie, Jenn Detellis, et al. "Phenotypic Correction of Murine Mucopolysaccharidosis Type II by Engraftment of Ex Vivo Lentiviral Vector-Transduced Hematopoietic Stem and Progenitor Cells." Human Gene Therapy 33, no. 23 (December 2022): 1279–92. https://doi.org/10.1089/hum.2022.141.	Animal/nonhuman or basic science
Sofronova, Viktoriia, Elizaveta Gurinova, Diana Petukhova, Hiroko Fukamatsu, Takenobu Yamamoto, Yumi Aoyama, Polina Golikova, et al. "A Case of Mucopolysaccharidosis II Caused by a Novel Variant with Skin Linear Hyperpigmented Streaks along Blaschko's Lines." International Journal of Molecular Sciences 24, no. 6 (March 2023): 5647. https://doi.org/10.3390/ijms24065647.	Natural history study w/ < 10 subjects
Spataro, Federico, Fabio Viggiani, Domenico Giorgio Macchia, Valentina Rollo, Albina Tummolo, Patrizia Suppressa, Carlo Sabba', et al. "Novel Approach to Idursulfase and Laronidase Desensitization in Type 2 and Type 1 S Mucopolysaccharidosis (MPS)." Orphanet Journal of Rare Diseases 17, no. 1 (December 2022). https://doi.org/10.1186/S13023-022-02556-7.	Wrong outcome
Tang, Jie, Guoying Chang, Meili Wei, Xin Li, Hongzhu Chen, Yanrong Qin, Jian Wang, Xiuming Wang, Ruimin Chen, and Niu Li. "Diagnosis of Patients with Mucopolysaccharidosis Type II via RNA Sequencing." Clinica Chimica Acta 537 (December 2022): 38–45. https://doi.org/10.1016/j.cca.2022.10.007.	Animal/nonhuman or basic science
Torres, Clarisse L., Fernanda B. Scalco, Maria Lúcia C. de Oliveira, Roy W.A. Peake, and Rafael Garrett. "Untargeted LC-HRMS Metabolomics Reveals Candidate Biomarkers for	Animal/nonhuman or basic science

Mucopolysaccharidoses." Clinica Chimica Acta 541 (February 2023): 117250. https://doi.org/10.1016/j.cca.2023.117250.	
Tylki-Szymańska, Anna, Zsuzsanna Almássy, Violetta Christophidou-Anastasiadou, Daniela Avdjieva-Tzavella, Ingeborg Barisic, Rimante Cerkauskiene, Goran Cuturilo, et al. "The Landscape of Mucopolysaccharidosis in Southern and Eastern European Countries: A Survey from 19 Specialistic Centers." Orphanet Journal of Rare Diseases 17, no. 1 (December 2022). https://doi.org/10.1186/s13023-022-02285-x.	Wrong population
Zhang, Haoyue, Sarah P Young, and David S Millington. "Quantification of Glycosaminoglycans in Urine by Isotope-Dilution Liquid Chromatography-Electrospray Ionization Tandem Mass Spectrometry." Current Protocols 3, no. 3 (March 2023): e701. https://doi.org/10.1002/cpz1.701.	Wrong outcome

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[1] Maurizio Scarpa, "Mucopolysaccharidosis Type II," in *GeneReviews®*, ed. Margaret P. Adam et al. (Seattle (WA): University of Washington, Seattle, 1993), http://www.ncbi.nlm.nih.gov/books/NBK1274/.

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Appendix B: Independent evidence report on GAMT Disorder

Evidence Report: Newborn Screening for Guanidinoacetate methyltransferase (GAMT) deficiency

Prepared for the Northwest Regional Newborn Bloodspot Screening Program Advisory Board

August 25, 2023

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Abbreviations:
ACHDNC - Advisory Committee on Heritable Disorders in Newborn and Children
GAMT - Guanidinoacetate methyltransferase
GUAC - guanidinoacetate
NWRNBS - Northwest Regional Newborn Screening Bloodspot Screening
OHSU - Oregon Health and Sciences University
RUSP - Recommended Uniform Screening Panel
TEP – Technical Expert Panel

Introduction

Background and Purpose

HB 2563 required the formation of Northwest Regional Newborn Screening Bloodspot Screening (NWRNBS) Advisory Board. HB 2563 tasked the board with reporting its findings and recommendations to the legislature. In addition, the board's charter states that it is to assist with modernization of the newborn bloodspot screening program including advising on changes to the newborn bloodspot screening panel.

The board has approved a process and criteria for evaluating addition of disorders to the bloodspot screening panel. The approval process stages are summarized below:

Stage 1: Addition to RUSP - Disorders that have been reviewed by the Advisory Committee on Heritable Disorders in Newborn and Children (ACHDNC) and have been added to the Recommended Uniform Screening Panel (RUSP) will be raised for further evaluation.

Stage 2: NWRNBS Program Evaluation using Category One Criteria: After a disorder has been added to the RUSP, the NWRNBS Program will evaluate the disorder using the criteria referred to as "Category One Criteria". This initial set of criteria will be answered using yes or no. If all the criteria are answered yes, the disorder will be moved to stage 3.

Stage 3: NWRNBS Advisory Board Evaluation and Recommendation using Category Two Criteria: Disorders that have met Category One criteria will be brought to the NWRNBS Advisory Board for evaluating using "Category Two criteria". These criteria will be evaluated using the consensus tool. The results of this evaluation will inform the recommendations to the NWRNBS Program.

Category one criteria and category two criteria are listed in the executive summary.

Scope of Review

This report follows the evidence outline as presented by ACHDNC for inclusion of guanidinoacetate methyltransferase (GAMT) deficiency to the RUSP. It begins with a discussion of natural history of GAMT deficiency, followed by incidence and prevalence estimates, discussion of screening, diagnosis, and treatment. This evidence report also provides context and implications for initiation of GAMT deficiency screening within the NWRNBS program.

The executive summary for GAMT deficiency, provided as separate document, presents evidence for each criterion as ordered by stages 1-3 above.

This evidence report documents, evaluates and summarizes available scientific evidence and expert opinion for evaluation by the board. This report is not intended to make recommendations for or on behalf of the board.

Methods

This report summarizes findings from the ACHDNC review of guanidinoacetate methyltransferase (GAMT) deficiency and more recently published literature. The ACHDNC initial literature search was conducted for references published between January 1, 2001-September 1, 2021, with a subsequent bridge search (September 1, 2021 – April 1, 2022) using the systematic evidence review (SER) methods.

To capture recent, relevant literature for this report, an updated literature search was conducted for publications between April 1, 2022 – April 13, 2023. In each section of the evidence review, a brief description of the ACHDNC review will be included, along with the recent updates. The focus of the evidence review is GAMT deficiency and newborn screening.

Subject matter experts, including medical consultants and NWRNBS Program staff and partners were consulted, and a summary of those discussions is also provided.

Documentation of literature review is in appendices A-B; Discussion with experts is in appendix C and a list of excluded articles is in appendix D.

Questions for Evidence Review: GAMT deficiency

Case Definition

Condition Overview: Guanidinoacetate methyltransferase (GAMT) deficiency is one of three metabolic disorders related to cerebral creatine deficiency. It is an autosomal recessive disorder due to variants in the gene, *GAMT*, which encodes for the guanidinoacetate methyltransferase. GAMT converts guanidinoacetate (GUAC) to creatine[1] (OMIM #601240)[2].

Patients with GAMT deficiency present with a neurologic phenotype including developmental delays particularly in speech, intellectual disability, behavioral issues including autism, seizures, and movement disorders like ataxia[3]. Pre-symptomatic treatment with dietary interventions and supplements has been shown to significantly improve outcomes with most individuals being neurologically typical[4,5,6].

Diagnosis of GAMT deficiency is confirmed by biochemical assessment of by a plasma GUAC (elevated) and creatine (reduced) levels. GUAC can also be detected at significant levels in urine and cerebrospinal fluid. Molecular testing of the *GAMT* gene supports the diagnosis[4]. Magnetic resonance spectroscopy can be used to measure creatine and GUAC levels in the brain and assist with diagnosis.

Natural History of GAMT deficiency with usual clinical detection

What is the natural history of this condition?

GAMT deficiency is a rare disorder. Its pathophysiology is due to the lack of the product, creatine, as well as the buildup of GUAC[1]. From the ACHDNC review, evidence indicates that the behavioral problems and intellectual disability are related to the creatine deficiency and intractable seizures and movement disorders are related to the elevated GUAC[4].

Clinical features include developmental delays (DD) particularly in speech development, intellectual disability (ID), behavioral concerns including aggression, autism like features, hyperactivity and self-injury, seizures, hypotonia, movement disorders including ataxia and chorea. Intellectual disability can range from mild to severe, however most individuals (50 to 75%) have severe developmental delay[3].

There is variability in neurologic features. Outlined in the ACHDNC review are several studies with 20 to 48 subjects[4]. Of note, patients overlap within these studies. The ACHDNC review accounts for this overlap in the reporting. Table 1 is a summary of the natural history studies from the ADHDNC.

Table 1 Summary of studies for natural history.

Reference	Subjects in study	Age of Diagnosis	Clinical Features
Khaikin et al 2018[7]	27	12.3 years (2 years-29 years)	78% with intellectual disability 28% intractable seizures 48% movement disorder
Stockler-Ipsiroglu et al 2014[6]	20	6.5 years (10 months – 20 years)	All with developmental delay/intellectual disability 75% with seizures 40% movement disorders 95% significant behavioral disorder
Mercimek-Mahmutoglu et al 2014[8]	22	8.5 years (9 months – 25 years)	All with developmental delay/intellectual disability 82% with seizures 36% movement disorders
Mercimek-Mahmutoglu et al 2016[9]	28	N/A	44 of 48 with developmental delay/intellectual disability (all started treatment after nine months) 35 of 44 with seizures

From the ACHDNC review, decrease in life expectancy is not reported, but neurologic sequelae including epilepsy may be related to an increased risk of mortality[4].

What are the ages of onset, diagnosis, and treatment without newborn screening?
Clinical features of GAMT deficiency develop in infancy or toddlerhood. The developing affected fetus is protected because creatine transport across the placenta occurs during pregnancy[10]. The earliest reported neurologic symptoms appear after 3-6 months[7].

Diagnosis can be identified in several ways. Clinical findings such as developmental delay/intellectual disability, hypotonia, seizures or epilepsy, movement disorders or behavioral problems or a family history may lead to a diagnostic evaluation. Laboratory findings including biochemical testing showing low creatine and elevated GUAC in urine and/or blood[3]. Molecular

DNA can identify variants in the GAMT gene[3]. Also, magnetic resonance spectroscopy (MRS) can show low or absent creatine peaks leading to suspicion of the diagnosis[3]. The age of diagnosis varies from neonatal to 34 years of age[3]. See Table 1 above for average age of diagnosis from various studies (adapted from ACHDNC review)[4].

Treatment of clinically identified patients does help improve symptoms. One study found 11 of 18 patients had seizures fully resolved on treatment[8]. Another study found treatment decreases seizures and movement disorders but did not change the underlying intellectual disability[7].

How is the condition defined in newborns?
The condition is not well defined in newborns, as most children are asymptomatic within the first 1-3 months of life. However, treatment should be started in this period to prevent clinical features of disease which may occur (at earliest) 3-6 months of life[6].

Incidence and Prevalence of GAMT deficiency
How many people are diagnosed with this condition clinically?
GAMT deficiency is a rare disorder. In 2022, GeneReviews estimated that only 130 individuals have GAMT deficiency[3].

At Oregon Health and Sciences University (OHSU), three patients are followed with GAMT deficiency. One patient presented clinically at one year of age with developmental delay and movement concerns and was started on dietary treatment. The other two patients are a sibship. The older sibling presented with seizures and developmental delay. The younger sibling was tested in early infancy after the sibling's diagnosis. Further details about these patients are provided below.

What is the incidence of GAMT deficiency? Are there specific populations where incidence increases?
The incidence, the number of newly identified cases over a specified timeframe, for GAMT deficiency is unknown. Based on clinically reported cases, an incidence of <0.3/100,000 live births can be estimated.

Several studies have estimated carrier frequency between from 1/250 to 1/812 to greater than 1/1475 newborns[9, 12, 15]. Based on this carrier frequency, the incidence would be calculated to be 1 in 250,000 to 1 in 2,640,0009[15,12].

Due to the rarity of GAMT deficiency and undiagnosed affected individuals, epidemiologic data is not complete assessing high risk populations[4]. Therefore, a specific population with an increased incidence of GAMT deficiency has not been identified[3].

What is the estimated birth prevalence?
The true birth prevalence of GAMT deficiency, defined as the proportion of the population with a condition at birth, is also unknown. From ACHDNC data, the systemic evidence review did not

find a clear birth prevalence, the likely range is between 1/200,000 births to 1/2,000,000 births[4]. The technical expert panel (TEP) supports a baseline estimate of birth prevalence to be 0.4 per 100,000 births based on Utah's case detection rate[4].

Table 2 – Represents table 6 from the ACHDNC - data use for the estimated birth prevalence of GAMT deficiency based on clinical case detection and newborn screening[6].

Description	Most Likely	Range (min-max)	Source
Birth prevalence of GAMT deficiency, clinical identification	Not available	0.5 per 100,000*	Published and unpublished literature on the prevalence of GAMT deficiency, TEP discussion
Birth prevalence of GAMT deficiency, NBS	0.2 per 100,000**	0.02-0.6 per 100,000***	Utah and New York newborn screening data

*1 in 2 million to 1 in 200,000
** 1 in 540,276
*** 1 in 4.4 million to 1 in 164,000. Minimum and maximum values derived from the 95th percentile confidence interval assuming a binomial distribution

Screening for GAMT deficiency

What screening method is used to detect GAMT deficiency among newborns?

Screening for GAMT Deficiency is performed by measuring GUAC and creatine within dried blood spots using flow injection tandem mass spectroscopy (MS/MS)[4]. GUAC and creatine detection can be multiplexed with other acylcarnitine and amino acid disorders using derivatized or non-derivatized MS/MS methods[14].

At present, there is no FDA - approved kit or testing method for GAMT screening. Incorporation of GUAC and creatine into the panel of acylcarnitines and amino acids would require the laboratory to make these modifications and validate this test.

One published article states the possibility of performing second tier testing for GAMT deficiency by measuring GUAC using liquid chromatography tandem mass spectrometry (LC-MSMS), which can increase specificity[4].

How well does the screening assay work? What is the sensitivity, specificity, and positive predictive value ?

With no false negatives known at this time, the sensitivity of this testing is 100% with specificity approaching 100%.

Table 3 Calculated Positive Predictive Value based on Pilot study data[4].

Pilot	Positive Predictive Value
Utah (Non derivatized)	33.3%
New York (cumulative)	4.1%
Pool US results	7.1%
All results	8.6%

What are the findings of pilot studies from other regions that have implemented screening?
For GAMT deficiency, there have been two state pilot studies as well as pilot studies done in British Columbia - Canada, and Australia.

Two states have piloted GAMT deficiency newborn screening. Both states had their screening protocols evolve over time including elimination of second tier testing due to improved accuracy of the first-tier test. The current method used by the Utah newborn screening program is a laboratory developed non-derivatized tandem mass spectrometry method that measures GUAC and GUAC:creatine ratio, along with amino acids and acylcarnitines[4]. In New York's pilot, initially there was a higher false positive rate thought due to an unknown isobaric interferant(s) of GUAC on the assay. Modification of the method decreases the false positives and increases the positive predictive value[14]. With this modification, the laboratory was able to discontinue the second tier of the assay. New York does follow biochemical screening with molecular sequencing of GAMT, but the sequencing is not part of the screening algorithm[4,14].

In an initial pilot study British Columbia - Canada, the assay included first tier of measurement of GUAC multiplexed with amino acids and acylcarnitine profiles, second-tier assay on liquid chromatography MS/MS and third tier testing of gene sequencing[17]. The pilot found a false positive rate of 0.1% was calculated for the first-tier screening based on normal second-tier screening. A third-tier genetic testing was completed in this study, which did not yield any variants in the specimens with screen positive, first-tier results[16].

For Australia's pilot study, the laboratory used flow injection MS/MS on a derivatized samples to evaluate GUAC concentrations. A positive initial screen led to a repeat of the dry blood spot.

Michigan attempted to add GAMT deficiency to its screening panel but was not initially able to complete assay validation. Michigan experienced challenges integrating GUAC and creatine into the pre-existing kit for amino acids and acylcarnitine analysis using proprietary reagents. However, from personal communication with Dr Held and the Michigan newborn screening laboratory, the laboratory was above to overcome challenges and is now screening for GAMT deficiency using a multiplex assay.

For calculated positive predictive value from pilots, see table 3 above. For a summary of the number of newborns screened, diagnosis of GAMT deficiency, and referral rate, see the ACHDNC report summarized in Table 4 below[4].

Table 4 Summary of Population-Based GAMT Deficiency Newborn Screening

Location	Time Period	Newborns Screened	Newborns Diagnosed with GAMT Deficiency	Diagnostic Follow-up Referral Rate per 100,000 Newborn Screened	Cases Detected per 100,000 Newborn Screened
Utah (Non-derivatized Approach)	June 2019 - December 2021	125,880	1	0.79	0.79
Utah (Cumulative)	May 2015 - December 2021	321,305	1	0.93	0.31
New York (Culminative)	October 2018-April 2022	759,246	1	3.2	0.13
British Columbia, Canada	October 2012-April 2022	428,140	0	0.7 (following second tier testing and genetic analysis)	0
Victoria, Australia	April 2002-April 2022	1.4 million	1	0.38	0.07
Pooled Screening Results – US only	May 2015-April 2022	1.08 million	2	2.6	0.19
Pooled Screening Results - All	April 2002-April 2022	2.9 million	3	1.2*	0.1

* Same case, reported from overlapping time.
** Assuming six referrals from Victoria newborn screening program based on average number of referrals per year provided for this report

Does it lead to improved outcomes compared to usual care?

Based on case series reports, early identification of individuals with GAMT deficiency changes the natural history of the disorder. The ACHDNC reviewed six studies that identified individuals treated prior to six months of age, comparing them to their older sibling who were identified clinically. This data is summarized in table 5 (below)[4]. Eight of the nine individuals identified from the prenatal period to five months of age were found to have normal developmental outcomes. One individual continued to have central hypotonia and developmental delays at 11 months follow up.

Table 5 Summary of GAMT Deficiency Studies with Treatment Within the First Few Months After Birth (Table 4 in ACHDNC review).

	Outcomes with treatment onset <6 months old			Outcomes of older sibling with later diagnosis when available		
	Age of diagnosis and treatment	Duration of treatment and follow-up	Developmental outcome at follow-up	Age of older sibling at diagnosis	Duration of treatment and follow-up	Developmental outcome at follow-up
El-Gharbawy et al (2013)[18]	Prenatal	42 months	Normal	10 months	6.5 years	Speech and fine motor delays
Stockler-Ipsiroglu et al. (2014)[6]	Prenatal 1 week 3 weeks	41 months 14 months 31 months	Normal Normal Normal	10 months 5.5 years 30 months	39 months 30 months 10 years	Mild DD Moderate DD Mild DD
Viau et al. (2013)[5]	Birth	12 months	Normal	--	--	--
Dhar et al (2009)[19]	8 days	11 months	Central hypotonia, developmental delay persists	2.5 years	4.5 years	Improved motor skills, started walking, improved tone, improved autistic features
Schulze et al (2006)[20]	22 days	14 months	Normal	2.75 years	2.25 years	Epilepsy, speaks “a few words”
Farshidi et al.(2011)[21]	5 months	11 months	Normal	15 months	21 months	Continues to have seizures (improved), cognitive impairment, learning disability (improved)

Potential Harms of Newborn Screening

What are the benefits and harms that could result from a newborn screening of GAMT deficiency?

The potential benefit newborn screening affords patients with GAMT deficiency is early diagnosis and treatment. Early treatment does appear to improve outcomes particularly for developmental delay and intellectual disability based on a limited case series.

Additionally, it is possible that the identification of a newborn may lead to the diagnosis of other family members particularly in older siblings. The older siblings would potentially be able to benefit from treatment, particularly with decreased seizure activity and improved movement, but would likely continue to have developmental delays/intellectual disability.

Potential harm may be the unneeded diagnostic workup for false positive screening results. Based on pilots in Utah and New York, false positives can be minimized through assay improvements. Other harms may include identification of a carrier.

The ACHDNC presented the following benefits and risks to screening in their summary of evidence advisory committee decision report presented May 12, 2022.

Table 6 Benefits and Risks of Screening (Summarize from Presentation of Recommendation to the ACHDNC for Newborn Screening of GAMT deficiency)[20]

Benefits	**Risks**
Presymptomatic therapy most often associated with normal neurologic outcome	Potential harms of the newborn screening process • False positive - low concern due to reliable confirmatory test • Indeterminate results are rare. • Potential for a loss to follow-up • Cost and burden of confirmatory testing - maybe lower than other conditions on the RUSP
Treatment is likely associated with better neurologic outcomes, cognitive development, and function	False negatives have not been reported.
Earlier initiation of treatment likely maximizes benefit of therapy.	At present, there is no clear case definition for GAMT deficiency.

Confirmatory Testing and Diagnosis

Is definitive diagnostic or specialty testing available to confirm or diagnose? positive screens? How well does it work?

Confirmatory testing can include blood and urine testing to demonstrate elevated GUAC as well as genetic testing to support the diagnosis[3]. Magnetic resonance spectroscopy can identify low

creatinine levels and elevated GUAC in the brain[4]. The American College of Medical Genetics and Genomics has completed a technical standards and guidelines for the laboratory diagnosis of creatine deficiency syndromes including GAMT deficiency[23]. This report notes that typically GUAC elevations are significantly increased although levels can vary particularly with supplementation of creatine or ornithine[16]. The report recommends follow up DNA testing to confirm biochemical findings. Molecular testing typically detects 100% of pathogenic variants with sequence analysis of GAMT[3].

Treatment for GAMT deficiency

What are the standard treatments for GAMT deficiency?

Current treatment involves dietary restriction of arginine as well as supplementation of creatine and ornithine. The goal of this treatment is to increase creatine levels and decrease GUAC levels.

Recent recommendations include emphasis on oral creatine (typically 400 mg/kg daily) and ornithine (typically 100-800 mg/kg daily)[24]. Dietary protein restriction of arginine with arginine free medical formula and sodium benzoate (typically 100 mg/kg daily) may also be added to the treatment regimen. A note made by the TEP committee stated that protein restriction is less than other metabolic disorders[4].

As part of dietary monitoring, regular blood GUAC and creatinine levels as well as plasma amino acids are obtained as frequently as every one to two months. Less frequent monitoring is needed as the individuals get older[6].

ACHDNC review does note that the treatments of creatine and orthenine are classified as dietary supplements; therefore, there is an increased risk of unknown substances in the manufacturing and distribution. The Association of Creatine Disorders (ACD) patient advocacy group has partnered with a laboratory to make high quality supplements. Sodium benzoate is available through compounding pharmacies. Medical metabolic formula is available through various companies.

Are there treatment guidelines for GAMT deficiency?

Per the ACHDNC review, there are no current conference or committee or society guidelines for treatment. However, there are several articles that provide current treatment recommendations for arginine restriction and supplementation of creatine and ornithine, as well as monitoring guidelines.

As for evidence of treatment efficacy prior to 12 months of age, there are no controlled treatment trials, but available case series suggest better developmental outcomes for those who start treatment earlier.

The ACHDNC review concludes that case series demonstrate that pre-symptomatic or early initiation of treatment is associated with improved neurologic outcomes[4]. These outcomes include a reduced risk of intellectual disability and a decrease in seizures and movement

disorders. There are no quantitative measures of developmental outcomes provided. Table 5 summarizes this data from the ACHDNC.

Future Treatments

Per ACHDNC review, there are no targeted treatments available. Gene therapy has been tested in a mouse model and was shown to normalized GUAC levels[25].

NWRNBS Program Impact Assessment

The program conducted an internal assessment which covered the following areas:

- Fiscal Analysis
- Availability of specialized medical consultants
- Capacity and expertise to implement and maintain testing and reporting.
- Capacity and expertise to implement short- and long-term follow-up.
- Capacity to provide education for providers and parents.
- Assessment of impact of implementing screen for NWRNBS program partners (readiness, barrier, etc.)

Fiscal Analysis

The ACHDNC used pilot data from Utah and New York to estimate the probability of a positive screen (2.6 per 100,000) and the probability of a confirmed diagnosis of GAMT deficiency (0.2 per 100,000). Based on these calculations and with approximately 60,000 births a year from Oregon and New Mexico:

- Positive screen for the NWRNBS program - ~1.5 positive screens per year.
- Diagnosis of GAMT after a positive screen for the NWRNBS program – 0.12 GAMT deficiency per year or 1 GAMT deficiency patient identified every 8 years.

Table 7 Cost associated with implementation of GAMT deficiency.

Stage of addition of GAMT deficiency	Items to consider	Cost
Development of assay and clinical care protocol and materials		
Assay development	Personnel, instrumentation time, reagents, and other supplies	Minimal - Extra staffing would not be required
LIMS set up	Personnel	Minimal - Extra staffing would not be required
Education materials	Personnel	Minimal - Extra staffing would not be required
Clinical care protocol	The Clinical consultants will create a workflow for practitioners to follow when a positive newborn screen is reported. The workflow will include recommended confirmatory testing, clinical care, and initiation of treatment, if required. Based on estimates from other conditions, the development of the workflow would cost approximately ~$4000.	4,000
Routine Screening		
Supplies	Internal standards for GUAC and creatine	Minimal

Instrumentation	No further instrumentation needed.	0
Personnel	Since GUAC and creatine will be multiplexed with amino acids and acylcarnitine on MS/MS, no additional staffing for the running of the assay will be needed.	0
Other Notes	No second-tier metabolite testing, or third tier molecular testing is planned.	0
Short term follow-up		
Cost of additional resources for follow-up.	Minimal funding with be required for follow-up based on the small number of screen positive call outs per year (estimated at 1.5 positive screens per year).	Minimal
Clinical Care		
	Yearly contract fee for inclusion*** Based on estimates calculated for grant to implement Mucopolysaccharidosis type 2. OHSU clinic estimated approximately $1000 for each screen positive.	<1000

Availability of Specialized Medical Consultants

The NWRNBS Program currently contracts with OHSU for medical expertise for metabolic disorders, therefore the expertise necessary for medical consultation exists for the program. However, adding GAMT deficiency could increase costs for the program if the burden of work exceeds a reasonable threshold for the current specialists. This is less likely due to the rarity of the disorder.

The four medical consultants at Oregon Health and Sciences University are:

- Cary Harding, MD hardingc@ohsu.edu
- Amy Yang, MD yangam@ohsu.edu
- Markus Grompe, MD grompem@ohsu.edu
- Kimberly Kripps, MD kripps@ohsu.edu

There are two nurse practitioners at Oregon Health and Sciences University, who also assist short- and long-term follow-up:

- Sarah Viall P.N.P
- Leah Wessenberg F.N.P.

There are two metabolic dietitians at Oregon Health and Sciences University, who also assist short- and long-term dietary management and follow-up:

- Sandra van Calcar PhD, RD, LD
- Laura Sliwoski MS, RD, LD, CNSC

Capacity and Expertise to implement and maintain testing and reporting
Per interview with Dr Held, there is expertise for assay development and implementation steps as well as maintaining testing and reporting.

The Oregon newborn screening laboratory would likely choose to develop and validate an assay for GUAC, and creatine multiplexed with its current amino acids and acylcarnitine assay on the MS/MS. With the addition of GUAC and creatine to the assay, validation for these analytes would need to be completed as well as revalidation of the amino acids and acylcarnitine. Expertise exists in the laboratory to complete the validation as well as technical support offered through the state's contract with Revvity. This process would take time to complete and Dr Held estimates 18 to 24 months to complete assay validation and updates to the laboratory information management system (LIMS).

More recently, the newborn screening laboratory for the state of Michigan has added GAMT deficiency to their newborn screening panel. Per personal communications between Dr Held and the Michigan newborn screening lab, Michigan was able to add single tier test for GUAC and creatine by multiplexing with its current amino acid and acylcarnitine assay on the tandem mass spectroscopy. Michigan newborn screening laboratory uses the same kit (neobase2, Revvity) as Oregon to measure amino acids and acylcarnitines. Michigan newborn screening lab would make their SOP available for review and would also be able to provide assistance to NWRNBS program. The Michigan newborn screening laboratory's development and implementation has not been published at this time.

The Association of Public Health Laboratories **(**APHL) has a readiness scale for the ability of newborn screening programs to adapt find new disorder into their existing newborn screening panel. The categories are:

- Ready - could implement within one year
- Developmental ready - could implement within 1-3 years
- Unprepared - would take more than 3 years

Per Dr Held, Oregon is developmental ready.

Capacity and expertise to implement short- and long-term follow-up
For short- and long-term follow-up of screen positive cases, the laboratory and OHSU medical consultants would need to develop an algorithm for reporting and a clinical care plan. The OHSU consultants have the expertise and capacity for this work per interview with Ms. Viall, Dr van Calcar, and Dr. Yang

The metabolic team has its routine clinic at OHSU main campus in Portland. The clinic has semi-annual outreach clinics in Eugene and Medford with limited staff. The clinic also frequently uses telemedicine, when possible, particularly for patients from rural areas (Ms. Viall interview).

Capacity to provide education for providers and parents
For educational materials, the current program resources include:

- Nurse Practitioner educators prepare high quality materials for education at the appropriate level for both providers and parents. The NPs have a long-term educator role within the NWRNBS program.
- Some materials may be able to be borrowed from other programs but will need to be adapted so they are specific to Oregon.

Assessment of impact of implementing screen for NWRNBS program partners (readiness, barrier, etc.)

The OSHU clinical consultants would be responsible for short-term follow-up for a screen positive GAMT deficiency including initial consult with PCP and follow-up of diagnostic labs. (Ms. Viall interview).

For New Mexico, Dr Michael Marble and Dr. Kiley Quintana would be responsible for clinical care of a confirmed GAMT deficiency. To assess readiness for the possible addition of GAMT deficiency, an email with questions was sent. Dr Marble did not have concerns for the addition of GAMT deficiency to the panel and New Mexico's capacity and ability to care for patients, including access to medical formula and supplements.

Access to Care and Equity of Treatment and Follow-up

Is this condition on the Prioritized List as determined by the Oregon Health Evidence Review commission?

No, GAMT deficiency does not appears in the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission ICD-10 codes.

Are experts available to provide treatment?

The NWRNBS Program currently contracts with OHSU for medical expertise for metabolic disorders, therefore the expertise necessary for medical consultation exists for the program. (Names of consultants listed on page 15).

For the state of Oregon, medical formulas and supplements are state mandated to be covered by insurances. The OHSU metabolic clinic distributes medical formula and high-quality supplements from their supply. Medical formula and supplements are usually covered without significant issue by insurances, but social work and financial assistance are both available at OHSU to assist families where difficulty may arise [Dr van Calcar interview].

As mentioned above, there are three patients with GAMT deficiency at receiving care at OHSU. All were started on diet and/or supplements at diagnosis and continue to follow in the metabolic clinic.

What is the availability and accessibility of care and treatment?

During interviews, accessibility of care and treatment was discussed.

For GAMT deficiency, the following barriers were discussed:

1) Geographic barriers to healthcare in the state of Oregon.
All pediatric and adult patients with GAMT deficiency would be seen by the metabolic specialist through Oregon Health and Sciences University (OHSU). There is only one metabolic clinic at OHSU with outreach. It can be a significant financial and logistical barrier for a family to travel to Portland for healthcare. Telemedicine is frequently used by the team to help with geographic barriers. Metabolic dietitians frequently deliver their care by telemedicine. As noted in the ACHDNC, remote care can be appropriate as clinical decisions are based on laboratory findings.

Dr. Yang does share that management of patients via telemedicine can be challenging, particularly with obtaining specialty labs. Small, local hospitals without relationships with specific metabolic reference laboratories (Baylor Genetics Clinical Diagnostic Laboratory) may find it challenging to send samples for GUAC monitoring.

2) Insurance barriers to healthcare
Ms. Viall relays that insurance coverage for Medicaid can be complicated by its organization into CCOs (Coordinated Care organization) managed by geographic area. CCOs can determine their own medical necessity criteria and coverage. Therefore, with new patients or if patients move, there may be issues with getting coverage for care.

In general, there is coverage for clinic appointments for patients on Medicaid and other private insurances. As far as telemedicine, this is frequently covered by both Medicaid and private insurance as well. With the change from the public health emergency, OHSU providers are expecting telemedicine coverage to continue (Dr Yang interview).

For medical formula and supplementation needed for dietary treatment of GAMT deficiency, access and coverage is available in Oregon.

3) Shortages in healthcare providers
Per interview with Ms. Viall, Oregon is the most medically underserved state with the fewest per capita hospital beds in America. The nursing shortage, all the shortages, and medical staffing burnout has been really felt here.

The overall shortage of healthcare providers can cause logistical concerns when caring for metabolic patients. However, Ms. Viall did feel there is an adequate number of providers for their institution.

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Appendix A: Systematic Literature Review
Guanidinoacetate methyltransferase (GAMT) deficiency and newborn screening.

PubMed

Set	Terms	4/2/2022-4/13/2023
#1	"guanidinoacetate methyltransferase deficiency"[Supplementary Concept] OR "guanidinoacetate methyltransferase deficiency"[All Fields] OR "GAMT"[All Fields] or "GAMT deficiency"[All Fields] OR ("Guanidinoacetate N-Methyltransferase"[MeSH] AND deficiency[tw])	
#2	English, Human, from 2022/4/2* - 3000/12/12	
	#1 and #2	
		12

CINAHL

Set	Terms	4/2/2022-4/13/2023
#1	guanidinoacetate methyltransferase deficiency OR gamt OR gamt deficiency OR gamt gene OR (Guanidinoacetate N-Methyltransferase AND deficiency)	
#2	English, Published Date: 20220101-20231231	
#3	#1 and #2	
		5

Cochrane

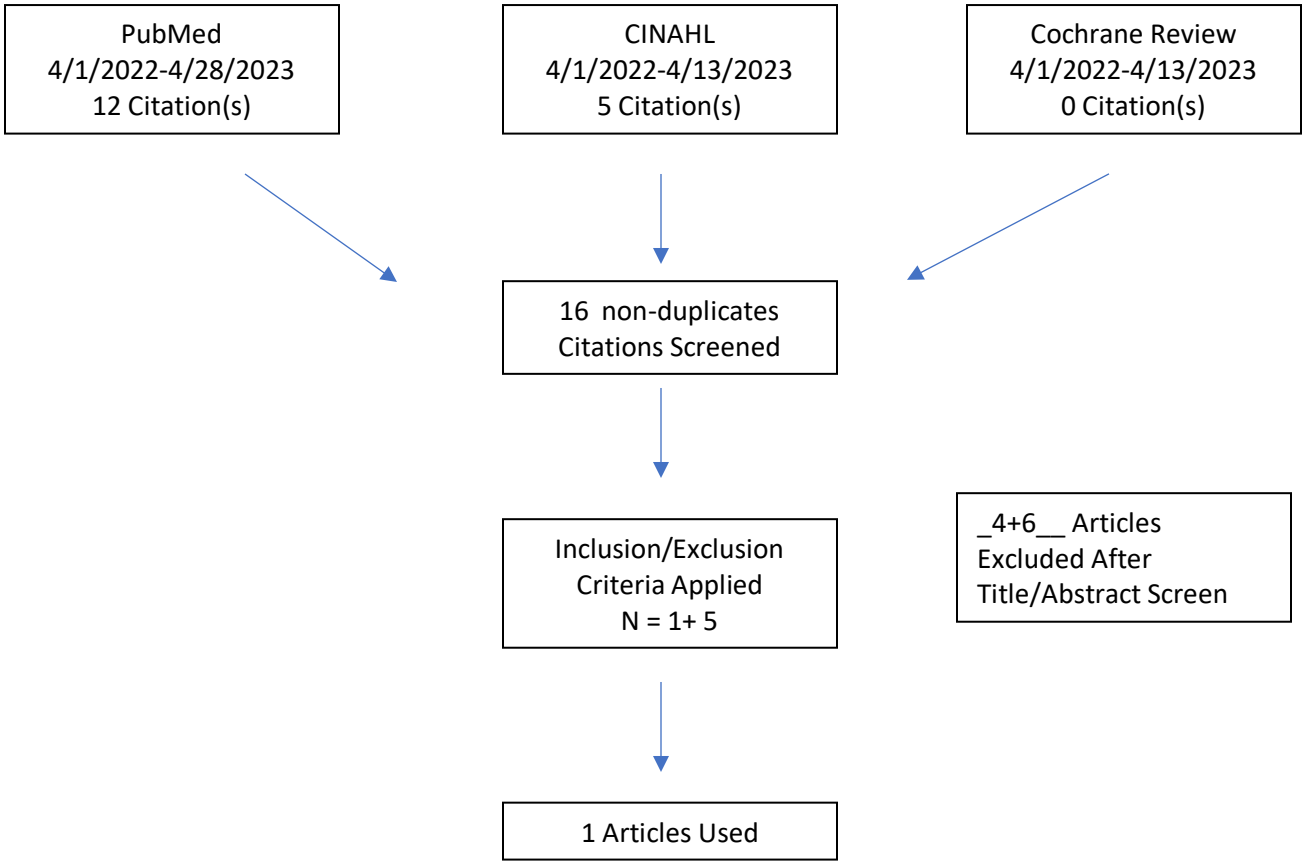
Set	Terms	4/2/2022-4/13/2023
#1	("guanidinoacetate methyltransferase deficiency"):ti,ab,kw or (GAMT):ti,ab,kw or ("GAMT gene"):ti,ab,kw or ("GAMT deficiency"):ti,ab,kw	
#2	MeSH descriptor: [Guanidinoacetate N-Methyltransferase] explode all trees	
#3	(deficiency):ti,ab,kw	
#4	#2 AND #3	11
#5	#1 OR #4	
	Date Range - **2022 – 2023**	
		0

GAMT deficiency inclusion/exclusion criteria. Criteria selected based on criteria used in ACHDNC review committee.

- Animal/non-human or basic science studies (N = 1)
- No original research or analysis (N = 0)
- Study with no primary data (N = 0)
- Natural History or Epi study with less than 10 subjects (N = 3)

- Study of dried blood spots without clinical correlations (N = 0)
- Study of urine for diagnosis (N=1)
- Screening study with less than five 1000 screened by one month (N = 0)
- Screening study only with no diagnosis (N = 0)
- Treatment study with no diagnosis of GAMT deficiency by 12 months (N =0)

Appendix B: PRISMA Diagram



Appendix C: Discussion with Experts - this section includes a summary of interviews with members of the Oregon newborn screening program. A full transcript is available upon request.

Medical Consultant	Title	Institution/ Affiliation	Date interviewed
Amy Yang, MD	Newborn Bloodspot Screening Medical Consultant	OHSU	5/4/2023
Sara Viall P.N.P.	Newborn Bloodspot Screening Medical Consultant	OHSU	4/19/2023
Sandra Van Calcar RD/PhD	Metabolic Registered Dietitian	OHSU	5/3/2023
Patrice Held, PhD	Manager of the newborn screening program in Oregon	Oregon Public Health Lab	4/21/2023

Interviewee: Dr. Amy Yang
Date of Interview: 5/4/2023
Position/Role in NBS Program: Clinical consultant from OHSU; Advisory Board Member
Information needed from interview: Patient care for individuals with GAMT deficiency.

Question(s)	Response
# of patients with GAMT in practice	Dr Yang identified two individuals GAMT deficiency - two family siblings in the same family. "The older child was diagnosed with global developmental delay hypotonia, cerebral palsy and seizures.... seizure gene panel was done and that's how the individual was diagnosed and then at that time the family had already had a newborn child … a couple of months old." The newborn the newborn child was also affected and "some signs and symptoms, but not seizures." These siblings are followed in clinic and receive dietary supplements, but there has been difficulty instituting a protein restricted diet.
Availability of Metabolic expertise? Capacity	Dr Yang relays that there is metabolic expertise. Included in their clinic are four metabolic genetics providers as well as two nurse practitioners, a genetic counselor, two dietitians and a nurse will be added soon. Dr Yang feels there is capacity particularly with the rarity of this disorder.
What is the availability and accessibility of supplements and medical formula?	For supplements, there have not been difficulty obtaining supplements for the family Dr. Yang treats with GAMT deficiency.

Barriers to capacity/assess of care?	"I don't see too much in the way of barriers, honestly, because this is GAMT and the management is supplements, low protein diet and creatine, all of which we're **p**retty skilled at getting from our patients with other for other disorders. So, I think we're OK. I don't think we'll **h**ave any extra challenges with getting the things that we need for our patients compared to other conditions that **we** help with."
Have you had good success with following up with metabolic disorders by telemedicine? Do you think this is a disorder that would lend itself to at least some follow up by telemedicine?	Dr Yang discuss the use of telemedicine for metabolic disorder "I think [issues] is …inherent in all the conditions that we struggle with to manage remotely… I think families who live far away from Portland…do appreciate telemedicine, so this way they don't have to drive the five hours to see us. But it's not ideal. I would say it's hard. It's difficult for us to struggle to get the specialty labs that we need… The monitoring for GAMT specifically we need metabolites like GAA measurements and creatine measurements, and it's really hard to get that sent out. We typically send to Baylor and it's this is not easily attainable for some of the local hospital labs that do not contract with Baylor. I can see as a potential barrier in terms of ongoing monitoring for those who don't live close to us."
Have you heard any concerns about your ability to continue telemedicine?	Dr Yang has not heard concerns about the ability of Oregon to maintain telemedicine to provide services. She states that it is difficult for some families to see specialists; therefore, institutions and coverage for telemedicine should continue.
Benefits and Harms of NBS for GAMT deficiency "What are the benefits and harms not related to treatment that could result from a newborn screening and early diagnosis to infants and to family members?"	"I think the benefit we clearly can identify individuals early on and that will be way more helpful in getting therapy started because the challenge with my family is that they can't seem to get the protein restriction diet down. It's just really, really hard for them. It's hard to start later in life than earlier in life. The difference between the two children, one who started much later in life versus one who started earlier in life, is huge. The younger child is speaking is using words. They're both on adequate therapies, as far as we can tell from their metabolites. So clearly there is a benefit to starting early. We haven't really employed the essential amino acid medical formulas for these individuals, but I can imagine that as we're doing newborn screening." For potential harms, Dr Yang mention false positives that "alarming a family that may not have a condition." She also mentions the potential for carriers to screen positive.
Neither GAMT deficiency nor creatine biosynthesis disorder are listed in that evidence	Dr Yang indicated that this is an important issue to bring to the advisory board. The Oregon Health Authority is aligned with the Oregon Medicaid program. The prioritized list would need to be changed. So, one of the things is asking these questions and whether we can change thing

Commission will. Will that be an issue or concern?	

Interviewee: Sarah Viall P.N.P Date of Interview: 4/19/2023 Title: Pediatric Nurse Practitioner Position/Role in NBS Program: Clinical consultant Information needed from interview: General information about OR NBS	
Question(s)	Response
What do short term follow-up for metabolic disorders (in lab or run by OHSU)?	Ms. Viall explains her role in short-term follow-up. This includes calling out screen positive metabolic diagnosis for newborns in Oregon and providing information to the PCP about confirmatory testing and follow up including its level of urgency. A spreadsheet is shared between the clinic and the laboratory to follow up on newborn screening. When confirmatory testing has been completed the clinical team and lab make a case determination for the screen. 4 New Mexico, the physician consultant speaks with the primary care physician and develops A follow-up plan. The case is handed to the local geneticist, Dr. Marble, when a referral needs to be placed either because confirmatory testing shows the diagnosis or clinical follow-up is needed prior to confirmatory testing being completed.
Clinic follow-up for diagnosis? Clinic follow-up for treatment? What is the availability and accessibility of care and treatment?	Ms. Viall that there is one metabolic clinic in Oregon located at Oregon Health Sciences university in Portland (the northwest corner of the state). The metabolic clinic does have outreach twice a year in Medford OR and twice a year in Eugene OR She points out that any patient "that doesn't live on the I-5 corridor is medically underserved, frankly." The clinic did start using telemedicine more, particularly with the recent COVID-19 pandemic. Ms. Viall discusses that telemedicine is often used for the first appointment after an abnormal newborn screen when clinically appropriate.
Are experts available to provide metabolic (and other) care? Who comprises your team? Is the Newborn Blood spot Screening Medical	"Currently we have four physicians routinely seeing patients. Two of those physicians only have clinic once per month at most. And then we have two full time nurse practitioners who see patients every week. We have one genetic counselor [for metabolism]… we have two metabolic dietitians." For outreach clinics, the schedule is made six months in advance. The team in Eugene is a physician, a nurse

Consultants list (revised May 2022) up to date?	practitioner, and a dietitian. The team in Medford is two physicians and a dietitian.
How do you view the capacity for the program to add new disorders in general?	"We have the capacity to see them. What we really struggle with is the capacity to coordinate complex care." "We have overwhelmed our bandwidth to continue to do that at this point already with what we have currently look, fortunately, OHSU is has supportive of us hiring new staff, which we plan to do. We're gonna get a nurse who's starting in May to help us with those court that coordination which is wonderful."
Are there barriers beyond the geography that you consistently identify for newborn screen follow up?	In Oregon, the Medicaid population is organized into groups of CCOs (Coordinated Care organization) managed by geographic area. A frequent issues for Medicaid is that there is variability between the CCOs in determining medical necessity criteria and coverage. If a patient changes CCO, new medical necessity criteria and coverage has to be completed. CCOs… "supposed to have more local governance and somebody can make their own decisions. And that's all really great. And it's better than just fee for service. It's not a strict fee for service model. But it just it's not equitable for our patients is what we find." Ms. Viall discusses that for several newborn screening disorders local care is important to coordinate, including when patients require enzyme replacement therapy (ERT). Barriers for local care include the CCO system and nursing and health care shortages in these local clinic settings. Both these factors can make it difficult to coordinate and optimize patient care locally. "Oregon is the most medically underserved state. …We have the fewest per capita hospital beds in America and that certainly doesn't help either, so the nursing shortage and medical staffing burnout shortage has been really felt here."
What are solutions or ways to resolve barriers to care?	Ms. Viall discussed that there may be changes to the CCO organization that may be helpful. This changed to thus CCO (i.e., the 1115 wavier) May lead to more equitable coverage with Medicaid.
Is there anything else I should know about the disease and potential addition to the newborn screening panel?	Ms Viall did not express concerns about the addition of GAMT deficiency. She noted for GAMT deficiency is a very sensitive test, rare disease, and has good treatment. She added that when considering a NBS disorder, she is concerned about false positives as she feels they impact the program. For GAMT deficiency she states that false positives

	are less likely, and the treatment is impactful. She states the clinic can provide management of medical diets throughout the state and can medical food and formula coverage without significant issue.

Interviewee: Sandra van Calcar, PhD, RD Date of Interview: 5/3/2023 Position/Role in NBS Program: Metabolic dietitian for OHSU and member of the Advisory Board. Information needed from interview: Patient care for individuals with GAMT deficiency.	
Question(s)	Response
# of patients with GAMT in practice Details of age of diagnosis, clinical features if available.	Dr van Calcar is aware of one patient in the metabolic clinic with GAMT deficiency. There may have been another patient in the past with this diagnosis but is not currently seen. This patient was presented clinically at one year of age with developmental delays and movement disorder, but no seizures. The patient continues to follow in clinic but does have residual developmental delays.
What is the clinic's current management for GAMT deficiency? Clinical follow-up and labs?	Per Dr van Calcar, current management for GAMT deficiency includes protein restricted diet placed on protein restricted diet, creatine, and ornithine. Follow-up in clinic every six months with laboratory monitoring including plasma amino acids and dietary adjustments. The clinic follows the current recommendations in the literature. There are no current guidelines including through GMDI for this disorder.
What is the availability and accessibility of supplements and medical formula?	Formula and supplements are supplied through insurance. There is a mandate to require insurance to cover formula and supplements. Dr van Calcar relays that they are normally able to get amino acid supplementation and formula, but it can depend on the insurance. "We have the Oregon Health Plan, which is also very good at allowing us to get the products people need." She states that it is rare to not get medical formula and supplements covered by insurance. Dr van Calcar also relays that OHSU has a good financial assistance program and there is a social worker in the clinic that can help with getting coverage for children.
Any concerns about the sourcing or quality of supplements?	The clinic distributes the supplements (and the medical formula) to the family rather than the parents purchasing supplements from other sources; therefore, Dr van Calcar has confidence in the high-quality supplements.
Metabolic RD expertise?	Currently OHSU has two metabolic dietitians with expertise in the dietary management of GAMT deficiency. They also have a food room coordinator who assists in billing and insurance for formula and supplements.
Barriers to capacity/assess of care?	Based on the rarity of this disorder, Dr van Calcar feels the metabolic dietitians have the capacity to care for patients found by newborn screening.

	As for barriers for dietary patients, "I think always it comes down to coverage [and] what they have initially it can be an issue… We have social workers here that can work with them to help them sign up for the Oregon Health Plan or whatever happens to be needed. We have financial services here. I think just getting that initial plan for the family is probably the, but once that's figured out seeing them or providing services isn't an issue."
Success with follow-up of metabolic disorders by TM?	"For the dietitians right now, it's probably a 50/50 split" for telemedicine appointments. Dr van Calcar feels that virtual is a good option for patients that are well settled and have a treatment plan that they are accustomed to. She feels initially it is important to see the patient in person, but patients can be transitioned to two more telemedicine appointments. She also notes that telemedicine does give them flexibility when there are issues like bad weather and people can't make the trip to Portland. They have used the local physician and virtual visits to initiate care. Dr van Calcar is not aware of changes to the ability to use telemedicine with the ending of the public health emergency.
What are the benefits and harms not related to treatment that could result from a newborn screening and early diagnosis to infants and to family members?	Dr van Calcar did not identify any harms with newborn screening for GAMT deficiency. GAMT deficiency has "all the hallmarks of something that should be added to newborn screening in my opinion."
Is there an advocate in the state for GAMT deficiency?	Dr van Calcar is not aware of a specific advocate or advocacy group for GAMT deficiency/creatine biosynthesis disorders in Oregon. She is familiar with advocacy for newborn screening through March of Dimes and the National Organization for Rare Disorders.

Interviewee: Patrice Held
Date of Interview: 4/21/2023
Position/Role in NBS Program: Manager of the newborn screening program in Oregon
Information needed from interview: Lab method for detecting GAMT, cost of addition, lab readiness

Question(s)	Responses
Duties related to the NBS	"I oversee the daily operations of both the laboratory testing and the short term follow up team." Within newborn screening, which

	includes education and outreach to people who submit specimens to U.S. hospitals, clinics, providers. It also includes the oversight of the transportation of the specimens, the testing of the specimens, and then the reporting of results to the PCP. Short term follow-up team…. acquires the confirmatory test results from cases that are referred because they screen positive, and so we also oversee that collection and then case determination. We contract with OHSU too, and they do the actual clinical care of the baby's patients that are identified through screening. OHSU covers metabolism, as well as other subspecialties that are needed for newborn screening."
GAMT deficiency. Have you had an opportunity to look into how Oregon might go about implementing that test?	Cases of GAMT deficiency are identified using creatine and elevated GUAC. Previously published literature has shown that these metabolites can be incorporated it into the amino acids and acylcarnitine assay. The Oregon newborn screening laboratory uses an FDA approved kit by PerkinElmer to measure amino acids and acylcarnitines. To add GUAC and creatine for screening of GAMT deficiency, the lab's assay would no longer be an FDA approved kit. This modification would require the laboratory to perform extensive validation of all the analytes prior to use of the multiplex.
Is [validation of the test with GUAC and creatine] something that you feel that you would be able to do with current supplies, machines, and staffing?	The lab has three mass spectrometers that run the multiplex amino acids and acyl carnitine assay. Since screening for GAMT deficiency would be the addition of metabolites to this multiplex, no additional instruments would be needed. Development of the assay would be identifying the parameters to best identify in quantity the additional analytes for GAMT deficiency and then revalidating the multiplex assay including amino acids and acylcarnitines. There is expertise in the laboratory for doing extensive validation. Also, the staff could utilize PerkinElmer research and development team as a lab has a contract with the company Perkin Elmer. There are other competing priorities within the newborn screening laboratory; therefore, it might take longer to implement GAMT deficiency because of the other projects the laboratory is currently working on.
Question about single tier vs multiple tier assay and parameters of sensitivity, specificity, and	Per Dr, Held, the newborn screening laboratory would aim for a single tier test multiplex with amino acids and acylcarnitines assay. "Probably the biggest technical hurdle would be to optimize the system so that you can get the sensitivity and specificity that you need with single tier approach."

positive predictive value?	
Is there a commercial essay from Perkin Elmer or another company?	Dr Held is not aware of a commercially available assay from PerkinElmer or other company.
After assay development, do you feel like you would have the supplies and the staff time to have this in an additional?	Yes. Because the assay is multiplexed, it would not take any additional staffing. "We can certainly manage the inclusion of this disease on our panel."
Timing of assay development? Other barriers?	The estimate for assay development is one year. The lab would be multiplexing the measurements of GUAC and creatine. For assay development, the laboratory would also have to revalidate all the other analytes since they have modified an FDA approved assay. This would mean revalidating the amino acid and acylcarnitine profile, at least 30 different analytes. The next hurdle would be to modify the laboratory information system (Laboratory Information Management system) to be able to analyze the data and generate reports. That process is estimated to take three to four months. Part of this can be completed at the same time as assay development. Developing the assay, validating the assay, then developing and validating the reporting structure, would likely take at least 12 to 18 months.
How is education for disorders on NBS completed for providers and patients?	Dr Held shares that part of contract with OHSU is for time for nurse health educators, Sarah Viall and Leah Wessenberg to help us develop our literature on GAMT deficiency, reach out to PCPs, clinics, hospitals, parents to be able to disseminate that information about the disease - the clinical findings, the treatment and care that is needed. The lab works closely with them and their clinical expertise for education.
Another question that comes up is the fiscal analysis. The RUSP mentions based on information from Utah and from New York, that it would be less	"I'm not surprised by that figure of less than a dollar because again, you're just simply adding on additional analyze, so you would need to the only additional reagent. Let's say that you would need is the internal standards for quantity GUAC and the creatine. Purchasing that and internal standard and then mixing it with other internal standards for all the other analytes, so that it's really just a relatively minimal cost."

than a dollar per infant.	
Is there a point in which the newborn screening lab does a fiscal analysis?	The Advisory Board does not have the ability to change the fees for the newborn screening program. If a new condition is added new condition, the Advisory Board would be making the decision to add the condition on its own merit and the factor of cost might be considered. Dr Held expresses that the fiscal impact of adding GAMT deficiency does need to be evaluated to see if any change in fees is needed with the addition of this disorder.
What barriers do you see for implementation of this of GAMT deficiency?	Dr Held identifies assay development as the biggest barrier. There is the expertise to complete the validation. After validation and implementation, screening for damp deficiency should run smoothly. She thinks it is unlikely to have very many false positives and does not anticipate a huge burden to this system. The other challenge that Dr Held mentions is a change to governmental rules to add this disorder to the panel. There is a legislative process that takes approximately one to two years to introduce this rule change. Dr Held does mention that GAMT deficiency is treated with dietary management which is accessible in Oregon.
APHL Readiness	Oregon - Developmental ready Scale for APHL Readiness - Ability to adopt GAMT deficiency onto the program's existing panel: • Ready - could implement within one year • Developmental ready - could implement within 1-3 years • Unprepared - would take more than 3 years
Other things that I should be asking you about adding GAMT deficiency to the Oregon newborn screen?	“For the committee to decide that balance between the number of cases versus so like the incidence versus the effort.” “I think for GAMT deficiency, what would make it challenging is that it's a very low incidence of disease, but on the flip side, it's also probably a very small amount of cost.”

Appendix D: Excluded Articles

CINAHL

Dong X, Dai H, Sun A, Yu Z, Du Y. Identification of Genes Predicting Poor Response of Trastuzumab in Human Epidermal Growth Factor Receptor 2 Positive Breast Cancer. Meng L, editor. Journal of Immunology Research. 2022 Jul 27;2022:1–14.

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Appendix C: Updated Disorder Review Protocol

Disorder Evaluation for the Northwest Regional Newborn Bloodspot Screening Testing Panel

In 2019, the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board established criteria and a process to evaluate conditions for inclusion on the NWRNBS Program testing panel.

Below is the process for disorder review and the criteria for disorder evaluation. This protocol was updated per approval of the Board on May 29, 2024.

Additional information on the US Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and the Recommended Uniform Screening Panel (RUSP) can be found here: https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html.

Proposed Procedure for Disorder Evaluation

Step 1: Addition to the RUSP

Determine if the disorder has been reviewed by the ACHDNC and added to the RUSP. Disorder recommended for addition to the RUSP by the ACHDNC will advance to step 2 for consideration to the NWRNBS Program testing panel.

Step 2: NWRNBS Program Evaluation

The NWRNBS Program will work with an outside consultant to provide a review of the condition and address the NWRNBS Program Criteria and the Advisory Board Criteria (see below). A report will be provided to the Advisory Board along with a presentation to assist in the deliberations.

Step 3: Public Input on Disorder Review

The Advisory Board will invite input from the public to inform deliberations and recommendation on the disorder to the Program. This public engagement process will be transparent and provide clear opportunities for participation with timely notices and using multiple communication venues. At least one Advisory Board meeting will dedicate time for public input on the disorder.

Step 4: NWRNBS Advisory Board Evaluation and Recommendation using Input from Steps 1–3

The NWRNBS Advisory Board will evaluate disorders using criteria and public input. A consensus tool (see below) will be used to gauge the Board's level of agreement or support for recommending the Program add a disorder to the panel.

Criteria for Disorder Evaluation

(Step 2) Program Review Criteria *The following questions will be reviewed by the consultant and offered as a starting place to the Advisory Board to inform deliberations.*

1. Is the condition well-defined in newborns? Do patients present within the newborn period or are there late-onset, mild presentations of the condition?
2. Will earlier intervention result in improved outcomes?
3. Is the population incidence / prevalence known?
4. Is there a Federal Drug Administration (FDA) approved testing method available or a peer-reviewed laboratory developed test for detecting the condition in dried blood spots? Does the method meet clinical laboratory requirements for validation?
5. Is diagnostic and specialty testing available?
6. Is a treatment available or expected to become available?
7. Is appropriate specialized medical consultation available or able to be obtained by the Program?
8. Does the NWRNBS Program have sufficient information to perform a fiscal analysis?
9. What capacity and expertise are available (or needed) in the NWRNBS program to implement and maintain testing and reporting?
10. What capacity and expertise are available (or needed) to implement and maintain follow-up and education for providers and parents?

(Step 4) Advisory Board Criteria *(Evaluated using the Consensus Method)* *Considering the above feedback from the Program, the Board will deliberate on the following additional criteria:*

1. What is the population level incidence, prevalence, and burden for this disorder for the state/territory?
2. Does diagnostic and specialty testing provide a definitive diagnosis for the intended screened disorder?

3. What is the risk for the family with a false positive newborn screen?
4. What is the risk for the family with an unintended diagnosis, such as late-onset disease?
5. Is an effective treatment for those with a diagnosis, proven to result in clinically significant benefits, available to families in Oregon?
6. What are the significant risks associated with treatment, if any?
7. Is equitable long-term follow-up and management of the disorder available to families in Oregon?
8. Do the population level public health benefits of screening outweigh the risks and harms?

After the above steps are completed, a consensus vote will be taken of all participating members of the Board to determine the level of agreement to recommend a condition being added to the screening panel using the following consensus tool described in the Advisory Board's Charter:

The Advisory Board will strive for consensus on recommendations provided to the NWRNBS Program and the Legislature.

Consensus is defined as "all group members can live with the recommendation or decision." Instead of simply voting for an item and having the majority of the group getting their way, a group using consensus is committed to finding solutions that everyone actively supports, or at least can live with.

A consensus tool using a range of 1-5 will be used to signify whether the group has reached agreement and the level of agreement on a given proposal which can inform the group, and the Agency, whether more work is needed to refine the proposal toward a stronger agreement.

Given the scale below:

- A **strong** consensus is one in which all or most Board members show 1's and 2's on a given proposal.
- A **weak** consensus is one in which some or several Board members show 3's and 4's.
- If anyone in the group shows a "5", the group does not have consensus.
- For weak or no consensus, the Advisory Board will frame up the points of divergence or minority perspectives on a given proposal.

The levels are:

“1” I enthusiastically agree with the proposal/recommendation.

“2” I agree with the proposal/recommendation.

“3” I am on the fence, have questions, or am neutral but can live with the proposal.

“4” I have serious questions or concerns but am not willing to block the proposal.

“5” I object and will block the proposal.

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200-705650a_24 (08/2024)