



Public Health Division

Center for Public Health Practice

Oregon State Public Health Laboratory

2026

Northwest Regional Newborn Bloodspot Screening

Advisory Board Report to the Legislature



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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](#)

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Executive summary

Background

This is the fifth report to the Oregon Legislature from the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board, fulfilling reporting requirements outlined in [HB 2563 \(2019\)](#).



Work of the NWRNBS Advisory Board: 2024–2026

Summary of 2024 to 2026 Board meetings

The Board met eight times in this report period, between September 2024 and May 2026, to review topics that included:

- Charter amendments
- Review of Infantile Krabbe Disease
- Disorder review protocols and criteria
- Modernization of the NBS Program — BRIDGES-NBS study
- Health equity assessment — screened and unscreened populations

Charter amendments

Through a strong consensus, the Advisory Board approved amendments to the NWRNBS Advisory Board Charter that streamlined decision making processes and clarified voting parameters.

Review of Infantile Krabbe Disease

The Board applied its disorder review criteria to Infantile Krabbe Disorder and concluded, by strong consensus, that the disorder met all criteria for addition to the screening panel.

Disorder review protocol

Due to the dissolution of the U.S. Health and Human Services Department HHS Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) in April 2025, the Board temporarily paused review of new disorders. The Board is presently revising the protocol to address issues resulting from the ACHDNC dissolution including ensuring sound scientific review. It is anticipated the Board will adopt a new disorder review protocol in the late fall or winter of 2026/2027.

Duchenne Muscular Dystrophy and Metachromatic Leukodystrophy Review

After the dissolution of the ACHDNC, on December 16, 2025, the U.S. HHS Secretary approved the addition of Duchenne Muscular Dystrophy (DMD) and Metachromatic Leukodystrophy (MLD) to the RUSP. Due to increased local advocacy of adding DMD and MLD to the Oregon screening panel, the Board decided to move forward with reviewing these disorders using the current protocol, instead of waiting for a newly revised protocol.

Modernization of NBS Program — BRIDGES-NBS

The BRIDGES-NBS study is a three-year research initiative funded by the NIH to assess the feasibility of incorporating whole genome sequencing into the existing public health newborn screening programs. The Oregon NBS program, with the support of the advisory board, applied for and was chosen to participate in the study.

Health equity evaluations

In Oregon, approximately 40,000 babies are born each year, and the majority receive newborn screening. While the success of screening programs is unequivocal; a growing number of families either decline or do not receive this essential public health service for their baby. The NWRNBS Program identified populations most at risk of not receiving screening and this data was shared with the Board.

Work within legislative sessions: 2025–2026

- HB 3192 (Rep. Nelson, McLain): Appropriates funds from the General Fund to the Oregon Health Authority to support adding testing for five specific diseases. This bill was sent to the Ways and Means Committee but did not move forward.
- HB 2741 (Rep. Nelson, Sen. Manning Jr.): This bill updates the statute language for the NBS program. It also specifies that OHA will implement an educational program for screening and conduct a follow-up program to improve the long term care of individuals with medical conditions. This bill was signed into law by the Governor, effective January 1, 2026.

Updates to Oregon Administrative Rules: 2025–2026

The Oregon Administrative Rules for newborn bloodspot screening OAR 333-024 were updated twice in 2025 with the support of the advisory board.

- The first rule making with changes implemented on November 1, 2025, updated newborn bloodspot screening definitions to add clarity, aligned with current practices, and added Infantile Krabbe Disease to the screening panel.
- The second updates to the rules went into effect on January 1, 2026. The rule amendments were made to align with the statute changes from the 2025 legislative session (HB 2741).

Introduction

This is the fifth report of the Northwest Regional Newborn Bloodspot Screening Program Advisory Board (Board). The Board was formed under HB 2563 (2019). This report fulfils the 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 Program of the Oregon State Public Health Laboratory and referred to here as the “Program”). The Board assists by providing the following:

- Advocacy
- Advice
- Recommendations
- Technical information

There are 13 seats on the Board, with members representing medical specialists, pediatricians, birth hospitals, community birth providers, Medicaid, advocacy organizations, and families. 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 4, 2024
- December 4, 2024
- March 4, 2025
- May 28, 2025
- September 3, 2025
- December 3, 2025
- March 3, 2026
- May 27, 2026



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 Program sells test kits to medical providers. The provider takes a small blood sample from the newborn's heel and sends the specimen to the Program. 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 Program sends the test results to providers who perform confirmatory testing, discuss any abnormal results with parents, and set up treatment plans, if needed. The Program 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.

Newborn bloodspot screening saves lives.

Detailed summaries of those meetings are available at the OHA website at: www.oregon.gov/oha/PH/LABORATORYSERVICES/NEWBORNSCREENING/Pages/advisory.aspx

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

- Revisions to the Board's charter to clarify voting processes and parameters.
- Information from experts on Infantile Krabbe Disorder. This disorder was evaluated and recommended by the Board for addition to the NBS Program's testing panel during this report period.
- Next steps in implementing addition of GAMT and MPSII disorders to the NBS Program's testing panel.
- Current consideration of revisions to the Board's disorder review protocol due to implications resulting from the dissolution of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC).
- NWRNBS Program's participation in BRIDGES-NBS.
- Health equity evaluations, as it pertains to access to screening.
- Future direction of the Board.

Charter amendments

In December 2024, the Board approved amendments to its Charter to clarify and streamline its decision-making processes.

The original Charter required all Board decisions to be made using a consensus tool where Board members were required to reach consensus and indicate a level of agreement on a scale of 1 to 5. While this tool is helpful and provides greater transparency in level of support for recommendations on adding conditions to the Program panel, it was cumbersome and unnecessary for routine and/or Board business decisions (e.g., meeting summary approvals). To allow for more expedient voting and decision-making, the Board approved an amendment that allows the 1 to 5 consensus tool for recommendations on disorder additions to the Program screening panel while allowing other Board business decisions to be decided by majority vote. Language requiring a consensus vote on all Board decisions was removed.



Clarification language was also added to the Charter stating proxy voting was not allowed for Board decisions.

Specific language additions are shown below in bold text:

“Absences: Board members must inform the co-chairs in advance of a Board meeting if they will be unable to attend. If a Board member knows they will be absent, they can submit written comments to the NWRNBS Manager in advance of The Board meeting **but cannot delegate a proxy vote.**”

“Quorum: A majority of the voting members of The Board constitutes a quorum for the transaction of business. Each Board member has one vote and cannot vote in absentia **or by proxy.**”

*“Vote **Required: The express approval of a majority of a quorum of The Board is necessary for any Board decision. Exceptions can be made to require a consensus of the quorum of The Board for the purpose of disorder review protocols should The Board formally adopt the process in advance of such decisions.***”

These amendments were approved by consensus at the Board's December 4, 2024, meeting. A copy of the adopted amended Charter is provided in [Appendix A](#).

Infantile Krabbe Disease: Criteria, public comment, consensus check, recommendation and implementation

Review to add Infantile Krabbe Disorder to the screening panel

The Board considered a proposal to add the Infantile Krabbe Disorder to the newborn bloodspot screening panel and reached a strong consensus that it should be added.

On July 1, 2024, Infantile Krabbe Disease was added to the Recommended Uniform Screening Panel (RUSP) by the Secretary of Health following the recommendation of the secretary's advisory committee on heritable disorders in newborn and children (SACHDNC).

<https://mchb.hrsa.gov/sites/default/files/mchb/programs-impact/recommended-uniform-screening-panel-table-december-15-2025.pdf>

This addition to the RUSP initiates the Board's review of IKD to determine if Oregon should screen for this condition (step 1). The Board reviewed, discussed, and evaluated the disorder based on its established protocol ([appendix B](#)). Following preparation of the executive review and summary ([appendix C](#) and [D](#)), the Program stated that IKD met all category one criteria (step 2). The Board provided an opportunity for public comments in favor or opposition for including IKD to the Oregon panel (step 3). The Board reviewed and discussed category 2 criteria and using a consensus tool came to a final recommendation to the NWRNBS Program in favor of adding IKD to the Oregon panel (step 4).

Infantile Krabbe Disorder background

Krabbe Disease (KD) (or globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme galactocerebrosidase (GALC) activity. Patients with KD present with a neurologic phenotype that varies based on age of onset. Infantile Krabbe Disease (IKD) (low GALC and psychosine > 10nM) typically presents within the first six months of life with irritability, feeding difficulties, abnormal neurologic exams including spasticity of the extremities with axial hypotonia and regression of developmental skills. Patients experience progressive neurodegeneration leading to early mortality, often by 2 years of life. Early identification of IKD by newborn screening allows

for treatment with hematopoietic stem cell transplantation. To obtain optimal results, transplant should occur before signs and symptoms of disease, ideally by four to six weeks after birth, as patients with an earlier transplant demonstrate better outcomes. Data indicates improved survival as well as developmental and neurologic benefits from transplantation, although individuals still experience ongoing developmental delays and motor disabilities. For additional details, please see the executive summary and evidence report in [appendix C](#) and [D](#).

Application of criteria for addition

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

Category 1 criteria: The following criteria were responded to by the NWRNBS Program:

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. 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 Program. 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 Program has sufficient information to perform fiscal analysis. Yes.

Category 2 criteria: The Board discussed category two criteria as is applied to IKD screening:

1. The population level public health benefits of screening outweigh the risks and harms.
2. There is adequate capacity and expertise in the NWRNBS Program to implement and maintain testing and reporting.

3. The NWRNBS Program has adequate capacity for conducting follow-up and education for providers and parents.
4. The NWRNBS Program 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 NWRNBS partners does not prohibit the addition or removal of the disorder.

Public comment

Verbal and video testimony from members of the public was shared during the March 2025 board meeting. Thirteen individuals provided input based on their personal experiences and/or knowledge of IKD. All verbal testimony was in favor of adding IKD to the Oregon NBS panel.

Written statements were submitted by four individuals and one organization. Four of the written testimonials supported adding IKD to the Oregon NBS panel. One testimony did not support adding IKD to the panel.

Consensus check

The Board conducted a consensus check to determine whether they would recommend adding IKD to the screening panel. The vote was made using the 1-5 consensus tool with 1 for full agreement and 5 for no agreement. The vote from individual board members ranged from 1 (full agreement) to 3 (neutral).

There was *consensus* to recommend adding Infantile Krabbe Disorder to the Newborn Screening Panel.

Consideration of late-onset forms of Krabbe Disease

The RUSP only recommends screening for the infantile form of Krabbe Disease, defined as a psychosine level above 10 nmol/L. Psychosine test results < 2 nmol/L are considered normal. Psychosine test results that are between 2 nmol/L and 10 are outside the normal range and indicative of a later onset or atypical form of Krabbe.

A question arose whether Oregon should set its psychosine cutoff at 10 nmol/L to only detect IKD cases or set its cutoff at 2nmol/L to capture all forms of Krabbe Disease.

After consultation with the Mayo Laboratories, who perform psychosine testing, and the OHA legal team, it was decided that all babies with an elevated psychosine greater than 2 nmol/L will be referred for additional testing and evaluation, even though our target of the screening test is IKD. The Board agreed with this decision.

Implementation of Infantile Krabbe Disease screening

Screening for IKD was implemented by the NWRNBS Program on November 1, 2025. **As of May 1, 2026, over 30,619 babies have been screened.** During this period, only one baby screened positive for IKD and is currently undergoing evaluation by the contracted medical consultants at Oregon Health & Science University.

Screening for GAMT Deficiency

On January 4, 2023, GAMT deficiency was added to the RUSP by recommendation of the ACHDNC. In the fall of 2023, GAMT deficiency was reviewed by the NWRNBS Advisory Board, and a recommendation was made to the Program to implement screening.

The NWRNBS Program is currently performing the method validation for GAMT deficiency. The NWRNBS Program anticipates implementation of screening prior to January 2027. Over the next couple of months, the Program will update the OAR to include screening for GAMT deficiency, outline appropriate reporting and follow-up actions for babies that screens positive, and notify providers and parents of this change to the panel of conditions.



Screening for Mucopolysaccharidosis Type II



On August 2, 2022, MPSII was added to the RUSP by recommendation of the ACHDNC. In the summer of 2023, MPSII deficiency was reviewed by the NWRNBS Advisory Board, and a recommendation was made to the Program to implement screening. To date, the Program has not implemented screening for MPSII.

The Program has encountered several barriers including the lack of an FDA approved kit for screening and acquisition of additional instrumentation and resources. The NWRNBS Program continues to work with OHA leadership on finding resources to help support the addition of MPSII, along with other conditions to the Oregon panel.

Disorder review protocol

The U.S. Health and Human Services (HHS) Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) was dissolved in April 2025. Previously, the ACHDNC had been charged with recommending disorders to be included on the HHS Recommended Uniform Screening Panel (RUSP).

The current NWRNBS Advisory Board disorder review protocol requires a condition be reviewed by the ACHDNC and added to the RUSP. With this requirement no longer possible to meet, and with questions remaining on how HHS planned to address the national review of disorders, the Board chose to pause on reviewing additional conditions for the Oregon screening panel pending greater clarity on HHS' disorder review and approval process. The Board also decided to focus on the implementation of two previously reviewed conditions, MPSII and GAMT Deficiency, during this interim period.

However, at the end of 2025, the U.S. HHS Secretary approved the addition of Duchenne Muscular Dystrophy (DMD) and Metachromatic Leukodystrophy (MLD) to the RUSP. Due to those decisions, and with increased local advocacy of adding those conditions to the Oregon Program screening panel, the Board decided to move forward in revising their review protocol to remove barriers for future disorder reviews.

At the time of this report, revisions to the review protocol were under discussion with a decision anticipated in late 2026 or early 2027. At a minimum, the Board intends to remove language referencing the now defunct ACHDNC.



DMD and MLD disorder review

Also at the May 27, 2026, meeting, the Board considered requests from state legislators and advocates to review the DMD and MLD. Due to the Board's preliminary agreement that protocol language referencing the ACHDNC is no longer relevant, the decision was made to move forward with reviewing these disorders using the current protocol.

Modernization of the NBS Program — BRIDGES-NBS



The BRIDGES-NBS study is a three-year research initiative funded by the NIH Common Fund Venture Program. The aim is to investigate if whole genome sequencing (WGS) can be responsibly and ethically integrated into existing public health newborn screening programs. Oregon was chosen to be one of the participating public health programs for the study, along with Iowa, Texas, Minnesota, South Carolina, New York, and Puerto Rico.

The study is not intended to replace the current newborn screening process, rather it will add additional testing for families who have consented to participate. Only one newborn bloodspot screening sample will be collected. Routine newborn bloodspot screening will proceed as typical. Once routine screening is completed, the sample will be sent for sequencing. Sequencing will be performed and results will be sent back to the existing public laboratories and the newborn screening follow-up teams for delivery to the baby's provider using existing mechanisms for communication. If the baby screens negative, the sequencing report will be faxed to the provider. If the baby screens positive, the Program will inform the primary care provider and associated specialists for a referral and additional testing.

The genomic sequencing will be looking at over 800 conditions in comparison to the 46 currently on the newborn screening panel. All of the conditions in the panel have actions that can be taken within the first year of life to prevent morbidity and mortality associated with the conditions.

The goal is to enroll and sequence 30,000 babies across all seven programs, with roughly 4,500 from Oregon over a two-year period. An expected 3-5% positivity rate is anticipated following sequencing. The Program anticipates enrolling families as soon as Fall of 2026.

There will be both active and passive recruitment of study participants in Oregon. Peace Health and OHSU have agreed to be sites for active recruitment. Passive recruitment will be done through social media, targeted campaigns, and parent groups to reach people statewide and direct them to website information and instructions.

GeneDx will perform sequencing and will hold the genomic data for up to five years, at which time it will be destroyed. Families can voluntarily share their baby's DNA analysis to public databases. Parents may request destruction of stored sample and data at any time.

The Board supported Oregon's engagement with the study. However, they did identify potential areas of concern, where the research study may have a negative impact on routine screening practices. The Program will take these concerns into consideration, as the study plan develops.

More information can be found on the study website: <https://www.bridgesnbs.org>

Health equity evaluations

Newborn screening (NBS) programs detect congenital conditions in babies, prior to the onset of symptoms, and escalate care for prevention of adverse outcomes. In Oregon, approximately 40,000 babies are born each year, and the majority receive testing for the 46 conditions on the panel, with more than 100 babies diagnosed with a disease. While the success of screening programs is unequivocal, a growing number of families either decline or do not receive this essential public health service for their baby. In alignment with Oregon's goal to end health inequities, it is imperative that the NWRNBS Program identify populations most at risk of not receiving screening and mitigate barriers in access.



To determine the number of unscreened babies over a four-year period and to assess attributes of this population that may have impacted screening uptake, a retrospective database match between vital statistics birth records and the NBS records was performed. Following analysis, babies were categorized as either screened or unscreened. Next, demographic data for each baby was extracted from the birth record, which included mother's race, age, and education, WIC status, prenatal care received, previous live births, type of birth attendant, birth setting and location, and payor

The results revealed that nearly 1% of the babies born in Oregon do not receive screening, with the number of unscreened babies increasing each year. Statistically significant differences in screening rates among key variables such as birth attendant type, birth setting, and payor were observed. Most unscreened babies are born at home or in a birth center under the care of a midwife (licensed or unlicensed) or a non-medical person. Fifty percent of families self-pay for the birth of their baby in the unscreened population, as opposed to public options and private insurance. Families who reside in frontier regions of the state have twice as many unscreened babies (versus screened) and the percentage of unscreened babies is also higher in rural areas, as compared to urban areas. Evaluation of the Kotelchuk Index, which measures the adequacy of prenatal care, in the unscreened population shows that 37% of babies and mothers received prenatal care considered inadequate. Additional information can be found within the [2025 NBS annual report](#).

The Oregon Health Authority has adopted the strategic goal of ending health inequities. To meet this objective all newborns must have access to screening. In 2024, OSPHL received one-time funds for subsidized cards from the legislature to be used for families who pay out of pocket for screening. At the end of 2025, 476 babies received screening at no cost because of this initiative. The Program plans to continue offering subsidized cards for as long as there are funds available addressing any financial barrier to screening. Additionally, the Program plans to improve content and delivery of educational materials to support the needs of different populations, exhibiting lower screening rates.

This data was presented to the NWRNBS Advisory Board. The Board advocates on behalf of the screening Program and the families it serves. Addressing health inequities, particularly in access to screening, is a key priority of the Board.

Future direction of the Board

As the Board moves forward within the environment of changing federal approaches, limited resources, new technologies, and public expectations, it will work to address the following objectives to the extent feasible:

- Improve newborn screening in the State of Oregon in all its facets including addressing equity concerns regarding access to screening, specifically within Oregon's frontier communities.
- Address perceived "unanswerable questions" with curiosity and tenacity.
- Explore opportunities to help fill the resource and technical support gap left by the ACHDNC dissolution that ensured scientifically sound determinations of which conditions should be added to state panels. These opportunities should address Oregon-specific needs as well as incorporating RUSP guidelines.
- Incorporate new knowledge before creating testing guidelines to avoid inadvertently causing harm and ensuring a plan for addressing data with no clear application.
- Address limited staff capacity to implement testing for new diseases.
- Anticipate impacts of new technological and scientific innovations including genomic sequencing and create a protocol that considers the pace of innovation and the current policy and resource parameters.
- Collaborate with subject matter experts in other states to consider applicable resources, in developing scientifically sound action plans.



Conclusion

The Board has proven to be effective in addressing disorder reviews, streamlining its decision-making processes, adapting to federal policy changes, providing advice on Program priorities, and supporting transparency and public engagement. It conducted an efficient review and recommendation to add Infantile Krabbe Disorder ensuring a sound, scientific review and a transparent and robust public input process. As significant changes took place at the federal level, most notably the dissolution of the ACHDNC, the Board strategically and thoughtfully adjusted their planning and approach to mitigate implications for the disorder review process. The Board also supported the Program by providing input on new initiatives, such as the BRIDGES-NBS study and helped the Program address inequities in access to screening.



Appendices

Appendix A: NWRNBS Advisory Board Charter



NORTHWEST REGIONAL NEWBORN BLOODSPOT SCREENING PROGRAM
ADVISORY BOARD CHARTER

Updated: December 4, 2024

Purpose and Scope of Authority

- I. The purpose of the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board (The Board) is to provide advocacy, advice, recommendations, and technical information based on members' respective areas of expertise. The Board shall assist NWRNBS Program with strategic planning and the development of policies, priorities, and services related to newborn screening including the addition or removal of tests; while considering the newborn screening system as a whole, to improve health outcomes for all infants and their families.

Sponsor

- I. *Executive Sponsor:* The executive sponsor of The Board shall be the Center Administrator for the Center for Public Health Practice, in the Public Health Division of the Oregon Health Authority.

Membership, Appointment and Service Terms:

I. Membership:

a. *Voting Members:*

- i. *Board Representation:* The Board shall be comprised of 13 voting members from the following:
 1. One member who is a person affected by a disorder included in the newborn screening panel or a family member of a person affected by a disorder included in the newborn screening panel;
 2. One member who is a licensed physician who by contract provides expert medical advice and consulting serves to the Northwest regional Newborn Bloodspot Screening Program;
 3. One member who is a representative of Medicaid or the insurance industry;
 4. Two members who are representatives of birthing centers or hospitals;
 5. One member who is a representative of an entity that contracts with the Northwest Regional Newborn Bloodspot Screening Program for newborn bloodspot screening services;
 6. Three members who are representatives of advocacy associations regarding newborns with medical conditions or rare disorders;
 7. One member who is a representative of a statewide association of nurses;

8. One member who is a representative of a statewide association of midwives; and
 9. Two members who are representatives of a statewide association of pediatricians.
- ii. *Discipline Representation:* One or more of the following professions must be represented as a voting member of The Board:
 1. Neonatal intensive care specialist;
 2. Licensed physician or nurse practitioner who is board certified in obstetrics, pediatrics or neonatology;
 3. Obstetrician or gynecologist;
 4. Nurse;
 5. Ethicist;
 6. Geneticist;
 7. Dietician; and
 8. Educator.
 - iii. *Inclusive Representation:*
 1. Newborn Screening touches all infants equally and is a system that requires representation from a diverse set of stakeholders to provide the best outcomes for infants and families. As much as possible, Board representation is intended to capture the diversity of the system to bring a balanced and inclusive view to inform the policies and priorities of the NWRNBS.
 2. To the greatest extent practicable, the Board shall have representation from a diverse range of socioeconomic, racial and ethnic backgrounds.
 - b. *Non-voting members:* Members of the Legislature or employees of the Oregon Health Authority may serve as honorary and non-voting members of The Board.
 - c. *Subject matter experts:* Subject matter or technical experts may be invited as guests to provide pertinent information for board consideration and contribute their expertise to specific topics of discussion. These subject matter experts shall not vote on board items unless they are already a voting member of The Board.
 - d. *Board Chairs and Vice Chairs:* The Board will have two Board chairs and one vice chair. One chair will be a voting Board member, the other chair will be the NWRNBS Manager or Manager designee, and the vice chair will be a voting Board member. The NWRNBS Manager or Manager designee must be a nonvoting member.

II. **Appointment and Service Terms:**

- a. *Appointment:*
 - i. *Appointment:* Board members shall be appointed by the Director of the Oregon Health Authority and serve at the pleasure of the director. Before the expiration of the term of a board member, the director shall appoint a successor whose term begins July 1st next following.
 - ii. *Vacancies:* If there is a vacancy, the director shall make an appointment to become effective immediately for the unexpired term.
- b. *Service Terms:*
 - i. *Board Membership terms:*

1. *Initial Board terms:*
 - a. Three members shall serve for a term ending July 1st, 2020
 - b. Three members shall serve for a term ending in July 1st, 2021
 - c. Three members shall serve for a term ending in July 1st, 2022
 - d. Four members shall serve for a term ending in July 1st, 2023.
2. *Routine Board membership:* After initial membership, voting members of The Board shall serve four-year terms. Members are eligible for reappointment.
 - ii. *Voting Board chair and vice chair terms:* The initial term for the chair and vice chair will be one year. After the initial term, the chair and vice-chair selected by The Board will serve a two-year term. Term lengths can be reviewed at the will of The Board.
 - c. *Resignation:* Board members can resign their membership by notifying the Director of the Oregon Health Authority and the NWRNBS Manager in writing that they wish to resign their position and the date their resignation will be official.
 - d. *Absences:* Board members must inform the co-chairs in advance of a Board meeting if they will be unable to attend. A Board member who is absent for two consecutive Board meetings will be considered to have resigned unless there are exceptional circumstances which have been conveyed to the co-chairs prior to their absence from the second meeting.

Sub-committees

- I. *Formation of Sub-committees:* Sub-committees with a defined purpose can be formed as necessary by the co-chairs.
- II. *Appointment:* The NWRNBS Manager shall appoint members and chairs of sub-committees. These appointments shall be reviewed by The Board chairs.
- III. *Operating Procedures:* Sub-committees will follow the same operating procedures as The Board. Sub-committee chairs shall provide feedback to The Board, as well as sub-committee meeting minutes and necessary reports.
- IV. *Dissolution of Sub-committees:* If it is determined that a sub-committee has fulfilled its purpose, it can be dissolved by the NWRNBS Manager upon recommendation of The Board.

Roles and Responsibilities

Board members bring their expertise from many parts of the newborn screening system including, but not limited to, clinical care, patient/family experience, and public health. Together members can provide a more holistic view of the newborn screening system and are expected to share information gained as a member of The Board with their represented organization, stakeholders, and others in their field.

- I. *All Board Members:* Board members shall:
 - a. Bring an open mind and be prepared to work collaboratively with others.
 - b. Review and agree to The Board charter and operations.
 - c. Sign a Conflict-of-Interest Disclosure form yearly.
 - d. Attend Board meetings either in person or by teleconference.
 - e. Inform the NWRNBS Manager of Board meeting absences in advance.
 - f. Review Board meeting materials and participate in Board meetings in representation of their expertise to provide advice and recommendations.
 - g. Participate in Rule Advisory Committees (RACs) for Newborn Screening rule changes.

- II. *Board Chairs and Vice Chair*: Board chairs and vice-chair shall:
 - a. Ensure a respectful, professional, and welcoming environment to encourage participation and collaboration
 - b. Assist in the creation of meeting agendas and meeting materials when appropriate.
 - c. Confirm sub-committee members.

Meeting Logistics and Operating Procedures:

I. Meetings

- a. *Frequency*: The Board shall meet at least once every six months. The Board may hold additional meetings by the call of one or both chairpersons or of a majority of the voting members of The Board.
- b. *Location*: The Board shall meet at a time and location determined by The Board. One meeting each year shall be an in-person meeting where all Board members shall attend in-person except for exceptional circumstances or as otherwise determined by The Board. All other meetings shall be attended remotely unless otherwise determined by the Board.
- c. *Absences*: Board members must inform the co-chairs in advance of a Board meeting if they will be unable to attend. If a Board member knows they will be absent, they can submit written comments to the NWRNBS Manager in advance of The Board meeting but cannot delegate a proxy vote.
- d. *Open to Public*: Board meetings shall be open to the public and adhere to Public Meeting requirements.
- e. *Compensation*: Voting board members are entitled to compensation and expenses as provided in ORS 292.495.

II. Operating Procedures

- a. *Voting on Board items*:
 - i. *Quorum*: A majority of the voting members of the board constitutes a quorum for the transaction of business. Each Board member has one vote and cannot vote in absentia or by proxy.
 - ii. *Consensus*: The Board will strive for consensus on recommendations provided to the NWRNBS Program and the Legislature.
 - iii. *Vote Required*: The express approval of a majority of a quorum of the Board is necessary for any Board decision. Exceptions can be made to require a consensus of the quorum of the Board for the purpose of disorder review protocols should the Board formally adopt the process in advance of such decisions.

Reports

I. Reports

- a. *Initial Report*: No later than December 15th, 2019 the Board shall conduct its first meeting and report its findings, which may include recommendations for legislative changes, to the committees or interim committees of the Legislative Assembly related to health.
- b. *Subsequent Reports*: The Board shall report its findings and recommendations for legislative changes to the committees or interim committees of the Legislative Assembly related to health no later than September 15th of each even numbered year.

- b. *Open comment period:* During every Board meeting there shall be a period for open public comments. The length shall be determined by the Board chairs.
- c. *Onboarding of new Board members:* New Board members shall review The Board charter and sign a conflict-of-interest form.

Values

- I. Respect – we value all members and welcome the uniqueness and diversity of their experience and viewpoints because it allows us to consider all sides of an issue.
- II. Inclusivity – we actively search for partners that will help represent diverse communities and viewpoints so that we can work for all infants and their families.
- III. Candor – honesty and willingness to share information are essential to the communication that will allow us to build a system that works to ensure the health of all infants and their families.
- IV. Collaboration- working collaboratively allows us to leverage each person's strengths and brings balance to our discussions and recommendations.

Appendix B: Current 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?
1. Will earlier intervention result in improved outcomes?
2. Is the population incidence / prevalence known?
3. 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?
4. Is diagnostic and specialty testing available?
5. Is a treatment available or expected to become available?
6. Is appropriate specialized medical consultation available or able to be obtained by the Program?
7. Does the NWRNBS Program have sufficient information to perform a fiscal analysis?
8. What capacity and expertise are available (or needed) in the NWRNBS program to implement and maintain testing and reporting?
9. 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.

Appendix C: Executive Summary — Newborn Screening for Infantile Krabbe Disease

Executive Summary: Newborn Screening for Infantile Krabbe Disease (low GALC and psychosine $\geq 10\text{nM}$)

Purpose:

This is a summary document for use by the Northwest Regional Newborn Screening Bloodspot Screening (NWRNBS) Advisory Board in their evaluation of Infantile Krabbe Disease (IKD) for inclusion on the NWRNBS testing panel. This document includes scientific evidence and an assessment of the NWRNBS Program and partner readiness. It is not intended to make decisions on behalf of the Advisory Board. The format of this document follows the criteria adopted by the Advisory Board for assessment of conditions:

Step 1: Addition to the RUSP

Determine if the disorder has been reviewed by the Advisory Committee on Heritable Disorders in Newborn and Children (ACHDNC) and added to the Recommended Uniform Screening Panel (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. Time will be dedicated during an Advisory Board 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 Program add a disorder to the panel.

Methods: This document summarizes evidence gathered in systemic evidence review (SER) process, including evidence published after the Advisory Committee on Heritable Disorders in Newborn and Children's (ACHDNC's) external evidence review report for Infantile Krabbe Disease (IKD). Subject matter experts, including medical consultants and NWRNBS Program staff and partners were consulted, and a summary of those discussions are provided here. A reference to a more detailed evidence report is provided for each of the criteria below.

Appendix D: Evidence Report — Newborn Screening for Infantile Krabbe Disease

Evidence Report: Newborn Screening for
Infantile Krabbe Disease

Prepared for the Northwest Regional Newborn
Bloodspot Screening Program Advisory Board

March 4, 2025

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Abbreviations:

ACHDNC - Advisory Committee on Heritable Disorders in Newborn and Children

NWRNBS - Northwest Regional Newborn Screening Bloodspot Screening

OHSU - Oregon Health and Sciences University

RUSP - Recommended Uniform Screening Panel

TEP – Technical Expert Panel

GALC – Glucocerebrosidase

HSCT - Hematopoietic stem cell transplantation

IKD - Infantile Krabbe Disease

LIKD – Late Infantile Krabbe Disease

Introduction

Background and Purpose

HB 2563 required the formation of the Northwest Regional Newborn 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 approved a process and criteria for addition of disorders to the bloodspot screening panel. This protocol was updated per approval of the Board on May 29, 2024.

The stages are summarized below:

Step 1: Addition to the RUSP

Determine if the disorder has been reviewed by the Advisory Committee on Heritable Disorders in Newborn and Children (ACHDNC) and added to the Recommended Uniform Screening Panel (RUSP). Disorders recommended for addition to the RUSP by the ACHDNC will advance to step 2 for consideration to the NWRNBS 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 both 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 recommendations 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. Time will be dedicated during an Advisory Board 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 Program add a disorder to the panel.

Scope of Review

This evidence report follows the evidence outline as presented by ACHDNC, beginning with discussion of natural history of the condition, followed by incidence and prevalence estimates, discussion of screening, diagnosis, and treatment. This report also provides context and implications for initiation of Infantile Krabbe Disease screening within the NWRNBS program.

The executive summary, which accompanies the evidence report, for Infantile Krabbe Disease presents evidence for each criterion as outlined in the updated protocol.

These documents, evaluate and summarize available scientific evidence and expert opinion on screening for Infantile Krabbe disease, for evaluation by the board. These reports are not intended to make recommendations for or on behalf of the board.

Methods

This report summarizes findings from the ACHDNC review of Infantile Krabbe Disease (low GALC and psychosine $\geq 10\text{nM}$) and more recently published literature.

Krabbe disease has undergone evidence review by ACHDNC on three separate occasions. The first evidence review captured literature from a 20-year period from January 1988 to November 2008. The subsequent review in 2023 evaluated the literature between 1/1/2010 – 1/10/2023 (through a primary search 1/1/2010-7/1/2022 and bridged search 7/1/2022-1/10/2023). For the third expedited evidence-based review, published literature between 1/10/2023 and 11/22/2023 was evaluated. To capture recent, relevant literature for the NWRNBS evidence report, an updated literature search was conducted for publications between 11/22/2023 – 1/5/2024.

In each section of the NWRNBS evidence review, a description of the ACHDNC review is included, along with the literature updates. The focus of the evidence review is Infantile Krabbe disease and newborn screening. Infantile Krabbe Disease (IKD) is defined as low GALC and psychosine > 10nM throughout the remainder of the report.

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

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

Evidence Review of Infantile Krabbe disease (low GALC and psychosine > 10nM)

Nomination history of Krabbe Disease to the Recommended Uniform Screening Panel (RUSP)

In 2009, full evidence review of Krabbe disease was performed by the Health and Human Services' ACHDNC. The natural history of early Infantile Krabbe disease (IKD) was well understood and there was a demonstrated benefit from early diagnosis and treatment. However, there were also recognized harms due to screening (1). These potential harms included: lack of consensus on case definitions, a need for additional information about testing algorithms, and more information on specific benefits of hematopoietic stem cell transplantation (HSCT) (1). At time, the committee **voted NOT to recommend** Krabbe disease to the RUSP.

In 2022, the nomination for Krabbe Disease: both infantile and late infantile phenotypes underwent the external evidence review. At a meeting in February 2023, the committee did not recommend KD to the RUSP due to a lack of sufficient evidence for a significant net benefit to the population (2). The committee cited the need for additional published data on efficacy of HSCT for early IKD and the need for data regarding outcomes of infants who are at risk for late infantile Krabbe disease (2). The committee again **voted NOT to recommend** Krabbe disease to the RUSP.

In 2023-2024, a revised, expedited external evidence review of only IKD (low galactocerebrosidase and psychosine greater than 10nM) was conducted. Evaluation by external committee liaisons to the evidence review group did not recommend addition to the RUSP, but the full committee assessed the data differently, and **voted to recommend** the addition of IKD (low galactocerebrosidase and psychosine greater than 10nM) to the RUSP in February 2024 (3).

Each nomination evaluated a different case definition for Krabbe disease. The case definitions included: Krabbe Disease in 2009 review, Infantile and Late Infantile Krabbe Disease (LIKD) in 2023, and only Infantile Krabbe Disease (low GALC and psychosine greater than 10nM) in 2024. The changes in the case definition modified the data review (the data met the case definition) and therefore revised the epidemiology, newborn screening and diagnostic algorithms, treatment outcomes, and the harms and risks associated with newborn screening.

Condition Overview

Krabbe Disease (or globoid cell leukodystrophy) is a lysosomal storage disorder caused by deficiency of galactocerebrosidase (GALC) activity. It is an autosomal recessive disorder due to pathogenic variants in the gene, *GALC*, which encodes for the galactocerebrosidase (OMIM #245200) (4). Accumulation of metabolites including psychosine lead to injury in neurologic cells and abnormal brain myelination (5).

Patients with Krabbe Disease present with a neurologic phenotype with signs and symptoms varying based on the age of onset. Those with an earlier onset of the disease often have developmental delay, loss of developmental skills, and early mortality (6). Infantile Krabbe Disease (IKD) typically show signs and symptoms within the first six months of life. Infants present with irritability, feeding difficulties, abnormal neurologic exam including spasticity of the extremities with axial hypotonia and regression of developmental skills (5). Progressive neurodegeneration leads to early mortality in these children often around age 2 (3).

Later onset Krabbe Disease represents anyone with signs or symptoms beginning after 12 months of age. This group of individuals can be further broken into Late infantile Krabbe Disease, Juvenile Krabbe Disease and Adult Onset Krabbe Disease. All have neurologic disease with symptoms including spasticity, seizures, and peripheral neuropathy.

Diagnosis of Krabbe Disease can be suspected and confirmed by a combination of (7):

- Clinical findings
- Newborn screen
- Biochemical evaluation of galactocerebrosidase activity and psychosine levels
- Molecular testing of the *GALC* gene
- Neuroimaging showing evidence of a leukodystrophy.
- Abnormal neurophysiological studies - nerve conduction velocity, brain stem auditory evoked response, visual evoked potentials
- Increased cerebrospinal fluid (CSF) protein concentration.

Treatment for Krabbe disease when found clinically is supportive care. If a patient is detected pre-symptomatically due to newborn screen or family history, treatment with HSCT improves survival and has developmental and neurologic benefits, but is not curative (8).

What is the pathophysiology of the disease?

The enzyme galactocerebrosidase breaks down specific galactolipids, including galactosylceramide and psychosine. Decreased enzyme activity leads to accumulation of ceramides which form a specific type of pathologic macrophage, called globoid cells, in the white matter of the brain. Krabbe disease is also referred to as globoid cell leukodystrophy (5).

Accumulations of psychosine leads to destruction of oligodendrocytes and Schwann cells and stops myelin formation, which leads to white matter damage in the central nervous system and demyelination in the peripheral nervous system (9).

Case Definition

Is the condition well-defined in newborns?

For the most recent review by the ACHDNC, the disorder was confined to IKD with biochemical markers of low GALC and elevated psychosine $\geq 10\text{nM}$. This case definition narrows the cohort of individuals to only those that are expected to present within the first six months of life and may benefit from treatment with HSCT(3).

Do patients present within the newborn period or are there late-onset, mild presentations of the condition?

Like many metabolic disorders, Krabbe Disease has significant clinical variability with presentation of disease between early infancy and adulthood. For this most recent review of Krabbe Disease, biochemical markers were used as part of the definition for disease (3). Use of the biomarkers is intended to allow for the identification of individuals with IKD, who are potentially amenable to treatment with HSCT (3). Please see Table 1 in the next section for categorization of Krabbe Disease based on age of onset. Patients with Krabbe Disease present with a neurologic phenotype that varies based on age of onset of signs and symptoms of the disease. Earlier signs and symptoms of disease are associated with more severe and rapidly progressive disease.

Table 1: Categories of Krabbe Disease based on age of onset – table adapted from A Summary of the Evidence and Advisory Committee Decision (3)(6)(5)(7).

	Age of onset	Typical Signs and Symptoms
Infantile Krabbe disease (IKD)	Signs and symptoms within the first six months of life.	Irritability Feeding difficulties Spasticity of lower extremities with axial hypotonia Peripheral neuropathy Regression of developmental skills Progressive neurodegeneration leading to early mortality often around age 2
Late Infantile Krabbe disease (LIKD)	7-36 months, typically starting around 14 months	Spasticity Developmental delay and/or loss of skills Visual impairment Seizures Peripheral neuropathy Regression
Juvenile Krabbe disease	3- 15 years; typically, 4-6 years of age	Behavioral difficulties including attention deficit hyperactivity disorder and mood disorders. Motor difficulties
Adult onset Krabbe disease	after 15 years of age; signs and symptoms usually appear around 32 years	Spastic paraplegia with or without peripheral neuropathy No cognitive deterioration

What is the age of onset, age of diagnosis without screening, and treatment without newborn screening?

Onset of symptoms is variable, but infants with IKD present within the first month of life suggesting that disease progression may start in utero for some individuals (9). Table 2 shows summaries of studies about individuals with Krabbe disease, many with IKD.

Table 2 reviews studies about the natural history of KD. Two studies reported on the average age of symptom onset versus diagnosis. Beltran-Quintero et al reported median age of symptoms at four months with diagnosis at six months of age (10). Bascou et al reported delay of diagnosis of approximately 3.5 months (11).

Table 2 - Summary of studies evaluating the distribution of IKD phenotype. (Table adapted from the 2023 ACHDNC Evidence based review of 248 reported cases including age of onset and survival spanning 1982 to 2017 (9)).

Report	Information on study	Early Infantile (%)	Diagnosis	Survival	Initial signs and symptoms
Komatsuzake et al (12)	Systematic review of case reports and case series Case total: 248 1982-2017	98 /248 (39.5%)	Age of onset 4 (3–5) months	Median: 1.5 years	N/A
Krieg et al (13)	Cross-sectional evaluation Germany Case total with data: 38/51 2003-2017	71%	Age of onset 0-6 months	For 12 patient, time of death known (Between 10 and 32 months, mean 13 months).	Agitation/ irritability 80% Movement problem and/or developmental regression (63%)
Beltran-Quintero et al (10)	Report of diagnosis of KD from age 0-5 months between 1999-2018	N/A	Reason for diagnosis • 13 Family history • 75 diagnosed due to symptoms that	70% died by 2.5 years	Irritability (54%) Feeding difficulties (36%) Spasticity (33%)

			developed on average at 4 months, with diagnosis at 6 months		
Bascou et al (11)	Report 35 subjects with onset of Krabbe disease between 6 and 36 months of age 2000 - 2017	N/A	Age of onset: 3.5 months (range: 0–21 months). Age of Diagnosis: 17.8 months of age (range: 0–39 months)	12 (34%) died, with a median survival time to 6.7 years	Developmental regression (41%) Irritability (38%) Abnormal gait (22%) Motor delay (16%) Abnormal muscle tone (13%).

Incidence and Prevalence of Infantile Krabbe Disease

What is the estimated birth prevalence? Are there specific populations where incidence increases?

Birth prevalence for Krabbe disease is estimated at 1 in 100,000 births in Europe and one in 250,000 births in the United states (7, 9). There are other studies that suggest there is a higher birth prevalence due to underestimation, as cases may not be identified with the appropriate diagnosis (9). Gene frequency studies suggest the prevalence could be as high as 8.3 per 100,000 live births (9).

Due to newborn screening, the incidence is being further refined. See sections below on screening outcomes.

There is no identified increased incidence in a specific population within the United States. In the Middle East, the Druze community in northern Israel and two Muslim Arab village near Jerusalem have been identified as having a carrier rate of one in six (7).

How many people are diagnosed with this condition clinically?

Until the start of newborn screening for Krabbe Disease, many individuals were found upon clinical presentation. A small number of individuals were identified due to a family history of Krabbe Disease.

At Oregon Health and Sciences University (OHSU), there has been only one recent case of childhood onset Krabbe Disease that clinicians are aware of during the last five years.

Screening for infantile Krabbe disease

What screening method is used to detect Krabbe disease among newborns?

Over time, the screening method for Krabbe disease has evolved. Initially, New York State (the first state to enact Krabbe newborn screening) used galactocerebrosidase enzyme activity with

second tier molecular GALC analysis (14). Psychosine has replaced molecular GALC testing as a second-tier screen for most programs (15).

More recently, data was evaluated to identify a specific cutoff for psychosine concentration that would identify IKD rather than LIKD in hopes of improving the net benefit of screening (3). Based on the data reviewed, a dried blood spot psychosine value of <10nM was determined to be very low risk of IKD (3). At the time of the expedited review, no state used a psychosine cut off of <10 nM (3).

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?

At present, there is an FDA - approved kit for measurement of the enzyme activity for galactocerebrosidase on dried blood spots (NeoLSD MSMS Kit by Revvity). This kit evaluates for galactocerebrosidase as well as the enzymes associated with other lysosomal storage disorders (Gaucher Disease, Niemann-Pick A/B Disease, Pompe Disease, Fabry Disease, and Mucopolysaccharidosis (MPS) Type I Disease) (16).

For second-tier testing of psychosine on dried blood spots, this is available and generally performed in reference laboratories rather than within the newborn screening laboratory (3). Reference laboratories that perform dried blood spot psychosine include Mayo Clinic Laboratories, Greenwood Genetics Center, Revvity, and Nationwide Childrens Hospital.

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

The use of second-tier psychosine testing allows for high sensitivity and specificity for Krabbe disease with the two-tier screening. Psychosine is specific for Krabbe disease as it is a metabolite related to the disease pathophysiology (3) (5). In a review of the specificity of psychosine for IKD versus a LIKD, 10 of 11 individuals with LIKD showed psychosine levels less than 10nM and one with a value of 12nM (17). Newborn screening programs already screening for Krabbe disease have not reported cases of IKD with psychosine <10 nM (3).

The technical expertise panel as part of the 2024 ACHDNC reviewed data about the sensitivity of psychosine >10 nM and found the sensitivity near 100% (3). Most cases of IKD have psychosine significantly >10 nM as reviewed by 26 cases of IKD with the range from 10 to 108nM (median 48.5nM) (17).

What are the findings for screening for Krabbe Disease in states that have implemented screening?

In the United States, multiple states screen for Krabbe Disease. Nine states use the combination of first-tier screening with low GALC activity and second-tier screen with psychosine (3). Other states that screen for Krabbe disease include Ohio and New Jersey but they do not use second-tier psychosine. The testing algorithm does vary from state to state including the cut-off used for psychosine to determine infants that should be referred for further evaluations. The table below

represents information requested from the nine newborn screening programs using psychosine as the second-tier and reviewed in the context in the use of a second-tier psychosine greater than 10 nM(3). This data was also recently published (18).

Table 3. Screening Results Reported by State Newborn Screening Programs (Adapted from 2024 Expedited Review and published literature) (3) (18).

Screening Program	Period	Number Screened	Positive First-tier	Psychosine ≥ 10 nM	Infantile Krabbe Disease	Known/Suspected Later-Onset KD not detected with Psychosine ≥ 10 nM **
GA	9/30/21-11/30/23	329,661	63 (19.1 per 100,000 screened)	1 (1.6% of positive first-tier screens)	1 (3.0 per million screened)	0
IL*	12/1/2017-9/30/2023	848,000	600 (70.8 per 100,000 screened)	5 (0.8% of positive first-tier screens)	5 (5.9 per million screened)	12 (14.2 per million screened)
IN	7/2020-11/2023	272,077	148 (54.4 per 100,000 screened)	0	0	10 (36.8 per million screened)
KY	2/15/16-6/30/23	404,626	128 (31.6 per 100,000 screened)	2 (1.6% of positive first-tier screens)	2 (4.9 per million screened)	0
MO	3/20/2020-8/31/2023	232,721	401 (172.3 per 100,000 screened)	3 (0.7% of positive first-tier screens)	1 (4.3 per million screened)	1 (4.3 per million screened)
NY	1/1/2021-9/30/23	572,197	38 (6.6 per 100,000 screened)	0	0	2 (3.5 per million screened)
PA	5/21/2021-10/31/2023	316,918	43 (13.6 per 100,000 screened)	1 (2.3% of positive first-tier screens)	1 (3.2 per million screened)	3 (9.5 per million screened)
SC	5/15/2023-11/27/2023	29,748	16 (53.8 per 100,000 screened)	0	0	0
TN	7/1/2017-9/30/2023	545,085	68 (12.5 per 100,000 screened)	1 (1.5% of positive first-tier screens)	1 (1.8 per million screened)	5 (9.2 per million screened)
Total		3,551,033	1,505 (42.4 per 100,000 screened)	13 (0.9% of positive first-tier screens)	11 (3.1 per million screened)	33 (9.3 per million screened)

*In Illinois, no information from the newborn screening program is available about the 5 cases of infantile Krabbe disease. However, information was obtained from a treatment center in Illinois regarding four of these cases of infantile Krabbe disease.

** Represents cases of late onset KD that would not be detected by use of a second-tier psychosine $\geq 10\text{nM}$.

The table above indicates that with the addition of psychosine as a second-tier metabolite would identify be 3.1 patients with IKD per million infants screened. The only false positive reported was in the Missouri program which upon further investigation was found to be a laboratory error (3). No false negatives have been reported.

Confirmatory Testing and Diagnosis

Is diagnostic testing available to confirm presence of disease in newborns who screen positive?

Diagnostic testing is available to confirm presence of disease in newborns who screen positive for IKD. Diagnostic testing can include galactocerebrosidase enzyme activity in leukocytes, blood psychosine levels, and molecular testing for variants in the *GALC* gene. 2021 guidelines recommend psychosine level greater than or equal to 10 nanomole consistent with IKD and should be immediately referred for evaluation (19).

Is diagnostic and specialty testing available?

Yes, galactocerebrosidase activity on leukocytes, blood psychosine level and *GALC* testing are all available. Technical standards do exist for testing of biomarkers including psychosine (20).

To make the diagnosis of KD clinically, a combination of factors including clinical findings, MRI spectroscopy, abnormal neurophysiological studies and other laboratories studies such as elevated protein in cerebrospinal fluid can prompt clinicians to complete further biochemical or molecular testing (7).

Treatment and its outcomes

What are the standard treatments for Infantile Krabbe disease? Are there treatment guidelines for Infantile Krabbe disease?

For patients clinically identified, only supportive care is available. HSCT must be completed in pre-symptomatically to be effective to reduce mortality and benefit the neurologic and developmental phenotype (8).

Current treatment for Krabbe disease involves hematopoietic stem cell transplant typically from umbilical cord blood. HSCT can also be completed from bone marrow or peripheral cells, but the current source for Krabbe disease is cord blood. This treatment can improve survival and developmental outcomes in those with IKD who are treated pre-symptomatically(8). For IKD, HSCT is recommended by four to six weeks after birth before significant disease involvement (9). One article comparing transplant before one month of age and after one month of age showed improved neurologic and developmental outcomes with transplantation before one month (21). Unfortunately, HSCT is associated with morbidity and mortality, particularly within the first ten days after transplantation (9) . Morbidity associated with HSCT includes graft versus host disease and infection (3). There is a 10% mortality rate with the transplant (22).

In 2018, consensus guidelines on newborn screening, diagnosis, and treatment of IKD were published based on the experience of New York and other states (15). In 2021 consensus recommendations for classification and long term follow up for screen positive patients were published and divided care into 3 pathways including Early Infantile Krabbe disease (19). There are also clinical practice guidelines about HSCT for Krabbe disease and other leukodystrophies (23).

Currently, there are no other clinically available treatments for IKD. Some families choose not to treat their infant with HSCT for IKD after informed counseling (3).

Will earlier intervention result in improved outcomes?

There is prior data on clinical outcomes with HSCT for patients with Krabbe disease. The earliest transplants were completed in the late 1990s. Data indicates that HSCT in IKD improves survival, but neurologic and development outcomes can be more variable.

In the ACHDNC report, clinical outcome data was limited to those individuals that had been diagnosed by newborn screening with low galactocerebrosidase and psychosine > 10nM to match the case definition(3). From that collected data, eleven patient cases were described (Table 4) including seven patients underwent HSCT, six of the seven infants were alive for at least two years after transplantation. (3).

Table 4 -Clinical outcome data available from 2024 expedited report outlining clinical treatment decisions and outcomes for individuals treated above(3).

Summary	Eleven cases detected on NBS with low GALC and psychosine > 10nM.
	Seven cases underwent HSCT

	6/7 are alive at 2 years or more (median 2.5 years, range 2-5 years).
	Three cases did not undergo treatment with HSCT. 1 patient death at 14 months 2 patients with unknown outcomes -up
	One case has no follow-up information.
Individual cases of HSCT	- HSCT at 24 days, now 5 years old - HSCT at 30 days, now 3 years old - HSCT at 1 month, now 2 years old, preparing for gene therapy to address persistent health problems including developmental impairment - HSCT at 34 days and again at 169 days, now 2 years - HSCT at 35 days, death around 7 months due to graft vs. host disease. - HSCT at 40 days, now almost 5 years - HSCT at 42 days, gene therapy at 24 months, now 28 months old

For more information about outcomes including survival and neurodevelopmental outcomes, the ACHDNC report summarizes seven cases (Table 5). Table 5 shares initial psychosine level, GALC genotype, age at transplant, and age at assessment.

- Five of six infants reviewed in the 2023 evidence review who received HSCT around one month of age were identified through newborn screening (9). Two of these patients overlap with patients described in table 4. One patient from that the 2023 review was lost to follow up.
- One infant not in the 2023 review who also who received HSCT around one month of age after IKD was identified through newborn screening.

Table 5 - Clinical data on patients with neurodevelopmental assessments completed. Adapted from table 4 in the 2024 expedited review (3).

Psychosine (nM)	GALC Genotype	Age at HSCT (days)	Age at Neurodevelopmental assessment (years)
70	30kb del (het, path) c.1851del(p.try617) (het, path) c.550C>T (p.Arg184Cys) (het, VUS)	32	2.2
35	c.1723_1724insT (p.G575Vfs*10) c.1913G>T (p.G638V) [het, path] c.1685T>C (p.I562T) [het, Pseudo]; c.742G>A (p.D248N) [het, Pseudo]	40	4.7
38	30kb deletion (het, path) [c.1270C>T 9p.Gln424Ter]] (het, path)	28	5.2
83	c.387c->g (homo, path).	31	5.8

	c.1885T->C (pseudo), c.550 C->T (pseudo)		
61	p.W629MfsX9 (Trp629MetfsX9); p.I562T (Ile562Thr) // delEx8-Ex9partial; p.I562T (Ile562Thr); p.R184C (Arg184Cys)	24	6.9
24	30kb deletion (loss of exons 11-17) (het, path*) and exon 4-c.379C>T (p.R127X) (het, path); (c.1161+6532_polyA+9kdel)	30	7.1

For the patients in Table 5, survival was reviewed and compared with historical data of patients who had not received HSCT. Figure 1 shows all treated patients survived, while no untreated patient survived.

Figure 1. Survival of IKD infants treated with HSCT compared to not treated. (Figure from 2024 expedited review (3)).

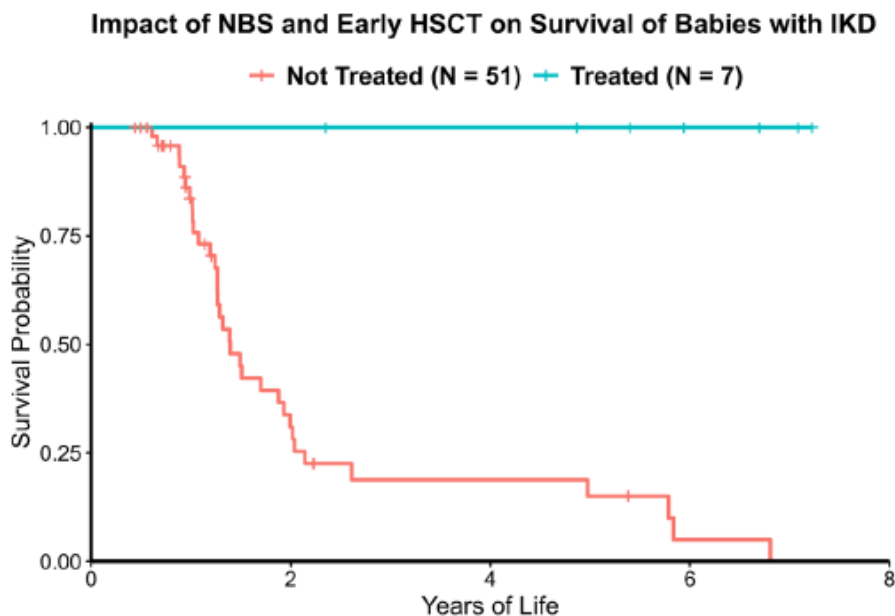
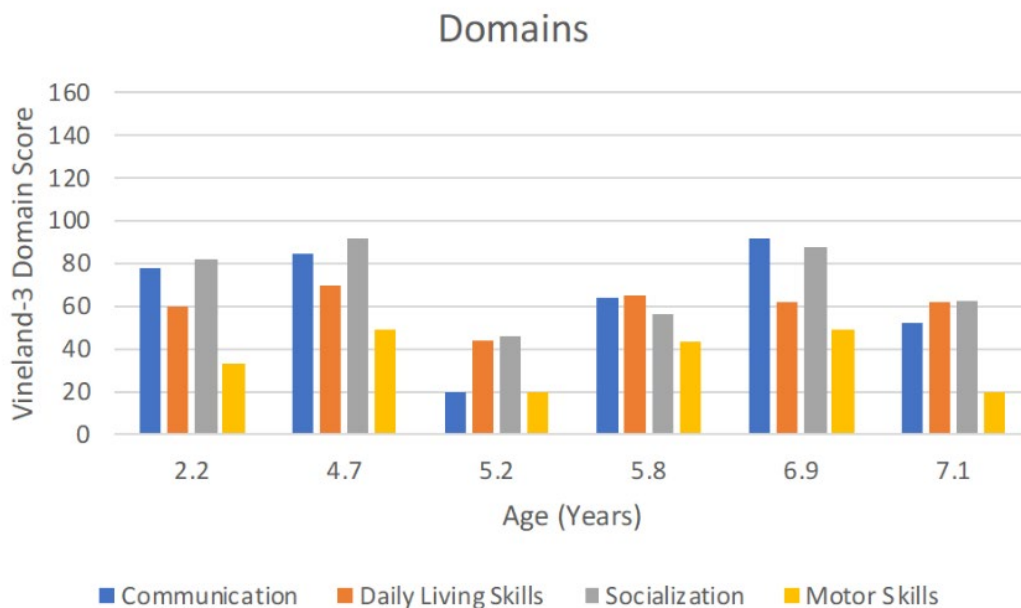


Figure 2, again data from the patients in Table 5, are evaluated for neurodevelopmental outcomes. The two neuropsychology assessments completed on this cohort were:

- Vineland-3 adaptive behavioral composite score (third edition) - Standardized assessment tool using parent/caregiver interview and checklist from parent/caregiver and/or teachers, to rate independent functioning in four adaptive domains (communication, daily living skills, socialization, and motor skills). Score interpretation is 40-60-Extremely Low; 60-70-Very Low; 70-80 – Low; 80-90 - Low average; 90 and above—Average (25).

Figure 2 Vineland-3 scores in the four domains of communication, daily living skills, socialization, and motor skills. (Figure from 2024 expedited review (3)).



Poster conclusions from the authors included (3):

- All seven individuals treated with HSCT around the first month of life for IKD were all alive compared to historical data where all individuals with IKD who did not undergo treatment (i.e., HSCT) died. Therefore, HSCT around the first month of life for IKD is associated with decreased risk of mortality (3).
- For the Vineland-3, all had markedly decreased gross motor subscores.
- “All [subjects] have deficits, which are most significant in areas affecting gross motor function. In contrast, social, communication, psychosocial, emotional and school performance were stronger and in the adequate range in half of the children tested.”

At the ACHDNC meeting, the Committee Liaisons to the Evidence Review Group presented on IKD (22). The presentation made several conclusions including the HSCT improves affected individuals’ lifespan and neurodevelopmental course, but some families of affected individuals may not find this improvement enough to undergo HSCT with its associated morbidity and mortality.

Is a treatment available or expected to become available?

As discussed above, disease modifying treatment for IKD is HSCT. OHSU does have a HSCT service which has performed transplantation in the past for Krabbe Disease.

Screening process

The ACHDNC expressed that the timeline from newborn screen to treatment with HSCT at 4-6 weeks of age is challenging. Each step in the newborn screening process (collection, transit, testing, reporting, referral, confirmatory testing, and preparation for HSCT), has the potential for errors and delay(22).

Oregon estimates a time from birth to a positive NBS for Krabbe disease would be 7 days, but potentially longer due to delayed collection of the screen or shipping issues. Screening steps include collection of the sample at 24-48 hours of life, shipping and processing at newborn screening laboratory, assay completion, and second-tier assay (shipping to reference lab and assay completion). A positive screen would then be called to a metabolic consultant to initiate confirmatory testing, evaluation and referral for HSCT. Dr Yang discussed hospital admission as an option to decrease the time to diagnosis and help with barriers like geography, specialty testing, and insurance.

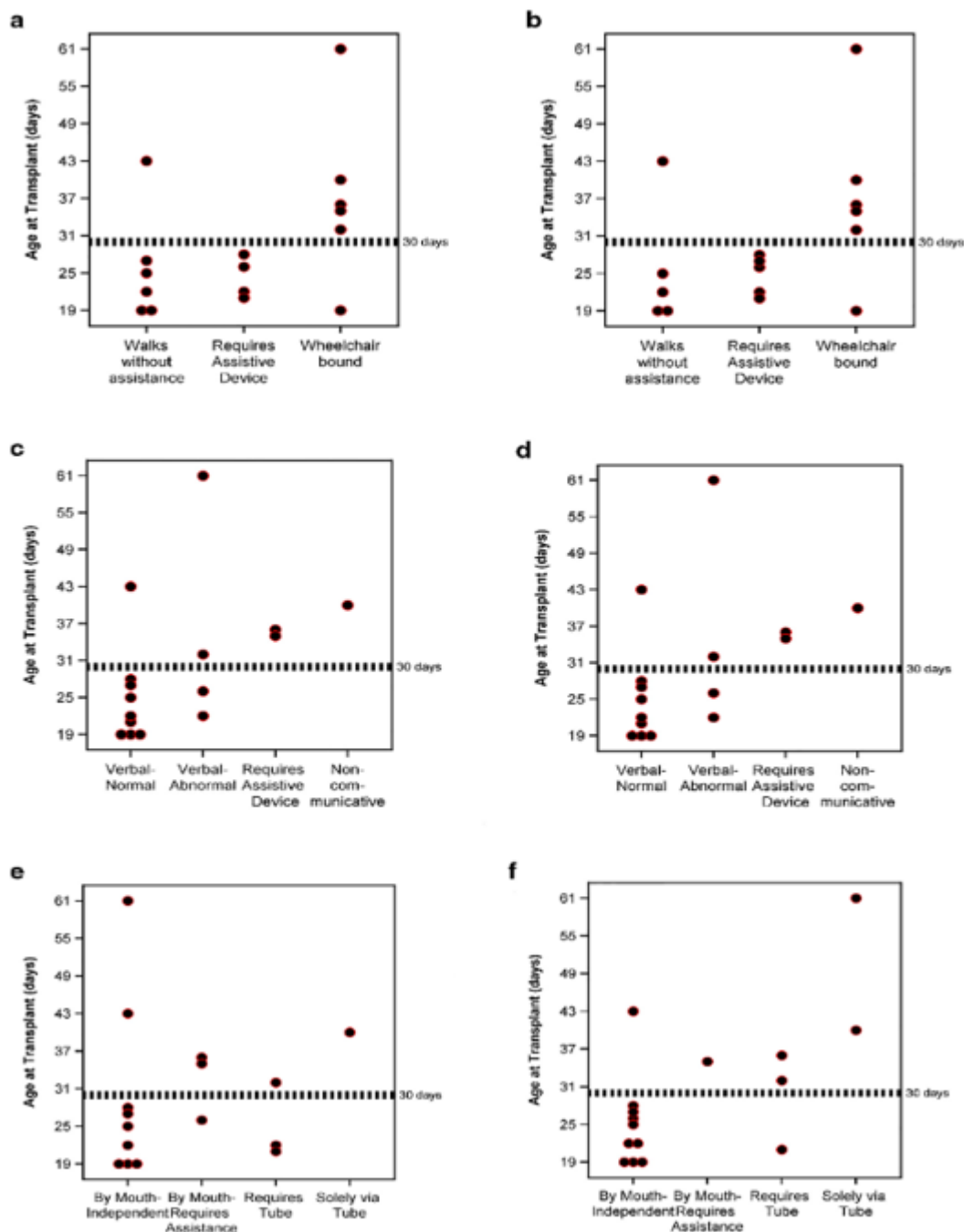
Transplant process

There are fourteen centers, none in Oregon, listed in the Leukodystrophy Care Network which meet the Leukodystrophy care network requirements. The list of centers including two in Northern California is available at www.hunterhope.org/family-care/leukodystrophy-care-network/lcn-care-centers.

In conversation with Dr Nemecek, director of the Pediatric Bone Marrow Transplant Program at Oregon Health Sciences University (OHSU/Doernbecher Children's Hospital), she felt HSCT could be completed by her team within one month of diagnosis (rather than age). Multiple guidelines stress the goal for transplant by one month of age, noting improved outcomes for patients when meeting this timeline (3) (8) (19) (15).

Figure 3 below presents data from a published review of 19 patients with IKD (diagnosed by family history or 3 by newborn screening in NY state) who underwent HSCT before 2 months of life between 1996-2010 (26). Three patients passed away prior to five year follow-up due to transplant related concerns (21). For the remaining 16 patients, the paper summarizes neurodevelopmental outcomes in mobility, communication, and feeding. In general, outcomes were better when transplant was completed prior to 30 days of age (21).

Figure3 from Allewelt et al. Graphs compare motor, communication and feeding abilities at five years post-transplant and with most current follow up. The dashed line represents individuals with transplant before or after 30 days of age. A – mobility status at 5 years post-transplant, B - mobility status at most recent follow-up, C- communication abilities at 5 years post-transplant, D - communication abilities at most recent evaluation, E- feeding abilities at 5 years post-transplant, F - mobility status at most recent evaluation.



Future treatment options

Currently, HSCT is the only treatment available for IKD. There is continuing research to evaluate the outcomes of HSCT in IKD, as well as LIKD (27) (28). Research includes working to establish meaningful clinical endpoints to help assess HSCT and monitor patients, as well as evaluate the effects of future therapies (29).

There is significant research looking into the underlying pathophysiology of leukodystrophies like Krabbe Disease with the hope that better understanding will lead to therapeutic interventions (30). A number of recent articles look at various therapeutic interventions from substrate reduction therapy, enzyme replacement therapy, chaperonin therapy, anti-inflammatory therapies, neuronal stem cell therapies, small molecule therapies and gene therapies (30) (31) (32) (33) (34) (35).

Potential Benefits and Risks of Newborn Screening

What are the benefits and risks that could result from newborn screening for infantile Krabbe disease?

The ACHDNC reviewed benefits and risks for families identified through IKD newborn screening. In a survey of family members impacted by Krabbe disease, 97% felt that Krabbe Disease should be implemented in every state (36). However, the survey only contacted patients in a family registry for Krabbe Disease or other leukodystrophies, therefore it may not represent the opinions of all families impacted by screening and the disease. The expedited report also adds that there have not been new studies to evaluate the family's experiences or perspective related to Krabbe disease and newborn screening (3).

Table 6. (Modified from Table 2 Newborn Screening for Krabbe Disease: A Summary of Evidence and Advisory Committee Decision 2023)(6).

Benefits	Risks
• Earlier detection and more direct diagnosis of Krabbe disease • Earlier access to treatment with HSCT. Although, it is not a cure of IKD, this treatment improves survival and clinical outcomes.	• False reassurance for families whose child has a later onset Krabbe disease • Mortality with treatment – for HSCT estimated at 10% • Treatment refusal after thorough counseling of treatment risks and outcomes

Of note, by adding psychosine as part of the case definition, it modifies benefits and risks of screening, by removing those attributed to LIKD including:

- Removes: Benefit of earlier monitoring for babies at risk for LIKD who do not need treatment right away
Removes: Risk of Individuals that would need monitoring for months or years for possible KD and possible unnecessary HSCT for LIKD.

Consultant views on benefits and harms to newborn screening

Clinical consultants for OHSU were asked about their point of view on newborn screening and care for IKD.

- Dr Yang notes that the current treatment with HSCT prolongs survival with less neurologic sequelae than without treatment, but there are neurologic sequelae. Dr Yang shares her experience with newborn screening for Krabbe disease during her training in New York State. She shares the difficulty of confirming the diagnosis of IKD prior to use of second-tier psychosine as well as the stress of the diagnosis and need for urgent decision making for treatment. For her experience, the initial positive newborn screen the family chose not to transplant, and the patient passed away. Their subsequent child also had was screened positive for IKD and passed away from complications from transplantation.

- Dr Starosta expresses his concerns about the outcomes for HSCT. He notes that few patients have undergone HSCT, and the data has not been replicated outside a couple transplant centers. He states he does not think there is sufficient evidence of the benefit of HSCT for patients with IKD. Dr Starosta shares his experience of positive newborn screen for IKD during training in Missouri where the infant had multiple complications from the transplantation as well as neurologic deterioration.
- Ms. Viall mentions concern that there is not clear information about expectations for neurodevelopmental outcome for a patient with IKD after HSCT.

NWRNBS Program Impact Assessment

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

- Screen numbers
- 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.)

ACHDNC screening outcome data

To estimate the number of newborn screens and IKD diagnoses resulting in the Oregon Newborn Screen program, data from other State Newborn Screening Programs provided in the 2024 ACHDNC was reviewed. Table 4 shows calculated first-tier positive screen with low GALC requiring second-tier psychosine as well as positive screens for IKD.

The following assumptions were made to calculate screening and IKD numbers:

- Approximately 60,000 births a year from Oregon and New Mexico
- Estimated positive first-tier screens of 42.4 per 100,000 screened. There was significant variability from state to state based on laboratory method and GALC cut-off values for the number of first-tier screens(3).
- All positive newborn screens for infantile Krabbe disease based on low enzyme activity and psychosine $\geq 10\text{nM}$ are expected to be a true positive.

Table 4. Projections for Oregon newborn screening numbers based on results reported by State Newborn Screening Programs (3) (18), (22).

Screening Program	Period	Number Screened	Positive First-tier	Psychosine $\geq 10\text{ nM}$	Infantile Krabbe Disease
Total from State Programs currently screening for Krabbe Disease	2016-2023	3,551,033	1,505 (42.4 per 100,000 screened)	13 (0.9% of positive first-tier screens)	11 (3.1 per million screened)
Oregon Newborn Screening program	N/A	~60,000 births per year	25.4 newborns per year*	< 1 positive screen per year	Estimate 1 positive screen per 5 years

* All low GALC screens would be sent in an expediated fashion to a reference laboratory for a psychosine level.

For the Oregon, screens with second-tier psychosine results greater than 10nM indicating a high likelihood of IKD will be reported to consultants for confirmatory testing and evaluation of the

newborn. There may be cases in which psychosine is elevated above the normal range (normal < 2nM), but not greater than 10nM. These individuals may represent late onset Krabbe disease (37). The reporting of these intermediate cases will need to be considered prior to the implementation of screening.

Does the NWRNBS Program have sufficient information to perform a fiscal analysis?

Dr Held and her colleagues at the newborn screening lab have had the opportunity to complete an initial fiscal analysis for the addition of IKD. This analysis was completed based on the request by a legislator in 2024.

The labs planned workflow would be first-tier analysis for IKD by enzyme activity of galactocerebrosidase. The lab uses an FDA approved kit to screen for four other lysosomal storage disorders on the Oregon newborn screen. Galactocerebrosidase can be assayed in this kit. Dr Held shared that the lab would then send samples to a reference lab for psychosine testing. The lab cost analysis estimated \$8.44 per infant screened.

Estimated Budget

Table 5 Laboratory and program cost associated with implementation of Infantile Krabbe Disease

Preparation or Preanalytical - Development of assay and clinical care protocol and materials		
- Assay development/validation (no cost) - LIMS computer system set-up (no cost) - Educational materials (no cost) - Clinical care protocol (estimated \$4,000 for the work of OHSU medical consultants)		
Ongoing Routine Screening		
Stage of addition of Infantile Krabbe Disease	Items to consider	Cost
Supplies including FDA approved kit	Lysosomal storage disorder enzyme kit has already purchased for screening of other places on all storage disorders in Oregon's newborn screen.	\$5000 for consumables
Second-tier Psychosine	Completed at reference laboratory. Estimate of 25.4 first-tier low GALC samples would undergo second-tier testing per year. Estimated cost of second-tier test - \$100/sample	\$2,544
Instrumentation	No further instrumentation needed.	\$0
Personnel	Microbiologist II (laboratory technician would be needed.)	\$71,576 annually
Short term follow-up		

Cost of additional resources for follow-up.	Program analyst II	\$65,030 annually
Clinical Care		
	Yearly contract fee	\$11,000

ACHDNC cost survey

In the 2023 ACHDNC review, the cost for addition of Krabbe disease varied considerably, up to \$7.00 per infant. This costing reflected equipment, reagents and additional laboratory technician and scientist time for the first-tier test (9). The Oregon cost estimate includes the additional staffing needed for the follow-up of screened positive cases and for education and outreach, second-tier testing, and cost of clinical care and protocol development.

Per Dr Held, screening for IKD would only be completed on first screen specimens. If the first screen was also deemed to be of poor quality (unsatisfactory specimen), then screening would also be performed on the repeat/second specimen.

Laboratory Assessment

What capacity and expertise are available (or needed) in the NWRNBS program to implement and maintain testing and reporting?

Laboratory assessment for testing and reporting for IKD shows that an additional microbiologist II would be needed. The laboratory has the expertise to perform the method validation and implementation.

What capacity and expertise are available (or needed) to implement and maintain follow-up and education for providers and parents?

Laboratory assessment for follow-up and education for IKD shows that an additional short-term follow-up coordinator would be needed.

Developmental Readiness

For readiness, Dr Held shared implementation would depend on circumstance. If the decision were for a more urgent addition of IKD, the laboratory could have the first-tier testing and second-tier workflow completed in 6-9 months.

In the ideal situation, the lab would bring on screening for IKD with adequate staffing for the laboratory and follow up. To have funding available for staffing, there would need to be an increase in general funds or a fee increase. Either of those two activities would take additional time, up to two years, to move through their respective processes.

Medical Follow-up Assessment

Is appropriate specialized medical consultation available or able to be obtained by the Program?

The NWRNBS Program currently contracts with OHSU for medical expertise for metabolic disorders, therefore the expertise necessary for diagnosis exists for the program.

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

- Cary Harding, MD
- Amy Yang, MD
- Markus Grompe, MD,
- Kimberly Kripps, MD
- Rodrigo Starosta, MD

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

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

The treatment for IKD is HSCT. HSCT is typically used to treat cancer diagnosis. Also, there are several metabolic disorders for which transplantation is used. At Oregon Health and Sciences University, pre-transplant evaluation, transplantation and initial follow-up would be completed by:

- Dr. Eneida Nemecek MD

By email, Dr Nemecek communicates that they do have a transplant program and have treated an individual with KD. She states, “if identified, we could treat here or send to a place where they could be treated, per patient/family preference just like any other metabolic disorder treated with BMT.” Dr Nemecek concludes that her program could “**transplant (cord only, as reported) within the first month of diagnosis (not life).**” She defers to the metabolic experts to determine what confirms the diagnosis of Krabbe disease

Per discussion with Dr Yang, two recent transplantations for other metabolic disorders have occurred at an outside site with significant expertise in HSCT in metabolic disorders (University of Minnesota).

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 and Dr. Yang.

Capacity to provide education for providers and parents

For educational materials, the current program resources include:

- Nurse Practitioner educators prepare high quality materials at the appropriate level for education of 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 able to help its partner, New Mexico, with short-term follow-up for a screen positive IKD including initial consult with PCP and follow-up of diagnostic labs and HSCT.

For New Mexico's point of view, Dr Michael Marble and Dr. Kiley Quintana would be responsible for clinical care of a metabolic patients. To assess readiness for the possible addition of IKD an email with questions was sent to these two providers. Dr Quintana shares that there would be access for diagnosis, but the family would have to go out of state for treatment with HSCT. Dr Quintana expressed her concern about the timeline from screen to treatment of 30 days. She is concerned that that would be difficult to achieve particularly with shipping of the sample and the need for the patient to go out of state for treatment. Dr Quintana would use expertise of the metabolic consultants with OHSU for the diagnostic evaluation.

Access to Care and Equity of Treatment and Follow-up

Impact on public health and health disparities

A recent publication evaluated if the recent addition of Krabbe Disease to newborn screening modified the number of individuals diagnosed within racial and ethnic minority populations (38). Results indicate increased rates of Krabbe Disease in individuals of Asian ancestry and a trend towards increase numbers in black individuals. This suggests that newborn screening has a potential to reduce disparities in diagnosis and treatment of Krabbe Disease (38).

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. Treatment with HSCT may be provided at OHSU or an alternate HSCT site.

What is the availability and accessibility of care and treatment?

During interviews, accessibility of care and treatment was discussed. For IKD, the following barriers were discussed:

1) Insurance barriers to healthcare

In a prior interview, Ms. Viall shared that insurance coverage for Medicaid in the state of Oregon can be complicated by its organization into CCOs (Coordinated Care Organizations) 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 care.

Dr Yang shares concerns about insurance coverage in an infant with IKD. Due to the time critical nature of the diagnosis and start of treatment, she is concerned about prior

authorization as a hurdle. She notes difficulties getting a timely response for prior authorizations in their coordinated care organizations in Oregon. Dr Starosta also expresses concern that insurance could be a barrier for care and paying for the necessary testing and transplantation.

2) Logistical barriers with diagnosis and treatment particularly with the short timeline

With the timeline of one month, logistics for obtaining all needed studies for diagnosis as well as preparation for transplantation will be difficult. Dr Starosta feels like the care coordination for the transplantation timeline would be difficult particularly for patients outside the Portland area. Dr Yang mentioned hospitalization at the time of a positive newborn screen to help with these logistical hurdles including short timeline, insurance issues and geographic issues for the family.

Ms. Viall mentions it will be important to have Dr Nemecke's involvement with the coordination of HSCT for patients in Oregon. She also notes that the metabolic team is good at overcoming challenges and barriers for patients but does worry about having to overcome these challenges within a short timeline.

3) Traumatization of families of patients with IKD

Dr Yang expresses concern about traumatization of the family with a positive newborn screen. In a very short period, the family will have to decide whether to do a significant medical procedure (HSCT) on their child who appears healthy. She expresses concern about the stress the family is being placed under. Ms. Viall shares the benefit of the family having the diagnosis up front, but the enormous decision the family will have to make in a short period of time which makes it hard to give them all the necessary information.

Ms. Viall does mention a concern of the distrust of the medical system and difficulties enacting a significant medical management in the short timeline. She realized that it may be difficult to develop good communication and trust with her family.

4) Experience of diagnosis and completing HSCT for IKD

OHSU does offer HSCT for metabolic disorders. Like most centers, a patient with IKD diagnosed from newborn screening has not been transplanted at OHSU. The timeline for transplantation is very short which will be a significant challenge.

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Appendix A: Systematic Literature Review - Krabbe disease/Infantile Krabbe disease and newborn screening.

PubMed

Set	Terms	11/23/2023 – 1/5/2024
#1	("Leukodystrophy, Globoid Cell"[Mesh] or "Globoid Cell Leukodystroph*" or "Galactocerebrosidase Deficienc*" or "GALC Deficienc*" or "Galactosylceramide beta-Galactosidase Deficienc*" or "Galactosylceramide Lipidosis" or "Galactosylcerebrosidase Deficienc*" or "Psychosine Lipidosis" or "Krabbe's Disease" or "Krabbes Disease" or "Krabbe Disease" or "Galactosylceramidase Deficiency Disease*" or "Globoid Leukodystroph*" or "Globoid Cell Leukodystrophy" or "Krabbe Leukodystrophy" or "Krabbes Leukodystrophy" or "Krabbe's Leukodystrophy")	
#2	("Leukodystrophy, Globoid Cell"[Mesh] or "Globoid Cell Leukodystroph*" or "Galactocerebrosidase Deficienc*" or "GALC Deficienc*" or "Galactosylceramide beta-Galactosidase Deficienc*" or "Galactosylceramide Lipidosis" or "Galactosylcerebrosidase Deficienc*" or "Psychosine Lipidosis" or "Krabbe's Disease" or "Krabbes Disease" or "Krabbe Disease" or "Galactosylceramidase Deficiency Disease*" or "Globoid Leukodystroph*" or "Globoid Cell Leukodystrophy" or "Krabbe Leukodystrophy" or "Krabbes Leukodystrophy" or "Krabbe's Leukodystrophy") AND ("Neonatal Screening"[Mesh] or "neonatal screening*" or "newborn screening*" or "infant screening*")	
#3	English, from 2023/11/5 - 2025/12/31	
	#1 and #3	40
	#2 and #3	4
	Number of Articles after Removing duplicates	40

Scopur

Set	Terms	11/22/2023 – 1/5/2024
#1	"Krabbe Disease"[Supplementary Concept] OR "Globoid Cell Leukodystrophy" [All Fields] and newborn screening	
#2	English, Published Date: 11/2023-1/2025	
		3

Cochrane

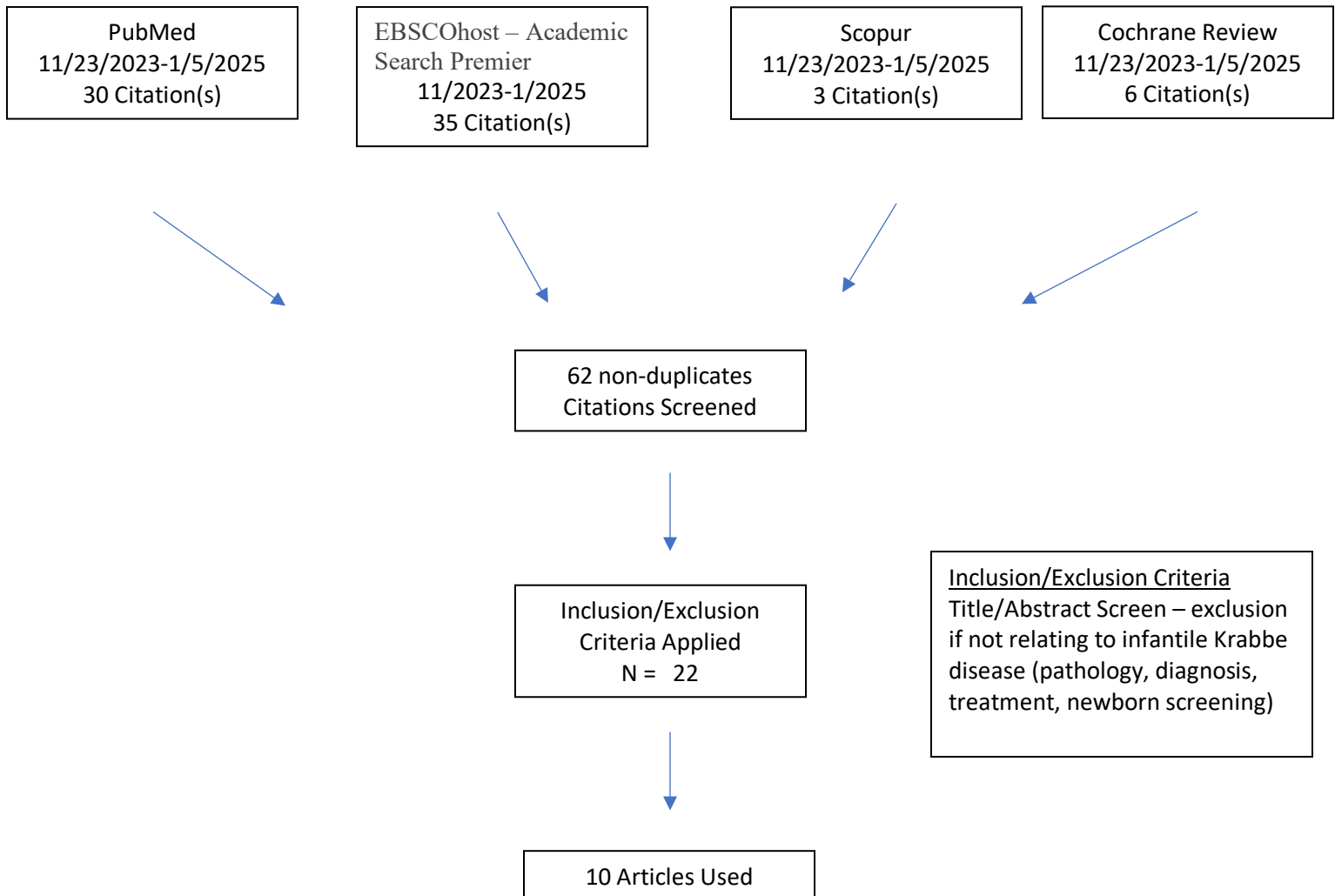
Set	Terms	4/2/2022- 4/13/2023
#1	MeSH descriptor: [Leukodystrophy, Globoid Cell] explode all trees	
#2	("Globoid Cell" NEXT Leukodystroph*) or (Galactocerebrosidase NEXT Deficienc*) or (GALC NEXT Deficienc*) or ("Galactosylceramide beta-	

	Galactosidase" NEXT Deficienc*) or "Galactosylceramide Lipidosis" or (Galactosylcerebrosidase NEXT Deficienc*) or "Psychosine Lipidosis" or "Krabbe's Disease" or "Krabbes Disease" or "Krabbe Disease" or ("Galactosylceramidase Deficiency" NEXT Disease*) or (Globoid NEXT Leukodystroph	
#3	#1 or #2	6
#4	MeSH descriptor: [Neonatal Screening] explode all trees	
#5	(newborn NEXT screening*) or (neonatal NEXT screening*) or (infant NEXT screening*)	
#6	#4 or #5	
#7	#3 and #6	0

EBSCOhost – Academic Search Premier

Set	Terms	11/2023-1/2025
#1	"Krabbe Disease"[Supplementary Concept] OR "Globoid Cell Leukodystrophy" [All Fields] and newborn screening	
#2	English, Published Date: 11/2023-1/2025	
#3	#1 and #2	
		35

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	11/25/2024
Sara Viall P.N.P.	Newborn Bloodspot Screening Medical Consultant	OHSU	11/22/2024
Rodrigo Starosta MD	Newborn Bloodspot Screening Medical Consultant	OHSU	11/22/2024
Eneida Nemecek MD	Nancy Jaggar Blount Endowed Professor of Pediatrics & Medical Oncology; Director, Pediatric Bone Marrow Transplant Program, Doernbecher Children's Hospital; Associate Director of Clinical Research, OHSU Knight Cancer Institute	OHSU	Email correspondence January 2025
Patrice Held, PhD	Manager of the newborn screening program in Oregon	Oregon Public Health Lab	11/22/2024
Kiley Quintana, MD Email correspondence	Medical genetics physician in New Mexico	University of New Mexico	12/11/2024

Position/Role in NBS Program:

Interviewee: Sarah Viall P.N.P Date of Interview: 11/22/2024 Title: Pediatric Nurse Practitioner Position/Role in NBS Program: Clinical consultant Information needed from interview: General information about OR NBS and patient care for individuals with Infantile Krabbe Disease Discussion prior to interview: Brief discussion clarifying case definition for this review. Discussed that this review is looking at adding IKD with low GALC and an elevated psychosine ≥ 10 nM	
Question(s)	Response
Please share OHSU experience with Krabbe disease including the number of patients with Infantile Krabbe disease in recent years.	There have not been many individuals with Krabbe at OHSU (expected for a rare disease). There has been one new case of Krabbe disease that Ms. Viall is aware of during the last five years. It was a later onset Krabbe disease.

Please discuss care for lysosomal storage disorders at OHSU including diagnosis, treatment including transplantation and expertise. Also, what is the availability and accessibility of this treatment and care?	OHSU cares for a variety of lysosomal storage disorders (LSDs). Oregon screens for Fabry and Gaucher disease which generates a lot of newborn screening referrals. Ms. Viall reports significant comfort with diagnosing and managing LSDs. She does mention there is not a lot of experience with severe infantile forms of LSD due to their rarity. Ms. Viall shares that there are challenges to caring for this group of patients particularly within certain communities with less medical resources. There are issues with finding infusion centers to treat patients in the rural community setting Ms. Viall shares that hematopoietic stem cell transplant/ bone marrow transplant is available at OHSU. The metabolic team is in regular contact with the head of transplantation at OHSU, Dr Nemecke, regarding transplantation for another newborn screening disorder X linked adrenoleukodystrophy. Ms. Viall states it will be important to have Dr Nemecke's involvement in the decision whether to newborn screen for Krabbe disease, "I would defer to her about the availability of this treatment for babies born in Oregon."
Challenges/Barriers to care for Krabbe Disease Note for question: There is a short timeline from a positive newborn screen to treatment (transplantation) for Infantile Krabbe disease. It was noted in the RUSP discussion that process of diagnosing and treating infantile Krabbe disease within 4 to 6 weeks will be challenging, with potential for errors and delays, unless state programs tightly coordinate NBS call-out, diagnostic testing, and HSCT referral.	Ms. Viall does note that there will be challenges including: • Organization/coordination of the treatment (HSCT) • Obtaining specialty laboratories for confirmation quickly and correctly – Ms. Viall shares two experiences this week where getting confirmatory testing for a newborn screening was challenging based on geography and laboratory error in processing of samples for infrequently obtained tests. • Geographic barriers for traveling for treatment in Portland (including weather) • Potential distrust of the medical system – “ when a child appears healthy...and you tell the family that they're not and they have to undergo a major medical procedure, I can see that being a challenge in some of our communities.” Regarding diagnosis, Ms. Viall states that psychosine greater than 10 is very sensitive and specific and the diagnosis should likely be trusted. Ms. Viall notes that the metabolic team is very good at overcoming challenges and barriers for appropriate care of metabolic patients but does worry about the need to overcome

	these challenges and barriers with the short timeline to when treatment should occur.
What are solutions or ways to resolve barriers to care?	For the concern about distrust of the medical system and difficulties with enacting a significant medical management on a short timeline. “I think that we do a great job of communicating, working with families to... However, it's very hard to do that overnight when they don't know us. And so that's why the timeline feels like a particular challenge.” She shares that due to the timeline, the family would need to decide quickly. She expresses that it does make her uncomfortable to have to press the family for decision in that timeline.
Insurance coverage and approval of HSCT	Ms. Viall reports that there are challenges and barriers for insurance coverage of care including transplantation but feels the metabolic team does have experience working hard to overcome these challenges. She notes that the team has overcome challenges with prior disorders to ensure high quality care for their patients. She does note that the short timeline for treatment to start will make overcoming these barriers more difficult.
Benefits of NBS for Infantile Krabbe Disease	Ms. Viall states that there is a clear benefit to families of identified children if they want treatment. For some families, it is going to be “an enormous decision and not enough time to make it in fully informed way. And I don't know what the downstream effects of that would be, but I think there certainly could be large.”
Possible Harms of NBS for Infantile Krabbe Disease	Ms. Viall mentions a general concern she has been hearing from others in the NBS field about whether this treatment is going to work for all children and families. She expresses concerns about outcomes and what is reasonable to expect for the outcomes for IKD after transplant. She expresses concern about whether transplantation will have a significant impact on the quality of life for all patients and their families.
Current advocacy for addition of Krabbe Disease to newborn screening in Oregon?	Yes, there is parent advocacy and an interested legislator promoting the addition of KD to the newborn screen.

Interviewee: Rodrigo Starosta

Date of Interview: 11/22/2024

Position/Role in NBS Program: Assistant professor at the Department of Molecular and Medical genetics at OHSU; training as a clinical and biochemical geneticist; involved in newborn screening for OHSU.

Information needed from interview: Patient care for individuals with Infantile Krabbe Disease; view of newborn screening for infantile Krabbe disease. Discussion prior to interview: Brief discussion clarifying case definition for this review. Discussed that this review is looking at adding infantile Krabbe disease with low GALC and an elevated psychosine ≥ 10 nM	
Question(s)	Response
Please share OHSU experience with Krabbe disease including the number of patients with Infantile Krabbe disease in recent years.	Dr Starosta is relatively new to OHSU. During his early training, he worked at a referral center in southern Brazil that cared for individuals with LSDs. He received his PhD focusing on LSDs. His specific area of interest during training and as an attending in LSDs. He sees individuals with LSDs on a regular basis.
Please discuss care for lysosomal storage disorders at OHSU including diagnosis, treatment including transplantation and expertise. Also, what is the availability and accessibility of this treatment and care?	Dr Starosta relays that OHSU is a large hospital and has the resources available to care for patients with LSDs. For the question of potential transplantation at OHSU, he defers to Sarah Viall for her experience as he is newer at OHSU and has not been part of a metabolic patient undergoing transplantation.
Above questions specific to Krabbe	During training, he was involved in one positive newborn screen for IKD in Missouri. Also, he has followed a few late onset KD patients. Dr Starosta shares his experience with transplantation of a baby at 29 days of age for IKD detected by newborn screening. Unfortunately, he reports that the patient did experience neurologic deterioration as well as multiple complications from her transplantation leading to a poor quality of life.
Challenges/Barriers to care for Krabbe Disease Note for question: there is a short timeline from a positive newborn screen to treatment (transplantation) for Infantile Krabbe disease. It was noted in the RUSP discussion that process of diagnosing and treating infantile Krabbe disease within 4 to 6 weeks will be challenging, with potential for errors and delays, unless state programs tightly coordinate NBS	Dr Starosta feels that the timeline is feasible for patients that live around Portland but mentions that many patients live several hours from Portland and frequent evaluations around pre transplantation would be difficult organization. Also, he does express concern that insurance could be a barrier for care. He relays that he has spent his morning talking with insurance to get enzyme replacement therapy for another LSD.

call-out, diagnostic testing, and HSCT referral.	
Benefits and Possible Harms of NBS for Infantile Krabbe Disease .	Dr Starosta does express concern about outcomes to transplantation. He notes that the data has not been replicated outside a couple of care centers. He expresses concern that there may not be enough outcome data to conclude that this is the right treatment for IKD. “Honestly, I don't think that the evidence for Krabbe screening and early treatment is good. As there seems to be some potential decrease in mortality for a very selected group of patients. Publications seem to be biased coming from a couple of centers. And I have not seen those data being replicated independently yet. Which makes me worry about how replicable this data is. And I don't think it's clear cut. The treatment itself can be fatal. The benefits are still need of further studies. So, I'm not sure how the benefits would play out scientifically. I don't think that we have a good basis for doing that at this moment that we are at, and I am skeptical of how this is being rolled out. And if new evidence comes up, that is independent and shows a clear benefit in an unbiased way, I will be very open to reassess, in my opinion. But I haven't seen that evidence yet.”

Interviewee: Dr. Amy Yang Date of Interview: 11/25/2024 Position/Role in NBS Program: Clinical consultant from OHSU; Advisory Board Member Information needed from interview: Patient care for individuals with Infantile Krabbe Disease Discussion prior to interview: Brief discussion clarifying case definition for this review. Discussed that this review is looking at adding infantile Krabbe disease with low GALC and an elevated psychosine ≥ 10 nM	
Question(s)	Response
Please share OHSU experience with Krabbe disease including the number of patients with Infantile Krabbe disease in recent years.	Since IKD is a rare disorder, there are limited number of patients cared for OHSU. Dr Yang is aware of one patient with late infantile onset Krabbe seen in the clinic prior to her arrival. From her knowledge of the case, there was a delay in diagnosis and the patient was

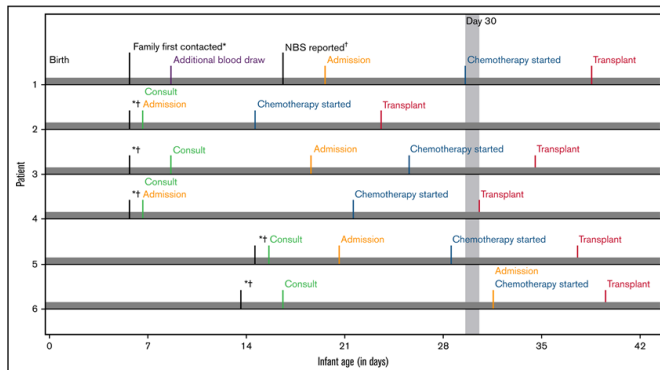
	not eligible for transplantation. The family of this infant is advocating for newborn screening for KD. Dr. Yang did share her experience with KD and newborn screening from her experiences in New York State during her medical training. New York was the first state to newborn screen for KD. They did not have a second-tier psychosine, “It was very fraught with lots of issues. Including not being able to differentiate on newborn screening early versus late infantile.” Dr Yang cared for two patients (siblings) with early IKD. She relays that experience as very difficult and traumatizing. For the first sibling, the family did not believe the infant was ill and went back to their home country and returned a few months later with a clearly symptomatic child. The second sibling was transplanted very quickly but she died of complications of the transplant. She states that New York State did publish their experience with screening for Krabbe disease and states “it wasn't very great.” Only two of the six infants initially found with infantile Krabbe disease survived. Dr Yang shares that psychosine will be helpful to help differentiate the type of onset Krabbe disease. She does mention that there is variation in assay and cut offs in each state therefore with implementation in Oregon, there still would be concerned for false positives or false negatives during the initial implementation. With the concern for false positives, there could be concern on treatment with transplant that it could not be necessary.
Please discuss care for Krabbe disease and lysosomal storage disorders at OHSU including diagnosis, treatment including transplantation and expertise. Also, what is the availability and accessibility of this treatment and care?	Dr Yang does mention the metabolism service would be prepared to evaluate and make the diagnosis of Krabbe disease for screen positive patients. She mentions barriers in the initial diagnostic evaluation that she thinks can be overcome by admission of the infant to the hospital for evaluation. Admission to the hospital would help overcome difficulties with the short timeline, insurance issues and geographic issues for the family.

	In addition to the testing to confirm the diagnosis, the patient would have to undergo a transplantation work up and find a match. Dr. Yang did not know whether the transplant for KD would be available at OHSU. She does report that there were previously transplant for metabolic disorders at OHSU, but it has been some time since a transplant for a metabolic disorder has occurred. She reports in recent memory a patient with Hunter disease and a patient with X linked ALD went to Minnesota to receive their transplantation.
Benefits to newborn screen/care for infantile Krabbe Disease	Dr. Yang notes the benefit to newborn screening for IKD is “to prolong life with less neurological sequelae. ... there's still... clearly there are going to be neurological sequelae.” Dr Yang mentions the difficult situation it is for a family of a screen positive infant. They are told that their currently healthy infant will neurodegeneration without a transplant, but this transplant has complications and potential mortality. She notes that the transplant is amelioration of IKD but is not a cure. Also, the family of the screen positive infant will have to decide whether to do the transplant or not. It would not be a required treatment.
Challenges/Barriers to care for Krabbe Disease Note for question: there is a short timeline from a positive newborn screen to treatment (transplantation) for Infantile Krabbe disease. It was noted in the RUSP discussion that process of diagnosing and treating infantile Krabbe disease within 4 to 6 weeks will be challenging, with potential for errors and delays, unless state programs tightly coordinate NBS call-out, diagnostic testing, and HSCT referral.	Dr Yang identifies the following challenges and barriers: 1) Concern for adequate insurance coverage for all aspects of diagnosis and management in a timely manner. She notes that prior authorization processes can take a long period of time. She mentions that it is common to have denials for needed treatments for other metabolic disorders such as enzyme replacement therapy. 2) Concerned for the traumatic experience for families with the diagnosis or with a false positive. 3) Concern that recent timelines for diagnosis and treatment are “highly unobtainable” in most states. “I think we'll be struggling to try and meet that, and we'll try to do the best we can... I don't see that happening in the state.”
Insurance coverage and approval of HSCT	Dr Yang does mention concerns about insurance coverage for care of an infant with IKD. She notes that there is increasing denial for care of newborn screening

	disorders. Her example is an infantile onset Pompe disease where they're having difficulties getting coverage for enzyme replacement therapy. She sees his prior authorization as a hurdle.
Neither Infantile Krabbe Disease are listed in that evidence Commission will. Will that be an issue or concern?	Dr Yang shares that this list is no longer the model for getting coverage. But she does mention worries about getting coverage through CCO (coordinated care organizations). Dr Yang relays that some CCOs are very responsive and timely with prior authorization. But there are other CCO where it is very difficult to reach an individual and there seems to be lack of experience in facilitating critical cases.
Asking about out of state client for if NM wanted to screen? Available to work with NM providers? How would you envision that partnership working?	Dr Yang relays that they have explored this issue with Dr Marble in the past. He has said that New Mexico does not have the capability for BMT within the state of New Mexico. In the past, they have forwarded cases to other states. With the lack of capacity for transplantation in New Mexico, there would be a limited role for Oregon's metabolic consultants outside initial discussion with the primary care physician about a screen positive result.

Interviewee: Eneida Nemecek MD Email correspondence Date of Interview: 1/4/2025-1/16/2025 Position/Role in NBS Program: None Medical Expertise Role: Nancy Jaggar Blount Endowed Professor of Pediatrics & Medical Oncology; Director, Pediatric Bone Marrow Transplant Program, Doernbecher Children's Hospital; Associate Director of Clinical Research, OHSU Knight Cancer Institute Information needed from interview: Transplantation for individuals with Infantile Krabbe Disease	
Question(s)	Response
Would OHSU and your care team be able to treat these identified newborns? (Dr Held)	We do have a transplant program and have treated one patient for this condition. I am in no position to comment or give my opinion on the disease itself (you will need a metabolics/genetics person for that), but can tell you that, if identified, we could treat here or send to a place where they could be treated, per patient/family preference just like any other metabolic disorder treated with BMT. We do not have expertise to get involved in the diagnostic part of this disease. In general, a specialist who makes the diagnosis would refer the patient to us

	for BMT consultation. Care of patients with metabolic disorders is multidisciplinary. We only care for them during the period of BMT and once recovered (usually the first 6 months-1yr) return to their pediatrician and specialist team for ongoing care.
Is [there] the feasibility of getting BMT before 1 month of life here at OHSU. (Dr Yang)	Yes, with a cord, impossible with an unrelated donor. We need at least 2 months. I can assure you that is the case everywhere else too!
Can you clarify what you mean by "diagnosis"? Is elevated psychosine in range consistent w/ Infantile Krabbe a "diagnosis" you would proceed with, or do you mean waiting for DNA results? (Dr Yang)	"We will let your knowledgeable team of experts to determine what a confirmed diagnosis of Krabbe is. We don't need DNA diagnosis specifically but do need a note from an expert in the field confirming the diagnosis and requesting BMT as a therapeutic option before we proceed. "
If there is a related stem cell donor available, the transplant before 1 month of life is doable. Would it matter if from individual vs cord? If there is not a related stem cell donor available and an unrelated cord donor is needed, 2 months is the timeline. The KD literature indicates that transplant should occur before 1 month of age for the best outcomes (article comparing < 30 days vs >30 days attached) and does not differentiate whether there is a related donor or not. There are now cases where transplant has started conditioning at ~ 2 weeks. Do you know how centers caring for infantile KD are able to meet the 1-month period if there is not a related donor?	This is the only paper that describes what was done to come up with these guidelines, which have been driven almost in their entirety by one physician group at Duke: https://ashpublications.org/bloodadvances/article/6/9/2947/483552/Benefits-of-newborn-screening-and-hematopoietic. It has data on 4 centers (but the 4 docs doing these were all Duke trained by that group) This is a retrospective report of 6 infants Cord blood only - which is the only way you can do a transplant by 1 month If we do the math on how long it takes for NB screening results to come back and all the tests described in the paper, a month to transplant will be the exception and not the rule, The only way I can see a transplant happening in a month is with prenatal diagnosis. We never start conditioning or transplant on a patient without a confirmed diagnosis (risks outweigh benefit of such approach), and I cannot see how we would start myeloablative chemotherapy of the intensity described in the paper by 2 weeks of life. Only one of the 6 kids did this, and I wonder if this was a family with known family history. See figure below for timeline reported.



I would say, when you are discussing this with state, you could accurately make a statement that we could get someone to transplant (cord only, as reported) within the first month of diagnosis (not life).

Interviewee: Patrice Held

Date of Interview: 11/22/2024

Position/Role in NBS Program: Manager of the newborn screening program in Oregon

Information needed from interview: Lab method for detecting Infantile Krabbe disease, cost of addition, lab readiness

Discussion prior to interview: Brief discussion clarifying case definition for this review.

Discussed that this review is looking at adding infantile Krabbe disease with low GALC and an elevated psychosine ≥ 10 nM

Question(s)	Responses
How would OR NBS lab implement testing for Infantile Krabbe disease?	The Oregon newborn screening lab has begun discussion for implementation of IKD. Oregon would use a first-tier and second-tier screen for IKD. The laboratory currently uses an FDA approved kit for four other LSDs. Included in the kit is the enzyme for IKD, galactocerebrosidase. The kit has already been validated for the four other enzymes and would need to undergo validation for galactocerebrosidase. For second-tier psychosine testing, Dr Held reports the laboratory would use a reference laboratory. That reference laboratory has not been chosen, but there are several laboratories in the United States. The

	laboratories initial estimation is that 0.5% of samples would require second-tier testing. Molecular testing is not planned. Oregon is a two screen state. Testing for IKD testing would only occur on the first screen unless the first screen is deemed unsatisfactory. In these situations, testing would be completed on both the unsatisfactory specimen and the second/repeat screen.
Would the lab be able to implement with current supplies, machines, and staffing?	Dr Held states this enzyme test is multiplexed with their current LSD assay; therefore, they would not need additional instrumentation. For laboratory staffing, an additional laboratory staffing would be optimal for routine testing and reporting. This assay does take a longer period to complete and will require a modification of the current workflow. Dr Held also anticipates additional staffing would be needed for short-term follow-up and education. Dr. Held shares that the kit is already being purchased for the other four LSDs, therefore there will be no additional cost for the kit (reagents). There will be a cost for the second-tier test, psychosine, that will be completed by a reference laboratory.
What laboratory barriers do you see for implementation of this of Infantile Krabbe Disease?	Dr Held notes that there could be some laboratory barriers to implementation. To include the enzyme, galactocerebrosidase, in the assay, the workflow would need to be modified to allow an 18-hour incubation (this incubation is currently three hours). The need for an increased incubation time would require a modification to the current workflow and the need for additional staffing. Also, the increase in incubation time would lead to delaying results for the other LSD and potentially the entire newborn screen report.
How is education for disorders on NBS completed for providers and patients?	Dr Held shares that the contract with OHSU includes 0.2FTE for a nurse health educator. Sarah Viall will work with the program to develop appropriate educational material for families and providers on Krabbe disease - the clinical findings, the treatment and care.

	Dissemination of this material will be performed by the nurse health educator and two public health nurses within the Oregon newborn screening program.
What would be the cost for adding infantile Krabbe disease to the Oregon newborn screen?	The Oregon newborn screening program has recently completed a cost calculation for adding Krabbe disease to the panel. This analysis was done at the request of a legislator, who is also interested in screening for Krabbe disease. Analysis, including needed increased staffing, estimated \$8.44 per infant screened.
APHL Readiness	Oregon – Developmental ready Scale for APHL Readiness - Ability to adopt infantile Krabbe disease 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 For readiness, Dr Held shared implementation would depend on circumstance. If the decision were for a more urgent addition of Infantile Krabbe disease, the laboratory could have the testing and second-tier workflow completed in six to nine months. In the ideal situation, the lab would bring on screening for infantile Krabbe disease with adequate staffing for the laboratory and follow-up units. To have funding available for staffing there would need to be an increase in general funds or a fee increase. Either of those two activities would take additional time to move through their respective processes, estimated at 2 years.
PROGRAM QUESTIONS	
NWRNBS Program have a relationship with the bone marrow transplant team? Are there contracts like there are with the metabolic team? If not, could one be organized?	NWRNBS Program would plan to continue its contract with the OHSU metabolic team for short-term follow-up of an IKD newborn screen. A contract with transplant at OHSU would not be necessary as they would become involved in the patient's care after short-term follow up was complete (i.e., diagnosis of IKD).
Other things that I should be asking you about adding Infantile Krabbe	From a technical standpoint, it is easy to bring on newborn screening for IKD. "I think the challenge really

Disease to the Oregon newborn screen?	is in the clinical care and access to treatment in a timely manner.” Considering the need for a quick turnaround for the newborn screening system (i.e., to transplant in approximately 4 weeks), the laboratory will want to closely monitor collection and transit times to allow for the sample processing to happen as quickly as possible. Some delays may be unavoidable, such as delays in transportation due to weather. The laboratory would aim for a return of second-tier testing by 7 days of life. This is where additional staff for follow-up, education and outreach to submitters on the importance of timely transport and monitoring of the courier would be needed.
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Interviewee: Kiley Quintana, MD Date of Interview: 12/11/2024 Position/Role in NBS Program: Medical genetics physician in New Mexico	
Question(s)	Responses
Would New Mexico plan to add Infantile Krabbe disease (low GALC and psychosine >10nM) to the New Mexico NBS?	I am not sure what the NM legislation has said (if anything) about Krabbe disease.
Is there access to urgent diagnosis and HSCT as well as expertise within your state?	Diagnosis - yes there is access. No, we do not have bone marrow transplant in NM. Would have to go out of state for that.
Are there barriers that you anticipate with caring for patients with Infantile Krabbe disease (low GALC and psychosine >10nM) to the New Mexico NBS?	We have very limited resources here. With the addition of Fabry disease recently it has been challenging to keep up with that from staffing/appointment perspective. For families in NM many would not have the ability to go out of state for a bone marrow transplant. Another consideration is that NM is a two-step NBS state. By the time it is shipped to Oregon, and we get the second result, it is frequently at least 2 weeks, often longer. So, if these kids need a transplant by age 30 days that would be nearly impossible to achieve.
What role (if any) would the metabolic consultants in Oregon	I would presume they would help with initial work-up for these patients.

play in the implementation of Infantile Krabbe disease (low GALC and psychosine >10nM)?	
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Appendix D: Excluded Articles

PUBMED

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200-705650a_26 (09/2026)