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Northwest Regional Newborn Bloodspot Screening

Advisory Board Report to the Legislature

Oregon Health Authority
PUBLIC HEALTH DIVISION

Acknowledgments

Authors

The Northwest Regional Newborn Bloodspot Screening Advisory Board

- Silke Akerson, representative of a statewide association of midwives
- Philip Dauterman, representative of an entity that contracts with the Northwest Regional Newborn Bloodspot Screening Program for newborn bloodspot screening services
- Anna Dennis, representative of an advocacy association regarding newborns with medical or rare disorders
- Cheryl Hanna, representative of a statewide association of pediatricians
- Dana Hargunani, representative of Medicaid or the insurance industry
- Marilyn Hartzell, person or family member of a person affected by a disorder on the newborn bloodspot screening panel
- Wannasiri (Awe) Lapcharoensap, representative of a statewide association of pediatricians
- Jill Levy-Fisch, representative of an advocacy association regarding newborns with medical or rare disorders
- Joanne Rogovoy, representative of advocacy association regarding newborns with medical or rare disorders
- Kara Stirling, representative of a birthing center or hospital
- Cate Wilcox, honorary non-voting representative
- Amy Yang, contracted medical consultant providing expert medical advice
- Collette Young, honorary non-voting representative

Staff

- Christianne Biggs, Newborn Screening Program Manager
- John Fontana, Laboratory Director
- Nicole Galloway, Laboratory Business Engagement Policy Analyst

Visiting experts

- Ladawna Gievers, MD, pediatric bio-ethicist
- Laurel Boyd, MPH, Contracted disorder researcher
- Erika Finanger, MD, Subject matter expert SMA
- David Koeller, MD, Subject matter expert X-ALD

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

For details about the work of the board, go to www.bitly.com/nbs-advisory

Contact

Oregon Health Authority
Public Health Division
Center for Public Health Practice
Oregon State Public Health Laboratory
503-693-4100
christianne.biggs@dhsoha.state.or.us

Contents

- Acknowledgments 2
- Executive summary 6
  - Background 6
  - Summary of 2020 board meetings 6
  - Disorders evaluated for addition to the testing panel 6
    - Spinal muscular atrophy 6
    - X-linked adrenoleukodystrophy 7
  - Need for additional resources 7
  - Future work of the board 7
- Introduction 8
- Background 10
  - Disorder evaluation criteria 10
- SMA background, discussion, evaluation and consensus process 13
  - Expert background on SMA 13
  - Program and board review for recommending the addition of SMA to the screening panel 14
    - Program's analysis of adding SMA to the panel 14
    - Board's analysis of adding SMA to the panel 15
    - Consensus check on proposal to add SMA to the screening panel with no carrier screening 16
- X-ALD background, discussion, evaluation and consensus process 17
  - Expert background on X-ALD 17

» Program and board review of adding X-ALD to the screening panel 18

» **Additional discussion of carrier and second-tier testing 23**

» **Disorder evaluation for removal from the testing panel 24**

» **Future advisory board work 25**

» **A note for funding 26**

» **Conclusion 27**

» **Appendix A: Guiding legislation and rules 28**

» **Appendix B: HB 2563 enrolled 29**

» **Appendix C: History of newborn bloodspot screening 32**

» **Appendix D: Disorder evaluation for addition to the Northwest Regional Newborn Bloodspot Program's screening testing panel 34**

» Procedure for disorder addition evaluation 34

» Stage 1: Addition to the RUSP 34

» Stage 2: NWRNBS program evaluation using category one criteria 34

» Stage 3: NWRNBS Advisory Board evaluation and recommendation using category two criteria 34

» Criteria for disorder addition evaluation 34

» Consensus method 35

» **Appendix E: Independent condition report regarding SMA—executive summary 37**

» Executive Summary: Spinal Muscular Atrophy (SMA) 37

» Stage 1: Addition to the RUSP 38

» Stage 2: NWRNBS Program Evaluation using Category One Criteria 38
» Stage 3: NWRNBS Advisory Board Evaluation and Recommendation using Category Two Criteria 42
» References 44

» **Appendix F: Independent condition report regarding X-ALD—executive summary 46**
» Executive Summary: X-Linked Adrenoleukodystrophy (X-ALD) 46
» Stage 1: Addition to the RUSP 47
» Stage 2: NWRNBS Program Evaluation using Category One Criteria 47
» Stage 3: NWRNBS Advisory Board Evaluation and Recommendation using Category Two Criteria 51
» References 54

» **Appendix G: Process for recommending the removal of a disorder from the Northwest Regional Newborn Bloodspot Screening Program's testing panel 56**
» Stage 1: Proposal to Remove a Disorder from the NWRNBS Panel 56
» Stage 2: Advisory Board Evaluation of a Proposal to Remove a Disorder 56
» Criteria for Evaluating a Disorder for Removal 56

» **Appendix H: Northwest Regional Newborn Bloodspot Screening Advisory Board 59**

Executive summary

Background

This is the second report to the legislature from the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board (the board). In the 2019 report, the board adopted a protocol and criteria for recommending the addition of disorders to Oregon's newborn bloodspot screening panel (Appendix D).

Summary of 2020 board meetings

The board met twice in 2020. During these meetings the board used its new protocol to evaluate and recommend the addition of two new disorders. The board also adopted a protocol and criteria to recommend the removal of disorders from the panel (Appendix G).

Disorders evaluated for addition to the testing panel

The board considered extensive expert information about two disorders for potential addition to the screening panel: 1.) Spinal muscular atrophy (SMA), and 2.) X-linked adrenoleukodystrophy (X-ALD).

See Appendices E and F for independent third-party expert analyses.

Spinal muscular atrophy

SMA is the most common cause of genetic death among infants. Early diagnosis results in better outcomes for the patient. The board determined that the disorder is: a.) well-defined in newborns b.) testable c.) treatable, and d.) met other criteria for addition.

As a result, they recommended the addition of SMA to the screening panel.

The board also considered the ethicality and costs of doing carrier screening as part of SMA screening. The board decided against carrier screening for SMA. See below.

- Their decision was based, in part, on prior consent issues, and the lack of enough genetic counselors to follow-up with identified carriers.

X-linked adrenoleukodystrophy

X-ALD interferes with the process for transporting fat molecules. The molecules are then toxic to myelin and the adrenal cortex. The disorder results in a.) adrenal insufficiency b.) cerebral damage c.) paralysis, and d.) sometimes death.

The board applied its criteria and they agreed to recommend the addition of X-ALD to the screening panel. Identifying parent carriers incidentally by screening for X-ALD was of concern to the board. However, the board determined that the benefits of identifying X-ALD in the child outweighed the harm of identifying parents who are carriers incidentally during the testing.

Need for additional resources

As a result of applying the protocol for recommending the addition of new disorders, the board identified that the NWRNBS Program (also called the Newborn Bloodspot Screening Program) would need additional resources to test and provide follow-up for SMA and X-ALD. At the next meeting, the Newborn Bloodspot Screening Program reported that its fee increase proposal for the 2021 legislature would not move forward due to fiscal consequences of the ongoing COVID-19 pandemic. As a result, addition of SMA and X-ALD to the screening panel will be delayed until a future legislative session. The board urges the legislature to give the fee proposal serious consideration in the next session as an important public health measure.

Future work of the board

In its next meetings, the board will:

- Conduct strategic visioning and planning for the Newborn Bloodspot Screening Program
- Use the protocol and criteria for recommending the removal of disorders from the screening panel to evaluate Gaucher and Fabry diseases
- Evaluate the costs and benefits of providing courier services or expedited shipping to improve timeliness
- Discuss newborn bloodspot screening education for providers and families, and
- Evaluate the equity of newborn bloodspot screening testing reimbursement.

For the full report, see https://www.oregon.gov/oha/ERD/Pages/Government-Relations.aspx or contact:

Christianne Biggs, MS
Newborn Screening Laboratory Manager
Oregon Health Authority
Public Health Division
Center for Public Health Practice
Oregon State Public Health Laboratory
503-693-4100
christianne.biggs@dhsoha.state.or.us

Introduction

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

The board meets a minimum of every six months to assist the Northwest Regional Newborn Bloodspot Screening Program (also called the Newborn Bloodspot Screening Program and referred to here as the "program"). The board assists by providing:

- Advocacy
- Advice
- Recommendations, and
- Technical information.

They assist based on members' 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 Feb. 4, 2020, and June 29, 2020 meetings. The report is designed to provide the legislature with the following:

- Information from experts about the disorders spinal muscular atrophy (SMA) and X-linked adrenoleukodystrophy (X-ALD). These disorders were evaluated for recommending addition to the program's testing panel during this report period.
- A summary of the board's discussion of the disorders. Also, the pros and cons for adding them to the testing panel.
- The board's recommendation about adding the disorders.

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 discuss any abnormal results with parents and set up treatment plans. Parents follow through with childhood health care. 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.

- A summary of next steps to implement adding the disorders.
- A summary of follow-up information from the program about SMA and X-ALD testing in other states.
- A summary of the board's discussion and recommendation about carrier screening for SMA and X-ALD second-tier testing.
- A record of board consensus about criteria to remove disorders from the screening panel.
- A summary of upcoming work of the board.

Background

Disorder evaluation criteria

In 2019, the board established criteria for recommending the addition of disorders to Oregon's newborn bloodspot screening panel. They identified key values for disorder evaluation as efficiency, timeliness and transparency. To support their work, the board requested:

- Information about the disorders be given before deliberation, and
- Subject matter experts and an ethicist be available to assist in board discussions about addition of disorders to the screening panel.

The board presented criteria for adding disorders to the panel in the 2019 report to the legislature. The description is in Appendix D.

Feb. 4, 2020, board meeting

At the Feb. 4, 2020 meeting, a quorum of the board members attended in person and by phone. (For a full list of board members, see Appendix H.) The board reported on work completed since the previous legislative report, which included:

- Clarification of roles of the board co-chairs and vice-chair, and
- Partial completion of a process for board members to offer input to improve board process.

The program reported on activities since the previous board meeting. This included:

- Minor rule changes by the program
- A legislative tour of the laboratory
- Public meeting law training for the program, and
- Creation of an email address for the public to submit comments (nbs.advisoryboard@dhsoha.state.or.us).

Laurel Boyd is an independent third-party consultant. She has a background in epidemiology and medical subject review. Ms. Boyd contracted with the program to develop independent disorder reports on SMA and X-ALD. Ms. Boyd briefly discussed her research. She explained that, in her research and report design, she used Systematic Evidence Review (SER) methods modified by the national Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and the board co-chairs. She also applied:

- Context about the program

- Knowledge provided by subject matter experts, and
- The program's perspective on feasibility of implementation.

In her work, Ms. Boyd looked at screening, treatment and policy-related articles. She also screened for bias and discussed bias in the reports. The executive summaries of the reports are in Appendix E (SMA) and Appendix F (X-ALD). The full reports are available on request.

Dr. Erika Finanger, an expert on SMA, gave a presentation to the board on SMA. Dr. David Koeller and board co-chair Dr. Cheryl Hanna, experts on X-ALD, gave presentations about X-ALD. In addition, Dr. LaDawna Gievers, a pediatric bio-ethicist, was present to help with ethical considerations during the board's discussions. The board offered two public comment periods at the meeting to help inform their deliberations.

The board discussed the presentations and their own knowledge about SMA and X-ALD. They reached consensus to add SMA and X-ALD to Oregon's newborn bloodspot screening test panel.

Content of the June 29, 2020, board meeting

At the June 29, 2020 meeting, a quorum of the board members attended via videoconferencing. The board reviewed and approved updates to the board charter. This includes additional clarification of roles of the board co-chairs and vice-chair. The program reported on activities since the last board meeting, including a survey of other states' X-ALD and SMA testing. The program also reported on the fee increase package for the legislature. This increase would have provided necessary funding to add SMA and X-ALD to the newborn bloodspot screening panel. It did not go forward this legislative session due to fiscal consequences of the ongoing pandemic. The board had follow-up discussions about:

- Second-tier testing for X-ALD, and
- Identifying carrier status for SMA.

The board also reviewed a protocol and criteria for determining when to recommend removal of disorders from the newborn bloodspot screening panel. The criteria are available in appendix H.

The board reached consensus on not recommending:

- Carrier screening for SMA, or
- Second-tier testing for X-ALD outside of additional tandem-mass spectrometry.

The board reached consensus on a protocol and criteria for the recommendation of removing disorders from the screening panel (Appendix G).

SMA background, discussion, evaluation and consensus process

Expert background on SMA

Dr. Erika Finanger, subject matter expert on SMA, gave a presentation on SMA. Highlights of the presentation follow:

SMA is the most common cause of genetic death among infants. SMA type I (the most common type) has been known since 1891. The gene for the disorder was not identified until 1995. After that, therapies developed quickly.

SMA types types 0-IV have the following outcomes without treatment:

- SMA type 0 often leads to fetal loss or newborns with significant involvement and death in early infancy.
- Type I leads to progressive weakness in the first six months of life and, without targeted intervention, death prior to two years of age.
- Type II is associated with progressive weakness by fifteen months of life and, without targeted intervention, respiratory failure and death after the third decade of life.
- Types III and IV are associated with progressive weakness that develops after one year of life or in adulthood. Most people have a normal lifespan.

There is generally a long delay between the onset of symptoms and diagnosis of SMA. It's a long and stressful diagnostic journey for parents. The sooner SMA is diagnosed, the better the outcomes are for the patient.

Current treatments include nusinersen and onasemnogene abeparvovec (gene therapy). Studies of nusinersen show significant improvement in outcomes for patients. The issues of treatment with nusinersen include the need to sedate the infant to administer the drug and risks related to the lumbar injection of the drug. Risks with gene therapy include a liver reaction due to the need for steroids. Gene therapy is a one-time treatment. Nusinersen is used for life.

No ethnic groups are at higher risk for SMA. However, there are concerns related to equity in current diagnosis and treatment of SMA, particularly in rural areas. So far, Dr. Finanger has been able to treat all patients with nusinersen. Oregon Health Plan (OHP) covers both treatments (nusinersen and gene therapy) with prior authorization. OHP sets the foundation for coordinated care organization (CCO) coverage. However, some patients are not authorized for coverage by their CCO. This may limit treatment options available to individual patients. Also, some insurance can have delays that affect the timing of treatment (The goal is to treat an infant within

days of diagnosis). Timely insurance coverage for treatment and medication is a challenge for many families.

Program and board review for recommending the addition of SMA to the screening panel

Program's analysis of adding SMA to the panel

The program reviewed SMA using the board approved criteria for recommending the addition of a disorder to the screening panel. It determined that SMA fulfills stage one of the review process: the disorder has been added to the Recommended Uniform Screening Panel (RUSP).* The results of the program's analysis of stage two, category one criteria are as follows:

The condition is well-defined in newborns.

- Earlier intervention results in improved outcomes compared to later identification.
- The population level incidence and prevalence of the disorder are known.
- There is either:
  - A Federal Drug Administration (FDA)-approved testing method available using dried blood spots, or
  - An accurate testing method available meeting clinical laboratory requirements for validation and testing by the laboratory using dried blood spots. (These are mostly molecular-based tests that are not FDA approved, however, they can be validated.)

    Note, the program analysis assumes there would be screening for infants with the disorder only. It assumes no screening for carriers because of the complexity of lab testing and follow-up.
- Diagnostic and specialty testing is available.
- A treatment is available.
- Appropriate specialized medical consultation is available to the program or can be obtained.
- The specific condition appears in the funded region of the OHP prioritized list as determined by the Oregon Health Evidence Review Commission.
- The program has sufficient information for a fiscal analysis.
- The impact to partners contracted with the program has been assessed.

* The RUSP (Recommended Uniform Screening Panel) is a list of disorders that the Secretary of the Department of Health and Human Services recommends for states to screen as part of their state universal newborn screening programs.

Board's analysis of adding SMA to the panel

Carrier screening. The board considered the ethicality and costs of performing carrier screening for SMA in addition to screening for the disorder itself. Five percent of SMA cases occur in compound heterozygotes detected by screening carriers. In opting not to do carrier screening that 5% would be missed. Essentially, every five years one infant would be missed. The board considered the question of whether that risk is acceptable given the impact on families. The incidence of SMA is 1 in 10,000 live births, whereas the carrier rate is approximately 1 in 30 live births. Detecting carriers would identify 800 to 1,300 carriers a year. The current capacity of genetic counselors would not be sufficient to respond to the needs of the families of infants who would be identified as carriers each year.

There was concern that:

- Carrier screening would deny children the right to informed choice about knowing their carrier status, and
- People who are ethically or religiously opposed to it may decline newborn bloodspot screening entirely as a result.

The board discussed delaying reporting until the child was legal age. However, if the program tests for carrier status, there is a regulatory obligation to report the results promptly. Identified carriers would need follow-up sequencing and follow-up surveillance.

The board examined the feasibility of implementing the SMA test now and later adding carrier screening. The program explained that to add the carrier screening later would require:

- Revalidating the methodology, and
- Adding more follow-up staff.

The program would need good data to support making the change.

At the February meeting the board agreed to follow up on the topic of SMA carrier screening at a future meeting. They will do so after the program gathers information from other states to inform the discussion. The board assumes for now that the program would not test for carrier status, and offer the following evaluation:

Benefit versus harm. The board affirmed that the population-level public health benefits of screening for SMA outweigh the risks and harms.

Program capacity. The program has adequate capacity and expertise to conduct SMA testing in its laboratory. However, they will need more staff to report results and conduct follow-up with parents and providers and to conduct education. Additional fiscal resources will also be needed if SMA is added to the screening panel.

Incidence, testing and treatment. The board determined that the following of SMA are significant enough to merit screening:

- Population level incidence
- Prevalence, and
- Disease burden.

The following is available and accessible:

- Diagnostic and specialty testing, that allows a definitive diagnosis to be made, and
- An effective treatment proven to result in clinically significant benefits.

Equity in care. The board agreed that there are equity concerns about delays in delivery of specimens from rural areas versus urban areas. However, time sensitivity is a concern with many conditions on the screening panel, not just SMA. Courier service or expedited shipping may be a solution. However, there is a need for more research (which is is forthcoming from the program). There needs to be work on educating rural hospitals about the importance of timely screening. The board concluded that SMA testing would be as equitable as newborn bloodspot screening can currently be.

Impact on program partners. The board assumed the addition of the disorder would not be prohibitive to screening partners contracted by the program. One program partner (Saipan) reported that, with a population of 50,000, they do see SMA cases and that testing would be beneficial. Other partners did not respond to the program's survey.

Consensus check on proposal to add SMA to the screening panel with no carrier screening

The board provided individual consensus ratings about adding SMA to the screening panel. They used the following consensus scale

1. Enthusiastic agreement
2. Agreement
3. On the fence or neutral
4. Serious questions or concerns but not going to block from moving forward
5. No agreement, would block action

Based on the ratings, there was strong consensus to add SMA to the program screening panel. All board members gave a consensus rating of 1.*

* A breakdown of consensus ratings by individual board member is available in meeting summaries at the advisory board website at www.bitly.com/nbs-advisory

X-ALD background, discussion, evaluation and consensus process

Expert background on X-ALD

Dr. David Koeller and Dr. Cheryl Hanna are both subject matter experts on X-ALD. Each gave a presentation on X-ALD. Highlights of the presentations follow:

X-ALD is an inherited genetic disorder caused by mutations on the ABCD1 gene located on the X chromosome. These mutations interfere with the process for transporting fat molecules, called very long-chain fatty acids. This leads to abnormally high levels of these fatty acids, which are thought to be toxic to myelin and the adrenal cortex.

There is a broad spectrum of disease, classified into three categories:

1. **Adrenocortical insufficiency**
   Eighty percent of patients with X-ALD will develop adrenal insufficiency. Steroid replacement therapy is effective at treating adrenal insufficiency.
2. **Cerebral demyelination (child, adolescent, and adult cerebral X-ALD)**
   The age of onset for cerebral X-ALD ranges from childhood to adulthood. Without treatment, cerebral X-ALD will result in progressive disability and death. The ACHDNC Evidence Committee recommends treatment with stem cell transplantation for early stage child cerebral X-ALD (shortly after brain involvement is demonstrated). However, the committee does not recommend transplant for those with:
   - Asymptomatic X-ALD, or
   - More severe neurologic impairment.

   For adults with cerebral X-ALD, there is no treatment.
3. **Progressive paralysis of the lower extremities (adrenomyeloneuropathy)**
   No treatment is available.

Treating X-ALD with bone marrow transplant cannot be done until a change shows on an MRI. Chances of survival without neurocognitive decline and death is improved if:

- Changes are detected, and
- A bone marrow transplant is performed on an X-ALD patient before the brain is significantly involved.

The challenge is that symptoms appear between 3 and 10 years of age. Early intervention is the only way to catch X-ALD before the brain is involved. If it is known that an infant has X-ALD, MRIs can be used to catch progression of the disease before symptoms surface. However, treatments have high morbidity rates and high cost.

Most children with X-ALD develop failure of the adrenal gland. They become unable to produce the stress hormone cortisol in the first decade of life. Deficiency of this hormone may be fatal and can occur as young as 6 months of age. Detection of cases of X-ALD allows infants to be monitored for adrenal gland failure.

Females have two X chromosomes, but males have only one. If a mother has a mutation on one X chromosome, her son will have a 50% chance of inheriting the mutation. Men with the gene will pass on an X-ALD gene to all daughters, who will then be carriers of the disease. Men will not pass the gene on to their sons. Male offspring of female carriers will have a 50% chance of having X-ALD, while 50% of female offspring will be carriers for the condition. Females who are carriers of X-ALD may develop mild symptoms with no central nervous system or adrenal impacts.

Historically, there has been insurance coverage for X-ALD when clinical symptoms are present. Experts expect that if X-ALD becomes part of the newborn bloodspot screening panel, there should be no problem with insurance coverage. There are potential equity issues due to limited imaging capacity in rural areas. If a patient needs a stem cell transplant, it is unclear whether it will be covered in Oregon. Patients currently must come to Portland for a transplant. Some are also sent to Minnesota.

Newborn bloodspot screening for X-ALD is not specific and diagnostic testing will produce some positive test results not related to X-ALD. Testing will identify untreatable disorders and adult onset of X-ALD for which there is no treatment.

Program and board review of adding X-ALD to the screening panel

Program's analysis of adding X-ALD to the panel

The program reviewed X-ALD for addition to the screening panel. The program assumed they would not be performing second-tier testing outside of additional tandem mass spectrometry. The program determined that X-ALD fulfills stage one of the review process: the disorder has been added to the RUSP. The results of the program's analysis of stage two, category one criteria are as follows:

- While the risk for the condition can be identified in the newborn period:

» The condition itself does not manifest until childhood, and
» The spectrum of disease is broad.

Currently there is uncertain clinical significance about the many genetic mutations. This is also uncertain penetrance of known mutations associated with disease.

- It is not clear that earlier detection by newborn screening results in improved outcomes compared to later identification. However, there is indirect evidence that earlier age of treatment for the cerebral form of adrenoleukodystrophy results in better outcomes.
- The population level incidence and prevalence are known.
- There is an FDA approved testing method available using dried blood spots. However, the screening test is not specific for X-ALD. It may pick up other conditions, some of which have no treatment (e.g., Zellweger syndrome).
- Diagnostic and specialty testing is available.
- A treatment is available.
- Appropriate specialized medical consultation is available or can be obtained.
- The specific condition appears in the funded region of the prioritized list as determined by the Oregon Health Evidence Review Commission.
- The program has enough information to perform a fiscal analysis.
- The program assessed the impact to the program's contracted partners.

Based on its analysis, the program gave a qualified "yes" for X-ALD to move on to stage three, category two review by the board.

Board's analysis of adding X-ALD to the panel

Benefit versus harm. The population level public health benefits of screening outweigh the risks and harms. Adrenal insufficiency is very common in childhood. The youngest affected children have been diagnosed in the first six months of life. The benefit of identifying the 80% of X-ALD affected children who get adrenal insufficiency outweighs the harm to families of getting incidental information about other disorders. It is important to treat cerebral X-ALD early.

Carriers. Identifying carriers incidentally by testing for X-ALD was of concern to the board. Ninety-five percent of mothers of boys with the X-ALD gene are carriers. These mothers will be identified by default through the detection of their sons. An identified female carrier will have a high likelihood of adult-onset symptoms with no known treatment. The mother may feel responsible for the child's disorder. The carrier information might also create a risk that insurers will treat the mother's X-ALD as a prior condition, which has implications for life and disability insurance. The board discussed whether it is ethical to identify female carriers without consent and whether it is ethical to not test a child due to the likelihood of discovering collateral information about the mother.

Resources needed. The program would require more staffing and resources in order to:

- Implement and maintain testing and reporting of X-ALD, and
- Provide follow-up and education for providers and parents.

Incidence, testing and treatment. One to five cases of X-ALD would be identified by newborn bloodspot screening per year. The board determined that the population level incidence, prevalence and disease burden are significant enough to merit screening.

Availability of testing. Diagnostic and specialty testing is available and accessible which allows a definitive diagnosis. The board felt that this criterion would be met if:

- The program administered only first tier testing with additional tandem mass spectrometry, and
- Primary care physicians did genetic and other specialized testing.

It was noted that DNA tests are complicated to order, and insurance often doesn't cover out-of-house testing. Some board members felt it would be better to keep genetic testing within the program. Given the large number of specimens that may require genetic testing, the program asked:

- If the need to increase fees to cover the cost of genetic testing for all screen-positive infants to identify the small number of true positives would be cost-effective, or
- If that testing would be better performed in a reference lab.

Treatment. The board determined that an effective treatment proven to result in clinically significant benefits is available and accessible.

Equity in care. Testing for X-ALD raises the same equity concerns about access in rural areas that SMA does. Such equity concerns are not unique to this disorder. In addition, some families will not be able to pay for genetic testing if they have to ask insurers to pay for it versus having the program do the testing. If the condition is not symptomatic until the future, low income families might not do genetic testing.

The program shared that adding tests to the panel would require a request to the legislature for a fee increase. The current cost for newborn bloodspot screening in Oregon is $80, which includes both a first and a second screen. Adding two more tests —SMA and X-ALD—along with other necessary testing, follow-up and program updates could nearly double the cost of the test kit. Additional cost is a consideration for whether the program should also do further testing beyond additional mass spectrometry for X-ALD.

Board members acknowledged cost concerns. Some members were concerned that a significant cost increase could have unintended consequences, such as decreased newborn screening rates. Others wondered whether cost is important enough on its own to determine whether to add the condition to the panel. It was noted that the disorders have been added to the RUSP. Twenty-three states are already testing for them.

Impact on program partners. The board assumes that the addition of the disorder is not prohibitive to the program's contracted screening partners. There are no X-ALD cases in Saipan. Other partners did not respond to the program's survey.

Consensus check on proposal to add X-ALD to the screening panel with no genetic second-tier testing by the program

The board provided individual consensus ratings about adding X-ALD to the screening panel. They used the following consensus scale:

1. Enthusiastic agreement
2. Agreement
3. On the fence or neutral
4. Serious questions or concerns but not going to block from moving forward
5. No agreement, would block action

Based on the ratings, the board reached consensus to add X-ALD to the program screening panel. The average consensus rating was 2. Ratings ranged from 1 to 4.

Next steps for adding SMA and X-ALD to Oregon's screening panel

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

- Finalize a fiscal analysis to inform the program's funding request to the legislature.
- Approach the legislature with a fee increase request. Note: After this discussion, it was determined that the program's fee increase package for the 2021 Oregon Legislature would not go forward. This is due to the fiscal consequences of the COVID-19 pandemic. Without this fee increase, SMA and X-ALD cannot be added to the testing panel until later.

- Obtain legislative approval of the fee increase request.
- Initiate a rule change to add the disorder. (This requires the board step into a role as a rules advisory committee.)
- Update the state's Oregon Newborn Bloodspot Screening Practitioner's Manual.
- Validate that the testing method works and how the test results will appear on the report.
- Determine the process for following up with providers after tests.
- Update the laboratory information system.
- Create and disseminate educational materials for parents and providers.
- Notify providers of the coming change.

Additional discussion of carrier and second-tier testing

After consensus decisions to recommend adding SMA and X-ALD to the screening panel, the group held additional discussion at the June 29, 2020, meeting about:

- Conducting second-tier testing for X-ALD, and
- Testing for carrier status for SMA.

The program provided the following follow-up information about approaches in other states.

- Twenty-three states implemented or are in the process of implementing SMA testing. Of those, 12 responded to the program's survey. Three are in pilot testing and nine have fully implemented SMA screening.
- All 12 use an opt-out process for consent, and all include SMA in that opt-out process.
- Half of the states do not do additional testing for SMA beyond the initial screen and repeat. Four states refer specimens out for survival of motor neuron 2 (SMN2) copy number and two do it in-house.
- No states test for SMA carriers.
- Of the 15 states that have implemented screening for X-ALD, five responded to the program's survey.
- No states screen only males for X-ALD.
- Three of the five states reported that the false positive rate for X-ALD testing is very low.
- Four of the five states do second-tier testing by mass spectrometry for X-ALD. One does third-tier testing (via a reference lab).
- All of the states reported that, after initial screening for X-ALD, providers are responsible for any confirmatory or additional testing.

Based on the discussion, the board confirmed agreements about SMA and X-ALD, as included above, would stand. Also, that the following would not be performed as part of screening by the program:

- Carrier testing for SMA
- Second-tier testing for X-ALD, except for additional mass spectrometry.

Disorder evaluation for removal from the testing panel

The program drafted, and the board considered, a set of criteria for recommending the removal of disorders from the newborn bloodspot screening panel. The criteria are available in Appendix G. The board clarified that in applying the criteria to disorders, it would take a holistic approach. They would not require that each criterion be met. They would instead:

- Consider all criteria, whether met or not
- Discuss the pros and cons, and
- Seek consensus on whether to remove a disorder from the panel.

The board made no changes to the draft criteria. They took a poll for consensus ratings about adopting the criteria. They used the following consensus scale:

1. Enthusiastic agreement
2. Agreement
3. On the fence or neutral
4. Serious questions or concerns but not going to block from moving forward
5. No agreement, would block action

Based on the ratings, the board reached a strong consensus (all 1s and 2s) to adopt the criteria for removing disorders from the program screening panel.

Future advisory board work

The board's goals for upcoming meetings are the following:

- Conduct strategic visioning and planning for the program.
- Use the protocol and criteria for recommending the removal of disorders from the screening panel to evaluate Gaucher and Fabry.
- Discuss recommendations for statute updates.
- Evaluate the costs and benefits of providing courier service or expedited shipping to improve timeliness.
- Discuss opportunities for and effectiveness of newborn bloodspot screening education for parents and providers.
- Evaluate the equity of newborn bloodspot screening testing reimbursement.

A note for funding

The advisory board wants to voice their concern that their recommendation to add SMA and X-ALD to the newborn bloodspot screening panel in Oregon will not be implemented at this time because the fee package needed is not moving forward to the 2021 legislative session. The package did not move forward due to the fiscal impacts of the COVID-19 pandemic on Oregon Health Authority. The fee proposal was designed to:

- Support crucial functioning and updates of the program, and
- Allow Oregon to start screening for SMA and X-ALD (two conditions this advisory board has recommended to be added).

The board would like to note to the Oregon Health Authority and the legislature, during this COVID-19 pandemic, that newborn screening is also a vital public health measure. It's one that Oregon has historically led in and not lagged on. It has contributed to many babies' lives saved and co-morbidities prevented. Already our health system is overburdened by COVID-19. This virus sidelines many other important health concerns. Let us not add to this with serious pediatric illnesses that could have been prevented. We strongly advise the legislature to consider the fee proposal at their next opportunity.

Conclusion

Efficient review and recommendations about SMA and X-ALD disorders are a sign of a high functioning board. The board ramped up quickly to develop protocols and criteria to evaluate practical and ethical questions about newborn bloodspot screening in Oregon. The board has used the consensus process in its operating procedures. The program has been effective in identifying and securing outside third-party expertise on ethics and disorders under review. Though established only a year ago, the board has already provided an active channel for addressing important questions about newborn bloodspot screening.

Appendix A: Guiding legislation and rules

The Newborn Bloodspot Screening Program's authority is set in the following statutes:

- ORS 433.285 to 433.295, which were established in 1963
- ORS 431A.750 (originally enacted as ORS 431.310 in 1919 and renumbered in 2015)

Excluding housekeeping amendments, ORS 433.285 was last revised in 1983 and ORS 433.295 has not been revised since its creation. ORS 433.290 was revised in 2017 to add "naturopathic physicians."

The Newborn Bloodspot Screening Program describes how to carry out the statutory authority in OAR 333-024-1000 and 333-024-1110.

HB 2563, passed into law in the 2019 regular session (see HB 2563 in Appendix B), sets up the board, specifies the board member representation categories, establishes the boards' governance framework and prescribes the frequency of meetings and reports to the legislature. The board has adopted a charter that conforms to this legislation.

Appendix B: HB 2563 enrolled

80th OREGON LEGISLATIVE ASSEMBLY--2019 Regular Session

Enrolled

House Bill 2563

Sponsored by Representatives MCLAIN, SOLLMAN, SCHOUTEN, HAYDEN; Representatives ALONSO LEON, KENY-GUYER, NOBLE, NOSSE, PRUSAK, SALINAS, SMITH WARNER, WILLIAMS, WITT, Senator HANSELL (Presession filed.)

CHAPTER .....

AN ACT

Relating to screening newborns for diseases; and declaring an emergency.

Be It Enacted by the People of the State of Oregon:

SECTION 1. (1) The Newborn Bloodspot Screening Advisory Board is established in the Oregon Health Authority.

(2) The board consists of 13 voting members appointed by the Director of the Oregon Health Authority as follows:

(a) 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;

(b) One member who is a licensed physician who by contract provides expert medical advice and consulting services to the Northwest Regional Newborn Bloodspot Screening Program;

(c) One member who is a representative of Medicaid or the insurance industry;

(d) Two members who are representatives of birthing centers or hospitals;

(e) One member who is a representative of an entity that contracts with the Northwest Regional Newborn Bloodspot Screening Program for newborn bloodspot screening services;

(f) Three members who are representatives of advocacy associations regarding newborns with medical conditions or rare disorders;

(g) One member who is a representative of a statewide association of nurses;

(h) One member who is a representative of a statewide association of midwives; and

(i) Two members who are representatives of a statewide association of pediatricians.

(3) In addition the requirements provided in subsection (2) of this section, one or more of the following professions must be represented as a voting member of the board:

(a) Neonatal intensive care specialist;

(b) Licensed physician or nurse practitioner who is board certified in obstetrics, pediatrics or neonatology;

(c) Obstetrician or gynecologist;

(d) Nurse;

(e) Ethicist;

(f) Geneticist;

(g) Dietician; and

(h) Educator.

(4) To the greatest extent practicable, the director shall appoint members from a diverse range of socioeconomic, racial and ethnic backgrounds.

(5) In addition to the 13 voting members provided for in subsection (2) of this section, members of the Legislative Assembly or employees of the Oregon Health Authority may serve as nonvoting members.

(6) The term of office of each voting member of the board is four years, but a member serves at the pleasure of the director. Before the expiration of the term of a member, the director shall appoint a successor whose term begins on July 1 next following. A member is eligible for reappointment. If there is a vacancy for any cause, the director shall make an appointment to become immediately effective for the unexpired term.

(7) A voting member of the board is entitled to compensation and expenses as provided in ORS 292.495.

(8) The board shall select two of its members to jointly serve as chairpersons and another as vice chairperson, for terms and with duties and powers necessary for the performance of the functions of the offices as the board determines. One chairperson must be a voting member and the other chairperson must be the manager of the Northwest Regional Newborn Bloodspot Screening Program or the manager's designee. The manager or manager's designee must be a nonvoting member.

(9) A majority of the voting members of the board constitutes a quorum for the transaction of business.

(10) The board shall meet at least once every six months at a time and place determined by the board. The board also may meet at other times and places specified by the call of one or both chairpersons or of a majority of the voting members of the board.

(11) The board shall report its findings and recommendations for legislative changes to the committees or interim committees of the Legislative Assembly related to health in the manner provided under ORS 192.245 no later than September 15 of each even numbered year.

SECTION 2. Notwithstanding the term of office specified by section 1 of this 2019 Act, of the members first appointed to the Newborn Bloodspot Screening Advisory Board:

(1) Three shall serve for a term ending July 1, 2020.

(2) Three shall serve for a term ending July 1, 2021.

(3) Three shall serve for a term ending July 1, 2022.

(4) Four shall serve for a term ending July 1, 2023.

SECTION 3. No later than December 15, 2019, the Newborn Bloodspot Screening Advisory 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.

SECTION 4. This 2019 Act being necessary for the immediate preservation of the public peace, health and safety, an emergency is declared to exist, and this 2019 Act takes effect on its passage.

Passed by House March 28, 2019

.....
Timothy G. Sekerak, Chief Clerk of House

.....
Tina Kotek, Speaker of House

Passed by Senate May 2, 2019

.....
Peter Courtney, President of Senate

Received by Governor:

.....M.,....., 2019

Approved:

.....M.,....., 2019

.....
Kate Brown, Governor

Filed in Office of Secretary of State:

.....M.,....., 2019

.....
Bev Clarno, Secretary of State

Appendix C: History of newborn bloodspot screening

Inception of newborn bloodspot screening

The push for newborn bloodspot screening nationally happened in response to incidences of intellectual disability in children in the 1960s. Phenylketonuria, a condition in which the body cannot break down phenylalanine, was found to be the cause of many of these cases, and a test was developed to allow widespread screening for phenylketonuria using dried bloodspots from infants. In 1963, the first states legislated newborn bloodspot screening for the disorder. Oregon was among these states. Newborn bloodspot screening became a rapidly changing field as researchers developed tests for other conditions that could cause death or severe impairment in the newborn period.

Standardization of screening

In 2002, the American College of Medical Genetics was asked by the federal government to create standard guidelines for screening. This was due to differences in states' approaches and the number and type of conditions screened for. They established the following minimum criteria for conditions to be screened:

- The condition could be detected within 24 to 48 hours after birth, when it could not be detected by a medical exam.
- There was a test that had sufficient sensitivity and specificity for the condition.
- Early detection, timely intervention and effective treatment existed and offered a proven benefit.

The college reviewed many conditions and placed 29 on a core screening panel and an additional 25 on a secondary screening panel because they lacked an effective treatment, or the disease was not well understood. The core screening panel of 29 conditions would become the first Recommended Uniform Screening Panel (RUSP). The Advisory Committee on Heritable Disorders in Newborns and Children was formed to advise the U.S. Secretary of Health and Human Services about whether the RUSP could become the national standard; the panel was approved in 2005. The RUSP is now the national standard and is used by newborn screening programs to help determine which conditions to add to their state screening panels. Today's panel covers 35 core conditions and 26 secondary conditions. Two of the core conditions, critical congenital heart disease and hearing screening, are point of care tests and are not performed by newborn bloodspot screening programs.

Timeliness of screening process

The U.S. Government Accountability Office (GAO) established standards for timeliness of the screening process. The overall goals set by the GAO are that time-critical disorders will be reported within five days of birth and all newborn screening results will be reported within seven days of birth. The screening process is divided into three stages with a benchmark of 95% for each:

1. Birth to collection of specimen — 48 hours
2. Collection to receipt of specimen in the lab — 24 hours
3. Laboratory testing and report — not specified

Appendix D: Disorder evaluation for addition to the Northwest Regional Newborn Bloodspot Program's screening testing panel

Procedure for disorder addition evaluation

Stage 1: Addition to the RUSP

Disorders that have been reviewed by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and that have been added to the RUSP will be raised for further evaluation.

Stage 2: NWRNBS program evaluation using category one criteria

After a disorder has been added to the RUSP, the NWRNBS program will evaluate the disorder using the criteria in "category one criteria" (please see below). This initial set of criteria will be answered yes or no. The NWRNBS program will share the evaluation of the category one criteria with the NWRNBS Advisory Board. If all criteria are answered yes, the disorder will be moved to stage three.

Stage 3: NWRNBS Advisory Board evaluation and recommendation using category two criteria

Disorders that have met category one criteria will be brought to the NWRNBS Advisory Board for evaluation using category two criteria. These criteria will be evaluated using the consensus tool (see below). The results of this evaluation will inform the recommendations to the NWRNBS program.

Criteria for disorder addition evaluation

Category one criteria (evaluated as yes or no)

1. The condition is well-defined in newborns.
2. Earlier intervention results in improved outcomes compared to later identification.
3. The population level incidence and prevalence are known.

4. There is an 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.
5. Diagnostic and specialty testing is available.
6. A treatment is available.
7. The contracted NWRNBS medical consultants have been consulted and appropriate specialized medical consultation is available or can be obtained by the program.
8. The specific condition appears in the funded region of the prioritized list as determined by the Oregon Health Evidence Review Commission.
9. The NWRNBS program has sufficient information to perform a fiscal analysis.
10. The impact to the NWRNBS contracted partners has been assessed.

Category two criteria (Evaluated using the consensus method)

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. There is adequate capacity and expertise in the NWRNBS program to implement and maintain follow-up and education for providers and parents.
4. The NWRNBS program has adequate fiscal resources for implementing the test, performing the test and conducting follow-up and education.
5. The population-level incidence, prevalence and disease burden are significant enough to merit screening.
6. Diagnostic and specialty testing is available and accessible that allows a definitive diagnosis to be made.
7. And effective treatment that is proven to result in clinically significant benefits is available and accessible. There is equitable care and treatment for the disorder.
8. Addition of the disorder is not prohibitive to NWRNBS contracted partners.

Consensus method

The 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 one through five 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 ones and twos on a given proposal.
- A **weak** consensus is one in which some or several board members show threes or fours.
- If anyone in the group shows a five, the group **does not have consensus**.
- For weak or no consensus, the 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/recommendation.

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

"5" I object and will block the proposal.

Appendix E: Independent condition report regarding SMA—executive summary

Executive Summary: Spinal Muscular Atrophy (SMA)

Purpose: This is a summary document containing information for use by the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board in their evaluation of the potential addition of SMA to the NWRNBS testing panel. This document is intended to summarize scientific evidence and assessment of NWRNBS Program and partner readiness and 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 proposed for addition to the panel:

Stage 1: Addition to the RUSP
Disorders that have been reviewed by the ACHDNC and have been added to the RUSP will be raised for further evaluation.

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

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

Methods: This document summarizes evidence gathered in a Systematic Evidence Review (SER) process, including evidence published after the Advisory Committee for Heritable Disorders in Newborns and Children's (ACHDNC's) External Evidence Review Report for SMA. Importantly, the scope of the literature review is limited to childhood disease onset. Subject matter experts, including medical ethicists, medical consultants, and NWRNBS Program staff and partners were consulted and a summary of those discussions is provided here. A reference to the more detailed Evidence Report is provided for each of the criteria below.

Condition overview: Spinal muscular atrophy is a group of genetic conditions caused by deterioration of motor neurons in the spinal cord. The focus of the ACHDNC review, and that of this review, is on SMA caused by mutations in the Survival Motor Neuron 1 (SMN1) gene. Like its name suggests, the SMN1 gene guides the production of survival motor neuron protein, which is found throughout the body, but especially in the spinal cord and which maintains the health of specialized nerve cells that connect brain signals to skeletal muscles.1 Ninety-five percent of SMA is caused by the same mutation (deletion of exon 7 in both alleles of SMN1), which leads to a deficiency of survival motor neuron protein and subsequent progressive motor weakness. 2,3 Another gene, SMN2, also produces a small amount of survival motor neuron protein. Normally a person has two copies of the SMN1 gene and one to two, but ranging up to five, copies of SMN2.43 Multiple copies of SMN2 are associated with less severe disease.

Stage 1: Addition to the RUSP

Disorders that have been reviewed by the ACHDNC and have been added to the RUSP will be raised for further evaluation.

Stage 1: Addition to the Recommended Uniform Screening Panel (RUSP)	Yes/No
Has the condition been added to the Recommended Uniform Screening Panel (RUSP)?	Yes

Stage 2: NWRNBS Program Evaluation using Category One Criteria

After a disorder has been added to the RUSP, the NWRNBS Program will evaluate the disorder using the criteria in "Category One Criteria" (Please see below). This initial set of criteria will be answered using yes or no. If all criteria are answered yes, the disorder will be moved to Stage 3.

Stage 2: NWRNBS Program Evaluation using Category 1 Criteria	Reference to Evidence Report (page)
1. **The condition is well-defined in newborns.** Yes, the condition is well-defined in newborns.	Case Definition (page 6)
Historically, SMA was thought to have five clinical phenotypes based upon "maximum motor function achieved," but with the advent of genetic testing, it is clear that mutations on the *SMN1* gene span a continuum of outcomes, blurring the lines between the conventional categories presented in the table below.[3] As the "Spinal Muscular Atrophy" Chapter in GeneReviews® points out, the conventional clinical categories may still be useful for understanding prognosis of disease based upon age of onset. Two of these "historical" categories of SMA affect	Natural History of SMA with Usual Clinical Detection (8)

newborns or infants less than 6 months of age.

- Type 0 often leads to fetal loss or newborns with significant involvement and death in early infancy.
- Type I leads to progressive weakness in the first six months of life and, without targeted intervention, death prior to 2 years of age.
- Type II is associated with progressive weakness by 15 months of life and, without targeted intervention, respiratory failure and death after the third decade of life.
- Types III and IV are associated with progressive weakness that develops after 1 year of life or in adulthood, and most individuals have a normal lifespan.

2. **Earlier intervention results in improved outcomes compared to later identification.**

   Yes, earlier intervention results in improved outcomes compared to later identification.

   According to the ACHDNC evidence review, "Data support that therapies such as nusinersen or gene therapy lead to a decreased risk of ventilator dependence or death and improved motor outcome within the first two years of life in those with SMA type I."[2]

   In addition, a recent, high-quality systematic review found high quality evidence for meaningful improvement in motor function and achievement of development of motor milestones in infants with SMA Type I treated with intrathecal nusinersen, particularly if started earlier in the disease course.[6]

   Treatment for SMA. (13)

3. **The population level incidence and prevalence are known.**

   Yes, population level incidence and prevalence are known.

   Birth prevalence for SMA from newborn screening pilot studies ranges from 1:4,000 to 1:17,000.[178]

   Incidence and Prevalence of SMA (9)

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, there are accurate testing methods available.

   Screening method summary:
   Screening is based on detection of a deletion in exon 7 in

   What is the screening method to detect SMA among newborns? (10)

SMN1 using Real-Time PCR.[2] Multiple screening methods are available, some of which only detect infants with deletions in both alleles (homozygotes). Other methods detect both deletions and deleterious mutations. Those methods detect carriers as well as newborns who have one deletion and a deleterious mutation in the other allele (i.e., compound heterozygotes). From 2-6% of cases of SMA are estimated to be compound heterozygotes or have de novo mutations. Screening for SMA can either be stand alone or multiplexed with screening for severe combined immunodeficiency (SCID).

5. **Diagnostic and specialty testing are available.**

Confirmatory Testing and Diagnosis. (13)

Yes, diagnostic testing is available.

Diagnostic testing:
Most DNA diagnostic laboratories use multiplex ligation probe amplification (MLPA) methods for deletion analysis of exon 7 of the SMN1 gene.[2] Electromyography or muscle biopsy are also used for confirmation.

6. **A treatment is available.**

Treatment for SMA (13)

Yes, two treatments are available.

Available treatment:
SPINRAZA® (nusinersen)
ZOLGENSMA® (onasemnogene abeparvovec-xioi)

7. **The contracted NWRNBS medical consultants have been consulted and appropriate specialized medical consultation is available or can be obtained by the Program.**

Availability of Medical Consultants ()

Yes, appropriate specialized medical consultation is available or can be obtained by the Program.

Type of medical consultation: Pediatric neurologists

Availability of medical consultants:
One multidisciplinary clinic located at Shriners Hospital on the campus of Oregon Health and Science University in Portland, Oregon. The Northwest regional Newborn Bloodspot Screening (NWRNBS) Program has identified one specialist in Oregon who could be added to the current contract for medical consultation. This would require an amendment to the current contract and would have a cost associated with the extra work. It is unknown if this would be sufficient for the volume of infants identified by screening.

8. **The specific condition appears in the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission.**

   Yes, SMA appears in the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission.

   Location on Prioritized List:
   Oregon's legislature approved funding for lines 1-469 of the prioritized list for January 1, 2018. SMA appears on Lines 71, 292, 345, and 377 and is therefore on the funded region of the Prioritized List.

Is this condition on the Prioritized List as determined by the Oregon Health Evidence Review Commission? (18)

9. **The NWRNBS Program has sufficient information to perform a fiscal analysis.**

   Yes, the NWRNBS Program has sufficient information to perform a fiscal analysis.

   Summary of available information:
   With the assumptions that the program will not detect carriers or do *SMN2* copy number or other second tier testing, information exists for testing and reagent costs. Prevalence estimates for other populations can be used as a starting point for follow-up cost analysis.

NWRNBS Program Impact Assessment (21)

10. **The impact to the NWRNBS partners has been assessed.**

    Yes, the impact to the NWRNBS partners has been assessed.

    List of partners assessed: Idaho, New Mexico, Saipan

    Type and date of assessment: Email survey sent on December 4, 2019

NWRNBS Program Impact Assessment (21)

Stage 3: NWRNBS Advisory Board Evaluation and Recommendation using Category Two Criteria

Disorders that have met Category One Criteria will be brought to the NWRNBS Advisory Board for evaluation using Category Two Criteria. These criteria will be evaluated using the consensus tool (see below). The results of this evaluation will inform the recommendations to the NWRNBS Program.

Stage 3: Category 2 Criteria (Evaluated Using the Consensus Method)	Reference to Evidence Report (page)
1. **The population level public health benefits of screening outweigh the risks and harms.** **Risks and harms of screening:** None identified by the ACHDNC Evidence Review.2 **Additional consideration:** The screening test under consideration by the NWRNBS Program would not detect carrier status.	Potential Harms of Newborn Screening for SMA. (13)
2. **There is adequate capacity and expertise in the NWRNBS program to implement and maintain testing and reporting.** The program has sufficient expertise to implement testing but will require additional personnel to maintain screening and reporting.	Capacity and expertise to implement and maintain testing and reporting (21)
3. **The NWRNBS Program has adequate fiscal resources for implementing the test, performing the test and conducting follow-up and education.** The program will require additional resources to implement and perform the test and to conduct follow-up and education.	Fiscal Analysis (21)
4. **The population level incidence, prevalence and disease burden are significant enough to merit screening.** Birth prevalence for SMA from newborn screening pilot studies ranges from 1:4,000 to 1:17,000.[178] Without treatment, early onset SMA (Type I) almost certainly results in severe disability and death. There is evidence from a high quality and a moderate quality randomized control trial to suggest short- or moderate-term treatment benefit from nusinersen, particularly for children treated pre-symptomatically, though the risk of adverse events appear high and long-term outcomes are not known.[6] There is emerging evidence about gene therapy for treatment of	What is the estimated birth prevalence? (9) What is the natural history of this condition? (8) Treatment for SMA. (13)

SMA, prompting approval from FDA for children ages 2 and under.[9]

5. **Diagnostic and specialty testing is available and accessible that allows a definitive diagnosis to be made.**

   Newborn screening pilot program results have reported definitive testing results, although the number of SMN2 copies could lead to uncertainty in diagnosis for patients with 4 or more copies who typically undergo monitoring without pre-symptomatic treatment.

Confirmatory Testing and Diagnosis (12)

6. **An effective treatment that is proven to result in clinically significant benefits is available and accessible.**

   Both nusinersen and gene therapy are FDA-approved and have evidence supporting their effectiveness.[101169] According to expert opinion, despite the cost ($4.1 million for ten years of treatment with nusinersen and $2.125 million for the same amount of time of treatment with gene therapy), coverage for treatment has not been an issue for patients seeking care in Oregon due to insurance coverage and financial assistance funded through pharmaceutical companies.[12]

Treatment for SMA. (13)

Appendix D: Discussion with Experts. (32)

7. **There is equitable care and treatment for the disorder.**

   Location of specialty care: One clinic in Portland, Oregon

   All pediatric patients with SMA must currently go to Portland for care at a multidisciplinary clinic at Shriners Hospital. Although patients can see a wide variety of providers at this clinic (ranging from Neurology to Pulmonology to Orthopedics), some families have to travel long distances to get to the clinic.

   Literature is emerging about the allocation of resources for care and treatment of patients with SMA in the setting of resource strain (due to newborn screening). This review does not estimate the number of patients estimated to be captured through screening, or the capacity of the health system to care for these patients. Additionally, it is not known which insurance companies will cover the cost of treatment and additional monitoring (and, potentially, family testing) of patients identified through a positive newborn screen.

What's the availability and accessibility of care and treatment? (19)

8. **The impact to the NWRNBS partners does not prohibit the addition or removal of the disorder.**

   Summary of impact to NWRNBS partners:
   3 partners were surveyed and one response received as of December 18, 2019 which was positive for SMA and neutral for X-ALD.

   "I think that the addition of these tests could be helpful and are unlikely to have any detrimental effects. We already see SMA somewhat frequently - more frequently than a population of our size in the mainland - so having this as a screening test could be greatly beneficial for counseling and prognostic considerations. I'm not aware of any cases of X-ALD ever on Saipan, but see no harm in testing for it, perhaps this could identify new cases.

   1. I anticipate the impact being earlier identification of those conditions leading to improved family counseling, education and management of expectations as well as early development of a treatment and emergency action plan.

   2. I am not aware of any activities that would need to be completed, however would be willing to entertain ideas I may not have considered if Oregon would be willing to offer some examples?

   3. Please see my intro above, I believe SMA is somewhat more common here than elsewhere and the addition of this test would likely be greatly beneficial to the CNMI."

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

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Appendix F: Independent condition report regarding X-ALD—executive summary

Executive Summary: X-Linked Adrenoleukodystrophy (X-ALD)

Purpose: This is a summary document containing information for use by the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board in their evaluation of the potential addition of X-ALD to the NWRNBS testing panel. This document is intended to summarize scientific evidence and assessment of NWRNBS Program and partner readiness and 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 proposed for addition to the panel:

Stage 1: Addition to the RUSP
Disorders that have been reviewed by the ACHDNC and have been added to the RUSP will be raised for further evaluation.

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

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

Methods: This document summarizes evidence gathered in a Systematic Evidence Review (SER) process, including evidence published after the Advisory Committee for Heritable Disorders in Newborns and Children's (ACHDNC's) External Evidence Review Report for X-ALD. Importantly, the scope of the literature review is limited to childhood disease onset. Subject matter experts, including medical ethicists, medical consultants, and NWRNBS Program staff and partners were consulted and

a summary of those discussions is provided here. A reference to the more detailed Evidence Report is provided for each of the criteria below.

Condition overview: X-ALD is caused by mutations in the ABCD1 gene located on the X chromosome, leading to defects in the transfer of very long-chain fatty acids into peroxisomes.1 The clinical phenotype is broad, with severe forms affecting hemizygous males much more often than heterozygous females.[2]

Stage 1: Addition to the RUSP

Disorders that have been reviewed by the ACHDNC and have been added to the RUSP will be raised for further evaluation.

Stage 1: Addition to the Recommended Uniform Screening Panel (RUSP)	Yes/No
Has the condition been added to the Recommended Uniform Screening Panel (RUSP)?	Yes

Stage 2: NWRNBS Program Evaluation using Category One Criteria

After a disorder has been added to the RUSP, the NWRNBS Program will evaluate the disorder using the criteria in "Category One Criteria" (Please see below). This initial set of criteria will be answered using yes or no. If all criteria are answered yes, the disorder will be moved to Stage 3.

Stage 2: NWRNBS Program Evaluation using Category 1 Criteria	Reference to Evidence Report (page)
1. **The condition is well-defined in newborns.** X-linked adrenoleukodystrophy is an inherited genetic disorder caused by mutations on the ABCD1 gene located on the X chromosome. These mutations interfere with the process for transporting fat molecules, called very long-chain fatty acids (VLCFAs), leading to abnormally high levels of these fatty acids, which are thought to be toxic to myelin and the adrenal cortex.[1] There is a broad spectrum of disease, historically classified into three categories of phenotypes (but now known to change and overlap over time):[2] • Adrenocortical insufficiency ("Addison's only" if the only symptom) • Cerebral demyelination (child, adolescent, and adult cerebral X-ALD) • Progressive paralysis of the lower extremities (adrenomyeloneuropathy, or AMN) Females have two X chromosomes, but males have only one; if a mother has a mutation on one X chromosome, her	Case Definition (6) What is the Genotype-Phenotype relationship? (7) Natural History of X-ALD with Usual Clinical Detection (6)

son will have a 50% chance of inheriting the mutation.

The genotype-phenotype relationship (link between individual mutations in the *ABCD1* gene and physical outcomes) is not very clear as affected individuals within the same family can have different forms of X-ALD disease.[1]

2. **Earlier intervention results in improved outcomes compared to later identification.**

Natural History of X-ALD with Usual Clinical Detection (7)

Treatment for X-ALD (15)

The ADHDNC Evidence Committee was not able to identify specific evidence for outcomes of individuals detected pre-symptomatically through newborn screening versus those diagnosed symptomatically but did conclude that "Indirect evidence suggests that earlier age of treatment with HSCT is associated with better outcomes."[2]

Adrenocortical insufficiency:
80% of patients with X-ALD will develop adrenal insufficiency.[3] Steroid replacement therapy is effective at treating adrenal insufficiency.

Cerebral demyelination (child and adolescent):
Age of onset for cerebral ALD (CALD) ranges from childhood to adulthood. Without treatment, cerebral ALD will result in progressive disability and death. The ACHDNC Evidence Committee recommends treatment with hematopoietic stem cell transplantation (HSCT) for early stage child cerebral X-ALD (shortly after brain involvement is demonstrated) but do not recommend transplant for asymptomatic or those with more severe neurologic impairment.4 The committee states that HSCT can be effective at slowing progression of cerebral disease but does not affect other major symptoms of X-ALD such as adrenal insufficiency or peripheral neuropathy.

Cerebral demyelination (adult cerebral XALD):
No treatment available.

Two low quality studies assessed outcomes of patients treated pre-symptomatically (identified through family screening or diagnosed because of adrenal insufficiency and monitored until the first signs of CALD) but there are no high-quality peer-reviewed published reports that compared outcomes for individuals with X-ALD identified pre-symptomatically versus usual case detection.

3. **The population level incidence and prevalence are known.**

Incidence and Prevalence of X-ALD (8)

Yes, clinical incidence and birth prevalence are known.

Newborn screening studies from North Carolina, Minnesota, and New York estimate birth prevalence of X-ALD from 1:5,000-1:17,000. 567 For male X-ALD hemizygotes, birth prevalence ranges from 1:8,000-1:31,000 and for female X-ALD heterozygotes, birth prevalence ranges from 1:14,000-1:35,000.

These estimates are much higher than clinical incidence estimates from the ACHDNC Evidence Review of 1:16,900 (all), 1:42,000 (male hemizygotes), 1:28,000 (female heterozygotes).[2]

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.** Screening (9)

   Yes, there is an FDA-approved testing method.

   Two-tier, tandem mass spectrometry (MS/MS) is available in the PerkinElmer® NeoBase™ 2 Non-Derivatized MSMS Kit or there are various lab-developed versions of this type of testing available.

5. **Diagnostic and specialty testing are available.** Screening (9)

   Yes. Diagnostic and specialty testing are available.

   Diagnosis of X-ALD is confirmed based on the presence of elevated serum VLCFA, as determined by C:26-LPC. Genotyping of the ABCD1 gene is supportive of the diagnosis, but the lack of genotype-phenotype correlation makes this test less helpful in predicting later phenotype.

6. **A treatment is available.** Treatment for X-ALD (15)

   Yes, a treatment is available for certain Types of X-ALD.

   Adrenal insufficiency:
   Adrenal replacement therapy is available for adrenal insufficiency.

   Childhood-CALD:
   According to the ACHDNC Evidence Committee:

   "Hematopoietic stem cell transplantation (HSCT) is recommended for early stage childhood-CALD after brain involvement is demonstrated. HSCT can be effective at arresting or slowing progression of cerebral demyelination.

HSCT does not appear to impact other major symptoms of X-ALD symptoms (e.g., adrenal insufficiency, peripheral neuropathy)."[2]

7. **The contracted NWRNBS medical consultants have been consulted and appropriate specialized medical consultation is available or can be obtained by the Program.**

Availability of Medical Consultants (22)

Yes, appropriate specialized medical consultation is available or can be obtained by the Program.

Type of medical consultation:
Pediatric metabolic specialists, pediatric endocrinologists

Availability of medical consultants:
The Northwest regional Newborn Bloodspot Screening (NWRNBS) Program currently contracts with OHSU for medical expertise for metabolic and endocrine disorders so the expertise necessary for medical consultation currently exists for the program. However, adding X-ALD could potentially require a contract amendment and increased costs for the program if the burden of work exceeds a reasonable threshold for the current specialists.

8. **The specific condition appears in the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission.**

Is this condition on the Prioritized List as determined by the Oregon Health Evidence Review Commission? (19)

Yes, X-ALD is on the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission.

Oregon's legislature approved funding for lines 1-469 of the prioritized list for January 1, 2018. X-ALD appears on Lines 60, 71, 292, 345, and 377 and is therefore on the funded region of the Prioritized List.

9. **The NWRNBS Program has sufficient information to perform a fiscal analysis.**

Yes, the NWRNBS Program has sufficient information to perform a fiscal analysis.

Summary of available information:
Information exists for testing and reagent costs and personnel for testing. Information about impact on follow-up due to identification of carriers requires further investigation to allow a better estimate of costs.

Determination by program:

A fiscal analysis can be performed by the program for the cost of the additional testing; however, the additional resources required for follow-up due to the identification of carriers will need to be further investigated in order to provide a more accurate estimate of the true workload and associated costs.

10. **The impact to the NWRNBS partners has been assessed.**

    Yes, the impact to the NWRNBS partners has been assessed.

    List of partners assessed:
    Idaho, New Mexico, and Saipan

    Type and date of assessment:
    Email survey sent on December 4, 2019

Stage 3: NWRNBS Advisory Board Evaluation and Recommendation using Category Two Criteria

Disorders that have met Category One Criteria will be brought to the NWRNBS Advisory Board for evaluation using Category Two Criteria. These criteria will be evaluated using the consensus tool (see below). The results of this evaluation will inform the recommendations to the NWRNBS Program.

Stage 3: Category Two Criteria (Evaluated Using the Consensus Method)	Reference to Evidence Report (page)
1. **The population level public health benefits of screening outweigh the risks and harms.** The ACHDNC Evidence Review states there is "Indirect evidence suggests that earlier age of treatment [of C-CALD] with HSCT is associated with better outcomes."[2] However, there are several known risks and harms of screening, including: **Identification of secondary findings:** Screening for X-ALD can lead to identification of patients with Zellweger syndrome which is rarer than X-ALD, associated with death in early infancy, and for which no specific treatment exists. **Process of follow-up for individuals with asymptomatic X-ALD:** Childhood CALD is the main target of newborn screening but adrenal insufficiency adrenomyeloneuropathy (AMN), and	What is the Genotype-Phenotype relationship? (7) Treatment for X-ALD (15) What are the benefits and harms (not related to treatment) that could result from newborn screening and early diagnosis, to the infant and to family members? (13)

cerebral adrenoleukodystrophy (CALD) will all be captured by newborn screening. Treatment is only available for childhood CALD. Additionally, rarely, individuals who may never go on to develop disease will be captured by screening.

Currently, the genotype-phenotype relationship (link between individual mutations in the ABCD1 gene and physical outcomes) is not well understood enough to predict the type of disease an infant with a positive newborn screen will develop.[1]

Identification of carriers through newborn screening:
Mothers of cases and additional female family members (sisters or other female relatives) identified as carriers may develop symptoms or may be asymptomatic but on the basis of this diagnosis they may be unable to qualify for life or long-term insurance or experience "guilt, shame, or depression around this diagnosis."[8] There is currently no information about the risks or harms of family testing.

2. **There is adequate capacity and expertise in the NWRNBS program to implement and maintain testing and reporting.**

   Testing and reporting assessment:
   Current personnel have the expertise to perform the testing, but additional capacity will be required to implement and maintain testing and reporting.

Capacity and expertise to implement and maintain testing and reporting (22)

3. **The NWRNBS Program has adequate fiscal resources for implementing the test, performing the test and conducting follow-up and education.**

   Fiscal resource assessment:
   Implementing and maintaining testing for X-ALD will require additional resources for reagents and personnel to perform testing and follow-up.

Fiscal Analysis (22)

4. **The population level incidence, prevalence and disease burden are significant enough to merit screening.**

   Estimated birth prevalence for all X-ALD cases ranges from 1:5,000-1:17,000.[5,6,7] For male X-ALD hemizygotes, birth prevalence ranges from 1:8,000-1:35,000. For female X-ALD heterozygotes, the range is 1:14,000-1:35,000.

   GeneReviews® estimates that about 35% of males with X-ALD will develop childhood CALD (presenting with learning or behavioral issues) with typical age of onset between 2-10 years.[9] They estimate another 40-45% of

Incidence and Prevalence of X-ALD (8)

Natural History of X-ALD with Usual Clinical Detection (7)

males will develop adrenomyeloneuropathy (progressive stiffness and weakness in legs and lower body) with onset between age 20 and middle age. About 1 in 10 males develop adrenal insufficiency (only), on average by age 7. These individuals may develop adrenomyeloneuropathy later in life. Similarly, patients with childhood cerebral ALD or adrenomyeloneuropathy typically also have adrenal insufficiency. One in five female carriers will develop adrenomyeloneuropathy in middle age or later. About 1 in 10 males develop adrenal insufficiency (only), on average by age 7; untreated, adrenal insufficiency can also result in death.

5. **Diagnostic and specialty testing is available and accessible that allows a definitive diagnosis to be made.**

   Confirmation of elevated VLCFA levels in plasma samples is a standard diagnostic procedure in males. Mutation analysis of the *ABCD1* gene can diagnose both males and females.

Confirmatory Testing and Diagnosis (14)

6. **An effective treatment that is proven to result in clinically significant benefits is available and accessible.**

   Published evidence consistently demonstrates differences in outcome following HSCT for mildly affected vs. severely affected individuals with C-CALD, as determined by an established MRI rating scale. There is emerging low-quality evidence to support HSCT gene therapy.

   Treatment for adrenal insufficiency is standard practice.

   Patients with X-ALD are typically monitored by a neurologist, a metabolic geneticist or both a neurologist and a metabolic specialist. There are pediatric endocrinology clinics at Oregon Health and Science University (OHSU), Providence, Emanuel, Kaiser (in Portland) and outreach clinics elsewhere in state (Medford, Eugene). There is only one metabolic clinic in Oregon and it is located at OHSU.

Treatment for X-ALD (15)

Appendix D: Discussion with Experts (31)

7. **here is equitable care and treatment for the disorder.**

   In Oregon context, it is not known which insurance companies will cover the cost of treatment and additional monitoring (and, potentially, family testing) of patients identified through a positive newborn screen, and experts point out that for care of X-ALD (particularly bone marrow transplant) to be equitable, insurance companies may be uniform in their coverage of monitoring, care and treatment.

Is care and treatment for this condition equitable? (21)

Is this condition on the Prioritized List as determined by the Oregon Health Evidence Review Commission? (19)

The Oregon Health Evidence Review Commission does not have criteria for approving HSCT or HSCT with gene therapy for treatment of X-ALD. The Oregon Pharmacy and Therapeutics Committee does not have prior authorization criteria for HSCT or HSCT with gene therapy. Medicaid fee-for-service, coordinated care organization (CCO) and private insurance criteria may differ from HERC.

8. **The impact to the NWRNBS partners does not prohibit the addition or removal of the disorder.**

   Summary of impact to NWRNBS partners:
   Only one response was received from program partners which indicated that Saipan was not opposed to the implementation of X-ALD and thought it could be helpful. It is unclear whether they considered the fiscal impact of adding the test based on their response.

Assessment of the impact of implementing screening (readiness, barriers, etc.) for NWRNBS Program Partners (23)

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Appendix G: Process for recommending the removal of a disorder from the Northwest Regional Newborn Bloodspot Screening Program's testing panel

Stage 1: Proposal to Remove a Disorder from the NWRNBS Panel

The NWRNBS Program may propose that a disorder that is currently on the NWRNBS testing panel be evaluated for removal if it meets one or more of the criteria below:

1. The disorder is not on the RUSP.
2. The disorder does not have an infantile or early childhood onset.
3. Available treatment options in the newborn period are not adequate to alleviate the symptoms of the disorder in early childhood.
4. The NWRNBS Program and OHSU NBS medical consultants have determined that discontinuing screening for the disorder does not have a significant public health consequence.
5. Screening for the disorder is not sustainable for the NWRNBS Program.

Stage 2: Advisory Board Evaluation of a Proposal to Remove a Disorder

The NWRNBS Advisory Board (the board) will be asked to evaluate each proposal to remove a disorder from the NWRNBS Program using the Criteria for Evaluating a Disorder for Removal and the consensus tool (below). This evaluation is the basis for recommendations from the NWRNBS Advisory Board to the NWRNBS Program.

Criteria for Evaluating a Disorder for Removal

1. The disorder does not have an infantile or early childhood onset.
2. There is not an effective treatment in the newborn period that is proven to result in clinically significant benefits in early childhood that is available and accessible.

3. Diagnostic and specialty testing is not available and accessible that allows a definitive diagnosis to be made.
4. Diagnosis or treatment for the disorder does not appear in the funded region of the Prioritized List as determined by the Oregon Health Evidence Review Commission.
5. There is not equitable care and treatment for the disorder.
6. The consequences of not screening for the disorder in the newborn period do not result in significant harm to the child.
7. The epidemiology and public health benefits do not outweigh the risks, harms and costs of screening.
8. There is not adequate capacity and expertise in the NWRNBS program to maintain testing, reporting, follow-up, and education for providers and parents.
9. The NWRNBS Program does not have adequate fiscal resources to maintain the testing, reporting, follow-up, and education.
10. Removal of the disorder does not negatively impact NWRNBS contracted partners.

Consensus Tool: 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 H: Northwest Regional Newborn Bloodspot Screening Advisory Board

Silke Akerson, representative of a statewide association of midwives

Philip Dauterman, representative of an entity that contracts with the Northwest Regional Newborn Bloodspot Screening Program for newborn bloodspot screening services

Anna Dennis, representative of an advocacy association regarding newborns with medical or rare disorders

Cheryl Hanna, representative of a statewide association of pediatricians

Dana Hargunani, representative of Medicaid or the insurance industry

Marilyn Hartzell, person or family member of a person affected by a disorder on the newborn bloodspot screening panel

Wannasiri (Awe) Lapcharoensap, representative of a statewide association of pediatricians

Jill Levy-Fisch, representative of an advocacy association regarding newborns with medical or rare disorders

Joanne Rogovoy, representative of advocacy association regarding newborns with medical or rare disorders

Kara Stirling, representative of a birthing center or hospital

Deb Wetherelt, representative of a birthing center or hospital

Cate Wilcox, honorary non-voting representative

Amy Yang, contracted medical consultant providing expert medical advice

Collette Young, honorary non-voting representative

Staff

Christianne Biggs, Newborn Screening Program Manager
John Fontana, Laboratory Director
Nicole Galloway, Laboratory Business Engagement Policy Analyst

Oregon Health Authority
PUBLIC HEALTH DIVISION
Phone: 503-693-4100
Fax: 503-693-5602

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