Oregon Health Authority
Northwest Regional Newborn Bloodspot Screening Advisory Board

Meeting Summary March 1, 2021

Location: Videoconference

Quorum
Board attendees constituted a quorum.

Board Members
Nicole Galloway, PhD, NWRNBS Interim Program Manager (co-chair)
Anna Dennis, MS, CGC, Advocacy association regarding newborns with medical or rare disorders
Cheryl Hanna, MD, Representative of a statewide association of pediatricians
Marilyn Hartzell, M.Ed., Person or family member of a person affected by a disorder on the Newborn Screening Panel
Wannasiri (Awe) Lapcharoensap, MD, Representative of a statewide association of pediatricians
Joanne Rogovoy, Advocacy association regarding newborns with medical or rare disorders
Kara Stirling, MD, representative of a birthing center or hospital
Amy Yang, MD, Contracted medical consultant
Jill Levy-Fisch, representative of an advocacy association regarding newborns with medical or rare disorders
Philip Dauterman, MD, FCAP, Entity that contracts with NWRNBS for newborn bloodspot screening

Absent
Silke Akerson, CPM, LDM Representative of a statewide association of midwives
Collette Young, PhD, Honorary Representative
Cate Wilcox, MPH, Honorary Representative
Dana Hargunani, MD, MPH, Medicaid or insurance industry representative

Guests
LaDawna Gievers, medical ethicist
Chris Biggs, MS, former NWRNBS Program Manager (former co-chair)

Members of the public
Sarah Viall
Paul Roesch
Leah Wessenberg
Carla Ortiz
Brenda Romero

Oregon Consensus Facilitation Team
Robin Harkless, Facilitator
Cat McGinnis, project associate

ACTION ITEMS

- Board submit to Robin Harkless (hrobin@pdx.edu) or Cat McGinnis (mcginnc@pdx.edu) input to the program regarding stakeholder/user needs for a more comprehensive electronic database.
- A point for potential future guidance from the board: how to allocate limited resources for impacting the highest number of children.
- The program doesn't currently do a cost/benefit analysis of removing versus adding disorders to the panel. Robin suggested that Nicole discuss this with the program.
- Flagged for program follow-up: can the program screen differently for different partners? What would that mean for second-tier testing and follow-up?
- Board members have requested a discussion on the overall scope of newborn bloodspot screening. Robin will send an inquiry to the board asking for input on information from the program to aid in discussions.
- Board members will email Robin regarding any blocks of dates when they are not available to meet in the June/July time frame, and the facilitation team will send out a doodle poll to get a date scheduled.

MEETING GOAL

Review information on Fabry Disease and Gaucher disease, walk through criteria for removing disorders from the screening panel, and gauge the level of consensus surrounding the board's recommendation to the program regarding removal of these diseases from the bloodspot screening panel.

MEETING AGENDA ITEMS

1. NWRNBS program updates

Efficiencies and process improvements. Nicole Galloway, now serving as the board co-chair on behalf of the program, shared updates. The Oregon State Public Health Laboratory (OSPHL) including the NBS program is working on developing the ability for electronic test orders and reports (ETOR). In support of this, the OSPHL is working on onboarding consultants to assist with interoperability. In addition, the program, in collaboration with Maternal and Child Health, has been selected as part of the first cohort to participate in an assessment and road map for interoperability. The program is also working on a more comprehensive electronic database of submitters in order to improve electronic communication of updates, etc. Currently the program is sending letters. Nicole invited the board to submit to Robin or Cat any suggestions or feedback on how best to compile this contact list and reach submitters.

New Mexico, Saipan, and Idaho. The program is adding two Lysosomal Storage Disorders (LSDs), Pompe and MPS-1, to New Mexico's screening panel. Idaho will be transitioning away from the NWRNBS program by the end of April. The NWRNBS program is meeting with Saipan soon to discuss how to best support Saipan's screening needs.

Legislative update. The program is tracking HB 2987 and HB 3107 related to newborn bloodspot screening and working with the government relations team to inform bill sponsors about the NWRNBS advisory board and share the board's past reports.

Funding for adding disorders. The program is looking for funding to add X-ALD and SMA to the screening panel as recommended by the board. Nothing concrete has been identified yet but the program is exploring all options.

2. Summary from last meeting

The meeting summary from the November 16, 2020, meeting was adopted without changes.

3. Presentation by Dr. Amy Yang, overview of Gaucher disease

(Note: prior to the meeting, board members also reviewed evidence reports regarding Gaucher disease and Fabry disease prepared by an independent consultant.)

- Gaucher is a lysomal storage disease. Enzymes are missing that break up large particles that build up in the body, including in bone marrow.
- Gaucher disease leads to death, disability, bone pain, and bone damage in various forms of the disease.
- It is an autosomal recessive condition—the gene must be inherited from both parents.
- It occurs in 1 in 40,000 births in the United States—1 in 60,000 worldwide. In Oregon, 1 in 31,000 screenings result in a true positive test result for the disease.
- One symptom is an enlarged liver and spleen, which are sometimes detected during a well-child visit. Most diagnoses occur before 5 years of age.
- Gaucher type 1 is the least severe, type 2 is the most severe, and type 3 is moderately severe. Ninety-six percent of cases are type 1. This type leads to few symptoms, but an increased risk of Parkinson's disease in late adulthood.
- Enzyme replacement therapy is effective for types 1 and 3, but not for type 2.
- Gaucher disease has never been nominated for review for inclusion on the United States Recommended Uniform Screening Panel (RUSP). It is screened for in some states.

Q&A

- With regular pediatric checkups, how likely is it that this disorder would be detected in time to reverse neurologic damage?
    - This is not easy to answer: In the example case of the 15-month old Gaucher patient who was put on enzyme therapy, the child was being monitored due to screening; a subsequent ultrasound identified an enlarged spleen, which was not apparent on palpation. Anemia was also present.
- By the time an enlarged liver or spleen could be visually or tactilely detected at a well-child visit, how bad would bone damage be? It is hard to say, but Dr. Yang has not seen any cases of bone damage in toddlers.
- Question about the variant ASN 409 noted in the documentation, suggesting this is "not always pathogenic."
    - This is a common mutation found in the United States, it predicts a very mild disease but also a huge range of time when this can present; so it's hard to predict.

4. Stage two review: application of removal criteria to Gaucher disease

General discussion

- Why was Gaucher up for removal from the Oregon screen? Program's response: Primarily because it's not on the RUSP, and the program has limited capacity and funding for second-tier

testing and follow-up. However, it also partially due to a combination of some of the other criteria in stage 1, such as the age of onset of most cases.

- How did Gaucher and Fabry get on Oregon's screening panel? It was part of the reagent panel and thought to assist with the screening for Pompe and MPS-1.
- How would savings from removing Gaucher and Fabry be used by the department? Could they offset the cost of adding SMA and X-ALD to the panel? No, the costs wouldn't exactly counterbalance. The main reason for removal would be that they are not on the RUSP, and there is limited capacity for follow-up.

Criteria 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.

Discussion of application of criteria to Gaucher disease

- Criterion 1: The disorder does have infantile onset.
- Criterion 2: The disorder does have effective treatments for some types of the disorder—it was noted that some inconclusive cases are identified by screening and those children are monitored for developing symptoms.
- Criterion 3: Diagnostic and specialty testing is available.
- Criterion 4: It is in the funded region of the HERC Prioritized List. Prior authorization is required and there is a preferred treatment.
- Criterion 5: There is equitable care and treatment for the disorder; Dr. Yang reported she has been able to find coverage for treatments, and copays are not especially burdensome. It was noted the screen catches all types of the disease, including adult onset cases where the family/patient will know they may develop the disease later in life.
- Criterion 6: Regarding the consequences of not screening, the following language from the evidence report was reviewed:

> A review of treatment for pediatric Gaucher disease summarizes the context as the following:
>
> Newborn screening and PND [prenatal diagnosis] for disorders like GD are a highly debated topic, because of the lack of consensus about when to initiate treatment; the

potential identification of infants with anticipated late-onset presentation, thereby creating a population of asymptomatic children who are essentially 'patients in waiting'[26]; possibly violating most of international pediatric genetic ethics guidelines that stipulate that screening is not advised for late-onset conditions that could lead to parental anxiety and substantial financial implications.[23]

The review goes on to say that because of the variable onset of Type 1 Gaucher disease (frequently before age 20), the benefits of early detection and symptom monitoring may outweigh the potential harms.

A question was raised whether the international ethics guideline referenced above is still current. Ethicist LaDawna Gievers was called away and unavailable to answer the question.

A question was raised whether the 15-month old child described in Dr. Yang's presentation might not have been identified until age 7 or 8 without bloodspot screening. Dr. Yang pointed out that another patient was identified at age 7 and already had lytic lesions in the bones. The most common path of diagnosis is identification of anemia leading to tests for lymphoma or leukemia and resulting in a Gaucher diagnosis.

Ultimately, the group found uncertainty with this Criterion.

- Criterion 7: Regarding the costs/benefits of screening: There was a discussion of the scope of the NWRNBS program in relation to adult onset disorders. The tenants of newborn bloodspot screening have been primarily to detect disorders in the infantile or early childhood period. There needs to be recognition that program resources are limited. The board may want to prioritize X-ALD and SMA. This was noted as a point for potential future guidance from the board regarding a discussion of how to allocate limited resources for impacting the highest number of children.

  The program doesn't currently do a cost/benefit analysis of removing versus adding disorders to the panel.

  ACTION: The board will revisit the topic of how a cost/benefit analysis could or should be done to weigh issues around adding and removing disorders from the screening panel.

  What is the screening philosophy regarding when the cut off is for how soon treatment is needed to justify newborn bloodspot screening? Program response: All newborn screening programs are grappling with the question of proper scope of newborn screening.

  Ultimately, the board found uncertainty with this Criterion.

- Criterion 8: There is adequate capacity and expertise for the lab to test for Gaucher (since they are currently testing for it.)

- Criterion 9: Primary capacity and funding challenges relate to follow-up and second-tier testing

- Criterion 10: New Mexico and Saipan responded to an inquiry on this criterion. Would the program be able to do the test for one program and not another if needed? Yes, but there are efficiencies and program considerations to doing the same test for all.

- **ACTION**: Nicole will follow up to determine if there is clearer guidance from the program about accommodating different screens for different partners.

5. Public comment period

No public comments were offered at this meeting.

6. Additional general discussion regarding Gaucher disease

- If there were no newborn bloodspot screening of Gaucher, is there confidence that a child with Gaucher would be identified by well-care visits? Dr. Yang: There are no guarantees of identification without newborn screening. The diagnostic odyssey would begin with anemia and/or enlarged spleen/liver. The majority of people at diagnosis do not have irreversible damage.
- Given the current technique of screening, would Gaucher continue to be flagged as a result but with no follow-up action? Program response: No, it would be a new test kit; the program would not be seeing Gaucher (or Fabry) results at all.
- Identifying adult-onset disorders presents a challenge for parents regarding when to tell the child; and potentially could be stress-inducing. Similarly, there is a concern about false positives.
- Krabbe also has an adult-onset form as well as an infantile-onset. Would not want states that are performing that testing to stop testing for that reason.
- There is a common Gaucher adult-onset variant among Ashkenazic Jewish people in New York. Prenatal testing is done as well as testing at birth. Dr. Yang has received uniform feedback from families that they are happy to have the knowledge.
- It's important to think about the implications of over-medicalizing a child or patient-in-waiting. What does it mean to have it in one's medical record? While there are protections in employment and health insurance, there are none for life or long-term disability insurance.
- Gaucher (and Fabry) are not on the RUSP. There's a question about keeping them on the panel when they have not had that broader, more expert review. How will keeping non-RUSP disorders on the panel impact the board's criteria regarding adding disorders that are not on the RUSP?
- Being consistent regarding the RUSP is important as there can be interest to add many different disorders. Need to respect RUSP expertise. RUSP puts a lot of thought into decisions.
- There may also be times when relying on the RUSP may not be in the best interest of families. For example, if the RUSP is not funded (which happened recently), it falls behind in addressing disorders.
- If Gaucher had been nominated for review by the RUSP, there is no way to know what the RUSP would have decided. We have to do what's best for Oregon, not necessarily for the nation as a whole.
- It was pointed out that whether a disorder is on the RUSP is not part of stage 2 board criteria for removal—it is only part of the program criteria.

7. Consensus check on removing Gaucher disease from the screening panel

Cheryl Hanna proposed that Gaucher disease be removed from the panel. Consensus check on proposal: (1=strong agreement, 2= agreement, 3= on the fence/neutral, = serious concerns or questions but won't block, 5=do not agree, would block action)

Anna Dennis—2
Cheryl Hanna—2
Marilyn Hartzell—3
Wannasiri (Awe) Lapcharoensap—2
Jill Levy-Fisch—5
Joanne Rogovoy—2
Kara Stirling—2
Amy Yang—3

There was not a full consensus for the board to make a recommendation to the program to remove Gaucher disease from the newborn bloodspot screening panel.

Facilitator's note: one board member, Silke Akerson, was unable to attend but registered in writing her support for removal of both Fabry and Gaucher from the screening panel.

Discussion of low/no consensus views:

- Marilyn Hartzell—Influenced by my family's own diagnostic odyssey. Would like the program to stay open to evolving science regarding Gaucher.
- Jill Levy-Fisch—Believe that if screening is available, and it will save one life, it should be done. Less concerned about privacy related to adult onset due to the Genome Act. Wishes the question of removal could be revisited in a year to see if the RUSP takes it up. Uncomfortable relying on a family-care doctor—a pediatrician missed my kid's disorder. Unless there is a reason to remove the disorder from the panel, I'd like to give it more time.
- It was also noted that several votes fell in the stronger consensus category.

8. Presentation by Dr. Amy Yang, overview of Fabry disease

- Fabry is an X-linked disorder. If the father has the gene, all daughters will have the disease and sons will not. If the mother has the gene, male and female children have the same 50 percent risk of having the disease.
- It is the most common lysosomal storage disorder.
- The disease spectrum includes classic disease and atypical or variant disease.
- It is a slowly progressive disorder.
- Males are more affected than females. Females experience milder affects later in life. In respect to newborn screening, it is hard to predict when a female will develop symptoms of the disease.
- Adult symptoms are hard to diagnose because they mimic many common adult disorders.
- There are potential incidental findings during newborn bloodspot screening. If a female is heterozygous, the test may capture Turner's syndrome. In a male, the Fabry test may reveal Klinefelter syndrome. The lab will not report on these conditions, but they can see if a child is heterozygous or homozygous.
- Enzyme replacement therapy will successfully treat a mild to moderate disease state, but will not reverse advanced disease.
- Some states screen for Fabry. It was nominated for review by the RUSP in 2008. They found that there are no detectable symptoms in newborns. There is data about early treatment early in life.
- False positive results are substantial.
- A143T mutation is identified in 65 percent of confirmed Fabry cases. A143T is treated differently. Females who have it do not need follow-up. Some males who have it are released from follow-up. Currently, of 23 babies detected with A143T, one male is receiving follow-up.

Q&A

- Why is Fabry under consideration for removal by the program? Program response: like Gaucher, it is not on the RUSP, it was added incidentally with the addition of Pompe and MPS-1, and there are resource challenges with the follow-up and second-tier testing.

9. Stage two review: application of removal criteria to Fabry disease

- Criterion 1: There is no infantile onset, but as childhood progresses there can be some debilitating bowel and nerve pain, treated with enzyme replacement.
- Criterion 2: There is effective treatment. Enzyme replacement therapy is effective, but depends on timing of treatment.
- Criterion 3: Diagnostic and specialty testing is available.
- Criterion 4: Fabry is on the funded list. Prior authorization is required and a preferred treatment is specified.
- Criterion 5: There is equitable care and treatment. Dr. Yang hasn't detected significant barriers to coverage; however, some convincing of insurers is needed because there is a paucity of data for treating children under 8.
- Criterion 6: This is difficult to qualify; not screening could harm children in that they are often not believed when they report bowel symptoms and are assumed to be shirking. Dr. Yang has heard of this childhood experience from many adults with Fabry.
- Criterion 7: Regarding whether the epidemiology and public health benefits outweigh the risks, harms and costs of screening: Fabry is not the classic condition for newborn screening. A bigger question is—are we going to start screening for other adult-onset diseases? This is outside the scope of NWRNBS.

  Will there be no impact on babies and young children? Dr. Yang response: Wouldn't expect to see symptoms in babies. Child might have nerve pain and GI symptoms. Children will have a normal working heart and kidneys until 20s and 30s. No heart failure or kidney failure for children.

- Criterion 8: There is adequate capacity and expertise for the lab to test for Fabry (since they are currently testing for it.)
- Criterion 9: Primary capacity and funding challenges relate to follow-up and second-tier testing
- Criterion 10: Same response as for Gaucher.

10. Additional general discussion regarding Fabry disease

- Fabry is different than Gaucher because the RUSP has reviewed Fabry (in 2008) and not added it to the panel. The condition happens later in life, and while it is hard to diagnose, that is not necessarily a good reason to include it.

11. Consensus check on removing Fabry disease from the screening panel

Consensus check on proposal:
(1=strong agreement, 2= agreement, 3= on the fence/neutral, 4= serious questions or concerns, 5=no agreement, would block action)

Anna Dennis—2
Cheryl Hanna—2
Marilyn Hartzell—4

Wannasiri (Awe) Lapcharoensap—2
Jill Levy-Fisch—4
Joanne Rogovoy—2
Kara Stirling—2
Amy Yang—3

There was weak consensus for the board to make a recommendation to the program to remove Fabry disease from the newborn bloodspot screening panel.

Facilitator's note: one board member, Silke Akerson, was unable to attend but registered in writing her support for removal of both Fabry and Gaucher from the screening panel.

Discussion of '4' consensus views:

- Marilyn Hartzell—Need a conversation about the overall scope of newborn bloodspot screening.
- Jill Levy-Fisch—The RUSP review was 13 years ago. I won't, personally, base my decision on that. Fabry impacts the quality of a child's life.

12. Next steps

- Robin reviewed the 2021 work plan, noting the intention to convene the group three times during the year (today, early/mid-summer, and fall/winter) likely over Zoom.
- At the next meeting, the board will revisit the topic surfaced and discussed today about the scope of newborn bloodspot screening and begin strategic planning from there.
- Other issues for future board discussion: Midwife reimbursement, categories on newborn screening card, revisit courier service discussion.
- Robin will send an inquiry to the board regarding what information from the program would be useful to the board to tee up the discussion of purpose and scope of the program.
- The board will email Robin regarding any blocks of dates when board members are not available to meet in the June/July timeframe.

Adjourned