

September 2022

# >> Northwest Regional Newborn Bloodspot Screening

Advisory Board Report to the Legislature

Oregon  
Health  
Authority  
PUBLIC HEALTH DIVISION

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# Acknowledgments

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

For details about the work of the board, go to [www.bitly.com/nbs-advisory](http://www.bitly.com/nbs-advisory).

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# Executive summary

## Background

This is the third report to the Legislature from the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Advisory Board (the board). Established in 2019, the board was required to submit a report to the Legislature in 2019 and is required to submit subsequent reports in each even-numbered year.

In the 2019 report, the board noted its adoption of a protocol and criteria to recommend adding disorders to Oregon's newborn bloodspot screening panel. In the 2020 report, the board recommended adding two disorders to the newborn bloodspot screening panel. In addition, the board noted its adoption of a protocol and criteria to recommend removal of disorders from Oregon's newborn bloodspot screening panel.

## Work of the NWRNBS Advisory Board: 2021 and 2022

### Summary of 2021 and 2022 board meetings

The board met seven times in this report period to review topics that included:

- Screening costs and equity
- Expediting transport of bloodspot specimens, and
- Reimbursing community birth providers for newborn bloodspot screening services.

In addition, board members also addressed changes to statutes and rules governing the NWRNBS Program and Board. They also reviewed the board's role and interface with the Legislature during legislative sessions.

### Disorders considered for removal from the screening panel

The board considered two disorders for potential removal from the screening panel: Gaucher disorder and Fabry disorder. These disorders were added to the panel before the board was established. They do not meet the board's criteria for board review for addition to the panel, as they have not been added to the United States Recommended Uniform Screening Panel (RUSP). The late age of onset for most cases of Gaucher was also a reason to consider removal of this disorder from the panel.

The board applied its criteria for removal of each disorder ([Appendix A](#)) and concluded that neither disorder meets all criteria for removal from the screening panel. The program will track data on the disorders. The board will review and discuss the information available and decide whether to conduct another review of the disorders in the future. See [appendices B and C](#) for independent expert analyses.

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## Statutory and legislative activity

The board also reviewed potential changes to the program's statute. The board supports the program proposing a legislative concept for the 2023 legislative session to propose statutory changes.

## Newborn bloodspot screening funding

The board reviewed a proposed fee increase for newborn bloodspot screening to cover increasing costs to operate the program, address the program's budget deficit and meet the needs of Oregon families. The board is interested in working with the program and Legislature to ensure adequate and sustainable funding for newborn bloodspot screening.

## Future work of the board

In its next meetings, the board will do the following:

- Evaluate other states' funding models for screening programs.
- Establish a subcommittee to obtain information about newborn bloodspot screening program funding, submitter payment and fee waivers.
- Continue to track RUSP activities and conduct a review of specific disorders for addition to or removal from Oregon's screening panel when indicated.
- Identify pathways for more parental involvement in adding disorders to the screening panel.

# Introduction

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

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

- Advocacy
- Advice
- Recommendations
- Technical information

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

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

- Nov. 16, 2020
- March 1, 2021
- July 12, 2021
- Nov. 1, 2021
- Jan. 31, 2022
- Feb. 23, 2022
- April 27, 2022

Detailed summaries of those meetings are available at the OHA website at [www.bitly.com/nbs-advisory](http://www.bitly.com/nbs-advisory).

## 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 more than 40 tests for heritable disorders. These conditions may not be clinically apparent in the first weeks after birth. However, they may lead to disability or death if not detected early.

The program sends the test results to providers who test to confirm the results, discuss any abnormal results with parents, and set up any needed treatment plans. 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, the following occur:

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

*Newborn bloodspot screening saves lives.*



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

- Information from experts about Gaucher and Fabry disorders, which were evaluated for recommended removal from the program's testing panel during this report period
- A summary of the board's discussion of the disorders, the pros and cons for removing the disorders from the testing panel, and the board's decisions about recommending removing the disorders
- The board's review of potential changes to the program's statute and rules, including a proposed fee increase to cover increasing costs to operate the program, address the program's budget deficit and provide necessary quality services for the program
- Discussion of expediting delivery of bloodspot specimens to the laboratory
- Discussions of HB 4109 from the 2022 legislative session, which proposed a number of changes to the board's makeup and function, and
- Strategic planning and board procedures.

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# Gaucher disorder background, discussion and consensus check

## Review to remove Gaucher disorder from the screening panel

The board considered a proposal to remove Gaucher disorder from the newborn bloodspot screening panel. Gaucher was added to the panel before the board was established. It does not meet the board's criteria to review for addition to the panel because it is not on the United States Recommended Uniform Screening Panel (RUSP). In addition, the age of onset does not meet the board's review criteria. Gaucher was added to Oregon's panel in 2018 to assist with screening for Pompe and MPS-1 disorders.

## Gaucher disorder background

Board members reviewed an evidence report regarding Gaucher disorder prepared by a consultant ([Appendix B](#)). Lysosomal storage expert and board member Amy Yang, M.D., shared her expertise.

Gaucher is an inherited metabolic disorder in which lipids accumulate in the body. The disorder leads to liver malfunctions, skeletal disorders, neurological problems, disability and, in some cases, death. Typical symptoms are 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; however, an increased risk of Parkinson's disorder in late adulthood is possible. Enzyme replacement therapy is effective for types 1 and 3, but not for type 2.

Gaucher disorder occurs in 1 in 40,000 births in the United States — 1 in 60,000 worldwide — and has highest incidence in the Ashkenazi Jewish population.

## Application of criteria for removal

The board discussed each of the removal criteria ([Appendix A](#)) as applied to Gaucher disorder:

- **Criterion one:** The disorder does not have infantile onset.
- **Criterion two:** The disorder does not have effective treatments for some types of the disorder. Some inconclusive cases are identified by screening and those children are monitored for developing symptoms.
- **Criterion three:** Diagnostic and specialty testing is available.

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- **Criterion four:** Gaucher is in the funded region of the OHA Health Evidence Review Commission (HERC) Prioritized List of Health Services. Prior authorization is required, and there is a preferred treatment.
  - **Criterion five:** There is equitable care and treatment for the disorder. Dr. Yang reported finding coverage for treatments, and copays that are not especially burdensome. The screen catches all types of the disorder, including adult-onset cases where the family or patient will know from infancy that they may develop the disorder later in life.
  - **Criterion six:** Regarding the consequences of not screening, the following language from the evidence report was reviewed:

Newborn screening and prenatal diagnosis (PND) for disorders such as Gaucher disorder are a highly debated topic. This is due to:

- The lack of consensus on when to initiate treatment, and
- The potential identification of infants with anticipated late-onset presentation, which creates a group of asymptomatic children who are essentially “patients in waiting.” This may violate most international pediatric genetic ethics guidelines stipulating that screening is not advised for late-onset conditions that could lead to parental anxiety and substantial financial implications.

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

The board expressed uncertainty with criterion six.

- **Criterion seven:** Regarding the costs and benefits of screening, the board discussed 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. Program resources are limited. The board may want to prioritize funding the addition of X-ALD and SMA. All newborn screening programs are grappling with determining the proper scope of newborn screening.

The board expressed uncertainty with criterion seven.

- **Criterion 8:** There is adequate capacity and expertise for the lab to test for Gaucher because 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. The program would be able to test for one program and not another if needed. However, there are efficiencies and program considerations to doing the same test for all programs that the NWRNBS Program serves.

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## Consensus check

The board conducted a consensus check (see [Appendix A](#)) to determine whether it would recommend removing Gaucher disorder from the screening panel.

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

## Next steps

The program will track data on Gaucher disorder throughout the next year. The board will review and discuss the information available at that time and decide whether to conduct another review regarding removal of Gaucher from the screening panel.

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# Fabry disorder background, discussion and consensus check

## Review to remove Fabry disorder from the screening panel

The board considered a proposal to remove Fabry disorder from the newborn bloodspot screening panel. Fabry was added to the panel before the board was established. The condition does not meet the board's criteria for board review to add it to the panel because it is not on the RUSP. Like Gaucher disorder, Fabry was added to the panel in 2018 with the addition of Pompe and MPS-1.

## Fabry disorder background

Board members reviewed an evidence report regarding Fabry disorder prepared by a consultant ([Appendix C](#)). Lysosomal storage expert and board member Amy Yang, M.D., shared her expertise.

Fabry is the most common lysosomal storage disorder and is linked to genetic changes on the X chromosome. It is slowly progressive. Enzyme replacement therapy will successfully treat a mild to moderate disorder state but will not reverse an advanced disorder.

Males are more affected than females. Females experience milder effects later in life. In respect to newborn screening, it is hard to predict when a female will develop symptoms of the disorder. Adult symptoms are hard to diagnose because they mimic many common adult disorders.

Some states screen for Fabry. It was nominated for review by the RUSP in 2008 but was not added to the RUSP because there were no detectable symptoms in newborns, and false positive results were substantial.

## Application of criteria for removal

The board had the following discussion around each of the removal criteria ([Appendix A](#)) as applied to Fabry disorder.

- **Criterion one:** There is no infantile onset. However, as childhood progresses there can be some debilitating bowel and nerve pain, which can be treated with enzyme replacement.
- **Criterion two:** Enzyme replacement therapy is effective but depends on timing of the treatment.
- **Criterion three:** Diagnostic and specialty testing are available.

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- **Criterion four:** Fabry is on the HERC funded list. Prior authorization is required, and a preferred treatment is specified.
  - **Criterion five:** There is equitable care and treatment.
  - **Criterion six:** Untreated children may experience debilitating nerve pain and gastrointestinal symptoms that can be avoided through early detection. A child with Fabry will have a normal working heart and kidneys until age 20 to 30.
  - **Criterion seven:** Fabry is not the classic condition for newborn screening. A bigger question is, “Are we going to start screening for other adult-onset disorders?” Such screening is outside the scope of the NWRNBS program.
  - **Criterion eight:** There is adequate capacity and expertise for the lab to test for Fabry.
  - **Criterion nine:** Primary capacity and funding challenges relate to lifespan follow-up and second-tier testing.
  - **Criterion ten:** New Mexico and Saipan responded to an inquiry on this criterion. The program would be able to do the test for one program and not another if needed. However, there are efficiencies and program considerations to doing the same test for all programs that the NWRNBS Program serves.

## Consensus check

The board conducted a consensus check to determine whether it would recommend removing Fabry disorder from the screening panel.

There was **weak consensus** for the board to make a recommendation to the program to remove Fabry disorder.

## Next steps

The program will track data on Fabry disorder throughout the next year. The board will review and discuss the information available at that time on removing Fabry from the screening panel.

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# Fees for newborn bloodspot screening

## Bundling screening reimbursement to providers

For purposes of insurance reimbursement, fees for the birthing package or supply kit are bundled under one code. The cost of newborn bloodspot screening is not broken out as a separate payment. This bundling may contribute to community birth providers not receiving adequate compensation for testing kits they purchase for use with their patients or may increase out-of-pocket costs for uninsured parents. A little used fee waiver is available.

Two Oregon Administrative Rules address the birthing fee bundling. OHA is also amending the rules to unbundle the newborn screening fee for community birth providers.

The board decided to establish a subcommittee to create a methodology to:

- Determine screening versus live births in Oregon, and
- Explore screening payment and reimbursement patterns.

## Proposed NWRNBS fee increase

The program presented a fee increase draft for newborn bloodspot screening. Program staff explained the following:

- Newborn screening is fee-based. The current fee is \$80 for a two-screen kit; the current draft proposed fee increase is \$175 per two-screen kit.
- The number and complexity of the disorders that newborn screening programs screen for continues to increase. Historically, newborn screening programs screened for well-defined disorders. Today, new disorders are being screened that are more complex and involve advanced testing methods.
- The program is estimated to cost approximately \$9.1 million per year and has \$7.2 million per year in estimated revenues.
- The program received \$440,770 in general funds to onboard SMA screening.
- The program will hold a rules advisory committee to obtain feedback about the proposed fee changes on April 27, 2022. The board participated in the rules advisory committee.

## Next steps regarding newborn bloodspot screening fees

The board wants to work with the program and the Legislature to identify a more sustainable funding model for newborn bloodspot screening.

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# Improving timeliness of specimen delivery

## Background on specimen transport

Ensuring optimal diagnosis and treatment of the disorders on the newborn screening panel requires timely specimen delivery, laboratory screening and results reporting. Efforts are underway to monitor and improve timeliness in each aspect of the work.

In a review of data from January through October 2020, 33,252 specimens were transported to the lab from across the state. Variations in transit times were not always associated with geographic location; facilities in the same area may have different transit times. Data suggests that midwives may face challenges to timely collection and transport.

### Average time from birth to reporting results (Jan.–Oct. 2020)

Hospital births	5.6 days
Out-of-hospital births (e.g., midwives)	7.7 days
All Oregon	5.7 days
National standard	7 days

## Next steps

The board requested the following additional information regarding expedited shipping to inform future recommendations:

- Assessment of barriers to timely specimen delivery in community birth settings
- Assessment of timely specimen delivery that includes birth day of the week, geography and shipping service, and
- Information from other states about their efforts to improve timeliness.



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# Strategic planning for the NWRNBS program

## Board's vision

Given program leadership and staffing changes and multiple work priorities, the program is not developing a strategic plan at this time, but it may work with the board on strategic topics in the coming year. Board responses could serve as a foundation for the program's work to build out a strategic plan in the future. Board members discussed the question below and provided the responses detailed.

If everything were working perfectly, what would the program look like in 10 years?

- No matter where or when a baby is born, the baby gets timely screening and is linked to any needed care.
- Families are centered in services and communications.
- Families have access to information about the value of newborn screening.
- Low-income families do not have financial barriers.
- Families receive culturally competent education.
- Providers have education and resources they need to address timeliness and quality of specimen delivery to the lab.
- Well-baby visits discuss screening results, even if results are negative.
- There is an efficient and effective system from specimen collection to treatment in place to prevent delays and improve health outcomes.
- The support team includes social workers and health system navigators.
- Families receive wraparound services with behavioral and mental health support.
- Providers seamlessly communicate.
- Every hospital medical record system has all results.
- There is long-term and robust case coordination for abnormal test results and follow-up.
- Affected families are offered timely consultation with an expert.
- Affected families have access to telemedicine and other forms of timely human connection.
- Program funding is sustainable and adequate.
- Disorders are added to the screening panel in a timely manner.
- The newborn screening system can easily transition to new technologies.

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- Insurance reimbursement for screening is adequate.
  - If a condition is recommended for the panel, diagnosis and treatment of the condition are covered by insurance.
  - The program includes genetic counselors and nurses.

## Planning for equity

Following that initial strategic visioning exercise, the board explored:

- The purpose of newborn screening
- Whether the current program is aligned with that purpose, and
- The priorities and principles to help guide the program moving forward.

The board also discussed strategic challenges the program is currently facing that the board will need to help work through, as well as external factors that could affect the program.

The board acknowledged that the overarching strategic planning priority was to focus on **improving equity**. Members identified the following elements and considerations for equitable testing and care:

- **Accessibility.** Making core screenings and treatment more accessible and maintaining cost effectiveness.
  - » There is a desire for equitable access to screening services around the state and country, regardless of where a newborn is delivered.
  - » For babies born at home or in birth centers (which account for 5 percent of Oregon births), there are currently reimbursement challenges for midwives. As a result, parents may opt out of the screening because of costs. At a future meeting, the board will address screening accessibility for out-of-hospital births, recognizing that midwives are being excluded from a type of billing.
- **Family-centered care.** Providing more effective family-centered care through social and emotional support, education and help navigating the system. Also ensuring that providers have needed resources.
  - » Families need established overall communication, outreach and follow-up around testing, particularly about what happens if a screening test is positive.
  - » Communication with the NWRNBS Program sometimes ends when a test result is positive. At this point, the family must seek follow-up tests. What are the available resources outside of the program and screening that could support follow-up testing?
  - » Families sometimes need education materials in languages other than English.

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- **Timeliness.** Delivering timely services and results by keeping pace with the available technology and improving electronic transmission of test orders, reports and information.
    - » In the future, the pace of treatments and ability to detect them may outpace the process or available funding.
    - » We must ensure that U.S. Government Accountability Office standards are being met.

## External forces

The board acknowledged financial limitations and cost increases of potential screening expansions as additional disorders are added to the United States Recommended Uniform Screening Panel (RUSP). Members noted the program may need to find supplementary funding. However, meaningful change and expansion requires sustainable funding, which is more challenging. As a next step, the board will identify activities within the scope of the program and set priorities accordingly. It will then identify funding pathways and potentially advocate for more funding if it uncovers gaps. Increased collaboration with community-based partners will play a key role in closing any system gaps around education, communication and other family support.

The board noted rapid development of technology as another external force, which can be a support and a challenge to the program. Effective data exchange, including data matches and electronic transmission of test orders and results, is a critical strategic challenge and opportunity.

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# Program developments, statute review and rule changes

## Program developments

During the report period, the program underwent the following changes and improvements:

**Streamlining.** The Oregon State Public Health Laboratory (OSPHL), including the program, is developing the ability to receive and transmit electronic test orders and results, which is one facet of interoperability. In support of this effort, the OSPHL is onboarding consultants to provide expertise and capacity-building toward this goal. In addition, the NWRNBS program, in collaboration with the Oregon Health Authority Public Health Division's Maternal and Child Health Section, is part of the first cohort to help assess and create a road map for interoperability. The program has also developed a more comprehensive electronic database of bloodspot screening test submitters; this improves electronic communication of updates.

Improved bloodspot screening report comments and results will streamline delivery to providers so information is more accessible and centrally located. In addition, the practitioners' manual and educational materials are being updated to improve satisfactory specimen rates and provide more support and resources.

**New Mexico, Saipan and Idaho.** Historically, the NWRNBS Program has provided testing services for New Mexico, Saipan and Idaho. The program added two lysosomal storage disorders, Pompe and MPS-1, to New Mexico's screening panel. Idaho has transitioned away from the NWRNBS Program. The program has held meetings with the Saipan program to best understand its screening needs.

**Board vacancies.** Several board positions are in transition and recruitment is underway for the following legislatively mandated seats:

- Representative of advocacy association regarding newborns with medical or rare disorders
- Representative of a statewide association of nurses
- Representative of an entity that contracts with NWRNBS for newborn bloodspot screening

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## Review of the NWRNBS Program statutes

The program provided the board with a marked-up version of the program's governing statutes showing proposed changes developed with the Oregon Department of Justice counsel for the program. The relevant statutes include ORS 433.285, ORS 433.290 and ORS 433.295. These statutes haven't been substantively updated for decades. The currently proposed changes would be included in a legislative concept for the 2023 legislative session.

Oregon Department of Justice advisors to the program are reviewing the changes with the program. The program will seek input from community partners and may look to the board to assist with connections.

Board discussion of the proposed changes was as follows:

- Language should be included to say that no one should be denied a test due to inability to pay.
- Should the statute require that the provider inform parents about the fee waiver? The statute includes that the program will provide education. Maybe this is a place to include more about providers informing parents about the fee waiver.
- The proposed revisions create immunity for the program regarding screening. What if there is gross negligence? It would be a policy question for the Legislature whether it wants to add an exception for gross negligence.
- Changes to ORS 433.295 establish responsibility of health care providers to report back to the program regarding confirmed conditions that were found through screening and conditions found later that weren't found through screening. This provides quality control for the program. This is not routinely done, but it will be a requirement under this amendment. The program will need to educate providers. One concern: It could prove difficult to reach providers and then they will be out of compliance. There was a suggestion that this be less formal and that the program simply ask subspecialists for the information.
- How do people know about the fee waiver? The program doesn't know if providers are telling parents about the waiver.

The board is generally supportive of the changes to update the language in the statute. The program has considered the board's feedback when developing additional proposed language for the legislative concept.

The board agreed it would be good for a subcommittee of the board to design a methodology to survey providers and parents about exchange of information regarding the fee waiver.

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## Rules changes

Twice the board stepped into its role as a rules advisory committee for the program. Other members of the rules advisory committee also attended and provided input. In both instances, the program provided drafts of proposed changes to specific Oregon Administrative Rules (OARs) and drafts of fiscal impact statements. At the first meeting, proposed rule changes for OAR 333-024-1020, 333-024-1025, 333-024-1040 and 333-024-1070 were discussed, including changes to the NWRNBS Practitioner’s Manual.

The program invited feedback from the rules advisory committee regarding the proposed rule changes and the statement of need and fiscal impact. Members of the rules advisory committee made the following comments:

- Practitioner’s Manual:
  - » “Identification of other medical conditions” — This change does not provide for fully informed consent for disclosure of other conditions found during screening. It is ethically thorny because there may not be effective prognoses or treatments. What other conditions? These need to be spelled out.
  - » The manual discusses fee waivers. The information needs to appear earlier in the document.
- General:
  - » Can parents opt out of the SMA carrier screening? Program response: It’s a panel of tests; parents can’t opt out of individual tests.
- Statement of Need and Fiscal Impact:
  - » It needs to discuss the impact on families who pay out-of-pocket as a racial equity consideration. If this is not added to this fiscal impact statement, it needs to be tagged for a future fiscal.
  - » The program needs to clarify in the fiscal statement that, though there is no fee change being proposed in this rule change, there are rule changes that contribute to a proposed fee increase. Need to make this more transparent.

At a subsequent meeting, the rules advisory committee reviewed proposed changes to OAR 333-024-1100, relating to a fee increase for screening. The committee raised similar concerns about the equity impacts of a fee increase on parents who pay out of pocket as well as impacts on providers of non-hospital births, such as midwives. Committee members suggested that sustainable funding sources be secured for the program in place of ongoing fee increases.

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# Board procedures

## NWRNBS Advisory Board governance and communication

**Governance.** The group reviewed and discussed the role of the board in advising the program. The board can advise and make recommendations to the program. Based on that input, the program will make decisions. There was no opposition to this process as it currently stands and all present were in favor.

**Communication.** The current statute requires the board meet at least once every six months. For agenda items, board members can email and provide input to the chairs, the program and the facilitator. The group discussed how the program can orient the board for broader communications and more timely organization between meetings. Per the board's bylaws, the co-chair will respond to communication submitted through the board's official email address.

The board questioned whether board input on the co-chair's email responses would constitute a serial communication under open records law. The Oregon Department of Justice shared that if the co-chair is delegated to respond to the public and the response doesn't include making decisions that are normally an item for board consensus-making, the co-chair can ask other board members for input. However, any substantive issue that could require a board decision would be better brought to the whole board.

## Expert presentation on public meeting laws

An Oregon Department of Justice counsel shared a presentation on public meeting laws, drawing from the Oregon Attorney General's Public Meetings and Public Records Manual 2019.

The presentation notes the following key points:

- When a quorum is required for public decision making, there must be public notice, documentation of the meeting, and public access.
- A series of private communications (serial communication) between board members that constitutes a quorum, even when through an intermediary, is considered a public meeting. Polling board members would constitute a serial communication.
- Meetings of two or more board members authorized to make recommendations to the board are considered subcommittee meetings and are subject to public meeting laws.
- One way communications with the board that do not request a response are not serial communications.

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- One-to-one communications between a board member and staff are not serial communications.
  - An individual board member putting together an individual recommendation is not subject to the public meetings law.
  - Communications between meetings that fall under the law can be accomplished quickly with internet notice and public access. A public comment period is not required.
  - Things to avoid because they do not allow public access: serial email communications and serial editing of a document.
  - Co-chairs can communicate with each other regarding meeting agenda items because the program manager makes the final decision on the meeting agenda.

## Board's roles related to legislative activity

The board raised the following questions regarding their role in the legislative process.

- How does a board member or the board as a whole interface with the Legislature?
- Can the board comment on legislation?
- How does the board coordinate with the program?
- Must feedback be from the board as a whole?
- How does the board comply with public meeting requirements in such cases?

Belle Shepherd, OHA government relations, responded as follows:

- OHA staff must follow OHA protocols that support OHA's and the Governor's bills and take no position on all others. OHA shares facts only, not opinions. The board is not under that guidance. The board can testify at legislative hearings, but would do so in cooperation with OHA government relations. Board members can testify alone in their professional and personal capacity, but should make clear they are not speaking on behalf of the board.
- If any board member wants the full board to review and respond as a board to legislation, they can request a special board meeting.
- Any board member who is interacting with the Legislature in a professional or personal capacity is invited to seek guidance from OHA government relations.

Ms. Shepherd described the following roles related to legislative activity:

- Legislators
  - » Introduce legislation to propose changes to government programs, and
  - » Work within the legislative process for appropriations and approval of their bills.



- 
- NWRNBS Program staff
    - » Perform functions established by legislation
    - » Share information regarding the potential impact of proposed legislation, and
    - » Suggest changes to bill language, if needed, to address unintended impacts to the NWRNBS Program.
  - NWRNBS Advisory Board
    - » Accomplish the intention established by the legislation
    - » Advise legislators regarding the impact of proposed legislation, and
    - » Suggest changes to bill language, if needed, to address unintended impacts to the NWRNBS Advisory Board.

## Legislation

**2021 legislative session.** Neither HB 2987 nor HB 3107 moved forward during the legislative session. Both bills would have had impacts on the board's and program's work, including the potential addition of disorders to the screening panel.

**2022 legislative session.** HB 4109 was introduced in this legislative session, which proposed changes to the statute establishing the NWRNBS Advisory Board. The board chose to hold a special emergency meeting to discuss the bill language.

The board did not achieve quorum to provide board testimony on HB 4109. HB 4109 did not pass out of the Ways and Means Committee before the close of the legislative session.

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# Conclusion

Efficient review and consensus decision making to remove Gaucher and Fabry from the panel demonstrated the value of the criteria the board established for evaluating removal. The carefully designed make-up of the board, with experts representing many fields and organizations, has provided robust and well-balanced discussion of the important issues that come before the board. The board has also continued to improve its effectiveness through further refining its processes and its relationships with the program and the legislative process. In this report period, the board has clearly demonstrated its maturity and its ability to move forward as the state's primary source of expert advising for the NWRNBS Program.

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# Appendix A: Process for recommending the removal of a disorder from the NWRNBS panel

**The following is a copy of the process voted on and approved by the advisory board:**

## **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 Oregon Health & Science University newborn screening 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.

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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.

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# Appendix B: Evidence Report: Newborn Screening for Gaucher

## **Evidence Report: Newborn Screening for Gaucher**

**Prepared for the Northwest Regional Newborn Bloodspot Screening Program Advisory Board**

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Author: Laurel Boyd, Consultant

Publication date: Draft prepared by Laurel 2019. Draft added to by Program 2021.

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Version: 1.0

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# Introduction

## Scope of Review

In accordance with ORS 433.299, the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Program has created an Advisory Board to assist with modernization of Oregon's newborn bloodspot screening. This Advisory Board is tasked with advising the NWRNBS Program on proposed changes to the Screening Panel, including additions or removals from the panel.

Gaucher disease is currently on the NWRNBS Screening Panel, but has been proposed for removal from the panel. The Advisory Board has approved a process and criteria to use when evaluating proposed removals from the screening panel.

This report follows the evidence outline as presented by ACHDNC, beginning with a discussion of the natural history of the condition, followed by incidence and prevalence estimates and a discussion of screening, diagnosis, treatment and context for NWRNBS Program. The Executive Summary for Fabry disease presents evidence for each criterion in the board's approved criteria.

## Purpose

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

## Methods

The focus of this evidence review is on childhood disease onset. This report summarizes evidence and findings from the GenReviews® Gaucher Disease Chapter (most recently updated: June 2018) and ClinGen Gaucher Disease Curation Summary review (most recently updated: April 2016).<sup>12</sup> This evidence report is intended to gather new, significant updates to evidence subsequent to the publication of these reports. A subsequent evidence (March 2018-November 2019) review was conducted using Systematic Evidence Review (SER) methods, as modified by the Advisory Committee on Heritable Disorders in Newborns and Children and the NWRNBS Program Advisory Board co-chairs. The focus of this review is on pediatric disease including evidence around newborn screening and treatment. This review does not cover updates to natural history (except as they relate to changes in treatment or outcome due to newborn screening).

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<sup>1</sup> Mehta A, Hughes DA. Gaucher Disease. 2002 Aug 5 [Updated 2017 Jan 5]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1292/>

<sup>2</sup> Clinical Genome Resource. [https://search.clinicalgenome.org/kb/conditions/MONDO\\_0018150](https://search.clinicalgenome.org/kb/conditions/MONDO_0018150) [11/23/19].

Literature review methods were created in consultation with subject matter experts and Advisory Board co-chairs. Documentation of literature review is in Appendices A-C; discussion with experts is in Appendix D and a list of included articles is in Appendix E.

## Key Questions for Evidence Review: Gaucher

### Case Definition

Gaucher disease is inherited in an autosomal recessive manner. Gaucher disease is characterized by hepatosplenomegaly (enlarged liver and spleen) and cytopenia (low red blood cell count). There is a spectrum of disease from three major clinical types (1, 2, and 3) and two other subtypes (perinatal-lethal and cardiovascular). Of the three main types, Type 1 is the most common form in North America and has variable onset (childhood through adulthood) and variable presentation (with splenomegaly or enlarged spleen as sometimes the only characteristic, but also with bone disease, lung disease, and cytopenia).<sup>3</sup> Patients with Type 3 disease experience similar clinical manifestations as Type 1, but also with eye or other neurological involvement, and typically childhood onset. Type 2 is also typically childhood onset disease characterized by liver and spleen enlargement and severe neurological impairment (e.g., severe swallowing disorders), and oculomotor paralysis (or bilateral fixed strabismus).<sup>4</sup>

Here are the broad categories of disease by age at onset:

Age	Subtype	Neurologic Involvement	Bone Disease	Other
Adult	Type 1	No	Yes	<ul style="list-style-type: none"><li>• Enlarged spleen</li><li>• Enlarged liver</li><li>• Cytopenia</li><li>• Pulmonary disease</li></ul>

<sup>3</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28218669>

<sup>4</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28218669>



Infancy - early childhood	Type 2 (acute or infantile)	<ul style="list-style-type: none"> <li>● Bulbar signs</li> <li>● Pyramidal signs</li> <li>● Cognitive impairment</li> </ul>	No	<ul style="list-style-type: none"> <li>● Enlarged liver</li> <li>● Enlarged spleen</li> <li>● Cytopenia</li> <li>● Lung disease</li> <li>● Skin changes</li> </ul>
Childhood	Type 3 (subacute; juvenile)	<ul style="list-style-type: none"> <li>● Oculomotor apraxia</li> <li>● Seizures</li> <li>● Progressive myoclonic epilepsy</li> </ul>	Yes	<ul style="list-style-type: none"> <li>● Enlarged liver</li> <li>● Enlarged spleen</li> <li>● Cytopenia</li> <li>● Lung disease</li> </ul>
Perinatal	Perinatal-lethal form	Pyramidal signs	No	<ul style="list-style-type: none"> <li>● Scaly or parchment-like skin changes</li> <li>● Fetal complications</li> </ul>
Cardiovascular-predominant variant	Cardiovascular form	Oculomotor apraxia	Yes	<ul style="list-style-type: none"> <li>● Calcification of mitral &amp; aortic valves</li> <li>● Corneal opacity</li> <li>● Mild spleen enlargement</li> </ul>

Table adapted from GeneReviews®

### What is the Genotype-Phenotype relationship?

According to GeneReviews almost 90% of Gaucher Disease is associated with seven pathogenic variants (see table below) of various levels of penetrance (e.g., the Asn409Ser variant is sometimes but not always pathogenic) and among various populations (this same

variant is found mainly among Ashkenazi Jews but not at all among Japanese or Chinese individuals).<sup>5</sup>

Variants	% of Affected Individuals	Notes
p.[Asn409Ser]+[Asn409Ser]	29%	Associated with mild Type 1 disease
p.[Asn409Ser]+[?]	20%	Associated with Type 1 disease; this variant is not always pathogenic.
p.[Asn409Ser]+[Leu483Pro]	16%	Associated with Type 1 and Type 2
p.Asn409Ser+c.84dupG	12%	Found in almost 1 in 4 Ashkenazi Jews but not at all in Non-Jewish populations
p.[Leu483Pro]+[Leu483Pro] 4	6%	Type 3
p.[Leu483Pro]+[?]	3%	Associated with Type 1 and Type 2
p.Asn409Ser+c.115+1G>A	3%	

Table adapted from GeneReviews®

## Natural History of Gaucher with Usual Clinical Detection

What is the natural history of this condition?

The natural history of Gaucher disease is below, reported by category of disease:<sup>678</sup>

Type 1: These individuals typically experience symptom onset (bone disease with or without neuropathy, enlarged spleen, low red blood cell count, blood clotting abnormalities, anemia, fatigue, and pulmonary disease) in childhood or adulthood and typically die in adulthood.

Type 2: This type is characterized by onset of severe neurological clinical features in early childhood or infancy resulting in impairment and death in early childhood. There is no effective treatment for this type.

<sup>5</sup> <https://www.ncbi.nlm.nih.gov/books/NBK1269/>

<sup>6</sup> <https://www.ncbi.nlm.nih.gov/books/NBK1269/>

<sup>7</sup> <https://www.ncbi.nlm.nih.gov/pubmed/17011471>

<sup>8</sup> <https://rarediseases.info.nih.gov/diseases/10675/gaucher-disease-perinatal-lethal>

Type 3: This is the more slowly progressive neurological type with onset of neurological (but also symptoms similar to Type 1) in childhood or early adulthood impairment. Without treatment, survival does not typically extend beyond the third decade of life.

Perinatal-lethal form: This type is the perinatal lethal type of Gaucher disease resulting in death *in utero* or within three months of birth. Characteristics of this type include: decrease in fetal movements, hepatosplenomegaly, low blood cell counts, edema, and skin changes. There is no treatment for this form.

Cardiovascular form: This type is characterized by calcification of the mitral and aortic valves and sometimes bone disease, eye abnormalities and splenomegaly, and is sometimes called Type 3C. This is the rarest of the types; no information about life expectancy was identified.

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

Without newborn screening, ages of onset range from perinatal through adulthood. Enlarged spleen and subsequent abdominal distention is typically the earliest health problem experienced by those with Gaucher disease, often resulting in diagnosis within a year of symptom onset.<sup>9</sup>

How is the condition defined in newborns?

Pathogenic variants of known significance can identify several types of Gaucher disease including childhood or adult onset. It is possible to instead identify variants of unknown significance, which complicates the condition definition in newborns.

## Incidence and Prevalence of Gaucher

How many people are diagnosed with this condition clinically?

GeneReviews® estimates that prevalence ranges from 1 in 57,000 to 1 in 88,000 with prevalence of specific types differing by ethnic group (1 in 855 Ashkenazi Jewish persons experience Type 1 and Types 2 and 3 are more common among non-European populations).

What is the estimated birth prevalence?

From screening studies, the estimated birth prevalence ranges from 1 in 4,000 in New York City to 1 in 48,000 in Missouri.<sup>10,11</sup>

### Prevalence estimates from additional evidence review, March 2018-November 2019:

Author, Pub Year	N (region)	Base Years	Estimated Birth Prevalence
Yang, 2019	Oregon	2018-2019	1 in 8,000

<sup>9</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28847676>

<sup>10</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30093709>

<sup>11</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25444528>

Wasserstein, 2019	New York City	2013-2017	1 in 4,000
Burton, 2017	Illinois	2014-2016	1 in 44,000
Hopkins, 2015	Missouri	2013	1 in 48,000
Burlina, 2018	Italy	2015-2017	1 in 22,000

## Screening

What is the screening method to detect Gaucher among newborns using dried blood spots?

Detection of 0-15% normal amount of glucocerebrosidase (glucosylceramidase) enzyme activity alone or paired with a genetic screening test. The level of glucocerebrosidase enzyme activity does not correlate with disease type or severity.

How well does it work? (Does it lead to improved outcomes compared to usual care?)

There is currently no information in published scientific literature that assesses long-term outcomes of newborns diagnosed with Gaucher disease following newborn screening. Illinois notes that of the 5 newborns diagnosed with Gaucher in their newborn screening pilot, none are receiving treatment.<sup>12</sup>

Can the severity or Types of Gaucher be predicted at the time of screening?

It is possible to predict some Types of Gaucher (e.g., late vs early onset, or Type 1) at screening but other variants have an uncertain phenotype. Illinois and Missouri both note identification of Gaucher disease of uncertain phenotype.<sup>1314</sup>

### Clinical laboratory testing methods for screening

Test name	Vendor	Method	FDA-approved	Meets clinical laboratory requirements for testing dried blood spots
DMF SEEKER® platform	Baebies Inc.,	digital microfluidic fluorimetry (DMF) kit	Yes	Yes
NeoLSD	Perkin Elmer	Tandem Mass Spectrometry *MS/MS)	Yes	Yes

<sup>12</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

<sup>13</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25444528>

<sup>14</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

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

Birth prevalence estimates from published newborn screening studies ranged from 1 in 4,000 in New York City to 1 in 48,000 in Missouri.<sup>15,16</sup> The authors of the New York City study point out the higher incidence of Gaucher disease in New York City is likely due to a larger Ashkenazi Jewish population and that if the study were repeated for New York State, they would anticipate an overall decrease in prevalence rates.<sup>17</sup> False positive rates were higher than true positives, ranging from 1 in 2,000 in Illinois to 1 in 5,000 in Missouri.<sup>18,19</sup> Comparison among these screening pilots is difficult due to differing case definitions (Missouri combined late onset and diagnoses of unknown significance together whereas New York and Illinois separated them out). Burton et al 2017 recommends against comparing false positive rates as cut-off values and other methodology differ across programs.<sup>20</sup> In this same timeframe, Italy also published newborn screening pilot results that indicated a birth prevalence of 1 in 22,000 (2 infants in 44,000 screened); both infants were homozygous for the .Asn370Ser mutation, which is associated with a variable onset (childhood through adulthood).<sup>21</sup> In New York City, all Gaucher variants identified were associated with late-onset Gaucher disease.

**Screening pilot study findings from New York City, 2013-2017**

	N	%*	Observed Birth Prevalence
Babies screened	65,605	-	
Normal	65,588	99.974%	
Suspected carrier	0	-	

<sup>15</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30093709>

<sup>16</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25444528>

<sup>17</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30093709>

<sup>18</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

<sup>19</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25444528>

<sup>20</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

<sup>21</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29143201>

Suspected case	17	0.026%	1 in 4,000
False Positive	2	0.018%	1 in 3,000
True Positive, Diagnosed	15	0.023%	1 in 4,000

\*Sum doesn't total 100 due to rounding

Illinois identified 5 newborns with Gaucher disease; at least one is Type 1 disease and the others are unspecified types. None of the infants were symptomatic (nor on treatment) at the time of publication. The authors also note identification of 2 more infants with "possible Gaucher disease" (phenotype of unknown significance) that they did not include in their totals. Assuming these children develop Gaucher disease, birth prevalence rates would increase to 1 in 31,000.

#### Screening pilot study findings from Illinois, 2014-2016

	N	%*	Observed Birth Prevalence
Babies screened	219,793	-	
Normal	219,676	99.947%	
Suspected carrier	-	-	
Suspected case	117	0.053%	1 in 2,000
False Positive †	112	0.051%	1 in 2,000
True Positive, Diagnosed	5	0.002%	1 in 44,000

\*Sum doesn't total 100 due to rounding

† Also includes undetermined status and lost to follow-up

Missouri identified a single infant with Gaucher, but classified this case as either later-onset or of unknown significance (differing from how New York City and Illinois classified late-onset cases as true positives). The authors report a high false positive rate (1 in 4,000) and a relatively low true positive rate (1 in 48,000).

### Screening pilot study findings from Missouri, 2013

	N	%*	Observed Birth Prevalence
Babies screened	47,701	-	
Normal	47,690		
Suspected carrier	-	-	
Suspected case	11	0.023%	1 in 4,000
False Positive	10	0.021%	1 in 5,000
True Positive, Diagnosed †	1	0.002%	1 in 48,000

\*Sum doesn't total 100 due to rounding

† Also includes undetermined status

### Screening pilot study findings from Italy, 2015-2017

	N	%*	Observed Birth Prevalence
Babies screened	44,411	-	
Normal	44,409	99.995%	
Suspected carrier	-	-	
Suspected case	9	0.020%	1 in 5,000
False Positive †	7	0.015%	1 in 6,000

True Positive, Diagnosed	2	0.005%	1 in 22,000
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\*Sum doesn't total 100 due to rounding

† Includes infants who did not undergo confirmatory testing.

### What is the experience in Oregon?

Preliminary results from Oregon's first six months of screening for Gaucher indicate a prevalence of 1:12,000 for Gaucher in Oregon, about four times higher as high as earlier estimates of 1:50,000 (as compiled by GeneReviews®).<sup>22</sup> These results, published in a conference proceeding, also indicate the NWRNBS Program is "experiencing higher than expected false positive rates" for Gaucher using only one tier testing (enzyme activity), but that adding a second-tier DNA analysis (genetic analysis) reduced the rate of false positive screens. The NWRNBS program identified 6 carriers through newborn screening and a false positive rate of 0.09% (calculated without carriers, below, the rate decreases to 0.06%). A breakdown of findings is presented in the table below.

### Screening pilot study findings from Oregon (NWRNBS Program), 10/2018-4/2019

	N	%	Observed Incidence
Babies screened	24,209		
Normal	24,186		
Suspected carrier	6	0.025%	1 in 4,000
Suspected case	17	0.070%	1 in 1,000
False Positive †	15	0.062%	1 in 2,000
True Positive, Diagnosed	2	0.008%	1 in 12,000

<sup>22</sup> A. Yang, A. Dennis, D. Koeller, S. Denniston, L. Flint, C. Biggs. "Newborn screening for lysosomal storage disorders in Oregon from results to clinical findings: a 6+ month retrospective" Poster presentation at the American Society of Human Genetics 2019 Annual Meeting. 2019-10-15



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From October 1, 2018 to December 21, 2020, the program has screened 93,081 infants for Lysosomal Storage Disorders. Of those, 275 specimens had an abnormal Gaucher first-tier test and were sent for second tier-testing genetic analysis. Of those, 5 were referred to OHSU medical specialists and 3 are being followed, 2 with early/classic disease and 1 with late/non-classic disease.<sup>31</sup>

In November 2019 the program adjusted cut-offs for Gaucher, which has reduced the number of second-tier genetic analysis tests performed.

## Potential Benefits and Harms of Newborn Screening for Gaucher

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?

Currently, there are no long-term follow-up studies of newborn screening for Gaucher disease so evidence for benefits of screening is not known. Published evidence from screening pilot programs yielded two conclusions: higher-than previously estimated birth prevalence rates and identification of majority late- or variable-onset mutations. None of the infants identified with Gaucher disease were on treatment at the time of publication.

Below are potential harms of screening.

### High rates of false positive screening

The majority of screening studies identified in this review reported high rates of false positive screens. One suggestion (from the six-month pilot screening project in Oregon) is to include a second, confirmatory step in screening.

### Identification of disease for which there is no treatment available

It is possible to identify Type 2 Gaucher disease patients on newborn screening; these are patients for whom treatment is not available and who typically die around age two.

### Identification of variants of unknown significance

Almost all the newborn screening pilot projects identified variants of unknown significance with their testing protocols. At the time of this review it is not clear that infants with these variants will develop Gaucher disease (or what type of disease they will develop).

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.<sup>23</sup>

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<sup>23</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30444430>

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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.

## Confirmatory Testing and Diagnosis

Is definitive diagnostic or speciality testing available to confirm or diagnose positive screens?

Definitive genetic testing is available to confirm positive glucocerebrosidase enzyme activity screens, via gene sequencing and through serial biomarkers. Due to presence of a pseudogene, GBA gene sequencing sometimes needs to be confirmed via Sanger method at another lab, typically, beyond what Baebies can provide. However, there will be cases where biomarkers may not be elevated in neonatal period, and/or DNA show variant of uncertain significance

How well does it work?

Please see above for the Oregon experience and data will be presented from the Oregon experience so far at the meeting. Overall, false positive rate is low.

How long does confirmatory testing and diagnosis take?

Generally, this may take one or two visits to make a diagnosis.

### Diagnostic and specialty testing methods

Test name	Vendor	Method
GBA gene sequencing	Baebies	Next-generation sequencing
GBA gene sequencing	Mayo Clinic Labs	Sanger sequencing
Chitotriosidase	Mayo, LabCorp, others	Fluorimetric enzyme assay
Plasma lyso-GL1	Mayo	Tandem mass spectrometry

## Treatment for Gaucher

What are the standard treatments for Gaucher?

Currently, enzyme replacement therapy or substrate replacement therapy are the standard treatments for Type 1 Gaucher disease and some patients with Type 3 Gaucher disease.

According to GeneReviews®:

*Prevention of primary manifestations:* ERT is usually well tolerated and provides sufficient exogenous enzyme to overcome the block in the catabolic pathway, clearing the stored substrate, GL1, and thus reversing hematologic and liver/spleen involvement. Although bone marrow transplantation (BMT) had been undertaken in individuals with severe GD, primarily those with chronic neurologic involvement (GD type 3), this procedure has been largely superseded by ERT or SRT. Miglustat may be indicated in symptomatic individuals with GD type 1 who are not able to receive ERT. Eliglustat has been shown to improve or stabilize key disease features in those naïve to or switched from enzyme replacement therapy.

ERT is not able to travel through the blood-brain barrier and is not used in controlling central nervous system disease; although clinical trials assessing the use of substrate replacement therapy for neurological involvement is ongoing, there is currently no standard treatment for Type 2 disease or perinatal lethal disease.<sup>24</sup>

### Approved treatment methods

Treatment name	Vendor	Method
imiglucerase (Cerezyme®)	Genzyme Corporation	Enzyme replacement therapy
taliglucerase alfa (Elelyso®)	Protalix and Pfizer	Enzyme replacement therapy
velaglucerase alfa (Vpriv®)	Shire Human Genetic Therapies	Enzyme replacement therapy
miglustat (Zavesca®)	Actelion	Substrate Reduction Therapy
eliglustat (Cerdelga®)	Genzyme Corp	Substrate Reduction Therapy

Cost for enzyme replacement therapy is estimated to be between \$139,000 to \$300,000/year.<sup>25</sup>

What is the evidence for their effectiveness?

A 2015 Cochrane review on the evidence for ERT in Gaucher describes the context for evidence as following:

<sup>24</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6687355/>

<sup>25</sup> <https://www.gaucherdisease.org/blog/national-gaucher-foundations-care-programs/>

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“The clear impact reported in the first patients receiving ERT was so remarkable (Barton 1991), that no randomized controlled studies investigating the absolute effects compared with placebo were carried out. However, with such an individual history of discovery, the ability to quantify the absolute effect of ERT and to describe the actual difference between treated and untreated individuals in a solid experimental fashion is diminished. Moreover, with the emergence of new enzyme preparations, experimental studies investigating their efficacy could only compare the new drugs with the acceptable gold standard (i.e. imiglucerase), since a randomized placebo-controlled study would no longer have been an ethical proposition.”<sup>26</sup>

They add that there are no long-term studies on the use of ERT that could answer questions about life expectancy, quality of life, or risk of Parkinsons (a later-in-life complication for some individuals with Type 1 Gaucher disease) but conclude that “it is unlikely that any randomised controlled study will successfully define the effect of current or future treatments on important outcomes such as Parkinsonism, malignancy, quality of life and mortality”.

What are the current treatments and guidelines for Gaucher, and do they address presymptomatic detection?

Several treatment guidelines exist for Gaucher which address presymptomatic detection along with treatment timing, types, details, changes and duration:

Kaplan et al 2013 offers guidance for treatment of Gaucher disease in children, recommending delaying treatment until symptom onset for Types 1 and 3 and modifying dosage on the basis of response.<sup>27</sup> Other guidelines identified by GeneReviews® offer guidance on treatment dose and initiation (typically 15-60 units of ERT per kg of body weight administered intravenously every two weeks) but note that the optimal dose and frequency for children with Type 1 Gaucher disease are not known.<sup>28,29,30</sup>

## Access to Care and Equity of Treatment and Follow-Up

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

Please see <https://www.orpd.org/drugs/drugclass.php?cid=1164> for prior authorization documents and other reference documents for Lysosomal Storage Disorders, including Gaucher treatments.

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<sup>26</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25812601>

<sup>27</sup> <https://www.ncbi.nlm.nih.gov/pubmed/22772880>

<sup>28</sup> <https://www.ncbi.nlm.nih.gov/pubmed/14677062>

<sup>29</sup> <https://www.ncbi.nlm.nih.gov/pubmed/14722528>

<sup>30</sup> <https://www.ncbi.nlm.nih.gov/pubmed/14677061>

**ICD-10 code:** E75.22 Gaucher disease

**Location on Prioritized List:**

Oregon's legislature approved funding for lines 1-469 of the prioritized list for January 1, 2018. Gaucher appears on lines 60, 71, 100, 292, and 345, 377, 650 and is therefore on **both** the funded and unfunded region of the Prioritized List.

**Location of Gaucher Disease (E75.22) on the Oregon Prioritized List\***

Line number	Description	Guideline Notes
Line 60:	METABOLIC DISORDERS Treatment: MEDICAL THERAPY	64,65
Line 71:	NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES (See Coding Specification) Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., G-TUBES, J-TUBES, RESPIRATORS, TRACHEOSTOMY, UROLOGICAL PROCEDURES)	6, 64, 65, 129, 170
Line 100:	END STAGE RENAL DISEASE Treatment: RENAL TRANSPLANT	-
Line 292:	NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., DURABLE MEDICAL EQUIPMENT AND ORTHOPEDIC PROCEDURE)	6, 64, 65, 170
Line 345:	NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS Treatment: MEDICAL THERAPY	6, 64, 65, 90
Line 377:	DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC	6, 38, 64, 65, 90

	CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION Treatment: MEDICAL THERAPY (SHORT TERM REHABILITATION WITH DEFINED GOALS)	
Line 650:	ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (See Coding Specification) -Unfunded region- Treatment: EVALUATION	64, 65, 74

\*As of 11/23/19

Are experts available to provide treatment?

The NWRNBS Program contracts with Oregon Health and Sciences University for Lysosomal Storage Disorders medical consultation, including Fabry.

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

To better understand the context of this condition in Oregon, Dr. Amy Yang, a medical geneticist who treats patients with Gaucher Disease was interviewed. Dr. Yang was asked about the availability and accessibility of treatment, barriers to care for patients and their families and solutions or possible ways to resolve barriers to care. See [Appendix D](#) for a summary of this discussion.

**Question:** Are treatments available and accessible?

Treatment is expensive but thus far has not presented a barrier to patients presenting for care because of support from patient advocacy organizations like National Organization for Rare Disorders who can often find funding for patients who can't afford treatment.

**Question:** What are barriers to care for patients and their families? Below is what is currently in the reports?

Because mainstay treatment for these two disorders for majority of patients is still ERT, which requires biweekly transfusions (60-90 minutes/every two weeks for life), treatment is burdensome but not insurmountable.

**Question:** What are solutions or possible ways to resolve barriers to care?

Patient advocacy groups as well as case management provided by the pharmaceutical companies have reduced many of these barriers to care.

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**Question:** Is care and treatment for this condition equitable?

Access to care and treatment is contingent upon access to a specialist familiar with these conditions. However, most patients with these diagnoses in Oregon are receiving access to care. The rate limiting step to getting access traditionally is due to delay in diagnosis, which NBS can address.

## NWRNBS Program Impact Assessment

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

- Fiscal analysis
- Availability of specialized medical consultancy services.
- Capacity and expertise to implement and maintain testing and reporting
- Capacity and expertise to implement and maintain follow-up and education for providers and parents
- Assessment of the impact of implementing screening for NWRNBS program partners

### Results

#### Fiscal Analysis

The removal of Gaucher from the Oregon screening panel would reduce costs associated with second tier testing and reagents costs.

#### Availability of Medical Consultants

The Northwest regional Newborn Bloodspot Screening (NWRNBS) program currently contracts with OHSU for medical expertise for Lysosomal Storage Disorders so the expertise necessary for medical consultation currently exists for the program.

#### Capacity and expertise for testing and reporting

The program has sufficient capacity and expertise for testing. There would be fewer retests on specimens, fewer inconclusive results that require additional collections and less send outs for second tier testing.

#### Capacity and expertise for follow-up and education for providers and parents

Currently there is limited follow-up staff capacity for follow-up activities related to abnormal results for Lysosomal Storage Disorders. There would be less tracking of second tier results, updating report results, and referrals to OHSU. In addition, there is limited follow-up capacity for data analysis and educational outreach.

#### Assessment of the impact for NWRNBS program partners

The program reached out to New Mexico and Saipan by e-mail on to ask the following

questions:

- What do you foresee the impact of Oregon removing Fabry to be for your jurisdiction? What about Gaucher?
- Is there any other feedback that you would like to provide for us regarding the possible removal of these two disorders and the impact on your jurisdiction? Are there any factors for your jurisdiction that we should be aware of?

Saipan provided feedback that removing Fabry and Gaucher from the Oregon screening panel would not impact them because their infants are not currently screened for Fabry and Gaucher.

New Mexico provided feedback that:

- NM state legislation in 2010 to implement 5 LSD's: Gaucher, Fabry, Pompe, Krabbe and Niemann pick.
- NM put a clause in the legislation when feasible and technology available for the testing.
- NM knew Oregon would be doing a pilot Oct 1st of 2018 with 3 out of the 5 required for our state.
- May 2019 Oregon presented the data to NM on high frequency of false positive results needing second tier testing and lack of long-term outcome data extra. So Fabry and Gaucher were not recommended at this time.
- Oregon mentioned the possibility of looking at a different platform that may decrease the false positives and this may cut down the need for several specimens going for second tier testing but unsure.
- NM at this point due the legislative law since 2010 in the future may be forced to look for another contractor with newborn screening capacity to meet more of our screening needs.
- NM at this point does not have the capability to remove the LSD legislation from our panel

## Appendix A: Systematic Literature Review

1. Query PubMed, Cochrane, Scopus
2. Gaucher inclusion/exclusion criteria:
  - Article language is English
  - Publication date is 3/1/2018, 3 months prior to the review date of the GeneReviews report (6/1/2018)
  - Not Full-text article
  - No original data or analyses
  - No Key Topic Areas or Key Topic Questions (KTA/KTQ) addressed (see table below)
  - No human subjects with Gaucher
  - Other (includes sample size requirements not met)

Condition	ACHDNC evidence review (timeframe of review)	GeneReviews (timeframe of review)	ClinGen review (Adult, Pediatric, Both; timeframe)
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Gaucher		July 2000 through June 2018	Adult; through April 2016
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### PubMed (core clinical journals)

Query	Items found	Time
Search (" <b>Gaucher Disease</b> "[Mesh] or " <b>Gaucher</b> "[tiab]) Sort by: <b>Author</b> Filters: <b>Publication date from 2018/31/01; Humans; Core clinical journals</b>	5	17:26:07

### PubMed (pediatric literature)

Query	Items found	Time
Search (#10 and #14) Filters: Publication date from 2018/03/01; Humans Sort by: Author	41	19:25:09
Search (((((((((((((((((((((((((((("Pediatrics"[MeSH Terms] OR "pediatric"[Title/Abstract]) OR "Pediatrics"[Title/Abstract]) OR "paediatric"[Title/Abstract]) OR "paediatrics"[Title/Abstract]) OR "juvenile"[Title/Abstract]) OR "juveniles"[Title/Abstract]) OR "Infant"[MeSH Terms]) OR "Infant"[Title/Abstract]) OR "infants"[Title/Abstract]) OR "infantile"[Title/Abstract]) OR "Child"[MeSH Terms]) OR "Child"[Title/Abstract]) OR "children"[Title/Abstract]) OR "childhood"[Title/Abstract]) OR "preadolescent"[Title/Abstract]) OR "preadolescents"[Title/Abstract]) OR "prepubescent"[Title/Abstract]) OR "Adolescent"[MeSH Terms]) OR "Adolescent"[Title/Abstract]) OR "adolescents"[Title/Abstract]) OR "youth"[Title/Abstract]) OR "youths"[Title/Abstract]) OR "teenager"[Title/Abstract]) OR "teenagers"[Title/Abstract]) OR "teenaged"[Title/Abstract]) OR "teen"[Title/Abstract]) OR "teens"[Title/Abstract]) NOT ("Adult"[MeSH Terms] NOT ("Adolescent"[MeSH Terms] OR "Child"[MeSH Terms]) OR "Infant"[MeSH Terms])))) Filters: Publication date from 2018/03/01; Humans Sort by: Author	134870	19:24:35
Search "Gaucher Disease"[MeSH] or "Gaucher"[tiab] Sort by: Author	5525	19:22:50

### Cochrane

Searched for "Gaucher disease" from 3/01/2018 to present (11/15/2019)  
No citations identified

## Scopus

### Search history

History Count	Search Terms	Results
47	#46 AND #45 AND #33	25 document results
46	( PUBYEAR > 2015 ) AND NOT INDEX ( medline ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) )	4,844,523 document results
45	TITLE-ABS-KEY ( gaucher AND disease )	7,849 document results
33	( TITLE-ABS-KEY ( infant* ) OR TITLE-ABS-KEY ( child* ) OR TITLE-ABS-KEY ( p*ediatric* ) OR TITLE-ABS-KEY ( juvenile* ) OR TITLE-ABS-KEY ( *adolescent* ) OR TITLE-ABS-KEY ( youth* ) OR TITLE-ABS-KEY ( teen* ) ) AND NOT ( TITLE-ABS-KEY ( adult ) OR TITLE-ABS-KEY ( elderly ) OR TITLE-ABS-KEY ( embryo ) OR TITLE-ABS-KEY ( fetus ) OR TITLE-ABS-KEY ( middle AND age* ) )	2,835,728 document results

### Key Questions for Literature Review\*

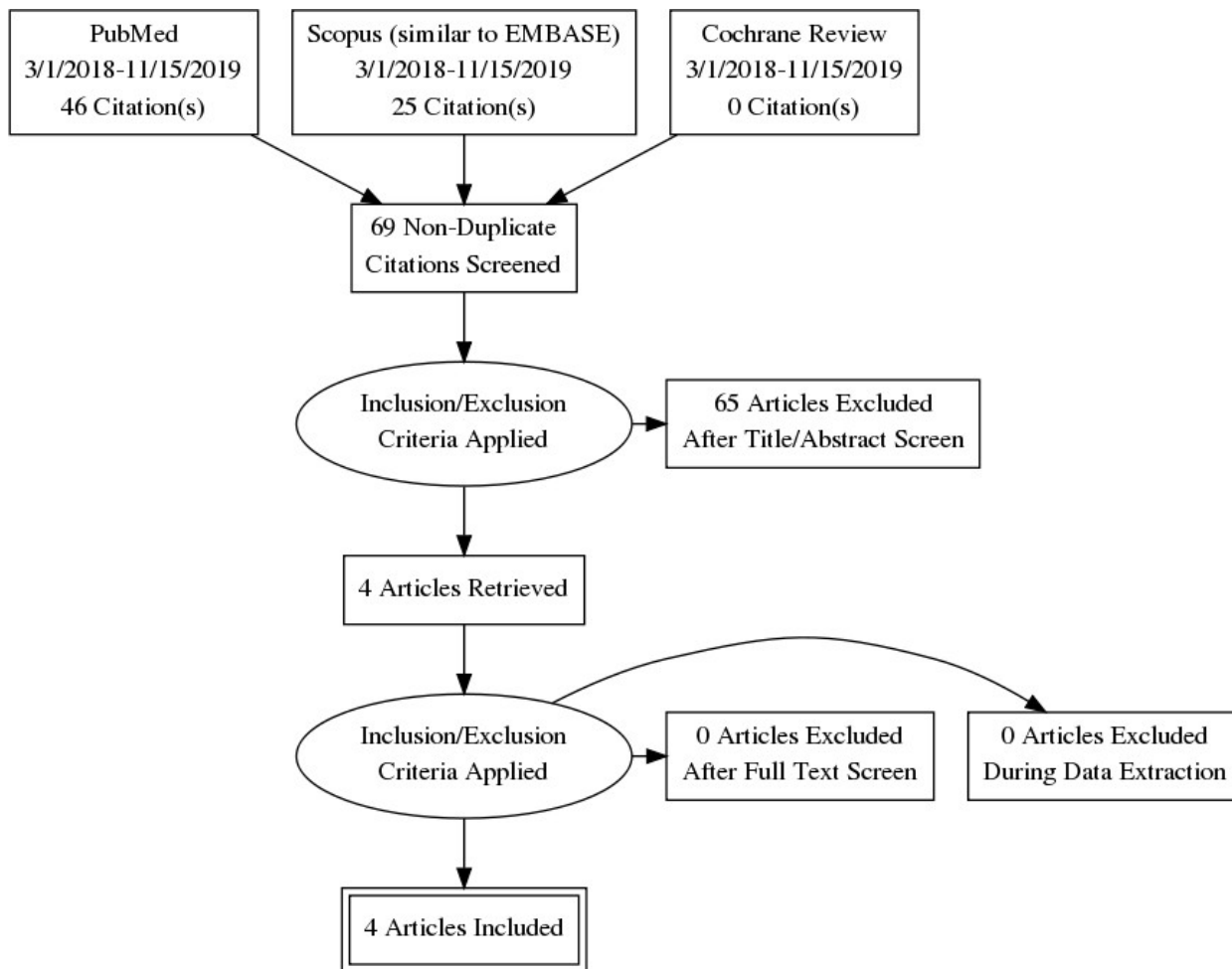
Key Question	Population	Interventions	Comparators	Outcomes
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Key Question 2: What is the direct and indirect evidence that newborn screening for this condition leads to improved health outcomes compared to usual clinical care?	n>5	Any care received subsequent to the screening test	Contemporaneous or historical controls affected by this condition	Overall Survival; Survival with major morbidity
Key Question 3: Screening and Short-term follow up/diagnostic confirmation methods	n>5, Newborns without known diagnosis of, or risk factor for this condition; deidentified dried-blood spots	Any screening methods for this condition conducted in the first month of life. For analytic validity, studies should also report proficiency	Diagnosis by genotype and follow-up evaluation or genotype alone Outcomes: Sensitivity, specificity, positive predictive value, negative predictive value, reliability, and yield (i.e., prevalence)	n/a
Key Question 4: What are the harms associated with newborn screening for this condition to the individual or the family?	n>5, Newborns screened for this condition and their families		Any newborn screening for this condition	Systematic assessment of harms, including harm related to false-positive screening results, false-negative screening results, early identification of later-onset disease, or perceived harms or acceptability of screening for this condition

<p>Key Question 5: What are the standard treatments for this condition and evidence for their effectiveness? Do follow-up protocols exist for the management of this condition that do not require immediate initiation of treatment? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes? Does early initiation of treatment improve primary health outcomes (overall survival, other important health outcomes) when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype?</p>	<p>n&gt;3, Newborns and others diagnosed with this condition through newborn screening or other methods of presymptomatic detection and diagnosis in childhood</p>	<p>Any approved disease-modifying therapy</p>	<p>Contemporaneous or historical controls with this condition disease or no comparison</p>	<p>Primary endpoint/outcome measures for Gaucher: Childhood onset</p>
<p>Key Question 8: What are the harms associated with treatments for this condition in early childhood, for symptomatic and presymptomatic patients? How does this vary by phenotype?</p>	<p>Any child (or caregiver of child) identified with this condition receiving a current treatment</p>	<p>Any approved disease-modifying therapy</p>	<p>Any</p>	<p>Any</p>

\*Key Questions 6 and 7 concern intermediate and secondary health outcomes and were considered to be outside the scope of this review.

## Appendix B: PRISMA Diagram



## Appendix C: Included Articles and Grading

Quality Assessment of Evidence: Screening and Treatment Articles

Key: Risk of Bias
Low
Unclear
High

Screening studies

Screening questions			Patient Selection		Newborn Screening Test		
Publication ( <i>First Author, Year of Publication</i> )	Therapy	Global Publication Rating	<p>Risk of Bias</p> <p>1. Was a consecutive or random sample of samples screened?</p> <p>2. Did the study avoid inappropriate exclusions?</p> <p>3. Could the selection of patients have introduced bias?</p>	<p>Applicability</p> <p>1. Was this a pilot test of a newborn screening test (i.e., not anonymized samples)?</p> <p>2. Did newborn screening occur within a defined population?</p> <p>3. Is there concern that the study does not reflect population-based newborn screening?</p>	<p>Conduct and Interpretation of Test</p> <p>1. Were the results of the newborn screening test interpreted without knowledge of the diagnostic test results?</p> <p>2. Was the threshold for a positive screen clear?</p> <p>3. Was the threshold for a positive screen pre-specified?</p> <p>4. Were alternative thresholds for a positive screen clear?</p> <p>5. Could the conduct</p>	<p>Reference Standard</p> <p>1. Is the reference standard likely to correctly classify the condition?</p> <p>2. Was the reference standard interpreted without knowledge of the newborn screening result?</p> <p>3. Could the reference standard, its conduct, or its interpretation have introduced bias?</p>	<p>Flow and Timing</p> <p>1. Did all positive newborn screens receive the reference standard?</p> <p>2. Was the same reference standard used for all who received diagnostic testing?</p> <p>3. Were all screening results used in the analysis?</p> <p>4. Could the newborn screening flow have introduced bias?</p>

					or interpretation of the screening introduce bias?		
Burton, 2017	Screening	Strong	Strong	Strong	Strong	Strong	Strong
Hopkins, 2015	Screening	Strong	Strong	Strong	Strong	Strong	Strong
Wasserstein, 2019	Screening	Strong	Strong	Strong	Strong	Strong	Strong
Burlina, 2018	Screening	Strong	Strong	Strong	Strong	Strong	Strong

### Appendix D: Discussion with Experts

Medical Consultant	Title	Institution/Affiliation	Date interviewed
<b>Amy Yang</b>	Medical Geneticist	Oregon Health and Science University	11/7/2019. Updated February 2021.

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## Summary of discussion with Dr. Amy Yang

Interview conducted on 11/7/2019. Updated in February 2021.

Thank you for agreeing to talk to me about Gaucher.

The objective of this discussion is for you to provide input and guidance as to the methods I use for a literature review before I begin collecting literature. I would also like to hear from you about equity in treatment and care for this condition. After I have reviewed and graded evidence, I would like to talk to you again about any questions for which there is less than high quality evidence (this could be in the next 2-5 weeks). You will also have an opportunity to review articles I've excluded from this review. Because the info you provide me will be summarized in an evidence report, I would like to transcribe this discussion and summarize it for appending to the report. Is that ok with you?

**Dr. Yang's response:** Yes

**Question:** Let's begin. Can you please tell me a little bit about your training and background in caring for patients with Gaucher?

**Dr. Yang's response:**

- Pediatric residency
- Then, clinical genetics residency at Mt. Sinai for 2 yrs (this is the place a large proportion of New Yorkers are referred to for genetic condition followup); meant a lot of experience with newborn screening
- 1:10 Ashkanizi people are carriers for Gaucher
- At Mt. Sinai, saw ~500 patients with Gaucher
- At OHSU, we actively follow ~20 pts w/ Gaucher

**Question:** Next, looking at methods for the literature review, can you tell me your thoughts on outcomes for key questions I've highlighted?

**Dr. Yang's response:** (no comments made regarding Gaucher.)

**Question:** For gaucher - does it make sense to think about restricting the review to a specific type (types 1-3) or subtype (perinatal lethal, cardiovascular)?

- For Key Question 2: What is the direct and indirect evidence that newborn screening for this condition leads to improved health outcomes compared to usual clinical care? Outcomes: Overall Survival; Survival with major morbidity?
- For Key Question 5: What are the standard treatments for this condition and evidence for their effectiveness? restrict to childhood onset? type 2 or type 3 or perinatal lethal?



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**Dr. Yang's response:** Literature for Gaucher is probably up to date. It's a done deal. We know a lot about natural history and we have an effective treatment that reverses organomegaly, improve growth, and prevent bone disease.

Majority of people have type 1 with large liver and spleen, can present in early childhood but not before 1 yr of life. ERT (enzyme replacement therapy) works well for type 1.

ERT works well for Type 3 (presents around age 1 yrs w/ organomegaly and gaze palsy. Those w/ type 3 will also benefit from NBS.

Even though newborn screening is great because there's an effective treatment, these people (Type 1 and 3) would still be picked up clinically with proper primary care. This would typically not lead to death since the organomegaly would alert the pediatrician immediately and further work-up would ensue. However, before someone start noticing the large liver and spleen, some children may develop bone infarcts that are quite painful and cause long-term disabilities; the bone damage cannot be reversed with enzyme replacement after they get a proper diagnosis.

Type 2 is most severe and have neurological issues. Usually die by age 1-2. ERT is generally not tried and child is usually referred for bone marrow transplant or palliative care. Picking up Type 2 Gaucher potentially would be a harm because despite bone marrow transplant and ERT, they have do not have a good neurological outcome. Is there something we could possibly offer these families if we can pick them up early through NBS? Ie, if bone marrow transplant is done very early on? We do not have the answer to that.

Literature overall is more limited on type 2 and type 3 due to rarity of cases.

From three patients I've cared for with type 3, all have done well with ERT. One is a lawyer. One is a kid. Going to kindergarten (kid has a vision issue with tracking). Accommodations for vision but beyond that he's learning and doing what he needs to. Baby with type 3 is doing well. Every geneticist encounters 1-3. Wouldn't mind treating them.

**Question:** What are some barriers to care for patients and their families?

Don't know if they are barriers but more like burdens. Haven't encountered a family that says this is too much.

These families have to come to Portland for care. And, treatment requires IV infusion. Requires care at a medical center. Some families have to drive an hour (every 2 weeks for life) for 60-90 minutes of infusion every two weeks.

**Question:** Cost: companies fund organizations that help with copays, transportation. If family speaks up, can usually help out by reaching out to patient groups like NORD - National Organization for Rare Diseases get funds from drug manufacture for certain disorders or PRI, another organization that get funds from pharmaceutical company. This helps families with copays (high deductible plan or maxed out).

**Is there other context that i should know about the disease?**

No

**What are potential harms for screening?** See above for type 2 cases, potentially.

## Appendix E: Included Articles

key	title	year	journal	volume	issue	authors	url
29143201	Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North East Italy.	2018	Journal of inherited metabolic disease	41	2	Burlina, Alberto B and Polo, Giulia and Salviati, Leonardo and Duro, Giovanni and Zizzo, Carmela and Dardis, Andrea and Bembi, Bruno and Cazzorla, Chiara and Rubert, Laura and Zordan, Roberta and Desnick, Robert J and Burlina, Alessandro P	<a href="https://www.ncbi.nlm.nih.gov/pubmed/29143201">https://www.ncbi.nlm.nih.gov/pubmed/29143201</a>
30444430	Pharmacological treatment of pediatric Gaucher disease.	2018	Expert review of clinical pharmacology	11	12	Gupta, Punita and Pastores, Gregory	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30444430">https://www.ncbi.nlm.nih.gov/pubmed/30444430</a>
30093709	The New York pilot newborn screening program for lysosomal storage diseases: Report of the First 65,000 Infants.	2019	Genetics in medicine : official journal of the American College of Medical Genetics	21	3	Wasserstein, Melissa P and Caggana, Michele and Bailey, Sean M and Desnick, Robert J and Edelman, Lisa and Estrella, Lissette and Holzman, Ian and Kelly, Nicole R and Kornreich, Ruth and Kupchik, S Gabriel and Martin, Monica and Nafday, Suhas M and Wasserman, Randi and Yang, Amy and Yu, Chunli and Orsini, Joseph J	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30093709">https://www.ncbi.nlm.nih.gov/pubmed/30093709</a>
28728811	Newborn Screening for Lysosomal Storage	2017	The Journal of pediatrics	190		Burton, Barbara K and Charrow, Joel and	<a href="https://www.ncbi.nlm.nih.gov/pubmed/28728811">https://www.ncbi.nlm.nih.gov/pubmed/28728811</a>

	Disorders in Illinois: The Initial 15-Month Experience.					Hoganson, George E and Waggoner, Darrell and Tinkle, Brad and Braddock, Stephen R and Schneider, Michael and Grange, Dorothy K and Nash, Claudia and Shryock, Heather and Barnett, Rebecca and Shao, Rong and Basheeruddin, Khaja and Dizikes, George	lm.nih.gov /pubmed/ 28728811
2544452 8	Lysosomal storage disorder screening implementation: findings from the first six months of full population pilot testing in Missouri.	2015	The Journal of pediatrics	166	1	Hopkins, Patrick V and Campbell, Carlene and Klug, Tracy and Rogers, Sharmini and Raburn- Miller, Julie and Kiesling, Jami	https://w ww.ncbi.n lm.nih.gov /pubmed/ 25444528

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# Appendix C: Evidence Report: Newborn Screening for Fabry

## **Evidence Report: Newborn Screening for Fabry**

**Prepared for the Northwest Regional Newborn Bloodspot Screening Program Advisory Board**

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Author: Laurel Boyd, Consultant

Publication date: Draft prepared by Laurel 2019. Draft added to by Program 2021. Northwest Regional Newborn Bloodspot Screening Program Contact: Nicole Galloway Contact

information: [NWRegional.NBS@state.or.us](mailto:NWRegional.NBS@state.or.us)

Version: 1.0

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# Introduction

## Scope of Review

In accordance with ORS 433.299, the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Program has created an Advisory Board to assist with modernization of Oregon's newborn bloodspot screening. This Advisory Board is tasked with advising the NWRNBS Program on proposed changes to the Screening Panel, including additions or removals from the panel.

Fabry disease is currently on the NWRNBS Screening Panel, but has been proposed for removal from the panel. The Advisory Board has approved a process and criteria to use when evaluating proposed removals from the screening panel.

This report follows the evidence outline as presented by ACHDNC, beginning with a discussion of the natural history of the condition, followed by incidence and prevalence estimates and a discussion of screening, diagnosis, treatment and context for NWRNBS Program. The Executive Summary for Fabry disease presents evidence for each criterion in the board's approved criteria.

## Purpose

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

## Methods

The focus of this evidence review is on childhood disease onset. This report summarizes evidence and findings from the GenReviews® Fabry Disease Chapter (most recently updated: January 2017) and ClinGen Fabry Disease Curation Summary review (most recently updated: April 2018).<sup>12</sup> This evidence report is intended to gather new, significant updates to evidence subsequent to the publication of the ClinGen report. A subsequent evidence (January 2018-November 2019) review was conducted using Systematic Evidence Review (SER) methods, as modified by the Advisory Committee on Heritable Disorders in Newborns and Children and the NWRNBS Program Advisory Board co-chairs. The focus of this review is on pediatric disease including evidence around newborn screening and treatment. This review does not cover updates to natural history (except as they relate to changes in treatment or outcome due to newborn screening).

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<sup>1</sup> Mehta A, Hughes DA. Fabry Disease. 2002 Aug 5 [Updated 2017 Jan 5]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1292/>

<sup>2</sup> Clinical Genome Resource. [https://search.clinicalgenome.org/kb/conditions/MONDO\\_0010526](https://search.clinicalgenome.org/kb/conditions/MONDO_0010526) [11/23/19].

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Literature review methods were created in consultation with subject matter experts and Advisory Board co-chairs. Documentation of literature review is in Appendices A-C; discussion with experts is in Appendix D and a list of included articles is in Appendix E.

## Key Questions for Evidence Review: Fabry

### Case Definition

Fabry disease is characterized by a pathogenic variant in the *GLA* gene, located on the X chromosome, that causes a deficiency of the enzyme alpha-galactosidase A ( $\alpha$ -Gal A), resulting in the buildup of globotriaosylceramide, a type of fat in blood vessels, the kidneys, the heart, nerves, and other organs. Males typically inherit a single X chromosome from their mother; if a pathogenic mutation in *GLA* is identified in a male, it is likely (but not certain, due to the possibility of *de novo* mutations) that his mother is also a carrier. There are several broad categories of disease:

- Males with < 1% of normal  $\alpha$ -Gal A enzyme activity have the so-called “classic” form of the disease, typically with childhood or adolescent onset of severe pain in the extremities, sweating abnormalities, vascular cutaneous lesions, corneal and lenticular opacities, and proteinuria. These individuals typically develop kidney disease (end-stage renal disease), cardiac and/or cerebrovascular disease by middle age.
- Males with >1% of normal  $\alpha$ -Gal A enzyme activity may develop other variants as adults: end-stage renal disease without other manifestations, cardiac or cerebrovascular disease but without end-stage renal disease.
- Disease varies widely for heterozygous females, who may be asymptomatic, have mild symptoms, or be as affected as severely as males with classic Fabry disease.

According to a listening session with the Food and Drug Administration, patients and their families living with Fabry identified gastrointestinal (bloating, diarrhea, abdominal pain), cold and heat intolerance (limiting seasonal outdoor activities), neuropathy, tinnitus, hearing loss, headaches and depression as the most impactful symptoms associated with Fabry.<sup>3</sup>

### What is the Genotype-Phenotype relationship?

There are some pathogenic variants of *GLA* that are known to be associated with the classic phenotype and others with later-onset phenotypes. There are also non-pathogenic mutations of *GLA*. The genotype-phenotype relationship in Fabry disease is complicated, due to these reasons:<sup>45</sup>

- Families with Fabry tend to have private (i.e., rare) pathogenic variants.

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<sup>3</sup> <https://www.fda.gov/media/120981/download>

<sup>4</sup> GeneReviews <https://www.ncbi.nlm.nih.gov/books/NBK1292/>

<sup>5</sup> <https://www.ncbi.nlm.nih.gov/books/NBK11584/>

- 
- Among people with the same variant, phenotypes can differ (one could have classic disease, another the cardiac variant).
  - Heterozygous females have two X chromosomes; parts of one X chromosome may be randomly inactivated, protecting against severe symptoms if the pathogenic region of *GLA* is silenced.
  - Because heart disease, neuropathic and abdominal pain are common in the general population, pathogenic mutations of *GLA* can be seen as risk factors for developing these conditions.

## Natural History of Fabry with Usual Clinical Detection

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

According to ClinGen and Gene Reviews®:

Without newborn screening, clinical detection is delayed upwards of 20 years after symptom onset, usually occurring in middle age.<sup>6</sup> With usual clinical detection people with Fabry disease have a shorter lifespan than the general population (50-57 years for males and 70-72 years for females), typically dying from renal or cardiac failure.<sup>7</sup> Before dialysis and transplantation became available, classically affected males did not typically survive beyond the first decade of life. Ages of onset for males with classic disease is typically 4-8 years with average life expectancy of 41; for later-onset, age of onset for renal variant is after age 25 with an average life expectancy of greater than 60 years. For the cardiac variant, the average age of onset is more than 40, with an average life expectancy of 60.

Without newborn screening, male patients are identified following symptom onset (unexplained pain in the extremities, sweating abnormalities, stroke, renal insufficiency, etc) via measurement of  $\alpha$ -Gal A enzyme activity in dried blood spot testing, followed by testing for a disease-causing mutation in *GAL*.<sup>8</sup> Diagnosis for females relies upon genetic testing as some heterozygous females may have  $\alpha$ -Gal A enzyme activity in the normal range.

How is the condition defined in newborns?

Depending on the variant of *GLA* it is possible to predict early vs. late onset of disease in newborns screened for the condition. Age of onset is typically not until age 4 (for classic disease) and much later for the renal, cardiac or cerebral variants.

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<sup>6</sup>Clin Gen <https://actionability.clinicalgenome.org/ac/Adult/ui/stg2SummaryRpt?doc=AC047>

<sup>7</sup> GeneReviews <https://www.ncbi.nlm.nih.gov/books/NBK1292/>

<sup>8</sup> [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3063537/pdf/10545\\_2010\\_Article\\_9261.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3063537/pdf/10545_2010_Article_9261.pdf)



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## Incidence and Prevalence of Fabry

What is the incidence (from clinical diagnosis) of this condition?

According to ClinGen:

The incidence of Fabry disease has historically been estimated as 1:50,000 to 1:117,000 births; however, more recent studies suggest the incidence may be as high as 1:1,600 to 1:3,100. This likely reflects a broader phenotypic spectrum identified in the last decade with a ratio of 11:1 of persons with the later-onset:classic phenotypes.

What is the estimated birth prevalence?

According to published and gray literature screening program results, estimated birth prevalence ranges from 1:3,000 to 1:24,000. See chart below for a summary.

### Prevalence estimates from additional evidence review, January 2018-November 2019:

Author, Pub Year	N (region)	Base Years	Estimated Birth Prevalence
Yang, 2019	Oregon	2018-2019	1 in 24,000
Wasserstein, 2019	New York City	2013-2017	1 in 9,000
Burton, 2017	Illinois	2014-2016	1 in 22,000
Hopkins, 2015	Missouri	2013	1 in 3,000
Burlina, 2018	Italy	2015-2017	1 in 9,000

## Screening

What is the screening method to detect Fabry among newborns using dried blood spots?

The NWRNBS Screening Panel uses a digital microfluidic fluorimetry (DMF) kit to test dried blood spots for lysosomal disorders, including Fabry. Another screening option is tandem mass spectrometry (MS/MS).

How well does it work? (Does it lead to improved outcomes compared to usual care?)

Newborn screening for Fabry is relatively new (implemented in 2018 in Oregon) and there is not enough information to date on long term outcomes such as prevention of premature death, or major morbidity.<sup>9, 10</sup> Hsu et al 2016 reported the Taiwanese experience of monitoring adults family members identified with late-onset Fabry disease after positive newborn screen (and familial screening).<sup>9</sup> The majority of these individuals did not have left ventricular hypertrophy before age 40 but “LVH was present and increased rapidly with age in the IVS4 adults >40

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<sup>9</sup> <https://www.ncbi.nlm.nih.gov/pubmed/27931613>

years of age and the frequency increased decade by decade.” They suggest initiating follow-up of these individuals before age 40 and conclude that newborn screening for Fabry “provides early detection of the future insidious and irreversible cardiac damage that occurs in adult type 2 later onset patients.”

Burton et al 2017 reports that in Illinois none of the infants identified with Fabry are receiving treatment and that one variant identified through screening, p.A143T, “suggests that it may be a benign or pseudodeficiency allele, or at most an incompletely penetrant mutation” the presence of which complicates genetic counseling.<sup>10</sup>

Can the severity or Types of Fabry be predicted at the time of screening?

There are known variants associated with classic disease and later onset disease that can be predicted at the time of screening. There are also rare variants that are not clearly associated with a phenotype and others that might be associated with more than one phenotype.

### Clinical laboratory testing methods for screening

Test name	Vendor	Method	FDA-approved	Meets clinical laboratory requirements for testing dried blood spots
DMF SEEKER® platform	Baebies Inc.,	digital microfluidic fluorimetry (DMF) kit	Yes	Yes
NeoLSD	Perkin Elmer	Tandem Mass Spectrometry *MS/MS)	Yes	Yes

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

Findings from other regions that have implemented screening pilots have identified birth prevalence rates that are higher than those historically estimated in the literature (1:50,000), ranging from 1:3,000 to 1:22,000.<sup>11</sup> Several states, including Oregon, have cited high false positive rates, ranging from 1:214 (Oregon) to 1:3,000 (Missouri and New York City).<sup>12,13</sup> Rates of false positives in identified screening studies are as high as true positive rates, due, in part to pseudodeficiencies (*GAL* variants) not associated with Fabry disease. Burton et al 2017 recommends against comparing false positive rates as cut-off values and other methodology

<sup>10</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

<sup>11</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25444528>

<sup>12</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25444528>

<sup>13</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30093709>

differ across programs.<sup>14</sup> Italy reported a birth prevalence rate of 1 in 9,000; 4 out of 5 infants diagnosed with Fabry had variants associated with later onset disease.<sup>15</sup> Taiwan analyzed their newborn screening results (published before the scope of this review) and identified a high rate of later-onset disease variants (381/441 or 5 out of 6 newborns diagnosed with Fabry had the IVS4 mutation).<sup>16</sup>

#### Screening pilot study findings from New York City, 2013-2017

	N	%*	Observed Birth Prevalence
Babies screened	65,605	-	
Normal	65,574	99.953%	
Suspected carrier	2	0.003%	1 in 32,000
Suspected case	29	0.044%	1 in 2,000
False Positive †	22	0.035%	1 in 3,000
True Positive, Diagnosed	7	0.011%	1 in 9,000

\*Sum doesn't total 100 due to rounding

† Also includes undetermined status and lost to follow-up

#### Screening pilot study findings from Illinois, 2014-2016

	N	%*	Observed Birth Prevalence
Babies screened	219,793	-	
Normal	219,686	99.951%	
Suspected carrier	-	-	
Suspected case	107	0.049%	1 in 2,000
False Positive †	97	0.044%	1 in 2,000
True Positive, Diagnosed	10	0.005%	1 in 22,000

\*Sum doesn't total 100 due to rounding

† Also includes undetermined status and lost to follow-up

#### Screening pilot study findings from Missouri, 2013

	N	%*	Observed Birth Prevalence
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<sup>14</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

<sup>15</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29143201>

<sup>16</sup> <https://www.ncbi.nlm.nih.gov/pubmed/27931613>

Babies screened	47,701	-	
Normal	47,673	99.941%	
Suspected carrier	-	-	
Suspected case	28	0.059%	1 in 2,000
False Positive †	13	0.0272%	1 in 4,000
True Positive, Diagnosed † †	15	0.031%	1 in 3,000

\*Sum doesn't total 100 due to rounding

† Also includes lost to follow-up

† † Also includes undetermined status

### Screening pilot study findings from Italy, 2015-2017

	N	%*	Observed Birth Prevalence
Babies screened	44,411	-	
Normal	44,405	99.986%	
Suspected carrier	-	-	
Suspected case	6	0.014%	1 in 7,000
False Positive †	1	0.002%	1 in 44,000
True Positive, Diagnosed	5	0.011%	1 in 9,000

\*Sum doesn't total 100 due to rounding

### What is the experience in Oregon?

An initial assessment of screening for Fabry in Oregon indicates a birth prevalence rate of 1 in 24,000, about twice as high as earlier estimates of 1:50,000 (as compiled by GeneReviews®). These results, published in a conference proceeding, also indicate the NWRNBS Program is "experiencing higher than expected false positive rates for Fabry" using only one tier testing ( $\alpha$ -Gal enzyme activity), but that adding a second-tier DNA analysis (genetic analysis) reduced the rate of false positive screens.<sup>17</sup> A breakdown of findings is presented in the table below.

<sup>17</sup> A. Yang, A. Dennis, D. Koeller, S. Denniston, L. Flint, C. Biggs. "Newborn screening for lysosomal storage disorders in Oregon from results to clinical findings: a 6+ month retrospective" Poster presentation at the American Society of Human Genetics 2019 Annual Meeting. 2019-10-15

### Screening pilot study findings from Oregon (NWRNBS Program), 10/2018-4/2019

	N	%*	Observed Birth Prevalence
Babies screened	24,209	-	
Normal	24,014	99.195%	
Suspected carrier	-	-	
Suspected case	195	0.805%	1 in 124
False Positive	194	0.801%	1 in 124
True Positive, Diagnosed	1	0.004%	1 in 24,000

\*Sum doesn't total 100 due to rounding

From October 1, 2018 to December 21, 2020, the program has screened 93,081 infants for Lysosomal Storage Disorders. Of those, 598 specimens had an abnormal Fabry first-tier test and were sent for second tier-testing genetic analysis. Of those, 47 were referred to OHSU medical specialists and 9 are being followed with Late/Non classic disease.<sup>31</sup>

In April 2020 the program adjusted cut-offs for Fabry, which has reduced the number of second-tier genetic analysis tests performed.

## Potential Benefits and Harms of Newborn Screening for Fabry

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?

At least one study recommends newborn screening for detection and diagnosis of infants and family members with Fabry (including late-onset disease) to allow for routine monitoring before development of severe, irreversible clinical manifestations.<sup>18</sup>

Findings from Illinois indicate detection of a “benign or pseudodeficiency allele” and conclude:

“A significant problem encountered in the follow-up of infants with abnormal newborn screening test results relates to those who cannot be positively identified as either affected or unaffected. Long-term follow-up of these infants, and of those detected with

<sup>18</sup> <https://www.ncbi.nlm.nih.gov/pubmed/27931613>

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later-onset disorders, will be essential to document the true risks and benefits of newborn screening for these disorders.”<sup>19</sup>

#### High rates of false positive screening

Initial findings from newborn screening programs indicate high rates of false positive screens (Oregon, New York City).

#### Secondary findings

The *GLA* gene is on the X chromosome, meaning that additional genetic testing of the X chromosome can identify secondary findings like identification of Klinefelter's disease, Turner's disease. Families have not been consented to receive secondary findings.

#### Medicalization of infants, children

Potential medicalization of babies who are identified as having late-onset disease. This means annual visits to a specialist from infancy onwards for a disease that may not manifest until adulthood.

#### Variants of uncertain significance

Burton 2017 highlights capture of 16 patients with the p.A143T variant in the Illinois screening pilot, stating:

“[The] uncertain significance of this mutation makes parental counseling very difficult, and also leads to questions regarding the appropriateness of testing other family members as is typically recommended in cases of a definite diagnosis of Fabry disease. The ambiguity surrounding the identification of this variant and the high frequency of its detection are factors that should be carefully considered when weighing the potential advantages and disadvantages of including Fabry disease in any newborn screening program.”<sup>20</sup>

See [Appendix D](#) for additional discussion from Dr. Yang.

## Confirmatory Testing and Diagnosis

Is definitive diagnostic or specialty testing available to confirm or diagnose positive screens?

Definitive genetic testing is available to confirm positive  $\alpha$ -Gal A enzyme activity screens, via DNA testing and biomarkers. However, there are still cases that potentially are going to be unresolved or not diagnostic. For example, a variant of uncertain significance DNA testing and/or equivocal biomarkers.

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<sup>19</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

<sup>20</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28728811>

How well does it work?

Please see above for the Oregon experience and data will be presented from the Oregon experience so far at the meeting. Overall, so far with screening through Baebies platform, there is high false positive rate, and there is contentious interpretation of a particular variant called A143T that is most commonly found in these babies w/ abnormal screening.

How long does confirmatory testing and diagnosis take?

Generally, this may take one or more visits to make a diagnosis. Sometimes, as in the case of A143T, testing additional family members needs to happen as well.

### Diagnostic and specialty testing methods

Test name	Vendor	Method
GLA gene sequencing	Baebies	Next-generation sequencing
Plasma lyso-GL3	Mayo Clinic Lab	Tandem Mass Spectrometry

### Treatment for Fabry

According to GeneReviews®:

*Prevention of primary complications:* The role of enzyme replacement therapy (ERT) in the long-term prophylaxis of renal, cardiac, and CNS manifestations is unproven; however, experts recommend that ERT be initiated as early as possible in all males with Fabry disease (including children and those with ESRD undergoing dialysis and renal transplantation) and in females with significant disease because all are at high risk for cardiac, cerebrovascular, and renal complications.

*Prevention of secondary complications:* Prophylaxis for renovascular disease, ischemic heart disease, and cerebrovascular disease as for the general population.

### Approved treatment methods\*

Treatment name	Vendor	Method	Cost <sup>21</sup>
agalsidase beta (Fabrazyme®)	Sanofi SA	Enzyme replacement therapy	average price is \$312,000 per year for each patient
migalastat (Galafold®)	Amicus Therapeutics	Pharmacological chaperone	average price is \$310,000 per year for each patient

<sup>21</sup> <https://www.ncbi.nlm.nih.gov/books/NBK533452/>

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\*agalsidase alfa (Replagal®) is available in Europe but is not currently approved by the FDA for use in the United States.

What is the effectiveness of treatment for Fabry disease?

GeneReviews® summarizes the effectiveness of ERT:

Two double-blind placebo-controlled trials found a short-term decreased risk of secondary or intermediate health outcomes (e.g, rate of decline of cardiac and renal function) after treatment with ERT. At least two other studies (one with 362 patients) also found a decreased risk of primary health outcomes (death, cardiac arrest, stroke ESRD) with ERT. At least two other observational or cohort studies found no difference in outcomes between patients treated with ERT and those (from the Fabry Registry) not treated. GeneReviews® notes the disparate findings in the medical literature, but states that physician experts in the United States recommend initiation of ERT as early as possible.

ClinGen summarizes the evidence on ERT as the following:

In practice, there is wide variability in the use of ERT even for hemizygotes, with some starting therapy at a young age even without symptoms and others waiting until end organ damage is evident. The decision to initiate ERT should be made according to the clinical judgment of the managing metabolic physician in conjunction with the family of the patient. (Tier 2)

Limited trial literature has been published regarding the use of ERT for Fabry disease. A systematic review of RCTs of ERT reported on nine studies of 351 patients; however, many of these studies reported only on the effect of ERT on levels of unmetabolized GL-3. Data from 2 trials (n=39) found no statistically significant differences in plasma GL-3 concentration and one trial (n=24) found no statistical differences in renal function between individuals treated with agalsidase alfa and placebo (up to 6-month follow-up). Similar results were seen for agalsidase beta. However, one trial (n=26) found a statistically significant difference in pain, favoring agalsidase alfa compared to placebo. No trial reported on the effect of agalsidase alfa on mortality or cardiac/cerebrovascular disease. One trial of agalsidase beta (N=82) found no difference in mortality, renal function, or symptoms or complications of cardiac or cerebrovascular disease over 18 months. (Tier 1)



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In January 2019 three review articles were published on ERT among adult males, adult females and pediatric patients.<sup>222324</sup> Although referenced in all three publications, a separate article with methods has not been published, and the reviews lack several characteristics of high quality systematic reviews: a clear objective, risk of bias assessment within or across studies, and discussion of limitations.<sup>25</sup> Thus, it is not clear the conclusions of the review articles are broadly generalizable.

What are the current treatments and guidelines for Fabry, and do they address presymptomatic detection?

Several treatment guidelines exist for Fabry which address presymptomatic detection along with treatment timing, types, details, changes and duration:

- Wang et al 2011 address diagnostic confirmation and management of presymptomatic individuals.<sup>26</sup>
- Hopkin et al 2016 recommend ERT at symptom development or 8-10 years of age (for males).<sup>27</sup>
- Eng et al 2006 recommend ERT at symptom development or 10-13 years of age (for males).<sup>28</sup>
- Desnick et al 2003 recommend ERT as early as possible after detection, regardless of symptom onset.<sup>29</sup>

European guidelines recommend presymptomatic treatment only for boys with classic variant, family history of severe disease or with undetectable levels of  $\alpha$ -Gal A enzyme activity or high levels of plasma globotriaosylsphingosine (a derivative of the fat that accumulates in Fabry disease).<sup>30</sup>

## Access to Care and Equity of Treatment and Follow-Up

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

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<sup>22</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30775256>

<sup>23</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30413388>

<sup>24</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29785937>

<sup>25</sup> <https://www.sciencedirect.com/science/article/pii/S2214426919300588>

<sup>26</sup> <https://www.ncbi.nlm.nih.gov/pubmed/21502868>

<sup>27</sup> <https://www.ncbi.nlm.nih.gov/pubmed/26546059>

<sup>28</sup> <https://www.ncbi.nlm.nih.gov/pubmed/16980809>

<sup>29</sup> <https://www.ncbi.nlm.nih.gov/pubmed/12585833>

<sup>30</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30941742>

Please see <https://www.orpdl.org/drugs/drugclass.php?cid=1164> for prior authorization documents and other reference documents for Lysosomal Storage Disorders, including Fabry treatments.

**ICD-10 code:** E75.21 Fabry (-Anderson) disease

**Location on Prioritized List:**

Oregon's legislature approved funding for lines 1-469 of the prioritized list for January 1, 2018. Fabry appears on lines 60, 71, 100, 292, and 345 and is therefore on the funded region of the Prioritized List.

**Location of Fabry Disease (E75.21) on the Oregon Prioritized List\***

Line number	Description	Guideline Notes
Line 60:	METABOLIC DISORDERS Treatment: MEDICAL THERAPY	64,65
Line 71:	NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES (See Coding Specification) Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., G-TUBES, J-TUBES, RESPIRATORS, TRACHEOSTOMY, UROLOGICAL PROCEDURES)	6, 64, 65, 129, 170
Line 100:	END STAGE RENAL DISEASE Treatment: RENAL TRANSPLANT	-
Line 292:	NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., DURABLE MEDICAL EQUIPMENT AND ORTHOPEDIC PROCEDURE)	6, 64, 65, 170
Line 345:	NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS Treatment: MEDICAL THERAPY	6, 64, 65, 90
Line 377:	DYSFUNCTION RESULTING IN LOSS OF ABILITY	6, 38, 64, 65, 90

	<p>TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION</p> <p>Treatment: MEDICAL THERAPY (SHORT TERM REHABILITATION WITH DEFINED GOALS)</p>	
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\*As of 11/23/19

Are experts available to provide treatment?

The NWRNBS Program contracts with Oregon Health and Sciences University for Lysosomal Storage Disorders medical consultation, including Fabry.

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

To better understand the context of this condition in Oregon, Dr. Amy Yang, a medical geneticist who treats patients with Fabry Disease was interviewed. Dr Yang was asked about the availability and accessibility of treatment, barriers to care for patients and their families and solutions or possible ways to resolve barriers to care. See [Appendix D](#) for a summary of this discussion.

**Question:** Are treatments available and accessible?

Treatment is expensive but thus far has not presented a barrier to patients presenting for care because of support from patient advocacy organizations like National Organization for Rare Disorders who can often find funding for patients who can't afford treatment.

**Question:** What are barriers to care for patients and their families? Below is what is currently in the reports?

Because mainstay treatment for these two disorders for majority of patients is still ERT, which requires biweekly transfusions (60-90 minutes/every two weeks for life), treatment is burdensome but not insurmountable.

**Question:** What are solutions or possible ways to resolve barriers to care?

Patient advocacy groups as well as case management provided by the pharmaceutical companies have reduced many of these barriers to care.

**Question:** Is care and treatment for this condition equitable?

Access to care and treatment is contingent upon access to a specialist familiar with these conditions. However, most patients with these diagnoses in Oregon are receiving access to

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care. The rate limiting step to getting access traditionally is due to delay in diagnosis, which NBS can address.

## NWRNBS Program Impact Assessment

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

- Fiscal analysis
- Availability of specialized medical consultancy services.
- Capacity and expertise to implement and maintain testing and reporting
- Capacity and expertise to implement and maintain follow-up and education for providers and parents
- Assessment of the impact of implementing screening for NWRNBS program partners

### Results

#### Fiscal Analysis

The removal of Fabry from the Oregon screening panel would reduce costs associated with second tier testing and reagents costs.

#### Availability of Medical Consultants

The Northwest regional Newborn Bloodspot Screening (NWRNBS) program currently contracts with OHSU for medical expertise for Lysosomal Storage Disorders so the expertise necessary for medical consultation currently exists for the program.

#### Capacity and expertise for testing and reporting

The program has sufficient capacity and expertise for testing. There would be fewer retests on specimens, fewer inconclusive results that require additional collections and less send outs for second tier testing.

#### Capacity and expertise for follow-up and education for providers and parents

Currently there is limited follow-up staff capacity for follow-up activities related to abnormal results for Lysosomal Storage Disorders. There would be less tracking of second tier results, updating report results, and referrals to OHSU. In addition, there is limited follow-up capacity for data analysis and educational outreach.

#### Assessment of the impact for NWRNBS program partners

The program reached out to New Mexico and Saipan by e-mail on to ask the following questions:

- What do you foresee the impact of Oregon removing Fabry to be for your jurisdiction? What about Gaucher?

- Is there any other feedback that you would like to provide for us regarding the possible removal of these two disorders and the impact on your jurisdiction? Are there any factors for your jurisdiction that we should be aware of?

Saipan provided feedback that removing Fabry and Gaucher from the Oregon screening panel would not impact them because their infants are not currently screened for Fabry and Gaucher.

New Mexico provided feedback that:

- NM state legislation in 2010 to implement 5 LSD's: Gaucher, Fabry, Pompe, Krabbe and Niemann pick.
- NM put a clause in the legislation when feasible and technology available for the testing.
- NM knew Oregon would be doing a pilot Oct 1st of 2018 with 3 out of the 5 required for our state.
- May 2019 Oregon presented the data to NM on high frequency of false positive results needing second tier testing and lack of long-term outcome data. So Fabry and Gaucher were not recommended at this time.
- Oregon mentioned the possibility of looking at a different platform that may decrease the false positives and this may cut down the need for several specimens going for second tier testing but unsure.
- NM at this point due the legislative law since 2010 in the future may be forced to look for another contractor with newborn screening capacity to meet more of our screening needs.
- NM at this point does not have the capability to remove the LSD legislation from our panel.

## Appendix A: Systematic Literature Review

1. Query PubMed, Cochrane, Scopus
2. Fabry inclusion/exclusion criteria:
  - Article language is English
  - Publication date is 11/1/2017, 3 months prior to literature review date of ClinGen review (4/26/2018)
  - Not Full-text article
  - No original data or analyses
  - No Key Topic Areas or Key Topic Questions (KTA/KTQ) addressed (see table below)
  - No human subjects with Fabry
  - Other (includes sample size requirements not met)
  - Search criteria are below

### PubMed (core clinical journals)

Search	Add to builder	Query	Items found	Time
<a href="#">#50</a>	<a href="#">Add</a>	Search (" <b>Fabry Disease</b> "[Mesh] or " <b>Fabry</b> "[tiab]) Sort by: <b>Author</b> Filters: <b>Publication date from 2018/01/01; Humans; Core clinical journals</b>	<a href="#">10</a>	17:26:07

**PubMed (pediatric literature)**

Search	Add to builder	Query	Items found	Time
#34	<a href="#">Add</a>	Search ((((((fabry disease[MeSH Major Topic] AND fabry[Title/Abstract])) AND (Humans[Mesh])) AND (("Pediatrics"[Mesh] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR juvenile[tiab] OR juveniles[tiab] OR "Infant"[Mesh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR childhood[tiab] OR preadolescent[tiab] OR preadolescents[tiab] OR prepubescent[tiab] OR "Adolescent"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR youth[tiab] OR youths[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab])) NOT ("Adult"[Mesh] NOT ("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh])) AND (Humans[Mesh]))) AND (("2018/01/01"[PDat] : "3000/12/31"[PDat]) AND Humans[Mesh] AND English[lang])	36	17:26:07

**Cochrane**

Searched for “Fabry” from 1/01/2018 to present (11/23/2019) No citations identified

**Scopus**

History Count	Search Terms	Results
36	#33 and #34 and #35	<a href="#">6 document results</a>
35	TITLE-ABS-KEY ( fabry AND disease )	<a href="#">6,222 document results</a>
34	(( ( TITLE-ABS-KEY ( fabry AND disease ) AND DOCTYPE ( ar ) AND PUBYEAR > 2017 )) AND NOT INDEX ( medline ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) )	<a href="#">77 document results</a>

33	( TITLE-ABS-KEY ( infant* ) OR TITLE-ABS-KEY ( child* ) OR TITLE-ABS-KEY ( p*ediatric* ) OR TITLE-ABS-KEY ( juvenile* ) OR TITLE-ABS-KEY ( *adolescent* ) OR TITLE-ABS-KEY ( youth* ) OR TITLE-ABS-KEY ( teen* ) ) AND NOT ( TITLE-ABS-KEY ( adult ) OR TITLE-ABS-KEY ( elderly ) OR TITLE-ABS-KEY ( embryo ) OR TITLE-ABS-KEY ( fetus ) OR TITLE-ABS-KEY ( middle AND age* ) )	<a href="#">2,835,728 document results</a>
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**Key Questions for Literature Review\***

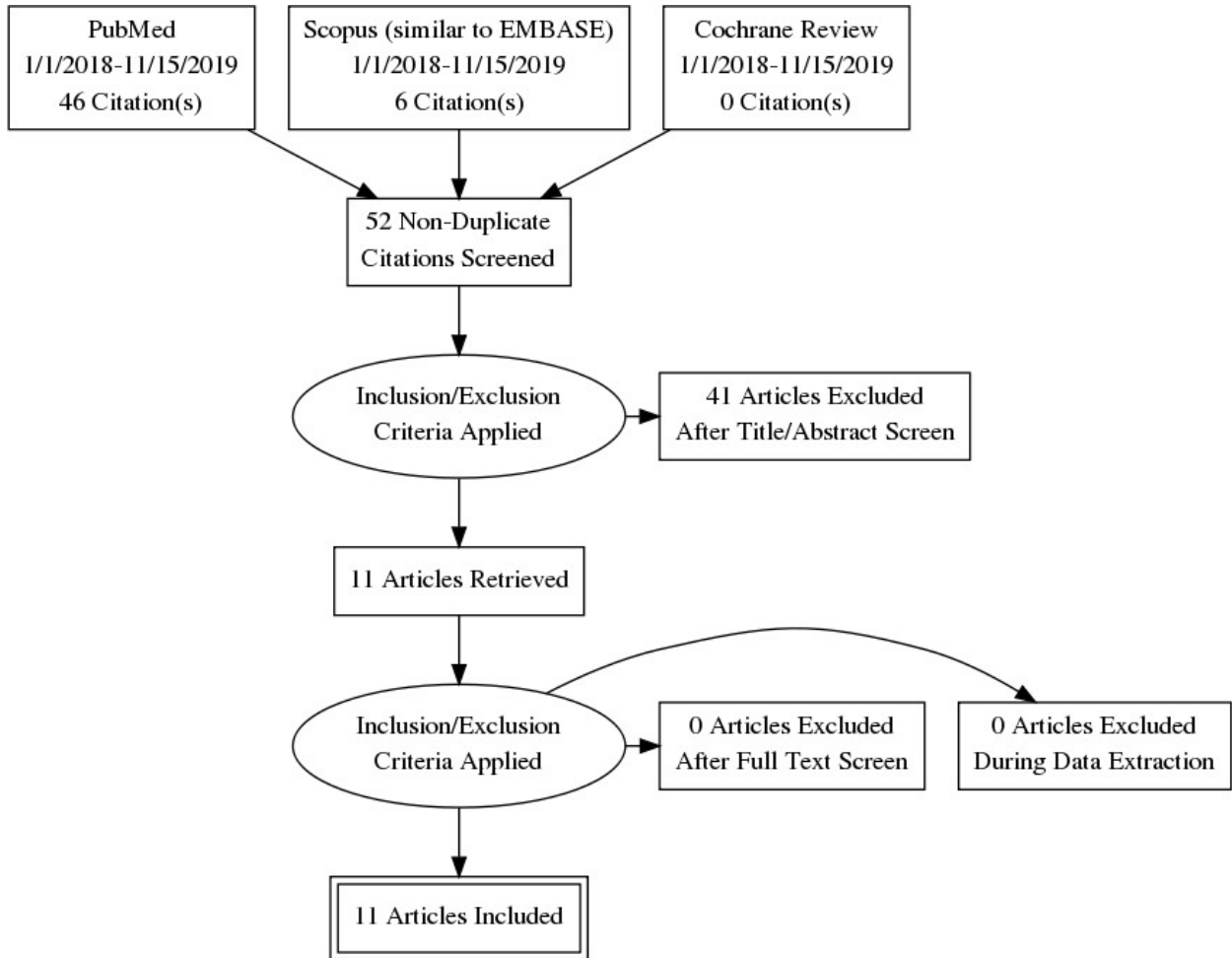
Key Question	Population	Interventions	Comparators	Outcomes
Key Question 1: What is the natural history and epidemiology of this condition? Typical course of disease (ages of reported onset, symptoms, diagnosis, treatment initiation, death; is the condition well-defined?) what phenotypes affect children/newborns? what factors predict morbidity/mortality? What are the estimated incidence rates for phenotypes associated with this condition?	n/a	n/a	n/a	n/a
Key Question 2: What is the direct and indirect evidence that newborn screening for this condition leads to improved health outcomes compared to usual clinical care?	n>5	Any care received subsequent to the screening test	Contemporaneous or historical controls affected by this condition	Overall Survival; Survival with major morbidity
Key Question 3: Screening and Short-term follow up/diagnostic confirmation methods	n>5, Newborns without known diagnosis of, or risk factor for this condition; deidentified dried-blood spots	Any screening methods for this condition conducted in the first month of life. For analytic validity, studies should also report proficiency	Diagnosis by genotype and follow-up evaluation or genotype alone Outcomes: Sensitivity, specificity, positive predictive value, negative predictive value, reliability, and yield (i.e., prevalence)	n/a

Key Question 4: What are the harms associated with newborn screening for this condition to the individual or the family?	n>5, Newborns screened for this condition and their families		Any newborn screening for this condition	Systematic assessment of harms, including harm related to false-positive screening results, false-negative screening results, early identification of later-onset disease, or perceived harms or acceptability of screening for this condition
Key Question 5: What are the standard treatments for this condition and evidence for their effectiveness? Do follow-up protocols exist for the management of this condition that do not require immediate initiation of treatment? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes? Does early initiation of treatment improve primary health outcomes (overall survival, other important health outcomes) when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype?	n>3, Newborns and others diagnosed with this condition through newborn screening or other methods of presymptomatic detection and diagnosis in childhood	Any approved disease-modifying therapy	Contemporaneous or historical controls with this condition disease or no comparison	Primary endpoint/outcome measures for Fabry: Death, neurologic or cardiovascular events
Key Question 8: What are the harms associated with treatments for this condition in early childhood, for symptomatic and presymptomatic patients? How does this vary by phenotype?	Any child (or caregiver of child) identified with this condition receiving a current treatment	Any approved disease-modifying therapy	Any	Any

\*Key Questions 6 and 7 concern intermediate and secondary health outcomes and were considered to be outside the scope of this review.

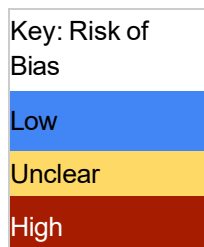


## Appendix B: PRISMA Diagram



## Appendix C: Included Articles and Grading

Quality Assessment of Evidence: Screening and Treatment Articles



Screening studies

Screening questions			Patient Selection		Newborn Screening Test		
Publication ( <i>First Author, Year of Publication</i> )	Therapy	Global Publication Rating	Risk of Bias  1. Was a consecutive or random sample of samples screened? 2. Did the study avoid inappropriate exclusions? 3. Could the selection of patients have introduced bias?	Applicability  1. Was this a pilot test of a newborn screening test (i.e., not anonymized samples)? 2. Did newborn screening occur within a defined population? 3. Is there concern that the study does not reflect population-based newborn screening?	Conduct and Interpretation of Test  1. Were the results of the newborn screening test interpreted without knowledge of the diagnostic test results? 2. Was the threshold for a positive screen clear? 3. Was the threshold for a positive screen pre-specified? 4. Were alternative thresholds for a positive screen clear? 5. Could the conduct	Reference Standard  1. Is the reference standard likely to correctly classify the condition? 2. Was the reference standard interpreted without knowledge of the newborn screening result? 3. Could the reference standard, its conduct, or its interpretation have introduced bias?	Flow and Timing  1. Did all positive newborn screens receive the reference standard? 2. Was the same reference standard used for all who received diagnostic testing? 3. Were all screening results used in the analysis? 4. Could the newborn screening flow have introduced bias?

					or interpretation of the screening introduce bias?		
Burton, 2017	Screening	Strong	Strong	Strong	Strong	Strong	Strong
Hopkins, 2015	Screening	Strong	Strong	Strong	Strong	Strong	Strong
Wasserstein, 2019	Screening	Strong	Strong	Strong	Strong	Strong	Strong
Burlina, 2018	Screening	Strong	Strong	Strong	Strong	Strong	Strong

## Appendix D: Discussion with Experts

Medical Consultant	Title	Institution/Affiliation	Date interviewed
<b>Amy Yang</b>	Medical Geneticist	Oregon Health and Science University	11/7/2019. Updated February 2021.

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## Summary of discussion with Dr. Amy Yang

Interview conducted on 11/7/2019. Updated in February 2021.

Thank you for agreeing to talk to me about Fabry.

The objective of this discussion is for you to provide input and guidance as to the methods I use for a literature review before I begin collecting literature. I would also like to hear from you about equity in treatment and care for this condition. Because the info you provide me will be summarized in an evidence report, I would like to transcribe this discussion and summarize it for appending to the report. Is that ok with you?

**Dr. Yang's response:** Yes

**Question:** Let's begin. Can you please tell me a little bit about your training and background in caring for patients with Fabry disease?

**Dr. Yang's response:**

- Pediatric residency
- Then, clinical genetics residency at Mt. Sinai for 2 yrs (this is the place a large proportion of New Yorkers are referred to for genetic condition followup); meant a lot of experience with newborn screening
- At Mt. Sinai, saw ~50 patients with Fabry, and followed
- At OHSU, we have over 50 patients with Fabry we are actively managing.

**Question:** Next, looking at methods for the literature review, can you tell me your thoughts on outcomes for key questions I've highlighted? For example, for Fabry, does it make sense to restrict to classic vs later-onset cases? Or male vs females?

**Dr. Yang's response:** Not sure about the right answer. Males with classic Fabry are suffering, even in childhood, and we will pick these people up along with asymptomatic female. Additionally, on NBS, we can pick up males and females with atypical disease. Problem is not that we don't know the natural history for those with atypical disease. How many of those w/ atypical disease may go through life and be well without treatment, and for how many years? These are the questions we do not yet have an answer.

However, I feel this is part of the burden of any NBS initiate, to eventually learn not only classic disease presentation, but the full spectrum of disease. Thus, we will be identifying those w/ atypical, milder disease on NBS, but it will be important for us to follow these patients and learn from them.

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**Question:** For Key Question 2 (What is the direct and indirect evidence that newborn screening for this condition leads to improved health outcomes compared to usual clinical care?) are the appropriate outcomes: Overall Survival; Survival with major morbidity?

I think we can look at our Oregon NBS experience so far since 2018. I will present this during our meeting.

**Question:** For Key Question 5 (What are the standard treatments for this condition and evidence for their effectiveness?) are the appropriate outcomes death, neurologic or cardiovascular events?

Since these two conditions do not present with neonatal or early infantile death, the standard guidelines on efficacy of a NBS program for these conditions may not apply. Perhaps efficacy of a NBS program for Fabry or Gaucher should be determined not by death or severe neurological or cardiovascular outcomes in infancy, but by efficacy in shortening the delay to diagnosis and treatment.

**Question:** Any other thoughts about methods for the lit review before we move on? No

**Question:** What is the availability and accessibility of treatment. See additional word document on this.

**Question:** What are some barriers to care for patients and their families?

**Dr. Yang's response:** Don't know if they are barriers but more like burdens. I haven't encountered a family that says this is too much.

ERT requires IV infusion. Requires care at a medical center. Some families have to drive an hour (every 2 weeks for life) to get a 2-3 hour infusion.

For example, I treat a family with Fabry:

- Mom gets infusion at clinic 30 min away
- Family has to drive the kid 90 min to get an infusion in a different clinic because mom's clinic doesn't see kids.

**Question:** What are some solutions or possible ways to resolve barriers to care?

**Dr. Yang's response:** Cost: companies fund organizations that help with copays, transportation. If a family speaks up, we can usually help out by reaching out to patient groups like NORD - National Organization for Rare Diseases get funds from drug manufacture for certain disorders or PRI, another organization that gets funds from pharmaceutical companies. This helps families with copays (high deductible plan or maxed out).

**Question:** Are there other experts I should contact (as time allows) for their input?

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**Dr. Yang's response:** Anna Davis, genetic counselor

**Question:** Is there other context that I should know about the disease?

**Dr. Yang's response:** I see patients w/ Fabry as adults that have kidney disease that were never diagnosed as kids, and they recall childhood pain and GI symptoms that were undiagnosed. They certainly could have benefited from earlier diagnosis and earlier treatment which would halt or slow progression of their kidney and heart disease as adults.

Fabry disease is not your traditional newborn screening condition in that patients do not present in early childhood with death or catastrophic events.

Fabry has nonspecific signs and symptoms in childhood but heart and kidney disease present later. If using traditional NBS criteria for childhood disease, Fabry would not qualify.

There are other potential issues with NBS, for example:

- Fabry is X-linked:
  - females are potentially less affected but we will pick them up with screening anyway.
  - Picking up a secondary finding, secondary diagnosis: for example, can potentially pick up a female with Turner syndrome (missing an X chromosome) or Klinefelter (male with extra X). Turner potentially has clinical issues. If we look at Klinefelter, these guys have testosterone deficiency and are infertile. Can feel slightly different from other guys but look normal, can have normal lives. Nothing to note on exam until they get tested for fertility issues (typically as adults). Male babies with Klinefelter have been picked up by newborn screening.

In X-linked disorders can pick up these secondary findings. Nowhere in the legislature is there guidance about giving these findings back to the family. In genetics lab, always consent patients first to risk of secondary findings. Problem with newborn screening is families don't consent for this. Newborn screening is an opt out. Most families don't know baby is being screened. Nurse says "baby's first blood test." Doesn't provide any other guidance. Family could potentially get very upset.

One of the considerations for Fabry NBS is we do not have all the systems in place to do right by the families for all possible outcomes; we don't have any mechanisms for giving these secondary findings to patients. All other conditions on the panel are autosomal recessive.

**Question:** What are potential harms for screening?

**Dr. Yang's response:**

There can be potential harm in identifying females w/ Fabry who may remain asymptomatic throughout their lifetime. There can be potential over medicalization of them, as well as the

males with atypical Fabry disease who may not experience any childhood symptoms, but still subjected to yearly evaluations and lab work.

## Appendix E: Included Articles

key	title	year	journal	volume	issue	authors	url
28728811	Newborn Screening for Lysosomal Storage Disorders in Illinois: The Initial 15-Month Experience.	2017	The Journal of pediatrics	190		Burton, Barbara K and Charrow, Joel and Hoganson, George E and Waggoner, Darrell and Tinkle, Brad and Braddock, Stephen R and Schneider, Michael and Grange, Dorothy K and Nash, Claudia and Shryock, Heather and Barnett, Rebecca and Shao, Rong and Basheeruddin, Khaja and Dizikes, George	<a href="https://www.ncbi.nlm.nih.gov/pubmed/28728811">https://www.ncbi.nlm.nih.gov/pubmed/28728811</a>
28723748	Clinical characteristics and mutation spectrum of GLA in Korean patients with Fabry disease by a nationwide survey: Underdiagnosis of late-onset phenotype.	2017	Medicine	96	29	Choi, Jin-Ho and Lee, Beom Hee and Heo, Sun Hee and Kim, Gu-Hwan and Kim, Yoo-Mi and Kim, Dae-Seong and Ko, Jung Min and Sohn, Young Bae and Hong, Yong Hee and Lee, Dong-Hwan and Kook, Hoon and Lim, Han Hyuk and Kim,	<a href="https://www.ncbi.nlm.nih.gov/pubmed/28723748">https://www.ncbi.nlm.nih.gov/pubmed/28723748</a>

						Kyung Hee and Kim, Woo-Shik and Hong, Geu-Ru and Kim, Su- Hyun and Park, Sang Hyun and Kim, Chan-Duck and Kim, So Mi and Seo, Jeong- Sook and Yoo, Han-Wook	
25444528	Lysosomal storage disorder screening implementation: findings from the first six months of full population pilot testing in Missouri.	2015	The Journal of pediatrics	166	1	Hopkins, Patrick V and Campbell, Carlene and Klug, Tracy and Rogers, Sharmini and Raburn-Miller, Julie and Kiesling, Jami	<a href="https://www.ncbi.nlm.nih.gov/pubmed/25444528">https://www.ncbi.nlm.nih.gov/pubmed/25444528</a>
27931613	Later Onset Fabry Disease, Cardiac Damage Progress in Silence: Experience With a Highly Prevalent Mutation.	2016	Journal of the American College of Cardiology	68	23	Hsu, Ting- Rong and Hung, Sheng- Che and Chang, Fu- Pang and Yu, Wen-Chung and Sung, Shih-Hsien and Hsu, Chia- Lin and Dzhagalov, Ivan and Yang, Chia- Feng and Chu, Tzu-Hung and Lee, Han-Jui and Lu, Yung- Hsiu and Chang, Sheng-Kai and Liao, Hsuan-Chieh and Lin, Hsiang-Yu and Liao, Tsan-Chieh and Lee, Pi-Chang and Li, Hsing- Yuan and Yang, An-	<a href="https://www.ncbi.nlm.nih.gov/pubmed/27931613">https://www.ncbi.nlm.nih.gov/pubmed/27931613</a>



						Hang and Ho, Hui-Chen and Chiang, Chuan-Chi and Lin, Ching-Yuang and Desnick, Robert J and Niu, Dau- Ming	
rayyan-45835400	Newborn screening for lysosomal storage disorders in Oregon from results to clinical findings: a 6+ month retrospective	2019	Poster Presented at the American Society of Human Genetics 2019 Annual Meeting			A. Yang, A. Dennis, D. Koeller, S. Denniston, L. Flint, C. Biggs.	
30941742	Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients.	2019	Clinical genetics	96	2	Germain, Dominique P and Foulhoux, Alain and Decramer, Stéphanie and Tardieu, Marine and Pillet, Pascal and Fila, Marc and Rivera, Serge and Deschênes, Georges and Lacombe, Didier	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30941742">https://www.ncbi.nlm.nih.gov/pubmed/30941742</a>

30775256	The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease: A systematic literature review by a European panel of experts.	2019	Molecular genetics and metabolism reports	19		Germain, Dominique P and Elliott, Perry M and Falissard, Bruno and Fomin, Victor V and Hilz, Max J and Jovanovic, Ana and Kantola, Ilkka and Linhart, AleÅj and Mignani, Renzo and Namdar, Mehdi and Nowak, Albina and Oliveira, JoÃo-Paulo and Pieroni, Maurizio and Viana- Baptista, Miguel and Wanner, Christoph and Spada, Marco	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30775256">https://www.ncbi.nlm.nih.gov/pubmed/30775256</a>
30093709	The New York pilot newborn screening program for lysosomal storage diseases: Report of the First 65,000 Infants.	2019	Genetics in medicine : official journal of the American College of Medical Genetics	21	3	Wasserstein, Melissa P and Caggana, Michele and Bailey, Sean M and Desnick, Robert J and Edelman, Lisa and Estrella, Lissette and Holzman, Ian and Kelly, Nicole R and Kornreich, Ruth and Kupchik, S Gabriel and Martin, Monica and Nafday, Suhas M and Wasserman, Randi and Yang, Amy and Yu, Chunli and Orsini, Joseph J	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30093709">https://www.ncbi.nlm.nih.gov/pubmed/30093709</a>

29785937	The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease - A systematic literature review by a European panel of experts.	2019	Molecular genetics and metabolism	126	3	Spada, Marco and Baron, Ralf and Elliott, Perry M and Falissard, Bruno and Hilz, Max J and Monserrat, Lorenzo and TÄ,ndel, Camilla and Tyłki-Szymańska, Anna and Wanner, Christoph and Germain, Dominique P	<a href="https://www.ncbi.nlm.nih.gov/pubmed/29785937">https://www.ncbi.nlm.nih.gov/pubmed/29785937</a>
30413388	The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease - A systematic literature review by a European panel of experts.	2019	Molecular genetics and metabolism	126	3	Germain, Dominique P and Arad, Michael and Burlina, Alessandro and Elliott, Perry M and Falissard, Bruno and Feldt-Rasmussen, Ulla and Hilz, Max J and Hughes, Derralynn A and Ortiz, Alberto and Wanner, Christoph and Weidemann, Frank and Spada, Marco	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30413388">https://www.ncbi.nlm.nih.gov/pubmed/30413388</a>
26546059	The management and treatment of children with Fabry disease: A United States-based perspective.	2016	Molecular genetics and metabolism	117	2	Hopkin, Robert J and Jefferies, John L and Laney, Dawn A and Lawson, Victoria H and Mauer, Michael and Taylor, Matthew R and Wilcox, William R and Fabry Pediatric	<a href="https://www.ncbi.nlm.nih.gov/pubmed/26546059">https://www.ncbi.nlm.nih.gov/pubmed/26546059</a>

						Expert Panel, [Collective Name]	
21502868	Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals.	2011	Genetics in medicine : official journal of the American College of Medical Genetics	13	5	Wang, Raymond Y and Bodamer, Olaf A and Watson, Michael S and Wilcox, William R and ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases, [Collective Name]	<a href="https://www.ncbi.nlm.nih.gov/pubmed/21502868">https://www.ncbi.nlm.nih.gov/pubmed/21502868</a>
29143201	Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North East Italy.	2018	Journal of inherited metabolic disease	41	2	Burlina, Alberto B and Polo, Giulia and Salviati, Leonardo and Duro, Giovanni and Zizzo, Carmela and Dardis, Andrea and Bembi, Bruno and Cazzorla, Chiara and Rubert, Laura and Zordan, Roberta and Desnick, Robert J and Burlina, Alessandro P	<a href="https://www.ncbi.nlm.nih.gov/pubmed/29143201">https://www.ncbi.nlm.nih.gov/pubmed/29143201</a>



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