HOUSE HEALTH COMMITTEE

INFORMATIONAL MEETING ON THE PENNSYLVANIA NEWBORN SCREENING PROGRAM

Tuesday, October 28th, 2025

9:00am

205, Ryan Office Building

Harrisburg, PA

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1. Call to Order

2. Attendance

First Panel:

Jerry Vockley, MD, PhD
Newborn Screening and Follow-up Technical Advisory Board, Newborn Screening Program

Debra Bogen, MD, FAAP, FABM
Secretary of Health, Commonwealth of Pennsylvania

Lesa Brackbill
Board Member, KrabbeConnect

Second Panel:

Aviva Rosenberg
Co-Founder/Co-President, Gaucher Community Alliance

Amy Aikins
Director of Patient Access, Little Hercules Foundation

3. Adjournment

Newborn screening priorities.

Good morning and thank you for the opportunity to bring my perspective on newborn screening to this meeting.

My name is Jerry Vockley, MD, PhD. I am the Cleveland Family Endowed Professor in Pediatric Research in the University of Pittsburgh School of Medicine, Professor of Human Genetics in the School Public Health, Chief of Genetic and Genomic Medicine for the University of Pittsburgh Medical Center, and Director of the Center for Rare Disease Therapy for the UPMC Children's Hospital of Pittsburgh.

I have served for many years on the Pennsylvania Newborn Screening Technical Advisory Board (NBSTAB), the group that helps guide newborn screening in PA, including 8 years as its chair. It is a committee mandated by State legislation that established newborn screening in PA and as its name suggests, advises the PA Secretary of Health and its newborn screening program on matters pertaining to newborn screening. It helps monitor the program's organization implementation and performance metrics, and advises on needed changes to program operation. One of its most important functions is to recommend adding new disorders to the PA newborn screening panel. I also served on the HRSA Secretary's Advisory Committee for Inherited Diseases in Children and Newborns. This is the group that, until its recent disbandment, developed and guided the federally curated Recommended Uniform Screening Panel for newborns, known as the RUSP. It was composed of government health officials, academic newborn screening professionals, and members of parent advocacy groups. As of 2025, this panel includes 38 core conditions and 26 secondary conditions. Core conditions are considered essential for newborn screening, while the secondary conditions may be detected during screening for the core conditions. States are not required to implement the RUSP, but most do so. In fact, the specific conditions included in some states' newborn screening programs, including PA, follow the RUSP by legislative mandate. Until its discontinuation, the RUSP was curated with the utmost scientific vigor, with the addition of new disorders when supported by the best available medical evidence.

The loss of the HRSA-sponsored committee provides both opportunities and challenges in the management of newborn screening programs in the coming years. As mentioned, PA law provides a mechanism for direct nomination of conditions to be added to the State newborn screening panel, allowing for careful review by the NBSTAB, with

recommendations provided to the PA Secretary of Health. The nomination process starts with the submission of a nomination form by a PA constituent, review of the medical literature on the disease with a focus on newborn screening tests and possible outcomes, and subsequent debate and vote by the TAB on the risks and benefits to all babies about inclusion of the disease in the newborn screening panel. This careful, methodical, and scientific process is the most appropriate mechanism for bringing new conditions to the state newborn screening panel, allowing for wise use of public health dollars. Recently, the NBSTAB added a new condition to the PA newborn screen known as metachromatic leukodystrophy, a devastating disease that leads to neurodegeneration and death in infancy, as a result of a constituent application. In short, the system works. I was gratified that the HRSA Secretary ultimately released a long-delayed opinion that coincided with ours.

I strongly urge the committee to allow the PA NBS TAB to do its good work serving the babies and families of the Commonwealth while ensuring a medically sound and economically robust newborn screening program. Of note, these recommendations are congruent with a recent report on newborn screening the the National Institute of Medicine and the introduction for reauthorization of the Newborn Screening Saves Lives Act into Congress (https://nap.nationalacademies.org/catalog/29102/newborn-screening-in-the-united-states-a-vision-for-sustaining). I also urge the legislature to continue to provide the funding necessary to bring this critical service to its constituents. Thank you for your attention.

Department of Health Written Statement

For the House Health Committee

Newborn Screening Informational Hearting

October 28, 2025

Chairs Frankel and Rapp, and members of the House Health Committee, thank you for the opportunity to talk about this important issue, and highlight the life changing work being done in the field of newborn screening. As a pediatrician who cared for newborns for decades, I want to emphasize how vital newborn screening is to families here in Pennsylvania and across the country.

Program Background

Pennsylvania's Newborn Child Screening and Follow-up Program was first established in 1965. It has evolved over the past six decades to keep pace with scientific discovery and innovation. The Program's goal is to eliminate or reduce mortality, morbidity and disabilities by screening for disorders included in the Pennsylvania Newborn Screening Panel to help affected babies live as long and as full of a life as possible.

The current program has three components. The first component is blood spot testing that screens for over 35 genetic conditions, such as congenital adrenal hyperplasia, congenital hypothyroidism, sickle cell disease, phenylketonuria and galactosemia to name a few. Second, the program screens for critical congenital heart defects (CCHD); and third, for newborn hearing loss. Together, these screening programs focus on diseases that present in the first year of life for which there are effective screening tests and effective treatment available to alter the course of the disease and improve outcomes.

Pennsylvania's program successfully screens over 95% of newborns born in the Commonwealth for all three components. The key is the importance of early recognition and treatment in altering the course of disease.

Newborn screening tests are just that – screenings. In nearly all cases, a positive screening test needs to be followed by additional, confirmatory testing.

It should also be noted that the newborn screen does not test for all diseases that affect newborns and that no test is perfect. Therefore, parents and health care providers must remain vigilant; even in the face of a normal newborn screen, if they suspect the infant has a medical problem they should seek further testing.

Staff from the Department of Health Newborn Screening Program work with all hospitals, midwives, and birthing centers to ensure that all newborns are offered all the screenings and when test results are inconclusive or unacceptable, families and physicians are notified and offered the opportunity to have further testing.

Newborn Screening and Follow-up Technical Advisory Board (NSFTAB)

The NSFTAB was renamed as a result of Act 133 of 2020, previously having been called the Newborn Screening and Technical Advisory Committee. The Board is tasked with providing recommendations and guidance to the Department of Health regarding newborn screening and works closely with the laboratories to ensure that screenings are accurate and are performed using current medical standards. NSFTAB approval is required for adding new screening tests to the screening panel. As required by the Act, the Board has 15 members (including pediatric physicians and geneticists) who are experts in various fields of newborn health. The Board meets 3 times per year to discuss new topics relevant to Pennsylvania's screening program, analyze new scientific data, and review screening applications presented to the board for consideration.

Program Highlights

Act 133 of 2020 requires the Department to add all tests that are recommended for inclusion on the Recommended Uniform Screening Panel (RUSP) by the federal Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) within 2 years. It should be noted that the ACHDNC was disbanded by the current federal administration and there has been no information on when, or if, it will be reconvened.

Currently Pennsylvania is one of only two states that screen for every condition on the RUSP. Mucopolysaccharidosis Type II Disorder (MPS II) was added to the RUSP on August 2, 2022, and to the PA newborn screening panel on July 1, 2023.

There is also a path for new conditions to be added that are not on the RUSP. For example, beginning in January 2026, PA added screening for Metachromatic Leukodystrophy (MLD). This condition, which is not currently on the RUSP, was reviewed by the NSFTAB, submitted for public comment and approved for addition. PA will be the second state to begin universally screening for this condition. (NY began screening just last month)

- There are three categories of screening results to identify and treat disorders. These screening categories are genetic, CCHD, and hearing. Recent results of these three categories of screenings:
    - Blood spot genetic screenings
        - In 2023, 307 infants were diagnosed with potential genetic disorders

        - In 2024, 326 infants were diagnosed with potential genetic disorders
    - CCHD screening
        - In 2023, 85 infants were diagnosed with CCHD
        - In 2024, 120 infants were diagnosed with CCHD
    - Hearing screenings
        - In 2023, 172 infants were diagnosed with potential hearing disorders
        - In 2024, 189 infants were diagnosed with potential hearing disorders
    - Because of these important screenings, hundreds of newborns in Pennsylvania receive life altering and lifesaving early identification and treatments to support their healthiest growth and development.

Other considerations in newborn screening

Newborn screening programs face significant dilemmas and challenges.

First, genetic testing has and will continue to evolve – opening the opportunity to identify more and more diseases in the newborn period with the blood spot testing. For example, some have argued that newborns should have whole genome sequencing – which can identify thousands of diseases. Some of these diseases will not present for decades (e.g. Huntington's chorea); for others, there is an increased risk but not absolute certainty that they will occur (e.g. breast cancer). There is concern that identifying diseases that will happen far beyond the immediate newborn period create distress for the parents. There is also the concern that identifying diseases that don't present until adulthood would violate the privacy of those adults. Others feel knowledge is power and all diseases should be identified as early as possible.

In addition, there is the issue of limited resources – including health care resources and financial resources. Infants identified with a newborn condition from the screen program are referred to a pediatric specialist for further testing, evaluation and treatment. There is a shortage of pediatric subspecialist even before expanding the need for them.

While Pennsylvania remains a state with a lower cost to hospitals/midwives for screening, there is a cost to the testing. Currently the cost of the PA newborn screening program is shared between the state and health care organization, with each paying approximately half of the cost of the screening panel. The cost per infant is approximately $57 paid by health care providers and $57 paid by the state. Each addition of a new disease/test increases the cost of the newborn screen by approximately $6 per infant.

Again, I appreciate the opportunity to highlight this extremely beneficial program offered by the Department of Health to ensure the health and safety of our newborns.

Testimony on the Integrity of Newborn Screening Policy

Good morning, and thank you for the honor of participating in this important discussion.

My name is Lesa Brackbill, and I am the parent advocate who helped make **Act 133 of 2020** a reality. To understand the importance of what we achieved, it is essential to understand the systemic issues that existed in Pennsylvania and what led me to pursue change.

Like so many in this space, I never imagined that I would be speaking to you today about Newborn Screening. But, on February 13, 2015, my life changed forever. My six-month-old daughter, **Victoria, was diagnosed symptomatically with Krabbe disease,** a terminal genetic disorder. After a six-week diagnostic odyssey, we were told three devastating things: our daughter was dying, there was nothing we could do, and, **"if we had caught it at birth, we could have treated it."** Those words became the catalyst for my advocacy. My mission became clear: to ensure no other family would endure the same fate. Victoria passed away in March 2016, at just twenty months of age.

Through research and conversations over the past ten years in this space, I've become a **state-level expert** on the process of newborn screening condition addition. My work has focused specifically on building relationships with state NBS leaders in order to understand and navigate the operational dynamics of state programs, to build relationships not barriers:

My advocacy is rooted in **direct collaboration**: I have established working relationships with **over half of all state newborn screening programs**, connections reinforced at when states seek me out for information.

My experience has consistently shown that Advisory Boards are partners, not adversaries, in effective NBS implementation.

The Broken System and the Need for Change

Three weeks after Tori's death, I attended a PA Newborn Screening Advisory Board meeting to listen and learn. Over the next year, through research and conversations, I uncovered the flaws in Pennsylvania's system. While **Act 148 of 2014** had attempted to add six conditions, it was never implemented because it did not address the system's operational or funding needs. It was a perfect example of a legislative mandate that failed because it didn't fix the core issues or provide necessary resources.

What I learned was that the system was fundamentally broken and unable to adapt to the times. We faced three critical barriers:

- **Authority Gap:** The Advisory Board, composed of scientific and clinical experts, **lacked the authority to add new conditions**. This forced critical medical decisions into the legislative arena.
- **Inequity:** A **"death by ZIP code"** problem existed because not all hospitals screened for all conditions on Pennsylvania's supplemental panel, creating unequal care across the state.
- **Process Frustration:** After a particular request to add a condition was denied by the legislature, the Advisory Board chair, Dr. Vockley, asked in an advisory board meeting, **"Why are we even here?"** They were volunteering their time, expertise, and passion only to be denied during the budget process.

It was that statement that caused me to pivot; my role was far greater than adding a single disease—I needed to be part of improving the entire process to pave the way for all future conditions. It was about filling the **"potholes"** in the road to evidence-based change.

I spent **five years** working with Pennsylvania stakeholders—the NBS program, the hospital association, the insurance federation, medical experts, and fellow advocates—to address these systemic failures. After two initial legislative attempts failed, we succeeded in November 2020. In just 65 days, the bill went from committee to the governor's desk, and my husband and I both cried tears of joy and relief as we watched the vote on television. This is our daughter's legacy.

The final bill, **Act 133 of 2020**, was stronger because it was informed by that comprehensive, collaborative effort over the course of five years.

Act 133 fixed the system by:

- **Empowering the Experts:** The law **empowered** the Advisory Board and the Department of Health to add new conditions based on scientific and clinical evidence, **removing the need for a legislative mandate**.
- **Establishing a Fair Standard:** It ensured that all conditions on the screening panel are mandatory, eliminating the "death by ZIP code" inequity.
- **Stabilizing Funding:** We were able to shift the majority of funding to insurance while maintaining stable funding for the NBS program, which allows for the flexibility to grow the program as science progresses without constant budget request battles.

The law went into effect 2,292 days after my daughter's diagnosis. This was not a quick process, but the work along the way is what has made our NBS program one of the

strongest in the country. Quick progress doesn't always mean effective progress. It also doesn’t mean ethical progress.

Ethical Advocacy: The Means Justify the Ends

It is tempting in advocacy to adopt the philosophy that the **ends justify the means**—that saving a child's life today is worth setting aside processes. But our five-year effort demonstrated the opposite: that the **means must justify the ends**. We were successful because we refused to adopt flawed shortcuts. We focused on building a durable, ethical process based on collaboration and science. When the legislature passed Act 133, they affirmed that our public health decisions must be supported by the experts and the evidence, ensuring the long-term integrity of newborn screening for all conditions.

Defending the Integrity of the Process

Though some might argue that the established process is failing them because it has not yet yielded the result they desire. I respectfully urge you to consider the precedent you would set with a legislative mandate.

When a state hesitates to add a condition to its panel, **advocates must** ask questions, learn what data the experts are missing, and work collaboratively with the advisory boards and state programs to fill those gaps in knowledge. By strengthening the evidence, we ensure the ethics of NBS are sustained.

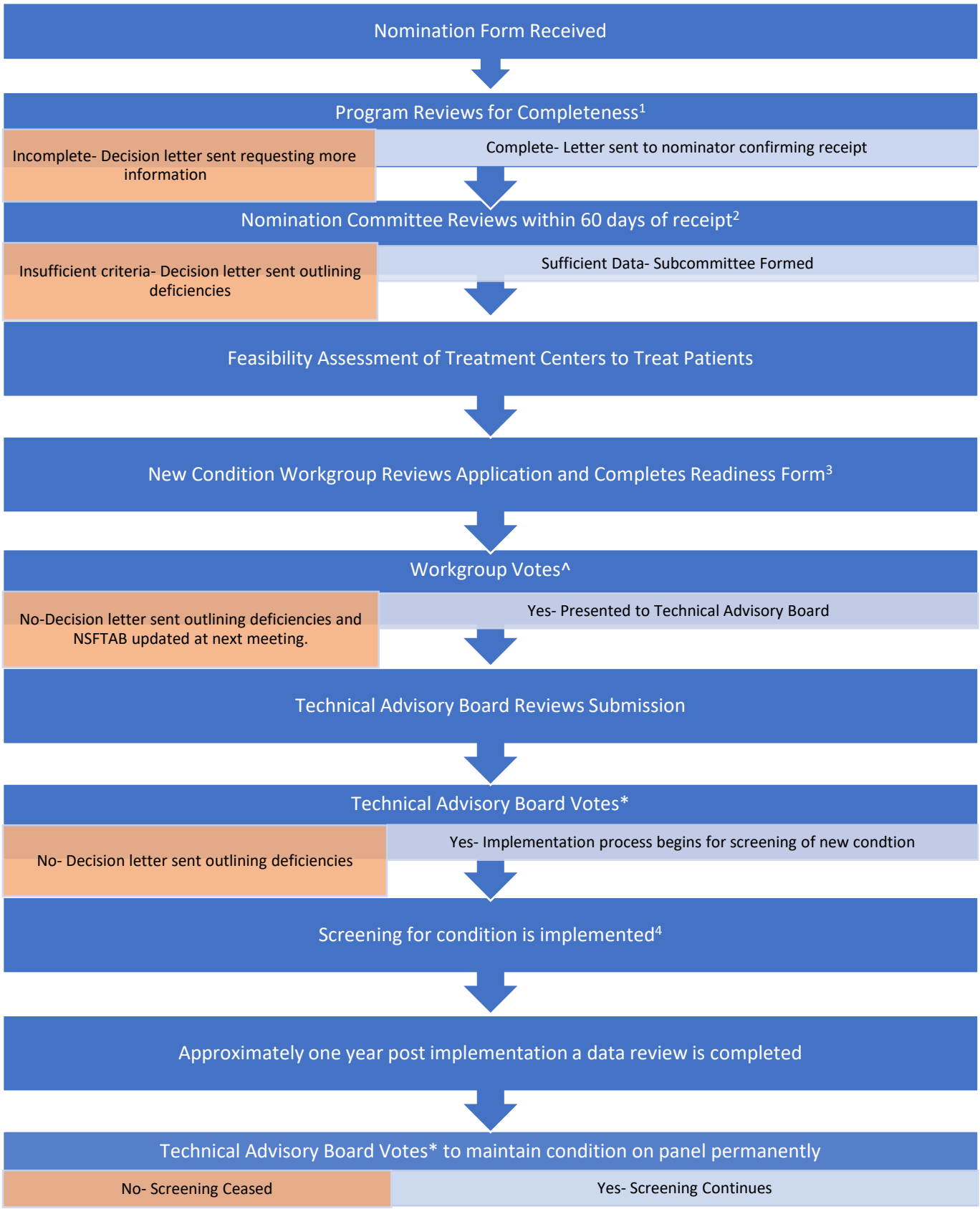
A "No" vote from the Advisory Board is not a failure of the system—it is a successful application of scientific rigor. And, a "No" from the board is not a "No" forever. It is an invitation to fill the evidentiary gaps and come back to the table with stronger data.

We fought for Act 133 precisely to ensure that medical decisions are made by **experts, not by politics**. These experts must serve as the gatekeepers, ensuring that the ethical standards of NBS are upheld. To step in now and mandate a condition be added would be to **invalidate the very authority you yourselves delegated** and the **five years of collaborative effort** that created this robust system. It would set a precarious precedent, inviting every special interest group to bypass scientific review and compromise the integrity of public health.

Act 133 is working. We did the hard work to establish a system that prioritizes the best possible, evidence-based medical outcomes for every child born in this Commonwealth. We urge you to uphold that precedent.

Thank you.

Lesa Brackbill, M.A.



1. Program staff consists of a minimum of two Department of Health delegates.
2. Nomination Committee consists of NSFTAB Chair, Vice Chair, and DOH Representative
3. New Condition Workgroup consists of NSFTAB Chair, Vice Chair, DOH Representative, Ethicist, selected providers with knowledge of the nominated condition. One condition will be reviewed at a time in the order in which a nomination or resubmission was received.
4. DOH will attempt to implement within two years after approval.

^Majority vote to continue to next phase.

*Per section 7 of the NSFTAB Bylaws only board members are eligible to vote. Majority vote to continue to next phase.

Newborn Screening at a Glance

- **Forty-eight states and D.C.** have **Newborn Screening Advisory Boards** or **Committees**,
  - Each has varying authority to add conditions independently
  - **All states** have a process that is **scientific** and **evidence-based**

- **Two** states (California and Arkansas) only add conditions as they are added to the Federal Recommended Uniform Screening Panel (RUSP).
  - With the dissolution of the ACHDNC and no mechanism to add conditions to the RUSP, it remains to be seen how these states will handle the expansion of their panels.

- **Ten** states have a transparent, publicly available nomination process on their website:
  - Georgia
  - Indiana
  - Louisiana
  - Massachusetts
  - Minnesota
  - Montana
  - Pennsylvania
  - South Dakota
  - Washington
  - Wisconsin

- **Pennsylvania** is the **ONLY state** screening for all RUSP disorders, plus additional ones that the Advisory Board has chosen to add.

Many other states are working to include this information on their websites. Each state has its own restrictions on what can and cannot be included on state websites, so each website contains different information. **Advocates are working to see that standardized** (see handout).

For more state-level information, view this spreadsheet developed and maintained by Lesa Brackbill.

Sources:

🌐 Newborn Screening Status for All Disorders

🌐 Home | Newborn Screening

https://everylifefoundation.org/newborn-screening-take-action/learn-more/

The Need for Transparent Condition Nomination Processes in State Newborn Screening Programs

Deterring Legislative Mandates Through Clear Policy

Newborn Screening (NBS) is a critical public health system that protects infants by identifying treatable conditions early. For the system to remain effective, it must adapt to new medical advancements by adding treatable conditions.

However, a lack of a clear process for adding new conditions often pushes well-meaning advocates to seek **legislative mandates**, bypassing your state's established public health review. In this current era, without a federal mechanism to add conditions to the RUSP, this is more necessary than ever.

If they aren't aware of the process, they aren't going to follow it.

At **Patient Advocacy Strategies**, we have done extensive research on the state-level NBS landscape to better understand how to guide advocates seeking to add a condition.

Current Reality	Desired Outcome
Only **ten states** currently provide a clear nomination pathway for advocates on their NBS website.	Every state NBS website should feature a **clear, accessible nomination process** for new conditions.
Advocates often engage in unpredictable and lengthy **legislative** actions to add conditions, which risk politicizing NBS and may lead to additional challenges for the NBS Program, such as unfunded mandates.	Advocates are empowered to use the state's **evidence-based, expert-driven** review process because it is easy to find.

The Pennsylvania Example: A Successful Model

After listening to advocate input, Pennsylvania's NBS Advisory Board developed a process modeled after other states that includes a **nomination form** and a clear **workflow** that advocates can easily access on the state's NBS website. This model channels advocacy efforts directly into the state's expert review system, strengthening the program while maintaining scientific rigor.

Patient Advocacy | Strategies

Five Key Elements for a Transparent NBS Website

If your state can add **non-RUSP** conditions, it is important to provide advocates with the process you have established. To proactively engage advocates and ensure the strongest possible NBS system, your state's website should provide unambiguous answers to the following questions:

Key Information	Why It Matters
Advisory Board Details	**Transparency:** Clearly state the **Board's authority** (add conditions vs. recommend to legislature), meeting schedule, and public access points.
Nomination Pathway	**Accessibility:** **Confirm that a process exists** for the public/advocates to officially nominate a condition for consideration.
Detailed Process Outline	**Clarity:** Publish the **step-by-step workflow** from initial submission to final decision. Provide a link to the official **nomination form**.
Criteria for Addition	**Expectation Setting:** Clearly list the **scientific, clinical, and public health criteria** a condition must meet (e.g., condition is serious, treatable, and a reliable screening test exists).
Community Engagement	**Partnership:** Articulate **how the advocacy community can best support** and strengthen the state's NBS system (e.g., help educate, fund pilot studies, or collect data).

Call to Action: Channeling Passion into Policy

A transparent, accessible process isn't just a convenience—it's a crucial component of sound public health policy. It gives rare disease families a roadmap to follow to effect change and benefit the work you do as a state NBS program.

By implementing a clear nomination process on your NBS website, your state can:

- **Deter legislative intervention** and protect the integrity of your expert-review process.
- **Empower advocates** by giving them an accessible, official pathway to contribute.
- **Ensure that all NBS additions are evidence-based**, maximizing public health benefit.

GAUCHER COMMUNITY ALLIANCE

NEWBORN SCREENING FOR GAUCHER DISEASE

Aviva Rosenberg, JD
Co-Founder/Co-President
Gaucher Community Alliance

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www.gauchercommunity.org

What is Gaucher Disease?

- Gaucher disease is a rare genetic disease, caused by mutations in the GBA1 gene, leading to deficient enzyme activity.
- Gaucher disease causes:
  - ❑ Enlarged liver and spleen
  - ❑ Bone pain and fractures
  - ❑ Easy brusing and bleeding
  - ❑ Anemia
  - ❑ Fatigue
  - ❑ Growth delays
  - ❑ Types 2⁄3: seizures, cognitive impairment, lung, heart and kidney problems, movement disorders, death
  - ❑ Increased risk of Parkinson's, osteoporosis, and some cancers

DOH Failed To Do It's Job

- Nomination submitted Oct. 30, 2023
- **Secret meeting** held March 28, 2024 - No notes, no attendance taken
- Letter received June 10, 2024, "no treatment available." **Denied**.
- Sept. 1, 2024 submitted addition information "proving" treatment.
- Letter received March 21, 2025 - "lack of treatment." **Denied**.
- Nomination packet never provided to the committee.

GAUCHER COMMUNITY ALLIANCE

Case for Newborn Screening

- Gaucher is a multisystem disease that leads to a spectrum of disease severity.
- Treatment is safe, effective and FDA approved since 1994.
- The diagnostic journey for Gaucher patients averages 7 years.
- The timing of treatment initiation can have a significant impact on the clinical outcomes. Delayed treatment, can cause irreversible complications such as osteonecrosis.
- Without diagnosis, treatment cannot begin. Early intervention offers the best outcomes and possibility of “normalcy” for Gaucher patients.

Case for Newborn Screening

- For Types 2 and 3, newborn screening gives the baby the best chance at life.
- Treatment must be intiated immediately after birth to provide the best possible outcome for the baby.
- Enzyme replacement therapy (ERT) is standard of care treatment and is used off-label for patients with Type 2 and Type 3.
- ERT is a live saving treatment if the patients are diagnosed through newborn screening.

States Currently Screening for Gaucher

- Illinois - 2014
- Missouri - 2013
- New Jersey - 2019
- Tennessee - 2017
- Oregon - 2018
- New Mexico - 2022
- Bill pending MA
- Approved in by committee in IN, pending start date
- Nominations under review MN, GA, WI
- Legislation soon: NY, Ohio, VA

GAUCHER COMMUNITY ALLIANCE

Missouri Newborn Screening

Year	Babies Screened	GD Cases detected
2013	91,074	3
2015	91,551	3
2016	92,294	2
2017	90,489	2

Missouri Newborn Screening Data (New)

	2024	2020-2024 (cumulative)
Total number of initial samples	67,600	339,256
Screen Positives	11	36
Confirmed Positives (no second tier testing)	1	10

Gender Breakdown (confirmed positives 2020-2024)

Males	4
Females	6

Gaucher Type (2020-2024)

Type 1	6
Type 2	0
Type 3	1
Genotype of unknown significance	3

Illinois Newborn Screening Data

Outcomes of newborn screening for Gaucher disease: Insights from a single-center experience (8 years of data from Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine)

2015-2022: 1.4 million newborns screened

21 confirmed positives

Tennessee Newborn Screening Data

Tennessee Department of Health. Division of Family Health and Wellness, Newborn Screening Follow-Up and Childhood Lead Poisoning Prevention Program.

2018-2024: 610,000 newborns screened

4 confirmed positives

New Jersey Newborn Screening

- **From July 1, 2019 to December 30, 2023, 439,000 newborns screened**
- **60 screen positives, 19 confirmed positives, 19 lost to follow-up, 23 false positives**

Hui Xing, New Jersey Department of Health, Newborn Screening and Genetic Services

Oregon Newborn Screening

October 2018-September 2023:

203,000 newborns screened

3 confirmed positives

New York Pilot Newborn Screening

Optional screening for panel of 14 conditions offered with informed consent to families at 8 birth hospitals in New York (5/2021 - 6/2025)

Study Opt-in Rate	~60%
Number of Infants Screened	29,097
Number Screen Positive for Gaucher Disease	6
Number Confirmed with Gaucher Disease	6

Thank you!

Please pass HB 1652 so Pennslyvania Gaucher families can have the same opportunity to live a full life.

Questions?

Children's Hospital of Philadelphia

Can Ficicioglu MD, PhD
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Perelman School of Medicine at the University of Pennsylvania
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Perelman School of Medicine
University of Pennsylvania

Pennsylvania House Health Committee

Harrisburg, PA

Re: Support for Pennsylvania HB 1652 – Inclusion of Gaucher Disease in Newborn Screening Panel

23-Sep-2025

Dear Chair and Honorable Committee Members,

As the leading Gaucher disease specialist in the Commonwealth of Pennsylvania and an internationally recognized expert in lysosomal storage disorders, I write to express my unequivocal and urgent support for HB 1652 and to urge its prompt passage. This bill proposes the inclusion of Gaucher disease (GD) in Pennsylvania's newborn screening (NBS) panel—a public health measure whose necessity I have seen firsthand through my care of affected infants and children in both Pennsylvania and New Jersey.

Clinical Experience Across State Lines

As Director of the Section of Biochemical Genetics and Newborn Screening at Children's Hospital of Philadelphia, I have the unique perspective of caring for infants diagnosed early by newborn screening in New Jersey as well as those identified later in Pennsylvania through traditional clinical pathways. The differences in outcomes are as dramatic as they are heartbreaking. In New Jersey—where NBS for GD has been in place since 2019—I have treated children identified presymptomatically. These patients benefit from close surveillance and, when necessary, timely initiation of enzyme replacement therapy (ERT). Early intervention has resulted in prevention of irreversible organ damage, normalization of blood counts, and normal growth and development. Parents benefit from clear information, reduced anxiety, and the assurance that a validated, treatable condition was not overlooked (1).

In stark contrast, Pennsylvania families without the benefit of newborn screening frequently endure years-long "diagnostic odysseys," multiple specialist consultations, and ultimately the discovery of advanced disease. Children often present with severe skeletal, hematologic, and visceral complications—many of which are irreversible by the time a diagnosis is made and treatment initiated. Published data from New Jersey confirm that among infants identified presymptomatically, treatment outcomes are superior by every measure to those identified after symptoms develop (2,3).

Evidence of Improved Outcomes with Early Detection

Expanding on our regional data, robust international evidence confirms that NBS for Gaucher disease enables:

- Timely initiation of ERT, resulting in normalized hematologic parameters, reversal of organomegaly, and prevention of bone complications (1,2,4).
- Substantial reduction in diagnostic delays—which literature shows can otherwise average seven years—leading to missed windows for optimal intervention (3,4).

- Enhanced parental support, reassurance, and healthcare navigation, with early genetic counseling and education (1,4).

New Jersey's experience, screening over 438,000 newborns between 2019 and 2023, resulted in identified cases that received early treatment and demonstrated improvement in clinical and biochemical markers, as well as quality of life. Notably, survival, growth, and bone health metrics are all improved compared to Pennsylvania counterparts, who frequently suffer avoidable complications due to diagnostic delays. These findings mirror results from other states and international cohorts (1,2,3,4).

The Need for Prompt Legislative Action

The technology for accurate and reliable Gaucher screening already exists and has been implemented successfully across several states. Cost-effectiveness studies indicate that early intervention is not only clinically prudent but also fiscally responsible, reducing lifetime costs linked to advanced disease and its management. Inclusion in the Pennsylvania panel would immediately redress the inequity now faced by Pennsylvania newborns compared to those in neighboring states (2,4).

Gaucher disease meets every established criterion for newborn screening: proven analytic validity, severe morbidity from delayed diagnosis, availability of effective treatment, and clear net benefit to affected children (1,2,4).

Conclusion

In closing, I urge the committee to act without delay and move HB 1652 forward. This is an opportunity to prevent avoidable suffering, align Pennsylvania with evidence-based best practice, and save lives. My medical colleagues, patient advocacy communities, and—most importantly—the children and families of Pennsylvania are counting on your leadership.

If I can provide further data or testimony, I am at your disposal.

Respectfully,

Can Ficicioglu, MD, PhD
Professor of Pediatrics
Distinguished Endowed Chair in the Department of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
The Children's Hospital of Philadelphia
Division of Human Genetics
Director, Biochemical Genetics
Director, Newborn Screening Program
Director, Lysosomal Storage Disorders (LSD) program

Attached papers:

1. Gaucher-NBS-letter-021025.pdf
2. Newborn Screening for Gaucher Disease: The New Jersey Experience
   Int. J. Neonatal Screen. 2025, 11, 34 .pdf
3. Diagnosis and Management in Gaucher Disease: A Case Series Emphasizing the Critical Role of Newborn Screening. MGMREPORTS 2025 (accepted for publication) .pdf
4. Inclusion-of-Gaucher-disease-in-newborn-screening-panels-across-the-U.S.pdf

Molecular Genetics and Metabolism Reports 45 (2025) 101256

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Early diagnosis and management in Gaucher disease: A case series emphasizing the critical role of newborn screening

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ABSTRACT

Type 1 Gaucher disease is a lysosomal storage disorder associated with marked phenotypic heterogeneity, including among individuals carrying genotypes historically defined as "mild". Early diagnosis, workup and follow-up care are crucial to avoid irreversible complications. We present a case series of 5 pediatric patients with type 1 Gaucher disease who had been identified based on newborn screening (NBS), parental carrier status, or clinical presentation. They were followed over time for monitoring of clinical status, hematologic indices, biomarkers including glucopsychosine, and imaging studies. Enzyme replacement therapy (ERT) was started when rising trends of biomarkers and/or new clinical symptoms appeared. Three patients were identified by NBS, one at birth due to parental carrier status, and one after symptomatic presentation with femoral fracture. All patients required initiation of ERT between 9 months and 5 years of age due to evidence of disease progression. Early diagnosis via NBS and proactive monitoring enabled timely ERT initiation in four cases, preventing irreversible organ damage and clinical complications. In contrast, the unscreened case presented with severe skeletal and hematologic involvement at baseline. Rising glucopsychosine was a sensitive early marker of disease activity and MRI was more sensitive at detecting organomegaly than ultrasound. These cases emphasize the vital importance of NBS, regular biomarker surveillance, and early intervention, even in presumed mild cases based on genotype. Early diagnosis via NBS, individualized monitoring and timely treatment are fundamental to optimizing outcomes in Gaucher disease type 1.

1. Introduction

Gaucher disease is an autosomal recessive lysosomal storage disorder caused by biallelic pathogenic variants in the *GBA* gene. This results in deficiency of glucocerebrosidase (β-glucosidase) and leads to deposition of glycosphingolipids within lysosomes [1]. There are three clinical subtypes: type 1 Gaucher disease, which can present at any age, is characterized by hepatosplenomegaly, bone disease, cytopenias, and pulmonary disease without central nervous system (CNS) involvement [2]. Type 2 Gaucher disease is characterized by early-onset, rapidly progressive neurologic impairment along with visceral involvement. Type 3 Gaucher disease typically presents in childhood with slowly progressive CNS disease, including oculomotor apraxia, seizures, ataxia, and cognitive impairment, along with features of visceral disease [1].

There are enzyme replacement (ERT) and substrate reduction therapies (SRT) available for Gaucher disease. There are 3 ERTs approved in the United States for types 1 and 3. The SRT available is only approved for adults with type 1 disease in the United States, though there are recent studies that describe its use in pediatric patients. Guidelines recommend that treatment be initiated at symptom-onset. However, diagnosis can be delayed because of the nonspecificity of clinical features and limited provider awareness of these features. Newborn screening (NBS) has the opportunity to identify individuals sooner to allow for more timely initiation of therapy. NBS for Gaucher disease has been implemented in some states but has not yet been added to the Recommended Uniform Screening Panel (RUSP).

Here, we present five patients with early-onset manifestations—some as young as within the first year of life—to underscore the pivotal importance of early recognition and timely initiation of therapy in type 1 Gaucher disease. We further explore the nuanced approach to monitoring individuals identified presymptomatically, highlighting evolving strategies aimed at optimizing long-term clinical outcomes in

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this population.

2. Material and methods

Individuals with type 1 Gaucher disease who required enzyme replacement therapy before 5 years of age were included in this case series. Cases 1, 2, and 4 were identified through NBS. Case 3 presented symptomatically at 4 years of age, and Case 5 was identified in the first year of life, as both parents were known carriers of Gaucher disease. Medical records were reviewed to collect data on newborn screening results, medical history, biochemical testing (including genotype, beta-glucosidase activity, glucopsychosine, chitotriosidase, ferritin, and complete blood count [CBC]), findings on physical examination, abdominal imaging (ultrasound or MRI), and treatment.

3. Results

3.1. Case 1

A 5-year-old female, the fifth of six children, was identified by New Jersey NBS for Gaucher disease, with beta-glucosidase activity <9.4 % (cut-off <12.0 %). Confirmatory testing revealed markedly reduced leukocyte beta-glucosidase (0.2 nmol/h/mg, ref. ≥8.7), elevated glucopsychosine (0.104 nmol/mL, ref. ≤0.040), and homozygosity for the *GBA* c.1226 A > G, p.N409S (N370S) variant, confirming type 1 Gaucher disease (Table 1).

Owing to the COVID-19 pandemic, initial evaluations occurred via telemedicine at 7 and 18 months. Her growth and development were appropriate per pediatrician report. At 12 months, delayed laboratory

Table 1

Table 1 presents labs values over time for all cases. These values do not represent all labs drawn for all cases but are meant to reflect pre-treatment and post-treatment trends. "Initial Value" refers to the first time the lab was drawn on the individual but does not mean it was drawn at the initial clinic visit. "Last Pre-Treatment Value" refers to the last time that lab was drawn before treatment was initiated. "First Post-Treatment Value" refers to the first time that lab was drawn after treatment was initiated. "Value at Last Clinical Evaluation" refers to the last time that lab was drawn as part of regular clinical monitoring. Case 1 does not produce chitotriosidase, so further lab values were not collected. For Case 3, the initial values for glucopsychosine, chitotriosidase, and ferritin were also the last pre-treatment values collected as she was exhibiting signs of active disease and was initiated on treatment. For Case 4, the initial value for ferritin reflects his first post-treatment value as pre-treatment lab values were not drawn. For Case 5, the last pre-treatment value for glucopsychosine is the last value that was collected. Subsequent glucopsychosine testing has not yet been performed. Additionally, the value at last clinical evaluation for chitotriosidase, hemoglobin, platelets, and ferritin are all reflected in the first post-treatment value. "NC" = not collected.

	Case 1	Case 2	Case 3	Case 4	Case 5
Genotype	Homozygous for *GBA* c.1226 A > G (p.N409S)	*GBA* c.1226 A > G (p.N409S) / *GBA* c.635C > G (p.S212*)	*GBA* c.1226 A > G (p.N409S) / *GBA* c.84dupG (p.L29fs)	*GBA* c.1226 A > G (p.N409S) / *GBA* c.84dupG (p.L29fs)	*GBA* c.1226 A > G (p.N409S) / *GBA* c.1448 T > C (p.L483P)
Confirmatory Enzyme	0.2 nmol/h/mg [≥8.7]	0.49 nmol/h/mg [≥3.53]	0.57 nmol/h/mg Prot [≥ 3.53]	0.77 μmol/L/h [>1.60]	0.67 nmol/h/mg [≥3.53)]
Glucopsychosine					
Initial Value	0.104 nmol/mL [≤0.040]	0.103 nmol/mL [≤0.040]	>2.000 nmol/mL [≤0.040]	89.12 ng/mL [<17.41]	0.089 nmol/mL [≤0.040]
Last Pre-Treatment Value	0.372 nmol/mL [≤0.040]	0.933 nmol/mL [≤0.040]	–	0.567 nmol/mL [≤0.040]	0.326 nmol/mL [≤0.040]
First Post-Treatment Value	0.199 nmol/mL [≤0.040]	0.534 nmol/mL [≤0.040]	1.001 nmol/mL [≤0.040]	0.142 nmol/mL [≤0.040]	–
Value at Last Clinical Evaluation	0.048 nmol/mL [≤0.040]	0.102 nmol/mL [≤0.040]	0.443 nmol/mL [≤0.040]	0.086 nmol/mL [≤0.040]	–
Chitotriosidase					
Initial Value	0 nmol/h/mL [4–120]	8721 nmol/h/mL [4–120]	27,540 nmoles/h/mL [4–120]	8714 nmoles/h/mL [4–120]	333 nmoles/h/mL [4–120]
Last Pre-Treatment Value	NC	9965 nmol/h/mL [4–120]	–	11,208 nmoles/h/mL [4–120]	471 nmoles/h/mL [4–120]
First Post-Treatment Value	NC	5239 nmoles/h/mL [4–120]	14,242 nmoles/h/mL [4–120]	4264 nmoles/h/mL [4–120]	70 nmoles/h/mL [4–120]
Value at Last Clinical Evaluation	NC	1033 nmoles/h/mL [4–120]	4794 nmoles/h/mL [4–120]	628 nmoles/h/mL [4–120]	–
Hemoglobin					
Initial Value	15.1 g/dL [12.5–20.5]	11.2 g/dL [10.5–13.5]	9.5 g/dL [11.5–13.5]	9.1 g/dL [11.5–13.5]	16.7 g/dL [13.5–19.5]
Last Pre-Treatment Value	11.3 g/dL [11.5–13.5]	8.1 g/dL [11.5–13.5]	7.3 g/dL [11.5–13.5]	9.1 g/dL [11.5–13.5]	9.9 g/dL [10.5–13.5]
First Post-Treatment Value	11.1 g/dL [11.5–13.5]	9.8 g/dL [11.5–13.5]	9.7 g/dL [11.5–13.5]	10.1 g/dL [11.5–13.5]	10.2 g/dL 10.5–13.5]
Value at Last Clinical Evaluation	12.1 g/dL [11.5–13.5]	10.7 g/dL [11.5–13.5]	11.8 g/dL [11.5–15.5]	11.3 g/dL [11.5–13.5]	–
Platelets					
Initial Value	325 × 10^3/μL [150–400]	197 × 10^3/μL [150–400]	14 × 10^3/μL [150–450]	126 × 10^3/μL [150–450]	275 × 10^3/μL [218–419]
Last Pre-Treatment Value	189 × 10^3/μL [150–450]	103 × 10^3/μL [150–450]	27 × 10^3/μL [150–450]	155 × 10^3/μL [150–450]	262 × 10^3/μL [150–450]
First Post-Treatment Value	234 × 10^3/μL [150–450]	105 × 10^3/μL [150–450]	77 × 10^3/μL [150–450]	183 × 10^3/μL [150–450]	222 × 10^3/μL [150–450]
Value at Last Clinical Evaluation	290 × 10^3/μL [150–450]	175 × 10^3/μL [150–450]	132 × 10^3/μL [150–450]	231 × 10^3/μL [150–450]	–
Ferritin					
Initial Value	74.7 ng/mL [10.0–99.9]	64.9 ng/mL [10.0–99.9]	675.1 ng/mL [10.0–99.9]	38.0 ng/mL [10.0–99.9]	112.6 ng/mL [10.0–181.9]
Last Pre-Treatment Value	232.2 ng/mL [10.0–99.9]	–	–	–	84.7 ng/mL [10.0–181.9]
First Post-Treatment Value	205.8 ng/mL [10.0–99.9]	129.1 [10.0–99.9]	644.3 ng/mL [13.7–78.8]	–	94.5 ng/mL [10.0–99.9]
Value at Last Clinical Evaluation	72.7 ng/mL [13.7–78.8]	44.2 [10–99.9]	310.2 ng/mL [13.7–78.8]	13.2 ng/mL [10.0–99.9]	–

evaluation revealed anemia (hemoglobin 9.8 g/dL; reference 10.9–14.8). Glucopsychosine was not obtained due to lab error, and chitotriosidase was undetectable. The family could not get the labs ordered at 18 months. Laboratory tests obtained at 24 months clinic visit revealed elevated glucopsychosine (0.194 nmol/mL; ref. ≤0.040) and anemia (hemoglobin 10.6 g/dL; ref. 10.9–14.8). Examination showed a spleen tip palpable 1–2 cm below the right costal margin.

At 30 months, her spleen tip was palpable 2 cm below the right costal margin. Laboratory evaluation showed anemia (hemoglobin 10.9 g/dL; ref. 11.5–14.8), normal platelet count (156 × 10^3/μL; ref. 150–400), mildly elevated ferritin (110.0 ng/mL; ref. 10.0–99.9), and persistently increased glucopsychosine (0.198 nmol/mL; ref. ≤0.040). Liver and spleen ultrasound at 33 months revealed mild hepatomegaly without splenomegaly.

At 36 months, laboratory studies showed anemia (hemoglobin 11.2 g/dL; ref. 11.5–13.5), stable platelets (162 × 10^3/μL; ref. 150–450), elevated ferritin (141.8 ng/mL; ref. 10.0–99.9), and a marked rise in glucopsychosine (0.372 nmol/mL; ref. ≤0.040). Angiotensin converting enzyme (ACE) was also elevated (176 U/L; ref. 18–90). At 3 years 5 months, metabolic MRI demonstrated hepatosplenomegaly (spleen 6.9× and liver 1.5× normal). Subsequent examination revealed liver and spleen tips palpable 3–4 cm below the right costal margin. Labs showed persistent anemia (hemoglobin 11.3 g/dL), normal platelets (189 × 10^3/μL), further elevated ferritin (232.2 ng/mL), rising glucopsychosine (0.504 nmol/mL), and ACE (190 U/L).

ERT was initiated at 60 units/kg biweekly and infusions were well tolerated with a favorable clinical response. Seventeen months later, metabolic MRI showed improved splenomegaly (spleen volume 5.6 multiples of normal) and stable hepatomegaly (liver 1.5 multiples of normal). At her most recent follow-up (age 5 years 9 months), physical examination revealed no hepatosplenomegaly, her parents reported no symptoms, and laboratory evaluation showed resolution of cytopenias and ferritinemia. Glucopsychosine levels markedly improved to 0.048 nmol/mL (ref ≤0.040).

3.2. Case 2

This 4-year-old male, the fourth child of his parents, was born at 36 + 5 weeks by cesarean section and identified by New Jersey newborn screening with low beta-glucosidase activity (<5.3 %). Confirmatory testing revealed markedly reduced leukocyte beta-glucosidase (0.49 nmol/h/mg; ref. ≥3.53), elevated glucopsychosine (0.103 nmol/mL; ref. ≤0.040), and compound heterozygosity for *GBA* c.1226 A > G (p.N409S) and *GBA* c.635C > G (p.S212*), confirming type 1 Gaucher disease (Table 1).

Due to the COVID-19 pandemic, initial care was virtual, with in-person evaluation delayed until 20 months of age. At 8 months of age the labs showed normal hemoglobin (11.2 g/dL), platelets, and stable glucopsychosine (0.104 nmol/mL; ref. ≤ 0.040), with appropriate growth and development.

At 14 months video visit, growth was appropriate per his growth chart. At 18 months, glucopsychosine had risen to 0.749 nmol/mL (ref ≤0.040) and chitotriosidase to 8721 nmoles/h/mL (ref 4–120), without anemia or thrombocytopenia.

At 20 months, his first in-person evaluation was limited by poor cooperation, precluding reliable assessment for hepatosplenomegaly. Laboratory studies revealed anemia (hemoglobin 9.5 g/dL; ref. 10.5–13.5), normal platelets (214 × 10^3/μL; ref. 150–450), stable glucopsychosine (0.780 nmol/mL), and markedly elevated chitotriosidase (10,486 nmoles/h/mL; ref. 4–120). Abdominal ultrasound with elastography showed normal liver and spleen size and stiffness, but diffuse hepatic coarse echotexture.

At 28 months, he developed pancytopenia (Hb 8.1 g/dL, platelets 103 × 10^3/μL, WBC 2.7 K/μL), with rising glucopsychosine (0.933 nmol/mL) and elevated chitotriosidase (9965 nmol/h/mL). He exhibited bruising, fatigue, slowed growth, and MRI showed marked splenomegaly (14.9×) and hepatomegaly (1.75×) with increased stiffness. ERT was initiated at 60 U/kg biweekly.

ERT was well tolerated and led to clinical improvement. After one year, MRI showed reduced hepatosplenomegaly (spleen 4.7×, liver 1.2× normal); spleen stiffness increased, but liver stiffness normalized. At 4 years, he reported only rare nosebleeds, with no other symptoms. Hemoglobin and platelet count improved (11.2 g/dL and 181 × 10^3/μL), and glucopsychosine decreased to 0.165 nmol/mL.

3.3. Case 3

Case 3, a 6-year-old female and third of five siblings, had mild motor delay and a plateau in linear growth from ages 3 to 4 years. Her height declined from the 60th percentile at age 2 to the 6th percentile at age 5.

At age 4 years 5 months, she developed pallor, fatigue, and splenomegaly. Initial evaluation done by her pediatrician revealed anemia and thrombocytopenia, for which she received iron supplementation without improvement.

Due to worsening cytopenias, she was referred to hematology, where bone marrow biopsy was performed. During the workup, she developed atraumatic left lower extremity pain and presented to the emergency department at the Children's Hospital of Philadelphia, where a left femoral neck fracture was diagnosed and surgically repaired. On admission, she had significant anemia (hemoglobin 9.5 g/dL; ref. 11.5–13.5) and thrombocytopenia (platelets 14 × 10^3/μL; ref. 150–450). Biomarkers were markedly elevated: glucopsychosine >2.0 nmol/mL (ref ≤0.040), chitotriosidase 27,540 nmol/h/mL (ref 4–120), and ferritin 675.1 ng/mL (ref 13.7–78.8) (Table 1). MRI revealed massive splenomegaly (27× normal), hepatomegaly (2× normal), increased organ stiffness, and left hip osteonecrosis. Confirmatory beta-glucosidase enzyme activity was reduced at 0.57 nmol/h/mg Prot (reference value ≥3.53), and bone marrow biopsy performed by the hematologist demonstrated Gaucher cells. *GBA* sequencing identified her as compound heterozygous for *GBA* c.1226 A > G (p.N409S) and *GBA* c.84dupG (p.L29fs).

She began inpatient ERT at 60 units/kg biweekly following surgical fracture fixation; the dose was subsequently increased to 80 units/kg to enhance bone response due to disease severity. Infusions were well tolerated, leading to increased energy and reduced splenomegaly. After 14 months of therapy, her spleen was no longer palpable, hemoglobin normalized (11.8 g/dL; ref. 11.5–15.5), platelets improved (132 × 10^3/μL; ref. 150–450), and biomarkers decreased (glucopsychosine 0.443 nmol/mL, chitotriosidase 4794 nmol/h/mL, ferritin 310.2 ng/mL). Linear growth improved from the 7th to the 24th percentile.

3.4. Case 4

This 3-year-old male, the younger brother of Case 3, was identified by New Jersey newborn screening with low beta-glucosidase activity (0.77 μmol/L/h; ref. >1.60). Confirmatory testing by his pediatrician showed markedly elevated glucopsychosine (89.12 ng/mL; ref. <17.41). *GBA* sequencing revealed compound heterozygosity for c.1226 A > G (p.N409S) and c.84dupG (p.L29fs). Despite these findings, the family declined further evaluation until he presented at 26 months following his sister's diagnosis.

At 26 months, he was found to have hepatosplenomegaly, anemia (hemoglobin 9.1 g/dL; ref. 11.5–13.5), thrombocytopenia (platelets 126 × 10^3/μL; ref. 150–450), and elevated biomarkers: glucopsychosine 0.550 nmol/mL (ref ≤0.040), chitotriosidase 8714 nmol/h/mL (ref 4–120), and ferritin 145.4 ng/mL (ref 10.0–99.9) (Table 1). Findings were consistent with active Gaucher disease, and ERT was recommended.

At 28 months, ERT (60 U/kg biweekly) was initiated and was well tolerated. After 12 months, hemoglobin improved to 11.3 g/dL, platelets normalized (231 × 10^3/μL), glucopsychosine declined to 0.086 nmol/mL, chitotriosidase to 628 nmol/h/mL, and ferritin normalized (13.2

ng/mL). He did not have hepatosplenomegaly on exam. MRI was deferred due to the family's concerns about the need for sedation. No imaging was performed.

3.5. Case 5

This 13-month-old male was born at 37 + 4 weeks via elective cesarean section. Parental carrier screening revealed the father carried c.1226 A > G (p.N409S) and the mother c.1448 T > C (p.L483P) in *GBA*. Cord blood testing confirmed the patient as a compound heterozygote, diagnosing Gaucher disease at birth.

At 7 weeks, his physical exam was unremarkable without hepatosplenomegaly. Growth parameters were: weight 4.5 kg (17th percentile), height 54.1 cm (7th), head circumference 37.1 cm (13th). Confirmatory labs showed reduced leukocyte beta-glucosidase (0.67 nmol/h/mg; ref. ≥3.53) and elevated glucopsychosine (0.089 nmol/mL; ref. ≤0.040), consistent with Gaucher disease (Table 1).

At 9 months, his growth had slowed (weight 7.4 kg, 4th percentile; height 67 cm, 1st percentile; head circumference 43 cm, 5th percentile). Examination revealed splenomegaly (spleen 3 cm below the left costal margin) without hepatomegaly. Labs showed normal blood counts and ferritin, but glucopsychosine rose to 0.343 nmol/mL (ref ≤0.040) and chitotriosidase to 333 nmol/h/mL (ref 4–120). MRI demonstrated hepatomegaly (1.6× normal), splenomegaly (5.1×), and normal bone marrow without avascular necrosis.

Given slowing growth, splenomegaly, and rising glucopsychosine, ERT (60 U/kg every two weeks) was initiated at 10 months, and infusions have been well tolerated. By 13 months, growth had improved (weight 8.8 kg, 14th percentile; height 74 cm, 10th percentile), he remained asymptomatic, and chitotriosidase normalized (70 nmol/h/mL). Splenomegaly persisted (spleen palpable 3 cm below the left costal margin).

4. Discussion

Gaucher disease is a rare disorder with non-specific signs and symptoms, often leading to delayed diagnosis and preventable complications. Studies underscored the diagnostic odyssey and showed that the average time from the first symptoms to final diagnosis was 4 years, leading to preventable complications in patients [5,11]. NBS allows for early identification, reducing diagnostic delays. Although a recent Delphi consensus group supported NBS for Gaucher disease [3], it is not yet included in the RUSP. Only six US states currently screen for it: Illinois, Missouri, New Jersey, New Mexico, Oregon, and Tennessee. [6] Limitations of NBS include the potential detection of later-onset cases and lack of treatment for neuronopathic forms [5,12].

We report five individuals with type 1 Gaucher disease who required treatment initiation between 9 months to 5 years. Three were identified through NBS, one at birth due to parental carrier status, and one following presentation with a femoral fracture. Some clinical details of NBS-identified cases (1, 2, and 4) have been previously published [6]. Individuals diagnosed at birth and closely monitored were started on ERT based on increasing biomarkers and mild clinical findings, prior to significant disease progression. Conversely, Case 3, who was not screened, presented with severe complications including left femoral neck osteonecrosis and fracture. Her sibling, Case 4, was identified on NBS but his parents elected not to follow with metabolism after birth. He presented to our care following his sister's diagnosis and was also found to have marked hepatosplenomegaly, anemia, and thrombocytopenia at presentation.

ERT has been shown to improve hematological, visceral, and skeletal manifestations of Gaucher disease [7] and to prevent complications, including severe bone disease, fractures [8], growth failure and delayed puberty [9]. Early initiation of ERT reduces the risk of avascular necrosis. [10] Treatment guidelines recommended treatment initiation in all symptomatic children [4] and recent Delphi consensus further supports early intervention to prevent adverse outcomes. [3] The severe complications observed in Case 3, including femoral neck osteonecrosis and fracture, could likely have been prevented with earlier diagnosis and timely treatment.

Current guidelines advise biannual monitoring for children detected by NBS with severe genotypes and annual monitoring for those with more benign genotypes, such as *GBA* p.N409S (N370S). [4,13]. Although this variant is generally associated with mild or late-onset disease, all individuals in our cohort - including those harboring the *GBA* p.N409S (N370S) variant - required early treatment, underscoring the limitations of genotype in predicting clinical course.

In our center, we follow presymptomatic individuals with type 1 Gaucher disease every six months, irrespective of genotype. Follow-up includes physical examination focusing on growth and organomegaly, and assessment of biomarkers such as glucopsychosine, chitotriosidase, complete blood count, and ferritin. Rising glucopsychosine, a reliable and sensitive biomarker, should prompt treatment initiation [14–16]. Imaging is performed to assess liver and spleen size, especially in the presence of rising biomarkers or clinical concern. While abdominal ultrasound is convenient and requires no sedation, MRI provides greater accuracy [3]. This was demonstrated in Cases 1 and 2, where normal ultrasounds underestimated splenomegaly that was subsequently identified by MRI.

Our experience underscores the critical importance of early diagnosis and timely intervention in the management of type 1 Gaucher disease, even among patients harboring genotypes traditionally associated with milder phenotypes, such as homozygosity or compound heterozygosity for the *GBA* p.N409S (N370S) variant. The cases demonstrate that pre-symptomatic identification via NBS combined with rigorous surveillance allows for timely initiation of ERT as early as 9 months as in the case 5.

Several key findings emerge from these cases. First, despite the theoretical expectation of a milder disease course or later onset symptoms associated with the *GBA* p.N409S (N370S) genotype, patients can and do develop clinically significant disease in early childhood. Decisions about disease onset or prognosis based solely on genotype may be unreliable, highlighting the need for individualized, phenotype-driven management and early diagnosis for all genotypes.

Second, the progressive elevation of sensitive biomarkers - most notably glucopsychosine (lyso-Gb1) -along with subtle but persistent hematologic abnormalities (e.g., anemia, thrombocytopenia), provided early objective evidence of disease activity prior to the onset of overt clinical symptoms. This is an important key finding that enables dynamic assessment of disease burden and informed decision-making regarding the timing of treatment initiation. Glucopsychosine proved highly sensitive in detecting early pathophysiological changes, as previously reported [14,17].

A third importance piece of observation is the limited sensitivity of imaging modalities such as abdominal ultrasound for early organomegaly; in contrast, MRI provided more accurate quantification of liver and spleen volumes and tissue characteristics. For example, both cases described here exhibited either normal or only mildly abnormal findings on ultrasound at time points when MRI revealed significant splenomegaly and hepatomegaly. These findings align with earlier studies advocating MRI as the gold standard for visceral involvement assessment in Gaucher disease, particularly in the surveillance of patients diagnosed pre-symptomatically [18,19].

Notably, early initiation of ERT in these patients led to demonstrable improvements in hematologic parameters, reductions in biomarker levels, and regression of organomegaly, as evidenced by follow-up MRIs. This supports a proactive therapeutic approach—initiating ERT based on objective evidence of disease activity rather than waiting for overt clinical deterioration. On the other hand, as illustrated by one patient who was diagnosed only after symptomatic presentation, late diagnosis and delayed initiation of therapy were associated with much higher disease burden, risk for sequala due to bone necrosis and preventable

complications at baseline.

These observations align with recent consensus guidelines [3] and longitudinal studies [10,12] recommending universal NBS in populations at risk, biomarker- and imaging-based surveillance for all patients regardless of genotype, and ERT initiation early during the latency phase to maintain organ reserve and quality of life. Ensuring close follow-up and parental engagement is also critical, as lapses in surveillance can result in missed opportunities for early intervention.

Our findings, though limited by the small sample size and observational nature of data, reinforce the paradigm that genotype-phenotype correlations in Gaucher disease should be interpreted cautiously, and that management decisions must be guided by comprehensive, dynamic assessment of each individual patient. The implementation of NBS and biomarker-based long-term monitoring provides an effective framework for maximize outcomes in Gaucher disease, and supports a shift toward earlier, personalized therapeutic intervention.

In summary, these cases highlight the necessity of newborn screening and comprehensive monitoring to ensure prompt initiation of ERT in Gaucher disease - even among those with so-called "milder" or late-onset genotypes. Such an approach is vital for preventing irreversible complications and optimizing long-term outcomes.

CRediT authorship contribution statement

Éliane Beauregard-Lacroix: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Data curation. **Madeline Steffensen:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Caitlin Menello:** Writing – review & editing, Investigation, Conceptualization. **Can Ficicioglu:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Data curation, Conceptualization.

Informed consent statement

Patient consent was waived for this study as this study met exemption criteria per 45 CFR 164.512(i)(2)(ii) per the Institutional Review Board of The Children's Hospital of Philadelphia.

Institutional review board statement

Ethical review and approval were waived for this study as this study met exemption criteria per 45 CFR 46.104(d) 4(ii) per the Institutional Review Board of The Children's Hospital of Philadelphia.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Data availability

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author(s).

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Newborn Screening for Gaucher Disease: The New Jersey Experience

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Abstract: Gaucher disease (GD) is a lysosomal storage disorder (LSD) characterized by glycosphingolipid accumulation. Age of symptomonset and disease progression varies across types of disease. Newborn screening (NBS) for Gaucher disease facilitates early identification of affected individuals and enables pre-symptomatic monitoring with the goal of starting therapies early and improving clinical outcomes. This multi-center study involved New Jersey NBS referral centers. Data regarding initial NBS results, confirmatory testing, diagnosis, and treatment were collected. For patients on therapy, monitoring biomarkers and exam findings are available as of the last clinical evaluation. Between July 2019 and December 2023, 438,515 newborns were screened, with 60 screen-positive cases. Of those positive screens, 19 cases with positive screens did not undergo confirmatory testing due to parental refusal, loss to follow-up, or death; 23 cases were false positives; 14 newborns were diagnosed with GD type I; 2 newborns were diagnosed with suspected type I GD; 2 newborns were diagnosed with GD type II; and 1 case is still pending. Three type I GD patients started enzyme replacement therapy, with the youngest starting at 28 months of age. Post-treatment data are available for these individuals. One type II case was referred to experimental gene therapy, and one was started on ERT. Our results demonstrate that NBS for GD is a valuable public health tool that can facilitate early diagnosis and intervention.

Keywords: Gaucher disease; lysosomal storage disorder; newborn screening

1. Introduction

Gaucher disease (GD) is a multi-systemic lysosomal storage disorder (LSD) caused by pathogenic biallelic variants in GBA and resulting in deficiency of β-glucosidase activity [1,2]. Consequent glycosphingolipid accumulation results in clinical manifestations of disease [3,4].

Gaucher disease is differentiated into three main forms based on the presence and rate of progression of neurologic disease [1,5,6]. Type I GD, considered the non-neuronopathic form, is characterized by visceral symptoms without primary neurologic involvement. Individuals with type I disease may present at any age with hepatosplenomegaly, periodic pain crises, bone disease, respiratory disease, cytopenia, anemia, and poor growth [6–8]. Type II GD typically presents in the first year of life and is characterized by rapidly progressive neurologic involvement, as well as marked organomegaly, cytopenia, and other visceral involvement [7,9]. Individuals with type III GD may present with similar symptoms as type I but do develop neurologic symptoms, including cognitive impairments, seizures, ataxia, and oculomotor abnormalities [6,10]. The global incidence of GD is believed to be between 0.45 and 25.0/100,000 live births [11]. The incidence is higher in the Ashkenazi Jewish population, with type I GD occurring in roughly 1 in 450 live births [12]. Type I GD is the more prevalent form found in affected individuals in Western countries, including the USA [7].

In the US, enzyme replacement therapy (ERT) is approved for type I and type III GD, though it does not slow neurologic progression [7,13]. Off-label use of ERT may be utilized palliatively for type II GD to address somatic involvement [14,15]. Substrate reduction therapy is approved for patients with type I GD 18 years of age and older.

Guidelines recommend initiation of ERT with development of manifestations in pediatric populations [7,16]. However, many patients with Gaucher disease experience a diagnostic odyssey. Roughly one in six affected individuals experience a delay of diagnosis ≥7 years from the first time they present to a doctor with symptoms [17]. Delays can be due to clinical heterogeneity, non-specific symptoms, and/or misdiagnosis [17,18]. Given the progressive nature of disease such delays may lead to poorer clinical outcomes.

Newborn screening (NBS) for Gaucher disease facilitates early identification of affected individuals and enables pre-symptomatic monitoring. Monitoring using non-invasive methods such as medical history, physical exams, and biomarker testing can reliably identify individuals who require therapy. Such surveillance is improved with the identification of lyso-Gb1, also known as glucosylsphingosine, as a sensitive and specific biomarker for accurate diagnosis, monitoring of glucosylceramide accumulation, and clearance with ERT [19]. A previous study demonstrated the utility of lyso-Gb1 in differentiating between types of Gaucher disease and monitoring for treatment response in pediatric populations [20]. Notably, patients with type I disease had lower elevations or even normal levels of lyso-Gb1 compared to individuals with types II and III [20]. Therefore, lyso-Gb1 may be useful in the differentiation of Gaucher disease subtypes and in monitoring treatment response.

Gaucher disease is not on the Recommended Uniform Screening Panel (RUSP) in the US. Currently, there are six states screening for GD in all infants: Illinois, Missouri, New Jersey, Tennessee, Oregon, and New Mexico [21–23]. Newborn screening for Gaucher disease is offered at certain hospitals in New York and Pennsylvania [24].

New Jersey implemented mandated newborn screening for Gaucher disease in July 2019. A tiered testing approach was implemented with confirmatory enzyme activity as first-tier testing and *GBA* sequencing as second-tier testing. However, second-tier testing was discontinued in 2020 due to the COVID-19 pandemic. There are nine NBS referral centers in the state of New Jersey. Here we present multi-center data from the New Jersey

NBS program and discuss clinical management of affected individuals identified through newborn screening.

2. Materials and Methods

2.1. Human Subjects Research

The Institutional Review Board at the Children's Hospital of Philadelphia determined that this study met exemption criteria per 45 CFR 102(e). A deidentified retrospective review of New Jersey's NBS results and outcomes from participating referral centers was performed for all cases reported from 8 July 2019 through 31 December 2023. Limited clinical data, including repeat β-glucosidase activity, glucopsychosine levels, and *GBA* sequencing and deletion/duplication analysis, were reported by participating referral centers.

2.2. New Jersey Newborn Screening Protocol

β-glucosidase activity is measured via tandem mass spectrometry using the NeoLSD™ MSMS Kit by Revvity, Inc. [25]. The NeoLSD™ MSMS Kit is commercially available and analyzes the activity of the six lysosomal enzymes associated with Gaucher disease, Pompe disease, Fabry disease, Krabbe disease, acid sphingomyelindase deficiency, and Mucopolysaccharidosis type I. The cutoff for the assay is expressed as the percentage of the daily median. Single enzyme deficiency of β-glucosidase is considered abnormal for Gaucher disease. If multiple enzymes are deficient, the sample is considered unsatisfactory and a repeat sample is requested.

2.3. Abnormal Newborn Screen Follow Up

Infants with decreased GBA enzyme on dried blood spot specimens were considered "positive", and referral to a biochemical geneticist was recommended. Families can decline further evaluation of an abnormal NBS after discussion with the primary care provider. Parental refusal must be documented by the state. Otherwise, selection of a particular referral center was at the discretion of the infant's primary care provider.

Screen-positive infants referred to a metabolic center were promptly evaluated by a physician and nurse practitioner or other advanced practice provider. A genetic counselor was available to provide counseling at most centers. The initial evaluation involved a physical exam and detailed collection of clinical and family history. Confirmatory β-glucosidase activity, lyso-Gb1 levels, and molecular *GBA* analysis were generally recommended at initial evaluation. Due to differences in provider preference across multiple institutions, confirmatory biochemical and molecular testing were performed at various laboratories. All laboratories that performed such testing were CLIA/CAP certified. Of the nine referral centers in the state, one declined to participate.

3. Results

From July 2019 to December 2023, 438,515 newborns underwent screening, resulting in 60 screen-positive cases. Of those positive screens, two cases were evaluated by specialists at external (non-referral) centers. One was reported as a false positive, while the other is pending with the state. Nineteen screen-positive newborns did not undergo confirmatory testing due to parental refusal, loss to follow-up, or death. Notably, 63% of the cases lacking confirmatory testing were attributed to parental refusal. Twenty-three screen-positive newborns were determined to be false positive cases after repeat enzyme was normal and/or *GBA* sequencing was non-diagnostic.

Out of 60 screen-positive newborns, 18 were ultimately diagnosed with GD: 14 were diagnosed with type I GD, 2 were diagnosed with suspected type I GD based on low

enzyme activity and compound heterozygosity of the GBA p.N409S allele with a variant of uncertain significance, and 2 were diagnosed with type II GD (Table 1). All subjects' NBS and confirmatory enzyme levels, genotypes, lyso-Gb1 levels, and treatment statuses are presented in Table 1.

Table 1. Clinical Data for Confirmed and Suspected Cases of Gaucher Disease.

Subject	NBS Enzyme	Confirmatory Enzyme	Lyso-Gb1	Genotype	Diagnosis	Treatment	Age at Treatment Initiation
1	9.4% [≥12.0%]	0.2 nmol/h/mg Prot [≥8.7]	0.104 nmol/mL [≤0.040]	*GBA* c.1226A>G (p.N409S) homozygous	Type I	Y	42 months
2	<5.3% [≥12.0%]	0.49 nmol/h/mg Prot [≥3.53]	0.103 nmol/mL [≤0.040]	*GBA* c.635C>G (p.S212*)/*GBA* c.1226A>G (p.N409S)	Type I	Y	29 months
3	8.1% [≥12.0%]	0.77 umol/L/h [≥1.60]	0.550 nmol/mL [≤0.040]	*GBA* c.1226A>G (p.N409S)/*GBA* c.84dupG (p.L29fs)	Type I	Y	28 months
4	11.6% [≥12.0%]	1.08 nmol/h/mg Prot [≤3.53]	0.066 nmol/mL [≤0.040]	*GBA* c.1226A>G (p.N409S) homozygous	Type I	N	N/A
5	9.3% [≥12.0%]	1.04 nmol/h/mg Prot [≤3.53]	0.113 nmol/mL [≤0.040]	*GBA* c.1226A>G (p.N409S)/*GBA* c.1448T>C (p.L483P)	Type I	N	N/A
6	5.6% [≥12.0%]	0.44 umol/L/h [≥1.60]	32.47 ng/mL [<17.41]	*GBA* c.1226A>G (p.N409S) homozygous	Type I	N	N/A
7	<5.3% [≥12.0%]	1.14 nmol/h/mg prot [≥3.53]	0.059 nmol/mL [≤0.040]	*GBA* c.1226A>G (p.N409S) homozygous	Type I	N	N/A
8	10.3% [≥12.0%]	0.5 [4.0–22.6 nmol/h/mg]	Not Performed	*GBA* c.1226A>G (p.N409S) homozygous	Type I	N	N/A
9	3.8% [≥12.0%]	0.774 nmol/h/mg prot [7.5–14.5]	Not Performed	*GBA* c.1448T>C (p.L483P)/*GBA* c.680A>G (p.N227S)	Type I	N	N/A
10	5.3% [≥12.0%]	0.4 nmol/h/mg [4.6–12]	Not Performed	*GBA* c.1226A>G (p.N409S) homozygous	Type I	N	N/A

Table 1. *Cont.*

Subject	NBS Enzyme	Confirmatory Enzyme	Lyso-Gb1	Genotype	Diagnosis	Treatment	Age at Treatment Initiation
11	4.9% [≥12.0%]	Not Performed	Not Performed	*GBA* c.1226A>G (p.N409S) homozygous	Type I	N	N/A
12	< 5.3% [≥12.0%]	Not Performed	Not Performed	*GBA* c.1226A>G (p.N409S) homozygous	Type I	N	N/A
13	9.0% [≥12.0%]	0.618 nmol/h/mg [7.5–14.5]	12 ng/mL [<1]	*GBA* c.84dupG (p.L29fs)/*GBA* c.1226A>G (p.N409S)	Type I	N	N/A
14	8.9% [≥12.0%]	Not Performed	Not Performed	*GBA* c.1226A>G, p.(N409S) homozygous	Type I	U	N/A
15	8.8% [≥12.0%]	1.06 nmol/h/mg Prot [≤3.53]	0.031 nmol/mL [≤0.040]	*GBA* c.1226A>G (p.N409S)/*GBA* c.1148G>A (p.G383D)	Suspected Type I	N	N/A
16	8.9% [≥12.0%]	0.93 umol/L/h [>1.60]	9.26 ng/mL [<17.41]	*GBA* c.1226A>G (p.N409S)/*GBA* c.686C>T (p.A229V)	Suspected Type I	U	N/A
17	<5.3% [≥12.0%]	0.31 umol/L/h [≥1.60]	>200 ng/mL [<17.41 ng/mL]	*GBA* c.203del (p.P68fs)/*GBA* c.1448T>C (p.L483P)	Type II	Y	1 month
18	5.3% [≥12.0%]	0.48 nmol/h/mg Prot [≥3.53]	Not Performed	*GBA* c.1448T>C (p.L483P) homozygous	Type II	Y	13 months

NBS results, baseline confirmatory enzyme, Lyso-Gb1 levels, and genotype are presented in this table. Whether or not the individual is on treatment is based on the last clinical evaluation, with age at treatment initiation listed for those on enzyme replacement therapy (ERT). Treatment statuses for Subject 14 and Subject 16 are unknown, as these individuals no longer follow up with the reporting referral center. Key: Y: yes, N: no, and U: unknown.

Subjects 1, 2, and 3 started ERT at 42 months, 29 months, and 28 months of age, respectively. Notably, Subject 3's parents initially refused further workup after discussion with the primary care physician. Subject 3 returned to care at 26 months of age after an older sibling was diagnosed with type I Gaucher disease. The older sibling had presented with a severe bone crisis and femur necrosis at age 4 years. Subjects 17 and 18 started off-label use of ERT as a palliative measure at 1 month and 13 months, respectively. Treatment information for subjects 1, 2, and 3 is presented below.

3.1. Treatment Initiation and Response in Type I GD

3.1.1. Subject 1

After the initial evaluation and diagnosis, follow-up appointments were recommended every six months. Interim history and exams from baseline to 24 months were considered normal, though physical exams were limited due to the need for telehealth visits during the COVID-19 pandemic.

The physical exam performed at 30 months was notable for mild splenomegaly. An abdominal ultrasound performed at 34 months demonstrated mild hepatomegaly with normal spleen size. Follow-up laboratory tests performed at 36 and 41 months revealed an increase in lyso-Gb1 levels up to 13 times the upper limit of normal (Table 2). An MRI of the liver, spleen, and bone marrow with elastography was performed at 40 months. The MRI demonstrated mild hepatosplenomegaly (liver volume 1.5 times normal with liver stiffness at EPI 2.65 kPa and spleen volume 6.9 times normal with increased splenic stiffness at EPI 5.43 kPa). The MRI also noted decreased T1-weighted signal intensity in the distribution of hematopoietic marrow without signs of osteonecrosis. The patient's family denied any other clinical symptoms in the child. Initiation of ERT was recommended.

Table 2. Laboratory evaluations for Subject 1.

	DOL 14	24 Months	30 Months	36 Months	41 Months	46 Months	52 Months	62 Months
Lyso-Gb1 [≤0.040 nmol/mL]	0.104	0.194	0.198	0.372	0.504	0.199	0.171	0.109
Chitotriosidase [4–120 nmol/h/mL]	--	--	--	--	--	--	--	--
WBC [4.9–13.2 K/uL]	NC	7.5	6.8	8.2	7.0	8.1	6.9	5.4
RBC [3.90–5.30 10^6/uL]	NC	4.29	4.12	4.21	4.23	4.07	4.38	4.33
Hgb [11.5–13.5 g/dL]	NC	10.6	10.9	11.2	11.3	11.1	12.1	12.3
PLT [150–450 10^3/uL]	NC	263	156	162	189	234	235	266

Laboratory values are presented here for Subject 1. Subject 1 does not produce chitotriosidase. Biomarkers improved with treatment initiation at 42 months. WBC = white blood cells, RBC: red blood cells, Hgb: hemoglobin, PLT: platelets, and NC = not collected.

Subject 1, aged 42 months at treatment initiation, received 60 u/kg of imiglucerase every two weeks. Infusions were tolerated well with no symptoms of hypersensitivity or anti-drug antibody development. Laboratory monitoring performed at 46 months demonstrated down-trending lyso-Gb1 level to 5 times the upper limit of normal (Table 2). Repeat MRI with elastography performed at 58 months demonstrated stable hepatosplenomegaly with liver volume 1.5 times normal and normal stiffness and a spleen volume 5.6 times normal with increased stiffness at EPI 4.05 kPa. Bone marrow findings were stable compared to the prior study. Lyso-Gb1 at the last clinical evaluation, at 62 months, decreased to 3 times the upper limit of normal (Table 2). A physical exam performed at that time noted resolution of hepatosplenomegaly. Other clinical symptoms of Gaucher disease were denied.

3.1.2. Subject 2

After initial evaluation and diagnosis, follow-up was recommended every six months. Exams and interim history from baseline to 16 months were considered normal, though physical exams were limited due to the need for telehealth visits during the COVID-19 pandemic. Biomarkers at 16 months of age demonstrated a 7-fold increase in lyso-Gb1 level and an initial chitotriosidase level of >70 times the upper limit of normal (Table 3). At 21 months of age, lyso-Gb1 increased to 20 times the upper limit of normal, and chitotriosidase increased to >85 times the upper limit of normal (Table 3). An abdominal ultrasound with elastography performed at that time demonstrated normal size and compliance of both the spleen and liver. However, at 25 months his weight gain stalled, though linear growth remained normal.

Table 3. Laboratory evaluations for Subject 2.

	DOL 12	9 Months	16 Months	17 Months	19 Months	28 Months	34 Months	43 Months	49 Months
Lyso-Gb1 [≤0.040 nmol/mL]	0.103	0.104	0.749	NC	0.780	0.933	0.173	0.102	0.165
Chitotriosidase [4–120 nmol/h/mL]	NC	NC	8721	NC	10,486	9965	5239	1033	NC
WBC [5.1–13.4 K/uL]	NC	5.7	7.0	10.7	6.0	2.7	3.7	4.8	4.3
RBC [3.90–5.30 10^6/uL]	NC	4.28	4.56	4.12	4.23	3.7	3.84	4.04	4.19
Hgb [11.5–13.5 g/dL]	NC	11.2	11.2	9.5	9.5	8.1	10.0	11.0	11.2
PLT [150–450 10^3/uL]	NC	197	214	202	214	103	193	198	181

Laboratory values are presented for Subject 2. Subject 2 demonstrated increasing lyso-Gb1 and chitotriosidase prior to treatment initiation with improved values after initiation at 29 months of age. WBC = white blood cells, RBC: red blood cells, Hgb: hemoglobin, PLT: platelets, and NC = not collected.

The follow-up evaluation at 28 months of age was remarkable for notable fatigue and easy bleeding and bruising. Laboratory tests at that time demonstrated pancytopenia; the lyso-Gb1 level was elevated at 23 times the upper limit of normal, and chitotriosidase was stably elevated at >80 times the upper limit of normal (Table 3). The physical exam was remarkable for splenomegaly. An MRI of the liver and spleen with elastography performed at 29 months revealed liver volume 1.7 times normal with increased stiffness at EPI 3.3 kPa and spleen volume 15.3 times normal with increased stiffness at EPI 6.1 kPa.

Subject 2 was 29 months old at treatment initiation, receiving 60 u/kg of imiglucerase every two weeks. Infusions were tolerated well with no symptoms of hypersensitivity or anti-drug antibody development. Laboratory evaluation at 34 months demonstrated improvement of hematologic parameters, decreasing lyso-Gb1 at 13 times the upper limit of normal, and decreasing chitotriosidase at 44 times the upper limit of normal (Table 3). An MRI of the liver, spleen, and bone marrow with elastography was performed at 41 months and revealed liver volume 1.2 times normal with normal stiffness at EPI 1.9 kPa, as well as spleen volume 4.7 times normal with increased stiffness at EPI 7.1 kPa. Bone marrow demonstrated normal marrow signal intensity without focal abnormality. The last clinical evaluation at 49 months of age demonstrated improved biomarkers with lyso-Gb1 elevated at 4 times the upper limit of normal (Table 3). The physical exam performed at that

time demonstrated resolution of splenomegaly with improvement in linear growth and weight gain.

3.1.3. Subject 3

After consultation with the primary care provider, Subject 3's parents declined a referral to a specialist for confirmatory testing. Subject 3 did not pursue any specialty care until his older sibling, who was born before the implementation of newborn screening, was diagnosed with type I GD. The older sibling had presented with a severe bone crisis and femur necrosis at age 4 years. Subject 3 presented for an initial evaluation by a specialist at 26 months of age. Hepatosplenomegaly was noted during the physical exam. Confirmatory lyso-Gb1 level was increased at 14 times the upper limit of normal, and chitotriosidase was increased at 73 times the upper limit of normal (Table 4). A complete blood count (CBC) demonstrated low hemoglobin and platelet counts (Table 4). Clinical symptoms were denied. An abdominal ultrasound at 27 months revealed hepatosplenomegaly and diffuse increased hepatic parenchymal echogenicity.

Table 4. Laboratory evaluations for Subject 3.

	26 Months	28 Months	30 Months	34 Months
Lyso-Gb1 [≤0.040 nmol/mL]	0.550	0.567	0.142	0.152
Chitotriosidase [4–120 nmol/h/mL]	8714	11,208	4264	1380
WBC [5.1–13.4 K/uL]	6.7	6.8	9.1	8.0
RBC [3.90–5.30 10^6/uL]	4.71	4.75	4.99	5.30
Hgb [11.5–13.5 g/dL]	9.1	9.1	10.1	11.3
PLT [150–450 10^3/uL]	126	155	183	227

Laboratory values are presented for Subject 3. There is a notable reduction in biomarkers after treatment initiation at 28 months. WBC = white blood cells, RBC: red blood cells, Hgb: hemoglobin, PLT: platelets, and NC = not collected.

Subject 3 began treatment at 28 months of age with 60 u/kg of imiglucerase every 2 weeks. Laboratory evaluation at 30 months demonstrated a decreased lyso-Gb1 level at 4 times the upper limit of normal and a decreasing chitotriosidase level at 36 times the upper limit of normal (Table 4). At his last clinical evaluation at 34 months of age, lyso-Gb1 remained stable at 4 times the upper limit of normal, and chitotriosidase decreased to 12 times the upper limit of normal (Table 4). The physical exam performed at that time was normal, with no detectable hepatosplenomegaly. Other clinical symptoms of Gaucher disease were denied.

4. Discussion

Newborn screening is a public health initiative that successfully identifies children with rare, treatable disorders to enable prompt access to disease-modifying therapies. Wilson and Jungner previously published criteria for adding conditions to population screening initiatives [26]. Gaucher disease appears to be a candidate for population screening based on the following criteria: (a) a specific screening test based on enzyme analysis is available, (b) confirmatory tests, including enzyme assays, specific biomarkers, and genetic tests, are accessible, (c) disease-modifying therapies exist, (d) diagnostic delays can extend

to 7 years or more in some cases, (e) the disease often has an early onset, presenting in the first years of life, and (f) irreversible bone disease, which could be prevented by early treatment, is a common presentation. These factors collectively support the consideration of Gaucher disease for population screening programs.

It is well established that early diagnosis and prompt initiation of therapy improve clinical outcomes in Gaucher disease [7,13,16]. Though some cases of type I Gaucher disease may present later in life, newborn screening enables early, non-invasive clinical monitoring for signs of disease, prevents the diagnostic odyssey, and allows early treatment.

In type II Gaucher disease, although treatment cannot prevent central nervous system (CNS) involvement, newborn screening can limit the diagnostic odyssey of affected newborns and lead to early initiation of enzyme replacement therapy (ERT) to reduce visceral disease manifestations [14,15].

The incidence of Gaucher disease across all subtypes in New Jersey was approximately 1 in 24,362 live births between July 2019 and December 2023. This incidence is higher than what was previously reported in other states, such as Illinois (1 in 43,959), Missouri (1 in 43,701), and Oregon (1 in 36,695), as well as other countries, such as China (1 in 80,855) [21–23,27]. Among the 18 confirmed cases of Gaucher disease within this population, pre-symptomatic monitoring enabled early identification of disease manifestations for three children within the first three and a half years of life. Early signs of disease included organomegaly, impaired growth, hematologic abnormalities, and elevated biomarkers of disease, most notably, lyso-Gb1 and chitotriosidase. Treatment was tolerated well in all three individuals, with no significant signs of hypersensitivity. ERT initiation resulted in reduction of biomarkers in all three patients. Subjects 1 and 2 demonstrated resolution of organomegaly during the follow-up period. Clinical symptoms, when reported, were resolved with therapy, and all three subjects are doing clinically well with no new reported issues. This report provides evidence that newborn screening for Gaucher disease benefits the general population by enabling pre-symptomatic diagnosis and monitoring of affected children during the latent period of this disease.

The high false positive rate in New Jersey indicates the need for improved screening methods for Gaucher disease. New Jersey newborn screening for lysosomal storage disorders, including Gaucher disease, is currently performed as a single-tier test. The false positive cases were cleared after repeat enzyme was normal and/or *GBA* sequencing was non-diagnostic. Carriers of Gaucher disease can have indeterminate or low enzyme levels on leukocyte testing. False positive cases with either negative or heterozygous pathogenic variants in *GBA* were found to have variable levels of enzyme activity reported on the newborn screen. The lowest reported enzyme activity in a false positive case was 7.4% [≥12.0%], while the highest was 11.6% [≥12.0]. However, one true positive, Subject 4, demonstrated borderline enzyme activity on newborn screening at 11.6%. This suggests that adjusting the enzyme activity cutoff may result in false negative cases. Therefore, a more nuanced approach to screening is needed to improve accuracy and reduce false positives while avoiding false negatives.

Illinois's pilot program reported that 74% of screen-positive newborns for Gaucher disease were premature [21]. While rates of false positives in screen-positive infants who were premature were not reported, this finding raises concern that gestational age may impact the ability to interpret screening results for Gaucher disease. The gestational ages and birth weights of false positives were not written on newborn screening records in New Jersey. It is possible that both resulted in false positive results in our cohort. Implementing cutoff values based on different gestational ages and birth weights may help reduce the number of false positives.

Tiered testing would be beneficial for Gaucher disease newborn screening. This approach is already utilized for newborn screening for other lysosomal storage disorders (LSDs) such as Pompe disease, Mucopolysaccharidosis type I (MPS I), and Mucopolysaccharidosis type II (MPS II) in some states. For Gaucher disease, a three-tiered approach is recommended, with enzyme activity measurement as the first tier, *GBA* sequencing as the second tier, and lyso-Gb1 as the third tier. The development of second- and third-tier tests, such as genotype and/or biomarkers, has shown effectiveness in reducing recall rates for certain LSDs, such as Pompe, MPS I, and Gaucher disease [28,29]. Utilization of a tiered approach can aid in the prompt identification of affected newborns while reducing false positives.

For twelve of the screen-positive cases, no initial confirmatory testing was performed due to parental refusal. Refusal for additional testing occurred both after an initial discussion with the pediatrician and after an initial evaluation by a specialist. The state does not require documentation of the reason for parental refusal. However, the higher-than-expected rate of parental refusal may reflect attitudes towards newborn screening for Gaucher disease. There might be parental concern about labeling their children with a rare disease such as Gaucher in certain cultures or ethnic groups. In addition, there might be a parental perception of Gaucher disease being a late-onset disorder that does not need early diagnosis and treatment.

Gaucher disease exists as a clinical spectrum. There are individuals with type I GD who remain asymptomatic throughout their lives. For individuals with a family history of type I GD or for those who are a part of ethnic groups in which type I Gaucher disease is highly prevalent, at-risk individuals may refuse confirmatory testing if they have personal experience with affected individuals who've not needed treatment. Knowledge of disease or carrier status may increase fears of stigma for children identified through newborn screening. A previous study revealed parental attitudes towards newborn screening for Pompe disease [30]. Further work is needed to elucidate specific reasons for parental refusal and understand attitudes regarding newborn screening for Gaucher disease in the general population.

Newborn screening for Gaucher disease has the potential to significantly improve clinical outcomes for affected children by enabling early diagnosis. Clinical monitoring using non-invasive methods can effectively identify affected individuals who need therapy. However, comprehensive guidelines for monitoring during the pre-symptomatic period are still needed. Methods to improve perinatal education regarding newborn screening for LSDs, as well as culturally competent counseling strategies, are needed to ensure families understand the implications of a positive newborn screen and can make informed decisions regarding follow-up.

To enhance the effectiveness of newborn screening for Gaucher disease, several improvements are necessary: (a) Developing more effective methods to educate expectant parents about newborn screening for Gaucher disease is crucial. This education should begin during prenatal care and continue through the immediate postnatal period. (b) Implementing culturally sensitive approaches to genetic counseling is essential. These strategies should ensure that families from diverse backgrounds can fully understand the implications of a positive newborn screen. (c) Providing families with comprehensive information and support is vital to help them make informed decisions regarding follow-up care and potential treatment options. (d) Ensuring that screening results are communicated clearly and promptly to both healthcare providers and families is critical for timely intervention. By addressing these areas, the newborn screening process for Gaucher disease can be optimized, leading to better understanding of screening for families of screen-positive newborns.

In conclusion, newborn screening for Gaucher disease has proven effective in identifying many newborns with the condition, allowing for early treatment in some cases. The success of the screening in New Jersey highlights the benefits of newborn screening for Gaucher disease. However, challenges remain, particularly with false positives and parental refusal to pursue confirmatory testing and follow-up care. These issues need to be addressed to enhance the effectiveness of newborn screening for Gaucher disease.

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Gaucher disease

Inclusion of Gaucher disease in newborn screening panels across the U.S.

This report presents a compelling case for the inclusion of Gaucher disease in newborn screening panels across the United States

March 7, 2025

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This report is produced as part of a collaboration between AllMyHealth and the Gaucher Community Alliance.

About the Gaucher Community Alliance

The Gaucher Community Alliance (GCA) is a dedicated patient advocacy organization committed to improving the lives of individuals affected by all types of Gaucher disease. Through educational outreach, patient support initiatives, and public health advocacy, the GCA strives to raise awareness, accelerate diagnosis, and ensure access to timely and effective treatment for all Gaucher patients and their families.

https://www.gauchercommunity.org/

About AllMyHealth

AllMyHealth is an innovative digital platform dedicated to empowering rare disease communities through reliable information, actionable insights, and community-driven support. By providing patients, caregivers, and healthcare stakeholders with high-quality resources and advocacy tools, AllMyHealth aims to improve health outcomes and facilitate informed decision-making for individuals affected by rare diseases, including Gaucher disease.

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Executive Summary

Gaucher disease (GD) is a rare genetic disorder with potentially life-threatening complications. Early detection through newborn screening (NBS) allows for timely intervention and improved outcomes for affected infants, for all types of the disease. This report presents a compelling case for the inclusion of GD in NBS panels across the United States. It highlights the clinical justification, technical feasibility, public health benefits and cost-effectiveness of screening for GD. Additionally, it examines state-level success stories and addresses common objections to NBS for GD.

Key points on the necessity of including gd in newborn screening panels

- GD is a serious genetic disorder with potentially life-threatening
- Early diagnosis and treatment through NBS can significantly improve health outcomes.
- Reliable screening tests and effective treatments are available.
- NBS for GD is cost-effective and aligns with public health goals.

Overview of benefits, urgency, and recommendations

- **Benefits**: Early diagnosis through NBS enables timely initiation of treatment, preventing irreversible organ damage and improving long-term health outcomes for individuals with GD.
- **Urgency**: Early detection is critical, especially for severe forms of GD, which can manifest with rapidly progressing symptoms [1].
- **Recommendation**: We advocate for the inclusion of GD in NBS panels nationwide.

Introduction

Gaucher disease (GD) is a rare, inherited metabolic disorder characterized by the accumulation of fatty substances (lipids) in various organs and tissues, primarily the spleen and liver [2]. This lipid buildup can lead to a range of symptoms, including enlarged organs, bone pain, anemia, easy bruising, and in severe cases, neurological complications [1].

Current landscape of GD newborn screening in the U.S.

Currently, only four states - Illinois, Missouri, New Jersey, and Tennessee - include GD in their NBS panels [3]. Screening for GD is also available at select New York hospitals and birthing sites through the ScreenPlus research study [3]. However, GD is not yet included in the Recommended Uniform Screening Panel (RUSP) provided by the Secretary of the U.S. Department of Health and Human Services to guide state health agencies [3]. It is important to note that newborn screening for GD may yield false-positive results, necessitating confirmatory testing to ensure an accurate diagnosis [4].

Purpose of this paper

This analysis aims to provide a comprehensive overview of GD and the compelling reasons for its inclusion in newborn screening (NBS) panels throughout the United States [5]. It will examine the clinical, technical, public health, and economic aspects of GD screening, while also addressing common objections and highlighting successful state-level implementations.

Background on gaucher disease

GD is a lysosomal storage disorder caused by a deficiency of the enzyme glucocerebrosidase [5]. This enzyme deficiency disrupts the breakdown of a fatty substance called glucocerebroside, leading to its accumulation in cells and tissues [5]. Over time, this excessive storage in the lysosomes can cause permanent cellular and tissue damage, particularly in the spleen, liver, bone marrow, and, rarely, the brain [6]. GD is classified as a "toxic accumulation" inborn error of metabolism, as the buildup of glucocerebroside lipids can have harmful effects on various organs and systems [7].

Types of GD and clinical manifestations

There are five known types of Gaucher disease: type 1, type 2, type 3, perinatal lethal, and cardiovascular [7]. The three major clinical types are:

- **Type 1 (non-neuronopathic)**: This is the most common type, affecting the spleen, liver, blood, and bones [8]. It typically does not involve the brain or spinal cord. Symptoms can range from mild to severe and may appear at any age [8].
- **Type 2 (acute neuronopathic)**: This rare form appears in infants younger than 6 months and causes severe brain damage [8]. It is typically fatal within the first few years of life.
- **Type 3 (chronic neuronopathic)**: This type is also rare and causes both organ and neurological problems [8]. Symptoms usually appear in childhood and progress more slowly than in type 2.

Clinical manifestations of GD vary depending on the type and severity of the disease. Common symptoms include [1]:

- Enlarged spleen and liver (hepatosplenomegaly)
- Low red blood cell count (anemia)

- Low platelet count (thrombocytopenia), leading to easy bruising and bleeding
- Bone pain and abnormalities
- Lung problems
- Neurological complications, such as seizures, muscle stiffness, and developmental delay (in types 2 and 3)

Genetic basis and prevalence

GD is caused by variants (mutations) in the *GBA1* gene, which provides instructions for making the enzyme glucocerebrosidase [1]. This enzyme plays a crucial role in the body by cleaving the beta-glucosidic linkage of glucocerebroside lipids [7]. GD is inherited in an autosomal recessive pattern, meaning that a child must inherit two mutated copies of the gene (one from each parent) to develop the disease [1].

GD occurs in approximately 1 in 50,000 to 1 in 100,000 people in the general population [1]. The incidence is higher among people of Ashkenazi Jewish descent, affecting approximately 1 in 450 live births within this population [9].

Challenges and delays in current diagnostic practices

Diagnosing GD can be challenging due to the variability of symptoms and the rarity of the disease [10]. Many patients experience diagnostic delays, sometimes consulting several specialists before receiving an accurate diagnosis [11]. This delay can lead to disease progression and irreversible complications, such as advanced bone disease [12].

Factors contributing to diagnostic delays include:

- **Variable clinical presentation**: GD symptoms can overlap with those of other disorders, making it difficult to recognize [13].

- **Low physician awareness**: Due to its rarity, many healthcare providers are unfamiliar with GD [13].
- **Nonspecific symptoms**: Mild or nonspecific symptoms may not prompt physicians to consider GD in their differential diagnoses [13].

The historical context of GD research sheds light on the challenges faced in understanding and diagnosing this disorder [14]. Early research focused on recognizing the enzymatic defect, isolating and characterizing the protein, and identifying the first mutant alleles in patients [14]. These efforts have paved the way for advancements in diagnostic techniques and treatment options.

Delayed diagnoses in GD patients contribute to slower-than-optimal initiation of treatment and can result in irreversible complications [12]. Early detection is critical, especially for severe forms of GD, which present with rapidly progressing symptoms [1]. These insights underscore the urgency of implementing effective strategies for early diagnosis, such as newborn screening.

The case for newborn screening

NBS for GD offers numerous benefits and addresses the challenges associated with current diagnostic practices.

Clinical justification: impact of early diagnosis and treatment

Early diagnosis of GD through NBS allows for timely initiation of treatment, which can significantly improve health outcomes [15]. Treatment options for GD include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) [15]. ERT aims to replace the deficient enzyme, while SRT reduces the production of the substance that accumulates in the body [15].

Early intervention can help prevent or reverse many of the non-neurological manifestations of GD, such as organ enlargement, bone disease, and blood abnormalities [16]. It can also improve overall quality of life and potentially normalize life expectancy for individuals with type 1 GD16. Additionally, early treatment may help prevent heart and lung problems that can occur in some GD patients [12].

Although there are currently limited treatment options for neuronopathic GD (Types 2 and 3), early diagnosis allows for optimized supportive care, participation in clinical trials and access to potential future therapies, such as gene therapy or chaperone-based treatments which are under development. Early identification can enable physicians to provide neuroprotective strategies, manage seizures and anticipate respiratory complications before they become life-threatening.

Technical Feasibility: Reliable Screening Tests and Their Advantages

Reliable screening tests for GD are available and can be readily incorporated into existing NBS programs. The primary screening method

involves measuring the activity level of the enzyme glucocerebrosidase in a dried blood spot sample collected from the newborn's heel [17]. This test is specific and sensitive, effectively identifying infants with low enzyme activity who may have GD [18].

Advantages of the screening test include:

- **Minimally invasive**: It requires only a small blood sample from the baby's heel.
- **High throughput**: It can be performed efficiently on a large scale.
- **Cost-effective**: It is relatively inexpensive to perform.

In addition to the primary screening test, imaging tests such as dual-energy X-ray absorptiometry (DXA) and MRI can be used to monitor GD progression [19]. DXA measures bone density, while MRI can assess organ enlargement and bone marrow involvement [19].

Public health perspective: addressing health disparities and improving outcomes

NBS for GD aligns with public health goals by promoting early detection and intervention for a serious genetic disorder. It can help address health disparities by ensuring that all infants, regardless of their background or access to healthcare, have the opportunity to benefit from early diagnosis and treatment.

By identifying and treating GD early, NBS can contribute to:

- **Reduced morbidity and mortality**: Preventing severe complications and improving long-term health outcomes.
- **Improved quality of life**: Enabling individuals with GD to live healthier and more fulfilling lives.
- **Reduced healthcare costs**: Early intervention can prevent costly hospitalizations and long-term care needs.

Early detection through NBS also facilitates comprehensive monitoring of bone health in GD patients, using tools such as MRI and DEXA scans [13]. This proactive approach can help prevent or mitigate bone complications, such as fractures and osteonecrosis.

Early intervention is particularly crucial for infants with Type 2 and Type 3 GD, as timely symptom monitoring can help prevent severe neurological decline. Identifying affected infants early allows families to access genetic counseling, supportive therapies, and emerging experimental treatments.

Cost-effectiveness: long-term healthcare savings through early intervention

While the initial costs of implementing NBS for GD may seem high, studies suggest that it is a cost-effective strategy in the long run [20]. Early diagnosis and treatment can lead to significant healthcare savings by preventing or reducing the need for expensive interventions, such as splenectomy, blood transfusions, and joint replacement surgery [20].

A study conducted in Taiwan found that the annual per-patient cost of illness for GD was USD 49,925 [20]. This cost included direct healthcare expenses, such as pharmaceuticals, inpatient care, and outpatient services, as well as indirect costs, such as productivity loss for caregivers [20]. Early intervention through NBS can potentially reduce these costs by preventing disease progression and the need for costly interventions.

State-level success stories

Several states have successfully implemented NBS for GD, demonstrating the feasibility and benefits of screening.

Highlights from states already screening for gd

- **Illinois**: Illinois began statewide screening for lysosomal storage disorders, including GD, in 2014 [6].
- **Missouri**: Missouri was one of the first states to include GD in its NBS panel [18].
- **New Jersey**: New Jersey also includes GD in its NBS program [18].
- **Tennessee**: Tennessee is another state that screens newborns for GD [18].

Outcomes and best practices from these implementations

These states have reported positive outcomes from their NBS programs for GD, including:

- **Increased detection rates**: Identifying more infants with GD, including those who may not have been diagnosed otherwise.
- **Timely intervention**: Enabling early initiation of treatment and preventing disease progression.
- **Improved health outcomes**: Reducing the incidence of severe complications and improving long-term health for individuals with GD.

It is important to acknowledge that false-positive newborn screening results can occur, highlighting the need for confirmatory testing to ensure accurate diagnosis and appropriate follow-up care [5].

Best practices from these state-level implementations include:

- **Collaboration among stakeholders:** Engaging healthcare providers, public health officials, and patient advocacy groups in program development and implementation.
- **Education and outreach:** Providing information to parents and healthcare providers about GD and the benefits of NBS.
- **Follow-up and diagnostic testing:** Ensuring timely and appropriate follow-up testing for infants with positive screening results.
- **Access to treatment and care:** Connecting families with specialized care centers and support services.

Overcoming common objections

While NBS for GD offers numerous benefits, some common objections have been raised.

Objection 1: GD is a rare disease, and screening all newborns may not be cost-effective.

- **Response:** While GD is rare in the general population, it is more common in certain ethnic groups, such as people of Ashkenazi Jewish descent [9]. Furthermore, the long-term healthcare savings from early intervention can outweigh the initial costs of screening [20].

Objection 2: Screening for a late-onset disorder like GD may cause unnecessary anxiety for parents.

- **Response:** While parental anxiety is a valid concern, studies have shown that providing education and support to families can effectively mitigate this anxiety [21]. Clear communication and support from healthcare providers are essential to address parental concerns and ensure informed decision-making [22]. Additionally, the benefits of early detection and intervention outweigh the potential risks of parental anxiety [23]. It is crucial to consider the potential psychological impacts of misdiagnosis and the lack of knowledge among medical providers, which can further contribute to parental anxiety [23].

Objection 3: There is limited genotype-phenotype correlation in GD, making it difficult to predict disease severity based on screening results.

- **Response:** While genotype-phenotype correlation can be complex, early diagnosis still allows for close monitoring and timely intervention if symptoms develop [25]. This can prevent irreversible complications and improve overall outcomes. Research in this area is ongoing, as demonstrated by a study conducted in Andalusia, Spain, which identified a novel mutation in the GBA gene [26].

Policy recommendation for newborn screening

Integrating Gaucher disease into newborn screening panels represents not just a clinical imperative but a decisive public health advancement. Early detection equips healthcare providers with the tools needed to prevent irreversible damage and improve long-term outcomes, while also reducing the burden on families and the healthcare system. By embracing evidence-based policy recommendations, fostering robust stakeholder engagement, and mobilizing advocacy efforts at both state and national levels, policymakers can drive a transformative change that ensures every newborn receives the opportunity for timely diagnosis and intervention. The time to act is now - by prioritizing Gaucher disease screening, we can pave the way for a healthier future and set a new standard in newborn care.

The rapid development of novel therapies, including cell and gene therapies, presents both opportunities and challenges for newborn screening programs [28]. To effectively accommodate these advancements, a coordinated national vision and solutions are needed to address issues such as cross-state variability, national harmonization, data collection, and support for state implementation [28].

Conclusion

The inclusion of GD in NBS panels across the U.S. is a critical step towards improving the lives of individuals with this serious genetic disorder. Early diagnosis through NBS enables timely intervention, prevents irreversible organ damage, and improves long-term health outcomes. Reliable screening tests and effective treatments are available, making NBS for GD both feasible and beneficial.

Policymakers should prioritize the inclusion of GD in NBS panels, considering the evidence of its effectiveness, the potential benefits for families and society, and the long-term cost-effectiveness of early intervention.

Patient advocacy groups are playing a vital role in raising awareness about GD, educating families, and advocating for policies that support early detection and access to treatment.

By overcoming common objections, learning from state-level success stories, and adapting to advancements in treatment and technology, stakeholders can work collaboratively to ensure that all newborns have the opportunity to benefit from early detection and treatment of Gaucher disease. This will ultimately improve public health and reduce healthcare disparities.

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GAUCHER COMMUNITY ALLIANCE

Gaucher Community Alliance, in collaboration with major national leaders and experts in Gaucher disease, newborn screening, and medical genetics (signatories to this) provide the following comments about the requirements for newborn screening. Herein, we address the specific questions required for newborn screening of Gaucher. Our responses and supporting references are included below.

Question 1. Is there a newborn screening test available?

We affirm that MS/MS is a reliable and validated method for assessing GCase activity in newborn screening programs. The strengths of MS/MS screening include:

High Sensitivity and Specificity: Can detect even minimal enzyme activity, reducing false negatives.

High Throughput: Suitable for large-scale population screening due to its ability to process many samples simultaneously.

Flexibility: Can be multiplexed to screen for multiple lysosomal storage disorders (e.g., Gaucher, Pompe, Fabry, Niemann-Pick).[1]

Question 2. Is there agreement about the case definition of the targeted condition and diagnostic confirmation after a positive newborn screen?

There is agreement on the targeted conditions. The case definition is non-neuronopathic Gaucher disease and chronic neuronopathic Gaucher disease.

The diagnosis of Gaucher disease is confirmed through two widely accepted methods:

1. Biochemical testing to assess deficient acid β-glucosidase (GCase) enzyme activity using MS/MS
2. Genetic testing to identify biallelic pathogenic variants in the *GBA* gene. We believe it is preferable to perform whole GBA gene sequencing as in the context of highly multi-ethnic populations; this approach can obviate the challenges arising in genotyping from highly homologous pseudogene, GBA.[2, 3]

For enhanced diagnostic precision, second-tier testing measuring glucosylsphingosine levels effectively distinguishes patients with Gaucher disease from false positives and it additionally provides a baseline for longitudinal monitoring of the total body burden of Gaucher cells. The gold standard for diagnosing Gaucher disease is the demonstration of acid β-glucosidase (GCase) enzyme activity <10% of normal, which may be additionally confirmed by its measurement in peripheral blood leucocytes if needed.[4] While GBA genotype-phenotype correlations are imperfect, biochemical and clinical monitoring provides the basis for effective individualized disease management.[2] Moreover, the presence of at least one p.Asn409Ser allele in the *GBA* gene absolutely predicts type 1 Gaucher disease while homozygosity for p. Leu 483Pro mutation is

strongly predictive of neuronopathic type 2 or type 3 Gaucher disease.[5] The presence of complex recombinant alleles with closely linked pseudogene also predicts more severe disease. Early identification allows for appropriate monitoring strategies tailored to each patient and treatment if indicated while avoiding diagnostic odysseys that can lead to irreversible complications.

a. *Which variants improve with treatment when identified before clinical symptoms appear?*

Both non-neuropathic Gaucher disease and neuronopathic Gaucher disease improve with treatment before clinical symptoms appear.

Enzyme replacement therapy (ERT) is the standard of care for pediatric patients with symptomatic Gaucher disease, regardless of the genetic variant.[3] ERT effectively reverses key manifestations, including hepatosplenomegaly, anemia, thrombocytopenia, and bone disease, while positively impacting growth and quality of life. [2] In Gaucher disease, as in other lysosomal disease, there is robust international evidence that earlier diagnosis and timely initiation of ERT prevents disabling complications even among patients designated to have type 3 Gaucher disease, initiation of ERT during infancy dramatically reverses hematological, visceral disease, and growth failure; children who otherwise have the life-threatening disease have a good survival rate into their second decades on ERT.[2, 3, 6, 7]

An issue that has hindered the application of NBS in Gaucher disease, is the perception that individuals who are homozygous for the Asn409Ser may have no disease manifestations and in such families the diagnosis could be overly burdensome. Emerging evidence is at variance with the earlier notion about the benign nature of this genotype.[8] We recognize that families identified in this category would receive counseling and monitoring that minimizes the burden and at the same time empowering for optimal health monitoring.

b. *How many infants have variants that are early onset Gaucher and require early treatment vs. infants with late-onset variants who need to be monitored?*

The world literature is mostly centered on Gaucher disease associated with the founder mutation from Eastern Europe p.ASn409Ser (as compound heterozygote or homozygous form). However, the GBA gene locus on chromosome 1q21 is vulnerable to gene-conversion events with closely linked, highly homologous pseudogene that harbors severe *GBA* mutations, i.e., p. Leu 483Pro.[9] Therefore, worldwide, severe GD appears to have been significantly underestimated in the literature, a significant issue given the multiethnic population structure of the US. The unprecedented collective experience of the signatories to our response clearly demonstrates dire consequences of prolonged diagnostic odysseys in babies with the most severe types of GD who suffer rapid progression of systemic (and neurological disease in GD2/GD3), missing optimal window for therapeutic intervention and maximal gains of QoL.

A study by Paige Kaplan et al in 2006 involving 887 children enrolled in the international Gaucher registry, ICGG, underscore that children with Gaucher disease are underserved by current nosology (i.e., type 1) and watchful waiting approach.[10] All 887 are designated as type 1, even though 14% had neuronopathic GBA genotypes (L444P homozygous + L444P/Recombinant allele). The majority of the children, regardless of GBA genotype, had significant disease manifestations involving the liver, the spleen, hematologic indices, the skeletal system, and slowed goth parameters. A significant confounder in the underestimation of the burden of neuronopathic genotypes is that care providers will err towards the designation of type 1 Gaucher disease to avoid pushback by insurance companies stating ERT is approved only for people with type 1 Gaucher disease.

Together, these issues underscore striking inequity faced by the most vulnerable individuals affected by Gaucher disease. We posit that the introduction of NBS will advance a new era to rectify these unmet needs and health transformation for individuals affected by Gaucher disease.

All variants of Gaucher disease are appropriate for newborn screening. The completed worksheet is below.

Name of Condition or Phenotype	Nominated Targeted Condition (Yes/No)	Case Definition Available (Yes/No)	Medically Serious (Yes/No)	Prospective Population-Based Screening Project (Yes/No)	Diagnostic Confirmation Process Available (Yes/No)	Early Identification Associated with Net Benefit for the Infant (Yes/No)	Estimated Birth Prevalence
Gaucher disease	Yes	Yes	Yes[3]	Yes	Yes[3]	Yes[3]	General population: 0.7-1.75:100,000 Ashkenazi Jewish descent: 118:100,000[11]

Question 3. Is there a prospective population-based newborn screening project that has identified at least one infant with the condition?

Yes

Question 4. Can identification of the targeted condition before clinical presentation allow provision of effective therapy and improve outcomes for screened infants?

Yes, early identification offers substantial benefits, including:

- **Timely initiation of treatment:** Early enzyme replacement therapy (ERT) has been shown to normalize hemoglobin and platelet counts, reduce organomegaly, and improve growth outcomes in symptomatic pediatric patients. Early treatment also minimizes irreversible complications such as bone deformities.
- **Monitoring asymptomatic cases:** For infants with late-onset variants, early identification enables regular monitoring to prevent disease progression and optimize health outcomes.
- **Reducing diagnostic delays:** Gaucher disease diagnosis can be delayed by up to seven years, leading to worsened outcomes. Newborn screening eliminates these delays.

a. *Is there published data from sibling studies or state newborn screening programs to support benefit of early identification and treatment?*

While published sibling studies on the benefits of newborn screening for Gaucher disease are unavailable, evidence supports the benefits of early treatment. Retrospective studies demonstrate significant improvements in outcomes when ERT is initiated promptly after symptom onset. [12],[13] Additionally, parents of children diagnosed early have reported reduced stress and improved confidence in managing their child's health through structured monitoring and treatment plans.

Due to clinical heterogeneity, an accurate diagnosis of GD1 can be delayed by 7 years or longer after symptoms and signs first appear.[2, 3, 14] Potential benefits of early diagnosis include infrastructure to provide support from genetic counselors and physicians familiar with Gaucher disease.[13] Such support may be useful for asymptomatic patients who would require monitoring throughout childhood and adulthood, as well as for symptomatic patients who require early treatment.

Gaucher disease is included in the newborn screens in Missouri, Illinois, New Jersey, Tennessee, Oregon, New Mexico, and at certain hospitals in New York.[15, 16] Missouri began screening in 2013 and Illinois followed in 2014. From November 2014 to August 2016, they performed a 5-plex LSD screen for Gaucher, Pompe, Fabry, MPS I, and Niemann-Pick diseases. Within that time frame, they screened 219,973 infants, with a reported incidence of Gaucher disease of 1:43,995 (n = 5).

Before ERT became standard of care treatment for the pediatric age group, children presented with more severe disease manifestations, including severe thrombocytopenia and anemia. These patients were often in need of splenectomy, which then was associated with a higher risk of bone complications.[12] A study in the International Collaborative Gaucher Group (ICGG) Gaucher Registry revealed that between 1991–1995, when ERT started to be used in clinical practice, and 2006–2009, the median interval between age at diagnosis and age at ERT initiation decreased from 2.5 to 0.5 years and the proportion of pediatric patients splenectomized prior to ERT initiation declined from 19.8% to 0%.[17]

Because Gaucher disease is a progressive condition, the disease stage at the time of treatment initiation and treatment adherence over time both influence outcomes.[12]

b. *In infants with neurological variants, is there evidence (e.g. family perspective) that treatment of other symptoms (e.g. hepatosplenomegaly) improves overall quality of life?*

For infants with neuronopathic Gaucher disease (GD2/GD3), ERT effectively treats visceral symptoms, improving overall quality of life and extending longevity. [2, 3, 6, 7] Experimental therapies such as venglustat (a CNS-penetrant substrate reduction therapy) and adeno-associated virus gene therapy are promising options for addressing neurological manifestations. These therapies underscore the growing potential of early diagnosis to enable timely access to innovative treatments.

There are other rapid developments in this area. Pre-clinical studies of neuronopathic GD models indicate that the blood-brain barrier is leaky in the setting of neuroinflammation allowing transfer of cells and ERT molecules.[18] This challenges the long-held belief that peripheral ERT is ineffective for CNS manifestations. With the advent of NBS, it will be timely to reevaluate ERT's (and other therapies in early development) role in neuronopathic GD at the earliest stages of disease.

Conclusion and Next Steps

The issues presented to medical professionals in Gaucher disease newborn screening are the same as other lysosomal storage diseases, such MPS II and Krabbe, in terms of their clinical variability. Furthermore, unlike the other conditions, in Gaucher disease, early intervention can lead to a healthy normal life. The inclusion of Gaucher disease in the newborn screening panel represents an opportunity to advance equitable access to early diagnosis and care for affected newborns. We hope this response addresses the requirements and supports moving Gaucher disease to the next step in NBS inclusion. We welcome the opportunity to discuss this further and provide additional supporting materials as needed.

Respectfully submitted,

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GAUCHER COMMUNITY ALLIANCE

Gaucher disease

Inclusion of Gaucher disease in newborn screening panels across the U.S.

This report presents a compelling case for the inclusion of Gaucher disease in newborn screening panels across the United States

April 9, 2025

Stay informed

This report is produced as part of a collaboration between AllMyHealth and the Gaucher Community Alliance.

About the Gaucher Community Alliance

The Gaucher Community Alliance (GCA) is a North American based patient advocacy organization committed to improving the lives of individuals affected by all types of Gaucher disease. Through educational outreach, patient support initiatives, and public health advocacy, the GCA strives to raise awareness, accelerate diagnosis, and ensure access to timely and effective treatment for all Gaucher patients and their families.

https://www.gauchercommunity.org/

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Executive Summary

Gaucher disease (GD) is a rare genetic disorder with potentially life-threatening complications. Early detection through newborn screening (NBS) allows for timely intervention and improved outcomes for affected individuals with all types of the disease.

This report presents a compelling case for the inclusion of GD in NBS panels across the United States. It highlights the clinical justification, technical feasibility, public health benefits and cost-effectiveness of screening for GD. Additionally, it examines state-level success stories and addresses common concerns to NBS for GD.

Key points on the necessity of including gd in newborn screening panels

- GD is a serious genetic disorder with potentially life-threatening symptoms.
- Early diagnosis and treatment through NBS can significantly improve health outcomes.
- Reliable screening tests and effective treatments are available.
- NBS for GD is cost-effective and aligns with public health goals.

Overview of benefits, urgency, and recommendations

- **Benefits**: Early diagnosis through NBS enables timely initiation of treatment, preventing irreversible damage and improving long-term health outcomes for individuals with GD, as well as allowing for genetic counselling for families affected and future children.

- **Urgency**: Early detection is critical, especially for severe forms of GD, which can manifest with rapidly progressing symptoms [1].

- **Recommendation**: We advocate for the inclusion of GD in NBS panels nationwide.

Introduction

Gaucher disease (GD) is a rare, inherited metabolic disorder characterized by the accumulation of fatty substances (lipids) in various organs, tissues and bone [2]. This lipid buildup can lead to a range of symptoms, including enlarged organs, bone pain, anemia, easy bruising, and in severe cases, neurological complications [1].

Current landscape of GD newborn screening in the U.S.

Currently, only six states - Illinois, Missouri, New Jersey, Tennessee, New Mexico, and Oregon - include GD in their NBS panels [3].Screening for GD is also available at select New York hospitals and birthing sites through the ScreenPlus pilot program [3]. However, GD is not yet included in the Recommended Uniform Screening Panel (RUSP) provided by the Secretary of the “U.S. Department of Health and Human Services” to guide state health agencies.

Purpose of this paper

This analysis aims to provide a comprehensive overview of GD and the compelling reasons for its inclusion in newborn screening (NBS) panels throughout the United States [5]. It will examine the clinical, technical, public health, and economic aspects of GD screening, while also addressing common objections and highlighting successful state-level implementations.

Background on Gaucher disease

GD is a lysosomal storage disorder caused by a deficiency of the enzyme glucocerebrosidase [5]. This enzyme deficiency disrupts the breakdown of a fatty substance called glucocerebroside, leading to its accumulation in cells and tissues [5]. Over time, this excessive storage in the lysosomes can cause permanent cellular and tissue damage, particularly in the spleen, liver, bone marrow, and brain [6]. GD is classified as a "toxic accumulation" inborn error of metabolism, as the buildup of glucocerebroside lipids can have harmful effects on various organs and systems [7].

Types of GD and clinical manifestations

There are various types of Gaucher disease and a wide spectrum of disease within each classification [7]. The three major clinical types are:

- **Type 1 (non-neuronopathic)**: This is the most common type in the United States affecting the spleen, liver, blood, and bones [8]. It typically does not involve the brain or spinal cord. Symptoms can range from mild to severe and may appear at any age [8].

- **Type 2 (acute neuronopathic)**: This rare form appears in infants younger than six months and causes severe brain damage [8]. It is typically fatal within the first few years of life.

- **Type 3 (chronic neuronopathic)**: This type causes both organ and neurological problems [8]. Symptoms usually appear in early childhood and progress more slowly than in type 2.

Clinical manifestations of GD vary depending on the type and severity of the disease. Common symptoms include [1]:

- Enlarged spleen and liver (hepatosplenomegaly)
- Low red blood cell count (anemia)
- Low platelet count (thrombocytopenia), leading to easy bruising and bleeding
- Bone pain and abnormalities
- Lung problems
- Cardiovascular manifestations, including pulmonary hypertension and cardiomyopathy
- Neurological complications, such as seizures, muscle stiffness, and developmental delay (in types 2 and 3)
- Increased risk of Parkison's and Multiple Myeloma

Genetic basis and prevalence

GD is caused by variants (mutations) in the GBA1 gene, which provides instructions for making the enzyme glucocerebrosidase [1]. This enzyme plays a crucial role in the body by cleaving the beta-glucosidic linkage of glucocerebroside lipids [7]. GD is inherited in an autosomal recessive pattern, meaning that a child must inherit two mutated copies of the gene (one from each parent) to develop the disease [1].

GD occurs in approximately one in 50,000 to one in 100,000 people in the general population [1]. The incidence is higher among people of Ashkenazi Jewish descent, affecting approximately one in 450 live births within this population [9].

Challenges and delays in current diagnostic practices

Diagnosing GD can be challenging due to the variability of symptoms and the rarity of the disease [10]. Many patients experience diagnostic delays,

sometimes consulting several specialists before receiving an accurate diagnosis [11]. This delay can lead to disease progression and irreversible complications such as advanced bone disease [12].

Factors contributing to diagnostic delays include:

- **Variable clinical presentation**: GD symptoms can overlap with those of other disorders, making it difficult to recognize [13].
- **Low physician awareness**: Due to its rarity, many healthcare providers are unfamiliar with GD [13].
- **Nonspecific symptoms**: Mild or nonspecific symptoms may not prompt physicians to consider GD in their differential diagnoses [13].

The historical context of GD research sheds light on the challenges faced in understanding and diagnosing this disorder [14]. Early research focused on recognizing the enzymatic defect, isolating and characterizing the protein, and identifying the first mutant alleles in patients [14]. These efforts have paved the way for advancements in diagnostic techniques and treatment options.

Delayed diagnoses in GD patients contribute to slower-than-optimal initiation of treatment and can result in irreversible complications [12]. Early detection is critical, especially for severe forms of GD, which present with rapidly progressing symptoms [1]. These insights underscore the urgency of implementing effective strategies for early diagnosis, such as newborn screening.

The case for newborn screening

NBS for GD offers numerous benefits and addresses the challenges associated with current diagnostic practices.

Clinical justification: impact of early diagnosis and treatment

Early diagnosis of GD through NBS allows for timely initiation of treatment, which can significantly improve health outcomes [15]. Treatment options for GD include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) [15]. ERT aims to replace the deficient enzyme, while SRT reduces the production of the substance that accumulates in the body [15].

Early intervention can help prevent or reverse many of the non-neurological manifestations of GD, such as organ enlargement, bone disease, and blood abnormalities [16]. It can also improve overall quality of life and potentially normalize life expectancy for individuals with type 1 GD [16]. Additionally, early treatment may help prevent heart and lung problems that can occur in some GD patients [12].

Although current treatment options for neuronopathic GD (types 2 and 3) do not eliminate all neurological symptoms, early diagnosis allows for optimized supportive care, participation in clinical trials and access to potential future therapies, such as gene therapy or chaperone-based treatments which are under development. Early identification can enable physicians to provide neuroprotective strategies, manage seizures, and anticipate respiratory complications before they become life-threatening. Furthermore, neuronopathic GD patients receive all the visceral benefits that current treatments provide.

Technical Feasibility: Reliable Screening Tests and Their Advantages

Reliable screening tests for GD are available and can be readily incorporated into existing NBS programs. The primary screening method involves measuring the activity level of the enzyme glucocerebrosidase in a dried blood spot sample collected from the newborn's heel [17]. This test is specific and sensitive, effectively identifying infants with low enzyme activity who may have GD [18].

Advantages of the screening test include:

- **Minimally invasive**: It requires only a small blood sample from the baby's heel.
- **High throughput**: It can be performed efficiently on a large scale.
- **Cost-effective**: It is relatively inexpensive to perform, as all states are already testing for other lysosomal storage conditions that use the same technology.

Public health perspective: addressing health disparities and improving outcomes

NBS for GD aligns with public health goals by promoting early detection and intervention for a serious genetic disorder. It can help address health disparities by ensuring that all infants, regardless of their background or access to healthcare, have the opportunity to benefit from early diagnosis and treatment.

By identifying and treating GD early, NBS can contribute to:

- **Reduced morbidity and mortality**: Preventing severe complications and improving long-term health outcomes.
- **Improved quality of life**: Enabling individuals with GD to live healthier and more fulfilling lives.

- **Reduced healthcare costs**: Early intervention can prevent costly hospitalizations and long-term care needs.

Early detection through NBS also facilitates comprehensive monitoring of bone health in GD patients, using tools such as MRI and DEXA scans [13]. This proactive approach can help prevent or mitigate bone complications, such as fractures and osteonecrosis.

Early intervention is particularly crucial for infants with type 3 GD, as timely symptom monitoring can help prevent severe neurological decline. Identifying affected infants early allows families to access genetic counselling, supportive therapies, and emerging experimental treatments.

Cost-effectiveness: long-term healthcare savings through early intervention

Studies suggest that NBS is a cost-effective strategy in the long run [20]. Early diagnosis and treatment can lead to significant healthcare savings by preventing or reducing the need for expensive interventions, such as splenectomy, blood transfusions, and joint replacement surgery [20].

State-level success stories

Several states have successfully implemented NBS for GD, including Illinois, Missouri, New Jersey, Tennessee, Oregon and New Mexico. Screening in several of these states has been done since 2014, demonstrating the feasibility and benefits of screening [6].

Outcomes and best practices from these implementations

These states have reported positive outcomes from their NBS programs for GD, including:

- **Increased detection rates**: Identifying more infants with GD, including those who may not have been diagnosed otherwise.
- **Timely intervention**: Enabling early initiation of treatment and preventing disease progression.
- **Improved health outcomes**: Reducing the incidence of severe complications and improving long-term health for individuals with GD.

It is important to acknowledge that false-positive newborn screening results can occur, highlighting the need for confirmatory testing to ensure accurate diagnosis and appropriate follow-up care [5].

Best practices from these state-level implementations include:

- **Collaboration among stakeholders:** Engaging healthcare providers, public health officials, and patient advocacy groups in program development and implementation.
- **Education and outreach:** Providing information to parents and healthcare providers about GD and the benefits of NBS.
- **Follow-up and diagnostic testing:** Ensuring timely and appropriate follow-up testing for infants with positive screening results.
- **Access to treatment and care:** Connecting families with specialized care centers and support services.

Overcoming common objections

While NBS for GD offers numerous benefits, some common objections have been raised.

Concern 1: GD is a rare disease, and screening all newborns may not be cost-effective.

- **Response:** While GD is rare in the general population, it is more common in certain ethnic groups, such as people of Ashkenazi Jewish descent [9]. Furthermore, the long-term healthcare savings from early intervention can outweigh the initial costs of screening in all populations [20]. In addition, as all states are already screening for other lysosomal storage disorders, the cost to add GD is minimal.

Concern 2: Screening for a late-onset disorder like GD may cause unnecessary anxiety for parents.

- **Response:** Gaucher disease is not a late-onset disorder. While parental anxiety is a valid concern, studies have shown that providing education and support to families can effectively mitigate this anxiety [21]. Clear communication and support from healthcare providers are essential to address parental concerns and ensure informed decision-making [22]. It is crucial to consider the potential psychological impacts of misdiagnosis and the lack of knowledge among medical providers, which can further contribute to parental anxiety [23]. Plus, the clinical harms to the patient and family without diagnosis comes with its own set of anxieties. Numerous disorders being screening for all have various onset times including neonates, older children, and adults. Gaucher is no different and has years of published data unlike other NBS conditions.

Concern 3: There is limited genotype-phenotype correlation in GD, making it difficult to predict disease severity based on screening results.

- **Response:** While genotype-phenotype correlation can be complex, early diagnosis still allows for close monitoring and timely intervention if symptoms develop [25]. This can prevent irreversible complications and improve overall outcomes. Research in this area is ongoing, as demonstrated by a study conducted in Andalusia, Spain, which identified a novel mutation in the GBA gene [26].

Policy recommendation for newborn screening

Integrating Gaucher disease into newborn screening panels represents not just a clinical imperative but a decisive public health advancement. Early detection equips healthcare providers with the tools needed to prevent irreversible damage and improve long-term outcomes, while also reducing the burden on families and the healthcare system. By embracing evidence-based policy recommendations, fostering robust stakeholder engagement, and mobilizing advocacy efforts at both state and national levels, policymakers can drive a transformative change that ensures every newborn receives the opportunity for timely diagnosis and intervention. The time to act is now. By prioritizing Gaucher disease screening, we can pave the way for a healthier future and set a new standard in newborn care.

The rapid development of novel therapies, including cell and gene therapies, presents both opportunities and challenges for newborn screening programs [28]. To effectively accommodate these advancements, a coordinated national vision and solutions are needed to address issues such as cross-state variability, national harmonization, data collection, and support for state implementation [28].

Conclusion

The inclusion of GD in NBS panels across the U.S. is a critical step towards improving the lives of individuals with this life-threatening genetic disorder. Early diagnosis through NBS enables timely intervention, prevents irreversible organ damage, and improves long-term health outcomes. Reliable screening tests and effective treatments are available, making NBS for GD both feasible and beneficial.

Policymakers should prioritize the inclusion of GD in NBS panels, considering the evidence of its effectiveness, the potential benefits for families and society, and the long-term cost-effectiveness of early intervention.

Patient advocacy groups are playing a vital role in raising awareness about GD, educating families, and advocating for policies that support early detection and access to treatment.

By overcoming common objections, learning from state-level success stories, and adapting to advancements in treatment and technology, stakeholders can work collaboratively to ensure that all newborns have the opportunity to benefit from early detection and treatment of Gaucher disease. This will ultimately improve public health and reduce healthcare disparities.

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Good morning! My name is Amy Aikins. I reside in Glenshaw, Pennsylvania, a suburb of Pittsburgh. I have a 21-year-old son, Elijah, who lives with Duchenne Muscular Dystrophy, or DMD. I am also a genetic carrier. Additionally, I work for the Little Hercules Foundation- a patient advocacy organization focused on access concerns for DMD and other rare conditions.

I'm here today in support of newborn screening for DMD. Duchenne is a genetic disorder that is characterized by progressive muscle loss. It is multi-systemic and affects multiple parts of the body, including skeletal, lung, and heart muscles.

Many parents of those with Duchenne recall the first time they heard the word Duchenne Muscular Dystrophy. This is not surprising, as we know that about one in every three cases of Duchenne is caused by a new or spontaneous mutation in the affected child with no known family history. I am unable to recall the first time I heard Duchenne because I don't remember a time when it was not part of my life.

My family has lost 4 boys to this disease: 2 uncles who passed before I was born, a cousin who succumbed at age 19, and my brother, who passed at 18 shortly after a bout with pneumonia.

As a toddler, I had concerns about Elijah's development compared to his peers. He never crawled and didn't walk independently until he was 17 months old. My fears were repeatedly calmed by the pediatrician, who attributed this to being an only child. In my work with families, I've learned that this is a common scenario. At age 2, I made a parent referral to the Early Intervention Birth to 3 Program. They completed their evaluation, and he passed the physical tests, qualifying only for education services and speech therapy.

When he turned three, Elijah transitioned to the early intervention preschool program. Sometime after being in the program, the physical therapist mentioned that she had some concerns about his muscle tone and development. Shortly thereafter, at the age of 4, he was diagnosed with DMD. At the time of Elijah's diagnosis, there were no approved treatments; only steroids to try to slow progression.

Elijah has followed the typical progression. Between the ages of 5 and 7, getting off the floor became difficult and then impossible without the use of furniture to drag himself upright. Between the ages of 8 and 11, the ability to climb stairs diminished to the point of nonexistence. At 13, he fractured his femur after a fall. As is common with these types of injuries and DMD, he never walked again and needed a powerchair for mobility. Through his teens, he continued to get weaker, and he lost the ability to do most daily living skills independently. He now requires a ventilator at night.

Even with family history, there was a big gap in time from symptom onset to final diagnosis. I know that had it not been for my family history, his diagnosis would have taken longer. Other parents have described scenarios where they have taken their young child to PTs who have implemented strength-building exercises. Weight resistance exercises can be very damaging to muscles that don't heal. Earlier diagnosis not only helps patients reach intervention sooner, but it also prevents these detrimental therapies from being administered by well-meaning professionals before the patient's diagnosis.

Currently, there are 8 approved treatments for DMD. Earlier initiation of treatments may preserve muscle longer. Newborn screening detects these patients early, allowing them to receive treatments sooner, possibly before any symptoms appear. Additionally, newborn screening helps identify children who may be eligible for clinical trials involving treatments in development.

It also identifies carriers, which is extremely important, as there is a subset of female carriers who have significant symptoms. I recently learned of a young 9-year-old girl who was very symptomatic. It took 7 years to obtain a diagnosis. Female carriers who appear asymptomatic, like me, are also at risk for health complications and need cardiac screening as adults.

I am in complete agreement that newborn screening for Duchenne should be added to Pennsylvania's newborn screening panel. Act 133 of 2020 provides this mechanism for expanding the conditions on the NBS Panel without the need for legislation. I supported the formal nomination for Duchenne to be added through the Newborn Screening Advisory Board this past spring and am grateful to the committee, which I understand will vote on Duchenne soon. I am also thankful for Representative Flood's expression of support for DMD newborn screening through HB 1715. I am in support of any method to expeditiously add Duchenne to the newborn screening panel, because the faster we get children diagnosed, the more time we give them with stronger muscles.

I appreciate the opportunity to testify to this issue and welcome any questions the committee may have.

PRINTER'S NO. 2005

THE GENERAL ASSEMBLY OF PENNSYLVANIA

HOUSE BILL

No. 1652 Session of 2025

INTRODUCED BY SALISBURY, McNEILL, HILL-EVANS, KAZEEM, FRANKEL, SANCHEZ, HANBIDGE, BOROWSKI, FLEMING, CIRESI, RIVERA, WAXMAN, KHAN, SCHLOSSBERG, T. DAVIS AND D. MILLER, JUNE 24, 2025

REFERRED TO COMMITTEE ON HEALTH, JUNE 24, 2025

AN ACT

Amending the act of September 9, 1965 (P.L.497, No.251), entitled "An act requiring physicians, hospitals and other institutions to administer or cause to be administered tests for genetic diseases upon infants in certain cases," further providing for Newborn Child Screening and Follow-up Program.

The General Assembly of the Commonwealth of Pennsylvania hereby enacts as follows:

Section 1. Section 3(a)(1) of the act of September 9, 1965 (P.L.497, No.251), known as the Newborn Child Testing Act, is amended by adding a subparagraph to read:

Section 3. Newborn Child Screening and Follow-up Program.--

(a) In order to assist health care providers to determine whether treatment or other services are necessary to avert intellectual disability, physical disability or death, the department, with the approval of the Newborn Screening and Follow-up Technical Advisory Board, shall establish a program providing for:

(1) The screening tests of newborn children and follow-up services for the following diseases:

* * *

(xi) Gaucher disease.

* * *

Section 2. This act shall take effect in 60 days.

PRINTER'S NO. 2111

THE GENERAL ASSEMBLY OF PENNSYLVANIA

HOUSE BILL

No. 1715 Session of 2025

INTRODUCED BY FLOOD, BRIGGS, COOK, CURRY AND McNEILL, JULY 9, 2025

REFERRED TO COMMITTEE ON HEALTH, JULY 10, 2025

AN ACT

Amending the act of September 9, 1965 (P.L.497, No.251), entitled "An act requiring physicians, hospitals and other institutions to administer or cause to be administered tests for genetic diseases upon infants in certain cases," further providing for Newborn Child Screening and Follow-up Program.

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(1) The screening tests of newborn children and follow-up services for the following diseases:

* * *

(xi) Duchenne muscular dystrophy.

* * *

Section 2. This act shall take effect in 60 days.