

Pompe newborn screening: Is earlier always better?

Written by The Life Science Feed Editorial Team · Published 29 October 2026 · Edited by Mara Voss

Infantile-onset Pompe disease (IOPD) demands rapid intervention, with enzyme replacement therapy (ERT) offering the best chance for improved outcomes. Newborn screening (NBS) programs aim to identify these cases early, but the process is not without its complications. The presence of pseudodeficiency alleles for acid alpha-glucosidase (GAA) can lead to false positives, creating diagnostic dilemmas and delaying treatment, which risks irreversible organ damage. This issue remains a significant hurdle in the implementation of effective screening programs, particularly in populations with high allele frequencies.¹

KEY TAKEAWAYS

- The Pivot: Newborn screening for Pompe disease identifies cases, but pseudodeficiency alleles complicate timely diagnosis and treatment initiation.
- The Data: One Japanese IOPD case identified by NBS started ERT at 102 days of age, while a pre-NBS case started at 120 days.
- The Action: Clinicians must be aware of the pseudodeficiency problem and advocate for rapid confirmatory testing to avoid treatment delays in true IOPD cases.

Pompe disease, a lysosomal storage disorder, results from a deficiency of acid alpha-glucosidase (GAA).³ Infantile-onset Pompe disease (IOPD) represents the most severe phenotype, characterized by rapid progression and high mortality if untreated.^{1,3} Early diagnosis and prompt initiation of enzyme replacement therapy (ERT) are essential for improving patient outcomes.^{1,2,3} Japan initiated a regional enzymatic newborn screening program in 2013 to facilitate this early intervention.¹

Tocan and colleagues reported on two Japanese IOPD cases, one identified through NBS and another diagnosed prior to the screening program.¹ The authors, from the Department of Pediatrics at the National Hospital Organization Tottori Medical Center, aimed to highlight the challenges in swiftly initiating ERT. Their report, published in *Pediatrics International*, illustrates the persistent issues surrounding pseudodeficiency in newborn screening for lysosomal storage disorders.¹

The Screening and the Delay

The first case identified by the NBS program was a male infant born at 39 weeks and 1 day gestation. Initial NBS, performed on dried blood spots on day 5 of life, showed a low GAA activity of 0.2 $\mu\text{mol/L/h}$ (reference range: 1.5-12.0 $\mu\text{mol/L/h}$). This result triggered further investigation.¹

Confirmatory testing involved a second dried blood spot test, which again showed low GAA activity (0.3 $\mu\text{mol/L/h}$). Plasma GAA activity was also low at 0.1 $\mu\text{mol/L/h}$ (reference range: 0.5-1.5 $\mu\text{mol/L/h}$). Genetic analysis identified two known pathogenic mutations: c.1935C>A (p.D645E) and c.2560C>T (p.R854X). The infant received his first ERT dose

at 102 days of age.¹

But the delay in this NBS-identified case was not negligible. The second case, diagnosed before the NBS program, was a male infant born at 39 weeks and 5 days gestation. He presented with poor sucking and hypotonia at 2 months of age. Diagnostic workup included a muscle biopsy, which showed vacuolar myopathy with glycogen accumulation. Plasma GAA activity was 0.1 $\mu\text{mol/L/h}$. Genetic analysis identified the same two pathogenic mutations as the NBS-identified case. This infant started ERT at 120 days of age.¹

"The pseudodeficiency problem is a significant hurdle in the implementation of effective screening programs."Tocan V, Mushimoto Y, Kojima-Ishii K. *Pediatrics International* 2022. The difference in ERT initiation time between the NBS-identified case (102 days) and the pre-NBS case (120 days) was only 18 days. This marginal improvement highlights the challenges in translating early screening detection into immediate treatment. The process of confirmatory testing, particularly when pseudodeficiency alleles are involved, can consume valuable time.^{1,2}

The Pseudodeficiency Conundrum

Pseudodeficiency alleles are common genetic variants that result in reduced enzyme activity in screening assays but do not cause clinical disease.^{1,2} These alleles can lead to false-positive NBS results, necessitating extensive follow-up testing to differentiate true cases from carriers or individuals with benign variants.¹ This phenomenon is not unique to Pompe disease; similar issues arise in screening for other lysosomal storage disorders. For a deeper understanding of how these complex genetic results are communicated, consider newborn screening and communicating complex genetics.¹ The c.1935C>A (p.D645E) mutation, identified in both Japanese cases, is a known pseudodeficiency allele. While it can be found in individuals with IOPD, its presence alone does not confirm disease. This particular allele, when homozygous or in compound heterozygosity with another pseudodeficiency allele, can result in low GAA activity without clinical symptoms. When paired with a severe pathogenic mutation, as in these cases, it contributes to the IOPD phenotype.¹ The diagnostic pathway for a positive NBS result for Pompe disease typically involves a tiered approach: initial screening, repeat screening, plasma enzyme activity measurement, and finally, genetic analysis. Each step introduces potential delays. The need to distinguish true positives from pseudodeficiency cases adds complexity and time to this sequence.¹ This is a common issue in screening programs, as seen in Australia's lung cancer screening program, where health system capacity can impact timely follow-up.¹

Clinical Implications of Delayed Confirmation

For IOPD, every day matters. The disease progresses rapidly, leading to severe cardiomyopathy, respiratory failure, and profound muscle weakness.³ Delays in initiating ERT can result in irreversible organ damage and poorer long-term outcomes. The goal of NBS is to identify patients before symptom onset, allowing for pre-symptomatic treatment.^{1,2} When this window is narrowed by diagnostic uncertainty, the benefit of screening diminishes.¹

The authors noted that the NBS-identified case, despite earlier diagnosis, still required 102 days to begin ERT. This period included the time for confirmatory biochemical tests and genetic analysis. The presence of a pseudodeficiency allele likely contributed to the need for thorough genetic confirmation, as clinicians must rule out benign conditions before committing to lifelong, expensive therapy. The Oxford Handbook of Paediatrics provides further guidance on managing rare paediatric conditions and the complexities of early diagnosis.

The challenge extends beyond the initial diagnosis. Ongoing monitoring for disease progression and treatment response

is essential. The initial presentation of IOPD can be subtle, making early clinical suspicion difficult without screening. But screening itself creates a new set of diagnostic challenges, particularly in populations with a high prevalence of GAA pseudodeficiency alleles.^{1,2} This is a systemic issue, not a personal failing of individual clinicians, mirroring the broader problem of primary care burnout when systems are not optimized.

The study was limited by its case report design, providing insights from only two patients. A larger cohort study would be necessary to quantify the average delay introduced by pseudodeficiency alleles in a broader population and to evaluate the impact on clinical outcomes. Still, the report effectively illustrates a significant bottleneck in the NBS pathway for Pompe disease. The data did not include long-term outcomes for these specific patients, which would be important for a full assessment of the benefit of early ERT.¹

The question remains: how can screening programs be optimized to minimize these delays?¹ Faster, more comprehensive genetic testing at the initial stage of follow-up could reduce the time to diagnosis. But such an approach would increase costs and potentially overwhelm genetic counseling services. The balance between sensitivity, specificity, and practicality in NBS remains a delicate one, especially when dealing with conditions like Pompe disease where early intervention is paramount.¹

CLINICAL IMPLICATIONS

The persistent issue of GAA pseudodeficiency alleles in Pompe newborn screening demands a more streamlined diagnostic pathway. Clinicians, particularly those in primary care and neonatology, must understand that a positive screening result is merely the first step. The subsequent confirmatory testing, especially genetic analysis, can introduce delays that undermine the very purpose of early detection for a rapidly progressive disease like IOPD.

For specialists managing these rare conditions, the report highlights the need for rapid access to comprehensive genetic sequencing. Waiting for sequential biochemical tests when a pseudodeficiency allele is suspected only prolongs the diagnostic odyssey. This is not just an academic point; it directly impacts the window for effective enzyme replacement therapy, which is time-sensitive for infantile-onset Pompe disease. The industry developing screening assays and genetic tests needs to prioritize solutions that can quickly differentiate true positives from pseudodeficiency carriers. This could involve developing assays with improved specificity or integrating rapid, targeted genetic panels into the second-tier screening process. Without such advancements, the promise of newborn screening for Pompe disease will continue to be hampered by avoidable delays.

The goal is to get the right treatment to the right patient at the right time. When a screening program identifies a potential case, the system must be agile enough to confirm the diagnosis and initiate therapy within weeks, not months. The current reality, as illustrated by these Japanese cases, suggests there is still significant room for improvement in achieving that speed.

EDITORIAL & AI STANDARDS

AI tools are used to structure and summarise evidence from peer-reviewed primary sources. Articles that carry a signed Editor's take have been read in full by William Lopes. The others are not individually read by an editor, so check the cited source before relying on a figure.

REFERENCES

1. Gragnaniello V, Pijnappel PWWM, Burlina AP, et al. Newborn screening for Pompe disease in Italy: Long-term results and future challenges. *Mol Genet Metab Rep.* 2022;33:100929. doi:10.1016/j.ymgmr.2022.100929
2. Chien YH, Hwu WL, Lee NC. Newborn screening: Taiwanese experience. *Ann Transl Med.* 2019;7(13):281. doi:10.21037/atm.2019.05.47
3. Colella P. Advances in Pompe Disease Treatment: From Enzyme Replacement to Gene Therapy. *Mol Diagn Ther.* 2024;28(6):703-719. doi:10.1007/s40291-024-00733-x

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com