Long-term Follow-up of Patients With Late-onset Pompe Disease Identified Through Newborn Screening

sanofi

MAT-US-2412105 v3.0 P Expiration Date: 01/29/2028

The 2024 Rare Disease Medical Advisory Board Meeting

In August 2024, the Sanofi Rare Disease Medical Team held a Medical Advisory Board Meeting with experienced specialist clinicians and other healthcare professionals (HCPs) from various regions throughout the United States (US).

The purpose of this meeting was to help advance patient monitoring and care by sharing insights, challenges, and real-world best practices for the long-term follow-up of patients with the lysosomal storage disorder late-onset Pompe disease (LOPD) who were identified through newborn screening (NBS). This monograph contains the views and real-world experiences of the Rare Disease Advisors and does not necessarily reflect the views of Sanofi.

Sanofi compensated the advisors for their participation in the meeting.

2024 Advisory Board Participants		
Advisors		
Jennifer Cohen, MD Duke University Durham, NC	**Christina Grant, MD, PhD** Children's National Hospital Washington, DC	**Tahseen Mozaffar, MD** University of California-Irvine Children's Hospital of Orange County Orange, CA
Tina Duong, PT, PhD Stanford University Stanford, CA	**David Kronn, MD** Westchester Medical Center Valhalla, NY	**Nishitha Pillai, MD** University of Minnesota Minneapolis, MN
Can Ficicioglu, MD, PhD Children's Hospital of Philadelphia Philadelphia, PA	**Linda Lowes, PT, PhD** Nationwide Children's Hospital Columbus, OH	**Katie Sapp, MS, CGC** Indiana University Health Riley Children's Hospital Indianapolis, IN
Amy Gaviglio, MS, CGC National Consultant, CDC and Association of Public Health Labs Minneapolis, MN	**Kimberly McDonald, MD** University of Louisville and Norton's Children's Hospital Louisville, KY	**Ayaka Suzuki, MS, CGC** University of California - Davis Health Sacramento, CA

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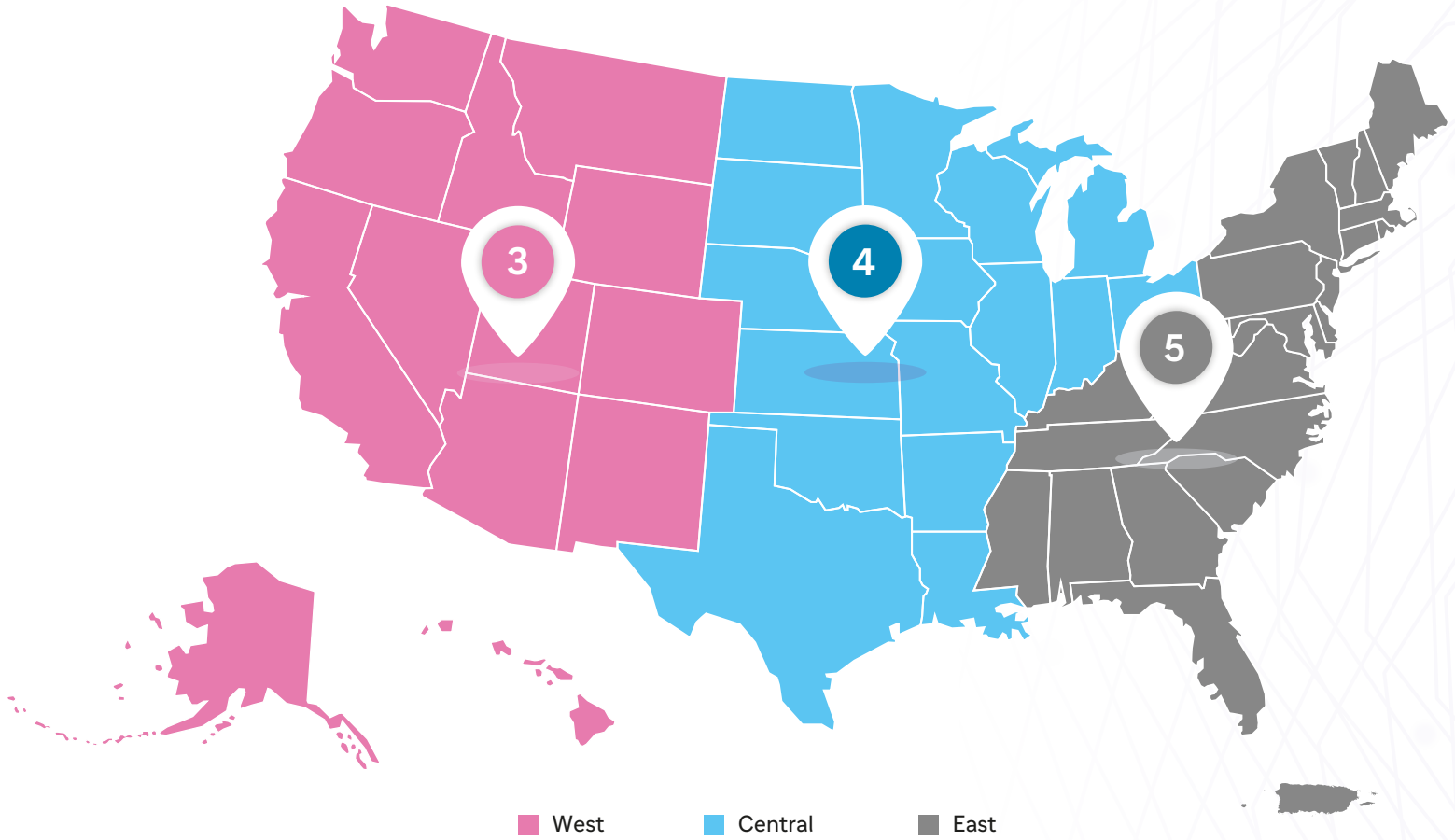

2024 Advisory Board Participants		
Sanofi		
Sarah Chadwell, MS, LCGC Senior Medical Science Liaison, Rare Disease	**Laura Croal, PhD** Senior Medical Science Liaison, Rare Disease	**Ann Lucas, MS, CGC** Field Science Director, Pompe Disease and MPS I
Rafaella Colzani, MD Senior Medical Director, Pompe Disease and MPS I	**Catherine Long, MS, LCGC** Senior Medical Science Liaison, Rare Disease	

Background on Newborn Screening for Pompe Disease

Pompe disease is an inherited, autosomal recessive lysosomal storage disorder caused by pathogenic variants in the *GAA* gene, localized on chromosome 17, resulting in deficient lysosomal acid α-glucosidase (GAA) enzyme activity. This loss of GAA enzyme activity leads to accumulation of intracellular glycogen in all tissues, especially muscles, resulting in progressive tissue damage and ultimately cardiac and/or respiratory disease, motor disability, and premature death.[1]

Pompe disease is classified as infantile-onset Pompe disease (IOPD) when cardiomyopathy and weakness occur <12 months of age, and as LOPD if symptoms occur in infancy without cardiomyopathy or after ≥12 months of age.[2,3] Overall, Pompe disease exhibits a continuum of disease severity, with considerable variation in age of symptom onset and rate of progression (**Figure 1**),[4] necessitating prospective follow-up and monitoring.

FIGURE 1. POMPE DISEASE CONTINUUM

Infantile-onset Pompe Disease (IOPD)[5] usually presents with symptoms within the first months of life and has a rapidly progressive disease course that is typically fatal by 2 years of age.

Late-onset Pompe Disease (LOPD) has a less rapid and more variable disease course, where symptoms may begin anywhere from infancy to adulthood.

IOPD image reproduced with permission from John R Bach, MD, published by Medscape CME & Education (https://www.medscape.org/), New Clinical Findings in Pompe Disease, Also Known as Acid Maltase Deficiency: Evidence-Based Cases in Infantile- and Late-Onset Patients, 2007, available at https://www.medscape.org/viewarticle/568049.

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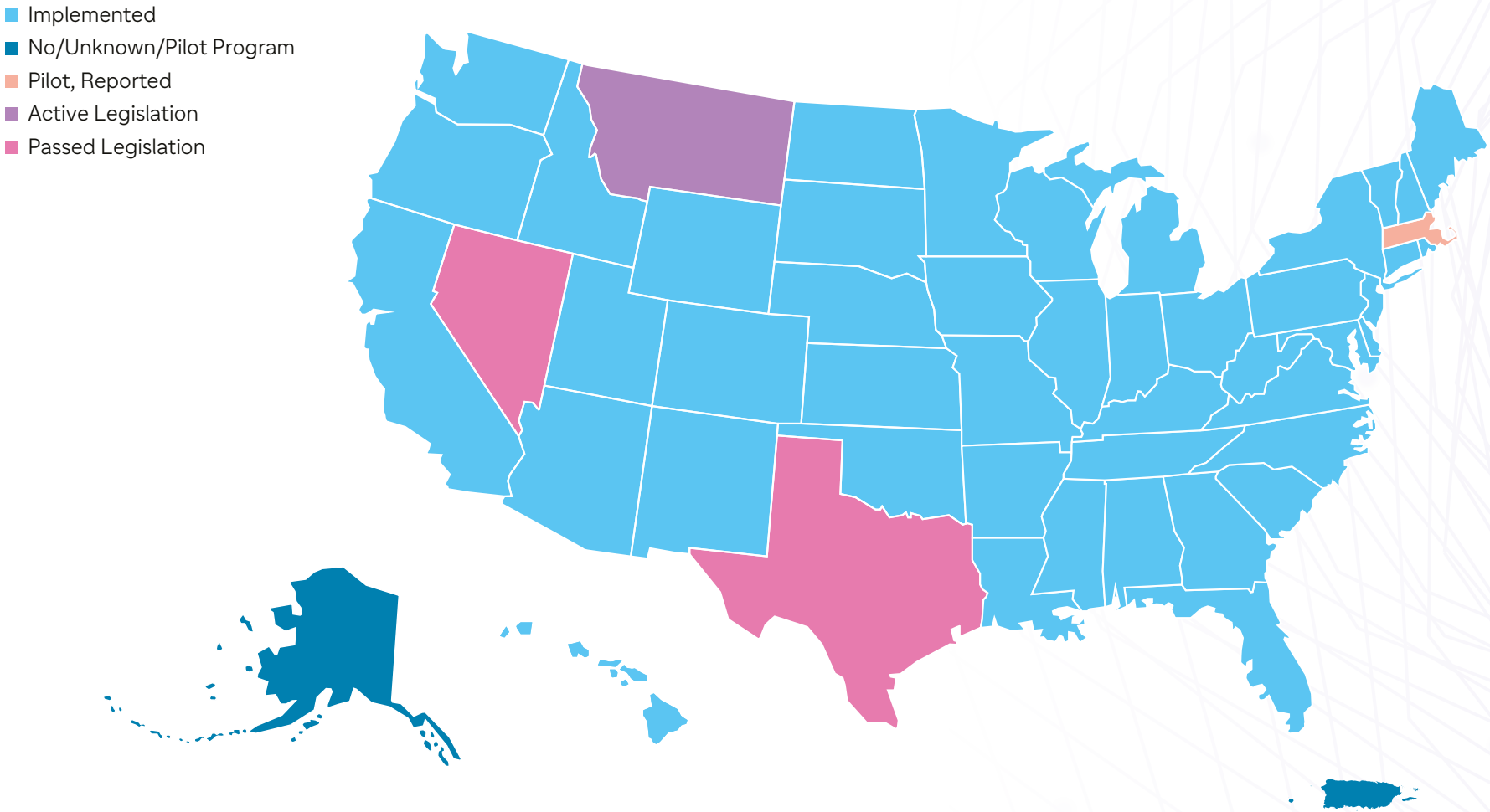
Newborn screening (NBS) is a public health initiative through which all newborns are screened for certain rare genetic or metabolic disorders through a group of biochemical and/or molecular tests conducted on a blood sample from a heel prick collected within 48 hours of birth. NBS is not diagnostic, but rather a screening procedure to identify newborns who are at risk to have a disease. Follow-up diagnostic testing is needed to confirm the diagnosis.

In 2015, Pompe disease was added to the Recommended Uniform Screening Panel (RUSP)[6,7]—a list of conditions that the US Secretary of Health and Human Services recommends for NBS programs. Each US state independently decides which conditions to screen for on its panel. As of 2024, most US states have implemented NBS for Pompe disease (**Figure 2**)[8]; for the most recent NBS implementation status across US states, visit NewSTEPs (a link can be found in "**Pompe Disease Relevant Resources**").

FIGURE 2. IMPLEMENTATION OF POMPE DISEASE NBS IN US STATES (AS OF AUGUST 2024)



NBS for Pompe disease can identify infants with IOPD and those considered to have LOPD (i.e., with genetic risk factors but may not have symptoms at birth).[4] Patients with LOPD represent most cases of Pompe disease identified on NBS in the US.[9]

Much variability exists in the NBS program across US states. NBS screening protocols differ by technology used to assess the GAA enzyme activity (first tier testing), use of reflex testing (not all states offer testing beyond first tier), type of additional reflex analyte (i.e., molecular or additional biochemical tests as second and/or third tier), and the degree of follow-up at the state health department level for patients with positive NBS.[6] The cutoff value for a positive Pompe disease NBS also varies by US state, as does the positive predictive value (PPV) of the NBS test (the ratio of newborns who are truly diagnosed as positive to all those who had positive test results). Studies have found the PPV may range from 17–81%.[10,11]

Furthermore, the patient referral process after a positive NBS for Pompe disease is also independent and may vary considerably. The initial positive result may go to a clinical specialist site or to providers who may have limited knowledge of Pompe disease such as primary care physicians (PCPs). Some states run their own test through their NBS departments or contract with laboratories who conduct the screening.[6,12,13]

Clinical Practice Insights from the 2024 Advisory Board

Advisors noted that inconsistencies in the Pompe disease NBS process are especially challenging for HCPs who receive abnormal Pompe disease NBS referrals from multiple states, and alignment across US states would be helpful.

Advisors noted that restructuring NBS reports to make them more user-friendly for HCPs by keeping them brief, listing actions/next steps at the top, and adding QR codes for additional resources would be helpful.

Advisors noted that providing more easily available and directly accessible education and training for HCPs (eg, handouts, podcasts, short videos, congress presentations) on NBS for Pompe disease and next steps following a positive NBS would be helpful.

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Diagnosing Late-onset Pompe Disease Following an Abnormal Newborn Screen

Clinical Practice Insights from the 2024 Advisory Board

Advisors noted that the NBS is a screening test only and that there may be newborns with LOPD who are not identified through NBS for a variety of reasons.

Confirmation of diagnosis of LOPD following an initial positive NBS for Pompe disease involves a series of biochemical assays, genetic testing, and clinical evaluations. Recommendations for diagnostic confirmation have been published by the American College of Medical Genetics (ACMG) Pompe Disease Newborn Screening Working Group.[4,14]

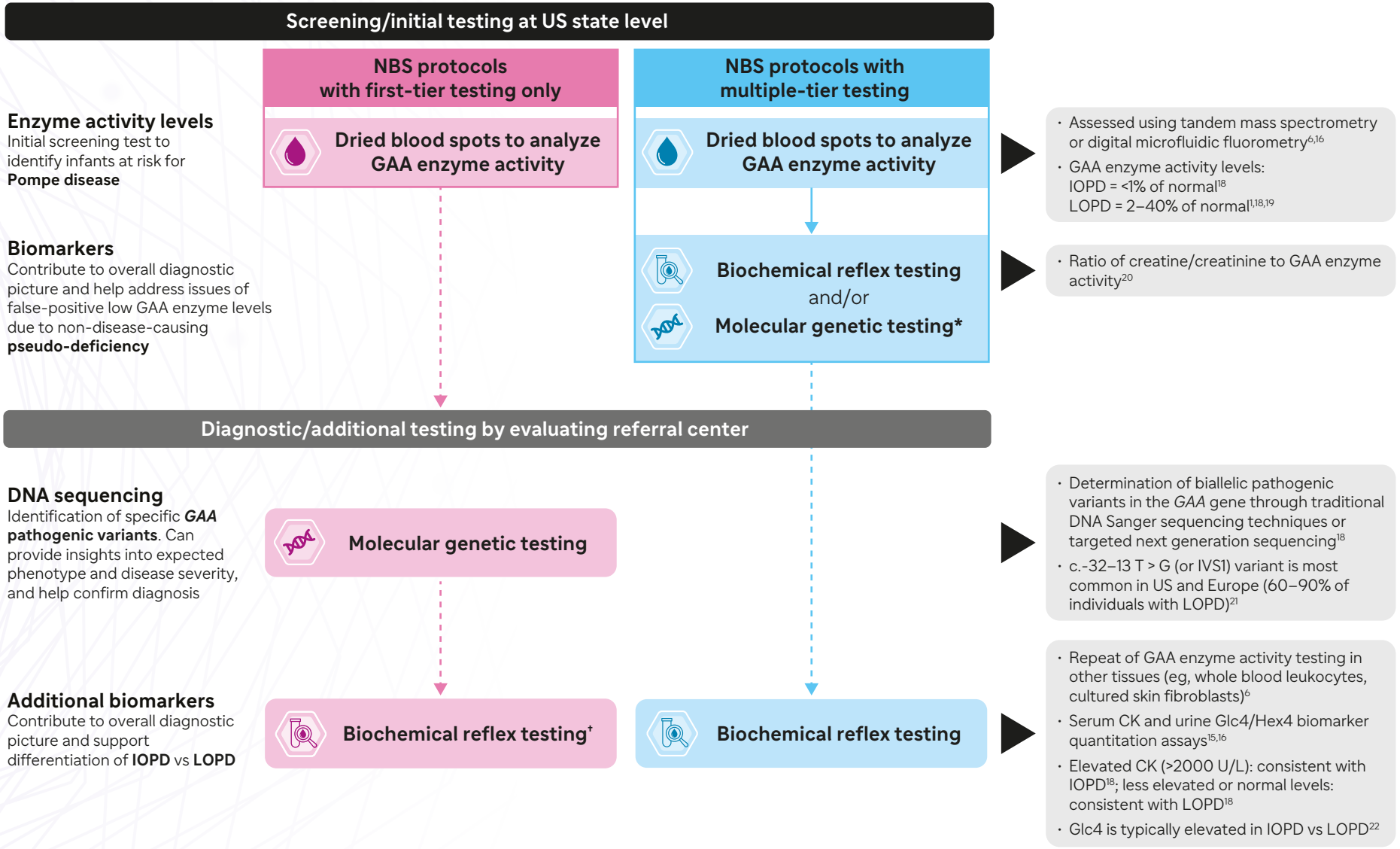
Rapid and accurate differentiation between patients with IOPD and LOPD is crucial for the implementation of appropriate management strategies, with an IOPD diagnosis requiring immediate intervention to improve patient outcomes and prevent early death.[3] DNA sequencing to confirm the *GAA* pathogenic variants can inform genotype-phenotype associations. If not done as part of the NBS, this should be conducted as quickly as possible to establish appropriate monitoring and management strategies based on a patient's predicted phenotype.[3,15] However, genetic testing is currently not consistently included in NBS protocols across US states, and the timing of DNA sequencing may therefore vary, causing delays in confirmation of diagnosis and unnecessary anxiety for families awaiting results.[6]

Tiered Testing

First tier testing measures GAA enzyme activity levels to determine risk for Pompe disease,[6,16] with any values below a previously established cut-off value suggesting presence of the disease (**Figure 3**).[17]

Newborns with an initial positive result require second or third tier confirmatory biochemical and/or molecular reflex testing, which may be completed by the state and/or by the clinical specialist. These additional tests can aid in phenotyping, as well as evaluating the patient for non-disease-causing pseudodeficiency alleles—molecular variants of the *GAA* gene that lower *in vitro* GAA enzyme activity but do not cause Pompe disease—and rule in/out a false positive result (**Figure 3**).[6]

FIGURE 3. OVERVIEW OF BIOCHEMICAL AND MOLECULAR TESTING FOR NBS AND DIAGNOSIS OF POMPE DISEASE



*DNA sequencing may be obtained as part of the state NBS protocol. †Biochemical reflex testing may include repeat GAA enzyme activity testing in other tissues and ratio of creatine/creatinine to GAA enzyme activity if not part of the state NBS protocol.

CK, creatine kinase; GAA, acid α-glucosidase; Glc4/Hex4, urine glucose tetrasaccharide/hexose tetrasaccharide; IOPD, infantile-onset Pompe disease; IVS, intervening sequence; LOPD, late-onset Pompe disease; NBS, newborn screening.

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Clinical Practice Insights from the 2024 Advisory Board

Advisors noted that genetic testing is an important component of NBS and that performing sequencing as soon as possible would be helpful to allow early differentiation of IOPD and LOPD and appropriate risk stratification, as well as to reduce anxiety in families awaiting results.

The advisors noted that specialists initially involved following a positive NBS for Pompe disease generally include geneticists, cardiologists, and physical therapists.

Genetic Testing for Pompe Disease

Some *GAA* biallelic pathogenic variants are particularly deleterious and cause a complete lack of enzyme (eg, nonsense variants); when both pathogenic variants are severe, these are assumed to result in IOPD.[18,23,24] Other less severe pathogenic variants (eg, missense variants) allow residual GAA enzyme activity in tissues,[18,25] resulting in heterogenous clinical severity of the disease; these are assumed to result in LOPD,[18] including cases with one severe and one less severe pathogenic variant.[18,23]

The spectrum of the pathogenic variants in the *GAA* gene includes more than 500 reported to date.[15] Various open access genetic databases for Pompe disease are available that provide information on *GAA* pathogenic variants, benign variants, and variants of unknown significance (VUS), as well as predicted associated clinical phenotypes[26,27]; see the section "**Pompe Disease Relevant Resources**" for details. Genotype-phenotype correlations are complex, and genotype alone cannot determine the predicted phenotype in a patient with LOPD; for example, variability in terms of age of onset, severity, and distribution have been observed in individuals carrying the same pathogenic variant.[25]

Initial Cardiac and Motor Assessments

Early clinical evaluations can support the biochemical and/or molecular diagnosis of Pompe disease and provide baseline values. Hypertrophic cardiomyopathy is a hallmark of IOPD but is rare in LOPD, and the presence of significant cardiac involvement in infancy is strongly suggestive of IOPD.[28] Assessments that may help rule out IOPD include an echocardiogram to assess left ventricular hypertrophy and an electrocardiogram to detect any conduction abnormalities.[28]

In addition, a thorough physical examination, focusing on neuromuscular status is crucial. Significant hypotonia and proximal muscle weakness in newborns are usually indicative of IOPD. In LOPD, although profound neuromuscular impairment is not typically present at birth, early symptoms including delay in achievement of gross motor milestones, signs of proximal muscle weakness, swallow and feeding difficulties, and sleep apnea have been reported in early infancy (from 10 days following birth).[29]

Long-term Follow-up of Patients With Late-onset Pompe Disease

Multidisciplinary Care Teams

LOPD is clinically heterogenous, and following a diagnosis, ongoing follow-up assessments to evaluate onset or progression of signs and symptoms are important to track disease state and monitor and adjust care.[4,18] **Figure 4** highlights the specialists usually involved in follow-up, with percentages representing the number of advisors that have had experience with these specialists for NBS-identified LOPD patients.

Some providers referred their patients with LOPD to Early Intervention Programs (EIPs). In the US, EIPs that provide support and services for infants and toddlers with developmental delays are often utilized.[30] EIP designs are state specific, but typically provide physical and speech therapy as well as access to other psychosocial family support services.[31] Providing a diagnosis to EIPs is important for the understanding of patient prognosis and decision-making, and partnering with caregivers in early discussions is essential to get their buy-in for disease management.

Clinical Practice Insights from the 2024 Advisory Board

Advisors noted geneticists, genetic counselors, cardiologists, and physical therapists are common denominators in long-term follow-up for patients with LOPD. Besides these care teams, the types of specialists involved and at what frequency is individualized to each patient and their needs.

Advisors noted that close communication with Primary Care Physicians (PCPs) and EIPs, although encouraged, does not consistently happen. Additionally, patients with LOPD may not qualify for early intervention, depending on their state eligibility criteria. They recommended early involvement of physical therapists, neuromuscular specialists and caregivers to help fill this gap.

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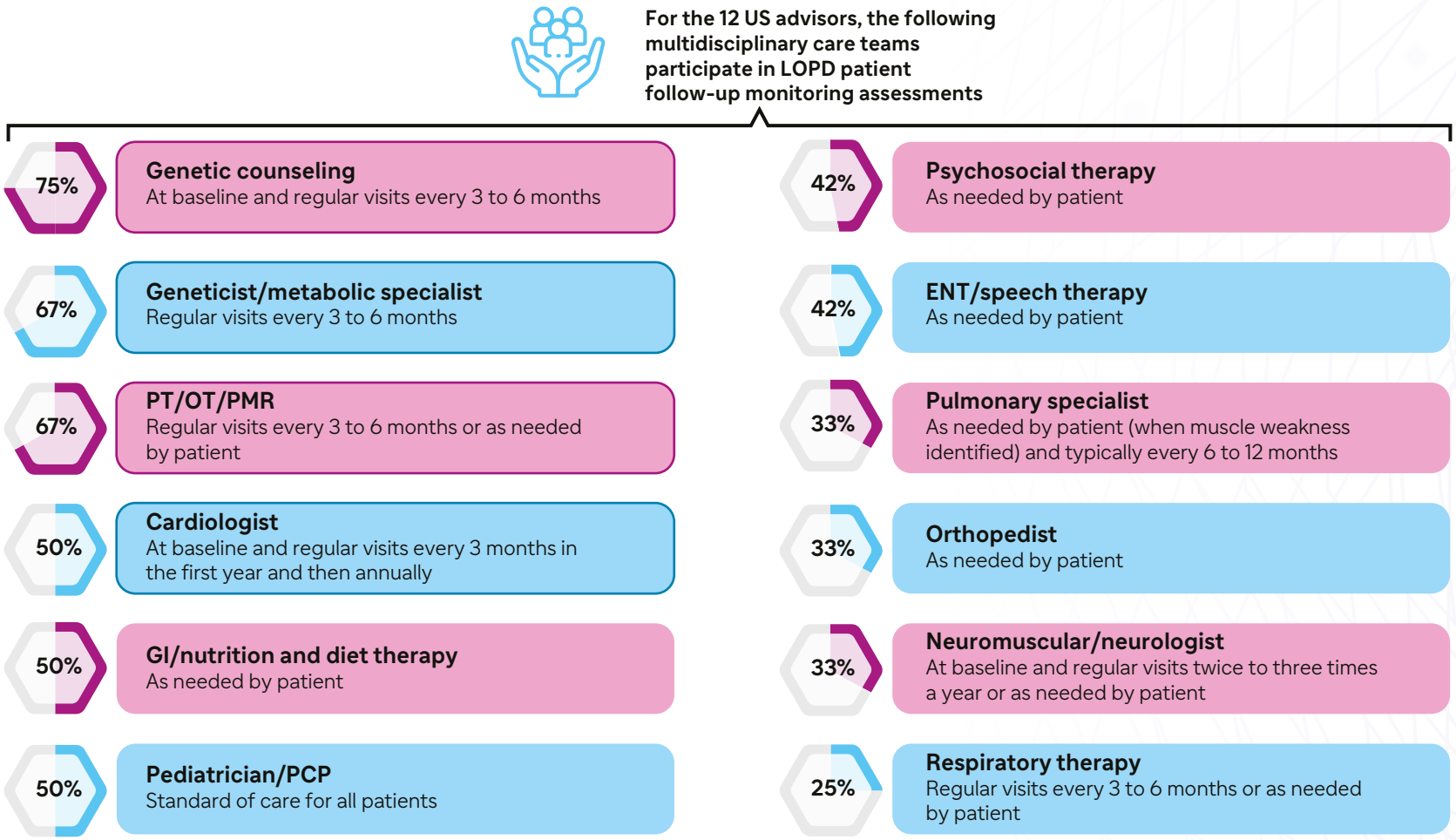
FIGURE 4. THE TYPES OF SPECIALISTS TYPICALLY INVOLVED IN FOLLOW-UP AND THE PERCENTAGE OF ADVISORS THAT USE THEM



Note that reported frequency of visits is based upon advisor experience only.
ENT, ears, nose, and throat; GI, gastroenterology; OT, occupational therapy; PCP, primary care physician; PMR, physical medicine and rehabilitation; PT, physcial therapy.

Long-Term Clinical and Physical Assessments

Identifying which clinical and physical assessments are appropriate for long-term follow-up in patients with NBS-identified LOPD is a challenge due to heterogeneity of patients. Clinical management algorithms are still being developed.[4] Decision-making for early intervention in LOPD is complex because patients diagnosed via NBS typically do not have measurable signs or symptoms or predictable time of symptom onset. It is thought that respiratory insufficiency, limb-girdle weakness, and elevated CK are early indications of disease progression.[32,33] Of note, although respiratory insufficiency is thought to follow musculoskeletal symptoms, respiratory muscle fatigue (particularly in the diaphragm) has been shown to be an early-stage symptom even in the absence of abnormal spirometry results.[34] **Table 1** summarizes advisor-recommended physical and clinical assessments for long-term follow-up and detection of symptoms.

Table 1. Long-term LOPD Assessment Overview

Assessment	Description	Important observations for LOPD
• **Glc4/Hex4 (urine)** • **ALT and AST (blood)** • **CK (blood)**	Glc4/Hex4 is a specific biomarker and correlates with muscle glycogen content[35] ALT, AST, and CK are non-specific markers of tissue damage[36]	Generally elevated, however can vary with some patients showing levels within the normal range[28,29] Biomarkers should be tracked over time and interpreted in context of clinical findings[28]
• **Echocardiogram or electrocardiogram**	Measures cardiac function including ejection fraction, vessel structure, and presence of arrhythmias	Life-threatening cardiac involvement is rare, but early assessment is needed to rule out IOPD Heart rhythm disturbances, aortic stiffness, and increased blood pressure are seen in some LOPD patients and should be monitored[29,37,38]
• **Cardiopulmonary exercise testing (CPET)**	Includes pulmonary function tests (PFTs),* maximal oxygen consumption (VO_2), functional aerobic impairment (FAI), respiratory exchange ratio (RER), dyspnea index (DI), and heart rate (HR) during exercise	Aerobic capacity measured via CPET has been shown to deteriorate over time (particularly in the absence of exercise)[39,40] Important to help establish customized home exercise programs
• **Six Minute Walk Test (6MWT)***	Walking on a looped track for 6 minutes to assess aerobic capacity and gait	Compared with healthy controls, a decline in walking ability is seen at an earlier age (mean age range in studies: 43–54.2 years)[41] Challenges with the 6MWT in NBS-identified LOPD patients are progressive musculoskeletal function decline and in some cases wheelchair dependence, which means they are unable to perform the test[41]
• **Pulmonary* and sleep assessments**	Sitting and supine forced vital capacity (FVC), inspiratory muscle pressure (MIP), expiratory muscle pressure (MEP), sniff nasal inspiratory pressure (SNIP), peak cough flow (PCF), sleep disordered breathing (SDB), respiratory failure (RF), and reduced quality of sleep	~75% of LOPD patients have some respiratory dysfunction.[42] FVC/MIP/MEP/SNIP can detect early diaphragmatic weakness; considered the principal cause of respiratory dysfunction in LOPD[43] SDB is an early symptom and is accompanied by reduced sleep quality. SDB symptoms indicate respiratory muscle weakness and can be a predictive sign of RF[44]

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Advisors agreed that a combination of biomarker changes and clinical signs is preferred to evaluate whether patients with LOPD are becoming symptomatic; these measurements must be repeated at different timepoints to understand evolution over time. Changes in biomarkers, respiratory insufficiency, and motor decline are all considered strong predictors of disease progression.

Table 1. Long-term LOPD Assessment Overview (continued)

Assessment	Description	Important observations for LOPD
• **Alberta Infant Motor Scale (AIMS) ≤18 months**[45]	Assesses gross motor skills against age-appropriate developmental milestones	Performance can be variable, but patients typically function below age level[29] Complementary physical therapist assessment is recommended to identify abnormal postures and/or movements[30]
• **Peabody Developmental Motor Scales-2nd Edition (PDMS-2) ≤5 years**	6 subtests assessing motor skills in young children: reflexes (<11 months), stationary, locomotion, object manipulation (≥12 months), grasping, and visual-motor integration	
• **Gross Motor Function Measure –66 (GMFM-66) or – 88 (GMFM-88) <5 months to 16 years**[46]	Ability to complete motor functions by grouped dimensions (lying and rolling, sitting, crawling and kneeling, standing, walking, running and jumping)[47]	LOPD patients score ~62% (scoring range: 0–100%)[48] 100% scores are expected by age 5 in normal development
• **Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)**[49] **≥3 months up to 2 years of age or children who cannot sit without support**[49,51]	Measures 16 muscle movements (head control, elbow flexion and knee extension, arm and leg mobility, and hand grip)[50]	No reported data in LOPD children younger than 11 years. Results in IOPD show low motor function, which deteriorates over time[51]
• **Physical medicine and rehabilitation**	Includes physical and occupational therapy; qualitative assessment of posture, movement, and musculoskeletal status	Characteristic patterns of posture and movement abnormalities including core and proximal muscle weakness, limb-girdle weakness, and impaired gait and standing posture[28,29]

* Patients must be ≥5 years of age, able to walk (to perform 6MWT), or follow directions for pulmonary function testing.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; Glc4/Hex4, urine glucose tetrasaccharide/hexose tetrasaccharide; LOPD, late-onset Pompe disease; NBS, newborn screening.

Other physical assessments in Pompe disease include kinematic analysis,[28] the expanded Hammersmith Functional Motor Scale,[51] the Gait, Stairs, Gower, Chair (GSGC) Scale,[52] and the Bayley Scales of Infant and Toddler Development.[53] There are also assessments aimed at limb-girdle muscular dystrophies of interest and include the North Star Assessment for limb-girdle type muscular dystrophies (NSAD), 100-meter timed test, and Performance of Upper Limb.[54]

Clinical Practice Insights from the 2024 Advisory Board

Advisors noted that more focused resources to improve adherence to assessment recommendations and reduce the risk of overmedicalizing healthy patients would be helpful.

Patients Lost to Long-term Follow-up and Unmet Needs

Patients with NBS-identified LOPD and/or their families and carers may find the commitment to long-term follow-up and continued assessments challenging, and some are lost (**Figure 5**).

Clinical Practice Insights from the 2024 Advisory Board

Advisors noted that reasons for NBS-identified LOPD patients being lost to follow-up include socio-economic factors, lack of noticeable symptoms by patients, migration, lack of access to academic centers, and insurance reimbursement issues. Lessons could be learned from other diseases and/or organizations to improve the lost to follow-up rate.

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FIGURE 5. REASONS PATIENTS WITH NBS-IDENTIFIED LOPD ARE LOST TO FOLLOW-UP AS PER ADVISORS' EXPERIENCES

20–30% of NBS-identified LOPD patients are lost to follow-up

Patient challenges

- At diagnosis it is unknown which patients will require the most care
- Subtle or no symptoms:
  - Lack of belief in danger
  - Uncertainty around when/if symptoms will arise and how
- Limited or misinformation about LOPD
- Language barriers
- Socioeconomic status

Geographical challenges

- Relocation (across state lines or country borders)
- HCPs limited to which patients they can see
- Difficulty accessing specialist Pompe disease centers or specialist HCPs due to distance

Financial challenges

- Lack of insurance reimbursement (eg, for telemedicine or specific assessments)
- Availability of funding or resources for NBS and assessments

Testing challenges

- Variability in US state post-positive NBS process
- Variability in timing of assays and sequencing
- Confidence of PCPs in specialist testing and process (eg, urine Glc4/Hex4)

Glc4/Hex4, glucose tetrasaccharide/hexose tetrasaccharide; HCP, healthcare professional; LOPD, late-onset Pompe disease; NBS, newborn screening; PCP, primary care physician; US, United States.

Clinical Practice Insights from the 2024 Advisory Board

Advisors suggested that systematically tracking patients with NBS-identified LOPD is important to know when follow-up care is needed. Electronic Health Record (EHR) Programs, such as EPIC or Cerner, can help ensure follow-up, as well as confirming patients have future appointments scheduled when completing a visit. Some state public health departments have robust follow-up care; however, others focus on confirming a case of LOPD and then transfer to clinical care.

Advisors acknowledged that consensus on Pompe disease nomenclature is challenging, but suggested the term "at risk" is appropriate for asymptomatic patients with enzymatic/genetic diagnosis of LOPD.

HCPs acknowledge that there is a need for better access to educational resources and support groups, as well as implementation of consistent management processes to improve loss to follow-up for patients with LOPD (**Figure 6**).

FIGURE 6. RECOMMENDED STRATEGIES AND TACTICS TO IMPROVE PATIENT UNMET NEED AND RELIABLE LONG-TERM FOLLOW-UP

Better access to education resources and support groups

Example issues

- Many caregivers are uncertain about what an NBS-identified LOPD diagnosis means, particularly those whose children are considered pre-symptomatic LOPD (often termed "patients in waiting")[55]
- During periods of waiting, caregivers' main source of information is the internet (eg, Google searches), which often increases their uncertainty and anxiety[56]

Strategies and tactics

From a patient/carer perspective:

- Early exposure to a specialist LOPD HCP/center following an NBS-confirmed diagnosis and providing appropriate and current disease education[57]
- Encouragement of patients/caregivers to be part of the Pompe Disease Registry and patient support groups, particularly those who have concerns about the financial and psychosocial impact of a LOPD diagnosis[57]

From a clinical/PCP perspective:

- Goal-targeted and time-sensitive education is necessary to ensure awareness of the current LOPD landscape (eg, newsletters, professional meetings, or regular user-friendly reports)

Consistent clinical management processes

Example issues

- Although clinical follow-up guidelines exist, assessments for patients with NBS-identified LOPD are not consistent[58]
- After referral for diagnosis, the public health mandate for most US states ends with the responsibility for care resting with pediatricians and other clinicians[58]
- Many patients/caregivers are frustrated at the lack of clarity on follow-up plans, citing that it prevents them from proactively managing their condition[56]

Strategies and tactics

From a patient/carer perspective:

- Systematic follow-up for children diagnosed via NBS[59]; patients/caregivers feel most comfortable with routinely scheduled follow-up assessments and being made aware of which tests are being performed and why[57]

From a clinical/PCP perspective:

- Utilizing national health systems such as EHR to track patients and share their medical data to ensure no gaps in care
- Standardized guidelines on the types and frequency of follow-up assessments to be performed
- Look to other less rare NBS-identified diseases to improve approaches in NBS-identified LOPD patient follow-up

EHR, electronic health record; HCP, healthcare professional; LOPD, late-onset Pompe disease; NBS, newborn screening; PCP, primary care physician; US, United States.

Emerging Technologies

Musculoskeletal signs and symptoms in patients with NBS-identified LOPD are highly variable/heterogenous, and physical therapy evaluation is necessary to assess these often-subtle signs.[28] Given these challenges, using a non-invasive and objective method to assess muscle involvement is important to follow progression. This is especially pertinent in those patients who may not show overt clinical symptoms or in those that have inconclusive or inconsistent values in other biomarkers (eg, Hex4/Glc4, CK, and AST).[21] Two emerging technologies to address this need are muscle magnetic resonance imaging (MRI) and muscle ultrasound **(Figure 7)**.

Clinical Practice Insights from the 2024 Advisory Board

Advisors noted that MRI and muscle ultrasound have the potential to help support clinical decisions for patients with LOPD, particularly those with inconsistent clinical assessments. Standardized guidelines on threshold values or images for patients with LOPD, and local expertise are needed before widespread adoption.

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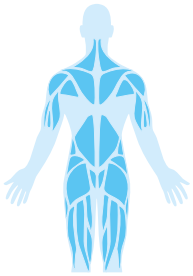
FIGURE 7. EMERGING TECHNOLOGIES FOR ASSESSMENT OF MUSCLE INVOLVEMENT IN PATIENTS WITH LOPD

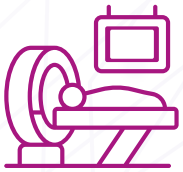
Muscle ultrasound

Ultrasonographic analysis of muscles in the extremities assessing echointensity (muscle quality) and muscle thickness to determine abnormalities



Muscle MRI

Detects changes in fat content in muscle. Increased fat content (fat fraction) is associated with a decline in muscle function



Studies

Studies in patients with LOPD have found that[21]:

- Muscle echointensity is elevated in muscles that generally fit the profile of physical and muscle exam findings in LOPD patients
- Muscle pattern is generally similar to MRI findings in children with LOPD

Studies in patients with LOPD have found that[60,61]:

- High fat fraction significantly correlates with performance in muscle function tests
- Fat muscle infiltration is observed in patients without any clinical symptoms of muscle weakness

Strengths

Strengths[21]

Inexpensive, rapid assessment provided at the point of care and does not require sedation

Strengths[62]

High sensitivity to detect subtle changes over time, quantifiable methods available, and propensity to detect changes in glycogen

Barriers

Barriers: Both require a technician and an expert to interpret the results. To date, there are no standardized protocols or specific guidance on insurance coverage

Both techniques are used for research purposes only in the US and are not currently standard of care for NBS-identified LOPD patients

LOPD, late-onset Pompe disease; MRI, magnetic resonance imaging; NBS, newborn screening; US, United States.

Pompe Disease Relevant Resources

Below are some resources for additional information relating to management of Pompe disease. These include educational materials and published recommended guidelines.

Guidelines

- Management of confirmed newborn-screened patients with Pompe disease across the disease spectrum[4]: https://pubmed.ncbi.nlm.nih.gov/29162675/
- Pompe disease diagnosis and management guideline[5]: https://pmc.ncbi.nlm.nih.gov/articles/PMC3110959/
- Consensus treatment recommendations for late-onset Pompe disease[63]: https://pubmed.ncbi.nlm.nih.gov/22173792/

Sanofi Resources

- Sanofi Rare Disease University: https://rdu-online.com/home
- Sanofi Medical Affairs Health Care Provider Portal: https://www.rarediseases.sanofimedical.com/
  - Pompe Physical Therapy Patient Video Library: Access via QR code
  - Or contact your local Sanofi medical science liaison: RareDiseaseMedical@sanofi.com
- Sanofi Rare Disease Registries: https://www.registrynxt.com/

Pompe Disease Genetic Databases

- The Pompe Disease *GAA* Variant Database: https://www.pompevariantdatabase.nl/
- Leiden Open Variation Database (LOVD): http://www.LOVD.nl/GAA
- The Pompe Disease Mutation Database: https://ngdc.cncb.ac.cn/databasecommons/database/id/5167

Other Resources

- Health Resources & Services Administration (HRSA) Newborn Screening: https://newbornscreening.hrsa.gov/
  - Pompe Disease Newborn Screening: https://newbornscreening.hrsa.gov/conditions/pompe-disease
  - Communicating Out-of-Range Newborn Screening Results to Parents and Families: https://newbornscreening.hrsa.gov/sites/default/files/newborn-screening/documents/nbsic-oor-results-guide.pdf
- UpToDate Newborn Screening for Inborn Errors of Metabolism: https://www.uptodate.com/contents/newborn-screening-for-inborn-errors-of-metabolism
- Baby's First Test: https://www.babysfirsttest.org/
- NewSTEPs: https://www.newsteps.org/
- Centers for Disease Control and Prevention (CDC)'s Milestone Tracker App: https://www.cdc.gov/ncbddd/actearly/milestones-app.html
- CDC. What is early intervention?: https://www.cdc.gov/ncbddd/actearly/parents/states.html
- Early Intervention and Special Education Services for Children: https://www.usa.gov/special-education
- Muscular Dystrophy Association: https://www.mda.org/disease/metabolic-myopathies/types/acid-maltase-deficiency-pompe-disease

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Clinical Practice Insights from the 2024 Advisory Board

Advisors noted that information regarding positive NBS-identified LOPD and long-term management are important resources for PCPs and pediatricians but recognized that a major barrier for HCPs is lack of time.

Glossary of Abbreviations and Acronyms

ACMG, American College of Medical Genetics

AIMS, Alberta Infant Motor Scale

ALT, alanine aminotransferase

AST, aspartate aminotransferase

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

CK, creatine kinase

CPET, cardiopulmonary exercise testing

DI, dyspnea index

EIP, Early Intervention Program

ENT, ears, nose, and throat

EHR, electronic health record

FAI, functional aerobic impairment

GAA, acid α-glucosidase

Glc4/Hex4, glucose tetrasaccharide/hexose tetrasaccharide

GMFM-66, Gross Motor Function Measure –66

GMFM-88, Gross Motor Function Measure –88

GSGC Scale, Gait, Stairs, Gower, Chair Scale

HCP, healthcare professional

HR, heart rate

IOPD, infantile-onset Pompe disease

IVS, intervening sequence

LOPD, late-onset Pompe disease

MRI, magnetic resonance imaging

NBS, newborn screening

NSAD, North Star Assessment for limb-girdle type muscular dystrophies

PCP, primary care physician

PDMS-2, Peabody Developmental Motor Scales-2nd Edition

PFT, pulmonary function test

PPV, positive predictive value

RER, respiratory exchange ratio

RUSP, Recommended Uniform Screening Panel

VO_2, maximal oxygen consumption

VUS, variants of unknown significance

References

1. van der Ploeg AT, Reuser AJ. Pompe's disease. *Lancet*. 2008;372:1342–1353. https://pubmed.ncbi.nlm.nih.gov/18929906/
2. Lee NC, et al. Outcome of later-onset Pompe disease identified through newborn screening. *J Pediatr*. 2022;244:139–147.e2. https://pubmed.ncbi.nlm.nih.gov/34995642/
3. Marques JS. The Clinical Management of Pompe Disease: A Pediatric Perspective. *Children (Basel)*. 2022;9(9):1404. https://pubmed.ncbi.nlm.nih.gov/36138713/
4. Kronn DF, et al. Management of Confirmed Newborn-Screened Patients With Pompe Disease Across the Disease Spectrum. *Pediatrics*. 2017;140(Suppl 1):S24–S45. https://pubmed.ncbi.nlm.nih.gov/29162675/
5. Kishnani PS, et al. Pompe disease diagnosis and management guideline. *Genet Med*. 2006;8(5):267–288. https://pubmed.ncbi.nlm.nih.gov/16702877/
6. Ames EG, et al. Current Practices for U.S. Newborn Screening of Pompe Disease and MPSI. *Int J Neonatal Screen*. 2020;6:72. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7569971/
7. Executive Summary of Adding Pompe to RUSP. 2015. Health Resources and Services Administration. Accessed October 21, 2024: https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/pompe-exsum.pdf
8. NewSTEPs. Accessed August 2024. https://www.newsteps.org/resources/data-visualizations/newborn-screening-status-all-disorders
9. Burton BK, et al. Newborn Screening for Lysosomal Storage Disorders in Illinois: The Initial 15-Month Experience. *J Pediatr*. 2017;190:130–135. https://pubmed.ncbi.nlm.nih.gov/28728811/
10. Klug TL, et al. Lessons Learned from Pompe Disease Newborn Screening and Follow-up. *Int J Neonatal Screen*. 2020;6(1):11. https://pubmed.ncbi.nlm.nih.gov/33073009/
11. Pillai NR, et al. Disparities in late and lost: Pediatricians' role in following Pompe disease identified by newborn screening. *Mol Genet Metab*. 2023;140(1-2):107633. https://pubmed.ncbi.nlm.nih.gov/37414610/
12. Lagler FB, et al. Extent, impact, and predictors of diagnostic delay in Pompe disease: A combined survey approach to unveil the diagnostic odyssey. *JIMD Rep*. 2019;49(1):89–95. https://pmc.ncbi.nlm.nih.gov/articles/PMC6718115/
13. HRSA.gov. Evidence report: newborn screening for Pompe disease. 2013. Accessed October 2024: https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/pompe-external-evidence-review-report-2013.pdf
14. Burton BK, et al. The Initial Evaluation of Patients After Positive Newborn Screening: Recommended Algorithms Leading to a Confirmed Diagnosis of Pompe Disease. *Pediatrics*. 2017;140(Suppl 1):S14–S23. https://pubmed.ncbi.nlm.nih.gov/29162674/
15. Smith LD, et al. Second Tier Molecular Genetic Testing in Newborn Screening for Pompe Disease: Landscape and Challenges. *Int J Neonatal Screen*. 2020;6(2):32. https://pubmed.ncbi.nlm.nih.gov/32352041/
16. Burton BK, et al. Newborn Screening for Pompe Disease in Illinois: Experience with 684,290 Infants. *Int J Neonatal Screen*. 2020;6(1):4. https://pubmed.ncbi.nlm.nih.gov/33073003/
17. Gelb M, et al. Newborn Screening for Lysosomal Storage Disorders: Methodologies for Measurement of Enzymatic Activities in Dried Blood Spots. *Int J Neonatal Screen*. 2018;5:1. https://pubmed.ncbi.nlm.nih.gov/30957052/
18. Leslie N, Bailey L. Pompe Disease. 2007 Aug 31 [updated 2023 Nov 2]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2024. https://pubmed.ncbi.nlm.nih.gov/20301438/
19. Niño MY, et al. Enzymatic diagnosis of Pompe Disease: Lessons from 28 years of experience. *Eur J Hum Genet*. 2021;29:434–446. https://pubmed.ncbi.nlm.nih.gov/33162552/
20. Tortorelli S, et al. Moonlighting newborn screening markers: the incidental discovery of a second-tier test for Pompe disease. *Genet Med*. 2018;20(8):840–846. https://pubmed.ncbi.nlm.nih.gov/29095812/
21. Jackson DG, et al. Muscle ultrasound in patients with late-onset Pompe disease identified by newborn screening. *Mol Genet Metab Rep*. 2023;36:100989. ttps://pubmed.ncbi.nlm.nih.gov/37670900/
22. Chien YH, et al. Baseline Urinary Glucose Tetrasaccharide Concentrations in Patients with Infantile- and Late-Onset Pompe Disease Identified by Newborn Screening. *JIMD Rep*. 2015;19:67–73. https://pubmed.ncbi.nlm.nih.gov/25681082/
23. De Filippi P, et al. Genotype-phenotype correlation in Pompe disease, a step forward. *Orphanet J Rare Dis*. 2014;9:102. https://pubmed.ncbi.nlm.nih.gov/25103075/
24. Rairikar MV, et al. Insight into the phenotype of infants with Pompe disease identified by newborn screening with the common c.-32-13T>G "late-onset" GAA variant. *Mol Genet Metab*. 2017;122(3):99–107. https://pubmed.ncbi.nlm.nih.gov/28951071/
25. Labella B, et al. A Comprehensive Update on Late-Onset Pompe Disease. *Biomolecules*. 2023;13(9):1279. https://pubmed.ncbi.nlm.nih.gov/37759679/
26. de Faria DOS, et al. Update of the Pompe variant database for the prediction of clinical phenotypes: Novel disease-associated variants, common sequence variants, and results from newborn screening. *Hum Mutat*. 2021;42(2):119–134. https://pubmed.ncbi.nlm.nih.gov/33560568/
27. Reuser AJJ, et al. GAA variants and phenotypes among 1,079 patients with Pompe disease: Data from the Pompe Registry. *Hum Mutat*. 2019;40(11):2146–2164. https://pubmed.ncbi.nlm.nih.gov/31342611/
28. Huggins E, et al. Early clinical phenotype of late onset Pompe disease: Lessons learned from newborn screening. *Mol Genet Metab*. 2022;135:179–185. https://pubmed.ncbi.nlm.nih.gov/35123877/
29. Herbert M, et al. Early-onset of symptoms and clinical course of Pompe disease associated with the c.-32-13 T > G variant. *Mol Genet Metab*. 2019;126(2):106–116. https://pmc.ncbi.nlm.nih.gov/articles/PMC9310053/
30. Early intervention and special education services for children. USA.gov. Accessed October 2024: https://www.usa.gov/special-education
31. Early Intervention Program. New York State Department of Health. Accessed October 2024: https://www.health.ny.gov/community/infants_children/early_intervention/
32. Preisler N, et al. Late-onset Pompe disease is prevalent in unclassified limb-girdle muscular dystrophies. *Mol Genet Metab*. 2013;110(3):287-9. https://pubmed.ncbi.nlm.nih.gov/24011652/
33. Lukacs Z, et al. Prevalence of Pompe disease in 3,076 patients with hyperCKemia and limb-girdle muscular weakness. *Neurology*. 2016;87(3):295–298. https://pubmed.ncbi.nlm.nih.gov/27170567/

34. Harlaar L, et al. Chest MRI to diagnose early diaphragmatic weakness in Pompe disease. *Orphanet J Rare Dis*. 2021 Jan 7;16(1):21. https://pubmed.ncbi.nlm.nih.gov/33413525/
35. Piraud M, et al. Urine glucose tetrasaccharide: A good biomarker for glycogenoses type II and III? A study of the French cohort. *Mol Genet Metab Rep*. 2020;23:100583. https://pubmed.ncbi.nlm.nih.gov/32382504/
36. Molares-Vila A, et al. Biomarkers in glycogen storage diseases: An update. *Int J Mol Sci*. 2021;22:4381. https://pmc.ncbi.nlm.nih.gov/articles/PMC8122709/
37. Palladino A, et al. Risk of Cardiac Arrhythmias in Patients with Late-Onset Pompe Disease—Results from a Long Follow-Up in a Group of 12 Patients and Review of Literature. *Cardiogenetics*. 2024;14:38–50. https://doi.org/10.3390/cardiogenetics14010003
38. Wens SC, et al. Increased aortic stiffness and blood pressure in non-classic Pompe disease. *J Inherit Metab Dis*. 2014;37(3):391-7. https://pubmed.ncbi.nlm.nih.gov/24407465/
39. Yang C, et al. Cardiopulmonary Exercise Testing in Two Patients with Late-Onset Pompe Disease Receiving Enzyme Replacement Therapy: A case report and Mini-review article. *Rehabilitation Practice and Science*. 2016;44(4):Article 5. Accessed October 2024: https://rps.researchcommons.org/journal/vol44/iss4/5/
40. Crescimanno G, et al. Role of the cardio-pulmonary exercise test and six-minute walking test in the evaluation of exercise performance in patients with late-onset Pompe disease. *Neuromuscul Disord*. 2015;25(7):542–547. https://pubmed.ncbi.nlm.nih.gov/25908581/
41. Lachmann R, Schoser B. The clinical relevance of outcomes used in late-onset Pompe disease: can we do better? *Orphanet J Rare Dis*. 2013 Oct 12;8:160. https://pubmed.ncbi.nlm.nih.gov/24119230/
42. van der Beek NA, et al. Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease. *Mol Genet Metab*. 2011 Sep-Oct;104(1-2):129-36. https://pubmed.ncbi.nlm.nih.gov/21763167/
43. Chan J, et al. The emerging phenotype of late-onset Pompe disease: A systematic literature review. *Mol Genet Metab*. 2017 Mar;120(3):163-172. https://pubmed.ncbi.nlm.nih.gov/28185884/
44. Boentert M, et al. Sleep-related symptoms and sleep-disordered breathing in adult Pompe disease. *Eur J Neurol*. 2015 Feb;22(2):369-76, e27. https://pubmed.ncbi.nlm.nih.gov/25367349/
45. Eliks M and Gajewska E. The Alberta Infant Motor Scale: A tool for the assessment of motor aspects of neurodevelopment in infancy and early childhood. *Front Neurol*. 2022;13:927502. https://pmc.ncbi.nlm.nih.gov/articles/PMC9515325/
46. Gross Motor Function Measure (GMFM). CanChild. Accessed October 2024: https://canchild.ca/en/resources/44-gross-motor-function-measure-gmfm
47. Russell DJ, et al. The gross motor function measure: a means to evaluate the effects of physical therapy. *Dev Med Child Neurol*. 1989 Jun;31(3):341–352. https://pubmed.ncbi.nlm.nih.gov/2753238/
48. Kishnani PS, et al. Clinical characteristics and genotypes in the ADVANCE baseline data set, a comprehensive cohort of US children and adolescents with Pompe disease. *Genet Med*. 2019;21(11):2543–2551. https://pmc.ncbi.nlm.nih.gov/articles/PMC8076035/
49. CHOP INTEND (Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders). Spinal Muscular Atrophy UK. Accessed October 2024: https://smauk.org.uk/treatments-research/measures-used-to-assess-a-drugs-effectiveness/chop-intend/
50. Glanzman AM, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord*. 2010;20(3):155–161. https://pubmed.ncbi.nlm.nih.gov/20074952/
51. Ricci F, et al. Functional assessment tools in children with Pompe disease: A pilot comparative study to identify suitable outcome measures for the standard of care. *Eur J Paediatr Neurol*. 2018 Nov;22(6):1103-1109. https://pubmed.ncbi.nlm.nih.gov/30166092/
52. Angelini C, et al. New motor outcome function measures in evaluation of late-onset Pompe disease before and after enzyme replacement therapy. *Muscle Nerve*. 2012;45(6):831-4. https://pubmed.ncbi.nlm.nih.gov/22581536/
53. Lai CJ, et al. Cognitive Development in Infantile-Onset Pompe Disease Under Very Early Enzyme Replacement Therapy. *J Child Neurol*. 2016;31(14):1617-1621. https://pubmed.ncbi.nlm.nih.gov/27655474/
54. James MK, et al. Validation of the North Star Assessment for Limb-Girdle Type Muscular Dystrophies. *Phys Ther*. 2022;102(10):pzac113. https://pubmed.ncbi.nlm.nih.gov/35932452/
55. Pruniski B, et al. Newborn screening for Pompe disease: impact on families. *J Inherit Metab Dis*. 2018;41(6):1189-1203. https://pubmed.ncbi.nlm.nih.gov/29594646/
56. Crossen K, et al. A Qualitative Study: Mothers' Experiences of Their Child's Late-Onset Pompe Disease Diagnosis Following Newborn Screening. *Int J Neonatal Screen*. 2022;8(3):43. https://pmc.ncbi.nlm.nih.gov/articles/PMC9326644/
57. Prakash S, et al. Newborn screening for Pompe disease: Parental experiences and follow-up care for a late-onset diagnosis. *J Genet Couns*. 2022;31(6):1404–1420. https://pubmed.ncbi.nlm.nih.gov/35915971/
58. Kemper AR, et al. Ensuring the Life-Span Benefits of Newborn Screening. *Pediatrics*. 2019;144(6):e20190904. https://pmc.ncbi.nlm.nih.gov/articles/PMC7202673/
59. Lisi EC and Ali N. Opinions of adults affected with later-onset lysosomal storage diseases regarding newborn screening: A qualitative study. *J Genet Couns*. 2021;30(6):1544–1558. https://pubmed.ncbi.nlm.nih.gov/33938615/
60. Alonso-Jiménez A, et al. Different Approaches to Analyze Muscle Fat Replacement With Dixon MRI in Pompe Disease. *Front Neurol*. 2021;12:675781. https://pubmed.ncbi.nlm.nih.gov/34305788/
61. Figueroa-Bonaparte S, et al. Muscle MRI Findings in Childhood/Adult Onset Pompe Disease Correlate with Muscle Function. *PLoS One*. 2016;11(10):e0163493. https://pubmed.ncbi.nlm.nih.gov/27711114/
62. Figueroa-Bonaparte S, et al. Quantitative muscle MRI to follow up late onset Pompe patients: a prospective study. *Sci Rep*. 2018 18;8(1):10898. https://pubmed.ncbi.nlm.nih.gov/30022036/
63. Cupler EJ, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45(3):319–333. https://pubmed.ncbi.nlm.nih.gov/22173792/

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MAT-US-2412105 v3.0 P Expiration Date: 01/29/2028