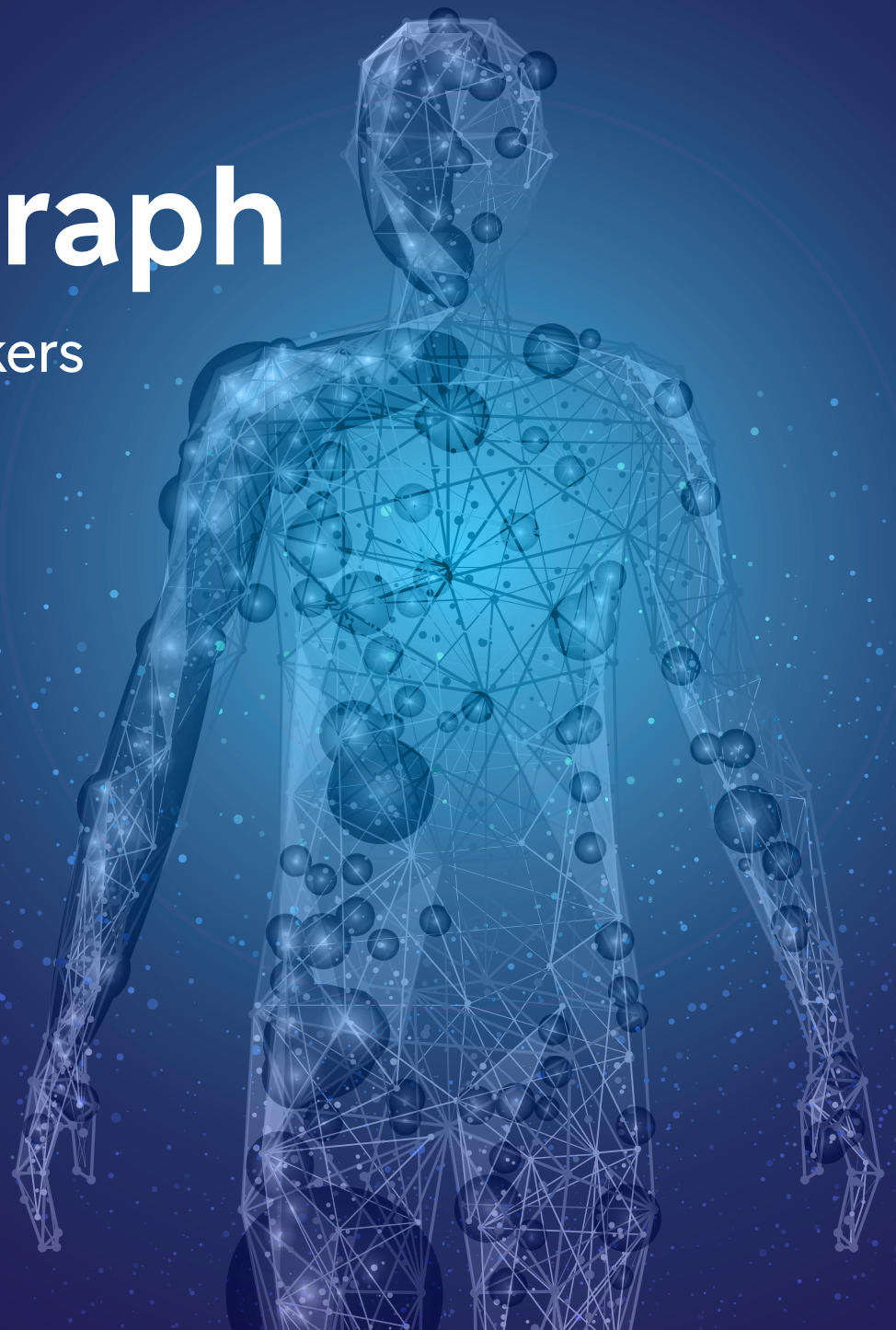
Clinical Monograph

Lysosomal Storage Disease Biomarkers



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The 2023 Rare Disease Advisory Council Meeting

In August 2023, the Sanofi Rare Disease Team conducted an Advisory Council Meeting to bring together experienced advanced practice providers (APPs) from various regions throughout the United States. The purpose of this meeting was to establish a network for education and communication to help advance patient care by sharing insights, resources, and best practices for obtaining and evaluating biomarkers for lysosomal storage diseases. The feedback from this meeting provided a basis for initiatives such as monographs, newsletters, and other educational materials available to APPs through the Sanofi Rare Disease Medical Team. The APP Advisory Council also helped identify knowledge gaps, educational resource needs, and potential topics for future initiatives, as part of Sanofi's ongoing commitment to APPs in their care of patients with rare diseases. This monograph contains the views, recommendations, and real-world experience of the attendees of the APP Advisory Council and does not necessarily reflect the views of Sanofi.

Sanofi compensated participants for their participation in the meeting.

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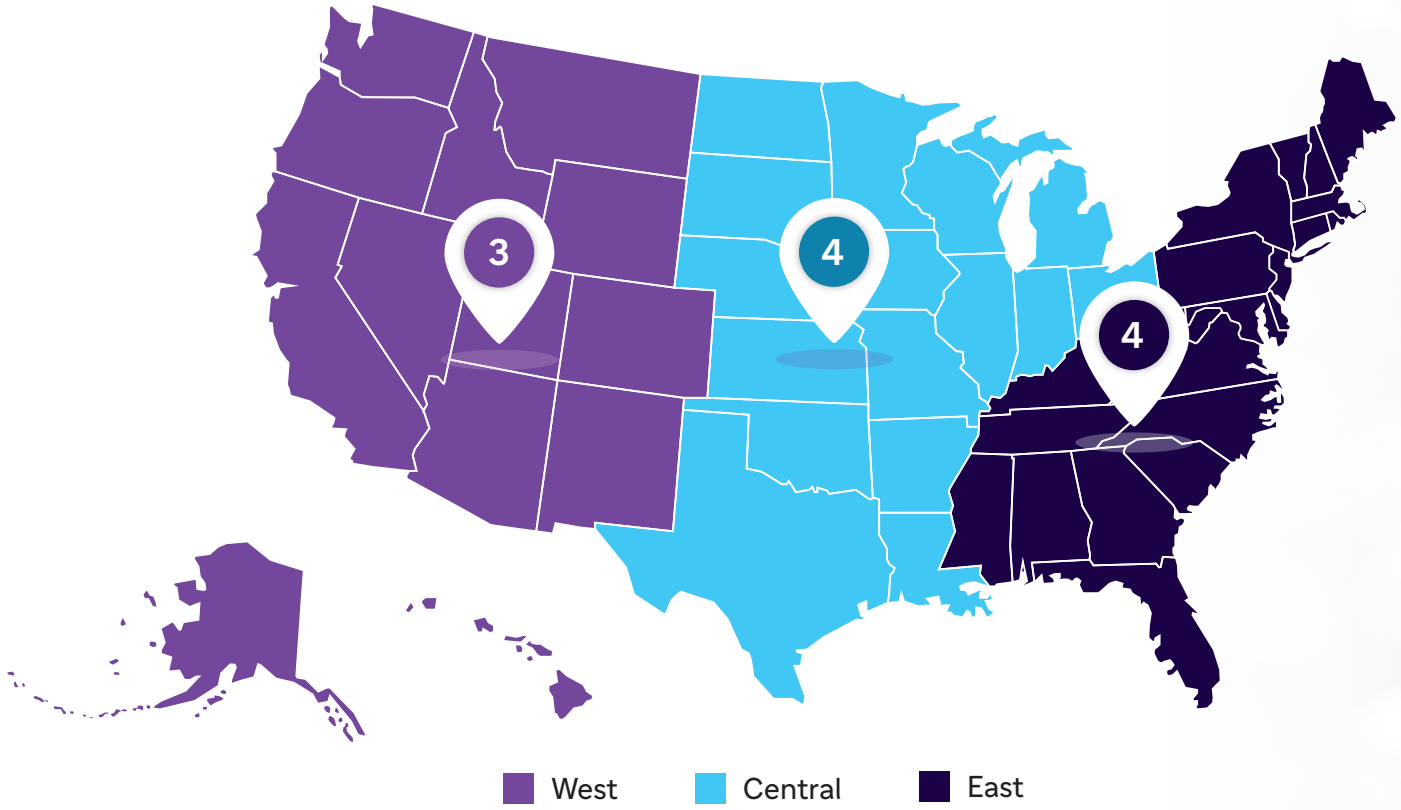

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Introduction to Biomarkers in Lysosomal Storage Diseases

A biomarker is a biological characteristic that can be objectively measured and evaluated as a signal of normal biological or pathological processes and thus has the potential to improve diagnosis, predict disease manifestations, and monitor responses to therapeutic intervention.[1]

A biomarker can be measured in body fluids such as blood, plasma, or urine to examine disease activity. Biomarkers are not necessarily specific to a disease but may indicate physiological processes that are happening as a result of disease (eg, inflammation). **Table 1** lists common terminology associated with biomarkers discussed in this monograph.

TABLE 1: GLOSSARY OF TERMS

Acid α-glucosidase (GAA)	A lysosomal enzyme that degrades lysosomal glycogen to glucose and is deficient in Pompe disease
Acid β-glucosidase (GCase) *Other names: glucocerebrosidase (GCase)*	A lysosomal enzyme that cleaves glucosylceramide to glucose and ceramide and is deficient in Gaucher disease
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Liver enzymes that are increased in the blood as a result of liver damage or disease
Angiotensin-converting enzyme (ACE)	An enzyme involved in blood pressure homeostasis by converting inactive angiotensin I to active angiotensin II and degrading bradykinin. Is a historic biomarker used in Gaucher disease
Biomarker	A biological molecule found in blood, other body fluids, or tissues reflecting a normal or abnormal process or disease
Ceramide	The precursor of complex sphingolipids such as glucosylceramides and sphingomyelin
Chitotriosidase	An enzyme produced by activated macrophages that can be elevated in many disorders including various lipid storage lysosomal diseases
Creatine kinase (CK)	An enzyme mainly present in skeletal muscle, myocardium, and brain that is released into the systemic circulation as a result of injury or disease
Globotriaosylceramide (GL-3)	A complex glycosphingolipid and the substrate that accumulates in cells as a direct result of α-galactosidase A deficiency in Fabry disease
Globotriaosylsphingosine (lyso-GL-3)	The deacylated form of the glycosphingolipid GL-3 that accumulates in Fabry disease as a direct result of α-galactosidase A deficiency
Glucose tetrasaccharide (Glc4)	One of multiple 6-carbon sugars (hexose tetrasaccharides, Hex4) resulting from amylolytic degradation of glycogen that is increased in several pathological conditions associated with increased storage of glycogen including Pompe disease. By measuring the total amount of Hex4, an indirect measure of Glc4 is obtained
Glucosylceramide (GL-1, or GlcCer) *Other names: glucocerebroside*	A central building block for more complex glycosphingolipids and the substrate that accumulates in cells due to the absence or deficiency of the enzyme GCase in Gaucher disease
Glucosylceramide synthase (GCS)	The key enzyme in glycosphingolipid synthesis catalyzing the transfer of glucose to ceramide to form GL-1
Glucosylsphingosine (lyso-GL-1)	The deacylated form of the glycosphingolipid GL-1 that accumulates in Gaucher disease as a direct result of GCase deficiency
Glycosaminoglycans (GAGs)	The major substrates (polysaccharides) that accumulate in cells as a direct result of deficiency of α-L-iduronidase in mucopolysaccharidosis I (MPS I)
Glycosphingolipid	A class of cell membrane lipids that serve important cellular functions including cell signaling
Lysosomal storage disease	A group of disorders caused by deficiency of specific lysosomal enzymes
Macrophage inflammatory protein 1-β (MIP-1β)	A protein produced by macrophages involved in cell activation of granulocytes and stimulation of lysosomal enzymes
Pathogenic variant	An alteration in a gene capable of causing a certain disease or disorder
Peripheral blood mononuclear cells (PBMCs)	Cells isolated from peripheral blood, including lymphocytes, monocytes, natural killer (cells), or dendritic cells
Tartrate resistant acid phosphatase (TRAP)	An enzyme that is highly expressed by osteoclasts and activated macrophages, and is a historic biomarker used in Gaucher disease
α-galactosidase A	A lysosomal enzyme that degrades the lysosomal glycosphingolipid GL-3 and is deficient in Fabry disease

Biomarkers are typically used to monitor disease activity over time and provide a bigger picture of a patient's long-term general condition and disease state, including tracking responses to therapeutic interventions. Hence, the main goal is to evaluate trends in biomarker values over the longer term rather than at single timepoints.

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Practice Insight From the 2023 Advisory Council

Advisors noted that they do not typically use lysosomal storage disease biomarkers for diagnostic purposes, but that they can be used as a follow-up to support the findings from genetic/molecular diagnostic testing and can help establish disease state and prognosis.

FIGURE 1: IDEAL CHARACTERISTICS OF A BIOMARKER (adapted from Burlina A, et al., 2023)[2,3]

1	**Disease monitoring/prognosis** 	Can be measured serially to assess the status of a disease	• High specificity • Low intra-individual variability • Responds to therapy and predicts treatment success
2	**Diagnosing** 	Can detect or confirm the presence of a disease	• Sufficient precision and reliability (high sensitivity) • Therapeutic implications • Low cost
3	**Screening** 	Can detect or confirm presence of a disease early/before clinical symptoms	• High specificity • Therapeutic and lifestyle implications • Low cost

Sensitivity: the ability of a test to correctly identify patients with a disease. Specificity: the ability of a test to correctly identify people without the disease. Sensitivity and specificity are inversely proportional, meaning that as the sensitivity increases, the specificity decreases and vice versa.

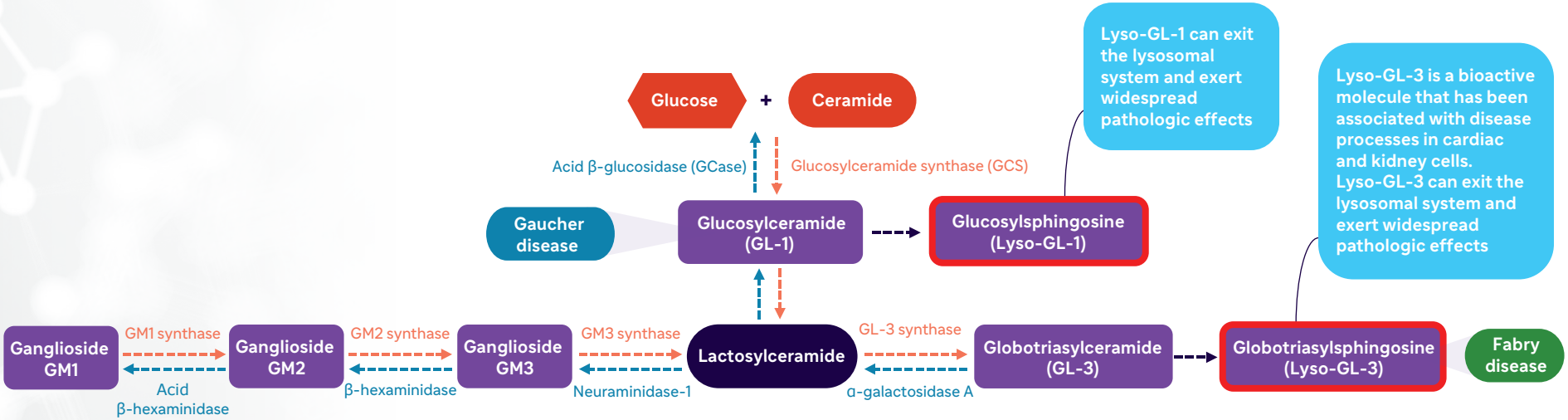
Guidance on Lysosomal Storage Disease Biomarker Monitoring for Healthcare Providers and Patients

Overview mechanism diagrams of the sphingolipid pathway (see **Figure 2** for an example) are helpful resources for healthcare providers (HCPs), particularly those who are unfamiliar with lysosomal storage diseases and their associated biomarkers. These diagrams are more technical and may not be useful guides when explaining biomarker assessments to patients.

Practice Insight From the 2023 Advisory Council

Advisors suggested using the term "disease marker" as opposed to "biomarker" to help patients understand the concept better. They also noted that digital or imaging markers may be more commonly referred to by the term "routine surveillance".

FIGURE 2: OVERVIEW OF THE SPHINGOLIPID PATHWAY



In lysosomal storage diseases, patients commonly have symptoms of organomegaly, pulmonary dysfunction, delayed growth, and bone pain.[4-8] Although some biological markers can indicate the status of these manifestations (eg, elevated liver enzymes and hepatomegaly[9]), imaging and digital markers are important clinical markers for monitoring patient disease status and the efficacy of therapeutic interventions. Common measures include high resolution computerized tomography, electrocardiograms, magnetic resonance imaging, pulmonary functions tests, and bone density scans.[4-8]

Biomarker testing and monitoring is becoming increasingly relevant and accessible in the management of patients with lysosomal storage diseases. However, understanding the utility and meaning of biomarkers, and how their levels change over time or from one measurement to the next can be difficult for patients (**Figure 3**).

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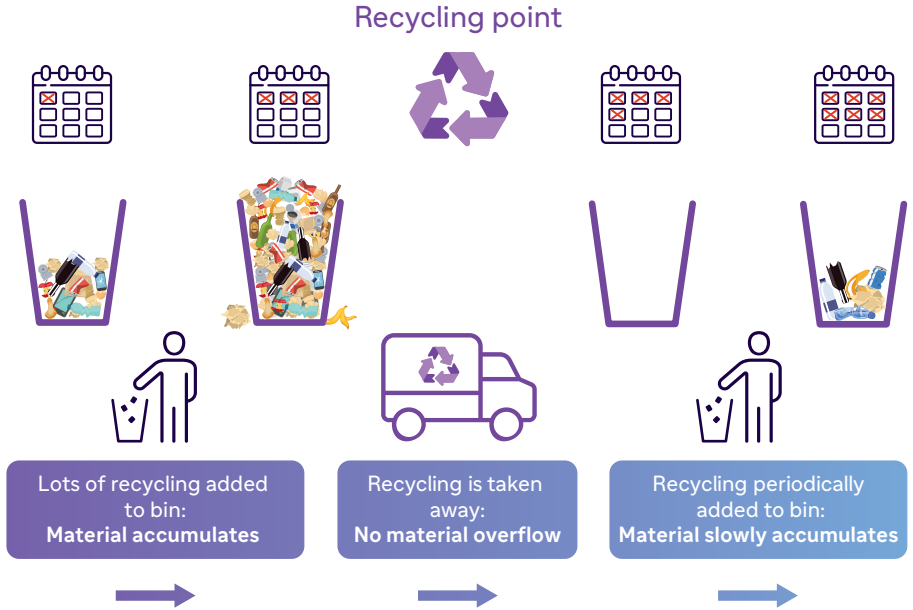
Practice Insight From the 2023 Advisory Council

Advisors recommend highly visual, simple to understand, patient-friendly educational resources on the meaning and utility of biomarkers. These need to consider language and cultural barriers and should be available to patients at the time of visit.

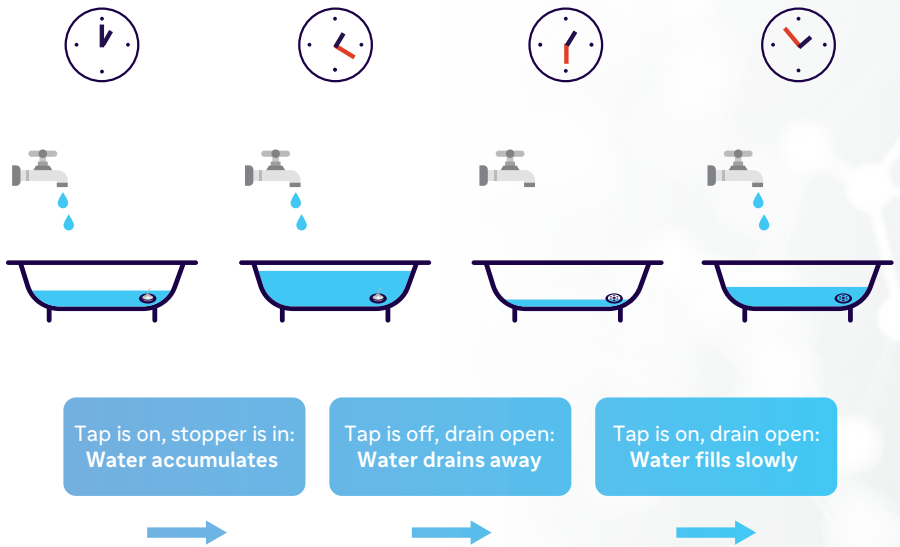
FIGURE 3: VISUAL GUIDES TO EXPLAIN BIOMARKER CHANGE OVER TIME

Substrate levels can change over time - biomarkers can help measure that change



Like recycling material (substrate), levels of a substrate can increase or decrease over time. In this analogy, the recycling truck can be considered the enzyme - if it is deficient or absent, the material will not only accumulate but will also not get to the recycling center (target organ) to be broken down and used elsewhere

Understanding how substrate levels change over time is important to help manage a patient's condition (eg, is the recycling material being taken away frequently enough?). Biomarkers can help measure the levels of a substrate

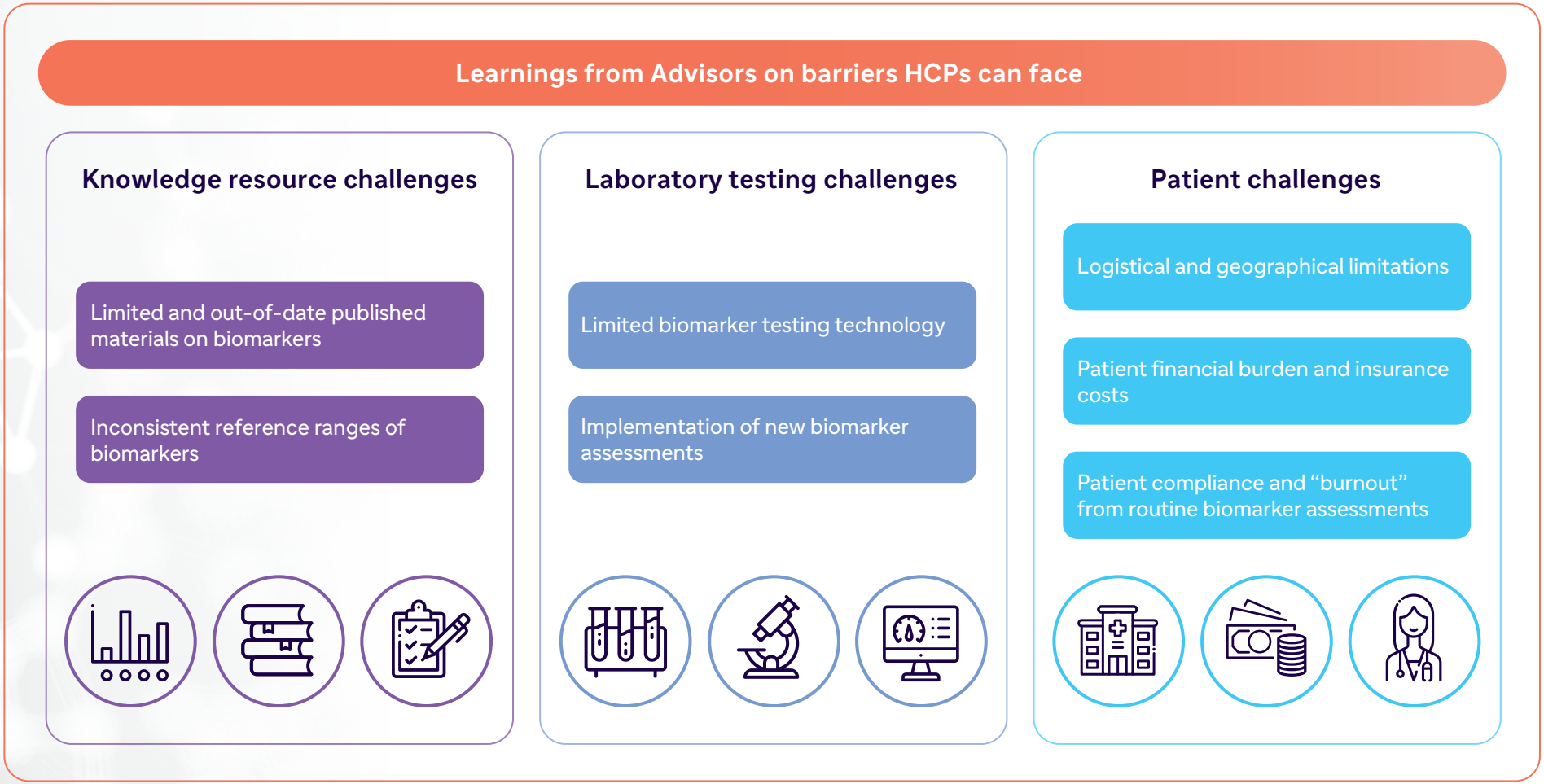


Like water (substrate) filling a bathtub, levels of a substrate can increase or decrease over time. In this analogy, the drain stopper can be considered as the enzyme - if it is deficient or absent, the water can accumulate and overflow

Understanding how substrate levels change over time is important to help manage a patient's condition (eg, is the water draining fast enough?). Biomarkers can help measure the levels of a substrate

For HCPs, learning about relevant biomarkers through literature is challenging as publications are limited, have varying reference ranges, and new information is not published in a timely manner. Other challenges and barriers advisors highlighted for HCPs include access to a reliable laboratory for testing, availability of biomarker testing technology, and patient factors including compliance and associated insurance costs (**Figures 4 and 5**).

FIGURE 4: ADVISOR LEARNINGS ON BARRIERS OF BIOMARKER TESTING FOR HCPS



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Advisors typically rely on other APPs, disease specialists, and medical science liaisons (MSLs) within the rare disease community to learn about new biomarkers. They also noted that they have a consistent laboratory they use for testing and consider each patient as an individual.

FIGURE 5: ADVISOR RECOMMENDATIONS FOR HCPS WHEN UTILIZING LYSOSOMAL STORAGE DISEASE BIOMARKERS

Top tips for HCPs from Advisors

- Reach out to APPs or specialists in the rare disease community to seek guidance
- Attend scientific meetings/conferences and advisory council meetings, and query rare disease registries
- Utilize MSLs as a resource

- Use the same laboratory whenever possible for long-term serial testing with reliable contacts
- Use laboratories that provide genetic counselling services to HCPs to help them understand results so they can discuss with their patients

- Ideal frequency for biomarker assessment is at baseline, and every 6 months to 1 year thereafter
- Consider each patient as an individual and personalize assessments to their needs

Biomarker Testing and Monitoring in Lysosomal Storage Diseases

When performing biomarker testing and monitoring patients with lysosomal storage disease, multiple factors must be considered. These include:

- Selection of the correct biomarkers/clinical team to monitor complex manifestations longitudinally
- Patient situational factors such as their ability to attend regular testing appointments at the clinic
- Difficulties in obtaining biomarker baseline values due to inconsistent disease reference ranges, disease status, or age of patient (eg, newborn screening)

The following are example case studies of patients with Gaucher disease, Fabry disease, and Pompe disease that may help illustrate patient monitoring and suggested approaches (note, results may vary for individual patients):

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Advisors highlighted the impact of situational factors on regular biomarker monitoring. These can include logistical and financial burdens for patients and lack of adherence and compliance to managing their condition.

Case study #1: Gaucher disease

Patient information

Profile:

- 14-year-old female patient presenting with an enlarged spleen, fatigue, and frequent nosebleeds
- Enzyme assay identified a diagnosis of **Gaucher disease**
- Genetic testing was not performed
- She has recently initiated enzyme replacement therapy

Symptoms:

- Hepatosplenomegaly, delayed growth, anemia, fatigue, and bruising

Biomarker monitoring assessments:

- Measurements of plasma chitotriosidase, ACE, TRAP, and lyso-GL-1 levels every 3-6 months
- Routine imaging of spleen and liver, and bone mineral density measurements

Challenge:

- The patient has recently relocated and, due to her worsening symptoms and cost of travel, is unable to attend regular clinical follow-ups and biomarker monitoring assessments at her hospital
- Due to similar somatic symptoms seen in Gaucher disease type 1 (GD1) and type 3 (GD3), a full diagnosis of type is yet to be determined and monitoring for neurological manifestations (eg, gaze palsy and cognitive impairment) is required

Solution/suggested approach:

- Explore potential collaborations with local clinical practices to the patient to obtain regular biomarker measurements
- Refer for a neurological work-up, including ophthalmology, to rule out symptoms consistent with GD3
- Obtain molecular testing of *GBA1* to determine whether the genotype is consistent with GD3
- Do regular virtual consultations with patient/caregiver via telehealth services

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Advisors typically associate biomarkers with tests that involve blood, plasma, urine, and cerebral spinal fluid, preferring "routine surveillance" to refer to imaging/digital. They emphasized the importance of having a multidisciplinary care team with other specialists such as radiologists and cardiologists.

Case study #2: Fabry disease

Patient information

Profile:

- A 25-year-old male presented to the genetics clinic with a 5-year history of intermittent episodes of burning pain, particularly in the hands and feet, and occasional gastrointestinal symptoms, including diarrhea and abdominal pain

Diagnosis:

- Family history was significant for a maternal uncle with a similar presentation. The patient's mother also has a history of arrythmias. Initial laboratory investigations showed elevated serum creatinine levels and significantly reduced α-galactosidase A enzyme activity (<5% of normal)
- Cardiac magnetic resonance imaging revealed left ventricular hypertrophy and late gadolinium enhancement, indicating myocardial fibrosis
- All findings were consistent with the progressive nature of **Fabry disease**, and treatment was initiated

Biomarker monitoring assessments:

- Every 3-to-6-month measurements of estimated glomerular filtration rate (via plasma) and proteinuria (via urine samples) to monitor kidney function (dependent on chronic kidney disease stage), and every 6- to 12-month measurements of plasma lyso-GL-3 levels. The patient needs evaluation by a nephrologist for the elevated creatinine

Challenge:

- In addition to biological samples, the patient requires routine surveillance via cardiac magnetic resonance imaging and echocardiography to monitor cardiac event risk and disease progression

Solution/suggested approach:

- Multidisciplinary clinical team was recommended including cardiologists, radiologists, nephrologists, and medical geneticists

Practice Insight From the 2023 Advisory Council

Advisors highlighted the importance of biomarker baseline values to monitor disease progression and inform therapeutic intervention. This can be a challenge particularly in newborns as multiple tests can be taxing on the patient and caregivers.

Case study #3: Pompe disease

Patient information

Profile:

- An 18-month-old female with a diagnosis of **late-onset Pompe disease** (LOPD) identified through newborn screening, confirmed through dried blood spot GAA enzyme activity and molecular testing
- The child was asymptomatic at birth, but the parents noted delayed milestones with difficulty crawling, standing, and walking, and some coughing/wheezing with colds in early childhood
- Medical examination identified muscle weakness in lower extremities and a history of frequent respiratory infections

Biomarker monitoring and other assessments:

- Biomarker baseline values of CK and urine Hex4 were obtained at birth through blood and urine samples, respectively. To monitor disease progression, values were also measured every 3 months. These values have remained relatively stable and within the normal reference range
- Physiotherapy assessment every 3 months and motor function evaluation every 6 months to monitor muscle strength and function

Challenge:

- The family has expressed concerns in the frequency of follow-up lab and appointments
- At newborn screening, LOPD patients typically have no measurable signs or symptoms or predictable time of symptom onset
- Regular and numerous tests at variable frequencies are required to monitor patients for onset or progression of signs and symptoms
- Published guidelines recommend pulmonary evaluations in symptomatic LOPD patients every 3–6 months for patients >12 months of age;[10] however, these assessments can be difficult to obtain in young pediatric patients

Solution/suggested approach:

- A personalized monitoring plan, tailored to the patient's disease progression including adjustments of the frequency of assessments as needed
- A multidisciplinary care team to ensure comprehensive monitoring and timely interventions

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Lysosomal Storage Disease-specific Biomarkers

Practice Insight From the 2023 Advisory Council

Advisors highlighted the need for resources listing relevant biomarkers for lysosomal storage diseases for HCPs who are unfamiliar with these conditions.

The following tables provide an overview of commonly measured biomarkers for MPS I, Fabry disease, Pompe disease, Gaucher disease, and acid sphingomyelinase deficiency (ASMD) and those (if any) that are still investigational and not typically available for commercial testing. Note that normal and pathological laboratory values may differ due to variability in methodology (techniques and protocols) used by different laboratories and may also vary according to age and sex of individuals. Reference ranges are therefore not included here.

Mucopolysaccharidosis I (MPS I)

MPS I is typically classified as severe (previously called Hurler syndrome) and attenuated (previously called Hurler-Scheie and Scheie syndromes). MPS I is seen worldwide in approximately 1/100,000 births (severe MPS I) or 1/500,000 births (attenuated MPS I).[11,12] People with MPS I have deficient α-L-iduronidase enzyme resulting in accumulation of glycosaminoglycans (GAGs), leading to developmental delay and regression, learning disabilities, as well as respiratory, cardiac, and musculoskeletal dysfunction ranging over a continuum of severity.[4,13] In severe MPS I, symptoms begin within the first few months of life with death occurring within the first 10 years of life.[4,11] In attenuated MPS I, symptoms often begin between the ages of 3–10 years and are associated with a significant disease burden; death occurs from the second decade of life but may also be associated with a normal lifespan.[4,11]

Common measured biomarkers in MPS I

Biomarker	Tissue sample	Typical unit of measurement	Pros/cons
Total GAGs: • Chondroitin sulfate • Dermatan sulfate • Heparan sulfate • Keratan sulfate	Urine	ng/mL	**Pro:** Non-invasive measurement; reduced after treatment initiation and responsive to changes in dosing[14] **Con:** Total GAGs cannot conclusively establish diagnosis, and there is no correlation between total GAG level and phenotype[15]
Total GAGs: • Dermatan sulfate • Heparan sulfate • Keratan sulfate	Whole blood Dried blood spots	nmol/L	**Pro:** Can be used to monitor disease burden,[16] and as a second-tier test in newborn screening to confirm diagnosis[17] **Con:** GAG levels are age-dependent[18]
Non-reducing ends (NREs) GAGs: • Dermatan sulfate • Heparan sulfate	Dried blood spots	nmol/L	**Pro:** Heparan sulfate analysis can distinguish MPS I from MPS II[19] **Con:** GAG levels are age-dependent[18]

For more information about MPS I and biomarkers, visit: https://www.rarediseases.sanofimedical.com/ or contact your local Sanofi Medical Science Liaison: RareDiseaseMedical@sanofi.com

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Fabry disease

People with Fabry disease are classified as having classic or late-onset (non-classic).[20] In classic Fabry disease, the incidence is approximately 1/40,000 in males and 1/20,000 in females.[20] Type classification is determined by the age of symptom onset and symptom presentation; patients with classic Fabry disease typically present in childhood/adolescence and have multi-organ involvement.[21] Patients with non-classic disease present later in life at variable ages, but most frequently between the 4th and 7th decades.[20] Patients with non-classic disease typically have fewer organ systems involved; most often primarily cardiac presentation.[18] People with Fabry disease have a lack of sufficient α-galactosidase A enzyme activity which results in progressive accumulation of the glycosphingolipid globotriaosylceramide (GL-3) causing multisystemic symptoms.[21] Symptoms range from mild to severe and for patients with classic Fabry disease, include neuropathic pain, gastrointestinal issues, renal dysfunction, cardiovascular disease, and cerebrovascular risk.[21] There is an approximately 16-year reduction in lifespan for classic males and a range of 5–14–year reduction in lifespan for classic females compared with the general population.[22–24]

Common measured biomarkers in Fabry disease

Biomarker	Tissue sample	Typical unit of measurement	Pros/cons
Globotriaosylceramide (GL-3)	Plasma/urine Dried blood spots	nmol/mL (plasma)	**Con:** Older biomarker of Fabry disease and less specificity than lyso-GL-3. Limited sensitivity in late-onset and female patients with some overlap in control populations[25]
Globotriaosylsphingosine (lyso-GL-3)	Plasma Dried blood spots Saliva	nmol/L	**Pro:** Higher specificity than GL-3, and correlates with disease progression and severity;[26] can be used to differentiate phenotypes[27,28] **Con:** Some overlap may exist between classic and non-classic females[29]
Urine albumin-creatinine ratio (UACR)	Urine (24 hours or dried urine spots)	mg/24 hours (day)	**Pro:** Non-invasive measurement and a well-established biomarker of renal Fabry disease. Albuminuria is an earlier pathological sign than proteinuria, and is a more sensitive marker of glomerular and podocyte injury[30] **Con:** Elevated levels can occur in the absence of renal damage, eg, in urologic or gynecologic disease[30]
Glomerular filtration rate (GFR) and estimated GFR (eGFR)	Plasma	mL/min/1.73 m^2/year	**Pro:** Well-established biomarker of renal dysfunction in Fabry disease[30] **Con:** Older people will have lower than normal levels as GFR decreases with age and estimated assessment is less accurate (measured GFR may not be feasible at regular intervals due to the complexity of the measurement)[21]

For more information about Fabry disease and biomarkers, visit: https://www.rarediseases.sanofimedical.com/ or contact your local Sanofi Medical Science Liaison: RareDiseaseMedical@sanofi.com

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Pompe disease

Pompe disease is seen in approximately 1/40,000 births worldwide and people are classified as having infantile-onset (IOPD) or late-onset (LOPD) Pompe disease.[6,31] In IOPD, symptoms present prior to 1 year of age whereas in LOPD, symptoms typically present in childhood or early adulthood.[6,31] People with Pompe disease have an absence or deficiency of acid α-glucosidase (GAA) enzyme, resulting in progressive accumulation of glycogen that affects all muscle types.[32] In IOPD, symptoms include rapidly progressive muscle weakness, cardiomyopathy and cardiomegaly, and hepatomegaly. If left unmanaged, IOPD typically leads to death by 2 years of age due to cardiorespiratory failure. In LOPD, symptoms include global muscle weakness and respiratory insufficiency, which also can lead to early mortality.[6,31]

Common measured biomarkers in Pompe disease

Biomarker	Tissue sample	Typical unit of measurement	Pros/cons
Glucose tetrasaccharide (Glc4/Hex4)	Plasma/urine (urine is the preferred sample due to higher concentration) Dried urine spots	mmol/mol creatinine	**Pro:** Non-invasive measurement; useful for adjunct diagnosis and monitoring treatment response.[33,34] Correlates with serum creatine kinase (CK), muscle glycogen content, and disease severity;[33,35] can be elevated in neonates with IOPD identified through newborn screening (prior to appearance of clinical symptoms)[33] **Con:** Sensitivity in newborns and prognostic value for monitoring asymptomatic patients not known[33]
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Serum	IU/L	**Pro:** Easily available laboratory tests[36] **Con:** Are non-specific and have limited prognostic value[36]
Creatine kinase (CK)	Serum	IU/L	
Lactate dehydrogenase (LDH)	Serum	IU/L	

For more information about Pompe disease and biomarkers, visit: https://www.rarediseases.sanofimedical.com/ or contact your local Sanofi Medical Science Liaison: RareDiseaseMedical@sanofi.com

Research/investigational biomarkers in Pompe disease

Biomarker	Tissue sample	Typical unit of measurement
Vacuolated periodic acid-Schiff (PAS) positive lymphocytes	Whole blood	Number per 100 lymphocytes
Peripheral blood mononuclear cell (PBMC) glycogen	Whole blood	µg/mg glycogen protein

References: 6. Leslie N, Bailey L. Pompe Disease. 2007 Aug 31 [Updated 2023 Nov 2]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. **31.** Kishnani PS, et al. Pompe disease diagnosis and management guideline. *Genet Med*. 2006;8:267–88. **32.** American Association of Neuromuscular & Electrodiagnostic Medicine. Diagnostic criteria for late-onset (childhood and adult) Pompe disease. *Muscle Nerve*. 2009;40:149–60. **33.** 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. **34.** Manwaring V, et al. Urine analysis of glucose tetrasaccharide by HPLC; a useful marker for the investigation of patients with Pompe and other glycogen storage diseases. *J Inherit Metab Dis*. 2012;35:311–16. **35.** An Y, et al. Glucose tetrasaccharide as a biomarker for monitoring the therapeutic response to enzyme replacement therapy for Pompe disease. *Mol Genet Metab*. 2005;85:247–54. **36.** Molares-Vila A, et al. Biomarkers in glycogen storage diseases: An update. *Int J Mol Sci*. 2021;22:4381.

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Gaucher disease

Gaucher disease is seen in approximately 1/40,000 births worldwide and, depending on genotype, phenotype, and symptom presentation, people can be diagnosed as having Gaucher disease type 1 (GD1), type 2 (GD2), or type 3 (GD3).[37] People with Gaucher disease have a deficiency in the enzyme acid β-glucosidase (GCase) which results in glucosylceramide (GL-1) progressively accumulating inside cells, which can cause a range of multisystemic symptoms.[7,37] Symptoms include progressive anemia, thrombocytopenia, hepatosplenomegaly, bone pain and increased likelihood of fractures, and neurological symptoms (seen in GD2 or GD3 only).[7]

Commonly measured biomarkers in Gaucher disease

Biomarker	Tissue sample	Typical unit of measurement	Pros/cons
Glucosylsphingosine (lyso-GL-1)	Plasma/serum Dried blood spots	ng/mL	**Pro:** Sensitive and highly specific biomarker for Gaucher disease.[38] Correlated with disease severity[39]
Chitotriosidase	Plasma Dried blood spots	μmol/L/hour, or nmol/mL/hour	**Pro:** Correlates with lyso-GL-1, spleen and liver volume,[40] and bone manifestations[41] **Con:** Non-specific and elevated in other lysosomal storage diseases (lower sensitivity and specificity than lyso-GL-1); cannot be tested in all patients due to natural genetic variation[38]
Angiotensin-converting enzyme (ACE)	Plasma	ng/mL	**Con:** Historic biomarker of Gaucher disease. Elevations not seen in all patients as not a specific marker for pathological Gaucher cells[42]
Tartrate resistant acid phosphatase (TRAP)	Serum	IU/L	**Con:** Historic biomarker of Gaucher disease. Elevations not seen in all patients as not a specific marker for pathological Gaucher cells[42]

For more information about Gaucher disease and biomarkers, visit: https://www.rarediseases.sanofimedical.com/ or contact your local Sanofi Medical Science Liaison: RareDiseaseMedical@sanofi.com

Research/investigational biomarkers in Gaucher disease

Biomarker	Tissue sample	Typical unit of measurement
Chemokine ligand 18 (CCL18)	Plasma	ng/mL
Macrophage inflammatory protein 1-β (MIP-1β)	Plasma	pg/mL

References: 7. Hughes DA, Pastores GM. Gaucher disease. 2000 Jul 27 [Updated 2023 Mar 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. **37.** National Gaucher Foundation. What is Gaucher disease? Accessed at: gaucherdisease.org/about-gaucher-disease/what-is/. **38.** Rolfs A, et al. Glucosylsphingosine is a highly sensitive and specific biomarker for primary diagnostic and follow-up monitoring in Gaucher disease in a non-Jewish, Caucasian cohort of Gaucher disease patients. *PLoS One*. 2013;8:e79732. **39.** Dekker N, et al. Elevated plasma glucosylsphingosine in Gaucher disease: relation to phenotype, storage cell markers, and therapeutic response. *Blood*. 2011;118:e118–27. **40.** Murugesan V, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. *Am J Hematol*. 2016;91:1082–89. **41.** Herrera S, et al. Assessment of bone health in patients with type 1 Gaucher disease using impact microindentation. *J Bone Miner Res*. 2017;32:1575–81. **42.** Aerts JM, et al. Biomarkers in the diagnosis of lysosomal storage disorders: Proteins, lipids, and inhibodies. *J Inher Metab Dis*. 2011;34:605–19.

Acid sphingomyelinase deficiency (ASMD)

ASMD is seen in 0.4–0.6/100,000 births worldwide and is associated with a broad spectrum of disease severity, ranging from infantile neurovisceral ASMD type A to chronic visceral forms (ASMD type A/B or type B).[43,44] People with ASMD have an absence or deficiency of acid sphingomyelinase enzyme resulting in progressive accumulation of sphingomyelin in cells and tissues, which can lead to hepatosplenomegaly, thrombocytopenia, interstitial lung disease, dyslipidemia, and/or neurologic involvement (ASMD type A or type A/B only).[43,44] ASMD type A is associated with death by ~3–4 years of age; ASMD type A/B or type B can be associated with a risk of early death due to primarily respiratory or liver failure.[43,44]

Common measured biomarkers in ASMD

Biomarker	Tissue sample	Typical unit of measurement	Pros/cons
Lyso-sphingomyelin	Plasma Dried blood spots	µg/mL	**Pro:** Elevated in all symptomatic patients and levels positively associated with clinical severity in patients[45] **Con:** Not known if levels are predictive of phenotype in pre-symptomatic patients. More information is needed on correlation with response to long-term treatment[45]
Chitotriosidase	Plasma/serum Dried blood spots	µmol/L/hour	**Con:** Levels in ASMD not as high as in patients with Gaucher disease; cannot be tested in all patients due to natural genetic variation[45]

For more information about ASMD and biomarkers, visit: https://www.rarediseases.sanofimedical.com/ or contact your local Sanofi medical science liaison: RareDiseaseMedical@sanofi.com

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Lysosomal Storage Disease Resources

Practice Insight From the 2023 Advisory Council

Advisors recommend that HCPs contact other APPs in their field, attend scientific conferences, and seek help from MSLs to learn about new and emerging biomarkers.

Below are some helpful resources for additional information relating to lysosomal storage diseases. These include educational materials and published recommended guidelines:

Recommended management guidelines	
MPS I	• Mucopolysaccharidosis I: management and treatment guidelines (Muenzer J, et al., 2009)[15]
Fabry disease	• Fabry disease revisited: Management and treatment recommendations for adult patients (Ortiz A, et al., 2018)[21] • The management and treatment of children with Fabry disease: A United States-based perspective (Hopkin RJ, et al., 2016)[46]
Pompe disease	• Pompe disease diagnosis and management guideline (Kishnani PS, et al., 2006)[31] • Consensus treatment recommendations for late-onset Pompe disease (Cupler EJ, et al., 2012)[47] • Management of confirmed newborn-screened patients with Pompe disease across the disease spectrum (Kronn DF, et al., 2017)[10]
Gaucher disease	• Revised recommendations for the management of Gaucher disease in children (Kaplan P, et al., 2013)[48] • The diagnosis and management of Gaucher disease in pediatric patients: Where do we go from here? (Weinreb NJ, et al., 2022)[49] • Gaucher disease type 1: revised recommendations on evaluations and monitoring for adult patients (Weinreb NJ, et al., 2004)[50]
ASMD	• Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD) (Wasserstein M, et al., 2019)[51] • Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B) (Geberhiwot T, et al., 2023)[52]

Other resources

- Sanofi Rare Disease University: https://www.rdu-online.com/home
- Medical Education for Rare Diseases: https://www.rarediseases.sanofimedical.com
- Pompe disease newborn screening: https://newbornscreening.hrsa.gov/conditions/pompe-disease

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