Catching the *Clues*, Changing the Course of Lysosomal Storage Disorders

Illuminating the Complex Pathways of Rare Disease with Fabry Disease and Alpha-Mannosidosis in Focus

Wednesday, September 3, 2025
12:45–13:45

15th International Congress of Inborn Errors of Metabolism (ICIEM 2025)

September 2–6, 2025
Kyoto, Japan

Veeva ID: GRDMA-GL-EF-00371

Chiesi

Disclaimer

- The following discussion does not focus on or depict any specific product manufactured by any pharmaceutical company

- Patient cases are for medical discussion only and reflect the faculty's own experience. They represent typical clinical practice scenarios

- This presentation, in part or in whole, may not be reproduced, copied, or recorded (including photography) without express written consent from Chiesi Global Rare Diseases

Today’s Chair and Speakers

Chair

Professor Yoshikatsu Eto

Advanced Clinical Research Center, Southern Tohoku Research Center for Neuroscience, Tokyo, Japan

Speaker

Dr Nicole Muschol

International Center for Lysosomal Disorders (ICLD), University Medical Center, Hamburg-Eppendorf, Germany

Speaker

Professor Patrício Aguiar

Inborn Errors of Metabolism Reference Center, Unidade Local de Saúde de Santa Maria / Faculty of Medicine, Lisbon University, Portugal

Speaker

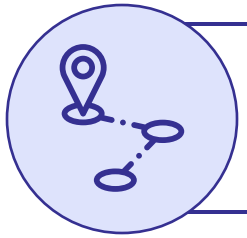
Dr Robert Hopkin

Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA

Interactivity – Polling Questions and Q&A

- There will also be a panel discussion with a live Q&A at the end of the presentation
  - Please enter your questions by scanning the QR code or entering the joining code at Slido.com
- Because this is a disease state symposium, we can address questions on disease state, but we are unable to answer questions about specific therapeutics today
- Any medical inquires, including specific treatment questions, can be made to the Chiesi Medical Information department (www.chiesiusamedical.com) or to us.medical@chiesi.com

Objectives



Explore the **patient journey** across the LSD continuum, focusing on the unmet needs in **diagnosis, treatment initiation,** and long-term **management**

Utilize **case-based discussions** focused on alpha-mannosidosis and Fabry disease to highlight disease-specific challenges

Assess where **challenges** persist in the patient journey, and where tailored **interventions** can improve outcomes

LSD, lysosomal storage disorder

Introduction to the LSD Patient Journey, with a Spotlight on Fabry Disease and Alpha-mannosidosis

Professor Yoshikatsu Eto

Disclosures: research grants from Alexion, JCR, and Sanofi; honoraria from Amicus, Chiesi, Sanofi, Sumitomo, and Takeda

Veeva ID: GRDMA-GL-EF-00371

Common Challenges For Patients with LSDs

LSD, lysosomal storage disorder

Common LSD Challenges Over the Patient Journey

Diagnosis

At least 70 different diseases, with an incidence of **1:5000–1:8000** in newborns[1,2]

Multiorgan manifestations and clinical heterogeneity complicate disease recognition[3–5]

New screening methods should be used to identify patients presymptomatically[6,7]

Treatment start

Early/presymptomatic treatment initiation is needed[6,8,9]

Usually **delayed** owing to **delayed diagnosis**[6]

Perceived burden of treatment may **delay treatment start** in patients with milder forms[10]

Monitoring

Monitoring relies on a **combination** of clinical assessments, laboratory tests, biomarkers, and imaging (e.g. echocardiograms and MRI)[11]

Biomarkers and **ADA assays lack standardization** and may not reflect **disease status** or **treatment response**[12,13]

Patient experiences between clinic visits and ERT infusions are **under-reported**[14]

ADA, anti-drug antibody; ERT, enzyme replacement therapy; LSD, lysosomal storage disorder; MRI, magnetic resonance imaging

1. Platt FM, et al. Nat Rev Dis Primers 2018;34:s41572-018-0037-0; 2. Mistry PK, et al. Orphanet J Rare Dis 2022;17:362; 3. Meikle PJ, et al. Mol Genet Metab 2006;88:307–314; 4. Parenti G, et al. EMBO Mol Med 2021;13:e12836; 5. Clarke LA, et al. Best Pract Res Clin Endocrinol Metab 2015;29:219–235; 6. Castaman G, et al. J Clin Med 2024;13:6981; 7. Koto Y, et al. Mol Genet Metab 2021;133:277–288; 8. Lenders M, et al. BioDrugs 2025;39:517–535; 9. Santoro L, et al. Mol Genet Metab 2024;142:108444; 10. Eskes EC, et al. Orphanet J Rare Dis 2022;17:383; 11. Ezgu F, et al. Orphanet J Rare Dis 2022;17:90; 12. Schiffmann R. J Inherit Metab Dis 2025;48:e70034; 13. Gómez-Cerezo JF, et al. Orphanet J Rare Dis 2025;20:253; 14. Berry L, et al. Orphanet J Rare Dis 2024;19:153

Veeva ID: GRDMA-GL-EF-00371

Disease Characteristics

Alpha-mannosidosis

- **Deficiency** of **α-mannosidase** (*MAN2B1* gene)[1]
- Accumulation of mannose-rich oligosaccharides[1]
- Autosomal-recessive inheritance[1]

- Age of onset from **infancy** to early **adolescence**[2]
- Incidence is approximately **1:500,000**[3]
- **Severe** or **attenuated** disease[2]

Fabry disease

- **Deficiency** of **α-Gal A** (*GLA* gene)[4]
- Accumulation of Gb3[5]
- X-chromosomal inheritance – both sexes affected[5]

- **First symptoms** can emerge at **any age**[6]
- Incidence in males is approximately **1:40,000–1:60,000**[7,8]
  - **Classic disease:** estimated incidence in males of **1:37,000–1:50,000**[9]
  - **Late-onset disease:** estimated incidence in males of **1:3100–1:4600**[9]

α-Gal A, α-galactosidase A; Gb3, globotriaosylceramide; *GLA*, galactosidase alpha

1. Malm D and Nilssen O. Orphanet J Rare Dis 2008;3:21; 2. Santoro L, et al. Mol Genet Metab 2024;142:1084444; 3. Guffon G, et al. Mol Genet Metab 2024;142:108519;
4. Mehta A and Hughes DA. GeneReviews 2002. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1292 (Accessed July 10, 2025)/; 5. Lerario S, et al. Int Urol Nephrol 2024;56:3161–3172;
6. Fabry Network 2022. Available from: https://www.fabrynetwork.org/new/wp-content/uploads/2022/05/Fabry-Findings-Issue-6_2022.pdf (Accessed July 10, 2025);
7. Fischer EG, et al. Mod Pathol 2006;19:1295–1301; 8. Frabasil J, et al. JIMD Rep 2019;48:45–52; 9. Spada M, et al. Am J Hum Genet 2006;79:31–40

Overview of Today's Presentations

Using alpha-mannosidosis and Fabry disease as illustrative examples, we will explore the shared hurdles and the unique challenges that patients face — spanning diagnosis, treatment initiation, and lifelong management

Common and Distinct Challenges Over the LSD Patient Journey

A Case-based Focus on **Diagnostic** Challenges Through the Lens of **Alpha-mannosidosis**

Dr Nicole Muschol

Disclosures: travel support, consulting fees and/or honoraria from Amicus, Biomarin, Chiesi, GC Biopharma, JCR Pharmaceuticals, Sanofi/Genzyme, and Takeda

Veeva ID: GRDMA-GL-EF-00371

Common Challenges For Patients with LSDs: Diagnosis

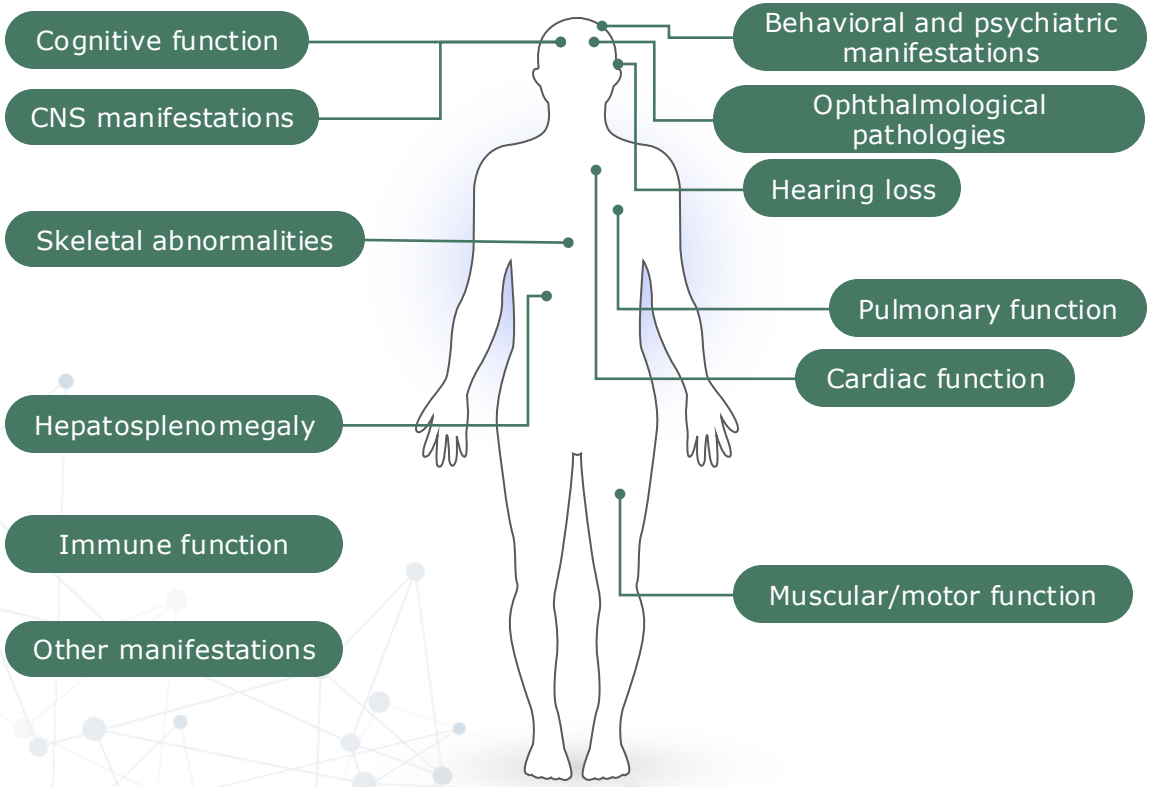
LSD, lysosomal storage disorder

Common Challenges For Patients with LSDs: Diagnosis

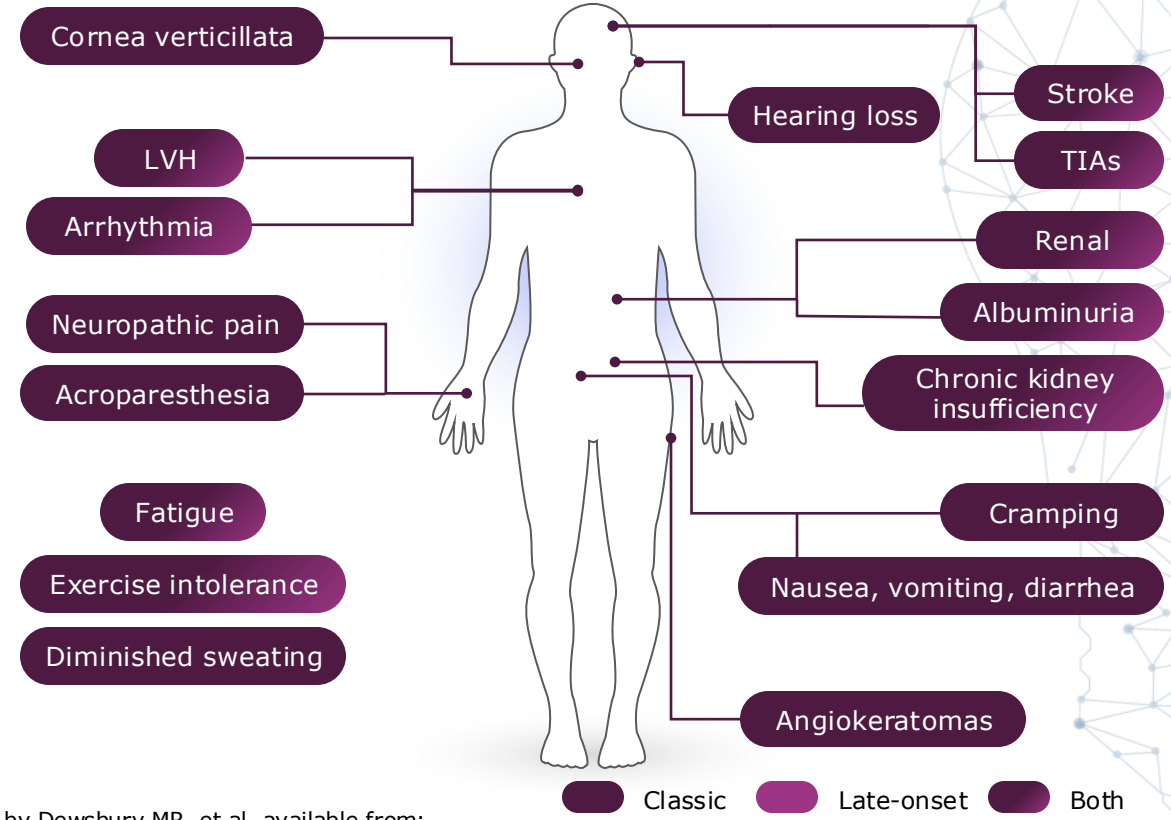
LSD, lysosomal storage disorder

Multiorgan Manifestations

Alpha-mannosidosis[1]



Fabry disease[2–4]



CNS, central nervous system; LVH, left ventricular hypertrophy; TIA, transient ischemic attack

1. Dewsbury MR, et al. J Transl Genet Genom 2014;8:85–101; 2. Lerario S, et al. Int Urol Nephrol 2024;56:3161–3172;
3. Fabry facts. Available from: https://www.fabryfacts.com/fabry-disease-phenotypes-and-their-associated-symptoms.php (Accessed July, 30 2025);
4. Fabry Australia. Available from: https://www.fabry.com.au/fabry-subtypes/ (Accessed July 30, 2025)

Veeva ID: GRDMA-GL-EF-00371

Diagnostic Considerations

Alpha-mannosidosis[1,2]

Clinical suspicion

- **First noticed by patients or caregivers:** frequent infections, hearing impairment, cognitive impairment
- **Noticed by specialists:** coarse facial features, skeletal dysplasia, hepatosplenomegaly, developmental delay

Diagnostics

- Screening of mannose-rich oligosaccharides
- α-mannosidase enzyme activity
- Genetic testing

Fabry disease[3,4]

Clinical suspicion

- **First noticed by patients or caregivers:** GI issues, angiokeratomas, acroparesthesias, hypohidrosis
- **Noticed by specialists**: early-onset stroke, unexplained LVH, CKD, cornea verticillata
- **Supported by:** positive family history of Fabry disease or sudden cardiac/renal deaths

Diagnostics

- α-Gal A enzyme activity (females: enzyme level might be normal)
- Lyso-Gb3 levels
- Genetic testing

α-Gal A, α-galactosidase A; CKD, chronic kidney disease; GI, gastrointestinal; lyso-Gb3, globotriaosylsphingosine; LVH, left ventricular hypertrophy

1. Guffon N, et al. Mol Genet Metab 2024;142:108519; 2. Santoro L, et al. Mol Genet Metab 2024;1:10844; 3. Germain DP, et al. Mol Genet Metab 2022;137:49–61; 4. Eng CM, et al. Genet Med 2006;9:539–548

Case Report 1

A patient with early-onset, nondifferentiating mucopolysaccharidosis symptoms

Dr Nicole Muschol

Veeva ID: GRDMA-GL-EF-00371

Early life

- Recurrent infections from third week of life (ENT, bronchitis)
- Independent sitting at 6 months
- Independent walking at 18 months
- First words at 20 months (speech delay)
- Pediatric consultation at 23 months before ENT surgery

35-year-old female patient

Birth

- First child of nonconsanguineous German parents
- Uneventful pregnancy and delivery

Disclaimer: this patient case study is a real case observed by the speaker. Patient photos presented with permission from the patient's family
ENT, ear, nose, and throat

Clinical presentation at 2 years old

- Coarse facial features
- Short neck (MPS-like phenotype)

- Skeletal abnormalities
- No joint contractures

- Systolic murmur
- No organomegaly

- Psychomotor development: not clearly abnormal

Investigations

Routine blood tests and urinary GAG	Normal
Cardiac echo	Small ASD II
Ultrasound	**Abnormal, slight enlargement of liver and spleen**
Ophthalmologist consultation	Normal, no corneal clouding
X-ray of head, thorax, spine, hips, and hand	Suspicion of bone dysplasia
Enzymatic testing for MPS I, MPS II, MPS III A–D, MPS IVB, MPS VI, MPS VII, mucolipidosis, MSD	Normal
Lymphocytes	Vacuolation

Disclaimer: this patient case study is a real case observed by the speaker
ASD, atrial septal defect; GAG, glycosaminoglycan; MPS, mucopolysaccharidosis; MSD, multiple sulfatase deficiency

Early life

- Recurrent infections from third week of life (ENT, bronchitis)
- Independent sitting at 6 months
- Independent walking at 18 months
- First words at 20 months (speech delay)
- Pediatric consultation at 23 months before ENT surgery

35-year-old female patient

Birth

- First child of nonconsanguineous German parents
- Uneventful pregnancy and delivery

Clinical course

Watch and wait, with annual follow-ups

- Persistent speech delay aged 3–4 years
- Diagnosis of sensorineural hearing impairment: hearing aids at 5 years
- Problems with fine motor function and coordination
- Macrocephaly (head circumference +2 SD)

Disclaimer: this patient case study is a real case observed by the speaker. Patient photos presented with permission from the patient's family
ENT, ear, nose, and throat; SD, standard deviation

Which further diagnostic steps would you choose for this patient?

- Enzymatic panel for a different MPS
- Go directly to genetic panel
- Liver biopsy
- Urine GAGs

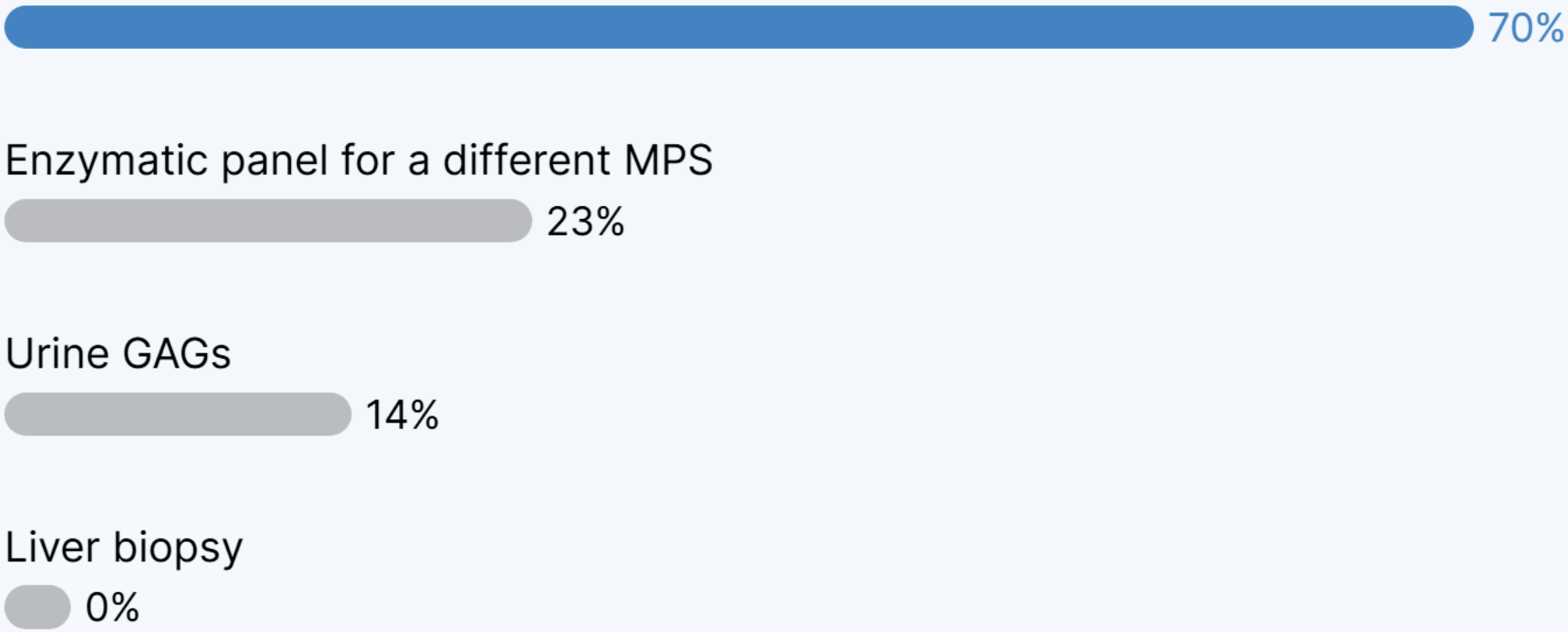
Disclaimer: this patient case study is a real case observed by the speaker
GAG, glycosaminoglycan; MPS, mucopolysaccharidosis

Active poll

43

Join at
slido.com
#6247 506

Which further diagnostic steps would you choose for this patient?



Diagnosis

Diagnosis of alpha-mannosidosis at 7 years old following enzymatic testing

Case Report 2

A 40-year-old undiagnosed male patient with early-onset symptoms

Dr Nicole Muschol

Veeva ID: GRDMA-GL-EF-00371

Medical history | Clinical presentation | Suspected diagnosis | Confirmed diagnosis

Birth

- Premature, uneventful delivery
- Neonatal jaundice

School age

- Learning difficulties, later regression
- Anxiety and hyperactivity
- Behavioral issues

40-year-old male patient

Early life

- Recurrent ENT surgeries and pulmonary infections in early childhood
- Nearly normal motor development
- Hearing impairment and hearing aids
- Speech delay

Clinical course

- Extensive metabolic work-up at 10 years old
- Suspicion of LSD owing to lymphocyte vacuolation and slightly increased GAG in urine

Disclaimer: this patient case study is a real case observed by the speaker
ENT, ear, nose, and throat; GAG, glycosaminoglycan; LSD, lysosomal storage disease

Clinical presentation at 40 years old

- Regression in cognitive and motor function
- Visual deterioration

- Angular facial features
- Fleshy earlobes
- Abnormal helix

- Able to speak in short sentences
- Blurred speech
- Able to follow simple instructions

- Able to walk independently
- Unsteady, broad gait, frequent stumbling
- Ataxia

- Long, narrow chest
- Kyphosis and scoliosis
- No joint contractures

Which disease would you suspect and test for first?

- MPS I–III
- Sialidosis
- Mucolipidosis
- FSASDs
- Alpha-mannosidosis

Disclaimer: this patient case study is a real case observed by the speaker
FSASD, free sialic acid storage disorder; MPS, mucopolysaccharidosis

Active poll

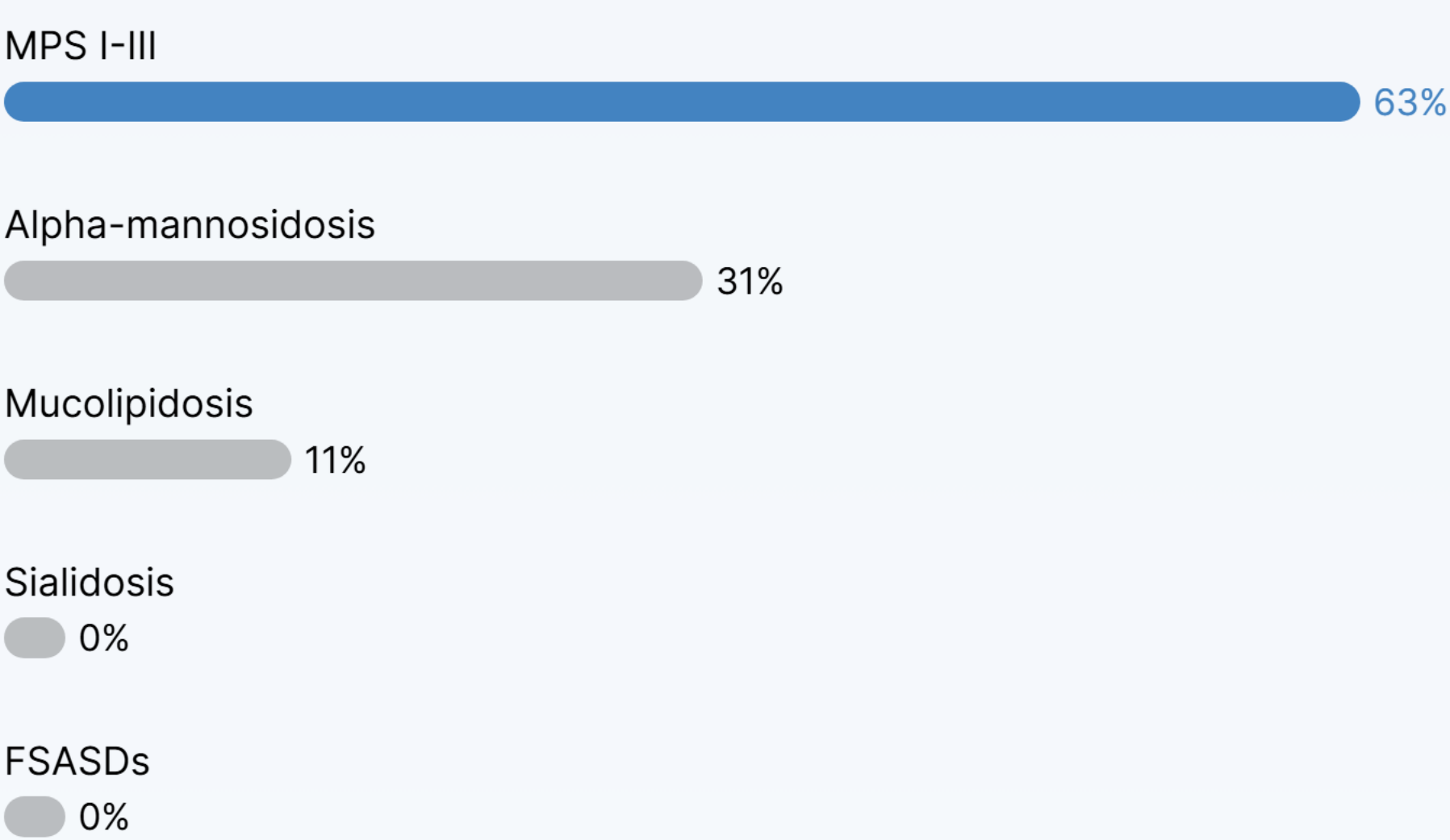
35

Join at

slido.com

#6247 506

Which disease would you suspect and test for first?



Investigations

Routine blood tests and urinary GAG	Normal
Enzymatic MPS panel	Normal
Alpha-mannosidosis activity	**0.01 nmol/spot*21 h** (normal range 0.3–1.3)
Oligosaccharides in urine	Abnormal pattern, consistent with alpha-mannosidosis
Cognitive testing (WISC-V)	Cognitive age equivalent of a 6-year old
Echocardiogram	Normal
Ultrasound	Normal
Ophthalmology	Progressed macular atrophy

Diagnosis

Diagnosis of alpha-mannosidosis at 40 years old following enzymatic testing

Disclaimer: this patient case study is a real case observed by the speaker
GAG, glycosaminoglycan; MPS, mucopolysaccharidosis; WISC-V, Wechsler Intelligence Scale for Children-Fifth Edition

Red Flags for Diagnosis of Alpha-Mannosidosis

Relative frequency of presenting symptoms in 111 patients with alpha-mannosidosis

Cognitive impairment **97%**

Bone anomalies **81%**

Coarse facies **70%**

Hearing loss **67%**

Respiratory tract infections **53%**

Dysmorphism **45%**

Organomegaly **41%**

Hernias **29%**

Ataxia **21%**

Short stature **21%**

Muscular hypotonia **13%**

Zielonka M, et al. J Inherit Metab Dis 2019;42:975–983

Conclusions

Diagnosis of lysosomal disorders can be challenging

- **Rarity of disease**
- **Clinical heterogeneity** (disease manifestations and severity)
- **Lack of specificity of early symptoms**
  - Early symptoms can be either unspecific or similar to other diseases

How to address these challenges

- **Familiarity with diagnostic algorithms** may support earlier recognition
- **Referral to specialized centers** can improve access to appropriate diagnostic tools
- Improved access to **enzymatic and genetic testing** and **interdisciplinary evaluation** may reduce diagnostic delays

Common and Distinct Challenges Over the LSD Patient Journey

A Case-based Focus on **Treatment Start** Through the Lens of **Fabry Disease**

Professor Patrício Aguiar

Disclosures: grant/research support from Takeda; honoraria from Alexion, Alnylam, Amicus, Biomarin, Chiesi, Sanofi, Takeda, and Ultragenyx

Veeva ID: GRDMA-GL-EF-00371

Common Challenges For Patients with LSDs: Treatment Start

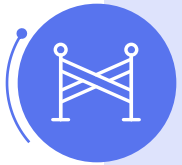
LSD, lysosomal storage disorder

Common Challenges For Patients with LSDs: Treatment Start

LSD, lysosomal storage disorder

Common Challenges For Patients with LSDs

Treatment start



Guidelines as barriers

Lack of biomarkers

Individualized treatment objectives

Patients at higher risk of IARs

IAR, infusion-associated reaction; LSD, lysosomal storage disorder

Therapeutic Landscape

Alpha-mannosidosis

ERT infusion (velmanase alfa)

- 1 mg/kg weekly for the treatment of non-neurological symptoms of alpha-mannosidosis (approved in the USA[1] and EU[2])

Hematopoietic stem cell transplantation

- Typically reserved for younger patients (<5-years old), and before neurological impairment is significant[3,4]

Fabry disease

ERT infusion

Agalsidase beta

- 1 mg/kg IV every 2 weeks; approved age: ≥8 years (EU),[5,6] ≥2 years (USA),[1] approved in Japan[7]

Agalsidase alfa

- 0.2 mg/kg IV every 2 weeks; approved age: ≥7 years (EU),[5,8] approved in Japan[7]

Pegunigalsidase alfa*

- 1 mg/kg IV every 2 weeks; approved age: ≥18 years (EU/USA)[5,9]

Pharmacological chaperone therapy

Migalastat

- 123 mg orally every other day[5,10]
- Approved age: ≥12 years ≥45 kg (EU),[5,11] ≥18 years (USA),[5] approved in Japan[12]
- Only for amenable *GLA* mutations[5]

*Pegunigalsidase alfa is not approved in Japan for Fabry disease. ERT, enzyme replacement therapy; *GLA*, galactosidase alpha; IV, intravenous

1. Chiesi Press Release. Available from: https://www.chiesi.com/en/chiesi-global-rare-diseases-announces-fda-approval-of-lamzede-velmanase-alfa-tycv-for-alpha-mannosidosis/ (Accessed July 11, 2025); 2. EMA Lamzede. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/lamzede (Accessed July 11, 2025); 3. Alpha-mannosidosis Society. Available from: https://mpssociety.org.uk/conditions/related-conditions/alpha-mannosidosis (Accessed July 11, 2025); 4. BIMDG Guidance. Available from: https://bimdg.org.uk/wp-content/uploads/2025/07/2025.05.30.Alpha-Mann-Clinical-Guidance.pdf (Accessed July 30, 2025); 5. Migani R, et al. Adv Ther 2024;42:597–635; 6. Fabrazyme EMA Scientific Discussion. Available from: https://www.ema.europa.eu/en/documents/scientific-discussion/fabrazyme-epar-scientific-discussion_en.pdf (Accessed July 30, 2025); 7. Arakawa M, et al. Mol Genet Metab 2024;40:101122; 8. Replagal EMA SmPC Available from: https://www.ema.europa.eu/en/documents/product-information/replagal-epar-product-information_en.pdf (Accessed July 30, 2025); 9. Elfabrio EMA SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/elfabrio-epar-product-information_en.pdf (Accessed July 30, 2025); 10. Migalastat hydrochloride deliberation report. Available from: https://www.pmda.go.jp/files/000233695.pdf (Accessed July 11, 2025); 11. Galafold EMA SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/galafold-epar-product-information_en.pdf (Accessed July 30, 2025); 12. Fabry Disease News. Available from: https://fabrydiseasenews.com/news/fabry-therapy-galafold-approved-japan-amicus-announces/ (Accessed August 12, 2025)

Case Report 1

Assessment of infusion-associated reaction risk in a patient with Fabry disease

Professor Patrício Aguiar

Veeva ID: GRDMA-GL-EF-00371

8-years old

- Acroparesthesia
- "Febrile crisis"
- Abdominal pain

→

- Rheumatic fever
- Rheumatological disorder

→

- Penicillin
- Painkillers and anticonvulsants

21-year-old male patient

21 years old

- Angiokeratomas

Clinic

- Hypohidrosis
- Scattered angiokeratomas
- Cornea verticillata
- Slight left auditory deficit

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
IAR, infusion-associated reaction

Initial investigations

Leukocytes	**Beta-galactosidase:** 160 nmol/h/mg protein (normal range 73–585) **Alpha-galactosidase:** 1 nmol/h/mg protein (normal range 36–80)
***GLA*-case index[1]**	[*GLA*] c.154T>G; p.C52G (exon 1) Hemizygous *Method: PCR sequencing* *OMIM: 300644* *Note: alteration not yet described in the scientific literature and not found in 100 chromosomes of control individuals from the population*
Lyso-Gb3 (plasma)	127 nmol/L (normal range 0–2)

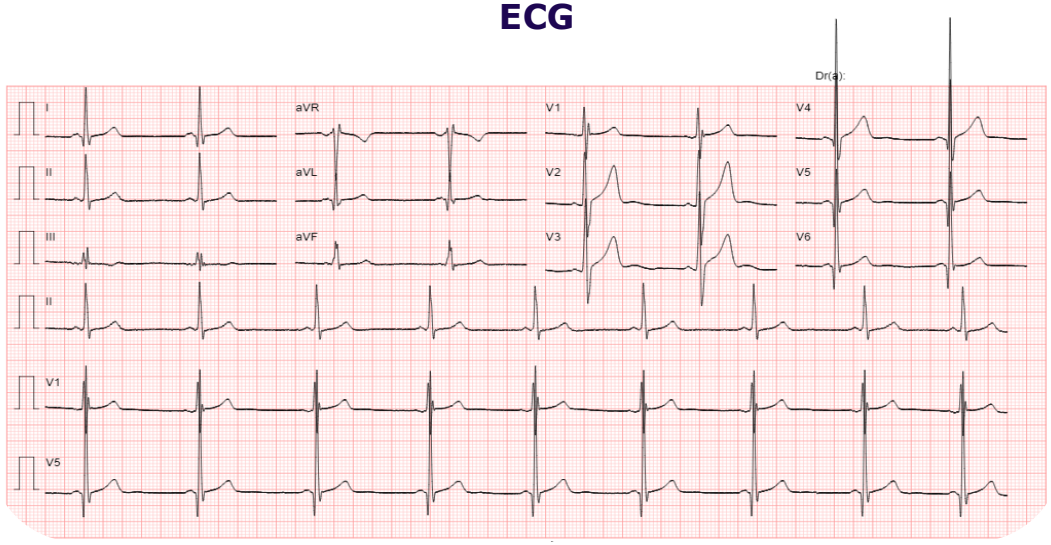
Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
GLA, galactosidase alpha; IAR, infusion-associated reaction; lyso-Gb3, globotriaosylsphingosine; PCR, polymerase chain reaction
1. OMIM. Galactosidase, alpha; GLA. Updated October 23, 2024. Available from: https://www.omim.org/entry/300644 (Accessed July 9, 2025)

Initial investigations

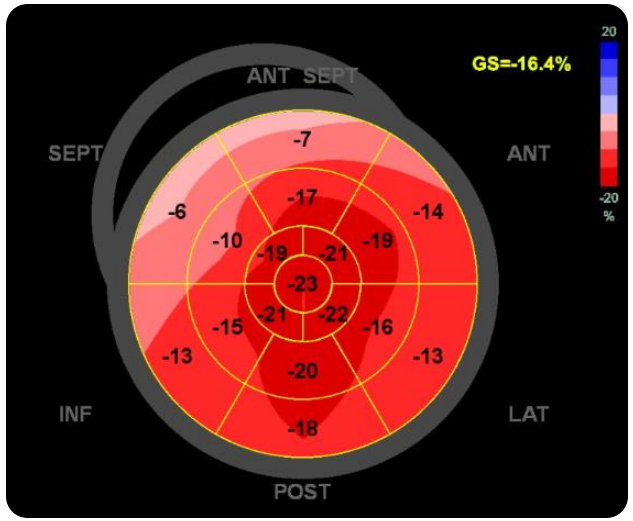
Leukocytes	**Beta-galactosidase: 160 nmol/h/mg protein** (normal range 73.0–585) **Alpha-galactosidase: 1 nmol/h/mg protein** (normal range 36–80)
***GLA*-case index[1]**	[*GLA*] c.154T>G; p.C52G (exon 1) Hemizygous *Method: PCR sequencing* *OMIM: 300644* *Note: alteration not yet described in the scientific literature and not found in 100 chromosomes of control individuals from the population*
Lyso-Gb3 (plasma)	**127 nmol/L** (normal range 0–2)

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
GLA, galactosidase alpha; IAR, infusion-associated reaction; lyso-Gb3, globotriaosylsphingosine; PCR, polymerase chain reaction
1. OMIM. Galactosidase, alpha; GLA. Updated October 23, 2024. Available from: https://www.omim.org/entry/300644 (Accessed July 9, 2025)

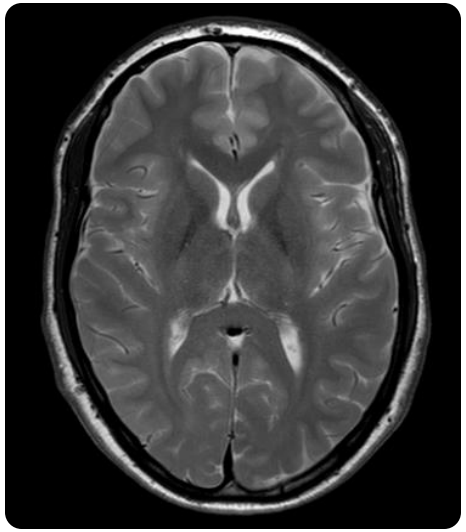
ECG



Speckle tracking ECG



Brain MRI



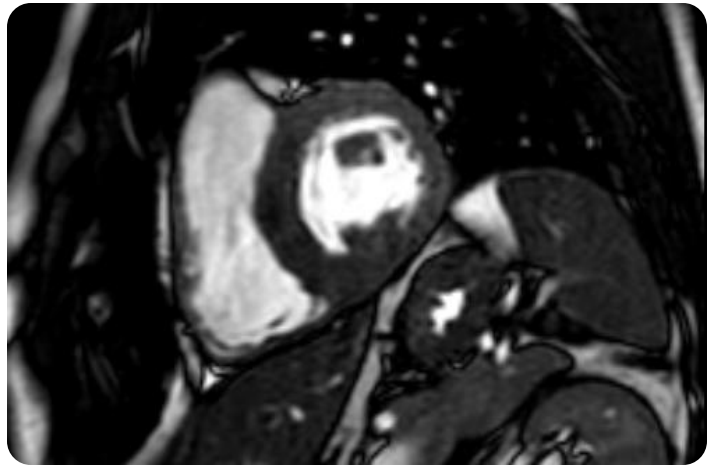
ECG results

Freq. Card	52 bpm
QRS duration	95 ms
QT/QTC	442/412 ms
PQ interval	112 ms
P/QRS/T	10/29/23

Investigations related to the kidney

Creatinine	0.89 mg/dL
Proteinuria	0.235 g/day
Albuminuria	77.2 mg/g

Heart MRI



Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker. Images provided by the speaker
bpm, beats per minute; ECG, echocardiogram; IAR, infusion-associated reaction; MRI, magnetic resonance imaging

Veeva ID: GRDMA-GL-EF-00371

Is this patient at high risk of infusion-associated reactions?

- Yes
- No

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
IAR, infusion-associated reaction

Active poll

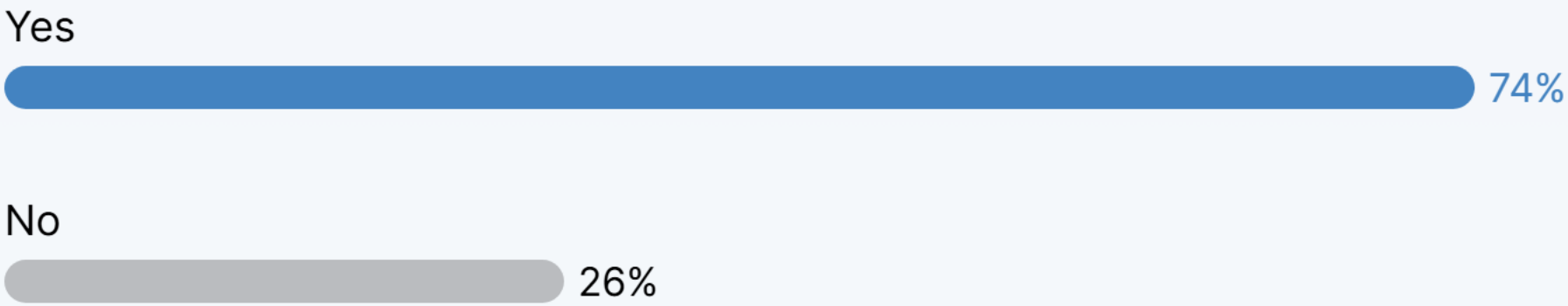
38

Join at

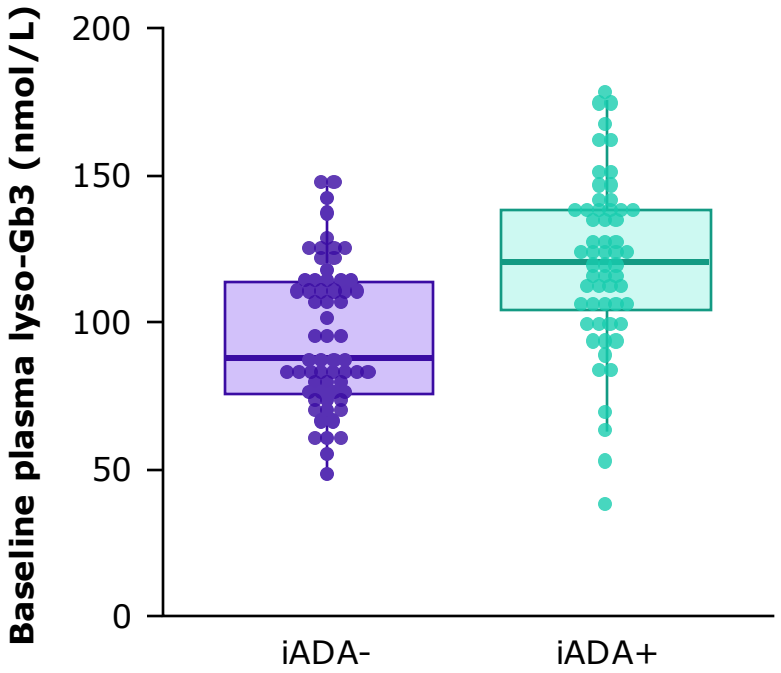
slido.com

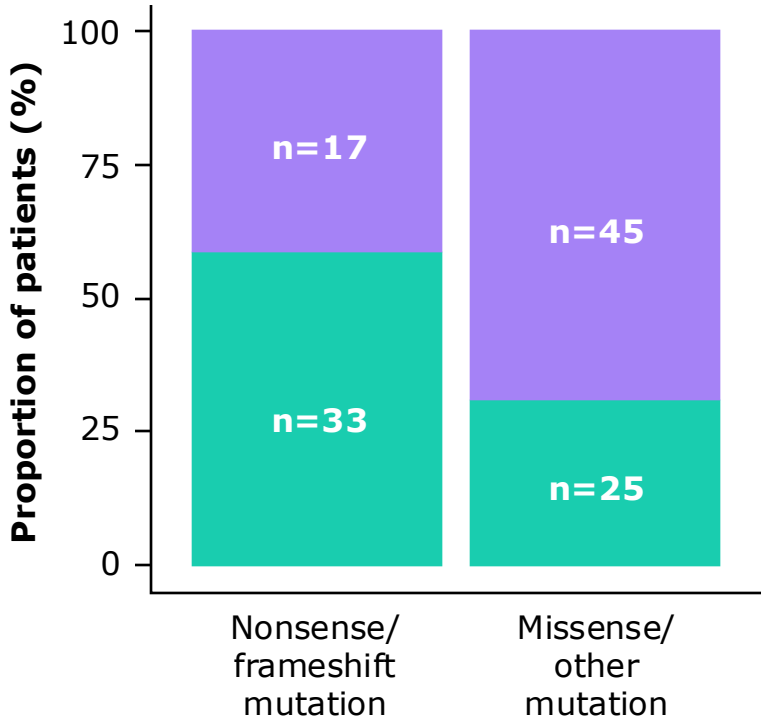
#6247 506

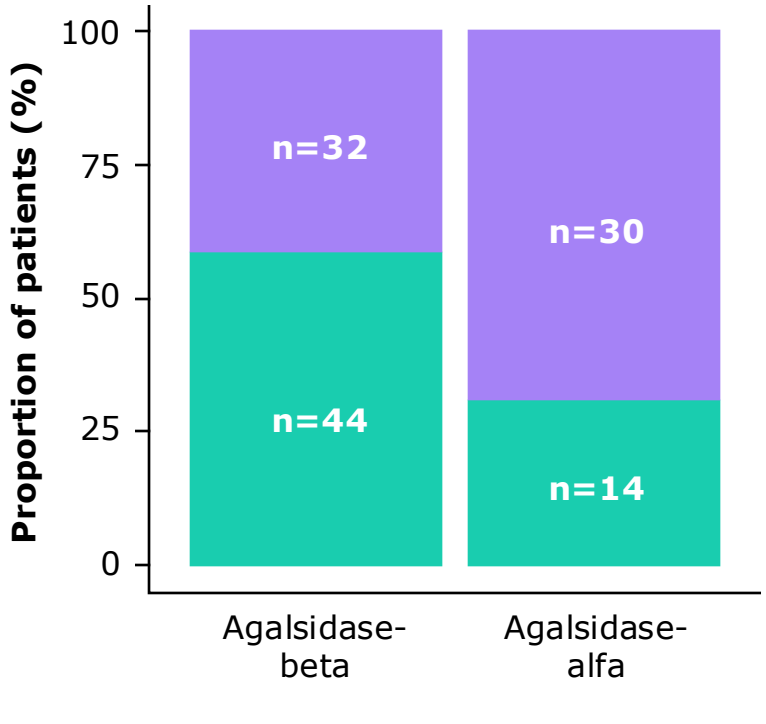
Is this patient at high risk of infusion-associated reactions?



Patients at High Risk of ADAs



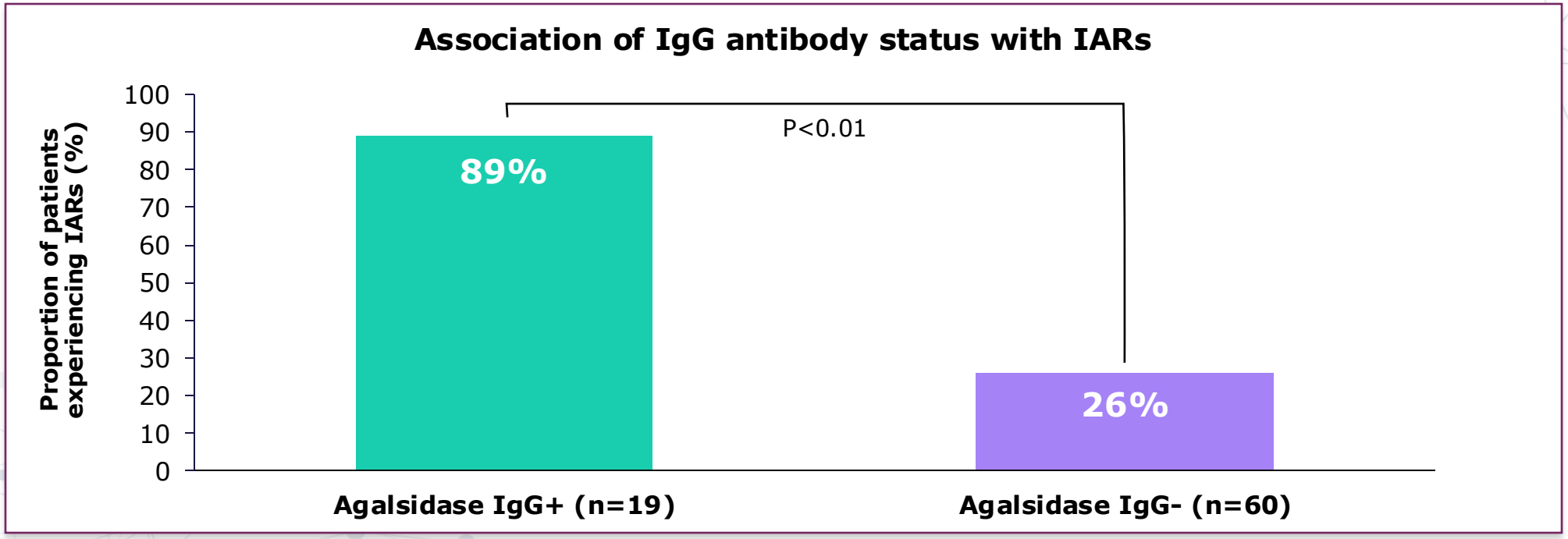




Figures by Van der Veen SJ, et al, available from: https://www.mdpi.com/1422-0067/21/16/5784, licensed under Creative Commons Attributions 4.0 International License
ADA, anti-drug antibody; iADA, inhibiting anti-drug antibody; lyso-Gb3, globotriaosylsphingosine
Van der Veen SJ, et al. Int J Mol Sci 2020;21:5784

Are IARs associated with ADAs?

A revised home treatment algorithm for Fabry disease: influence of antibody formation



ADA, anti-drug antibody; IAR, infusion-associated reaction; Ig, immunoglobulin
Smid BE, et al. Mol Genet Metab 2013;2:132–137

8-years old

- Acroparesthesia
- "Febrile crisis"
- Abdominal pain

- Rheumatic fever
- Rheumatological disorder

- Penicillin
- Painkillers and anticonvulsants

21-year-old male patient

21 years old

- Angiokeratomas

Clinic

- Hypohidrosis
- Scattered angiokeratomas
- Cornea verticillata
- Slight left auditory deficit

Key investigations

- [*GLA*]c.154T>G; p.C52G (exon 1), hemizygous
- Lyso-Gb3 (plasma): 127 nmol/L (normal range: 0–2)

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
GLA, galactosidase alpha; IAR, infusion-associated reaction; lyso-Gb3, globotriaosylsphingosine

8-years old

- Acroparesthesia
- "Febrile crisis"
- Abdominal pain

- Rheumatic fever
- Rheumatological disorder

- Penicillin
- Painkillers and anticonvulsants

21-year-old male patient

21 years old

- Angiokeratomas

Clinic

- Hypohidrosis
- Scattered angiokeratomas
- Cornea verticillata
- Slight left auditory deficit

Key investigations

- [*GLA*]c.154T>G; p.C52G (exon 1), hemizygous
- Lyso-Gb3 (plasma): 127 nmol/L (normal range: 0–2)

Key takeaways

The highlighted factors are associated with an increased risk of IARs[1]

Disclaimer: This patient case study is representative of patients seen in clinical practice by the speaker
GLA, galactosidase alpha; IAR, infusion-associated reaction
1. Speaker's opinion

Case Report 2

Initiation of disease-specific treatment in a patient with Fabry disease

Professor Patrício Aguiar

Veeva ID: GRDMA-GL-EF-00371

Medical history | Investigations | Treatment consideration

Disease history

- No known previous disease

Laboratory results

- α-gal A leukocytes: 10 nmol/h/mg
- α-gal A plasma: 5 nmol/h/mg
- *GLA*: p.G35E

46-year-old female patient

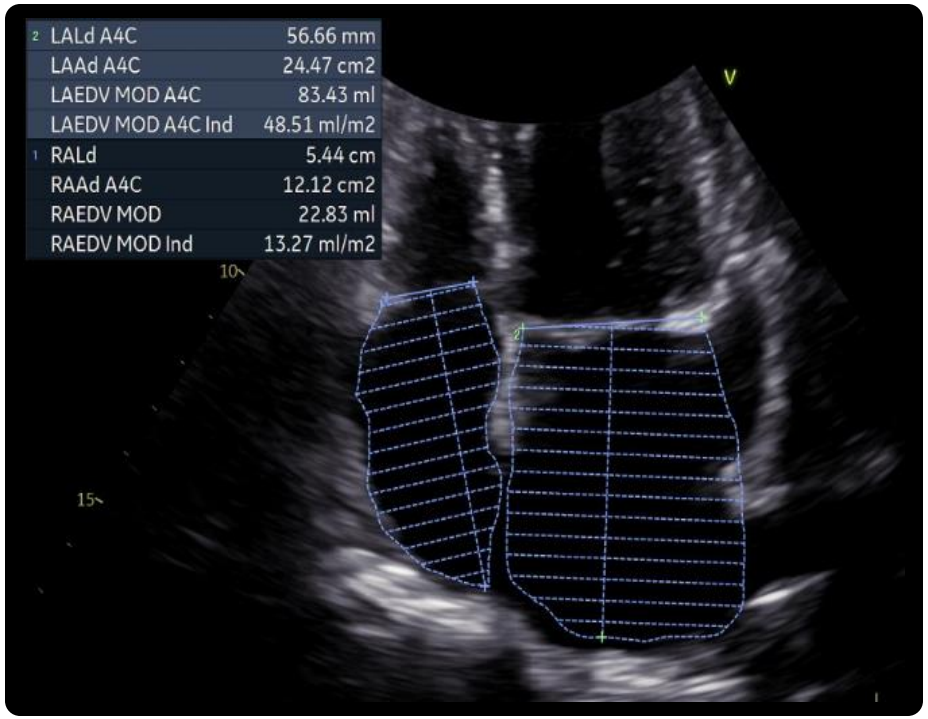
Family screening

- Classic phenotype in males

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
α-Gal A, α-galactosidase A; *GLA*, galactosidase alpha

Investigations

Echocardiogram	Mild LA enlargement (45 mL/m^2)
Cardiac MRI	Low T1
Head MRI	Normal
PNS	No complaints
Audiogram	Normal
Ophthalmology	Cornea verticillata
Skin	No angiokeratomas
Plasma lyso-Gb3	12.3 nmol/L
Creatinine	0.72 mg/dL
Proteinuria	0.122 g/24 hours
Albuminuria	26.7 mg/g



Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker. Image provided by the speaker
A4C, apical four-chamber view; LA, left atrial; lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging; PNS, peripheral nervous system

Would you start disease-specific treatment?

- Yes
- No

Veeva ID: GRDMA-GL-EF-00371

Active poll

31

Join at

slido.com

#6247 506

Would you start disease-specific treatment?

Guidelines: Treatment Initiation

Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document

Orphanet Journal of Rare Diseases (2015) 10:36

Marieke Biegstraaten[1*], Reynir Arngrímsson[2], Frederic Barbey[3], Lut Boks[4], Franco Cecchi[5], Patrick B Deegan[6], Ulla Feldt-Rasmussen[7], Tarekegn Geberhiwot[8], Dominique P Germain[9], Chris Hendriksz[10], Derralynn A Hughes[11], Ilkka Kantola[12], Nesrin Karabul[13], Christine Lavery[4], Gabor E Linthorst[1], Atul Mehta[11], Erica van de Mheen[14], João P Oliveira[15], Rossella Parini[16], Uma Ramaswami[17], Michael Rudnicki[18], Andreas Serra[19], Claudia Sommer[20], Gere Sunder-Plassmann[21], Einar Svarstad[22], Annelies Sweeb[14], Wim Terryn[23], Anna Tylki-Szymanska[24], Camilla Tøndel[25], Bojan Vujkovac[26], Frank Weidemann[27], Frits A Wijburg[28], Peter Woolfson[29] and Carla EM Hollak[1]

- Microalbuminuria*
- Proteinuria*
- Renal insufficiency

- Cardiac hypertrophy (MWT >12mm) without (or only minimal signs of) fibrosis
- Signs of cardiac rhythm disturbances†

- Neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication

- WMLs
- TIA/stroke
- Hearing loss, corrected for age

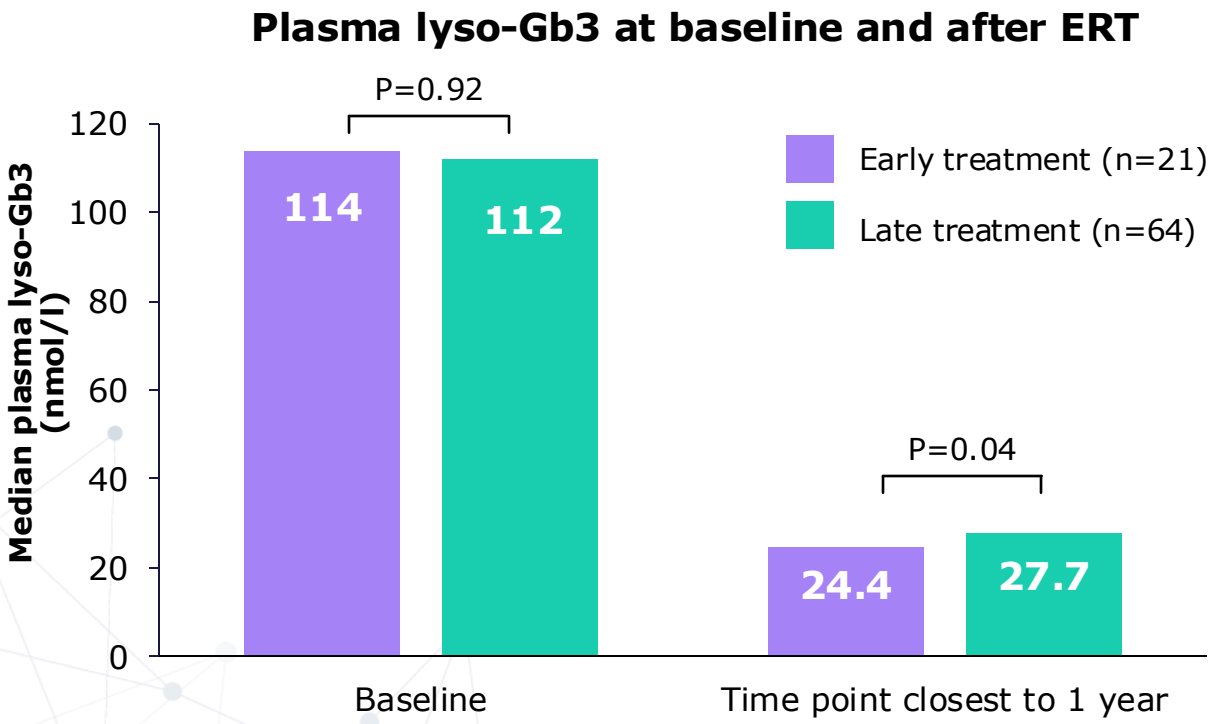
- GI symptoms

*According to international guidelines of kidney disease, KDIGO criteria; †sinus bradycardia

GFR, glomerular filtration rate; GI, gastrointestinal; KDIGO, Kidney Disease: Improving Global Outcomes; MWT, maximum wall thickness; TIA, transient ischemic attack; WML, white matter lesion

Biegstraaten M, et al. Orphanet J Rare Dis 2015;10:36

Earlier Treatment: Better Outcomes?



Age at treatment initiation[2], years	eGFR slope[2], mL/min/1.73m^2	LVMI slope[2], g/m^2
≤18	0.44	−0.17
18–30	−1.12	0.11
>30	−2.60	0.59

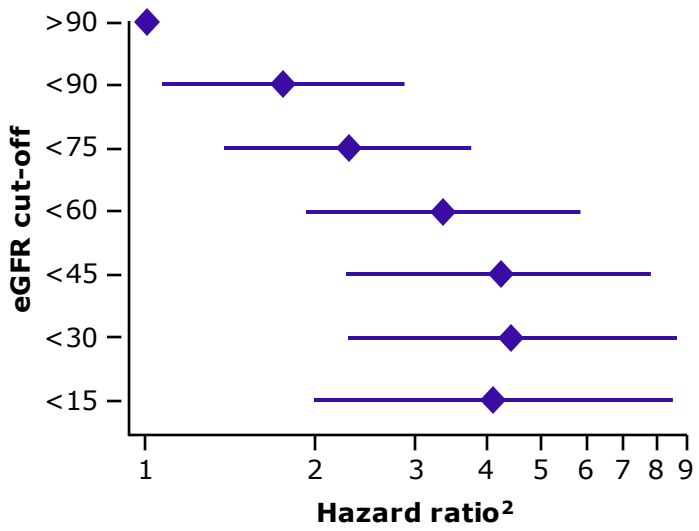
- Percentage of early vs. late treatment patients reaching a lyso-Gb3 concentration of <20nmol/l: **48%** vs **22%**

eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; LVMI, left ventricular mass index; lyso-Gb3, globotriaosylsphingosine

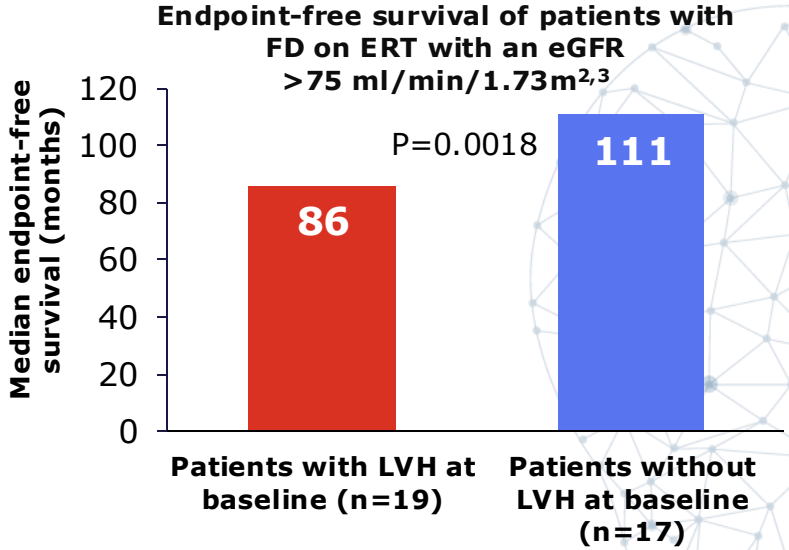
1. Arends M et al. Mol Genet Metab 2017;121:157-161; 2. Parini R et al. Drug Des Devel Ther 2020;14:2149–2158

Per Guidelines: Treatment and Outcomes Can Be Improved

- Microalbuminuria[1]*
- Proteinuria[1]*
- Renal insufficiency[1]



- Cardiac hypertrophy (MWT >12mm) without (or only minimal signs of) fibrosis[1]
- Signs of cardiac rhythm disturbances[1†]



	HR[2]	95% CI[2]
eGFR (per –10 ml/min/1.73m^2)	1.12[‡]	1.03–1.22
LVMI (per 10 gram/m^2)	1.16	0.99–1.36
Event(s) before ERT	1.45	0.85–2.53

*According to international guidelines of kidney disease, KDIGO criteria; †sinus bradycardia
CI, confidence interval; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FD, Fabry disease; GFR, glomerular filtration rate; HR, hazard ratio; LVH, left ventricular hypertrophy; LVMI, left ventricle mass index; MWT, maximum wall thickness; TIA, transient ischemic attack; WML, white matter lesion
1. Biegstraaten M, et al. Orphanet J Rare Dis 2015;10:36; 2. Arends M et al. PlosOne 2017;12:e0182379; 3. Lenders M et al. Nephrol Dial Transplant 2017;32:2090–2097

Conclusions

Diagnostic delay and misdiagnosis are the most important barriers to timely treatment initiation

Identifying patients at higher risk of IARs/ADAs is paramount to optimize treatment strategies

Emerging data suggest early treatment may benefit some patients, while delaying until guideline-based criteria are met could potentially affect long-term outcomes

There remains a significant unmet need for reliable biomarkers to guide prognosis and predict treatment response

ADA, anti-drug antibody; IAR, infusion-associated reaction

Common and Distinct Challenges Over the LSD Patient Journey

A Case-based Focus on **Treatment Monitoring** Through the Lens of **Fabry Disease**

Dr Robert Hopkin

Disclosures: consulting/advisory/speaking/research agreements (in compliance with conflict of interest policies at Cincinnati Children's Hospital Medical Center): Amicus, Chiesi/Protalix, Denali Therapeutics, Sangamo Therapeutics, Sanofi/Genzyme, and Takeda

Veeva ID: GRDMA-GL-EF-00371

Common Challenges For Patients with LSDs: Monitoring

LSD, lysosomal storage disorder

Common Challenges For Patients with LSDs: Monitoring

LSD, lysosomal storage disorder

Veeva ID: GRDMA-GL-EF-00371

Guideline Recommendations for the Monitoring of Alpha-Mannosidosis and Fabry Disease

Alpha-mannosidosis

- The first international clinical guidelines were published in 2024[1]
- Owing to the rarity of the condition, guideline awareness remains low, especially outside of specialized centers

- Ongoing efforts are needed to expand guideline use and integrate it into routine diagnostics for MPS-like disorders

Fabry disease

- Fabry disease guidelines have been available since the mid-2000s, with periodic updates from expert panels[2]

- Despite broader recognition, variability in awareness persists across regions and clinical specialties

MPS, mucopolysaccharidosis

1. Guffon N, et al. Mol Genet Metab 2024;108519; 2. Germain DP et al. Clin Genet 2019;96:107–117

Veeva ID: GRDMA-GL-EF-00371

Consensus Statement on the Monitoring of Alpha-Mannosidosis

- Patients with alpha-mannosidosis are followed by different specialists depending on their age and symptoms[1]
- Disease monitoring visits and assessments are generally more frequent and standardized for Fabry disease compared with alpha-mannosidosis[1,2]
- A recent consensus publication outlined 60 best-practice statements, highlighting comprehensive alpha-mannosidosis monitoring from diagnosis to long-term management[1]

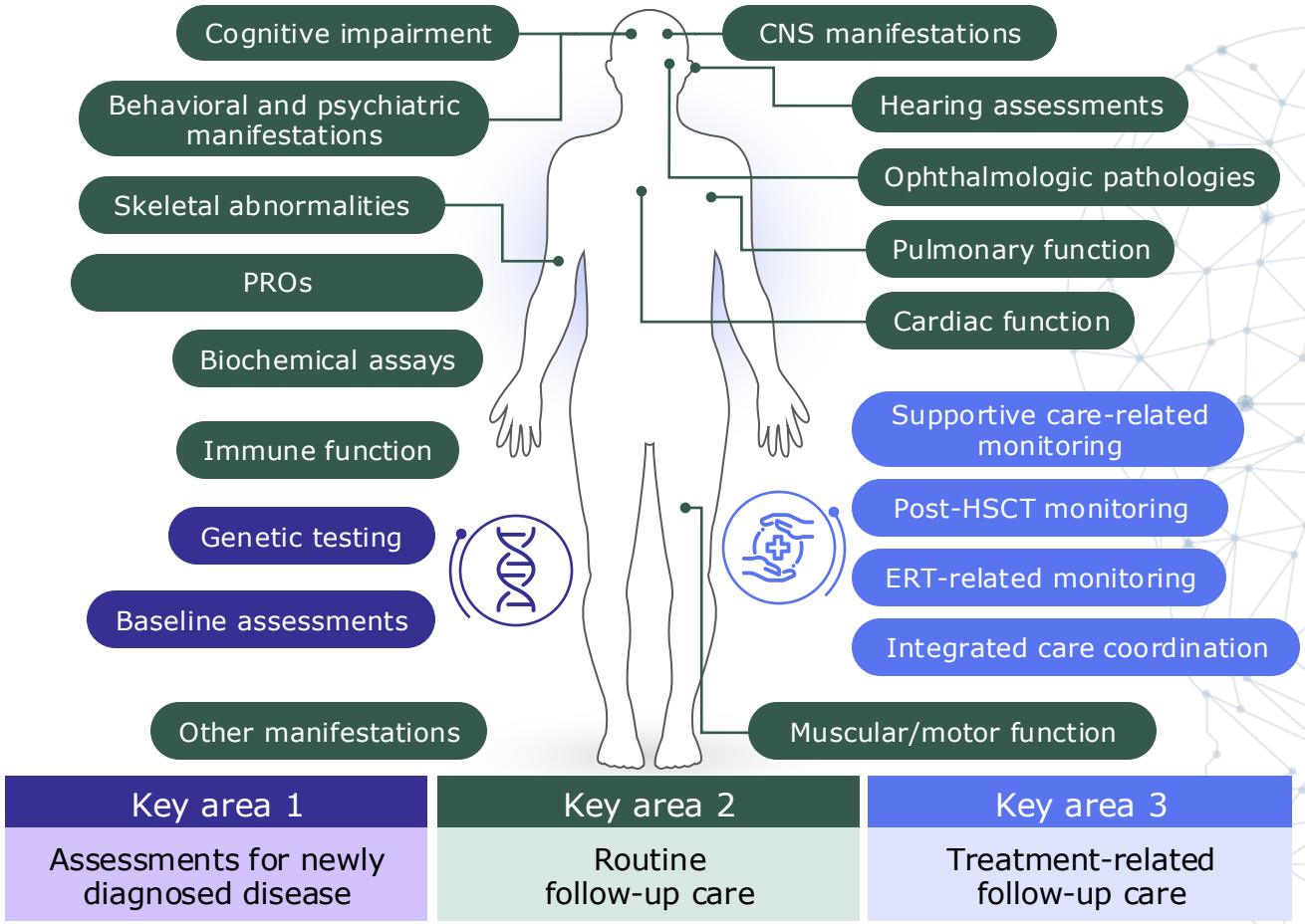


Figure by Guffon N, et al, available from: https://www.sciencedirect.com/science/article/pii/S1096719224004037, licensed under Creative Commons Attributions 4.0 International License (https://creativecommons.org/licenses/by/4.0)

CNS, central nervous system; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplant; PRO, patient-reported outcome

1. Guffon N et al. Mol Genet Metab 2024;142:108519; 2. Ortiz A, et al. Mol Genet Metab 2018;123:416–427

Opinions on Alpha-mannosidosis Treatment Goals

A more holistic approach to monitoring alpha-mannosidosis would allow for a more thorough evaluation of the patient's condition[1]

It is important to assess whether a patient's treatment plan is meeting all their needs, and to consider other options that are available[1]

1. Speaker's opinions

Guideline Recommendations for the Monitoring of Fabry Disease

Guidelines for Fabry disease treatment include monitoring recommendations

Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

Alberto Ortiz[a,*], Dominique P. Germain[b], Robert J. Desnick[c], Juan Politei[d], Michael Mauer[e], Alessandro Burlina[f], Christine Eng[g], Robert J. Hopkin[h], Dawn Laney[i], Aleš Linhart[j], Stephen Waldek[k], Eric Wallace[l], Frank Weidemann[m], William R. Wilcox[i]

Table 4
Recommended assessments and schedule for monitoring organ involvement in adult patients with Fabry disease.

Organ/system	Assessment(s)	Monitoring schedule
General	Complete history and physical examination including family history and evaluation of quality of life [94], gastrointestinal symptoms, work/study performance, level of depression/anxiety	Every clinic visit
	α-Gal A enzyme activity and *GLA* mutation analysis	If not previously determined
Renal	Glomerular filtration rate (measured GFR [preferred] or estimated [eGFR] using appropriate formulae)	Annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk;[a] measured GFR only once yearly because of complexity
	sensitive) and/or proteinuria (24-h or spot	Annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk
	nine and albumin/creatinine ratios)	As clinically indicated; vitamin D levels in late fall/early winter
		As clinically indicated. Podocyte foot process effacement may precede pathological albuminuria
	hythm	Every clinic visit
		Annually, and as clinically indicated
	tect intermittent rhythm abnormalities;	Annually, but may be assessed more or less frequently depending on age and other risk factors; if arrhythmias detected, more frequent/detailed rhythm surveillance should be instituted (schedule determined individually)
	er recommended for patients with	
	omyopathy [96]	
		If available, whenever there is evidence of clinical progression of disease or regularly at an interval > 2 years
	g	Investigational tool, should be interpreted with caution
		At least annually for patients with cardiomyopathy or bradycardia
	assessment in male patients aged over 21	Every 3 years and when clinically needed (e.g., presence of neurological
	then according to the clinical picture)	changes that could potentially relate to stroke) [37]
		In case of acute stroke and only if MRI is contraindicated due to cardiac pacing
	pain measurement scale such as the	Annually
	nventory or Brief Pain Inventory	
	bratory thresholds (quantitative sensory	Annually (less frequently in older patients)
	on by orthostatic blood pressure	Annually
	skin biopsy (for IENFD assessment, if available)	Consider
ENT	Audiometry [17]	As required [17]
Pulmonary	Spirometry, including response to bronchodilators, treadmill exercise testing, oximetry, chest X-ray	Every 2 years or more frequently for clinical indications; [17] chest X-ray according to clinical indications
Gastrointestinal	Referral to gastroenterology specialist for endoscopic or radiographic evaluation	If symptoms persist or worsen despite treatment
Overall glycolipid burden	Plasma and urinary sediment lyso-GL-3, GL-3	At baseline and then annually (at the moment, this is for research purposes only); biobanking of plasma/serum samples recommended if feasible
Skeletal	Bone dual-energy X-ray absorptiometry (DEXA)	Consider
Ophthalmological	Ophthalmological screening	Ophthalmological screening as clinically indicated

Rationale and details for each organ system are provided in online Appendices A (renal), B (cardiac), C (peripheral nervous system), D (central nervous system), and E (involvement of other organs). Baseline values should always be obtained; longer intervals between more complex organ assessments can be considered in asymptomatic female patients with a normal initial evaluation and/or favorable X chromosome inactivation pattern.
CKD, chronic kidney disease; CT, computed tomography; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; GFR, glomerular filtration rate; IENFD, intra-epidermal nerve fiber density; MRI, magnetic resonance imaging; TOF MRA, time-of-flight magnetic resonance angiography (head and neck).
[a] Risk levels based on KDIGO 2012 chronic kidney disease classification scheme. Low risk, CKD Stage G1/2 A1; moderate risk, CKD stage G3a A1, G1/2 A2; high to very high risk CKD Stage G4 or 5, G3b A1, G3 A3 [90]. See also online Appendix A, including Fig. 1S.

1. Ortiz A, et al. Mol Genet Metab 2018;123:416–427

Monitoring Strategies for Patients with Fabry Disease[1–3]

Assessment	Complete history and physical examination	Renal function and biomarkers	Cardiac function and biomarkers	Cerebrovascular manifestations	Gastrointestinal symptoms	Pain	QOL and levels of depression /anxiety
Schedule	Every clinical visit*	Every 3–12 months†	Every 1–>2 years‡	Every 3 years and when clinically needed§	Based on symptoms	Annually	Every clinic visit

Monitoring challenges[1–3]

- Biomarkers: inconsistent correlation with disease phenotypes and underlying pathology
- Assessments of ADAs: nonstandardized lab assays
- Symptom breakthrough between ERT infusions: usually patient-reported and not easily tracked
- Criteria for treatment switch

*Including family history and evaluation of QOL, gastrointestinal symptoms, work/study performance, level of depression/anxiety, α-Gal A enzyme activity, and *GLA* mutation analysis; †eGFR, albuminuria, and/or proteinuria: annually if low risk, every 6 months if moderate risk, and every 3 months if high-to-very-high risk; 25-hydroxyvitamin vitamin D and kidney biopsy: as clinically indicated; ‡blood pressure and cardiac rhythm: every visit; ECG: annually and as clinically indicated; cardiac MRI (MRI with gadolinium): regularly (>2-year interval) or when disease clinical progression is evident; MRI with T1 mapping: used as an investigational tool; §CT imaging: in case of acute stroke and only if MRI is contraindicated due to cardiac pacing
α-Gal A, α-galactosidase A; ADA, anti-drug antibody; CT, computed tomography; ECG, echocardiogram; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; *GLA*, galactosidase alpha; MRI, magnetic resonance imaging; QOL, quality of life

1. Burlina A et al. Mol Genet Metab 2023;139:107585; 2. Ortiz A et al. Mol Genet Metab 2018;123:416-427; 3. Panel experience

Veeva ID: GRDMA-GL-EF-00371

Assessment of ADAs

ADAs can:

- Inhibit drug efficacy[1]
- Affect patient safety[1]
- Increase risk of IRRs, with **51–76%*** of ADA+ patients experiencing reactions[2,3]
  - However, IRRs may still occur in those without ADAs

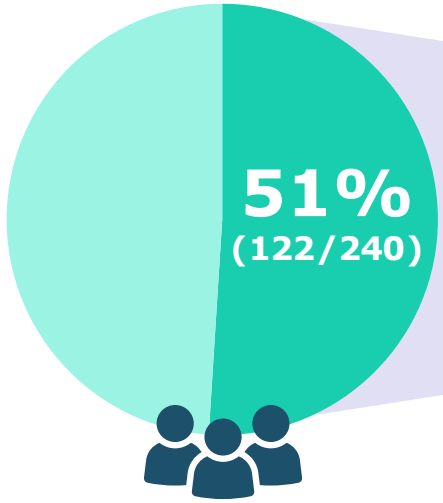
- **ADA assessments typically measure IgG, although multiple isotypes (e.g. IgA, IgM, IgE) and subclasses (e.g. IgG1–4) exist[4,5]**
  - However, ADA assays are not standardized and do not always predict IRRs
  - Characteristics other than presence of ADAs are important, including titer, affinity of binding, neutralization capacity, and subclass
- **The roles of these different ADAs remain to be determined**

*Not reported in agalsidase alfa product information
ADA, antidrug antibody; Ig, immunoglobulin; IRR, infusion-related reaction
1. FDA. Immunogenicity assessment for therapeutic protein products. 2014. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-assessment-therapeutic-protein-products (Accessed July 10, 2025); 2. Fabrazyme [Package Insert]. Cambridge, MA. Genzyme Corporation; 2023;
3. Elfabrio [Package Insert]. Parma, Italy: Chiesi Farmaceutici S.p.A; 2023; 4. Gunn GR, et al. Clin Exp Immunol 2016;184:137–46;
5. Baldwin T, et al. Mol Genet Metab 2024;141:107962; Poster Presented at WORLDSymposium 2024 (Poster 27)

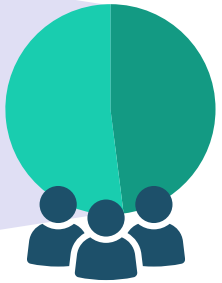
Symptom Breakthrough Between Infusions

Patient experience between clinic visits is often underreported, limiting insights into the true long-term burden of disease and treatment effects

In a comprehensive survey of 280 patients with Fabry disease



at the time of the survey experienced **temporary symptom worsening** between infusions



Only 48%
(59/122)

of those experiencing symptom worsening reported it to their physician

Of those who reported it, 41% (24/59) noted that their physician prescribed medication to manage symptoms or changed treatment regimen

ERT, enzyme replacement therapy
Berry L, et al. Orphanet J Rare Dis 2024:19:153

Case Report 1

A female patient with Fabry disease experiencing breakthrough symptoms between infusions

Dr Robert Hopkin

Veeva ID: GRDMA-GL-EF-00371

Disease history

- Diagnosis of Fabry disease

Background

- Demanding work and social life

Female patient

Treatment

- Receiving ERT
- Tolerating infusions well with minimum premedications

Clinical presentation

- In the last 4–5 days before the infusion is due, the patient has started experiencing fatigue, lack of energy, and worsening pain that interferes with her daily activities
- Following the infusion, these symptoms are relieved; however, they recur just before the next infusion in each cycle

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
ERT, enzyme replacement therapy

Have any of your patients reported symptom breakthrough before their next infusion?

- I don’t ask about this, and I’m not sure if it’s real
- Some patients mention this, but there isn’t much we can do about it
- It is common, but difficult to manage
- It is common and I try different symptomatic medications

Active poll

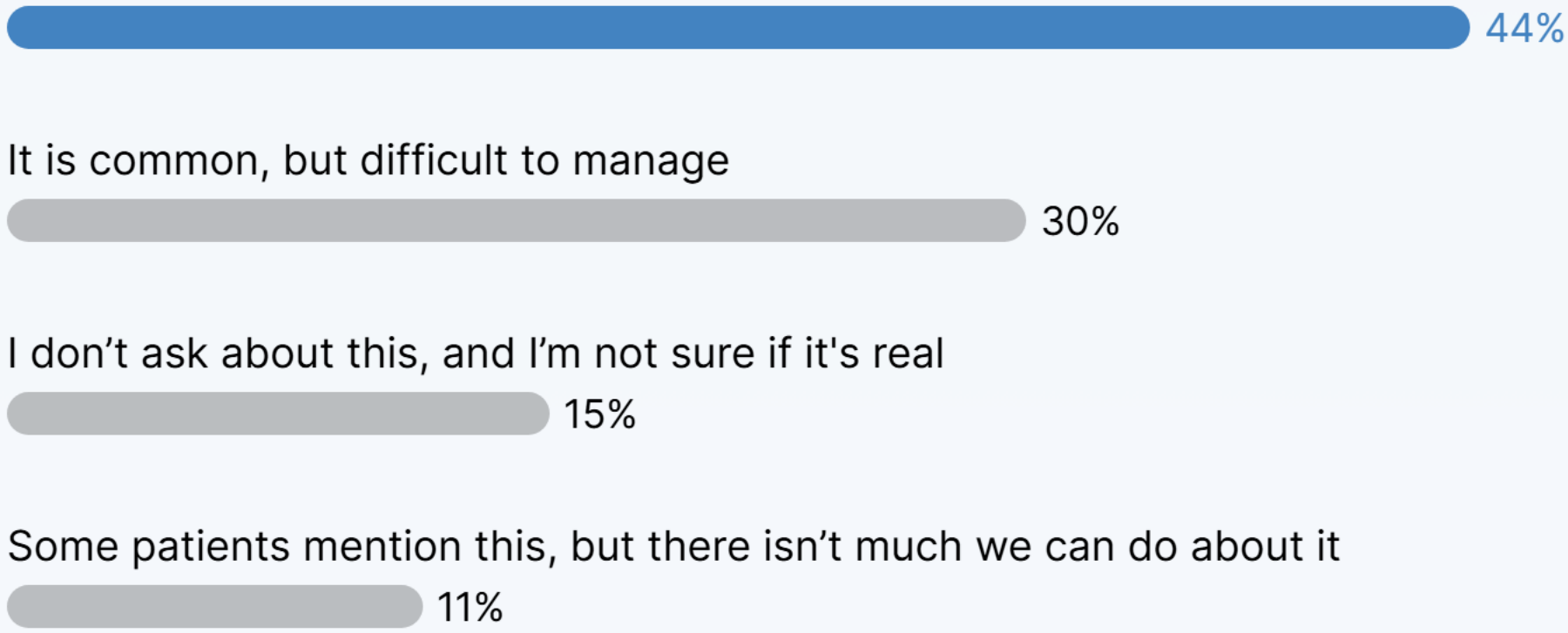
27

Join at

slido.com

#6247 506

Have any of your patients reported symptom breakthrough before their next infusion?



Case Report 2

A female patient with Fabry disease experiencing fatigue after infusions

Dr Robert Hopkin

Veeva ID: GRDMA-GL-EF-00371

Medical history

- Receiving ERT for over 2 years
  - Has always reported fatigue and dizziness the day after ERT
  - Infusion duration slowly reduced to 2 hours within 6 months
- Premedication: none at first infusion
  - Initiated antihistamine/ anticholinergic after 6 months of ERT to understand if it can improve symptoms – no symptom improvement

35-year-old female patient

Disease history

- Diagnosis of classic Fabry disease

Clinical presentation

- Presents with fatigue and dizziness the day after ERT

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
ERT, enzyme replacement therapy

How would you manage the patient's fatigue post-infusion?

- ADHD treatment
- Add steroids
- Discontinue antihistamines
- Further increase infusion duration
- Lifestyle changes to adapt
- Switch to another ERT
- Do not do anything

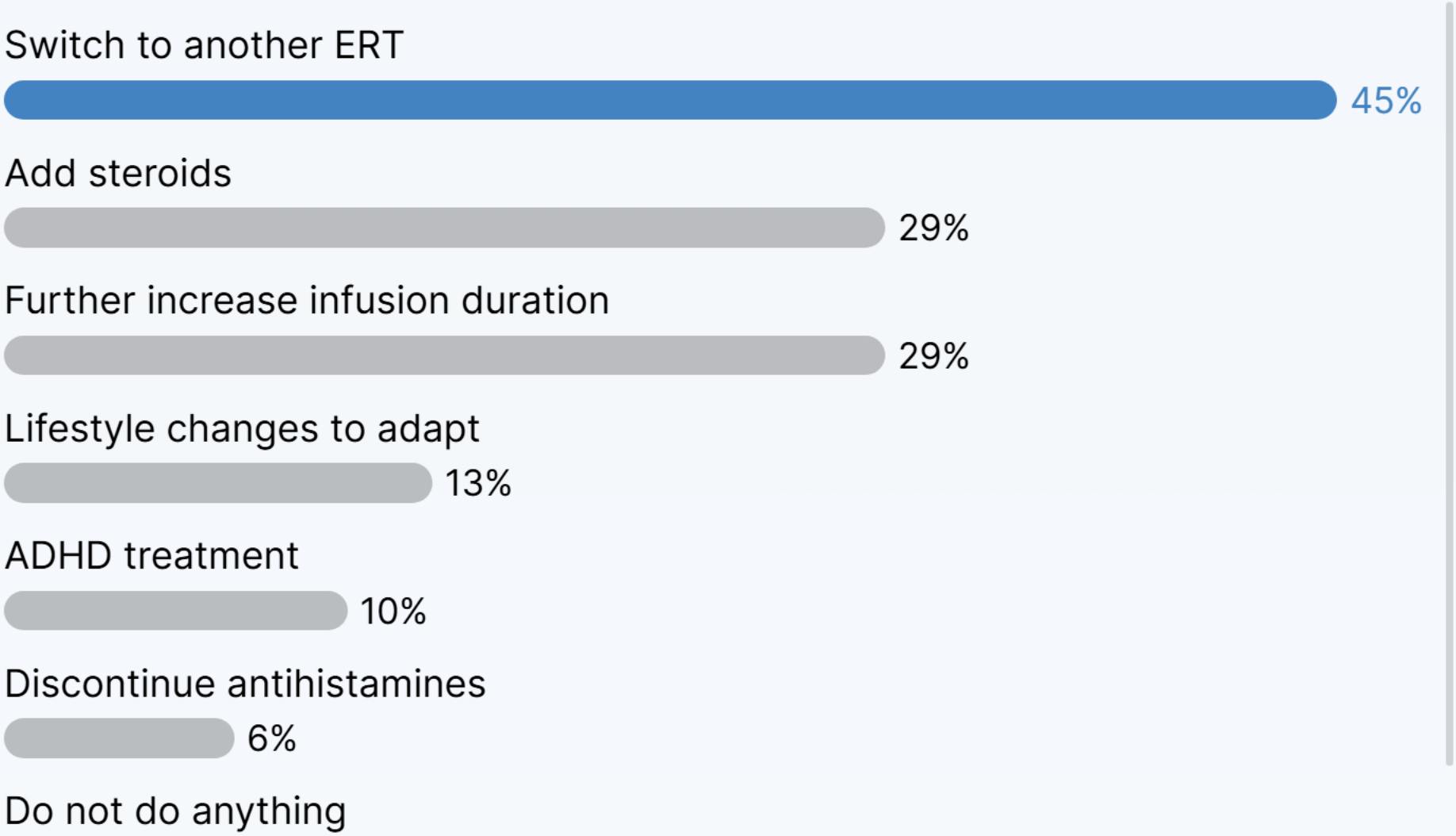
Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
ADHD, attention-deficit hyperactivity disorder; ERT, enzyme replacement therapy

Active poll

31

Join at
slido.com
#6247 506

How would you manage the patient's fatigue post-infusion?



Medical history

- Receiving ERT for over 2 years
  - Has always reported fatigue and dizziness the day after ERT
  - Infusion duration slowly reduced to 2 hours within 6 months
- Premedication: none at first infusion
  - Initiated antihistamine/ anticholinergic after 6 months of ERT to understand if it can improve symptoms – no symptom improvement

35-year-old female patient

Disease history

- Diagnosis of classic Fabry disease

Clinical presentation

- Presents with fatigue and dizziness the day after ERT

Symptom management

- After a 1-year, stepwise reduction of antihistamine, symptoms are a little less intense
- The patient still experiences fatigue and dizziness the day after ERT

Disclaimer: this patient case study is representative of patients seen in clinical practice by the speaker
ERT, enzyme replacement therapy

Conclusion

The following are important to improve monitoring of LSD treatments

Focus on patient-centered monitoring by assessing QOL factors such as fatigue, pain, and symptom recurrence

Use open communication and PROs to tailor treatment, considering patient and drug characteristics to optimize ERT tolerability

Consider the symptoms that the patients are most concerned about

Regularly monitor for ADAs and evaluate treatment adjustments, including switching when appropriate

ADA, anti-drug antibody; ERT, enzyme replacement therapy; LSD, lysosomal storage disease; PRO, patient-reported outcome; QOL, quality of life

Key Take-home Messages

Professor Yoshikatsu Eto

Perspectives from Japan and Key Take-home Messages

Diagnosis

- **Fabry disease**
  - Benefits from family-tree analysis, screening of high-risk patients, and diagnosis by DBS and newborn screening in Japan/Taiwan/Italy/USA
- **Alpha-mannosidosis**
  - Difficult to diagnose because it is not included on testing panels
  - Alpha-mannosidosis should also be considered if MPS is suspected
  - Diagnosis is made via DBS, leukocyte enzyme assay, and skin fibroblast testing

Key insight: greater awareness and access to testing is essential, and referral to expert centers improves diagnostic accuracy

Treatment start

- **Fabry disease**
  - >1300 patients treated with ERT in Japan (chaperone therapy is also available)
  - Treatment guidelines for late-onset Fabry disease are not well-established
- **Alpha-mannosidosis**
  - Few cases reported
  - ERT not yet approved in Japan, though available in the EU and USA

Key insight: diagnostic delays hinder timely treatment; early intervention is linked to better outcomes; identification of patients at risk for IARs and ADAs is key

Monitoring

- **Fabry disease**
  - Incorporates PROs and individualized ERT management based on patient and drug characteristics
- **Alpha-mannosidosis**
  - Structured monitoring is less common; symptom tracking, QOL measures, and preparation for future therapeutic options are essential

Key insight: a patient-centered approach is critical to improve long-term outcomes

ADA, anti-drug antibody; DBS, dried blood spot; ERT, enzyme-replacement therapy; IAR, infusion-associated reaction; MPS, mucopolysaccharidosis; PRO, patient-reported outcome; QOL, quality of life

Panel Discussion With Q&A

All

Q&A

- To submit your questions, please scan the QR code
- If you are having difficulty with submitting your questions, please refresh the app

Thank You!

Veeva ID: GRDMA-GL-EF-00371