The path from detection to personalized long-term care for Fabry disease

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A journey to diagnosing Fabry disease: An individual approach

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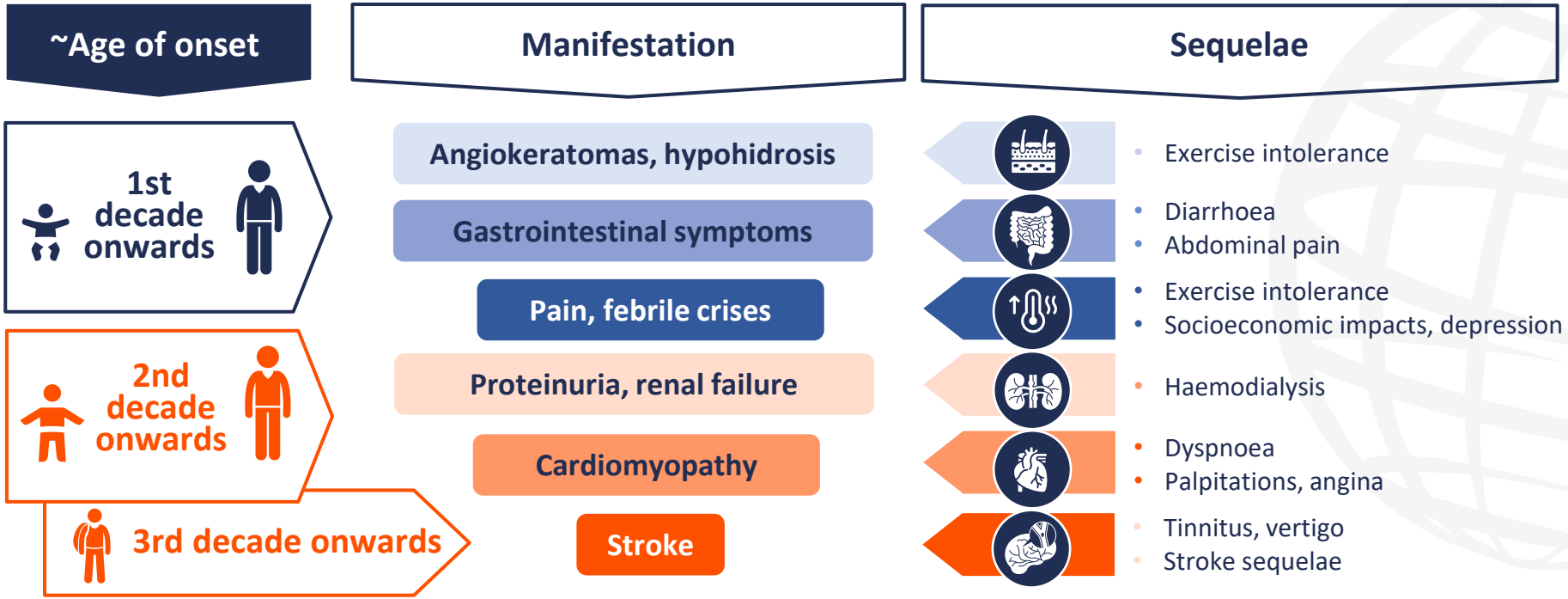
How can we improve early recognition of the multisystem manifestations of Fabry disease to support timely diagnosis?

Timeline of manifestations in hemizygous male patients



Schematic adapted from Figure 1 in Linhart A, Elliott PM. *Heart*. 2007;93:528–35; Ortiz A, et al. *Mol Genet Metab.* 2018;123:416–27.

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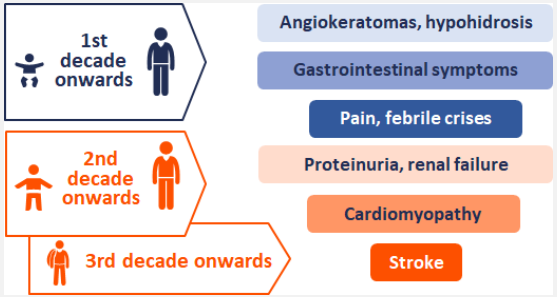
Phenotypic variation in Fabry disease

Age of onset?[1] Affected organ(s)?[2]

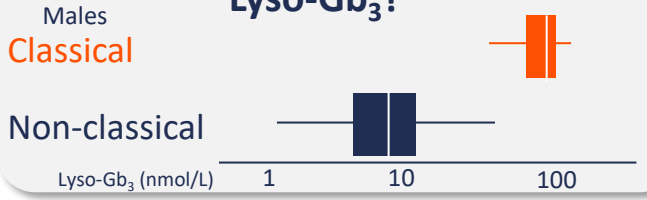


More than ? one disease

Genetic variant?[1]

- Pathogenic classic phenotype
- Pathogenic later-onset phenotype
- Variants of unknown significance
- Non-pathogenic polymorphisms

Lyso-Gb_3?[3*]



Residual enzyme activity?[4]

Leukocyte α-Gal A in males with FD
(normal range = 33–134 nmol/mg protein/h)

	N215S	non-N215S
Median (range)	**7.0** (2.1–14)	**2.3** (0.1–8.3)

*Median and interquartile range (IQR); whiskers extend to the most extreme data point that is no more than 1.5 times the IQR.
α-Gal A, alpha galactosidase A; FD, Fabry disease; lyso-Gb_3, globotriaosylsphingosine. 1. Ortiz A, et al. *Mol Genet Metab.* 2018;123:416–27; 2. Linhart A, Elliott PM. *Heart.* 2007;93:528–35; 3. Arends M, et al. *J Am Soc Nephrol.* 2017;28:1631–41; 4. Lavalle L, et al. *PLoS One.* 2018;13:e0193550.

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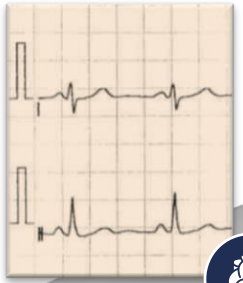
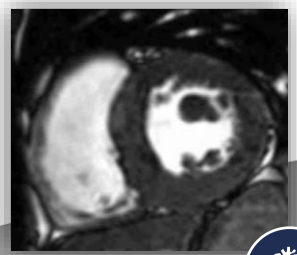
What organ assessments are needed, and when, to best support long-term outcomes?

Progression of cardiac involvement in Fabry disease[1]

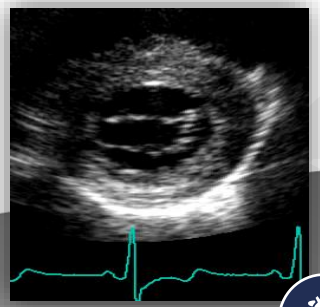
Storage without apparent structural and functional abnormality[2]



Borderline LV mass
No fibrosis
- Functionally normal
- Preclinical structural and functional abnormality



LVH
Minimal fibrosis
- Compensated HF
- Mildly decreased functional capacity
- Arrhythmias



Severe LVH
Severe fibrosis
- Decompensated HF
- Arrhythmias

HF, heart failure; LV, left ventricle; LVH, left ventricular hypertrophy.

1. Faculty (Linhart A) clinical expert perspectives from personal communication 17 June 2024. Images provided by Prof. Aleš Linhart.
2. Linhart A, Elliott PM. *Heart*. 2007;93:528–35.

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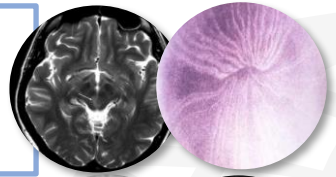
Multiorgan disease with substantially reduced QoL

Fabry disease

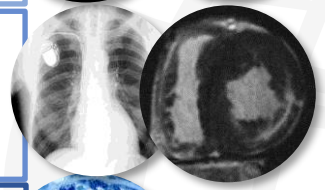
Cardiac hypertrophy
Heart failure
Arrhythmias

- Cardiac MRI
- ECG/Holter
- Echocardiogram
- hs-cTn
- NT-proBNP
- NYHA/CCS class



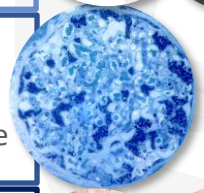
Peripheral neuropathy
Stroke/TIA
White matter lesions

- Audiogram
- Autonomic dysfunction
- Brain MRI
- Eye exam
- Surveys (BPI)
- Vestibular function



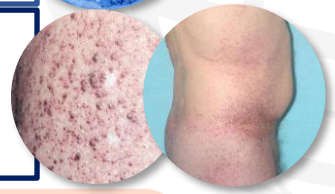
Proteinuria
Impaired renal function

- Albuminuria/ proteinuria
- eGFR
- Kidney biopsy
- Cystatin C
- Serum creatinine



Skin lesions (angiokeratomas)
Hypohidrosis

- Angiokeratoma assessment
- Sudomotor function



Assessments

- QoL questionnaires
- Biomarkers: lyso-Gb_3
- Multiorgan scoring: MSSI; Fastex; FabPRO

BPI, Brief Pain Inventory; CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; hs-cTn, high-sensitivity cardiac troponin; lyso-Gb_3, globotriaosylsphingosine; MRI, magnetic resonance imaging; MSSI, Mainz Severity Score Index; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA; New York Heart Association; PRO, patient reported outcomes; QoL, quality of life; TIA, transient ischaemic attack.

Faculty (Linhart A) clinical expert perspectives from personal communication 17 June 2024. Images provided by Prof. Aleš Linhart.

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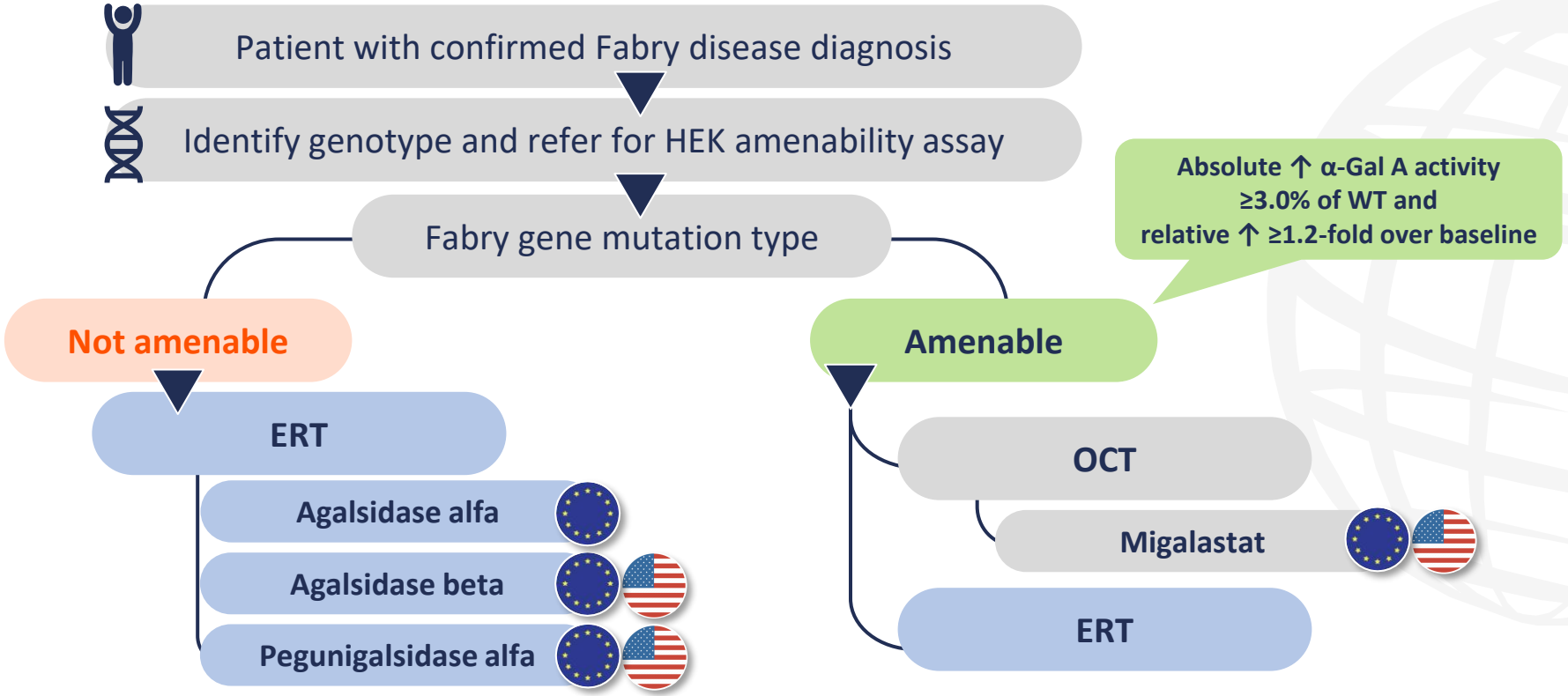
How do you approach Fabry disease in your clinic? What therapies are currently available?

Treatment options in Fabry disease



α-Gal A, alpha galactosidase A; ERT, enzyme replacement therapy; HEK, human embryonic kidney; OCT, oral chaperone therapy; WT, wildtype.

Bichet DG, et al. *Front Med (Lausanne)*. 2023;10:1220637.

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When should pharmacotherapies be considered in Fabry disease?

Knowing when to treat, and who

Treatment initiation

'Easy' scenarios?

- Classically affected patients
- Males
- Preventing irreversible changes
- QoL improvements
- Life expectancy?

'Difficult' scenarios?

- Late-onset variants
- Females
- Cost effectiveness
- Uncertainty of impacts on:
  - Cardiac involvement
  - QoL

Who should be treated?

Classical phenotype

- Known classical mutations
- Low α-Gal A activity
- High lyso-Gb_3
- At first clinical symptom, or earlier in males

Who may be treated?

Late-onset phenotype

- Known late-onset variants
- Residual α-Gal A activity
- Low-to-intermediate lyso-Gb_3
- At 1st clinically relevant sign of cardiac damage

Who should not be treated?

Non-pathogenic mutations or pseudovariants

- Known benign variants/polymorphisms
- High residual α-Gal A activity
- Borderline or normal lyso-Gb_3
- When in doubt, confirmed by biopsy

α-Gal A, alpha galactosidase A; lyso-Gb_3, globotriaosylsphingosine; QoL, quality of life.

Faculty (Linhart A) clinical expert perspective and own opinion from personal communication 17 June 2024, modified from Ortiz A, et al. *Mol Genet Metab.* 2018;123:416–27.

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Continuing the journey: Long-term management of Fabry disease

Dr Eric Wallace

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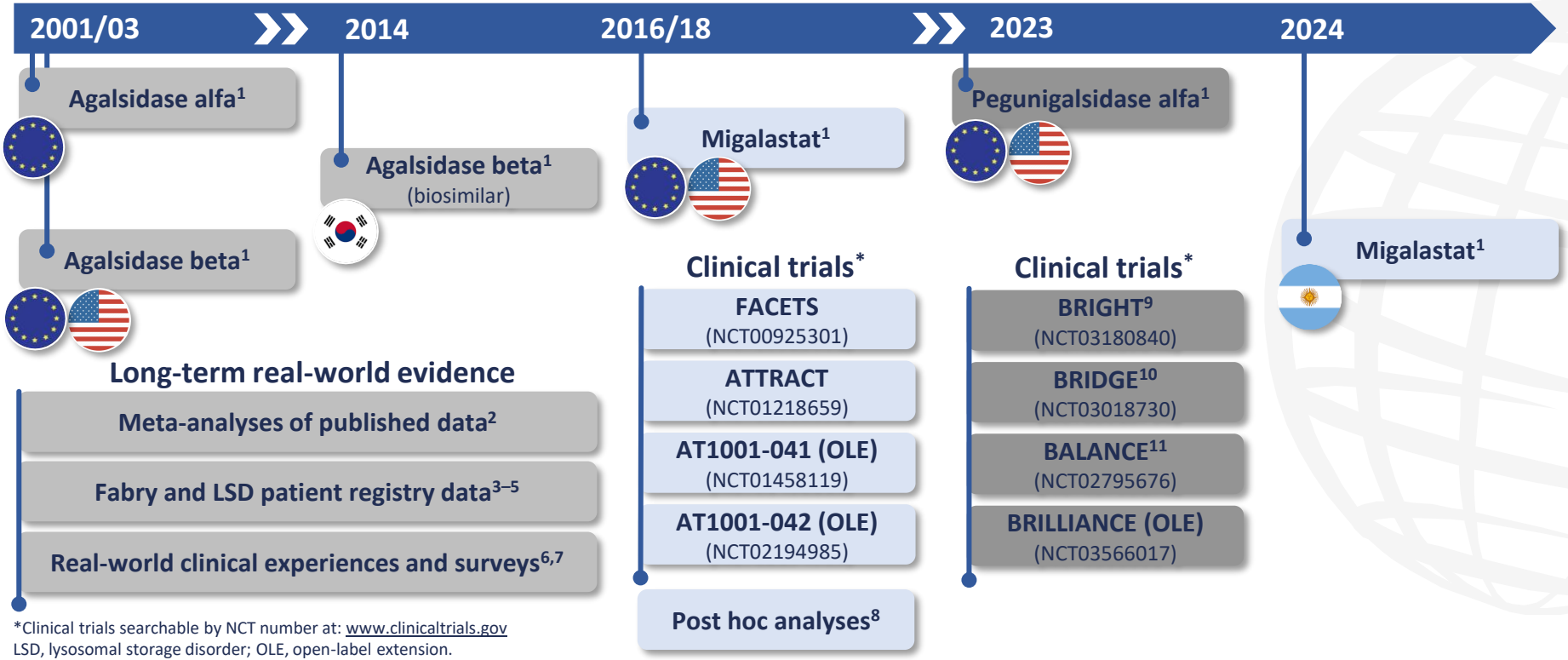
What do we currently know about long-term use of ERT and chaperone therapy?

A growing evidence base of clinical and real-world data



*Clinical trials searchable by NCT number at: www.clinicaltrials.gov

LSD, lysosomal storage disorder; OLE, open-label extension.

1. Germain DP, Linhart A. *Front Genet.* 2024;15:1395287; 2. Feriozzi S, et al. *Drug Des Devel Ther.* 2024;18:1083–101; 3. Beck M, et al. *Orphanet J Rare Dis.* 2022;17:238; 4. Wanner C, et al. *Mol Genet Metab.* 2023;139:107603; 5. Mistry PK, et al. *Orphanet J Rare Dis.* 2022;17:362; 6. Pisani A, et al. *Nephrol Dial Transplant.* 2024;39(Suppl. 1):2456; 7. Berry L, et al. *Orphanet J Rare Dis.* 2024;19:153; 8. Hughes DA, et al. *J Med Genet*. 2023;60:722–31; 9. Bernat J, et al. *Genet Med.* 2022;24(Suppl. 3):S91–2; 10. Linhart A, et al. *Orphanet J Rare Dis.* 2023;18:332; 11. Wallace EL, et al. *J Med Genet.* 2024;61:520–30.

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Insights on long-term use: Early intervention is needed

ERT: *Early intervention intended to reduce disease progression and protect against organ damage*

Agalsidase alfa[1]

FOS data show benefits of early ERT:

- **Attenuates progression** of **renal disease** and **cardiomyopathy**
- **Reduces risk** of **CV** (heart failure) and **renal** (dialysis) **events**, regardless of Fabry disease type (late-onset vs classic)
- Starting ERT in adulthood (aged >18 years vs ≤18 years) was associated with significant worsening in outcomes e.g. eGFR

Agalsidase beta[2]

Data collated from the **Fabry registry** show:

- **Reduction in clinical events**, with some patients remaining clinical event-free during defined periods of follow-up
- **Favourable treatment responses** measured by eGFR and ECG parameters
- Even in patients with **advanced disease**, **ERT may have slowed progression** of renal disease and cardiomyopathy
- **Positive impact on GI symptoms** in male and female patients

Pegunigalsidase alfa[3]

2-year data from the BALANCE trial show:

- **Non-inferiority to agalsidase beta** based on eGFR decline over 2 years
- Δ median eGFR slopes: -0.36 mL/min/1.73 m^2/year
- Lower exposure-adjusted rates of mild or moderate infusion-related reactions

Currently available ERTs are associated with infusion-site reactions and development of anti-drug antibodies[3]

CV, cardiovascular; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FOS, Fabry outcomes survey; GI, gastrointestinal.

1. Beck M, et al. *Orphanet J Rare Dis.* 2022;17:238; 2. Wanner C, et al. *Mol Genet Metab.* 2023;139:107603; 3. Wallace EL, et al. *J Med Genet.* 2024;61:520–30.

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Insights on long-term use: Early intervention is needed

Chaperone therapy: *An effective long-term treatment option*

Migalastat

Post hoc analysis of pooled clinical trial data from FACETS, ATTRACT and OLE studies (AT1001-041 and AT1001-042) showed **low incidence rates** of **Fabry-associated clinical events, comparable to** those in **previous ERT trials**:

Overall
48.3

Renal
4.4

Cardiac
30.7

Cerebrovascular
13.2

per 1,000 patient-years

ERT, enzyme replacement therapy; OLE, open-label extension.
Hughes DA, et al. *J Med Genet*. 2023;60:722–31.

How should we monitor our patients on ERT or chaperone therapy?

Monitoring recommendations (1 of 3)

	Clinical evaluations and assessments	Monitoring schedule
General	1. History including family history, physical examination, symptom and QoL assessment e.g. GI symptoms, study/work performance, mental health evaluation 2. α-Gal A enzyme activity and *GLA* mutation analysis	• Each clinic visit • If not previously established
Renal	1. GFR (measured [preferred] or eGFR using appropriate formulae) 2. Albuminuria (preferred) and/or proteinuria (24-h or spot urine for total protein/creatinine and albumin/creatinine ratios) 3. 25-hydroxycholecalciferol; vitamin D 4. Kidney biopsy	• 1 and 2. Low-risk: annually; moderate risk: 6-monthly; high-risk: 3-monthly (measured GFR once yearly only, as complex) • As clinically indicated; vitamin D late autumn/early winter • As clinically indicated. Podocyte foot process effacement may precede pathological albuminuria
Cardiac	1. Blood pressure and cardiac rhythm 2. Electrocardiography and echocardiography 3. 48-h Holter monitoring to detect intermittent rhythm abnormalities; implantable loop recorder recommended for patients with significant hypertrophic cardiomyopathy 4. Cardiac MRI with gadolinium 5. Cardiac MRI with T1 mapping 6. Brain natriuretic peptide	• Each clinic visit • Annually and as clinically indicated • Annually; adjust frequency depending on risk factors; where arrhythmias detected, more frequent/detailed surveillance should be tailored to the individual patient • Where evidence of clinical disease progression, or at regular >2-year intervals (if available) • Investigational tool: interpret with caution • ≥ annually in patients with cardiomyopathy or bradycardia

α-Gal A, α-galactosidase A; GI, gastrointestinal; GFR, glomerular filtration rate; eGFR; estimated GFR; MRI, magnetic resonance imaging; QoL, quality of life.

Ortiz A, et al. *Mol Genet Metab.* 2018;123:416–27.

Monitoring recommendations (2 of 3)

	Clinical evaluations and assessments	Monitoring schedule
PNS	1. Pain history and evaluation (pain measurement scale e.g. NPSI or BPI) 2. Cold and heat intolerance, vibratory thresholds (quantitative sensory testing, if available) 3. Autonomic symptom assessment (orthostatic blood pressure) 4. Skin biopsy for IENFD evaluation, if available	• Annually • Annually (reduced frequency in older patients) • Annually • Consider
Cerebro-vascular	1. Brain MRI (TOF MRA at 1st assessment in men ≥21 years and women ≥30 years; then per clinical scenario) 2. CT imaging	• Every 3 years and as clinically needed (e.g. presence of neurological changes suggestive of stroke) • In the event of acute stroke and only if MRI contraindicated due to cardiac pacing
ENT	• Audiometry	• As required
Pulmonary	1. Spirometry (including bronchodilator response) 2. Treadmill exercise test 3. Oximetry 4. Chest X-ray	• 1–3 every 2 years or more frequently for clinical indications • According to clinical needs
GI	• Gastroenterology referral for endoscopic/radiographic evaluation	• If symptoms persist or worsen despite treatment

BPI, Brief Pain Inventory; CT, computerized tomography; GI, gastrointestinal; IENFD, intra-epidermal nerve fibre density; MRI, magnetic resonance imaging; NPSI, Neuropathic Pain Symptom Inventory; PNS, peripheral nervous system; TOF MRA, time-of-flight magnetic resonance angiography (head and neck).

Ortiz A, et al. *Mol Genet Metab.* 2018;123:416–27.

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Monitoring recommendations (3 of 3)

	Clinical evaluations and assessments	Monitoring schedule
GL burden	• Gb_3; lyso-Gb_3 (plasma and urinary sediment)	• At baseline, then annually (currently for research purposes only); biobanking of samples is recommended if feasible
Skeletal	• DEXA bone scan	• Consider
Ophthalmol-ogical	• Ophthalmological screening	• As clinically indicated

DEXA, dual-energy X-ray absorptiometry; Gb_3, globotriaosylceramide; lyso-Gb_3, globotriaosylsphingosine.
Ortiz A, et al. *Mol Genet Metab.* 2018;123:416–27.

How can we support adherence to these therapies in our patients with Fabry?

Addressing treatment challenges to support adherence

Factors affecting adherence[1]

Treatment related

- **Route of administration** (IV infusion vs oral)
- **Complexity of dosing schedule** (daily infusions vs oral tablet on alternate days)
- **Common reactions/side effects**[2] (e.g. infusion-associated reactions)

Patient perceptions

- **Underestimation of disease effects** if slowly progressing with insidious symptom onset
- **Under-recognition of protective effects** of therapy on organs
- **'Forgetfulness'** in missing doses

Supporting adherence

- **HCP–patient communication and trust**[1,2]
- **HCP encouragement surrounding adherence to achieve treatment goals**[1,2]
- **Telemedicine**[3]
- **MDT monitoring**[4]
- **Timely and effective side-effect management**[3]
- **Patient/caregiver education**[1,2]

IV, intravenous; HCP, healthcare provider; MDT, multidisciplinary team.

1. Müntze J, et al. *Mol Genet Metab.* 2023;138:106981; 2. Berry L, et al. *Orphanet J Rare Dis.* 2024;19:153; 3. Nowicki M, et al. *Int J Environ Res Public Health.* 2021;18:8242; 4. Bichet DG, et al. *Front Med (Lausanne).* 2023;10:1220637.

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Charting the future:
The evolving landscape of Fabry disease

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What's on the horizon for Fabry disease, in terms of new treatments?

Identifying treatment gaps and need for new therapies

Patient survey data highlight treatment gaps in Fabry disease[1]

in 280 respondents with Fabry disease

Most respondents received ERT[1]

- ERT – 89%
- OCT – 11%

2003: First ERT approval[2]

2018: First OCT approval[3]

More than half of respondents reported symptom burden[1]

- 'Bothersome' – 38%
- 'Difficult to control' – 14%

Common symptoms[1*]

- 72% low energy/fatigue
- 62% tingling in hands/feet
- 60% pain in hands/feet
- 54% ringing in ears/hearing loss
- 51% general body pains/pain crises
- 50% abdominal/stomach pain

Temporary symptom worsening between infusions reported in:[1]

- 51% currently receiving ERT
- 48% previously receiving ERT

Symptom worsening is underreported[1]

- 48% reported to their physician
- Of those, 41% were prescribed medication to manage symptoms or changed their treatment regimen

*Symptoms reported by ≥50% of respondents.

ERT, enzyme replacement therapy; OCT, oral chaperone therapy.

1. Berry L ,et al. *Orphanet J Rare Dis.* 2024;19:153; 2. FDA. Agalsidase beta PI. 2024. Available at: https://shorturl.at/miGzq (accessed 12 July 2024); 3. FDA. Migalastat PI. 2024. Available at: https://shorturl.at/uE4fq (accessed 12 July 2024).

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New and emerging therapies in Fabry disease

Next-generation ERT

Moss-αGal[1,2]

- Mannose-dependent uptake r-α-Gal A

Completed phase I trial

- Single dose was safe, well-tolerated, and led to a prolonged reduction in Gb_3 excretion[2]
- Phase II/III clinical trials are in preparation[2]

Pegunigalsidase alfa[1,3,4]

- PEGylated r-α-Gal A

Approved in 2023

- In first head-to-head trial of ERTs: comparable to agalsidase beta based on eGFR decline over 2 years[5]
  (in adult males previously treated with agalsidase beta)

SRT

Venglustat (ibiglustat)[1,6–8]

- CNS penetrant GCSi

Completed phase IIa trial

- Reduced markers of synthetic/degradative pathways of major GSL pathways[6]
- Reduced biomarkers (plasma Gb_3; lyso-Gb_3)[6]
- No biochemical or histological indications of disease progression over 3 years' follow-up[6]
- In phase III trials[7,8]

Lucerastat[1,9–12]

- Iminosugar GCSi

Completed phase III trial; OLE ongoing

- Did not reach primary endpoint to reduce neuropathic pain vs placebo over 6 months[10,11]
- OLE: Long-term safety, tolerability and impact on renal and cardiac outcomes[10,12]

α-Gal A, alpha-galactosidase A; CNS, central nervous system; ERT, enzyme replacement therapy; Gb_3, globotriaosylceramide; GCSi, glucosylceramide-1 synthase inhibitor; GSL, glycosphingolipid; lyso-Gb_3, globotriaosylsphingosine; OLE, open-label extension; PEG, polyethylene glycol; r, recombinant; SRT, substrate reduction therapy.

1. Yoo H-W. *J Genet Med.* 2023;20:6–14; 2. Hennermann JB, et al. *J Inherit Metab Dis.* 2019;42:527–33; 3. FDA. Pegunigalsidase alfa PI. 2023. Available at: https://shorturl.at/Az4uf (accessed 12 July 2024); 4. EMA. Pegunigalsidase alfa SPC. 2023. Available at: https://shorturl.at/icGIW (accessed 12 July 2024); 5. Wallace EL, et al. *J Med Genet.* 2024;61:520–30; 6. Deegan PB, et al. *Mol Genet Metab.* 2023;138:106963; 7. NCT05206773; 8. NCT05280548; 9. Lenders M, Brand E. *Drugs.* 2021;81:635–45; 10. Maia M. Fabry Disease News. Available at https://shorturl.at/mevSJ (accessed 12 July 2024); 11. NCT03425539; 12. NCT03737214. Clinical trial information searchable by NCT number at: https://clinicaltrials.gov (accessed 12 July 2024).

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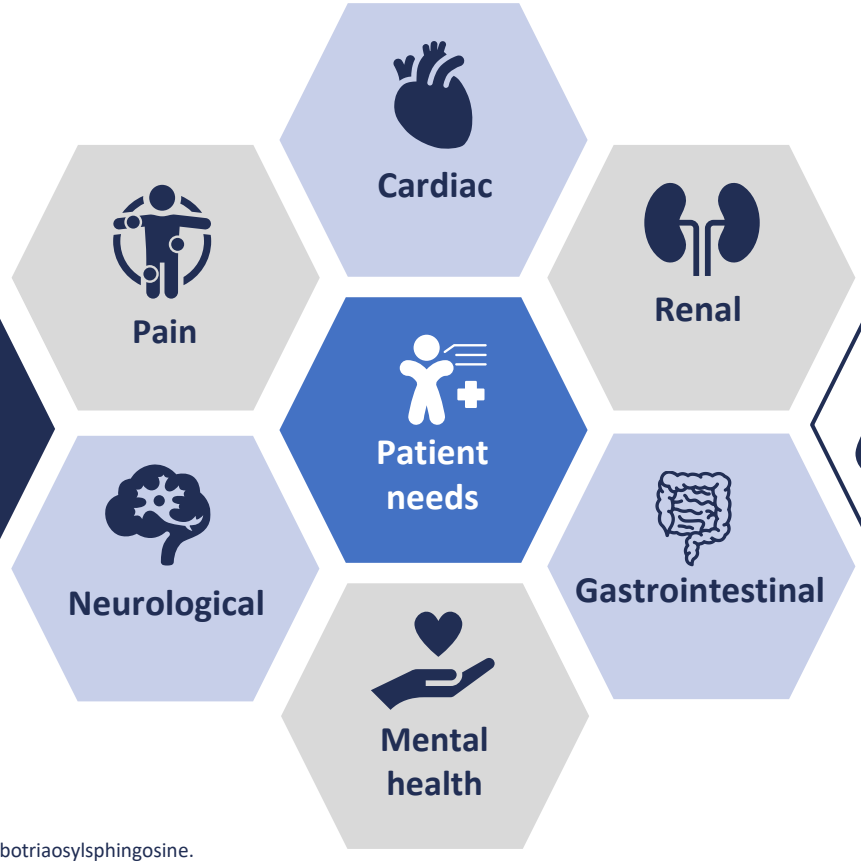
Why is interdisciplinary collaboration important in the management of Fabry disease?

Managing multisystem manifestations in Fabry disease

Fabry-related symptoms, organ involvement and effects on QoL require effective interdisciplinary collaboration[1]



Pathology Biomarker evaluation

- α-Gal A activity
- Lyso-Gb_3

Emerging role of telemedicine[2]

- Supporting home-based management and patient preferences
- Reducing travel burden and costs
- Improving access to care

α-Gal A, alpha-galactosidase A; lyso-Gb_3, globotriaosylsphingosine.

1. Bichet GD, et al. *Front Med (Lausanne).* 2023;10:1220637; 2. Nowicki M, et al. *Int J Environ Res Public Health.* 2021;18:8242.

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How might new therapies impact current standards of care and clinical outcomes?

Currently approved treatments in standards of care

Features of ERT[1–3]

- **IV infusion of exogenous α-Gal A enzyme** to reduce lysosomal Gb_3 accumulation
- **Mutation-independent** therapeutic activity
- **Long-term data show efficacy,** with stabilization or even improvement of disease load

Considerations

- Weight-based dosing
- Short half-life requiring short therapy intervals
- Tissue uptake and CNS penetrance
- Biodistribution and clearance e.g. clinically relevant cells (renal podocytes; cardiomyocytes) vs endothelium
- High immunogenicity – ADAs; infusion-related reactions

Features of OCT[1–5]

- **Oral corrective for misfolded protein** to increase endogenous α-Gal A trafficking and activity
- **Amenable *GLA* mutation-dependent** therapeutic activity
- **Growing clinical evidence base shows efficacy** reducing cardiac hypertrophy and stabilizing renal function

Considerations

- Weight-independent fixed dosing
- Convenience of oral administration
- Adherence challenges with alternate-day dosing

ADA, anti-drug antibody; α-Gal A, alpha-galactosidase A; CNS, central nervous system; ERT, enzyme replacement therapy; Gb_3, globotriaosylceramide; Q; OCT, oral chaperone therapy.

1. Umer M, Kalra DK. *Pharmaceuticals (Basel).* 2023;16:320; 2. Yoo H-W. *J Genet Med.* 2023;20:6–14; 3. Lenders M, Brand E. *Drugs.* 2021;81:635–45;
4. Nowicki M, et al. *Orphanet J Rare Dis.* 2024;19:16; 5. Müntze J, et al. *Mol Genet Metab.* 2023;138:106981.

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What are your hopes and expectations for the management of Fabry disease in 2024, and beyond?

Tailoring treatment to individual needs and outcomes

Individualize care, maximize outcomes?

Emerging genomic medicines

In phase I/IIa trials:

- 4D-310[1]
- AMT-191[2]
- Isaralgagene civaparvovec[3]

Next-generation ERTs and emerging SRTs

- Expanding treatment options?
- Wider access to therapy?
- Improving outcomes?

Long-term OCT data and role in treatment paradigm

- Front-line use?
- Switching from prior ERT?
- Improving treatment experience and outcomes?

ERT, enzyme replacement therapy; OCT, oral chaperone therapy; SRT, substrate replacement therapy.
1. NCT04519749; 2. NCT06270316; 3. NCT04046224.
Clinical trial information searchable by NCT number at: https://clinicaltrials.gov (accessed 12 July 2024).