Fabry masterclass

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Na investigação • No tratamento • Na garantia de um futuro

European Reference Network
for rare or low prevalence complex diseases

Network
Hereditary Metabolic Disorders (MetabERN)

Member
Hospital Senhora da Oliveira, Guimarães, FPF — Portugal

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Lyso-GB3: Usefulness and limitations

No disclosure

Fabry Disease: A Rare Genetic Disorder

X-linked Inheritance

Lysosomal storage disorder caused by α-galactosidase A deficiency affecting predominantly males

Cellular Accumulation

Progressive accumulation of glycosphingolipids, primarily globotriaosylceramide (Gb3) in lysosomes

Multi-organ Impact

Systemic involvement affecting kidneys, heart, nervous system, skin, and gastrointestinal tract

Clinical Variability

Manifestations vary between classic and late-onset forms, with gender differences

Gb3 Synthesis and Pathway

Golgi Apparatu

Gb3 synthesis occu
via the enzyme alp
galactosyltransfera

Location

It has a particular
membranes of crit
including the kidne
nervous system, ar
endothelium. This
directly correlates
manifestations obs
disease, explaining
nature of this diso

1

Vascular Endothelium

Gb3 deposits trigger endothelial dysfunction and microvascular complications

2

Cellular Inflammation

Accumulated lipids activate inflammatory cascades leading to tissue fibrosis

3

Apoptosis

Cellular stress pathways culminate in programmed cell death and organ failure

ha-
somes

Gb3 and Lyso-Gb3: Molecular Players

Structural Differences

The fundamental structural distinc
between Gb3 and lyso-Gb3 lies in t
of the fatty acid chain in the latter
This deacylation dramatically increases wa
solubility whilst simultaneously enhancing
bioactivity. The resulting molecule can mo
readily interact with cellular receptors and
transport mechanisms, potentially
contributing to disease pathogenesis beyo
simple accumulation.

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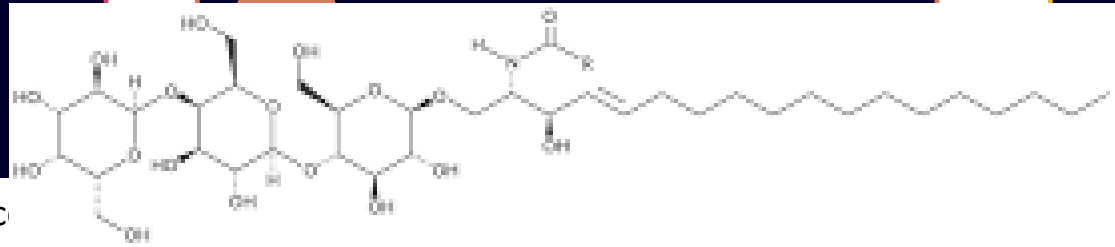
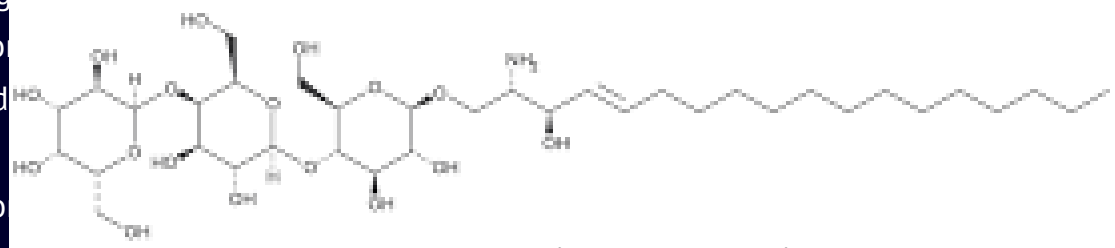


Globotriosylceramide



Lyso-Globotriosylceramide

Biological Sgnificance

ction,

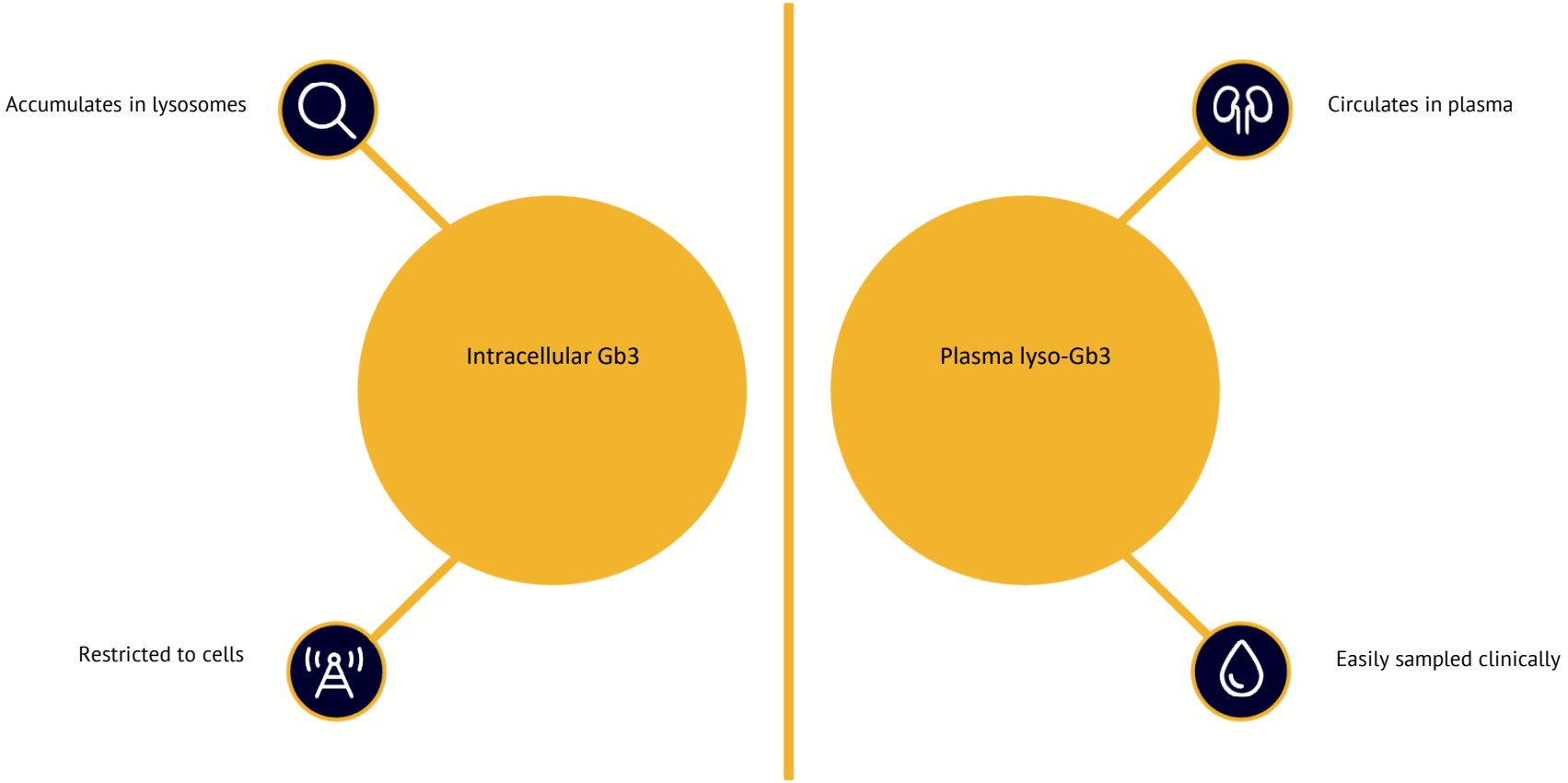
ctively promotes disease
n and cellular dysfunction.
ase biomarker: Accumulates due to
galactosidase A enzyme deficiency

oactive properties: Influences cellular
gnalling and inflammatory, induces fibrosis,
d cellular dysfunction

thological impact: Directly implicated in
organ damage and symptom manifestation

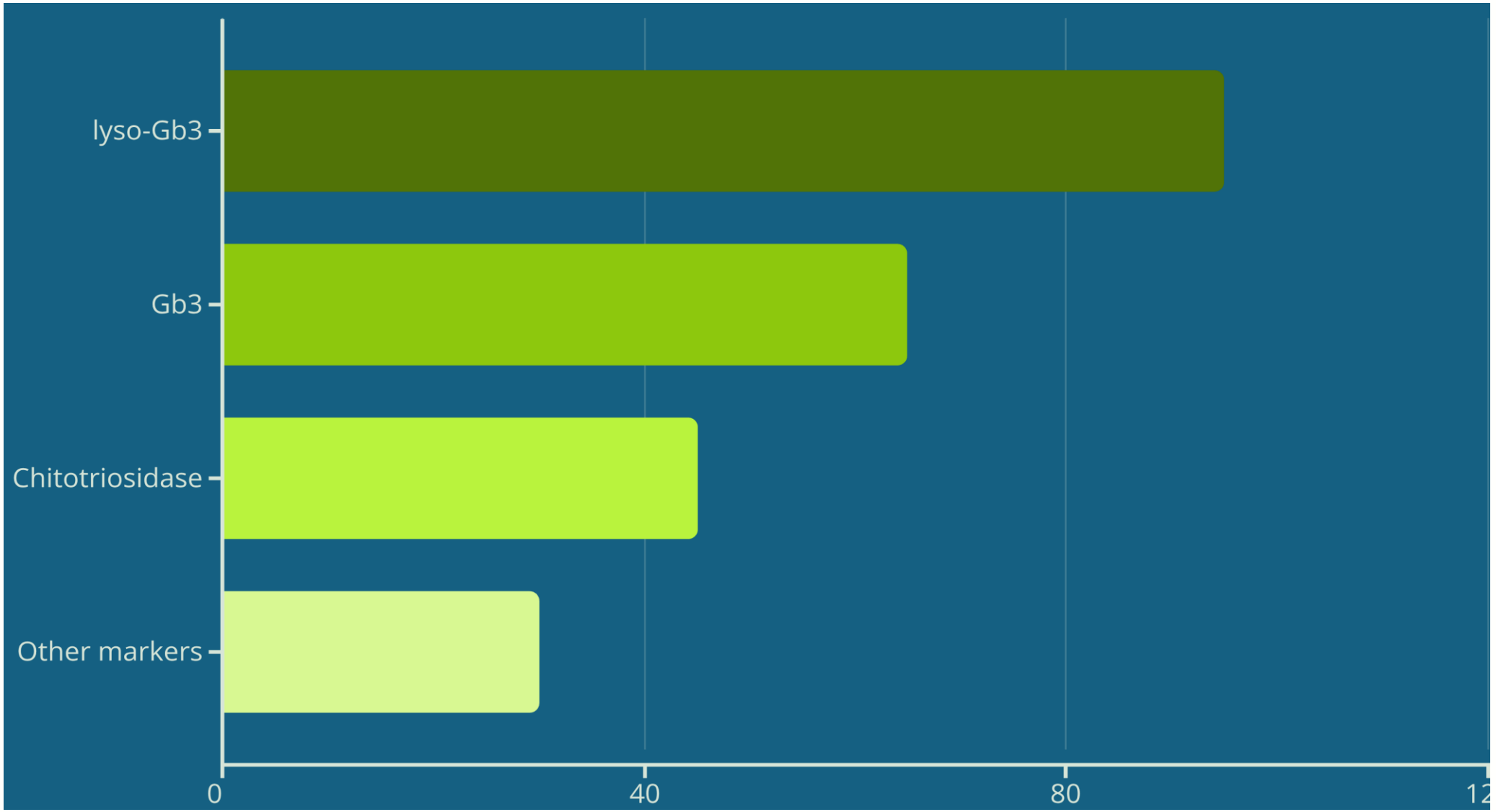
Understanding these molecular distinctions is crucial for interpreting lyso-Gb3 measurements in clinical practice, as structural variants may exhibit different kinetics of accumulation and clearance during treatment.

Cellular Pathophysiology

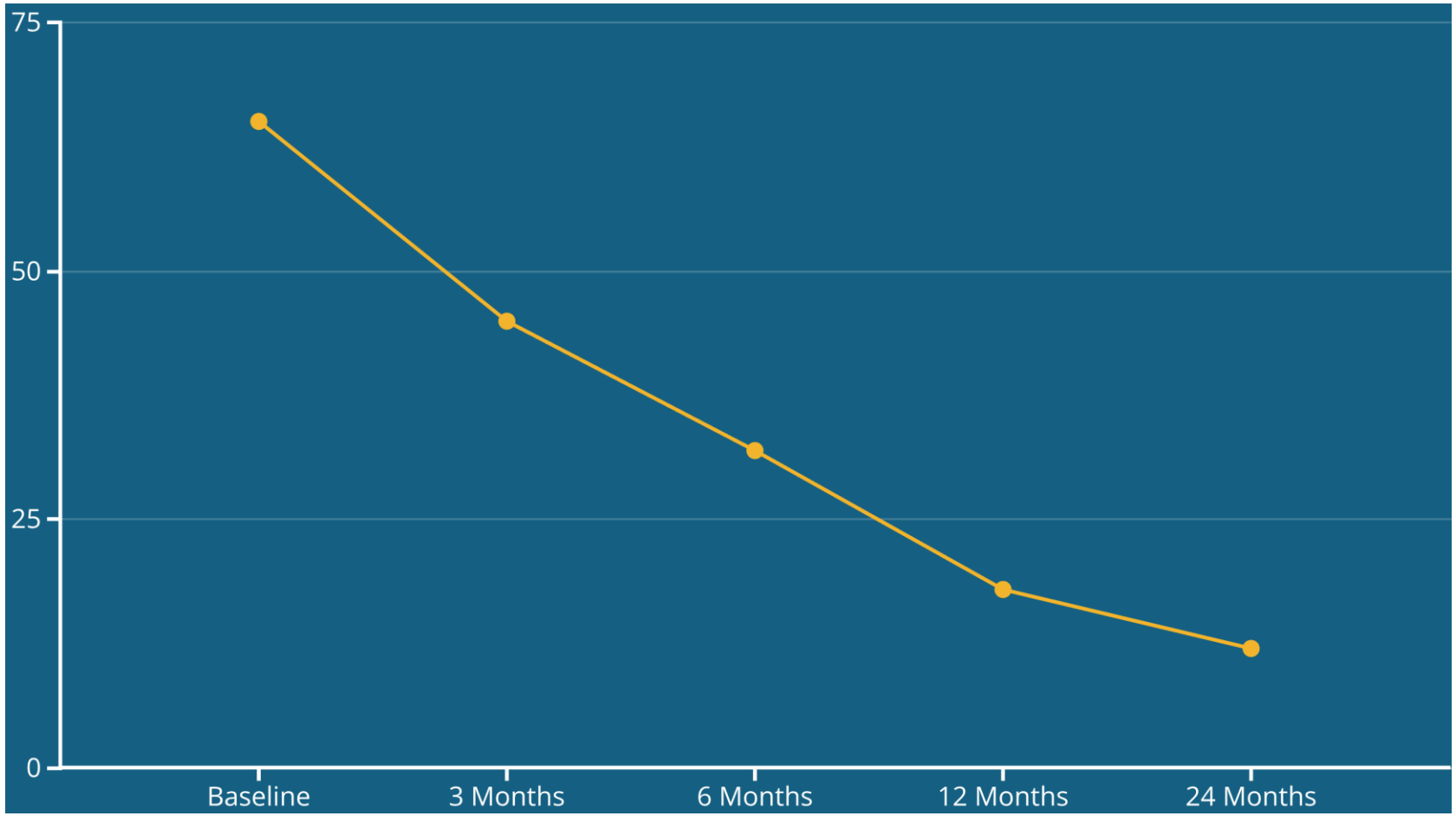


Understanding the distinct cellular locations and behaviours of these biomarkers is crucial for selecting appropriate diagnostic and monitoring strategies

Comparison with Other Biomarkers



Treatment Evolution: LysoGb3 Level Changes



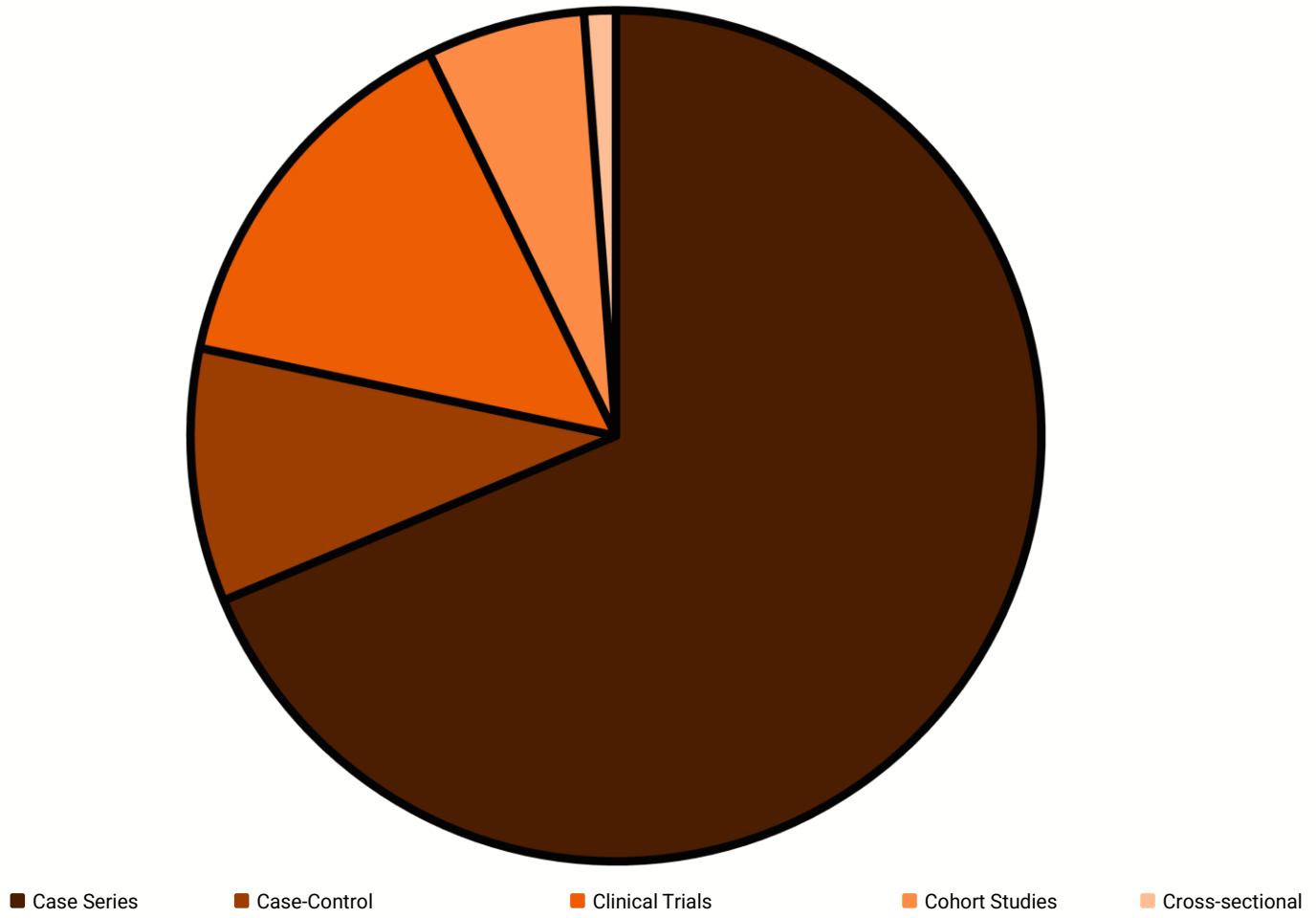
Typical response pattern showing progressive reduction in LysoGb3 levels following enzyme replacement therapy initiation.

Study Characteristics Overview

83

Total Studies

Eligible publications included

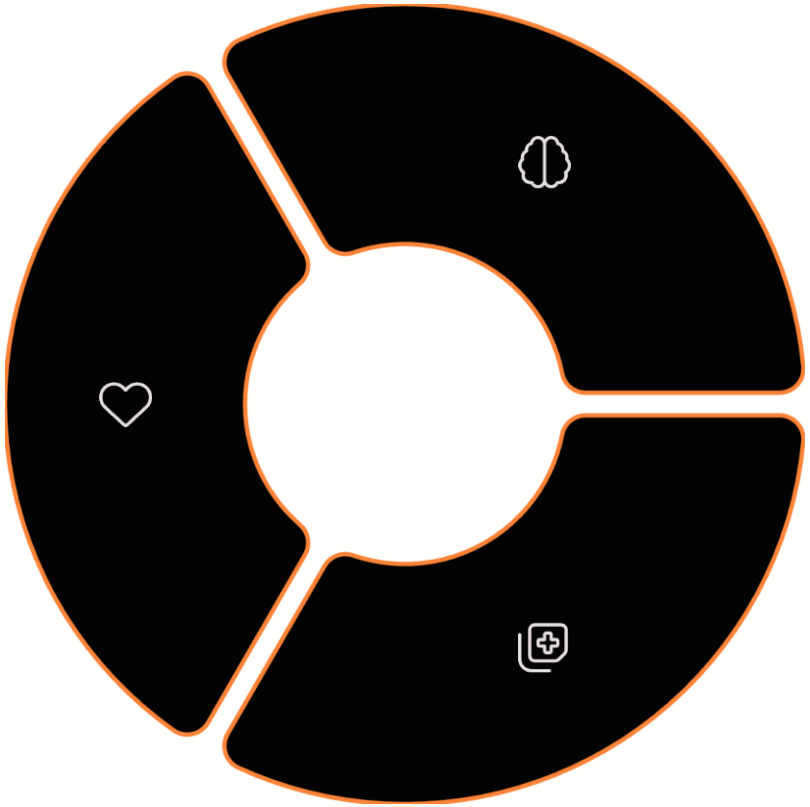


High-Risk Population Screening

Seven studies evaluated lyso-Gb3 screening in high-risk populations, including patients with unexplained left ventricular hypertrophy, early-onset stroke, and Fabry-related symptoms.

Cardiac Patients

Left ventricular hypertrophy screening identified 2 patients with Fabry disease among 277 tested



Stroke Patients

Ischemic stroke screening showed specificity in identifying Fabry disease cases

Symptomatic Patients

Family history or Fabry-related symptoms screening in 2,381 patients identified multiple cases

Treatment Monitoring Applications

Eleven real-world studies and twelve clinical trials reported lyso-Gb3 testing patterns during treatment with enzyme replacement therapy or chaperone therapy.

Baseline Assessment

Pre-treatment lyso-Gb3 levels established as reference point

Regular Monitoring

Testing frequency varied from 3-6 months to annually depending on study design

Treatment Response

Changes in lyso-Gb3 levels used to assess therapy effectiveness

Long-term Follow-up

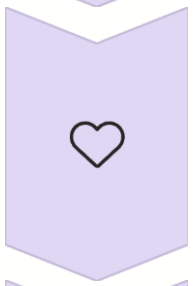
Extended monitoring up to 7 years in some studies

Various sample types used including plasma, serum, urine, and dried blood spots. No standardized testing patterns identified, suggesting need for clinical guidelines.

Diagnostic Utility Across Fabry Phenotypes

Classic Males

Markedly elevated Lyso-Gb3 correlates directly with severe multi-organ disease manifestations and early symptom onset



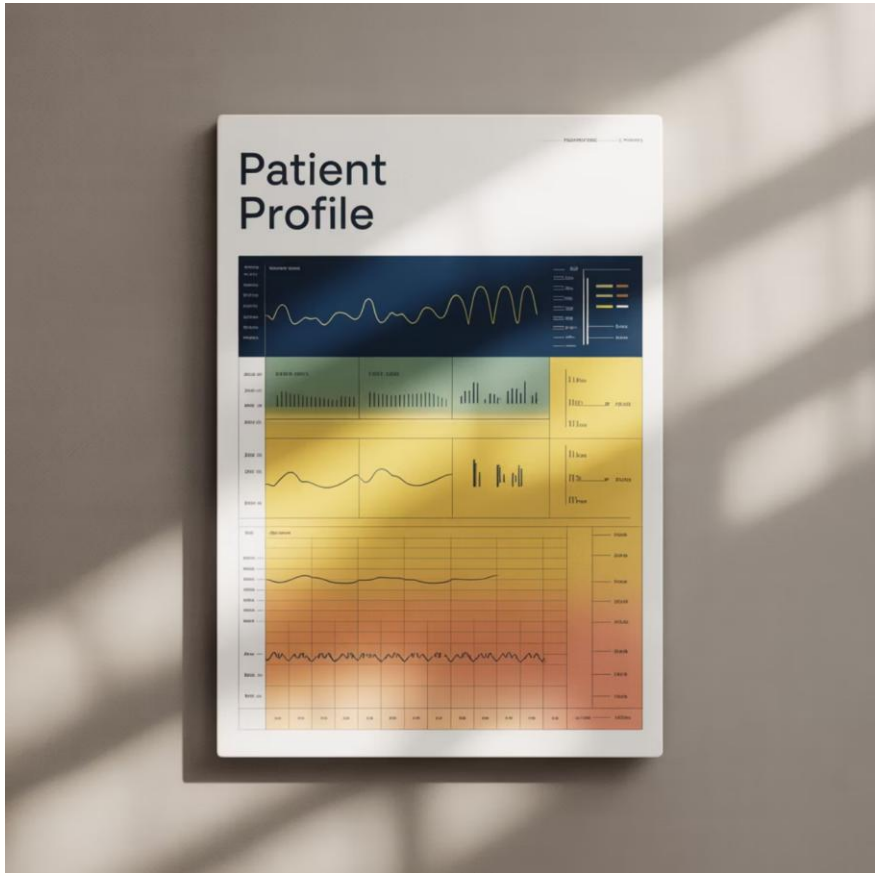
Late-Onset Cardiac (N215S)

Intermediate Lyso-Gb3 levels effectively distinguish patients from healthy healthy controls, facilitating accurate diagnosis

Female Heterozygotes

Variable Lyso-Gb3 levels reflect the broad phenotypic spectrum, serving as serving as valuable adjunct to genetic testing

Limitations in Diagnosis



Despite its diagnostic strengths, lyso-Gb3 measurements face significant limitations that complicate clinical interpretation, particularly in specific patient populations and genetic variants.

- **Phenotype Variability:** Lyso-Gb3 levels in late-onset and female patients often fall within lower ranges with substantial variability, potentially overlapping with normal population values and reducing diagnostic confidence.
- **Genetic Complexity:** Certain GLA variants produce atypical lyso-Gb3 profiles that don't conform to expected patterns, complicating interpretation and potentially leading to diagnostic uncertainty or misclassification.
- **Analytical Challenges:** The existence of multiple analogues and isoforms of lyso-Gb3 requires sophisticated analytical techniques for accurate detection and quantification, which may not be universally available.
- **Population Variations:** Reference ranges may vary across different ethnic populations, necessitating population-specific validation studies for optimal diagnostic accuracy.

These limitations underscore the importance of integrating lyso-Gb3 measurements with comprehensive clinical assessment, genetic analysis, and additional biomarkers for definitive diagnosis, particularly in challenging cases.

Clinical Interpretation Challenges

The complexity of lyso-Gb3 interpretation extends beyond simple elevation detection, requiring nuanced clinical understanding.

Organ-Specific Prediction

Lyso-Gb3 levels do not consistently predict organ-specific involvement patterns or disease progression rates in rates in individual patients.

High Exposure Paradox

Some patients with substantially high high lyso-Gb3 exposure remain relatively relatively mildly affected, challenging challenging traditional severity assumptions.

Female Complexity

Female disease expression, influenced by influenced by X-chromosome inactivation patterns, significantly complicates biomarker interpretation interpretation and clinical utility.

Renal Correlations

Three studies examined renal correlations:

- Weak positive correlation with serum creatinine (r=0.28)
- Weak positive correlation with protein/creatinine ratios (r=0.33)
- No significant correlation with estimated glomerular filtration rate

Sample Type Considerations

Plasma/Serum

Standard sample type with established reference ranges and highest concentrations

Urine

Higher proportion of analogues, valuable for comprehensive metabolite profiling

Dried Blood Spots

Convenient collection, ~50% lower concentrations requiring sensitive methods

Limitations and Clinical Challenges

Biological Variability

Influenced by sex, age, genotype, phenotype, and sample type. DBS concentrations ~50% lower than serum, requiring assay-specific reference ranges.

Reduced Sensitivity

Limited effectiveness in non-classical phenotypes, heterozygous females, and late-onset forms. Many symptomatic women may have normal LysoGb3 levels.

Treatment Confounders

Anti-drug antibodies can affect levels and treatment response. Correlation with clinical outcomes inconsistent, particularly with migalastat therapy.

Clinical Case: Male Patient with Classic Disease

Initial Presentation

Diagnosis confirmed with LysoGb3 >45 nmol/L alongside clinical symptoms

Monitoring Protocol

Quarterly assessments demonstrated progressive reduction following treatment initiation

Clinical Outcomes

Concurrent improvement in renal and cardiac function parameters observed

Diagnostic Limitations in Women and and Late-onset Forms

Reduced Sensitivity

Lower diagnostic accuracy in women with late-onset disease presentations

Combined Approach

Necessity of combining with other diagnostic tests to prevent false negatives

Clinical vigilance required when interpreting results in heterozygous females and patients with atypical presentations.

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Variable Female Response

Female patients and those with late-onset disease show more modest and variable responses, with lyso-Gb3 levels typically stabilising rather than dramatically declining. This pattern reflects the complex interplay between residual endogenous enzyme activity and tissue-specific accumulation patterns.

3

Antibody Impact

Development of neutralising antibodies against infused enzyme can significantly blunt lyso-Gb3 reduction, leading to treatment resistance and potential clinical deterioration. Regular monitoring becomes crucial for detecting this complication.

Conclusion: Promise and Limitations

LysoGb3 has proven to be a sensitive and practical biomarker for Fabry disease, enabling identification of unrecognized cases and facilitating risk stratification. However, concerns about prognostic utility remain, as levels don't consistently correlate with clinical endpoints.

Key Strengths

High diagnostic accuracy, responsiveness to therapy, robust analytical performance, and emerging analogue applications enhance clinical utility.

Critical Limitations

Reduced sensitivity in certain populations, lack of clinical correlation, and need for comprehensive diagnostic approach limit standalone use.

Future Outlook

Integration with multiplex panels, standardized protocols, and longitudinal studies will optimize LysoGb3 utility in personalized Fabry disease management.

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