ERNDiM
Quality Assurance in Laboratory Testing for IEM

Celebrating 30 years of ERNDiM 1994–2024

SSIEM 2024
Annual Symposium
03-06 September
Porto, Portugal
Exploring New Horizons

Contribution of biomarkers in the diagnosis and follow-up of sphingolipidoses

ERNDIM Participant Workshop

Tuesday 3rd September 2024

Dr Magali PETTAZZONI, Pharm D

HCL HOSPICES CIVILS DE LYON

LBMMS – Biochemichal and molecular laboratory
Inborn Errors of Metabolism unit
HOSPICES CIVILS DE LYON - France

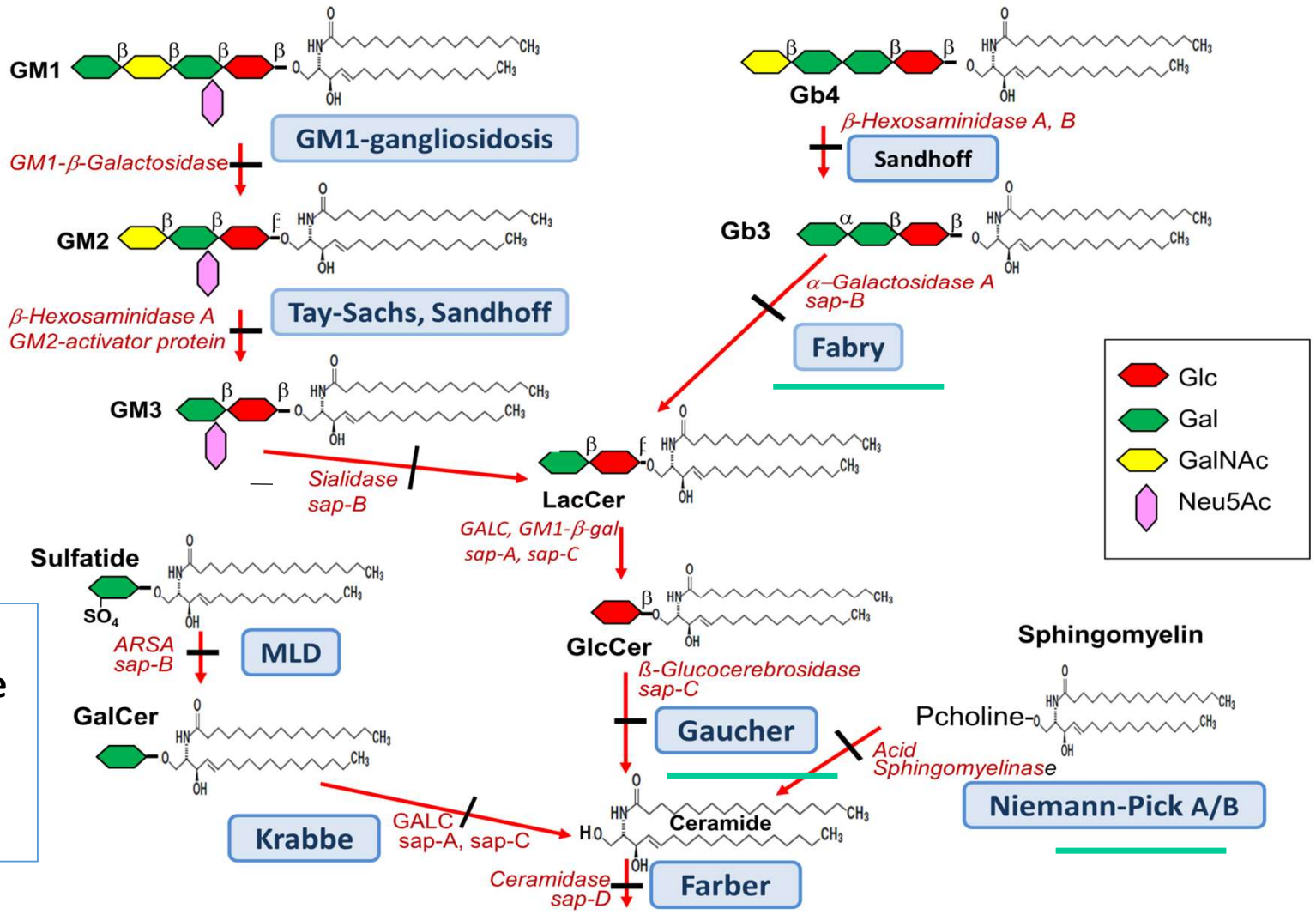
Disclosures

Participation in Board (Sanofi, Takeda, Chiesi)
Invitation to IEM Congress (Sanofi, Orchard, Biomarin)
Carrying out analyzes for the Lysodiag Plateform on DBS (Takeda)

Sphingolipidoses

- **Sphingolipidoses = group of Lysosomal Storage Diseases affecting the metabolism of Sphingolipids**
- **Several enzymatic deficiencies are known, corresponding to disorders**
- **The diagnosis is based on enzymatic activity measurement**

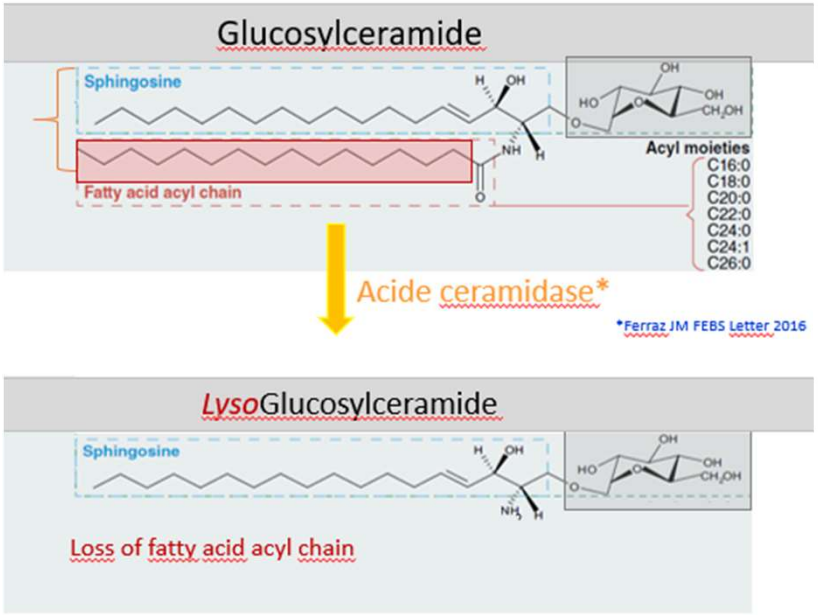
With the use of MS/MS: Lysosphingolipids have become biomarkers for screening and follow-up of Sphingolipidoses



Courtesy of Dr M-T. Vanier, Lyon France

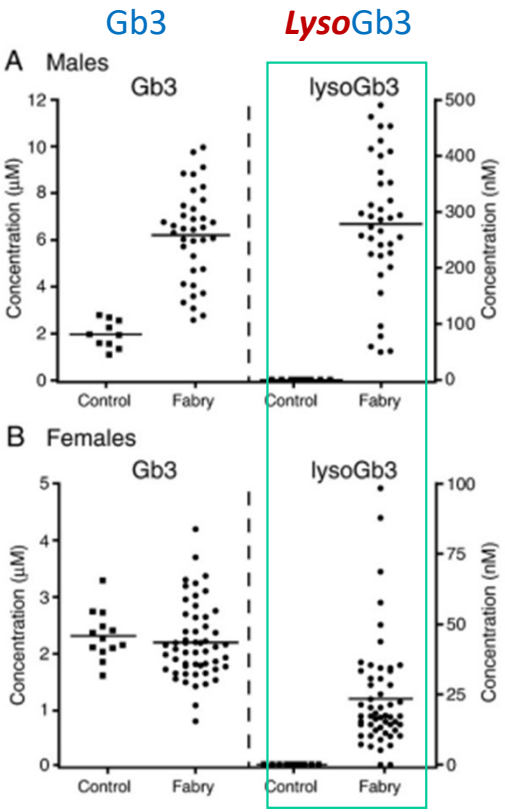
Lysosphingolipids: Biomarkers of Sphingolipidoses

Lysosphingolipids (LysoSL)
- deacylated form of the sphingolipids
- role in pathophysiology ?

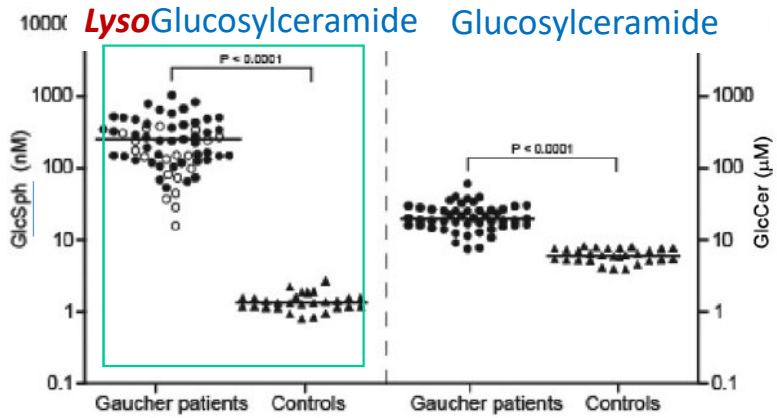


Adapted from Advances in Gaucher Disease: Basic and Clinical Perspectives. Future medicine. 2013. Glycosphingolipid aspects of Gaucher disease lipidomics. Sun and Zhang.

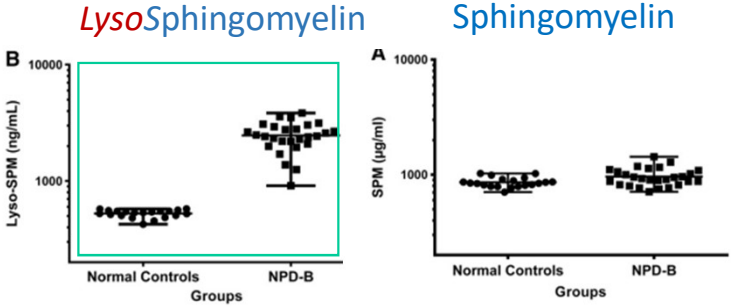
Measurement of the primary accumulated SL poorly informative in plasma
LysoSL: **A thousand time less important** in plasma (nmol/L vs µmol/L)
BUT more discriminant



Rombach et al. Biochim Biophys Acta 2010



Dekker et al. Blood 2011



Chuang et al. Mol Genet Metab 2014

Lysosphingolipids: measurement by tandem mass spectrometry (MSMS)

Since 15 years, many reports state of the measurement of LysoSLs by MSMS either isolated, or in multiplex,
in plasma, urine or dried blood spots (DBS)

LysoGlobotriaosylceramide (LysoGb$_3$)	**Fabry**	*Aerts et al.* Proc Natl Acad Sci USA, 2008
Lysogalactosyl-ceramide (LysoGalCer)	**Krabbe**	*Chuang et al. Clin Chim Acta 2013*
Lysoglucosyl-ceramide (LysoGlcCer)	**Gaucher**	*Dekker et al. Blood 2011*
Lysosphingomyelin (LysoSM)	**ASMD (Niemann-Pick A/B)**	*Chuang et al . Mol Genet Metab 2014*
LysoSM509/N-palmitoyl-O-phosphocholineserine	**ASMD and NPC**	*Giese et al.* Orphanet J Rare Dis 2015

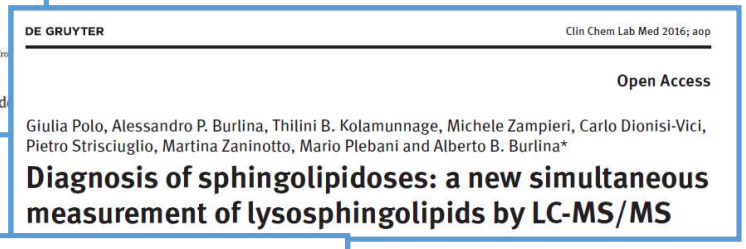

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Simultaneous quantitation of sphingoid bases by UPLC-ESI-MS/MS with identical ^{13}C-encoded internal standards

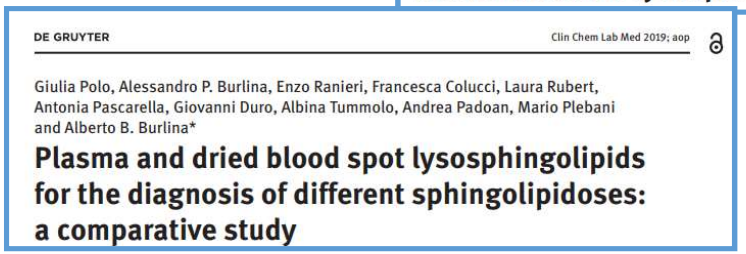
M. Mirzaian [a], P. Wisse [b], M.J. Ferraz [a], A.R.A. Marques [c], P. Gaspar [d], S.V. Oussoren [a], K. Kytidou [a], J.D.C. Cod
G. van der Marel [b], H.S. Overkleeft [b], J.M. Aerts [a,*]


DE GRUYTER Clin Chem Lab Med 2016; aop

Open Access

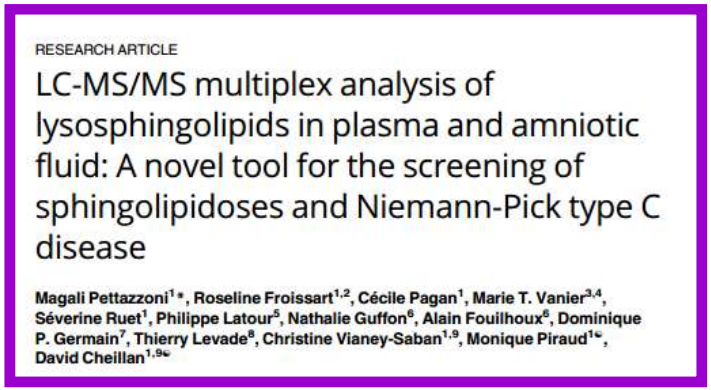
Giulia Polo, Alessandro P. Burlina, Thilini B. Kolamunnage, Michele Zampieri, Carlo Dionisi-Vici, Pietro Strisciuglio, Martina Zaninotto, Mario Plebani and Alberto B. Burlina*

Diagnosis of sphingolipidoses: a new simultaneous measurement of lysosphingolipids by LC-MS/MS


DE GRUYTER Clin Chem Lab Med 2019; aop

Giulia Polo, Alessandro P. Burlina, Enzo Ranieri, Francesca Colucci, Laura Rubert, Antonia Pascarella, Giovanni Duro, Albina Tummolo, Andrea Padoan, Mario Plebani and Alberto B. Burlina*

Plasma and dried blood spot lysosphingolipids for the diagnosis of different sphingolipidoses: a comparative study


RESEARCH ARTICLE

LC-MS/MS multiplex analysis of lysosphingolipids in plasma and amniotic fluid: A novel tool for the screening of sphingolipidoses and Niemann-Pick type C disease

Magali Pettazzoni[1]*, Roseline Froissart[1,2], Cécile Pagan[1], Marie T. Vanier[3,4], Séverine Ruet[1], Philippe Latour[5], Nathalie Guffon[6], Alain Fouilhoux[6], Dominique P. Germain[7], Thierry Levade[8], Christine Vianey-Saban[1,9], Monique Piraud[1☯], David Cheillan[1,9☯]

Pettazzoni et al. PLoS One. 2017

+ measurement in DBS since 2023

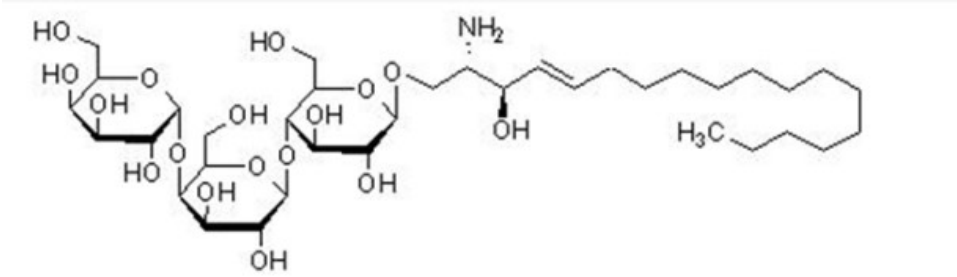

Measurement of lysosphingolipids in dried blood spots by LC-MSMS:
A useful tool for the diagnosis of sphingolipidoses

Julie Rochat[1], Roseline Froissart[1], Nathalie Guffon[2], Alain Fouilhoux[2], Bastien Feirrera[1], Emilien Ville[1], Séverine Ruet[1], Cécile Acquaviva-Bourdain[1], Magali Pettazzoni[1*]

[1] Laboratory of Inborn Error of Metabolism, Hospices Civils de Lyon – 69500 Bron, France
[2] National Reference Centre for Hereditary Metabolic Diseases, Hospices Civils de Lyon – 69500 Bron, France
* Presenting author, magali.pettazzoni@chu-lyon.fr

Contribution of biomarkers in the diagnosis and follow-up of sphingolipidoses

Are they usefull for diagnosis ?
Are they linked to the severity of the disease ?
Are they usefull for monitoring patients ?
Could DBS replace plasma ?



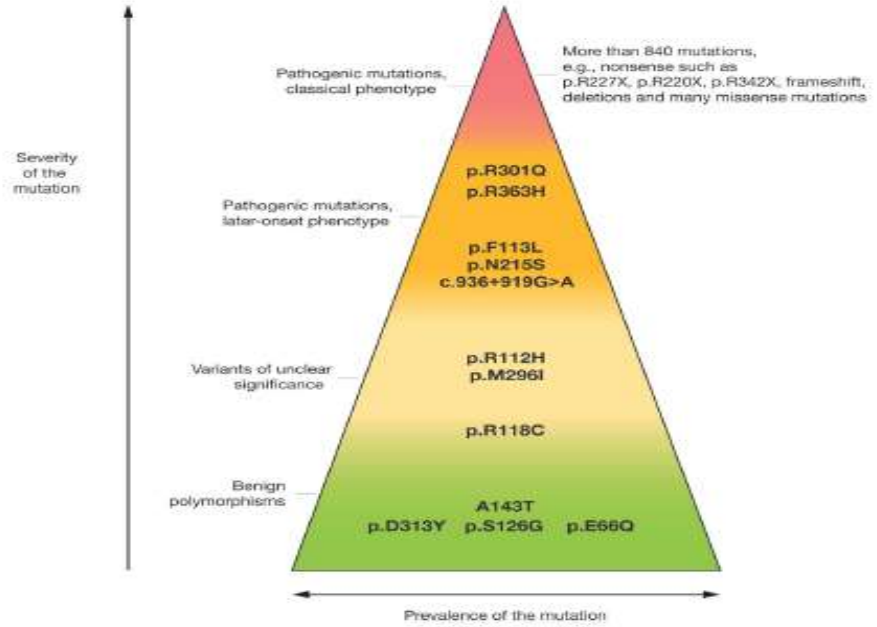
LysoGlobotriaosylceramide (LysoGb3): biomarker of Fabry disease

LysoGL3

Globotriaosylsphingosine

Fabry disease (X-linked)

Fabry disease is an X linked disorder caused by mutation on *GLA* gene with 2 phenotypes :
Classical Form and Variant form corresponding to specific mutations

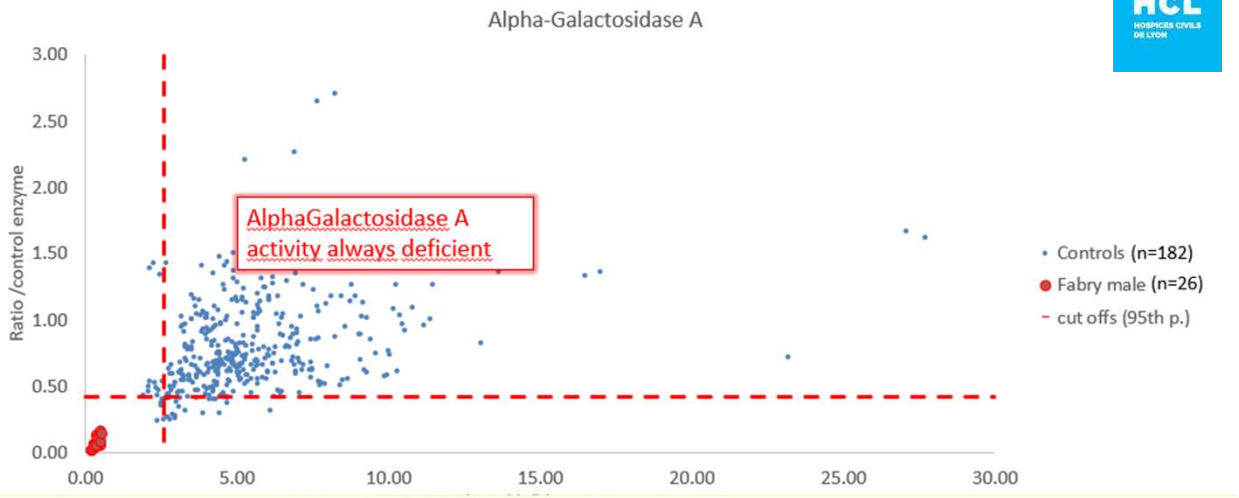


Ortiz et al., MGM 123 (2018) 416–427

Male diagnosis: AlphaGalactosidase A activity measurement

NeoLSD kit Perkin Elmer (1)

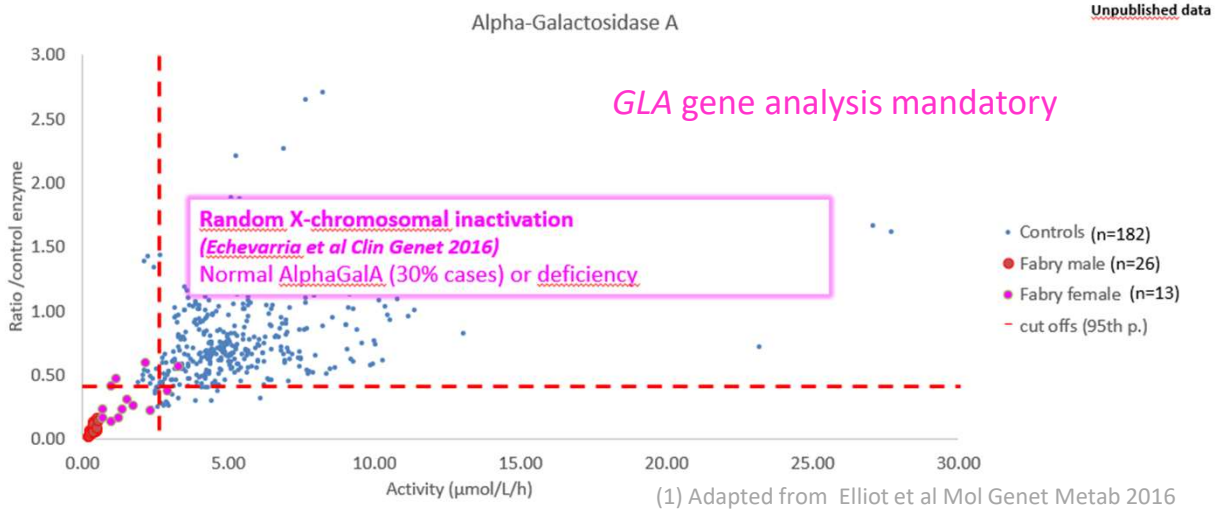
Results LYON, France
Unpublished data



Female diagnosis: alpha-Galactosidase A activity measurement

NeoLSD kit Perkin Elmer (1)

Results LYON, France
Unpublished data



GLA gene analysis mandatory

(1) Adapted from Elliot et al Mol Genet Metab 2016

Fabry disease (X-linked)

LysoGb3: a diagnostic biomarker in plasma

Elevated globotriaosylsphingosine is a hallmark of Fabry disease

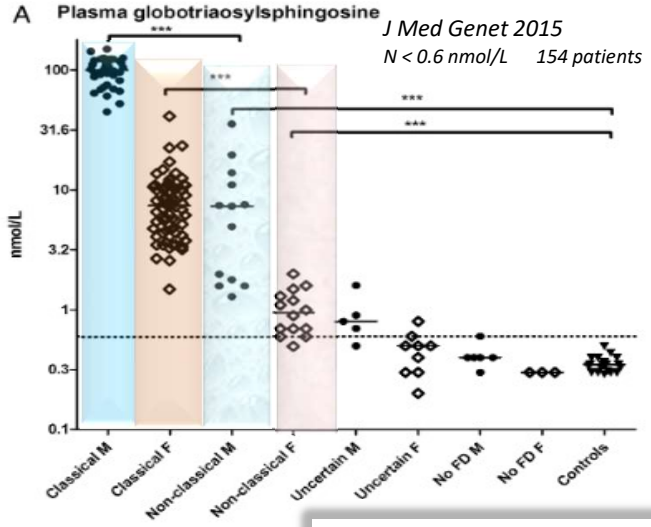
PNAS 2008

Johannes M. Aerts*†, Johanna E. Groener*, Sijmen Kuiper*, Wilma E. Donker-Koopman*, Anneke Strijland*, Roelof Ottenhoff*, Cindy van Roomen*, Mina Mirzaian*, Frits A. Wijburg*, Gabor E. Linthorst*, Anouk C. Vedder*, Saskia M. Rombach*, Josanne Cox-Brinkman*, Pentti Somerharju‡, Rolf G. Boot*, Carla E. Hollak*, Roscoe O. Brady†§, and Ben J. Poorthuis*

ORIGINAL ARTICLE

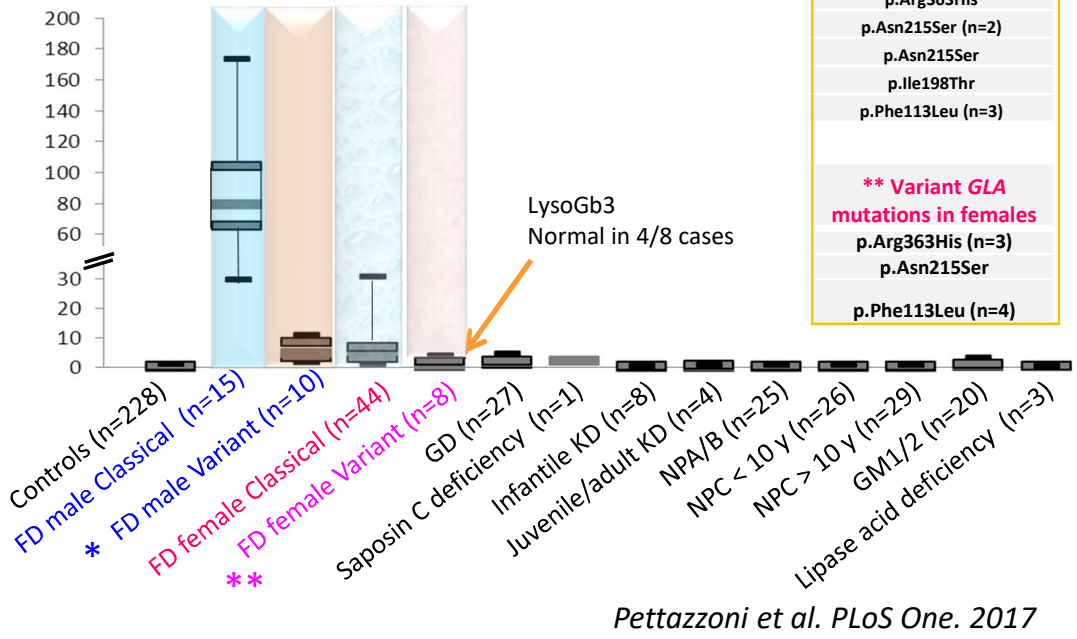
Plasma globotriaosylsphingosine in relation to phenotypes of Fabry disease

Bouwien E Smid,[1] Linda van der Tol,[1] Marieke Biegstraaten,[1] Gabor E Linthorst,[1] Carla E M Hollak,[1] Ben J H M Poorthuis[2]



J Med Genet 2015
N < 0.6 nmol/L 154 patients

HCL HOSPICES CIVILS DE LYON



*** Variant *GLA* mutations in males**

- p.Ile232Thr
- p.Met296Val
- p.Arg301Gln
- p.Arg363His
- p.Asn215Ser (n=2)
- p.Asn215Ser
- p.Ile198Thr
- p.Phe113Leu (n=3)

**** Variant *GLA* mutations in females**

- p.Arg363His (n=3)
- p.Asn215Ser
- p.Phe113Leu (n=4)

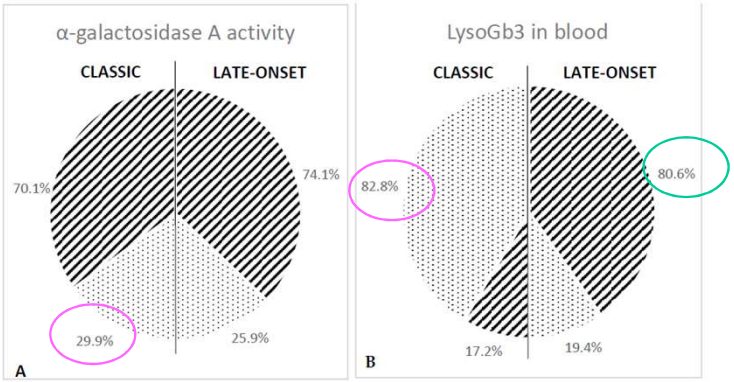
Pettazzoni et al. PLoS One. 2017

Plasma $LysoGb_3$ is a sensitive biomarker of screening,
LESS OVERLAP than U Gb3 between patients and controls, but can be normal in females

Fabry disease (X-linked)

Ratio AGAL/LysoGb3 could increase the sensitivity in females

In females
lysoGb3 more sensitive than AGalA in classical forms
BUT 80% of late onset forms had normal LysoGb3 !



268 females with classical form:
30% AGalA activity decreased vs
80% lysoGb3 increase

185 females with late onset form

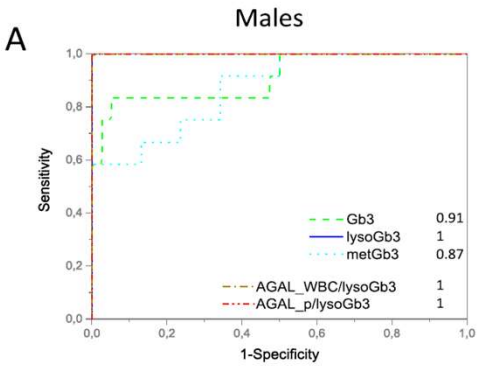
Duro et al Int. J. Mol. Sci. 2024, 25, 5158

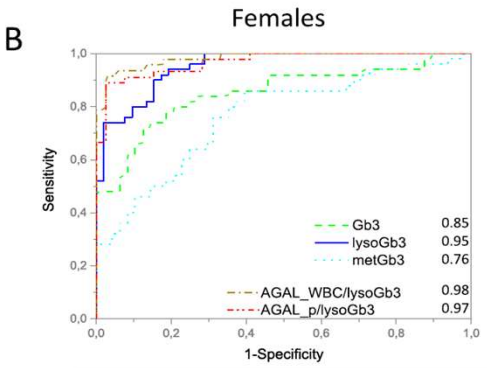

Clinica Chimica Acta
Volume 501, February 2020, Pages 27-32

α-Galactosidase A/lysoGb3 ratio as a potential marker for Fabry disease in females

G.V. Baydakova [a], A.A. Ilyushkina [a], S. Moiseev [c], I.O. Bychkov [a], N.V. Nikitina [b], T.A. Buruleva [d], E.Y. Zakharova [a]

Baydakova et al Clin Chim Acta. 2020 Feb





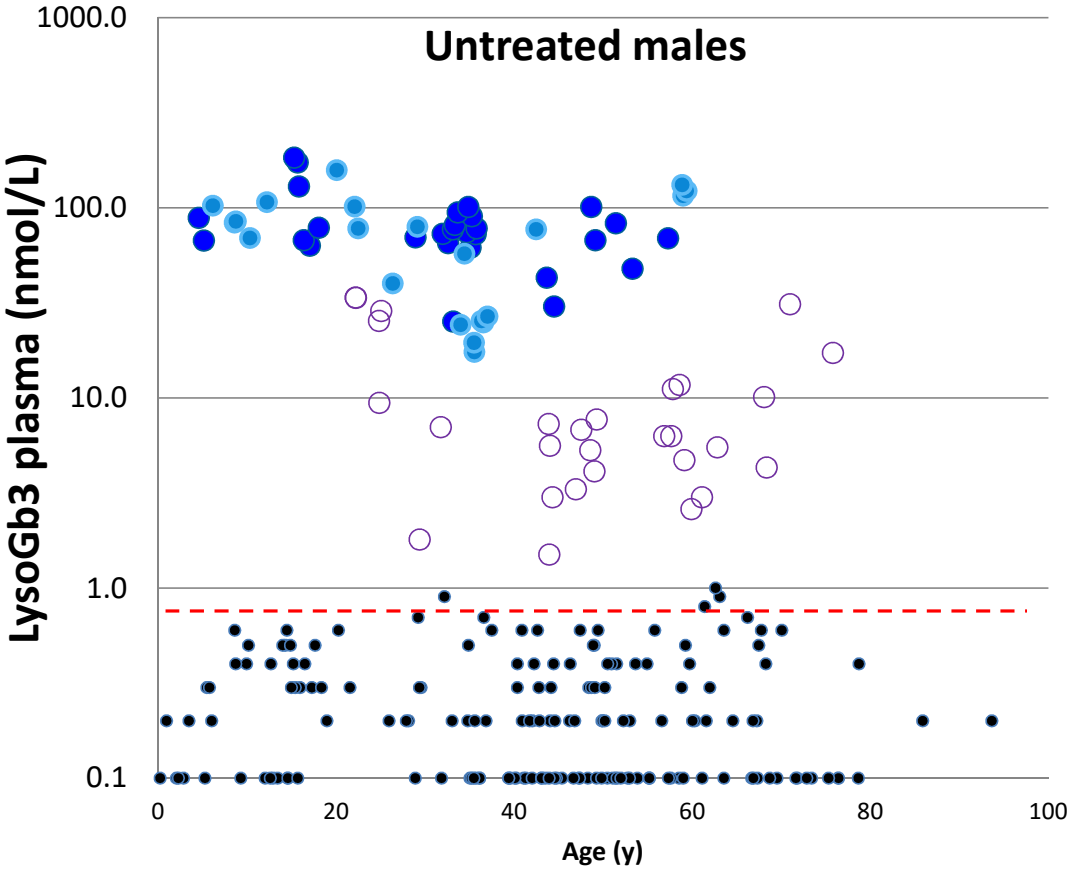
12 untreated male FD patients (6 classic FD and 6 late-onset cardiac FD), and 50 untreated heterozygous female FD patients (25 classic FD and 25 late-onset cardiac FD)

Ratio AGAL WBC/lysoGb3 sensitivity 98%

L. Kuchar et al.
Clinica Chimica Acta 561 (2024) 119824

Fabry disease (X-linked)

LysoGb3: A phenotype biomarker in males



Results LYON, France
Unpublished data

- Controls (n=117)
- Severe mutation (n=28)
- Variant mutation (n=28)
- Classical form missense mutation (n=21)

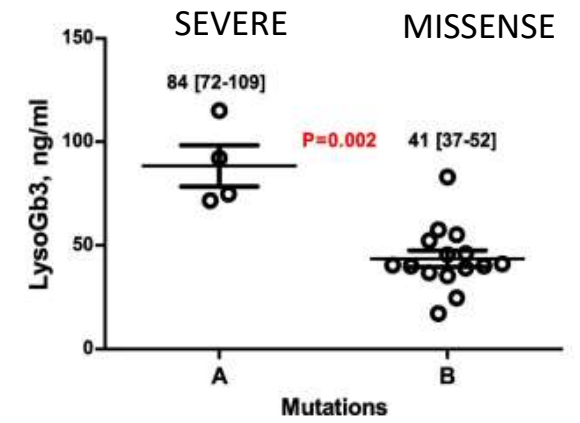


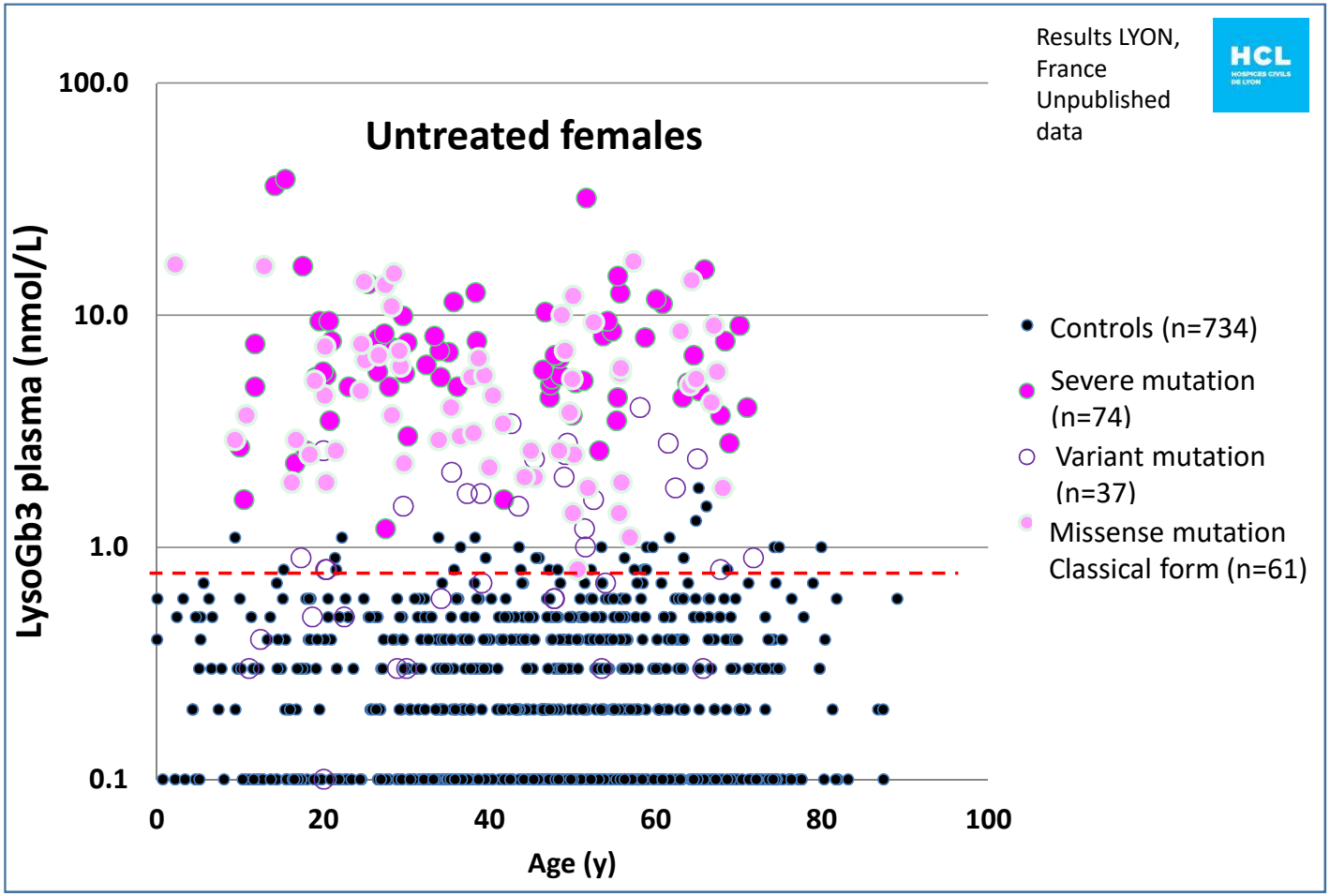
Fig. 3. Serum Lysob3 levels in affected males* according to mutation severity by structure and function: A) frame-shift and nonsense-mutation versus B) missense mutations. *Included only males with the same ERT preparation (α-agalsidase) at a stable dose of at least 5 years.

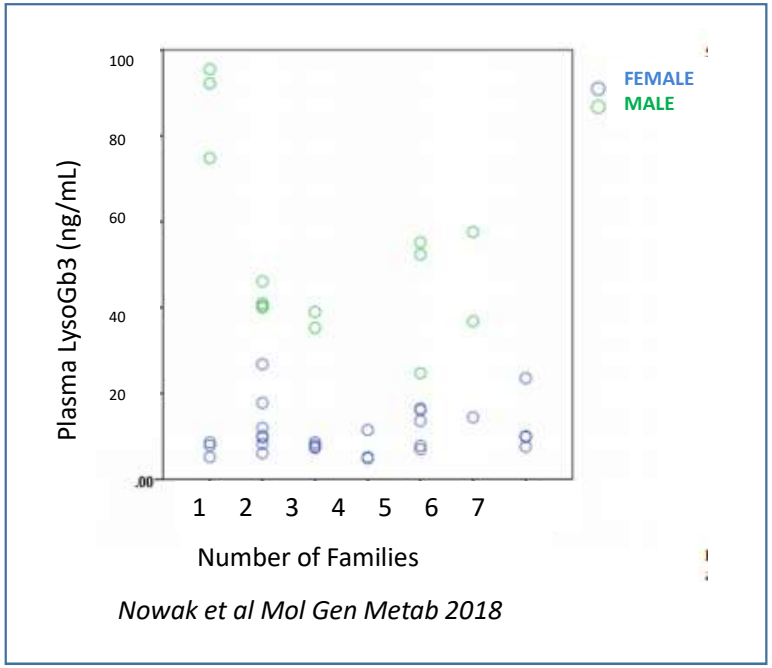
Nowak et al Mol Gen Metab 2018

The biomaker is higher in case of severe variant in *GLA* gene (frame-shift and nonsense variants)
Useful for Variant of Uncertain Significance (VUS)

Fabry disease (X-linked)

LysoGb3: A phenotype biomarker not always informative in females



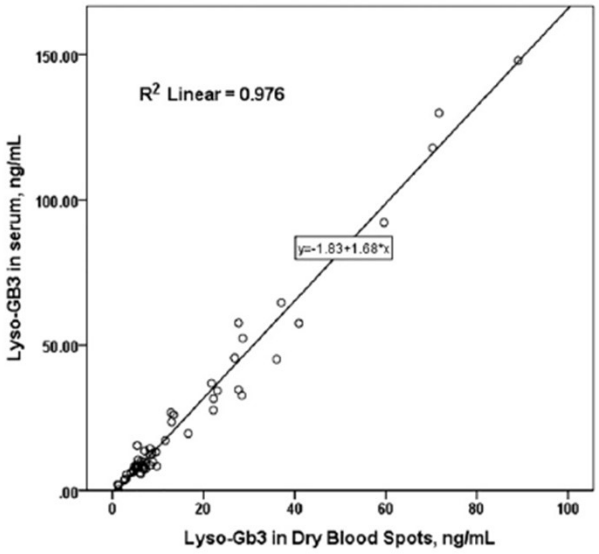


In females, LysoGb3 levels did not depend on the mutation severity

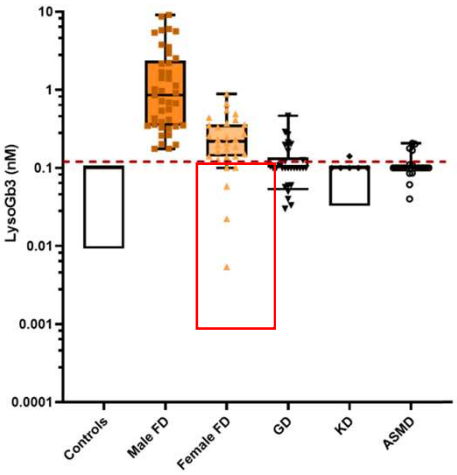
In a same family LysoGb3 values **are lower in females** than males

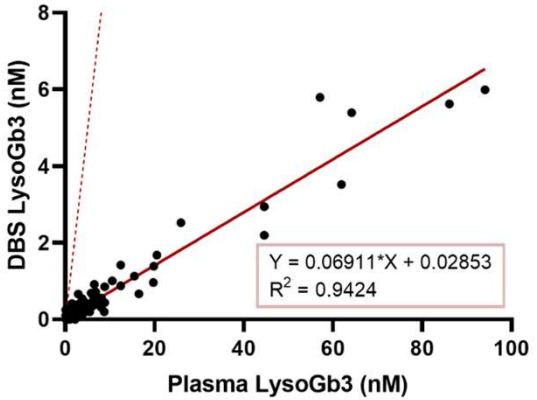
Fabry disease (X-linked)

LysoGb3 in dried blood spots (DBS): correlated but less sensitive than in plasma



A. Nowak et al. Molecular Genetics and Metabolism 121 (2017) 320–324





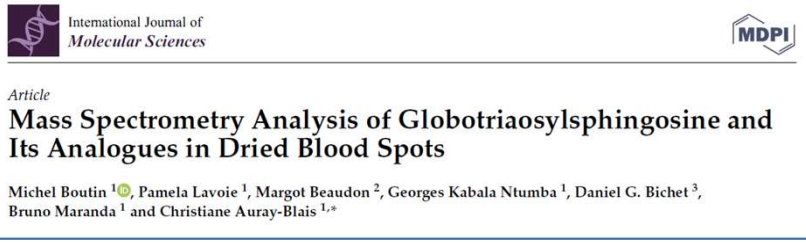
Results LYON, France
Unpublished data

Fabry patients
N=41 males
N=30 females
Controls N=265

- Values in DBS were well correlated with paired plasma (R^2 =0.94)
- All male FD values were elevated
- but 5/30 female FD values were under the cut-off in DBS, vs only 3/30 in plasma

=> DBS LESS SENSITIVE THAN PLASMA

In good accordance with literature
(Polo et al 2019 (1))


International Journal of *Molecular Sciences*

MDPI

Article

Mass Spectrometry Analysis of Globotriaosylsphingosine and Its Analogues in Dried Blood Spots

Michel Boutin [1], Pamela Lavoie [1], Margot Beaudon [2], Georges Kabala Ntumba [1], Daniel G. Bichet [3], Bruno Maranda [1] and Christiane Auray-Blais [1,*]

Boutin et al Int. J. Mol. Sci. 2023, 24, 3223.

(1) Polo et al Clin Chem Lab Med 2019

Fabry disease (X-linked)

LysoGb3: Treatment follow-up

Enzyme Replacement Therapy

EARLY-TREATMENT
Treatment started before the age of 25y in males

LATE-TREATMENT
Treatment started after the age of 25y in males

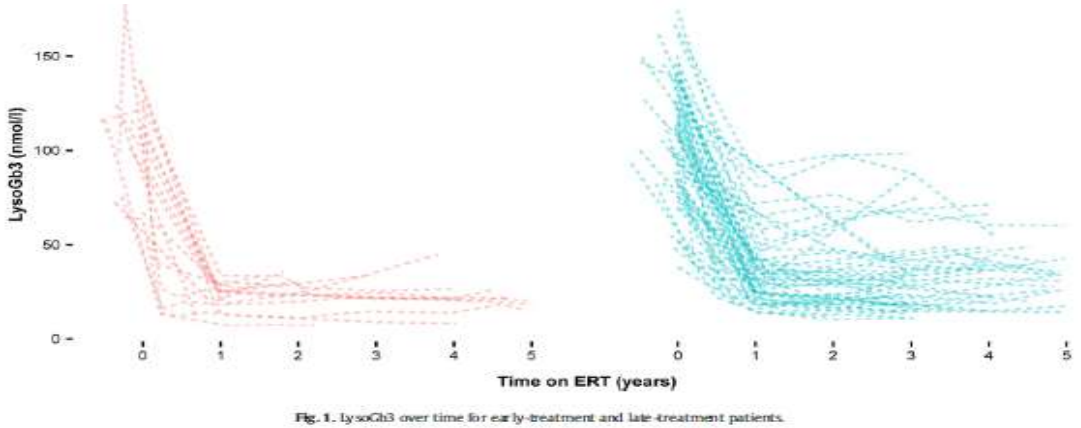
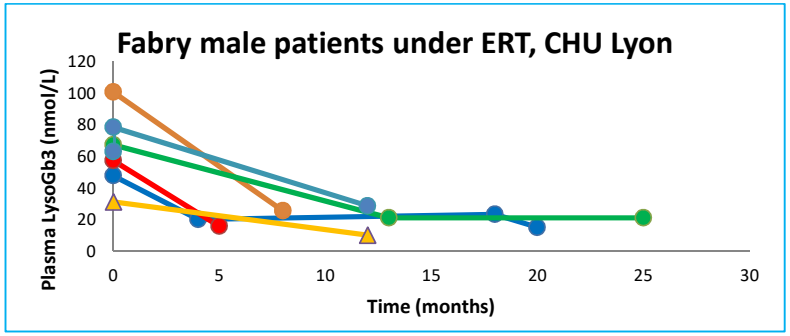


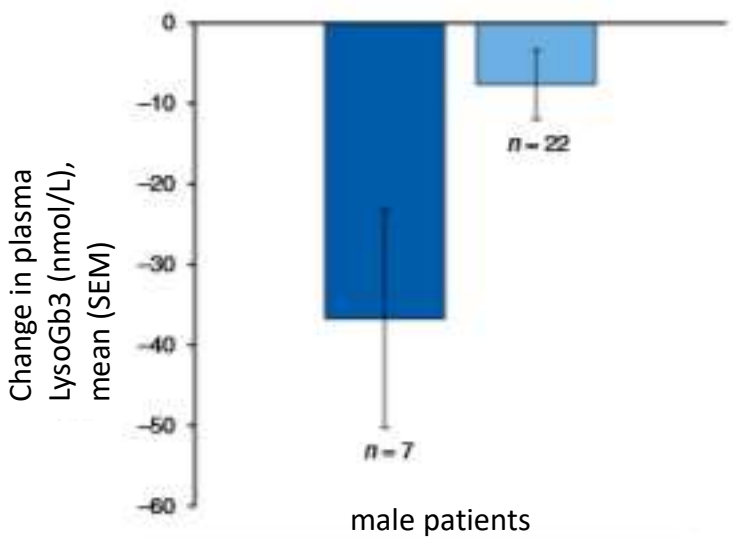
Fig. 1. lysoGb3 over time for early-treatment and late-treatment patients.

Arends et al. Molecular Genetics and Metabolism 2017



Results LYON, France
Unpublished data

Pharmacologic Chaperone Migalastat



male patients

Baseline values	Lyso-GB3	
	Classic	Other patients
n	7	24
Mean (SD)	99.8 (35.3)	29.3 (48.3)

Germain et al. Genet Med. 2019

Fabry disease (X-linked)

LysoGb3: utility of lyso-Gb3 as a biomarker to monitor treatment response ?

However, its usefulness in monitoring the effectiveness of the treatment is debated within the literature[1, 2, 3, 4].

frontiers | Frontiers in Medicine

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Bichet DG, Hopkin RJ, Aguiar P, Allam SR,

Consensus recommendations for the treatment and management of patients with Fabry disease on migalastat: a modified Delphi study

Daniel G. Bichet[1], Robert J. Hopkin[2], Patrício Aguiar[3,4], Sridhar R. Allam[5,6], Yin-Hsiu Chien[7,8], Roberto Giugliani[9,10], Staci Kallish[11], Sabina Kineen[12], Olivier Lidove[13,14], Dau-Ming Niu[15,16], Iacopo Olivotto[17], Juan Politei[18], Paul Rakoski[12], Roser Torra[19], Camilla Tøndel[20,21] and Derralynn A. Hughes[22]*

"Although plasma lyso-Gb3 has been shown to **decrease or stabilize** in patients receiving treatment with ERT and migalastat, several studies demonstrated that **neither lyso-Gb3 concentration nor rate of change predicts the risk of Fabry-associated clinical events** in either ERT-or migalastat-treated patients [2, 3].

Additionally, the **exact mechanism** by which substrate accumulation acts in Fabry disease **is not completely understood** [2,6]."

1. Arends M, et al J Am Soc Nephrol. (2017) 28:1631–41.
2. Bichet DG, et al Genet Med. (2021) 23:192–201.
3. Arends M, et al PLoS One. (2017) 12:e0182379.
4. Nowak A, et al J Med Genet. (2022) 59:287–93.
6. Rozenfeld et al. Mol Genet Metab. (2017) 122:19–27.

Fabry disease (X-linked)

LysoGb3: role in pathophysiology

LysoGb3

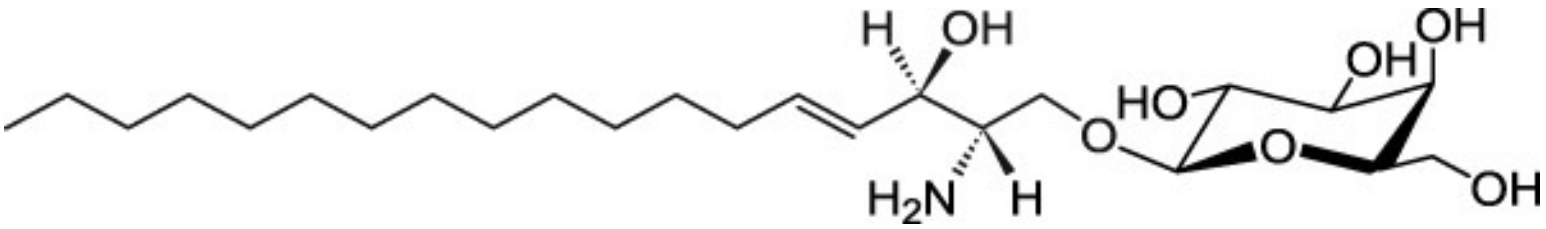
Correlated to the disease severity
Smid BE et al. J Med Genet 2015

Activates a **signaling pathway causing podocyte damage**
Sanchez-Nino et al Hum Mol Genet 2015

Risk factor **of ventricular hypertrophy** in female
Rombach SM et al. Biochim Biophys acta 2010

Risk factor for white matter lesions in male
Rombach et al. Biochim Biophys acta 2010

Activation **of calcium channels in sensory neurons**
Choi et al Nerosci Lett 2015



Lysoglucosylceramide (LysoGb1): biomarker of Gaucher disease

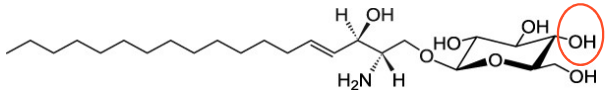
LysoGb1

Glucosylsphingosine

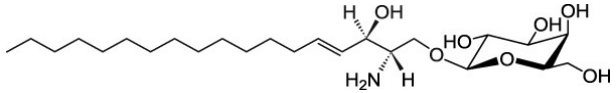
Lysoglucosylceramide

LysoGl1

LysoHexosylceramide



LysoGalactosylceramide (Psychosine)



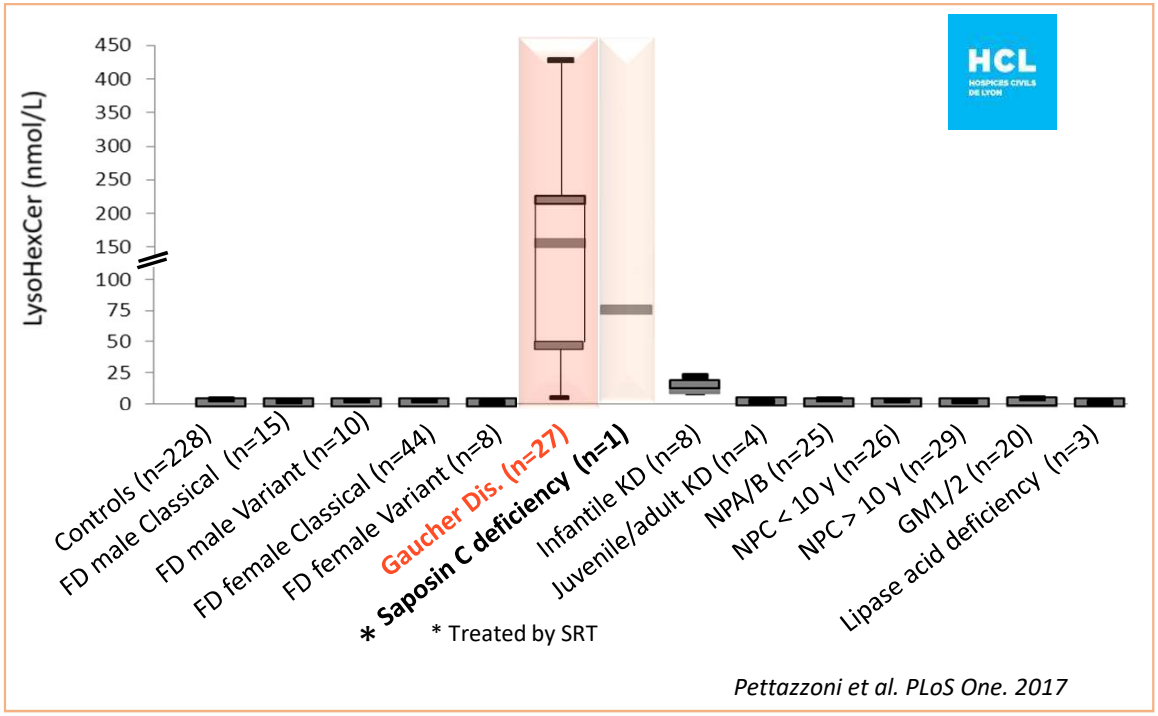
LysoGlucosylceramide

isomeric compounds

Psychosine < 3% of LysoHerCer in controls
Chuang et al, clin chim acta 2019

Gaucher disease

LysoHexCer (LysoGb1): the most specific and sensitive biomarker for the diagnosis than chitotriosidase or CCL18



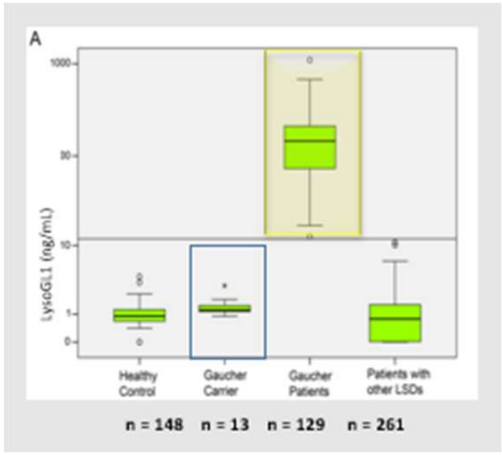
Pettazzoni et al. PLoS One. 2017

- **Sensitive:** Highly elevated in Gaucher, large range of values, sometimes very moderately
- Elevated in case of **saposin C deficiency** (Dekker et al 2001, Motta et al 2016, Pettazzoni et al 2017), **LIMP2 deficiency (**Dubot P et al 2022 Jan;94:124-126)
- **Specific:** Not elevated in other LSD, in carriers (Pettazzoni et al 2017, Dekker et al, 2001, *Rolfs et al. PLoS One 2013)* with or without Parkinson disease (*Dinur et al* Int. J. Mol. Sci. 2022)

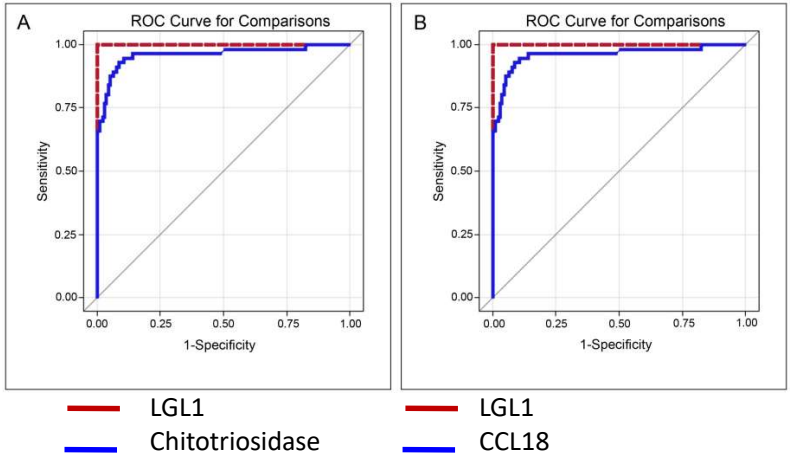
e-Blood

Elevated plasma glucosylsphingosine in Gaucher disease: relation to phenotype, storage cell markers, and therapeutic response

Nick Dekker,[1] Laura van Dussen,[2] Carla E. M. Hollak,[2] Herman Overkleeft,[3] Saskia Scheij,[1] Karen Ghauharali,[1] Mariëlle J. van Breemen,[1] Maria J. Ferraz,[1] Johanna E. M. Groener,[1] Mario Maas,[4] Frits A. Wijburg,[5] Dave Speijer,[1] Anna Tylki-Szymanska,[6] Pramod K. Mistry,[7] Rolf G. Boot,[1] and Johannes M. Aerts[1]

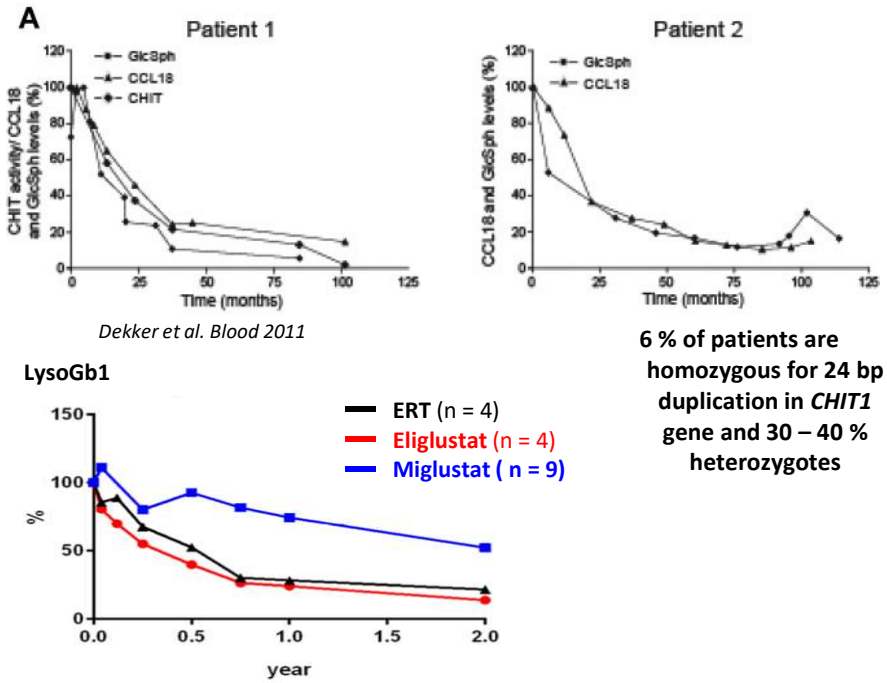


Rolfs et al. PLoS One 2013



Gaucher disease

Reliable response biomarker (ERT or SRT)

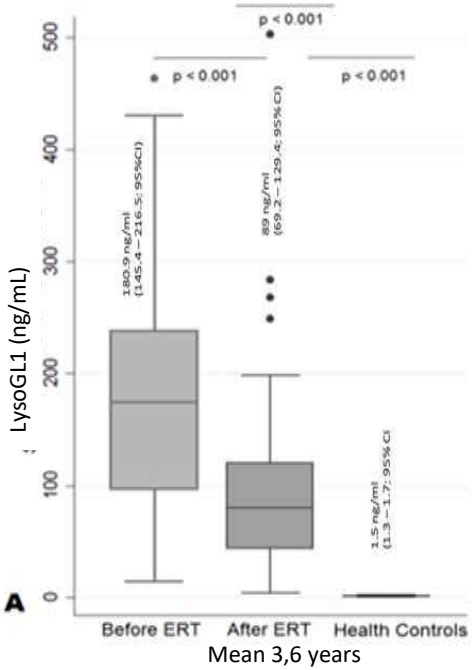


Dekker et al. Blood 2011

6 % of patients are homozygous for 24 bp duplication in *CHIT1* gene and 30 – 40 % heterozygotes

Smid et al. Orphanet J Rare Dis 2016

Decreases under treatment
Correlation with chitotriosidase and CCL18
(= indirect and non specific biomarkers)



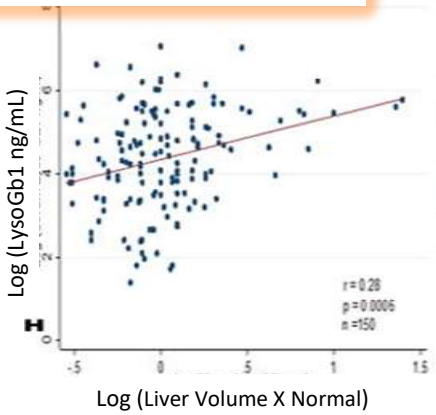
Murugesan et al. Am J Hematol 2016

LGL1 levels decrease after
Enzyme Replacement Therapy (ERT)

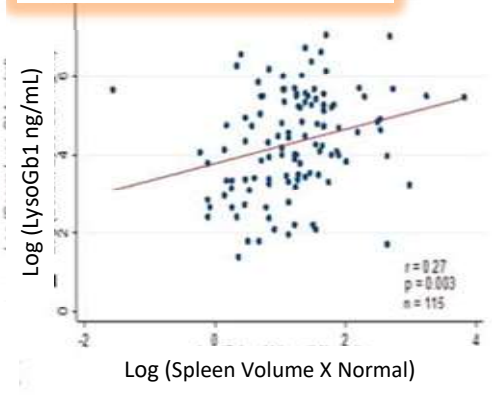
Gaucher disease

LysoGb1: correlated with visceral and haematological parameters (1-3)

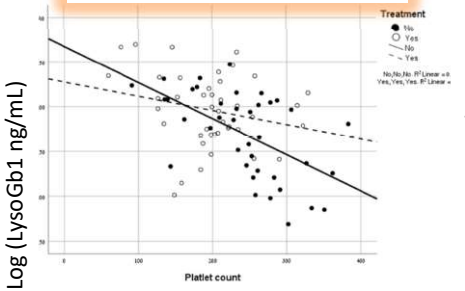
Liver volume



Spleen volume



Platelets count



Hemoglobin level

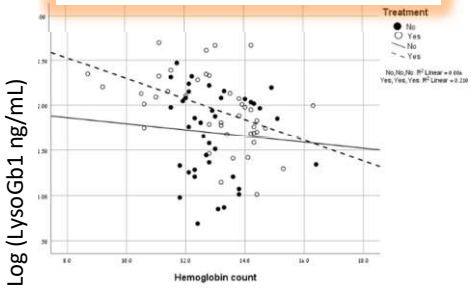
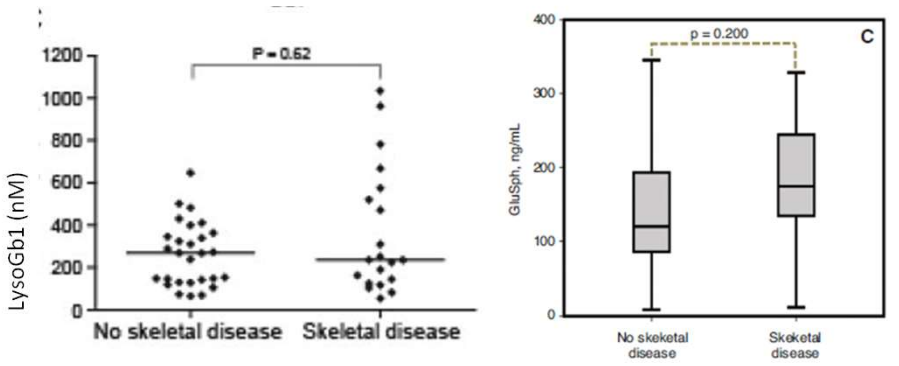


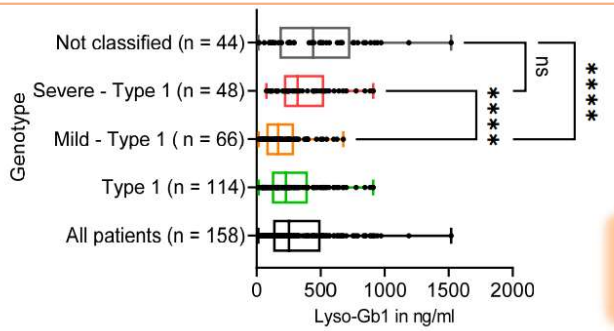
Figure 1. (**A**) Correlation analysis between lyso-Gb1 levels and the platelet count in treated (hollow dots, dotted line) and untreated children (full dots, continuous line). (**B**) Correlation analysis between lyso-Gb1 levels and the hemoglobin level in treated (hollow dots, dotted line) and untreated children (full dots, continuous line).

NOT correlated with skeletal disease (1, 7)



But decreased levels of LysoGb1 correlated with decreased probability of avascular osteonecrosis (4)

LysoGb1: correlated with SEVERITY in pediatric, and adult population (5,6)

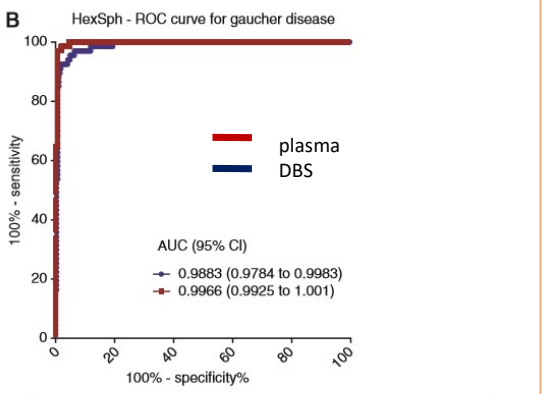


Adults GD type I - LysoPROOF study

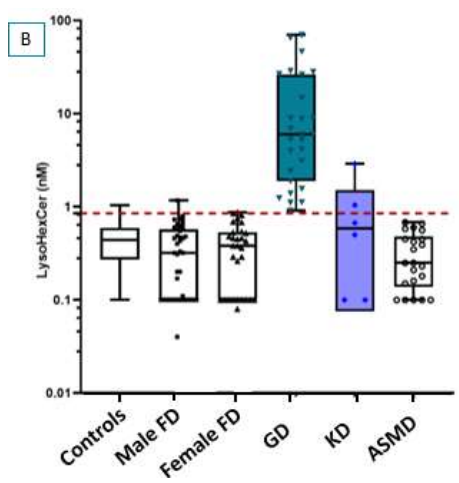
(1) Dekker et al. Blood 2011 (2) Murugesan et al. Am J Hematol 2016 (3) Hurvitz et al. Int J Mol Sci 2019 (4)Basiri et al. Elife 2023 (5) Hurvitz et al. Int J Mol Sci 2019 (6) Curado et al Diagnostics 2023 (7) Irún et al, Clin Chem Lab Med 2020

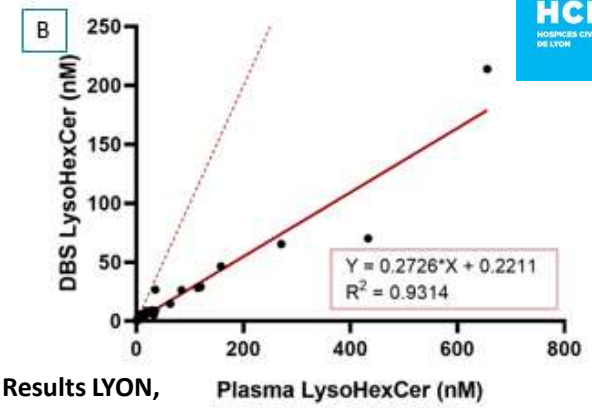
Gaucher disease

LysoGb1 in Dried blood spots: good correlation with plasma but less sensitive



Less sensitive than plasma





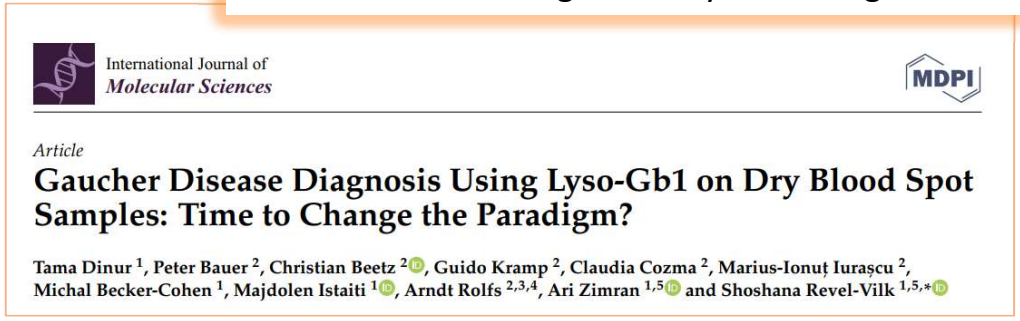
Results LYON, France
Unpublished data

All GD patients had elevation of LysoGb1 in DBS (n=30)

Correlated with paired plasma (R^2=0.93)

Polo et al Clin Chem Lab Med 2019

LysoGb1 in DBS: First tier analysis for diagnosis
Combined with *GBA* gene analysis for diagnosis confirmation



International Journal of *Molecular Sciences*

MDPI

Article

Gaucher Disease Diagnosis Using Lyso-Gb1 on Dry Blood Spot Samples: Time to Change the Paradigm?

Tama Dinur [1], Peter Bauer [2], Christian Beetz [2], Guido Kramp [2], Claudia Cozma [2], Marius-Ionuț Iurașcu [2], Michal Becker-Cohen [1], Majdolen Istaiti [1], Arndt Rolfs [2,3,4], Ari Zimran [1,5] and Shoshana Revel-Vilk [1,5,*]

Dinur et al. Int J Mol Sci. 2022

Gaucher disease

LysoGb1 levels in plasma as a treatment decision criteria

International Journal of *Molecular Sciences*

MDPI

Article

Contribution of Glucosylsphingosine (Lyso-Gb1) to Treatment Decisions in Patients with Gaucher Disease

Tama Dinur [1], Peter Bauer [2], Christian Beetz [2], Claudia Cozma [2], Michal Becker-Cohen [1], Majdolen Istaiti [1], Arndt Rolfs [2,3,4], Volha Skrahina [2,4], Ari Zimran [1,5] and Shoshana Revel-Vilk [1,5,*]

Table 4. Suggested updated criteria for initiation of Gaucher disease-specific treatment.

Israeli Ministry of Health Criteria for Imiglucerase, 1998 [28]	Suggested Updated Criteria for ERT/SRT
• A family history in a sibling with a rapid acceleration in the course of the disease.	When symptomatic or **high lyso-Gb1** *
• Age of onset of signs or symptoms of the disease below 5 years of age	Age is not a criterion by itself
• At any age, enlargement of the spleen and liver is accompanied by signs of hypersplenism, abnormal liver function tests, or other complications	Stays as is
• Hypersplenism expressed as serious pancytopenia: hemoglobin below 9 g%, white count below 3000/mm^3, platelet count of 50,000/mm^3 or less, in consecutive blood tests during a three-month approximated	Gaucher-related significant, symptomatic cytopenia and/or bleeding disorder, **irrespective of lyso-Gb1 levels**
• Symptomatic anemia which is not the result of iron deficiency or due to other causes unrelated to Gaucher disease, or thrombocytopenia with a tendency to bleeding, or a consistently decreasing platelet count.	Redundant

Dinur et al Int J Mol Sci 2023

BUT

LysoGb1 intraindividual variability in DBS: a limitation for treatment follow-up ?

biomolecules

MDPI

Communication

Long- and Short-Term Glucosphingosine (lyso-Gb1) Dynamics in Gaucher Patients Undergoing Enzyme Replacement Therapy

Pawel Dubiela [1,2,†], Paulina Szymanska-Rozek [3,†], Piotr Hasinski [4], Patryk Lipinski [5], Grazina Kleinotiene [6], Dorota Giersz [1] and Anna Tylki-Szymanska [7,*]

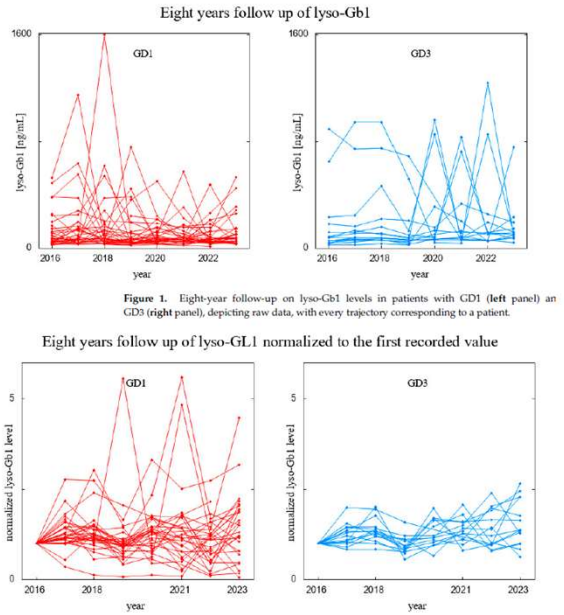
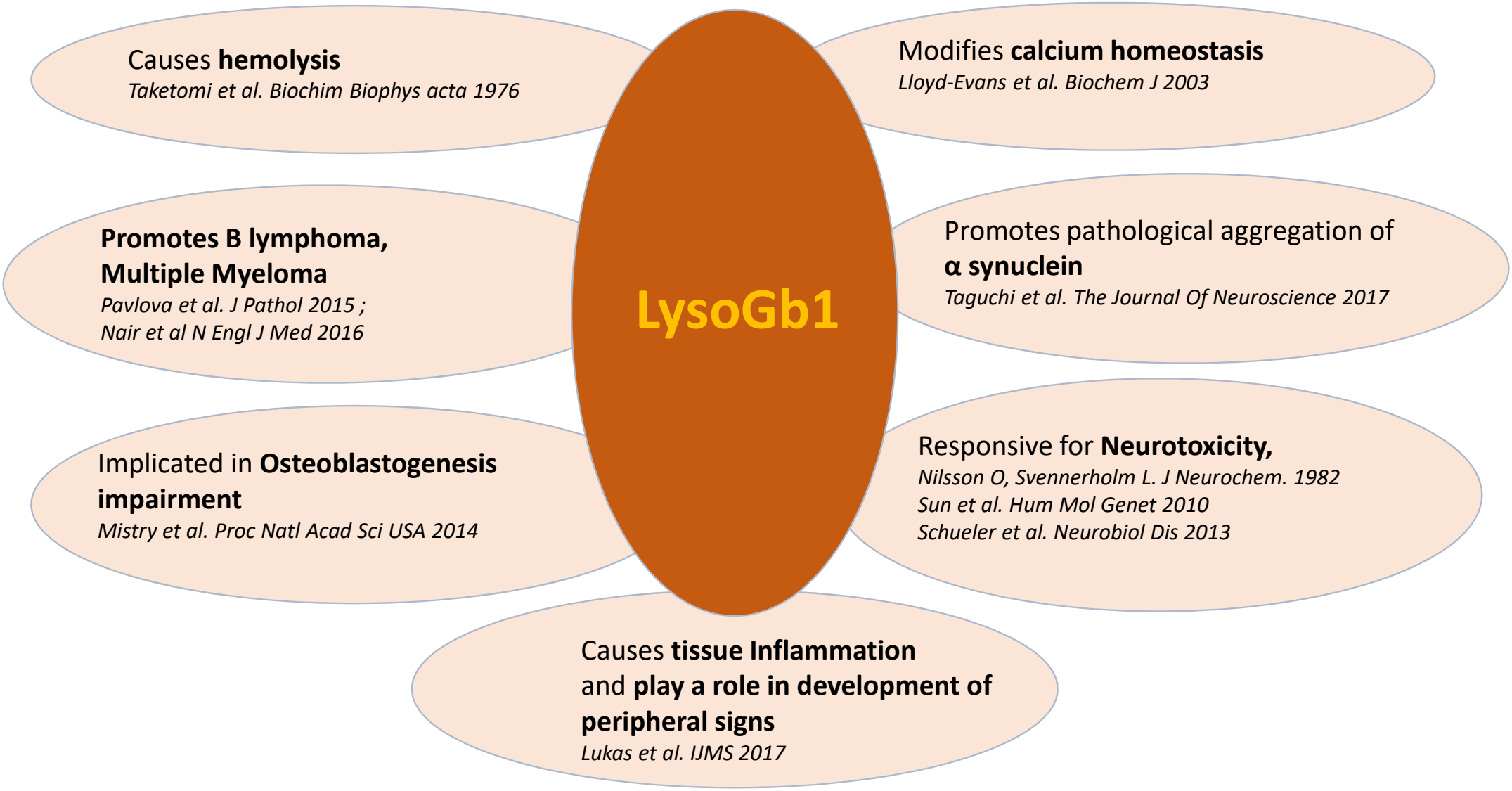
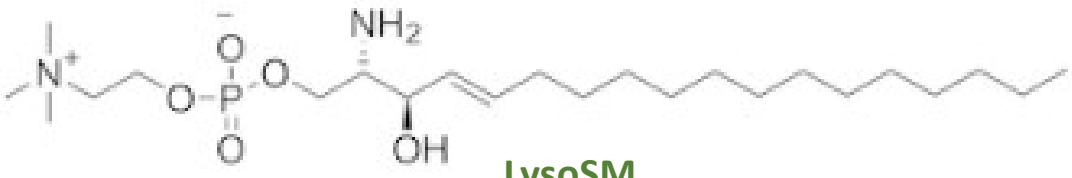


Figure 1. Eight-year follow-up on lyso-Gb1 levels in patients with GD1 (**left** panel) and GD3 (**right** panel), depicting raw data, with every trajectory corresponding to a patient.

Dubiela et al. Biomolecules 2024

Lysoglucosylceramide (LysoGb1): role in pathophysiology





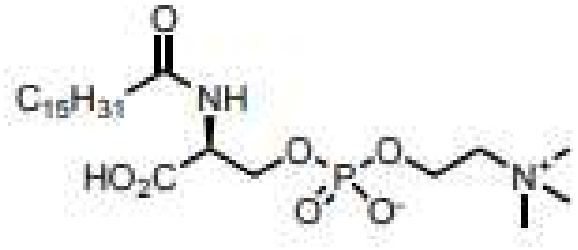
LysoSM

Lysosphingomyelin (LysoSM) and LysoSM509/PPCS: biomarkers of Acid SphingoMyelinase Deficiency (ASMD / Niemann-Pick type A,B or AB)

LysoSM

Sphingosylphosphorylcholine

SPC

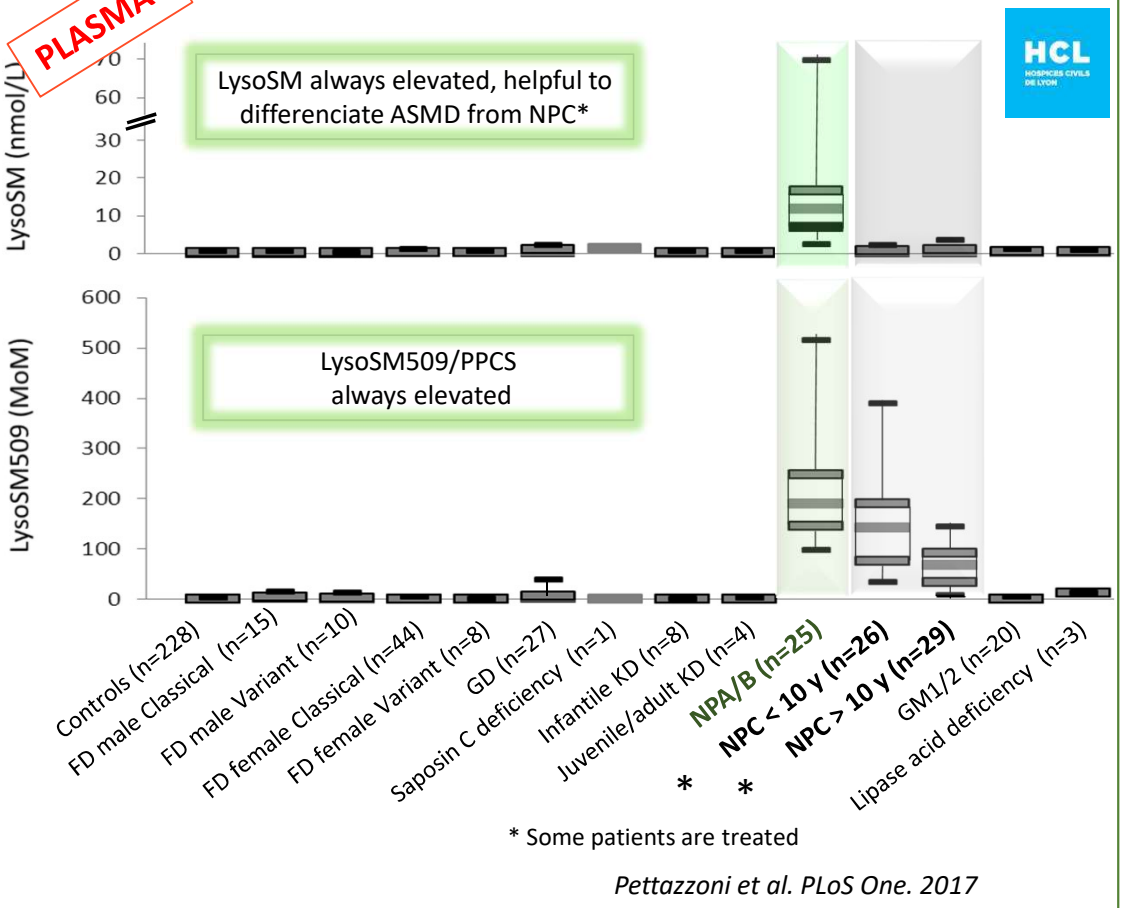


LysoSM509 / N-palmitoyl-O-phosphocholineserine (PPCS)

Acid SphingoMyelinase Deficiency (ASMD – Niemann-Pick A, AB and B)

LysoSM and LysoSM509 increase allows orientation to ASMD

PLASMA

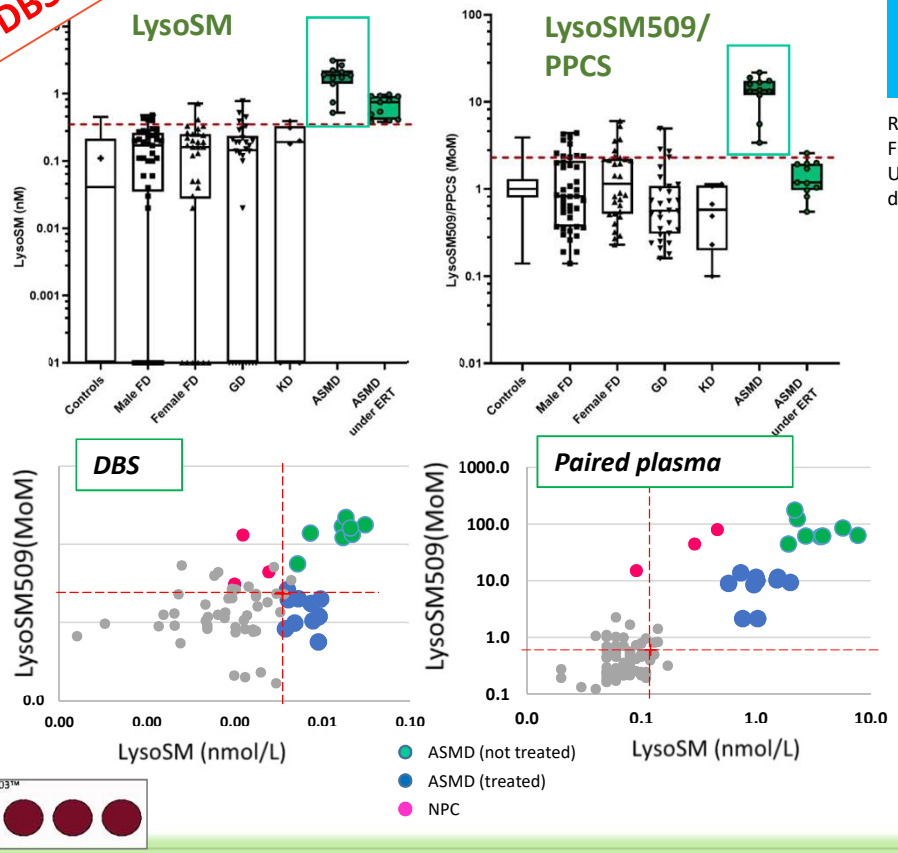


* Some patients are treated

Pettazzoni et al. PLoS One. 2017

*LysoSM very slightly increased in about 30% Niemann-Pick type C (Pettazzoni et al 2017, Welford et al 2016)

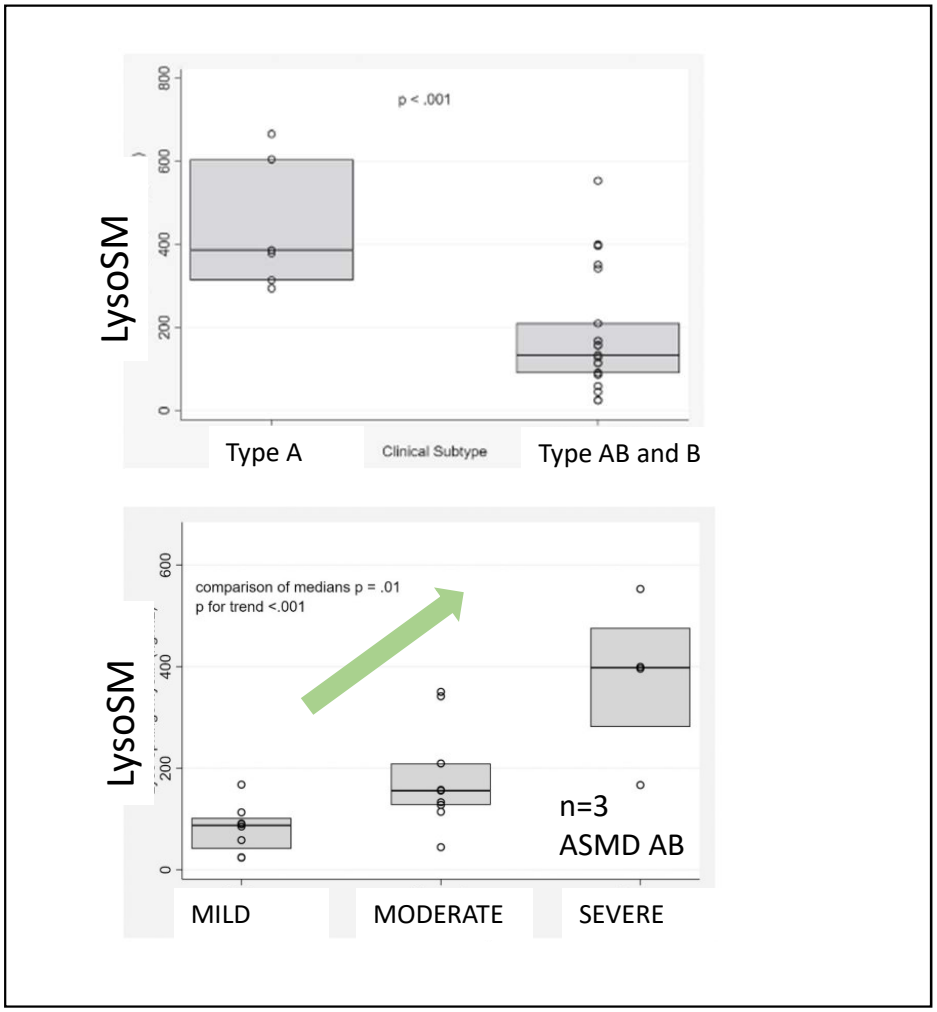
DBS



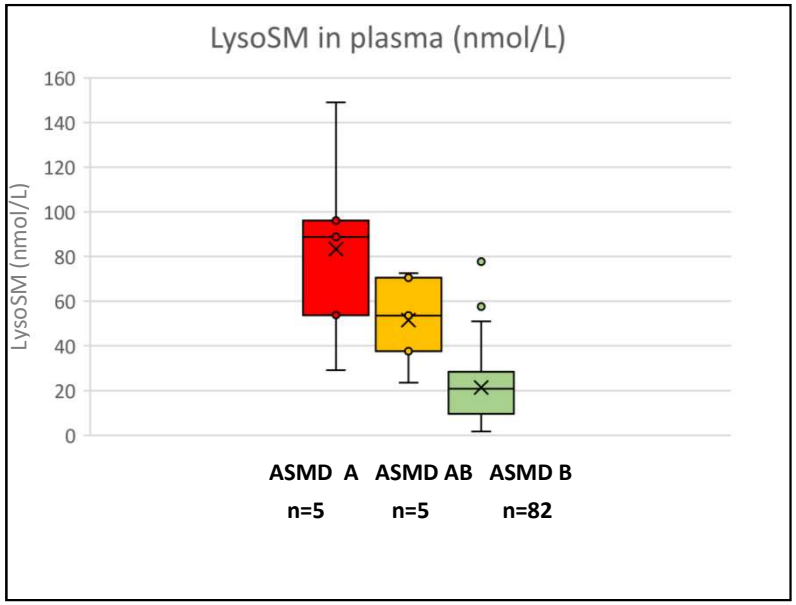
Results LYON, France Unpublished data

Not correlated with plasma (data not shown)
LysoSM and LSM509 **always elevated in untreated ASMD patients** (n=11)
Better discrimination in plasma than DBS between controls and ASMD patients (in good accordance with Polo et al 2019)

LysoSM in plasma correlates with clinical subtype and severity



Breilyn MS. Mol Genet Metab Rep. 2021 Jul 7;28:100780.



Results LYON, France Unpublished data 2018-2024

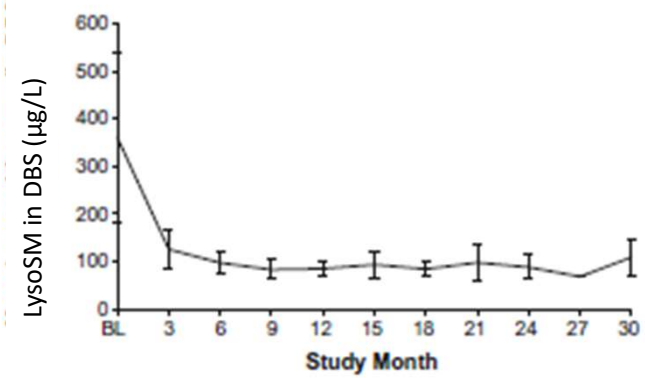
HCL HOSPICES CIVILS DE LYON

All ASMD patients (n=92) have elevated LysoSM in plasma at diagnosis

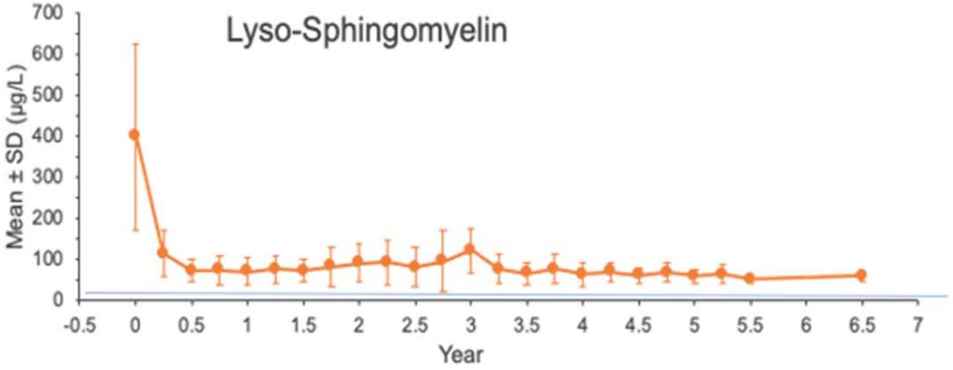
LysoSM higher in type A and AB compared to type B, with an overlap

Acid SphingoMyelinase Deficiency (ASMD – Niemann-Pick A, AB and B)

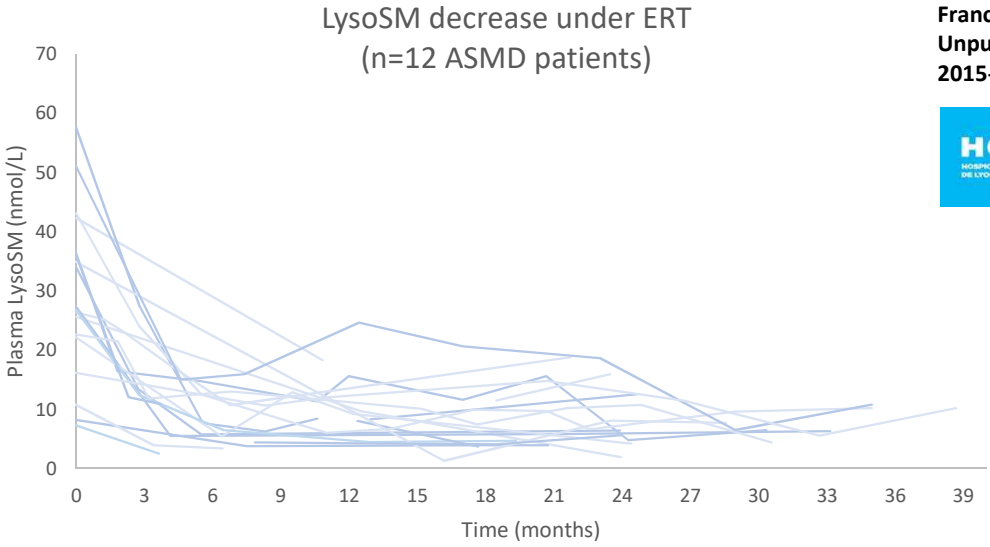
LysoSM as a biomarker of treatment follow-up (ERT)



Wasserstein et al J Inherit Metab Dis. 2018 Sep;41(5):829-838.



Lachmann et al. Orphanet J Rare Dis. 2023 Apr 25;18(1):94.



Results LYON, France
Unpublished data
2015-2024

Conclusion

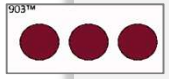
- **Lysosphingolipids multiplex measurement by MSMS in plasma**
  = Efficient and rapid biochemical screening tool

PLASMA

  - ✓ **Useful for diagnosis purpose: Sensitive and Specific biomarkers**
    Better screening of **Fabry females** than alphaGalA activity or urinary Gb3
    But possibly normal screening (Fabry females: variant cases), mild forms ?
  - ✓ **Related with the severity** of the disease
  - ✓ **Differential screening of ASMD, NPC and Gaucher disease** in the same run
  - ✓ Useful for the **monitoring** of patients under treatment (ERT, SRT, Chaperon therapy) and **therapeutic decisions**
  - ✓ **In connection with pathophysiology**

- **Lysosphingolipid measurement in DBS**

DBS



  - ✓ **Second-tier test** after enzymatic studies in the same DBS sample (routin diagnosis or newborn screening programs)
  - ✓ Might be the **first diagnostic step** (Gaucher disease) ***BUT* less sensitive than plasma**:
    Normal values should be interpreted with caution (false negative results in mild clinical forms?)
  - ✓ **Would facilitate the patient follow-up compared to plasma *BUT* great intra-individual variability**
    => More studies are needed, interest of analogues ?

Acknowledgement

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Thank you for your attention !

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