GROUPE HOSPITALIER DIACONESSES CROIX SAINT SIMON

Centre de Référence des Maladies Lysosomales

Fondation Ophtalmologique Adolphe de Rothschild

Fabry disease: the new great imposter

Olivier Lidove, MD;
Wladimir Mauhin, MD, PhD.

olidove@hopital-dcss.org

Service de Médecine Interne-IMIEP
GH Diaconesses-Croix Saint Simon,
125 rue d'Avron, 75020 Paris, France
Centre de Référence Maladies Lysosomales

UMRS 974, UPMC - INSERM

Collège national des Enseignants de Médecine Interne

Inserm

centre de référence maladies rares

ERKNet The European Rare Kidney Disease Reference Network

– December 03, 2019

Disclosure

- Travel grants and speaker honoraria from:
  - Amicus
  - Genzyme/Sanofi
  - Shire HGT

Menu

1 Introduction

2 Fabry disease: the new great imposter

3 Care of patients with Fabry disease in France and in Europe
- 1998-2019: > 20 years of work for Fabry patients

4 Enzyme therapy and chaperone therapy

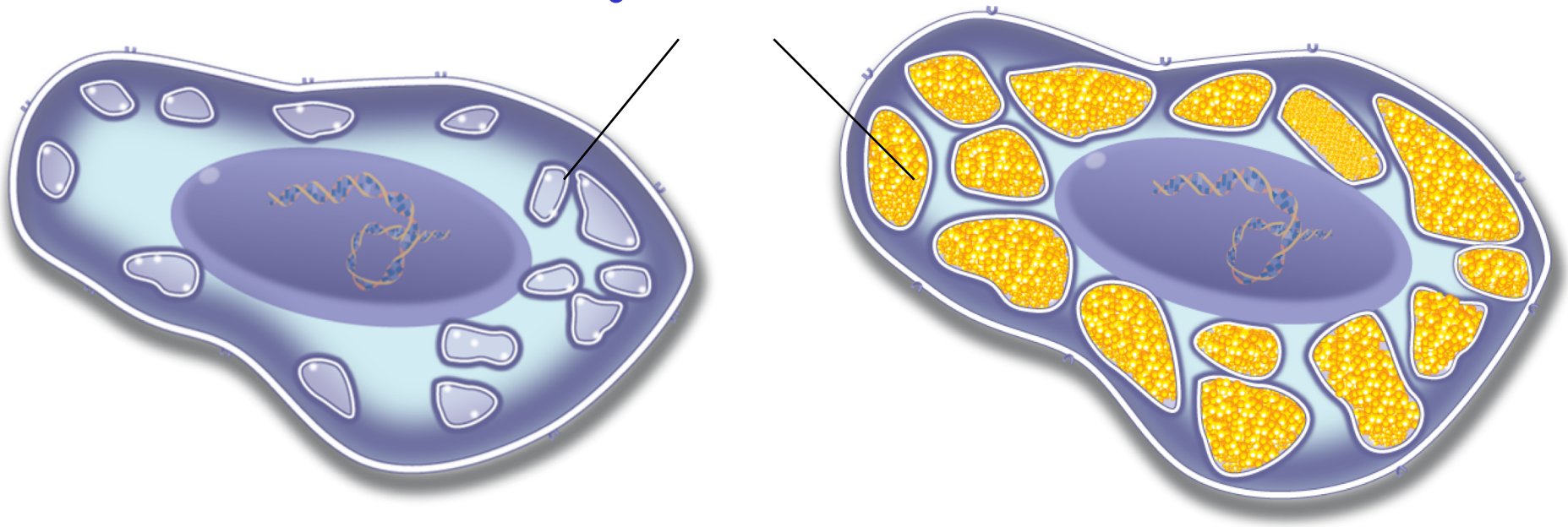
5 Perspectives - Conclusions

6 Acknowledgements

1. Introduction

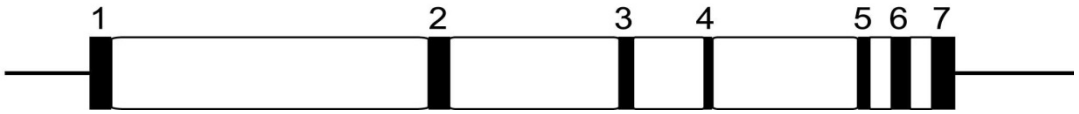
Pathophysiology

Lysosome



No disease ⇨ DISEASE

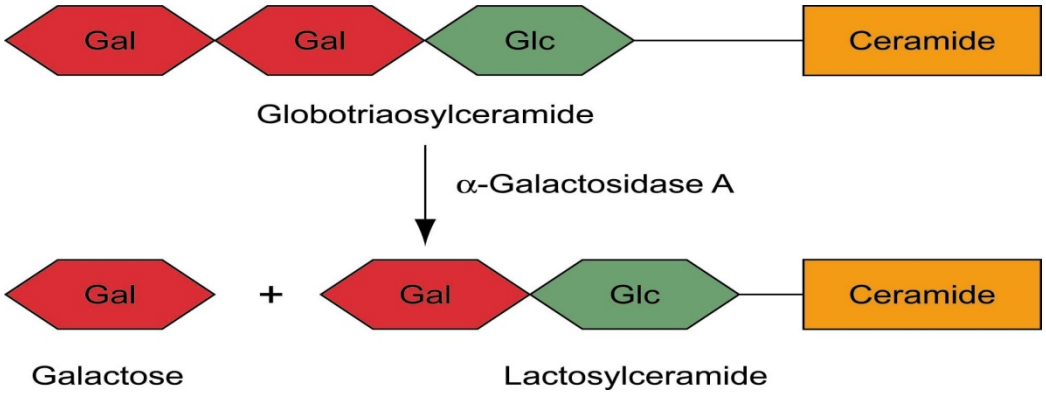
X chromosome



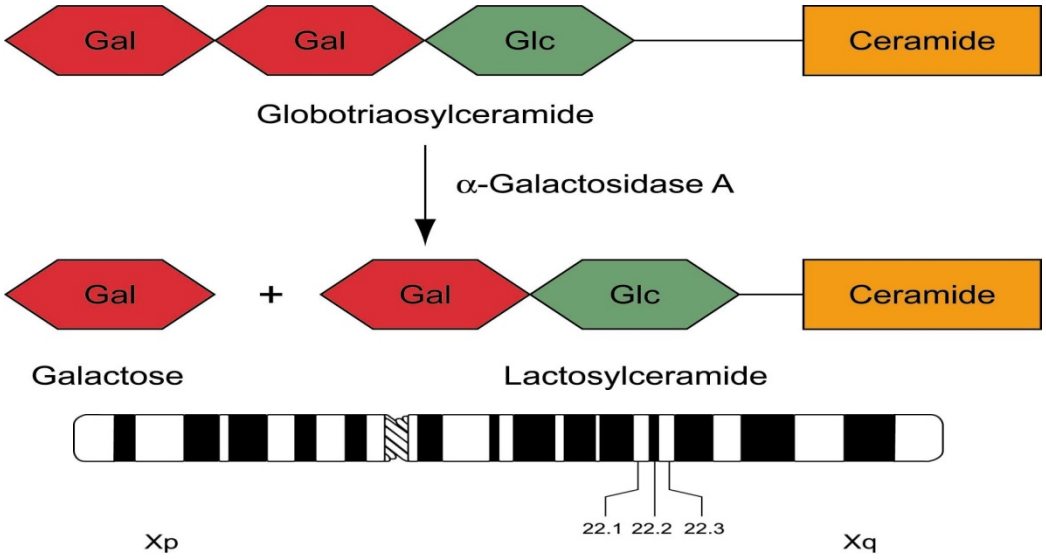
Bishop *et al. Proc Natl Acad Sci USA* 1988; 85: 3903–7.

Definition of Fabry disease?

Fabry?


Gal
Gal
Glc
Ceramide
Globotriaosylceramide
α-Galactosidase A
Gal
+
Gal
Glc
Ceramide
Galactose
Lactosylceramide

Fabry?


Gal
Gal
Glc
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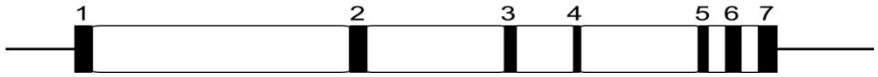
Globotriaosylceramide
α-Galactosidase A
Gal
+
Gal
Glc
Ceramide
Galactose
Lactosylceramide
22.1 22.2 22.3
Xp
Xq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2
3
4
5 6 7

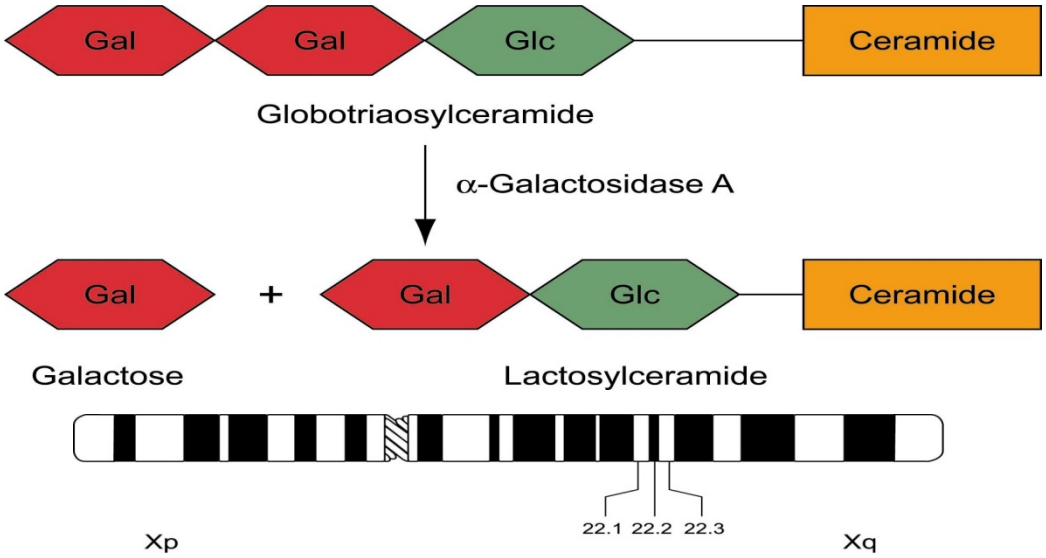
Fabry?

- Nephrology
- Adulthood
- Mutation or sequence variant?

- Kidney biopsy with ultrastructural examination can be useful for diagnosis

Van der Tol L, et al. Mol Genet Metab 2015

Fabry?


Gal
Gal
Glc
Ceramide
Globotriaosylceramide
α-Galactosidase A
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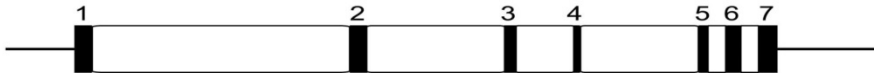
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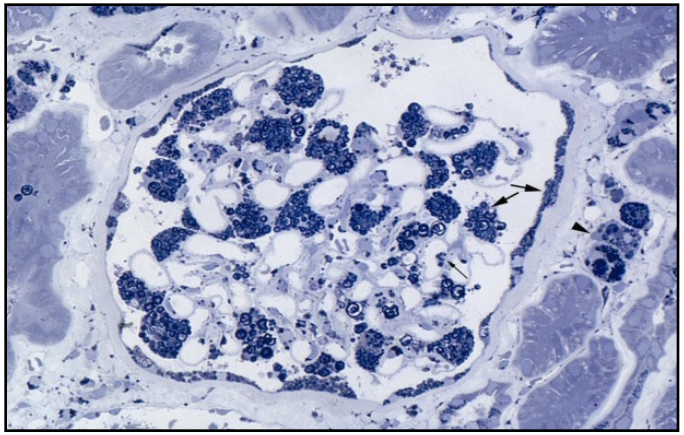
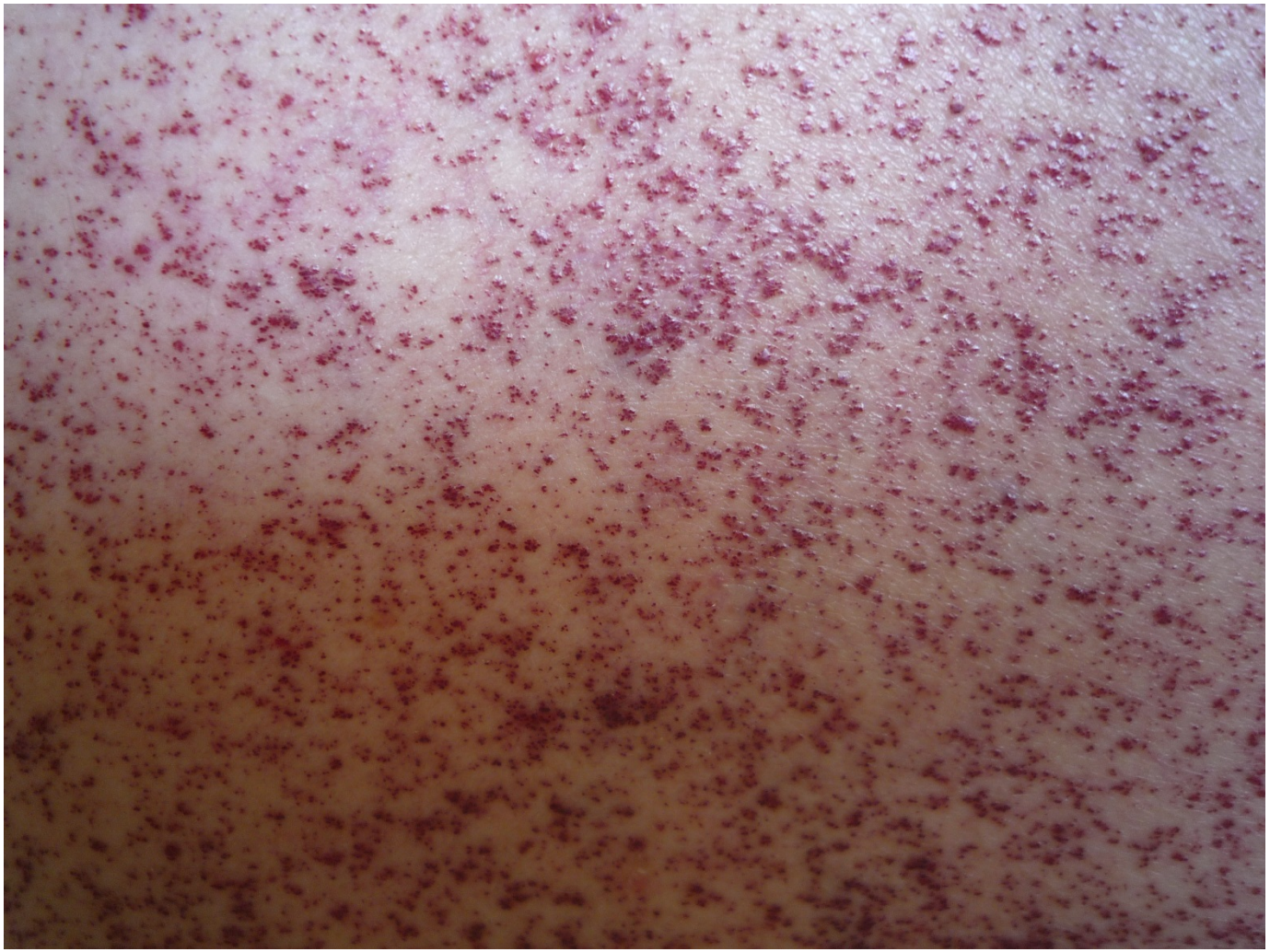


What is the diagnosis ?



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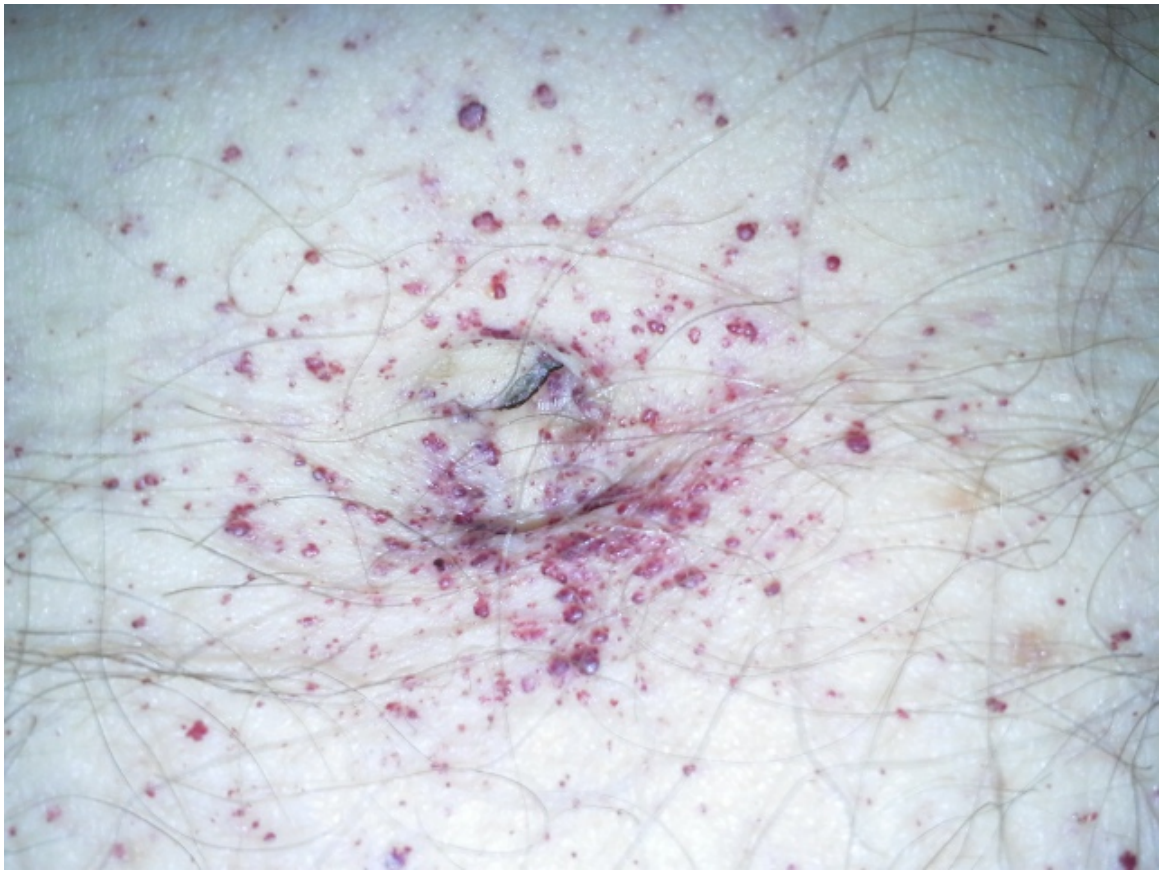
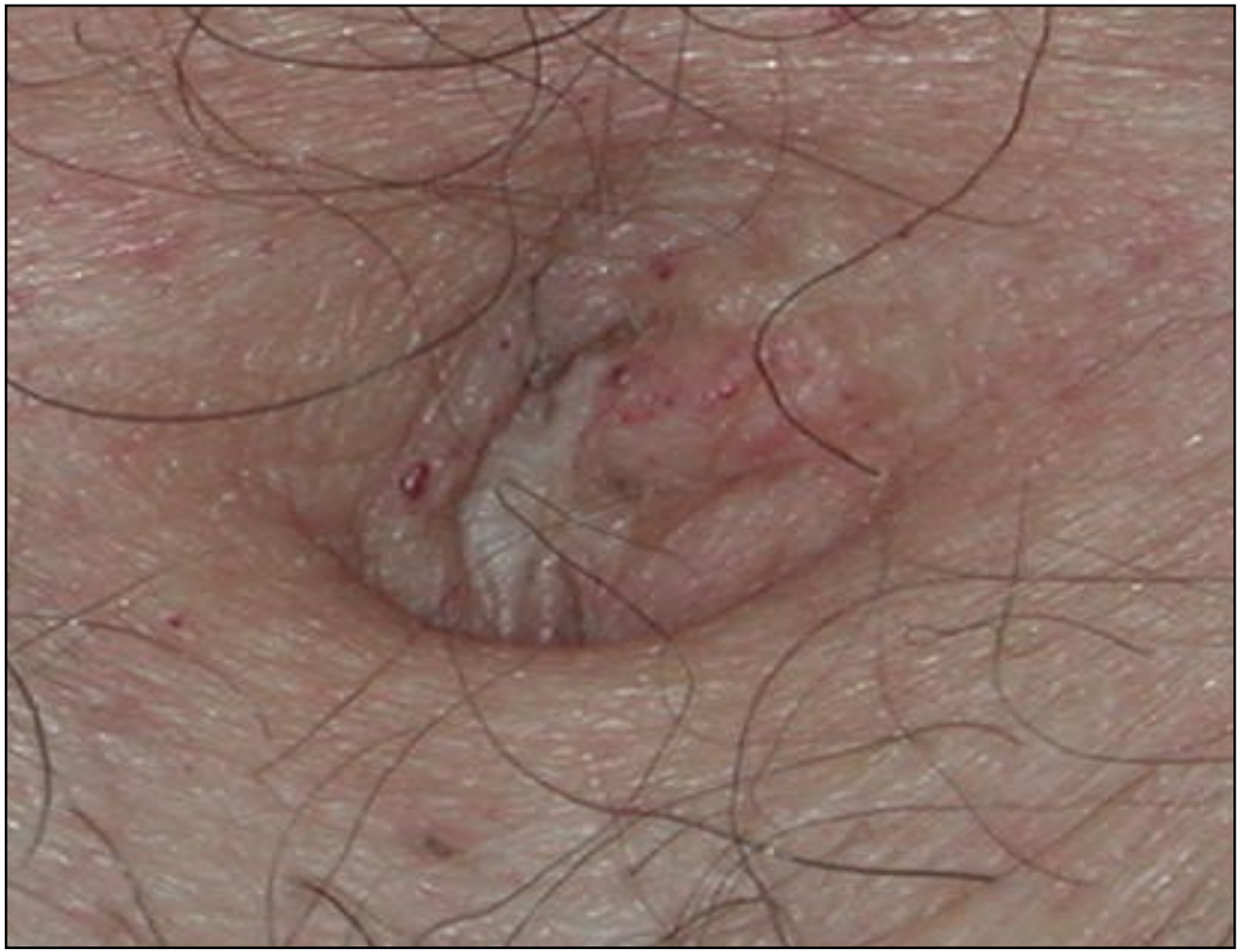
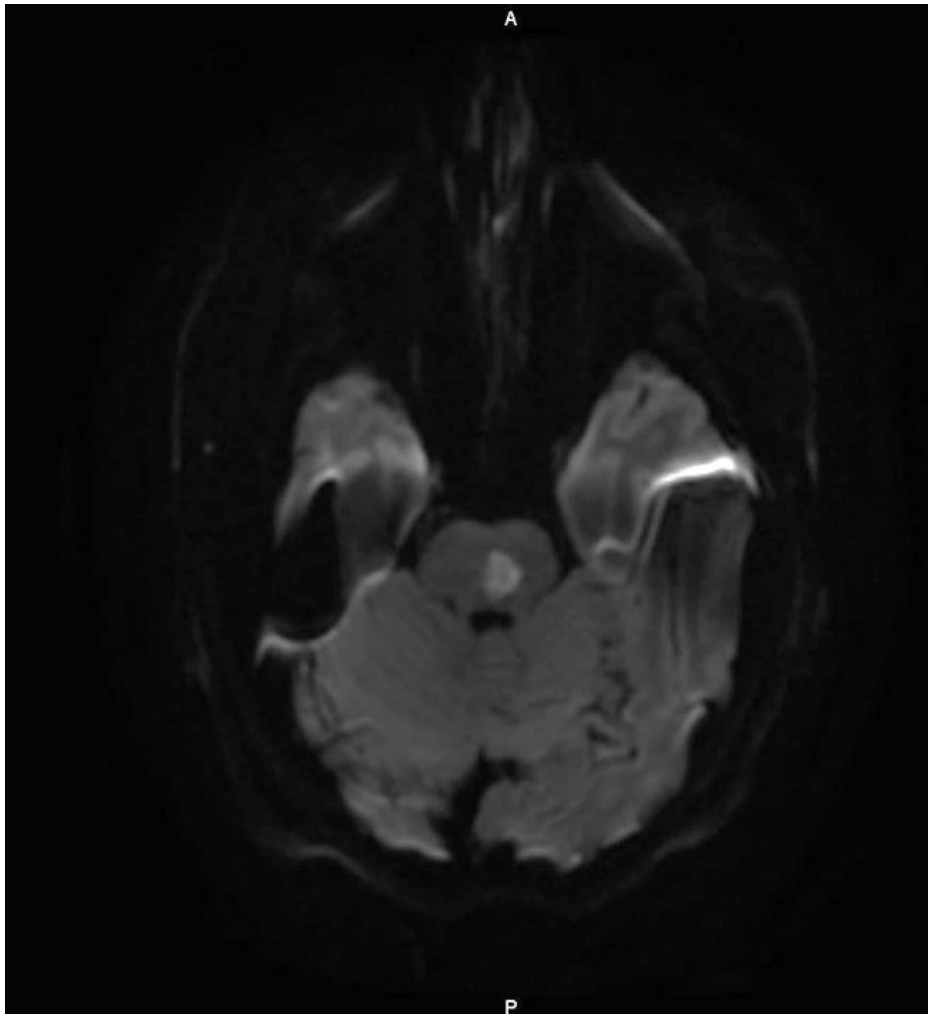


What is the diagnosis ?

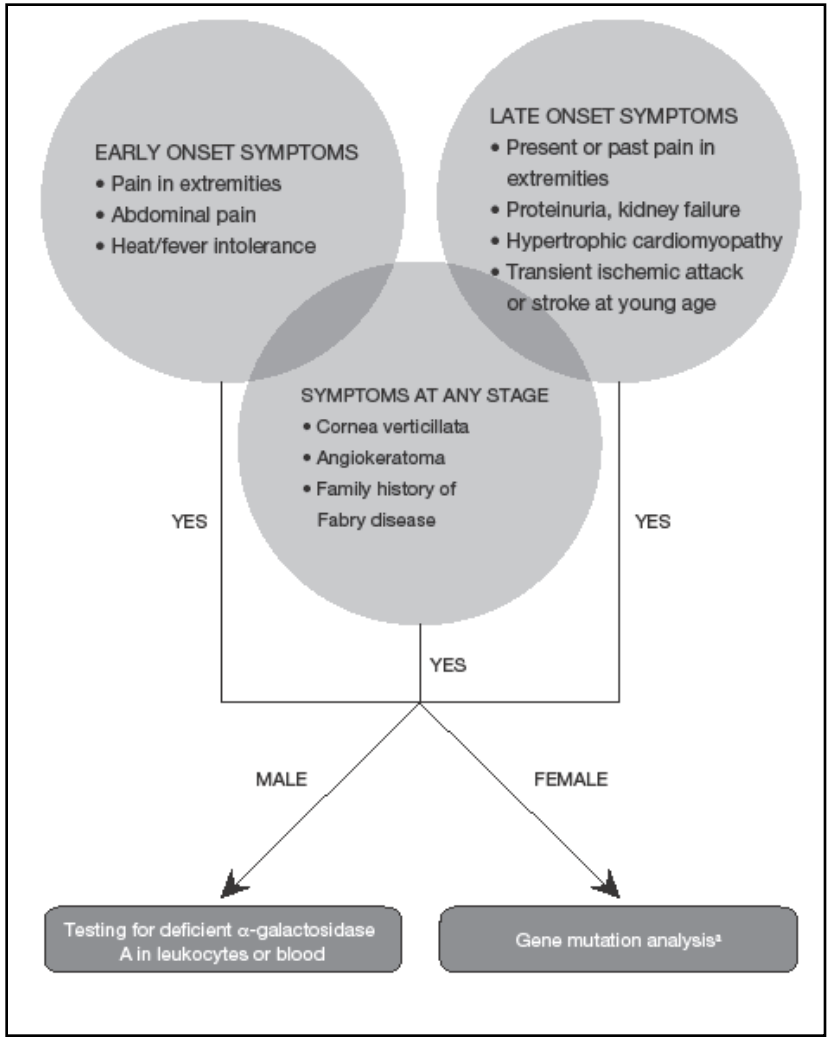


What therapy ?



2. Fabry disease: the new great imposter

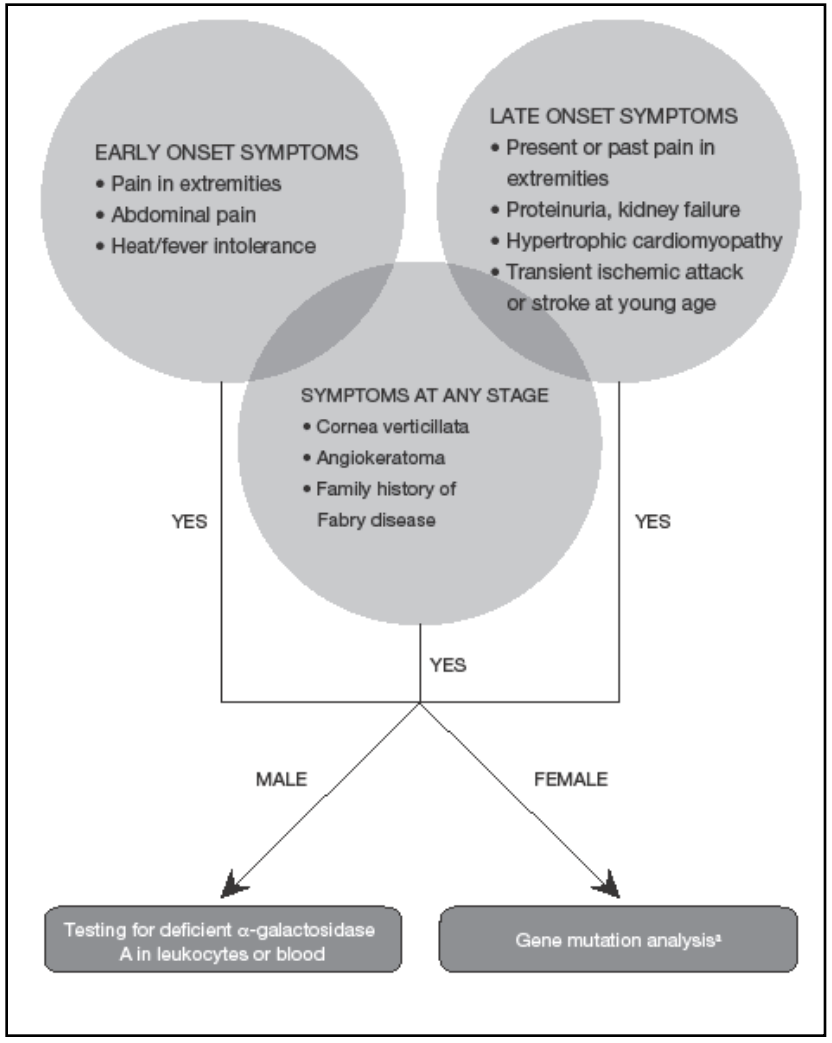
Fabry disease: the « new great imposter »



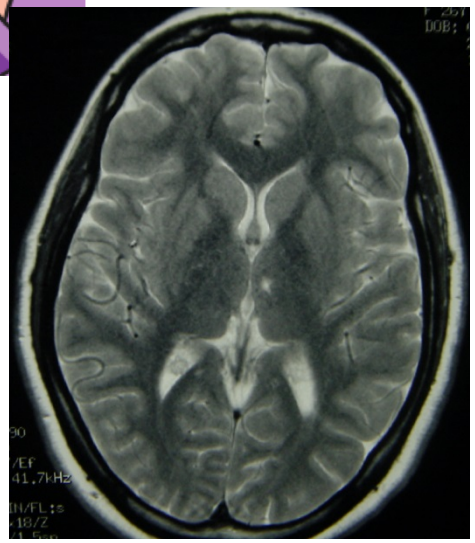
Early Onset

Lidove O, et al. Clin Genet 2012.

Fabry disease: the « new great imposter »

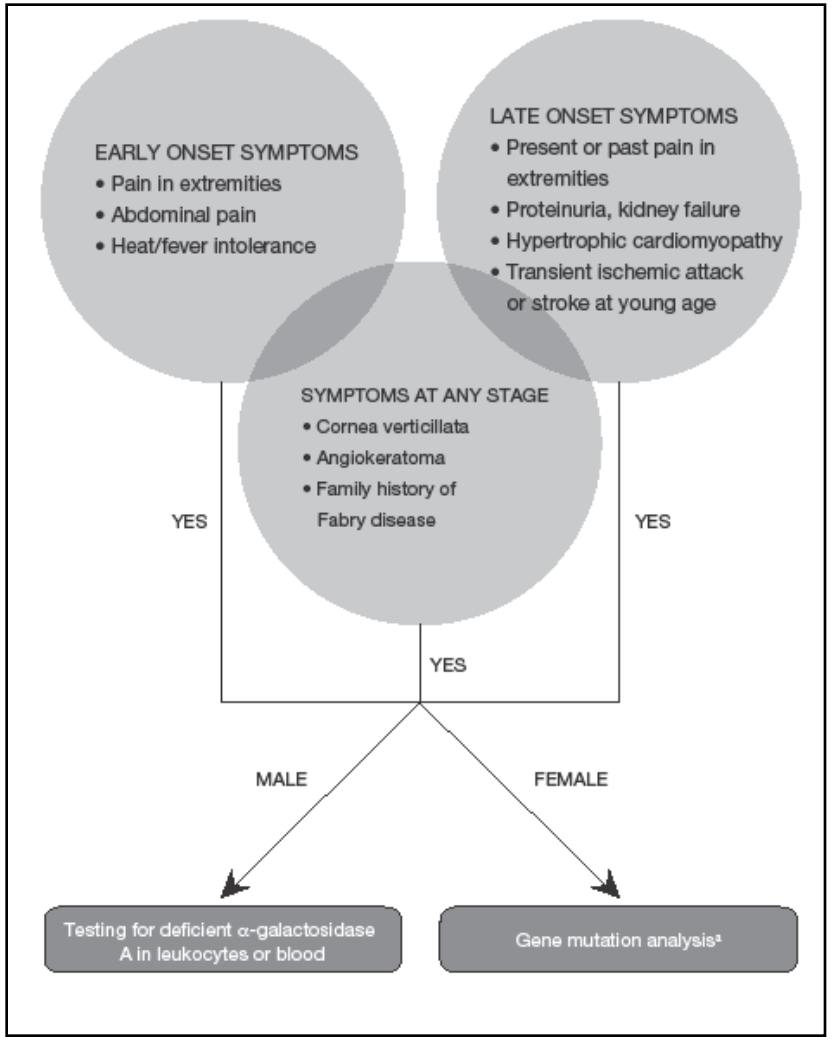


Late Onset

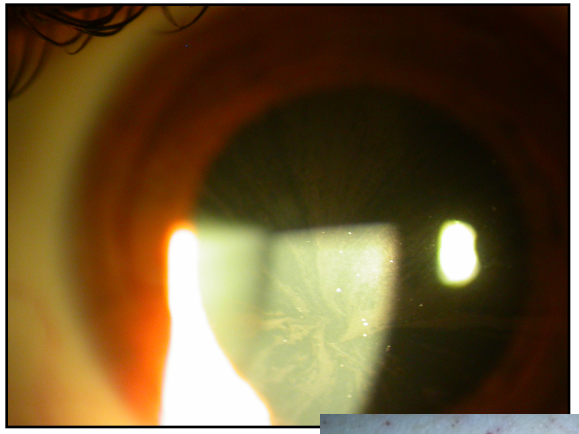


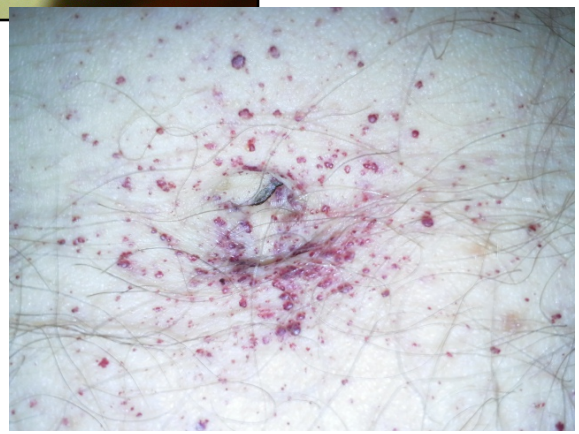
Lidove O, et al. Clin Genet 2012.

Fabry disease: the « new great imposter »



Any Stage





Lidove O, et al. Clin Genet 2012.

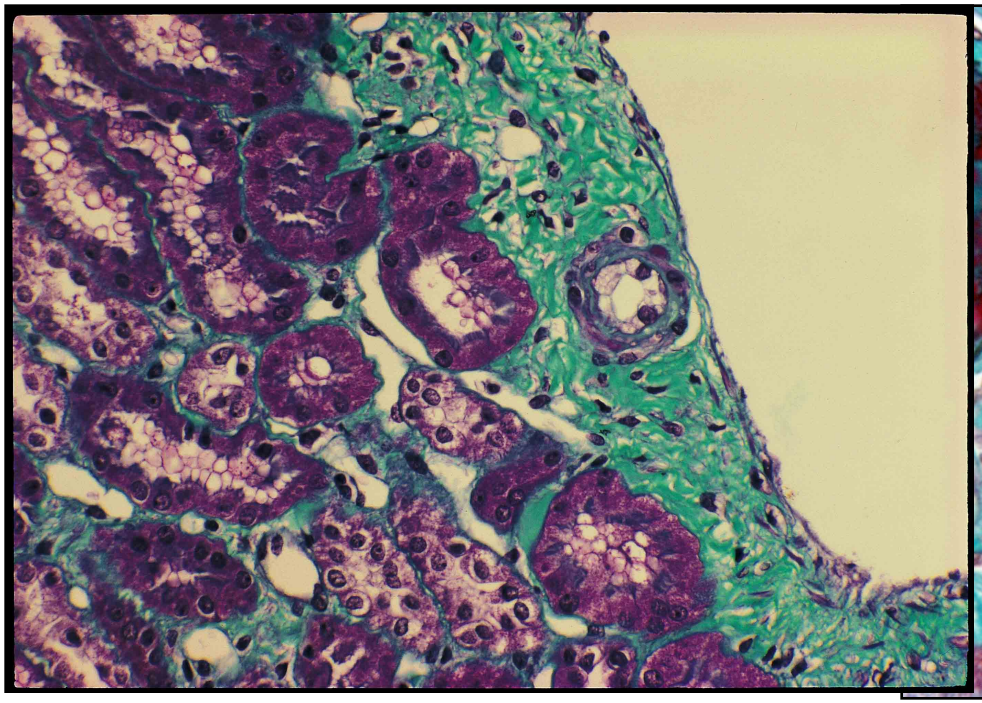
Late Onset Symptoms

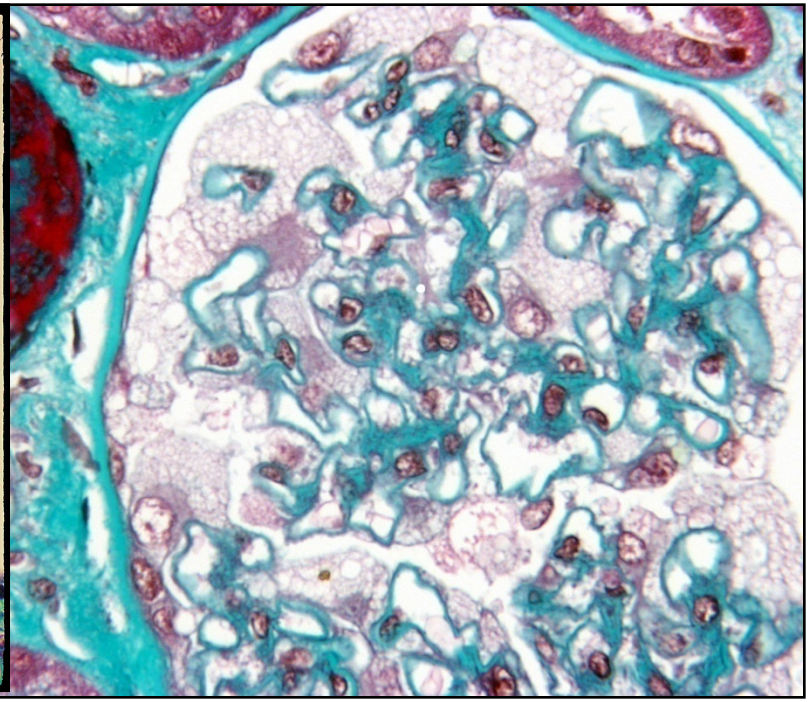
- **Stroke at young age**
- **Kidney involvement**
- **Heart involvement (main cause of death)**
- **Life expectancy: 58 years in males**

Waldek S, et al. Genet Med 2009.

Late Onset Symptoms

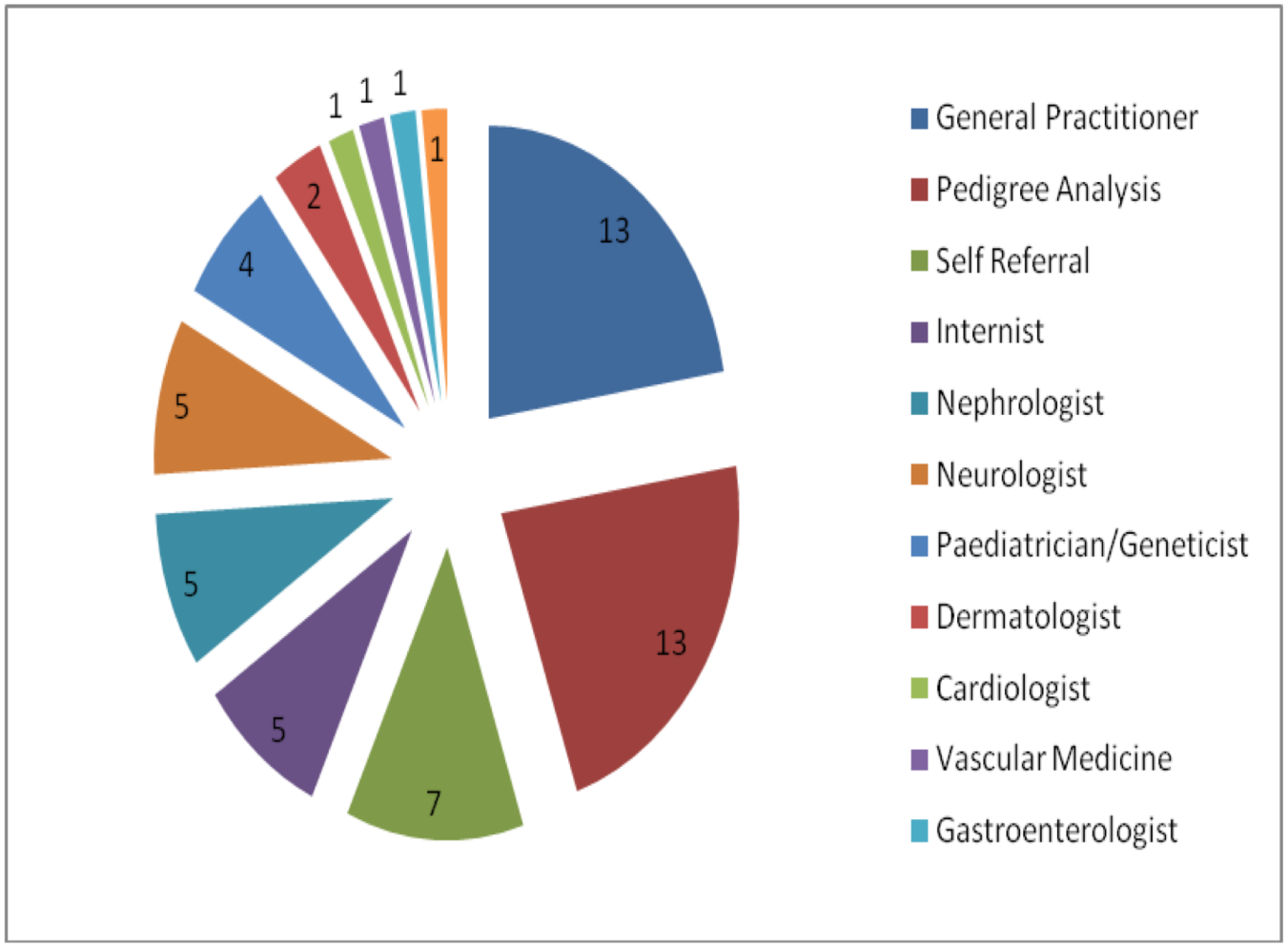
- **Ischemic Nephropathy**



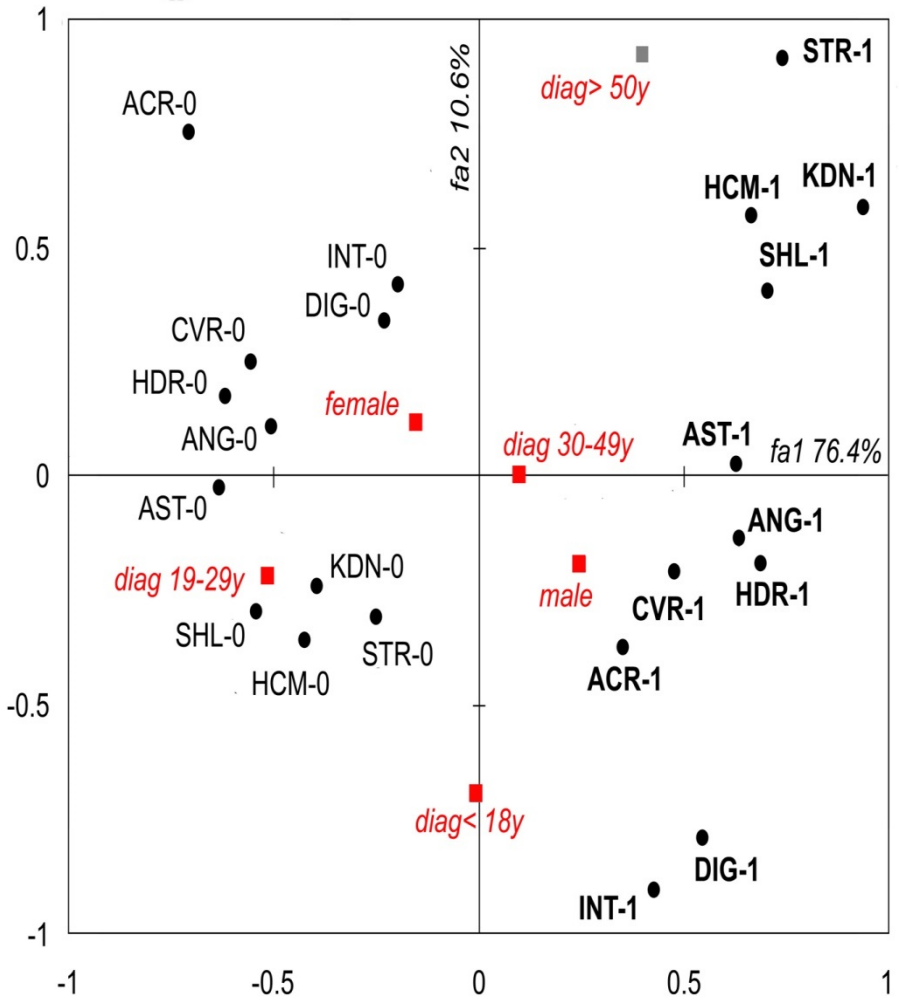


Acknowledgments : Dr LH Noël Hôpital Necker

Fabry disease: the « new great imposter » (n=58)



Lidove O, et al. Clin Genet 2012

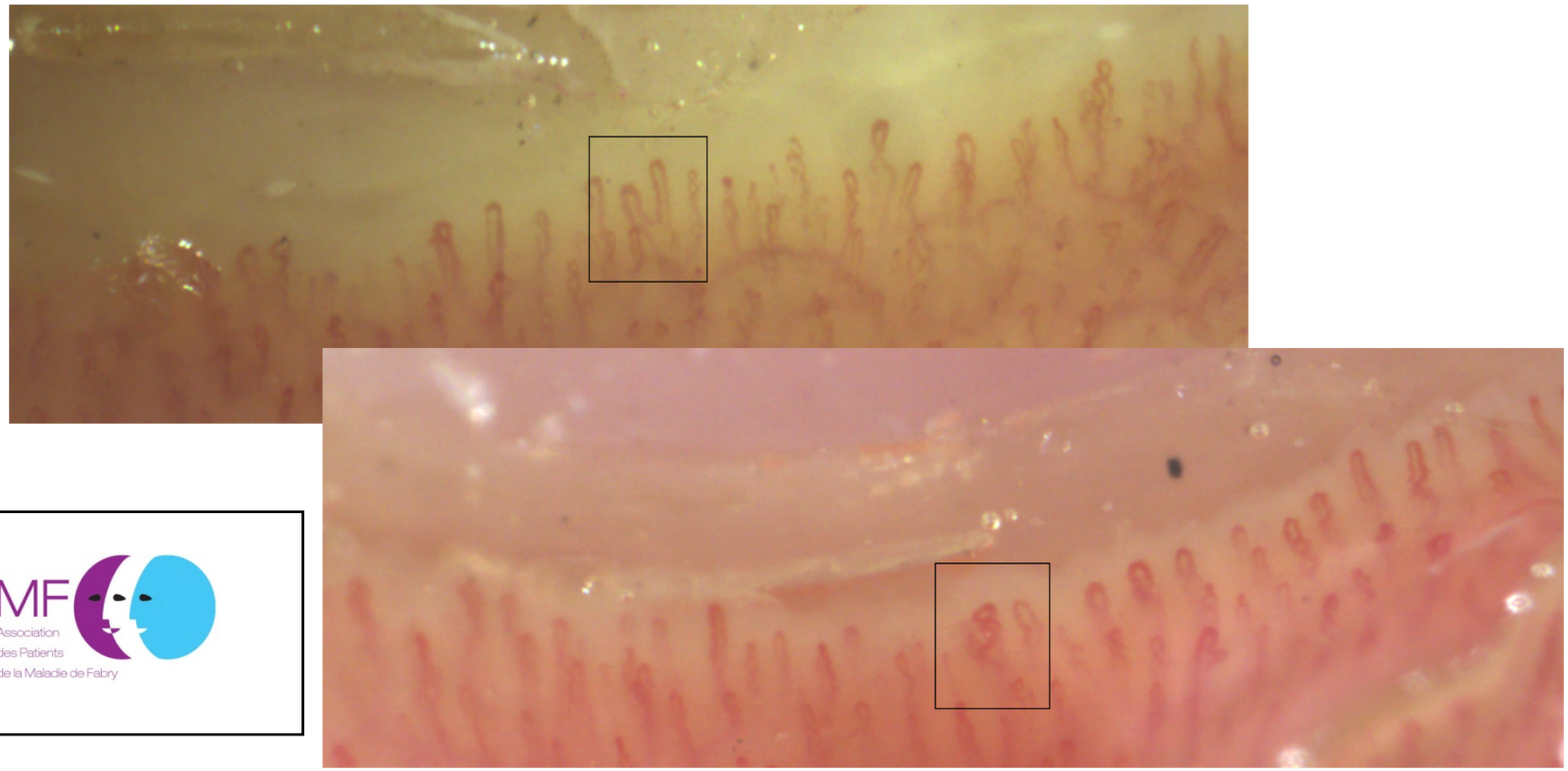


Multiple analysis of correspondence (n = 108)

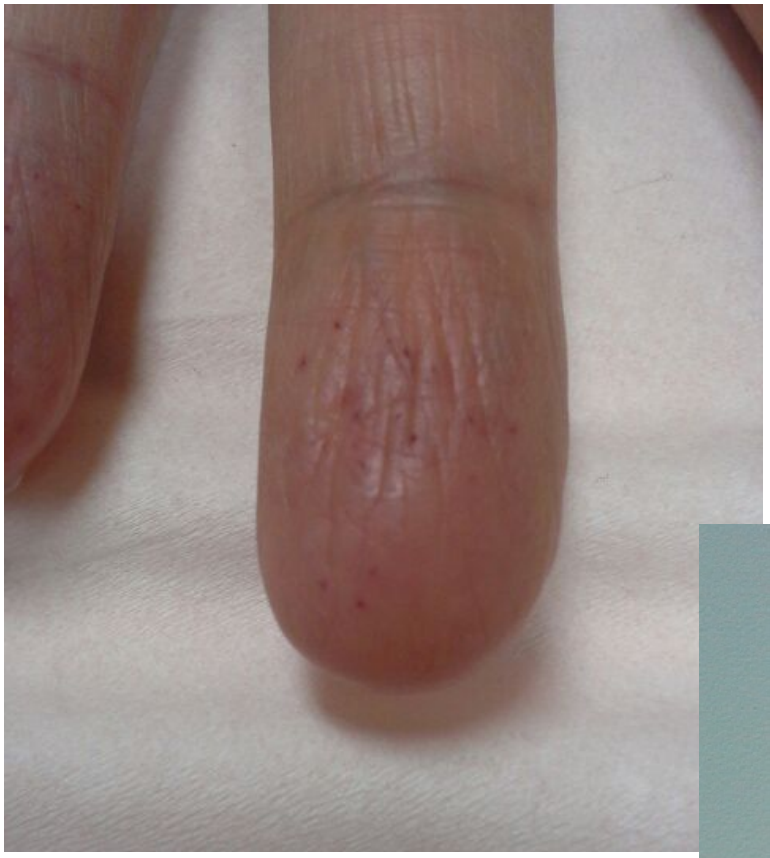
Kaminsky P, et al. Int J Clin Pract 2013.

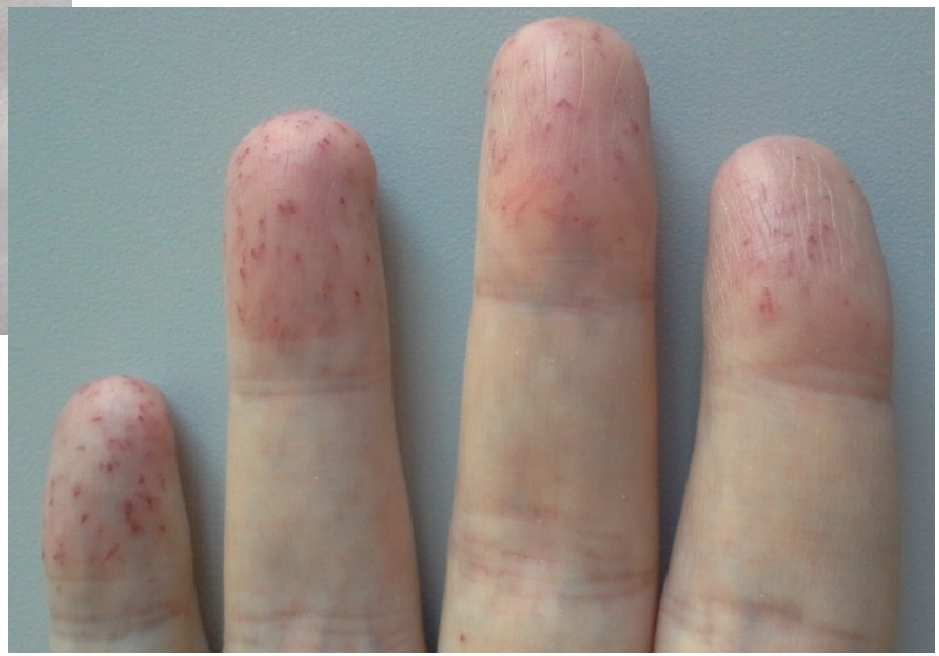
Prevalence of Raynaud Phenomenon and Nailfold Capillaroscopic Abnormalities in Fabry Disease: A Cross-Sectional Study. Medicine 2015;94:e780.

Deshayes, Samuel MD; Auboire, Laurent MD; Jaussaud, Roland MD, PhD; Lidove, Olivier MD; Parienti, Jean-Jacques MD, PhD; **Triclin, Nathalie;** Imbert, Bernard MD; Bienvenu, Boris MD, PhD; Aouba, Achille MD



APMF
Association des Patients de la Maladie de Fabry





Fredeau L, et al. Br J Dermatol, in press.

Question 1

- What is the « gold-standard » for the diagnosis of Fabry disease in **male** patients ?
  - Clinical phenotype
  - Alpha-galactosidase A in leukocytes
  - LysoGb3 in plasma
  - LysoGb3 in urine
  - GLA gene mutation analysis

Question 1

- What is the « gold-standard » for the diagnosis of Fabry disease in **male** patients ?
  - Clinical phenotype
  - **Alpha-galactosidase A in leukocytes**
  - LysoGb3 in plasma
  - LysoGb3 in urine
  - GLA gene mutation analysis

Question 2

- What is the « gold-standard » for the diagnosis of Fabry disease in **female** patients ?
  - Clinical phenotype
  - Alpha-galactosidase A in leukocytes
  - LysoGb3 in plasma
  - LysoGb3 in urine
  - GLA gene mutation analysis

Question 2

- What is the « gold-standard » for the diagnosis of Fabry disease in **female** patients ?
  - Clinical phenotype
  - Alpha-galactosidase A in leukocytes
    - **Normal in 40% of cases**
  - LysoGb3 in plasma
  - LysoGb3 in urine
  - **GLA gene mutation analysis**

Women are not only carriers

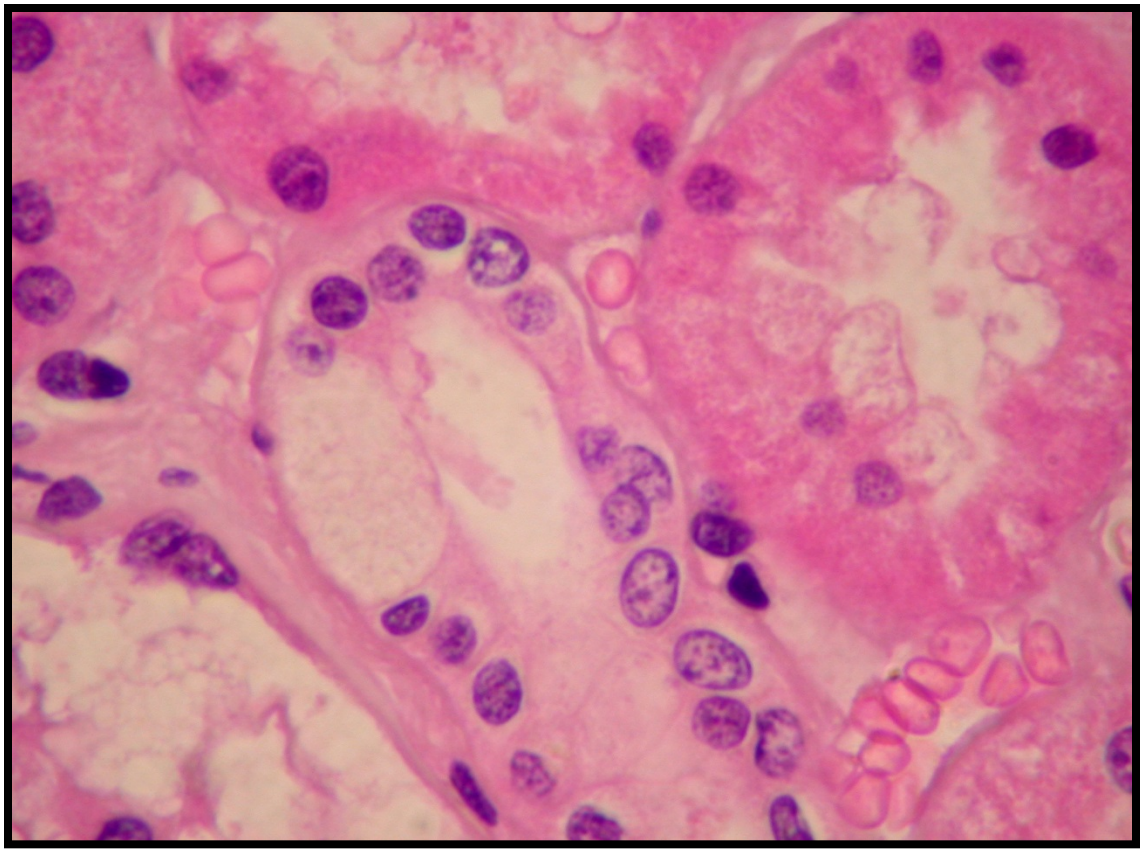
Comparison of frequency of symptoms:

- **Male versus female (%)**
- **Cornea verticillata: 75% each**
- **Dialysis: 12% of Fabry patients are female patients (USA and EU)**

Tsakiris D, Nephrol Dial Transplant 1996

Thadhani R, Kidney Int 2002

Lyonisation



With Courtesy F Barbey, Lausanne.

Globotriaosylsphingosine (LysoGb3)

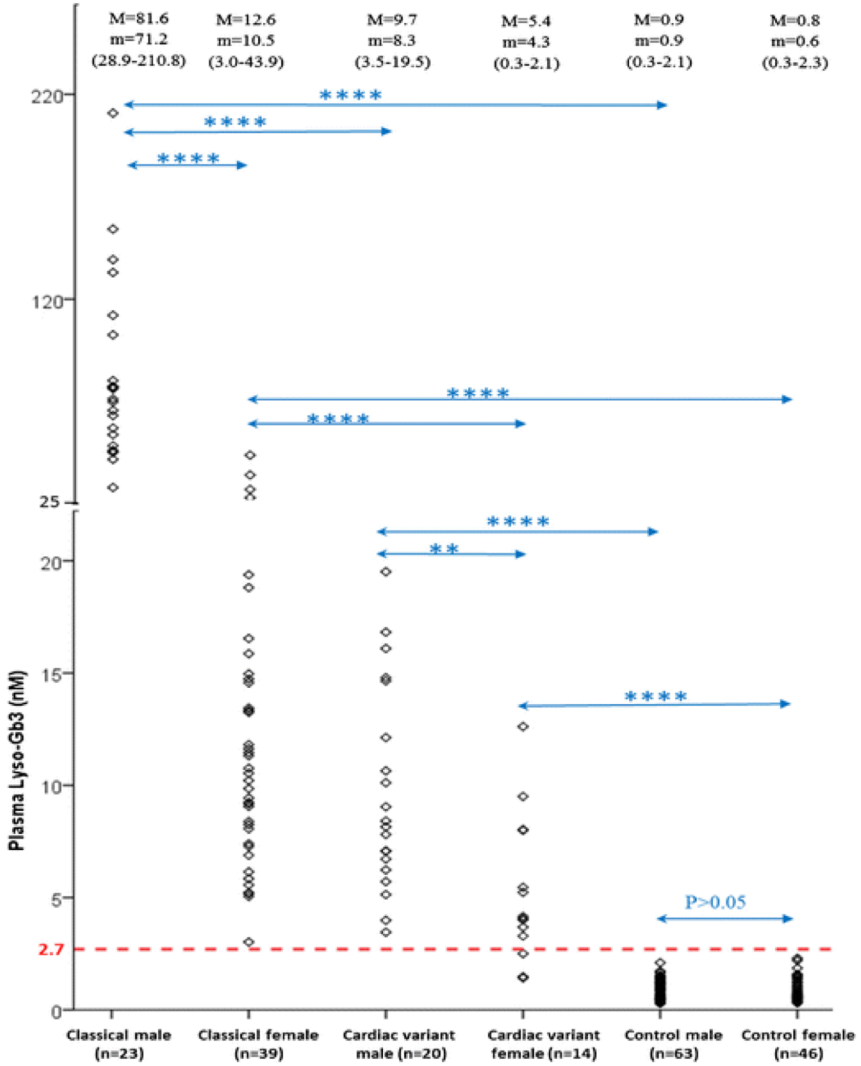


Fig. 2

Plasma Lyso-Gb_3 levels, baseline characteristics of 34 cardiac variant patients carrying ***N215S* mutation**: Data were pooled from Fabry patients and control subjects and presented as dot plots. The concentrations were measured using Lyso-Gb_3 calibration curves. Data were analyzed using SPSS. The subjects were divided into six groups as follows: classical Fabry males, classical Fabry females, cardiac variant Fabry males, cardiac variant Fabry females, control males, and control females. For each group: n = number of subjects; M = mean; m = median; the range of minimum and maximum values in brackets. Various groups were compared using the Mann-Whitney U tests. Differences were considered statistically significant if the *p* value <0.05 (** = $p < 0.01$ and **** = $p < 0001$). (Red dashes: cut-off value, n: number, M: mean & m: median)

Alharbi FJ, et al. JIMD 2018

« There is no evidence that lyso-Gb3 can inform on clinical events »

Talbot A, et al. Mol Genet Metab 2017

3a. Care of patients with Fabry disease in France and in Europe

PLAN NATIONAL MALADIES RARES 2018-2022

Partager l'innovation,
un diagnostic et un traitement
pour chacun

maladies rares

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

MINISTÈRE
DES SOLIDARITÉS
ET DE LA SANTÉ

MINISTÈRE
DE L'ENSEIGNEMENT
SUPÉRIEUR,
DE LA RECHERCHE
ET DE L'INNOVATION

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maladies rares

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DES SOLIDARITÉS
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MINISTÈRE
DE L'ENSEIGNEMENT
SUPÉRIEUR,
DE LA RECHERCHE
ET DE L'INNOVATION

Ministère de la Santé
et des Solidarités
Direction Générale de la Santé

Carte de soins et d'urgence

Emergency Healthcare Card

Maladie de Fabry

Fabry disease

La maladie de Fabry est une maladie génétique héréditaire de surcharge (groupe des maladies lysosomales) caractérisée par une atteinte pluriviscérale, principalement cérébrale, cardiaque et rénale.

- Risque accru d'accident vasculaire cérébral, d'infarctus du myocarde, de troubles de la conduction et du rythme cardiaque et de complications aiguës liées à l'insuffisance rénale chronique.
- Risque d'accident allergique grave au cours du traitement substitutif par enzymothérapie.

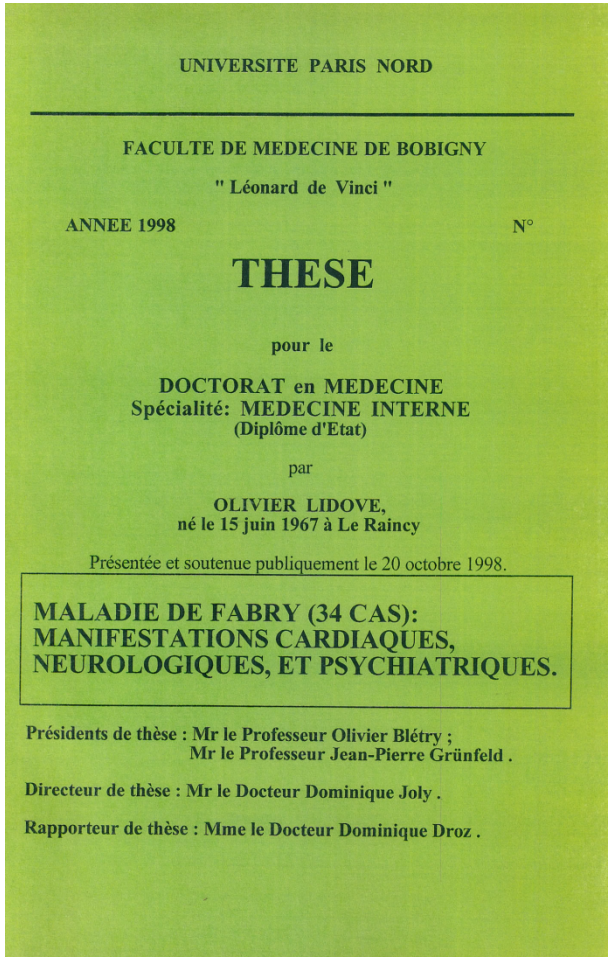
Cette carte est remplie et mise à jour par le médecin, en présence et avec l'accord du malade qui en est le propriétaire.

Ce document est confidentiel et soumis au secret médical.

Nul ne peut en exiger la communication sans autorisation du titulaire ou de son représentant légal.

3b. 1998-2019:
20 years of work
for
Fabry patients

Fabry disease : 20 years of work



UNIVERSITE PARIS NORD

FACULTE DE MEDECINE DE BOBIGNY

" Léonard de Vinci "

ANNEE 1998 N°

THESE

pour le

DOCTORAT en MEDECINE
Spécialité: MEDECINE INTERNE
(Diplôme d'Etat)

par

OLIVIER LIDOVE,
né le 15 juin 1967 à Le Raincy

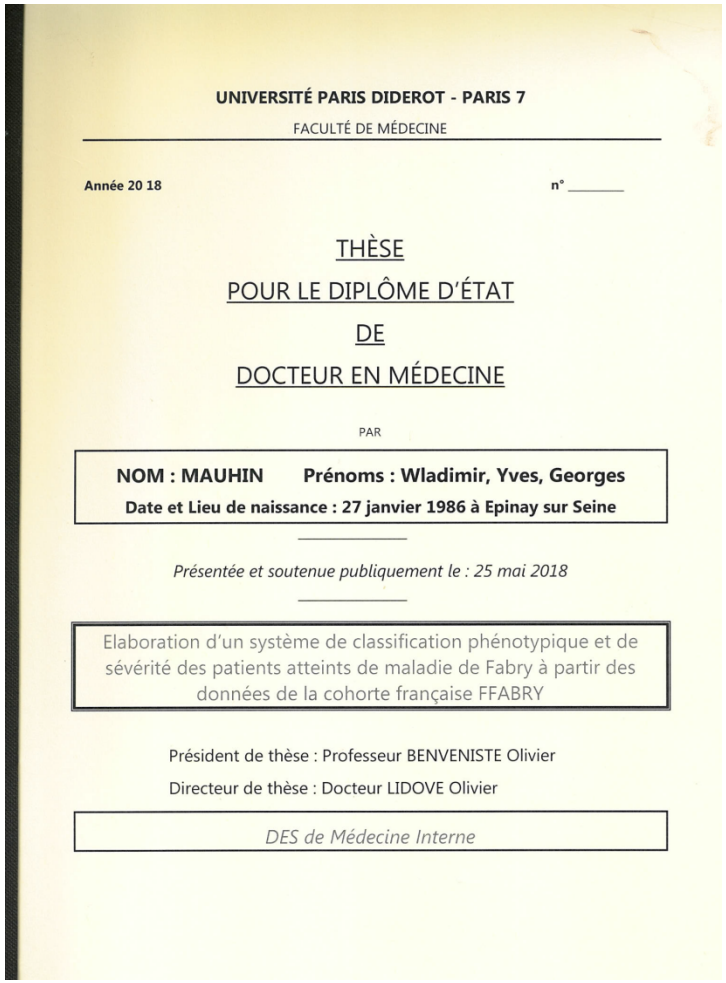
Présentée et soutenue publiquement le 20 octobre 1998.

MALADIE DE FABRY (34 CAS): MANIFESTATIONS CARDIAQUES, NEUROLOGIQUES, ET PSYCHIATRIQUES.

Présidents de thèse : Mr le Professeur Olivier Blétry ;
Mr le Professeur Jean-Pierre Grünfeld .

Directeur de thèse : Mr le Docteur Dominique Joly .

Rapporteur de thèse : Mme le Docteur Dominique Droz .



UNIVERSITÉ PARIS DIDEROT - PARIS 7

FACULTÉ DE MÉDECINE

Année 20 18 n° _____

THÈSE

POUR LE DIPLÔME D'ÉTAT

DE

DOCTEUR EN MÉDECINE

PAR

NOM : MAUHIN Prénoms : Wladimir, Yves, Georges

Date et Lieu de naissance : 27 janvier 1986 à Epinay sur Seine

Présentée et soutenue publiquement le : 25 mai 2018

Elaboration d'un système de classification phénotypique et de sévérité des patients atteints de maladie de Fabry à partir des données de la cohorte française FFABRY

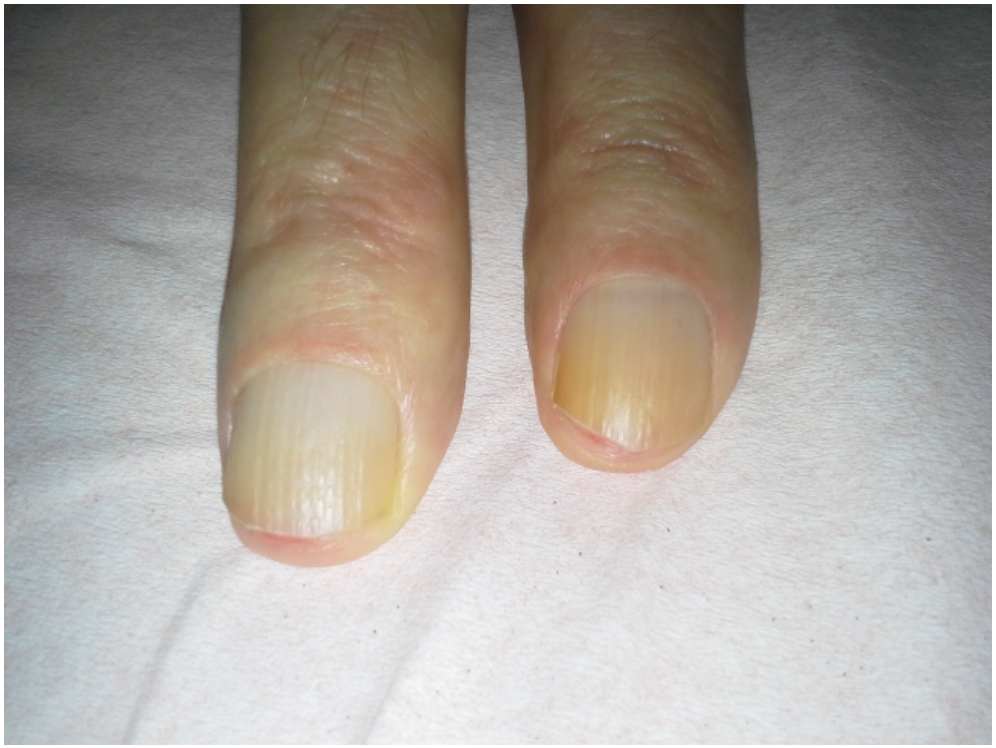
Président de thèse : Professeur BENVENISTE Olivier

Directeur de thèse : Docteur LIDOVE Olivier

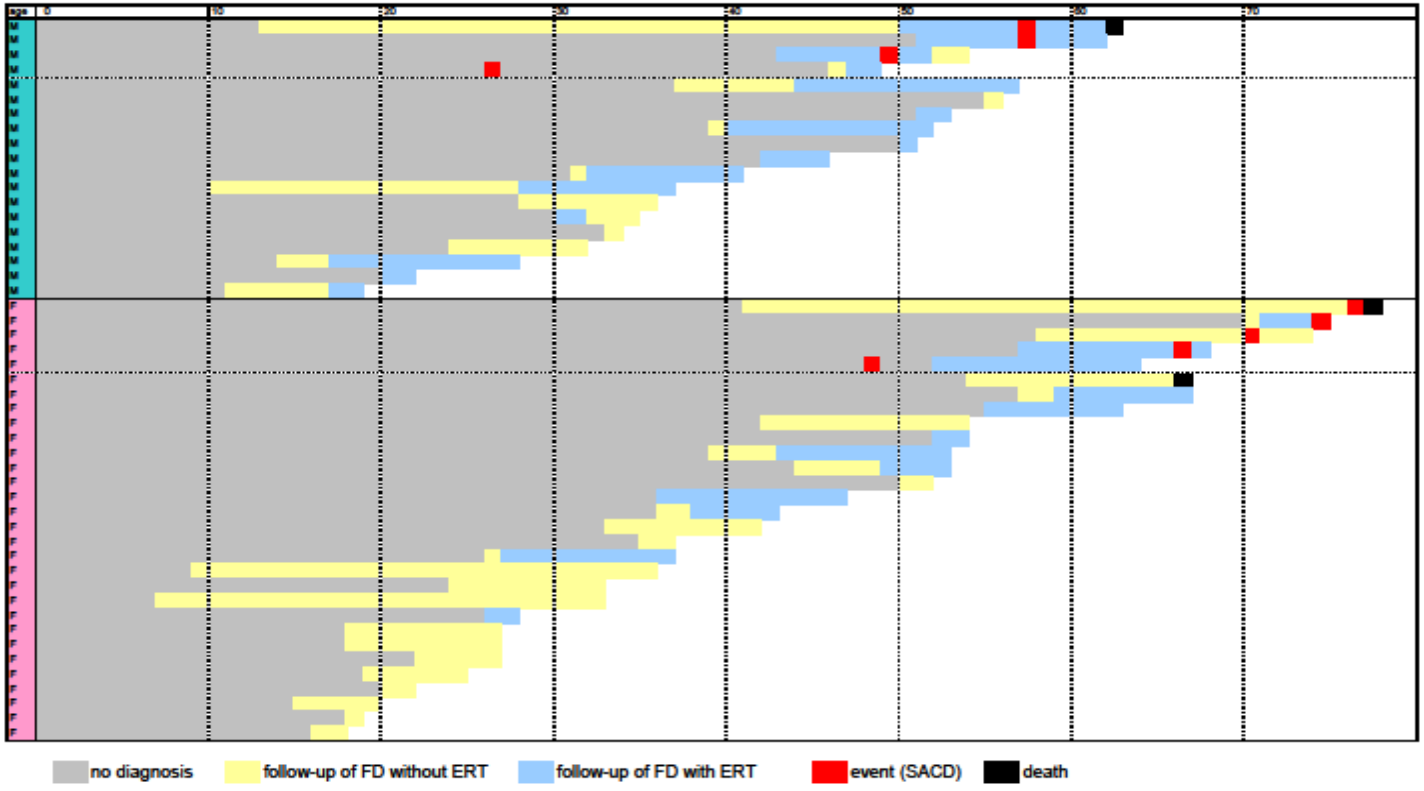
DES de Médecine Interne

At the beginning, only symptomatic therapy…

Stop tobacco



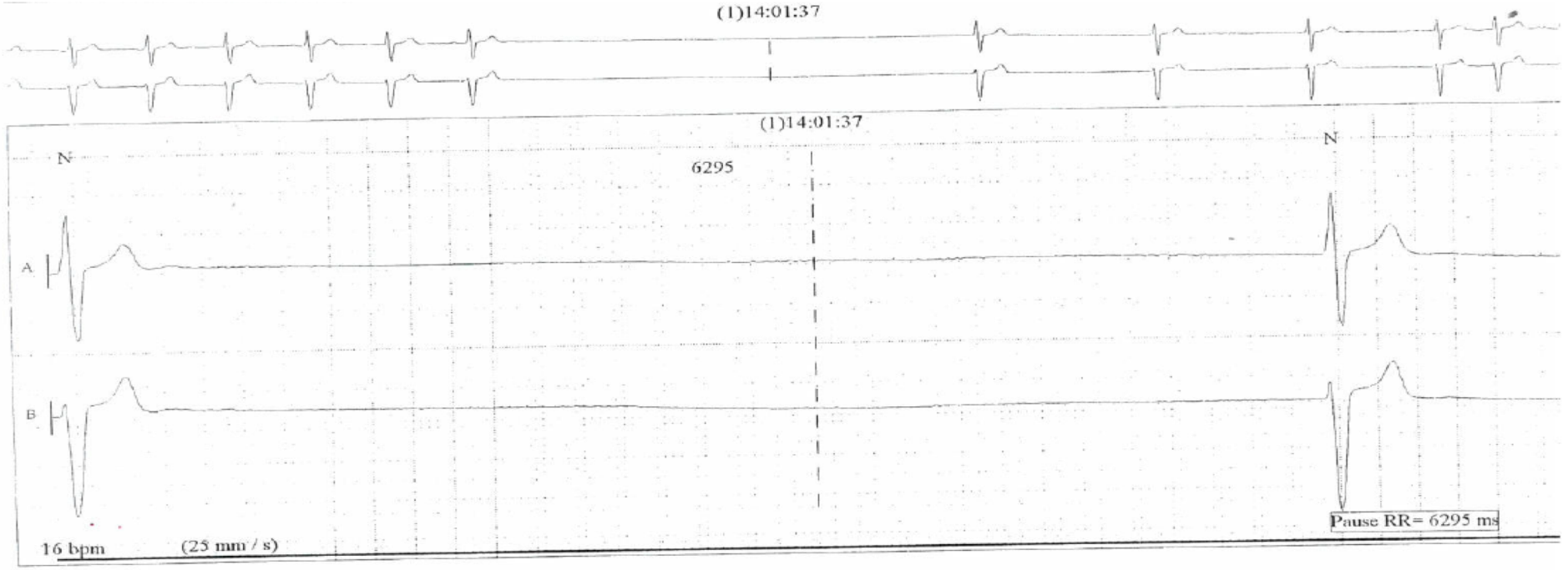
Cardiac device implantation in Fabry disease



SACD: severe arrhythmia or conduction defect

Sené T, Lidove O *et al.* Medicine (Baltimore). 2016 Oct;95(40):e4996

76 year-old female: syncope



Question 3

- One of your patient who is diagnosed with Fabry disease suffer from a nephrotic syndrome: albumin 28g/l, daily proteinuria 4g/day

- Is nephrotic syndrome usual in Fabry disease?

  - Yes

  - No

Question 3

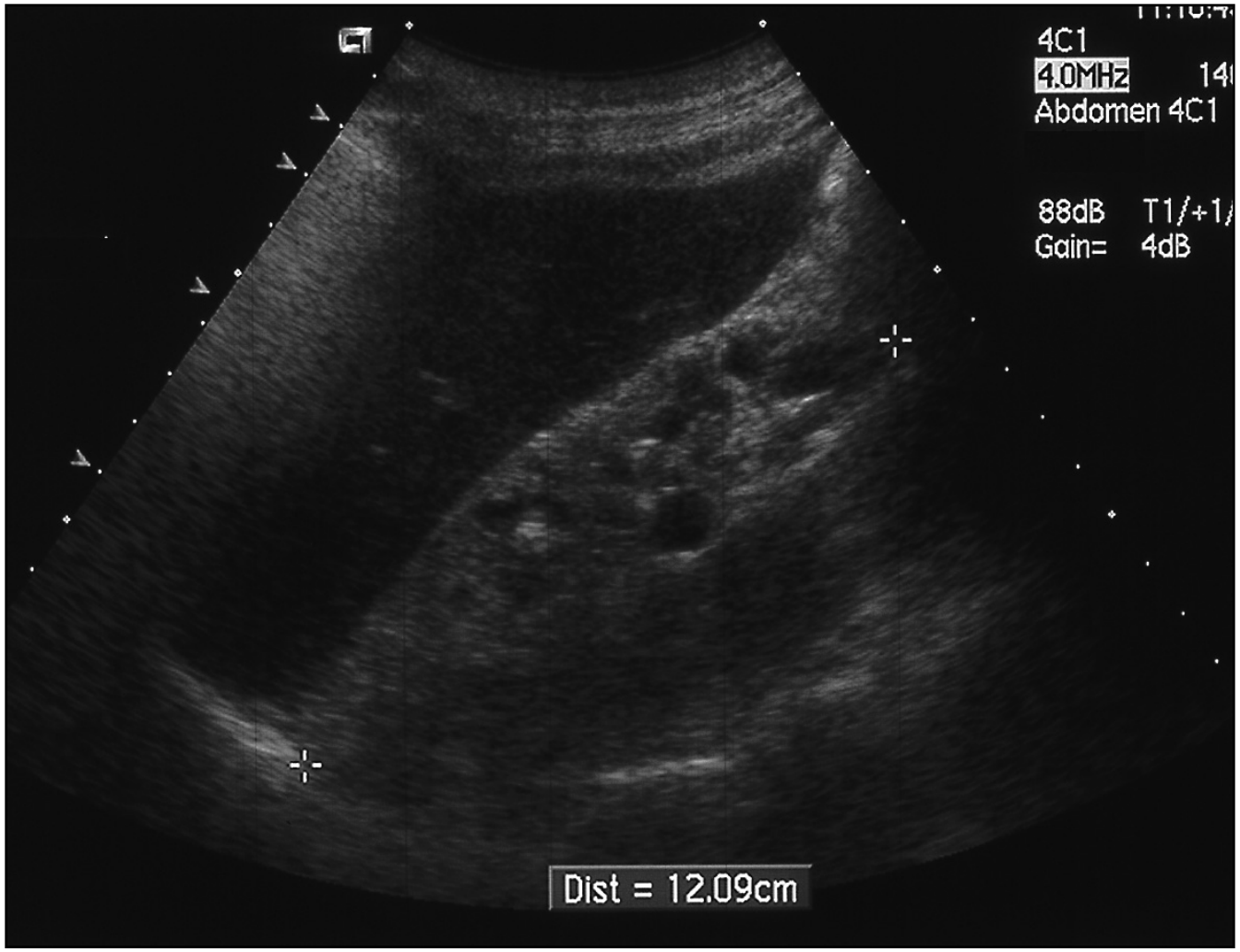
- One of your patient who is diagnosed with Fabry disease suffer from a nephrotic syndrome: albumin 28g/l, daily proteinuria 4g/day

- Is nephrotic syndrome usual in Fabry disease?

  - Yes

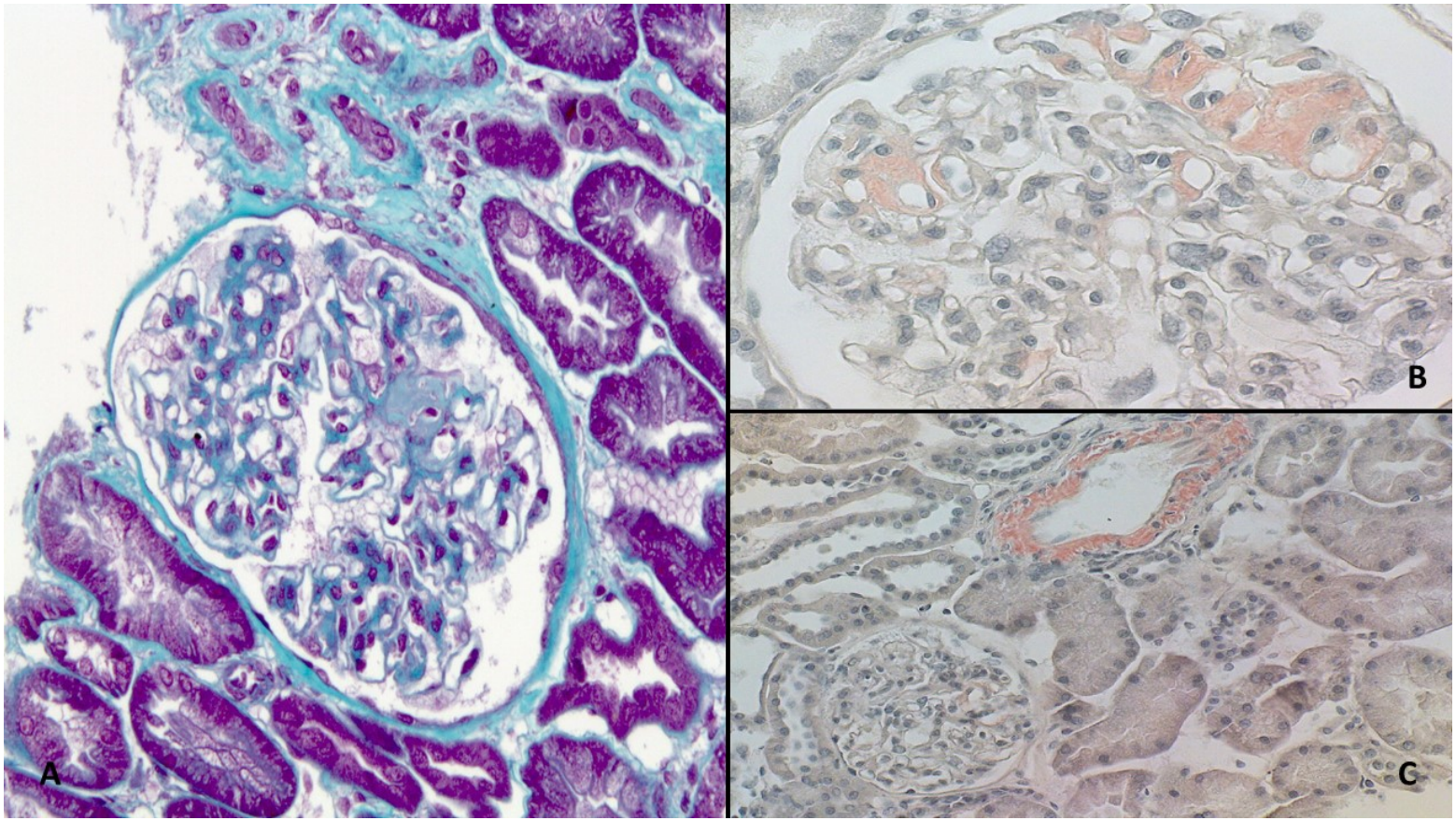
  - **No**

    - **Kidney biopsy is mandatory**

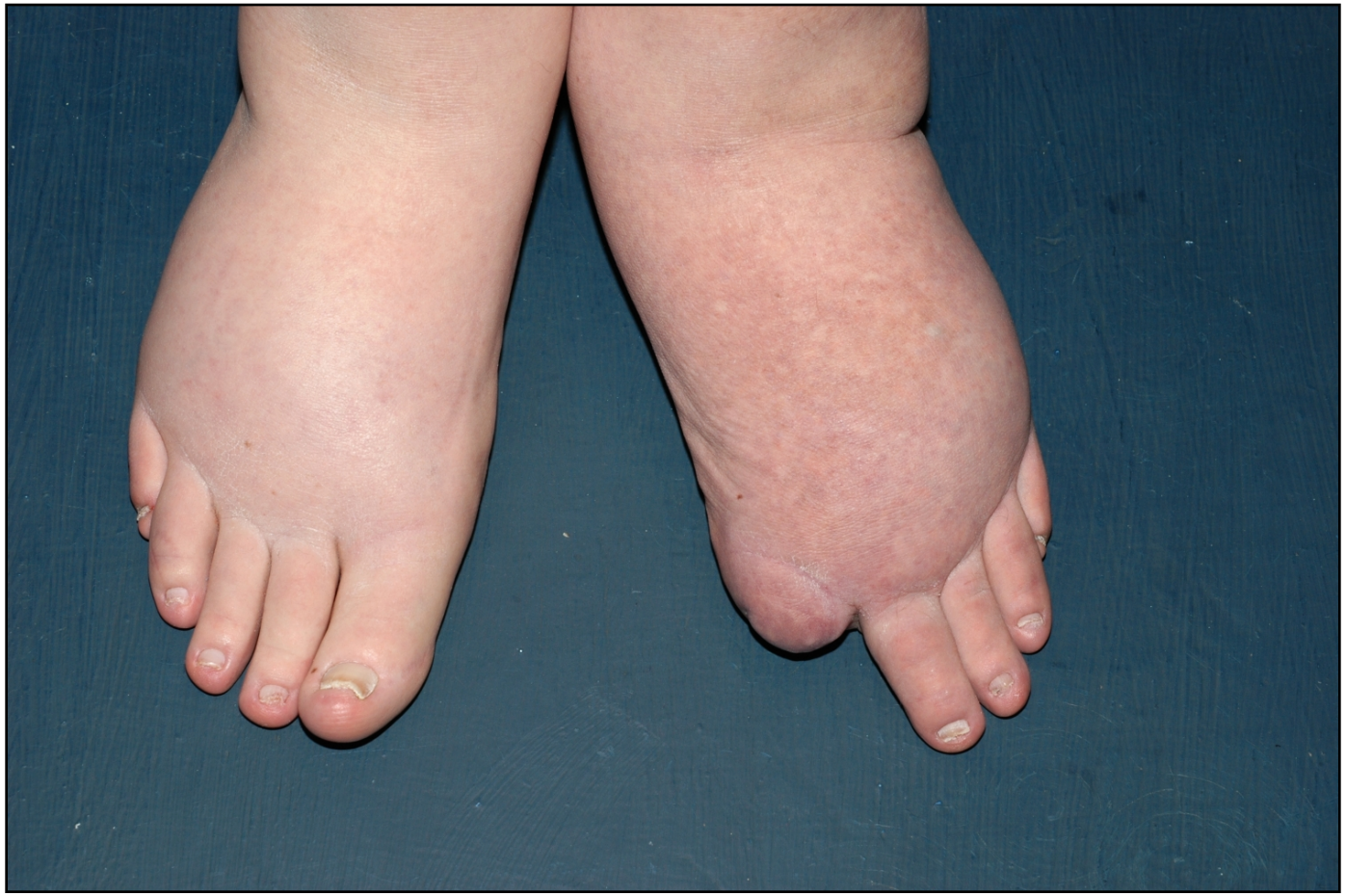


Lidove O, et al. Am J Roentgenol 2006.

55 year-old female FD patient (diagnosis at 21)



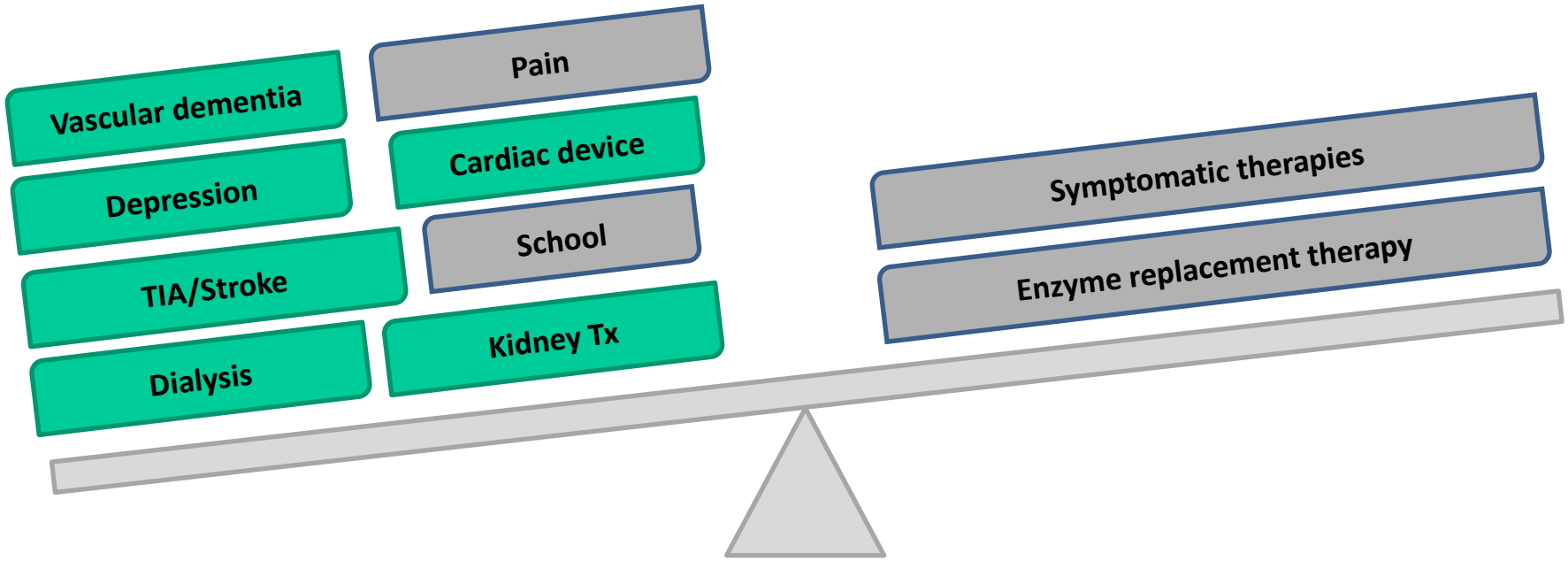
Terré A, et al. Submitted



Lidove O, et al. Joint Bone Spine 2016

4a. Enzyme therapy

Tøndel C, et al.
J Am Soc Nephrol 2013



Early diagnosis +++

Enzymatic substitution

Agalsidase alpha
Replagal® (TKT) Shire

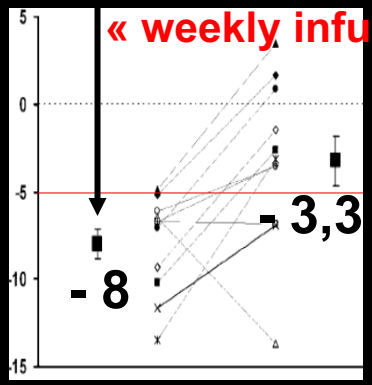
extension
follow-up

Agalsidase beta
Fabrazyme®, Genzyme

PROGRESSION

Δ DFG > 5 ml/mn/an

12/41 patients
29%



Schiffmann, JASN 2007

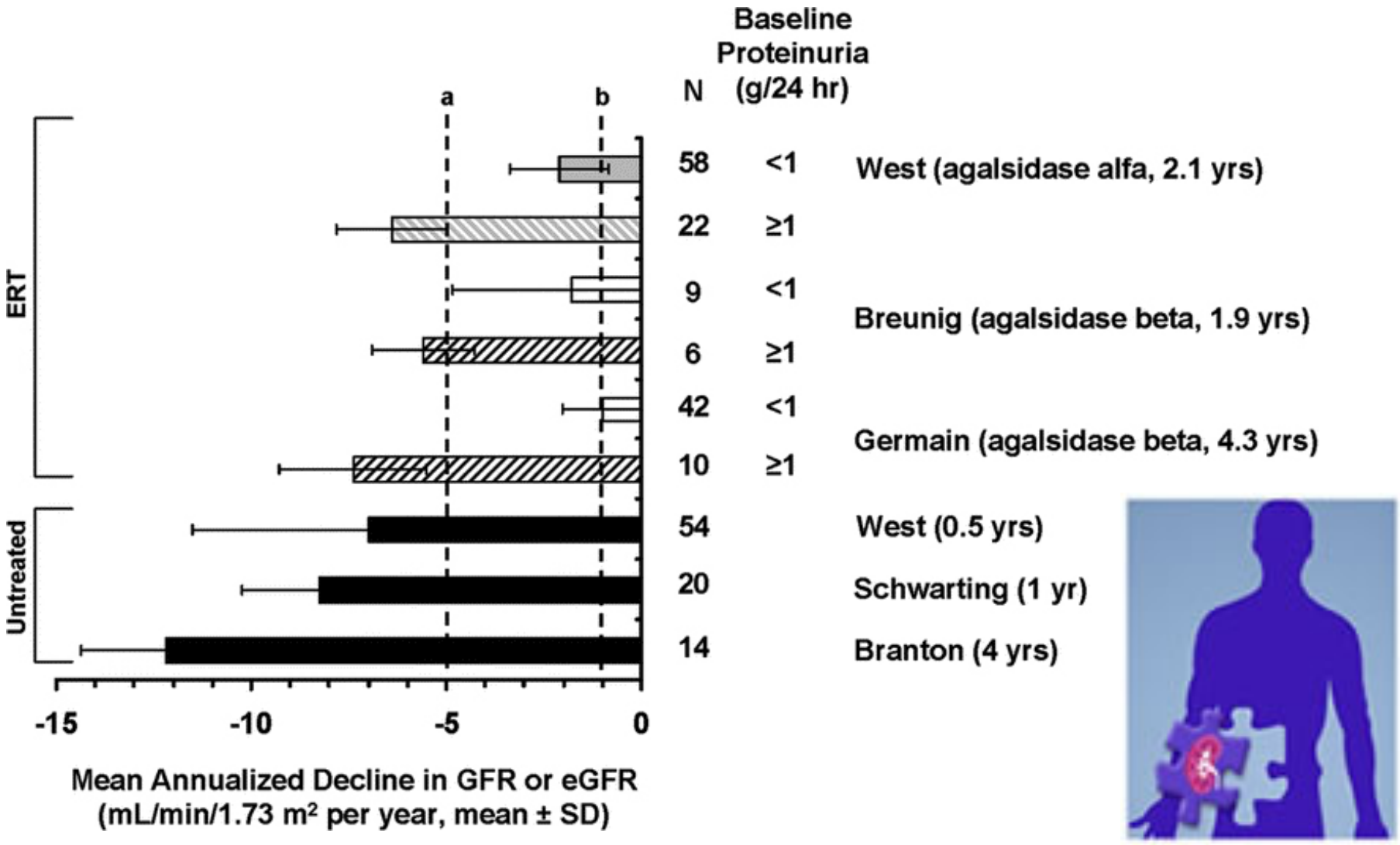
Δ DFG 3.5 à 12 ml/mn/an

6/54 patients
11 %

?

- **Protéinurie**
- **GS > 50 %**
- **(âge > 40 ans)**
- **(DFG < 55)**

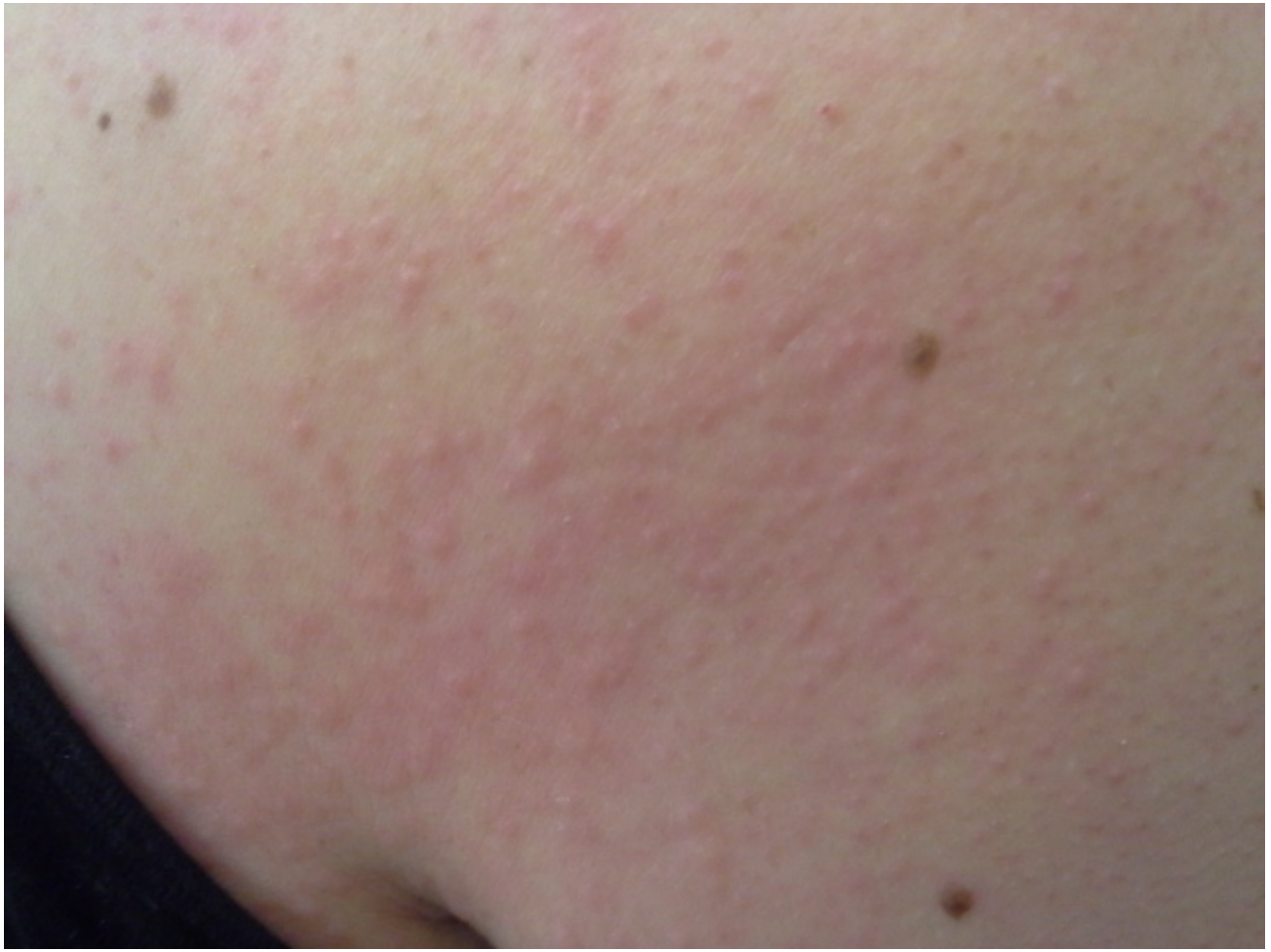
Germain, JASN 2007



(Adapted from Journal of the American Society of Nephrology, Volume 20, West M et al., pages 1132-1139, 2009, with permission from the American Society of Nephrology).

Lidove et al. Genet Med 2010.

Hypersensitivity reaction

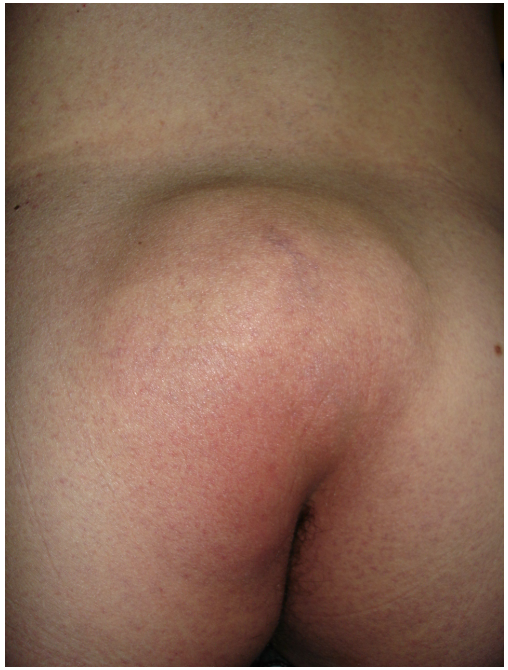


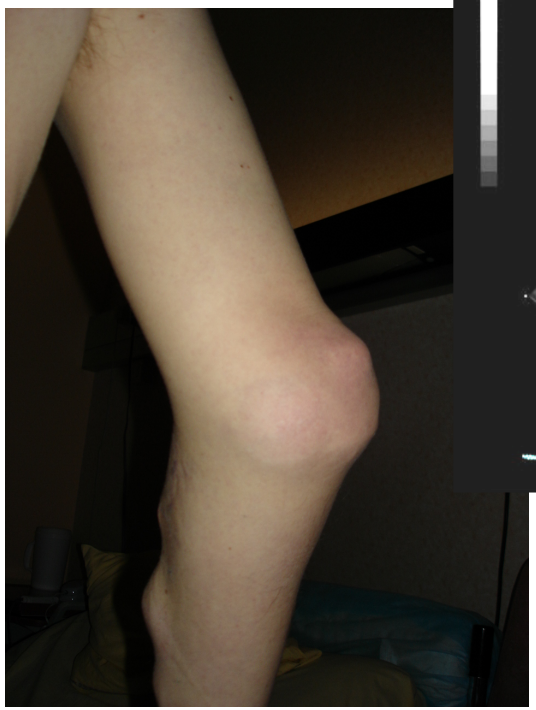
Prognosis

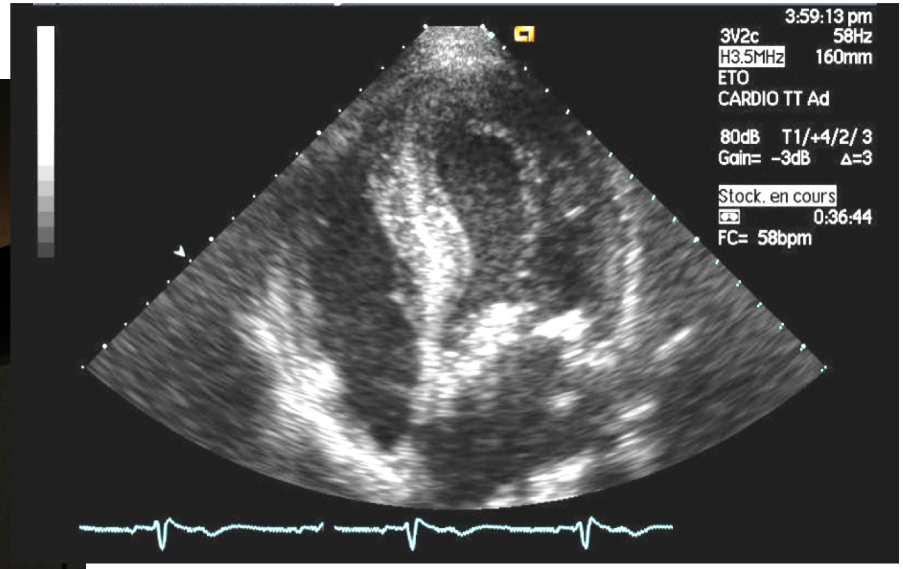
- To date, no proof of improvement of patients under ERT (**life expectancy**)

- Treat EARLY!!!
  - Fibrosis
    - Glomerulosclerosis
    - AV block
  - Dialysis

Treat Early !!!





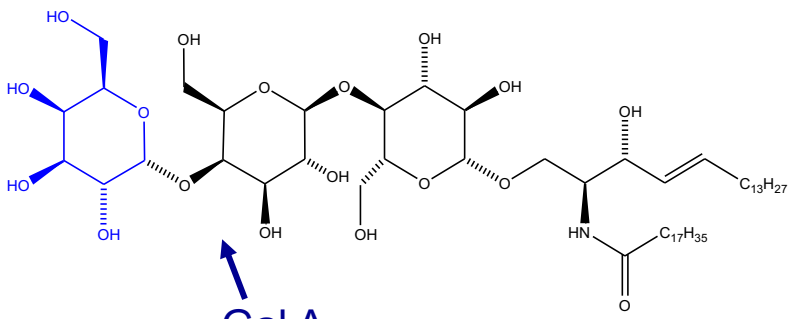


Karras A, et al. Am J Transplant 2008;8:1345-8
Tran Ba S-N. Rev Med interne 2017;38:137-42.

4b. Chaperone therapy

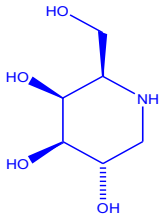
1-deoxygalactonojirimycin (DGJ) = migalastat : a pharmacological chaperone for certain mutant forms of a-Gal A associated with Fabry disease

Natural Substrate



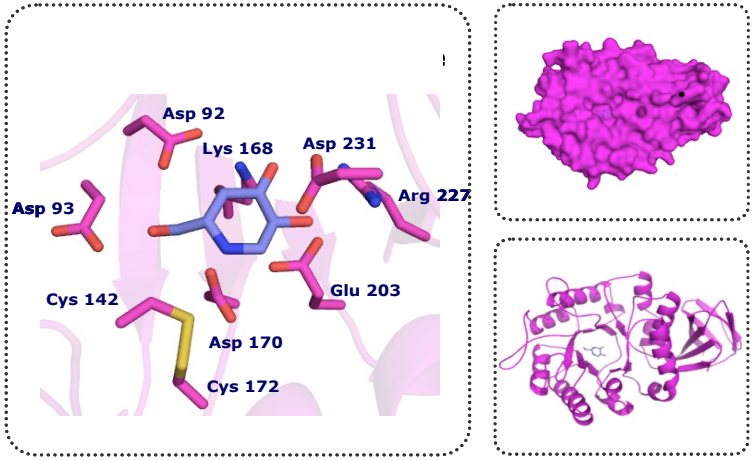
α-Gal A

Pharmacological Chaperone



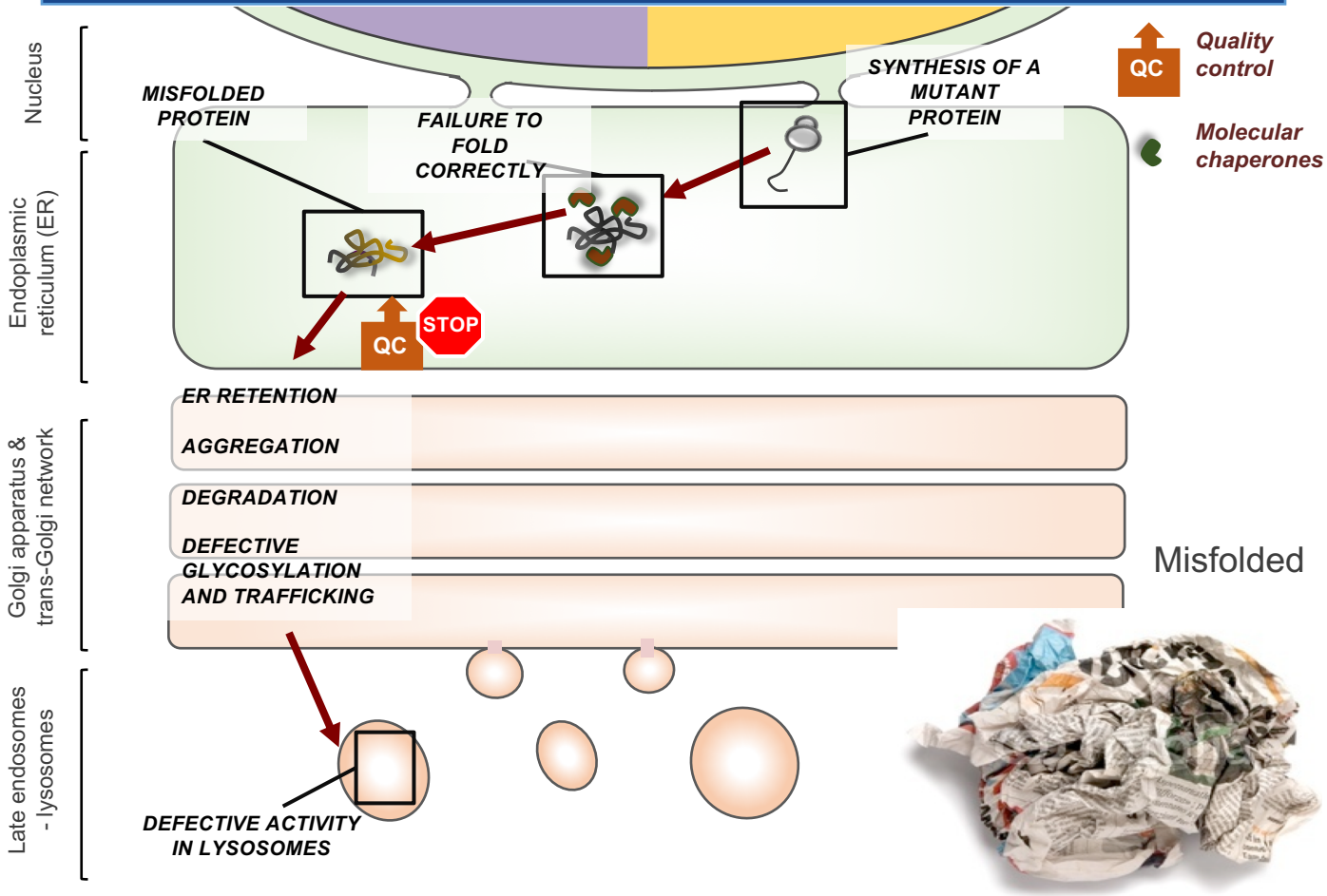
1-deoxygalactonojirimycin (DGJ) = Migalastat HCl
(referred to as 'AT1001' in preclinical studies)

Globotriaosylceramide (Gb3)
Lyso-Gb3



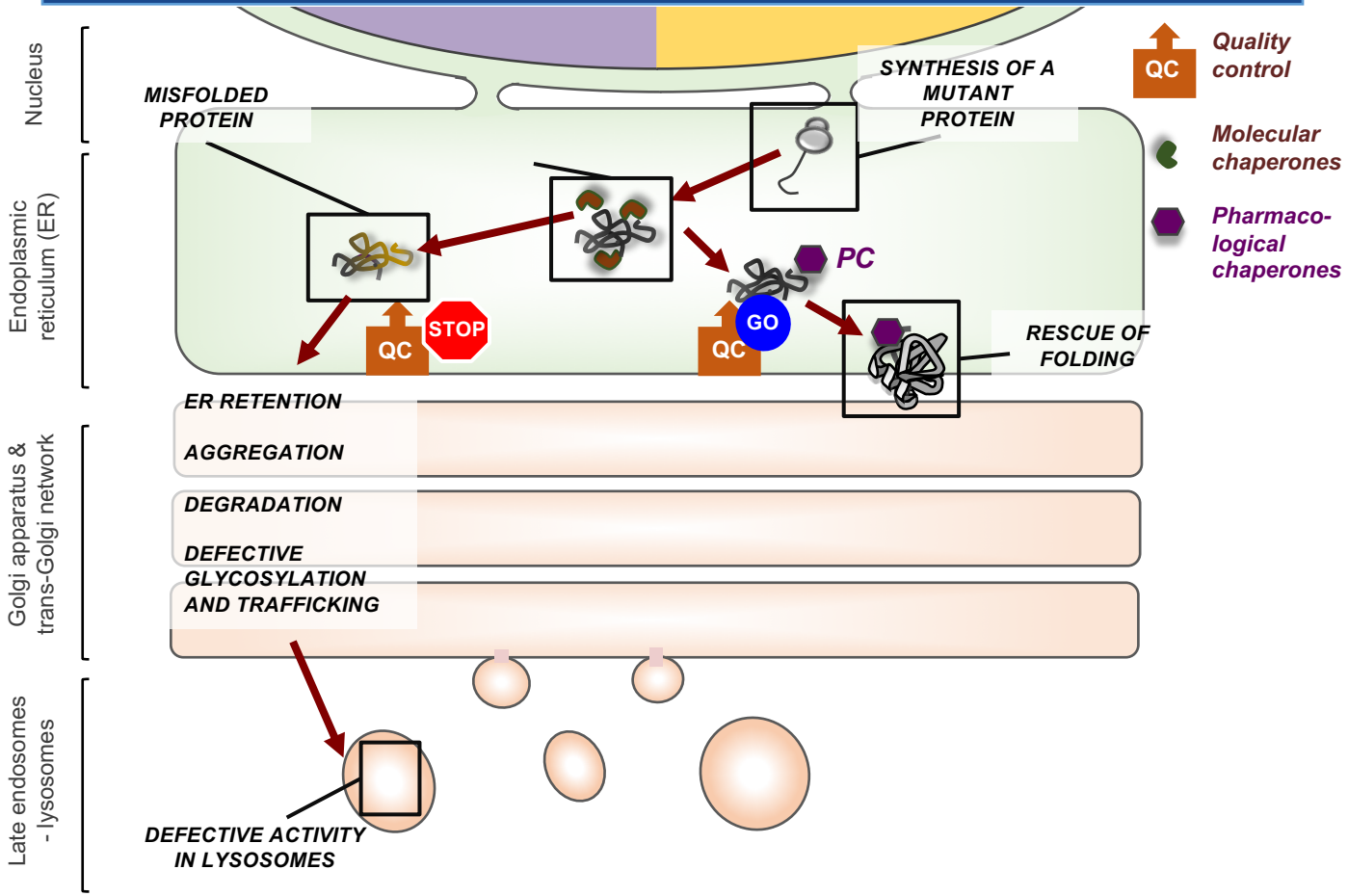
Migalastat **reversibly binds** certain mutant forms of a-Gal A associated with **at the active site** of α-galactosidase

Mechanism of action of chaperones



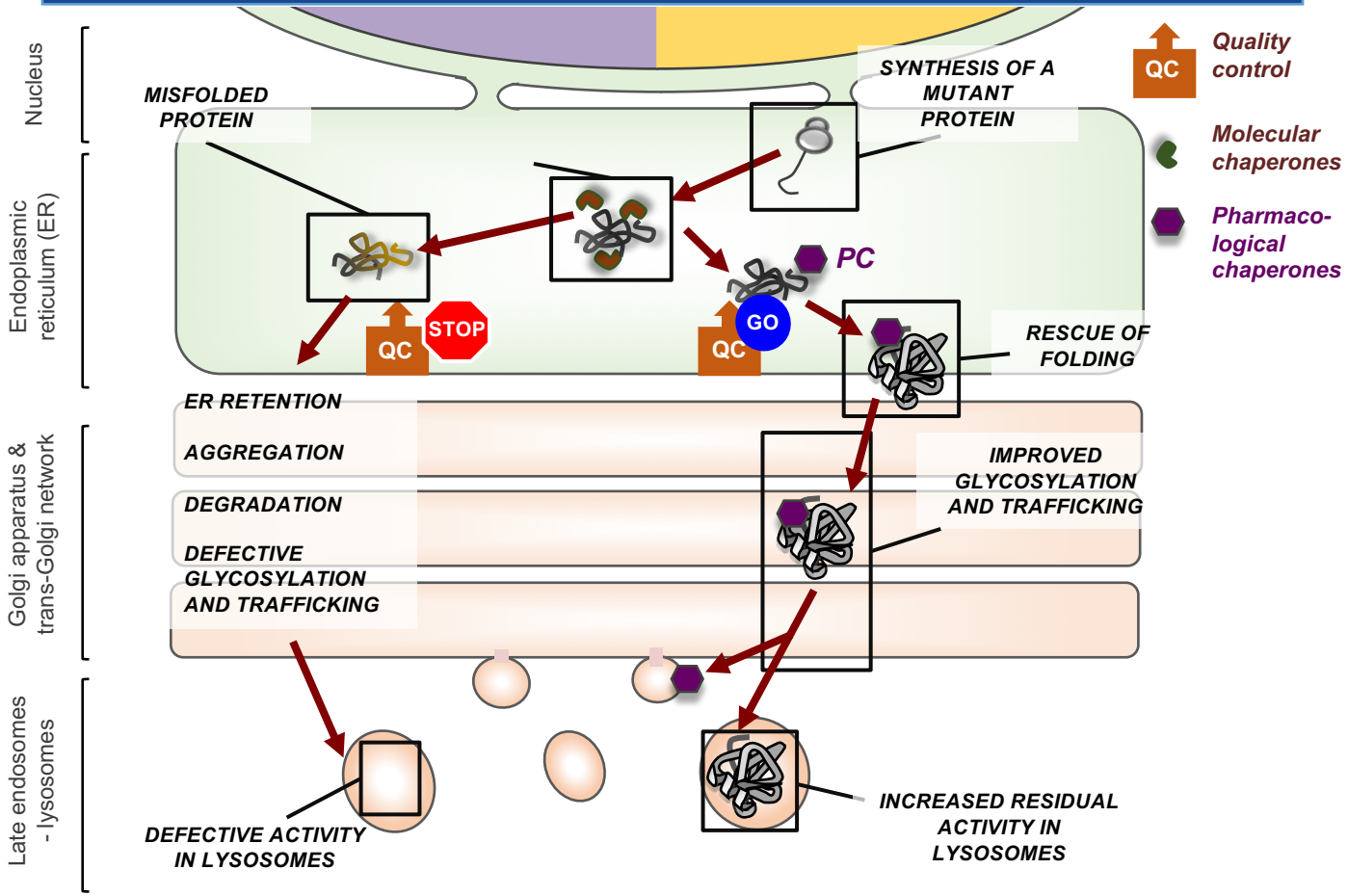
Adapted from: Parenti G, Andria G, Valenzano K, *Mol Ther*; 23:1138-48, 2015

Mechanism of action of chaperones



Adapted from: Parenti G, Andria G, Valenzano K, *Mol Ther*; 23:1138-48, 2015

Mechanism of action of chaperones

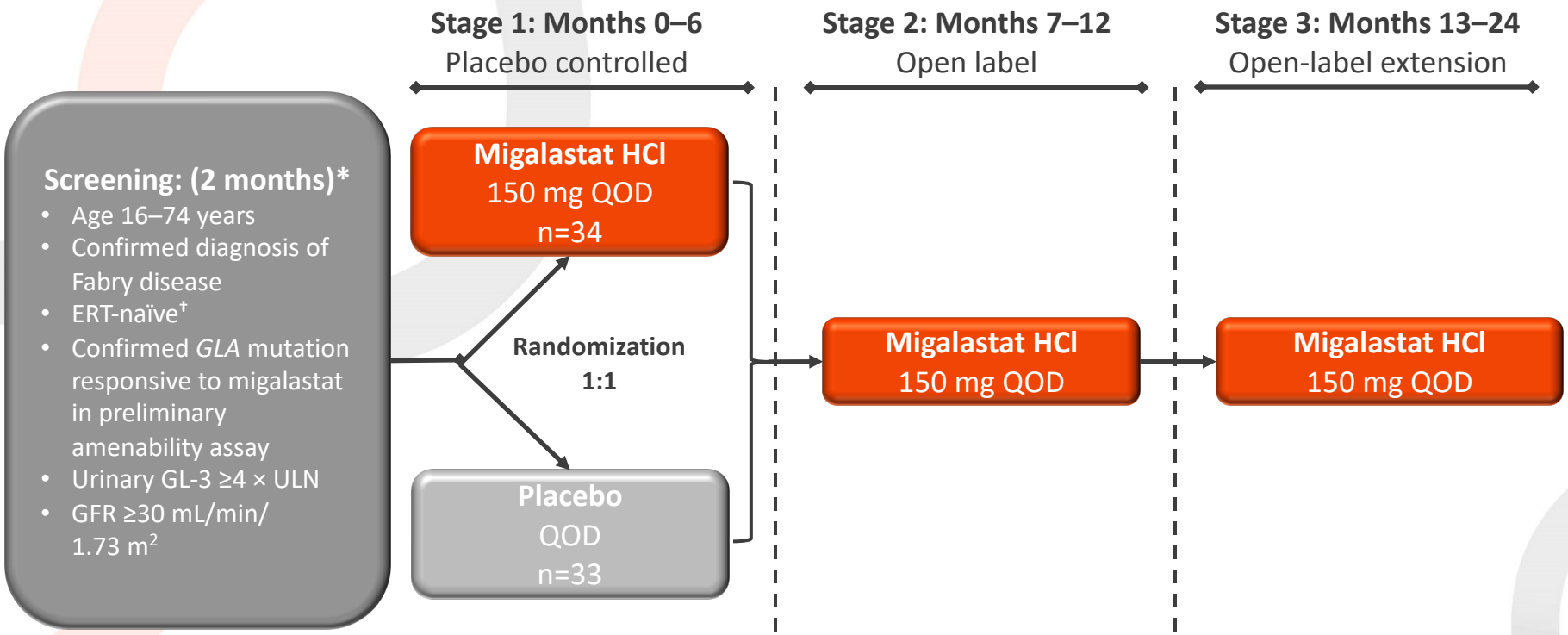


Adapted from: Parenti G, Andria G, Valenzano K, *Mol Ther*; 23:1138-48, 2015

Results

- **Methodology** of the 2 phase 3 studies
- **Kidney**
- Heart
- Surrogate markers
- **Safety**

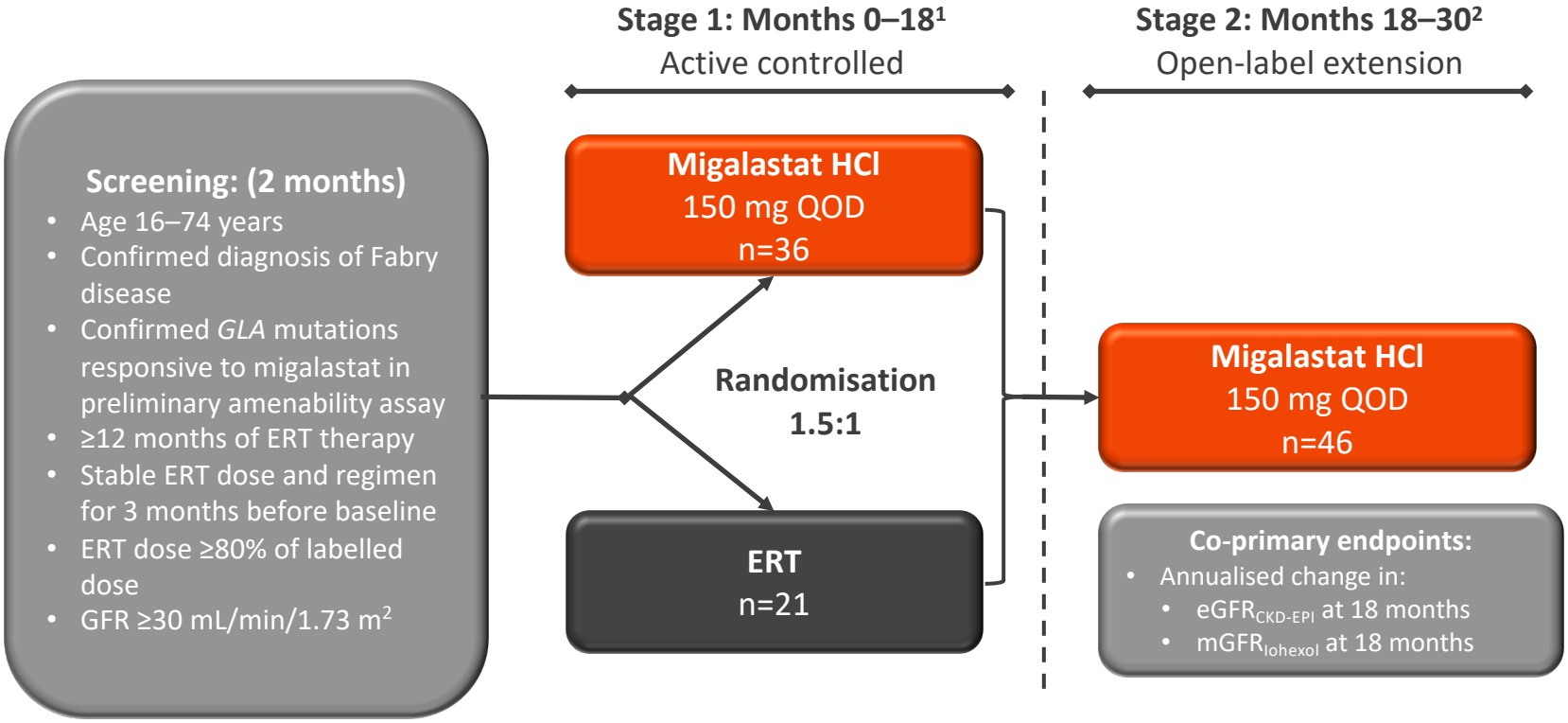
FACETS: Migalastat comparison with placebo in patients with amenable mutations



Double-blind, 6-month study of the efficacy, safety, and PD of migalastat in ERT-naïve patients with amenable mutations, followed by a 6-month open-label extension and an optional 12-month open-label extension[1]

*Patients were untreated for at least 6 months prior to screening and during screening; †Either ERT naïve or willing to stop ERT for the study period
ERT, enzyme-replacement therapy; α-GAL A, α-galactosidase A; GFR, glomerular filtration rate; GL-3, globotriaosylceramide; QOD, every other day; ULN, upper limit of normal
1. Bichet D et al. Presented at: 12th Annual WORLDSymposium™ 2016; February 29-March 4, 2016; San Diego, CA; 2. Barlow et al. Mol Genet Metab 2014;111:S24

ATTRACT: Comparison of migalastat with ERT in previously treated patients[1,2]



Randomised, open-label study to compare the efficacy and safety of migalastat and ERT in patients with Fabry disease and amenable mutations who were previously treated with ERT[1,2]

ERT, enzyme-replacement therapy; GFR, glomerular filtration rate; QOD, every other day

Hughes DA, Nicholls K, Shankar SP, et al. J Med Genet 2017;54(4):288-296.

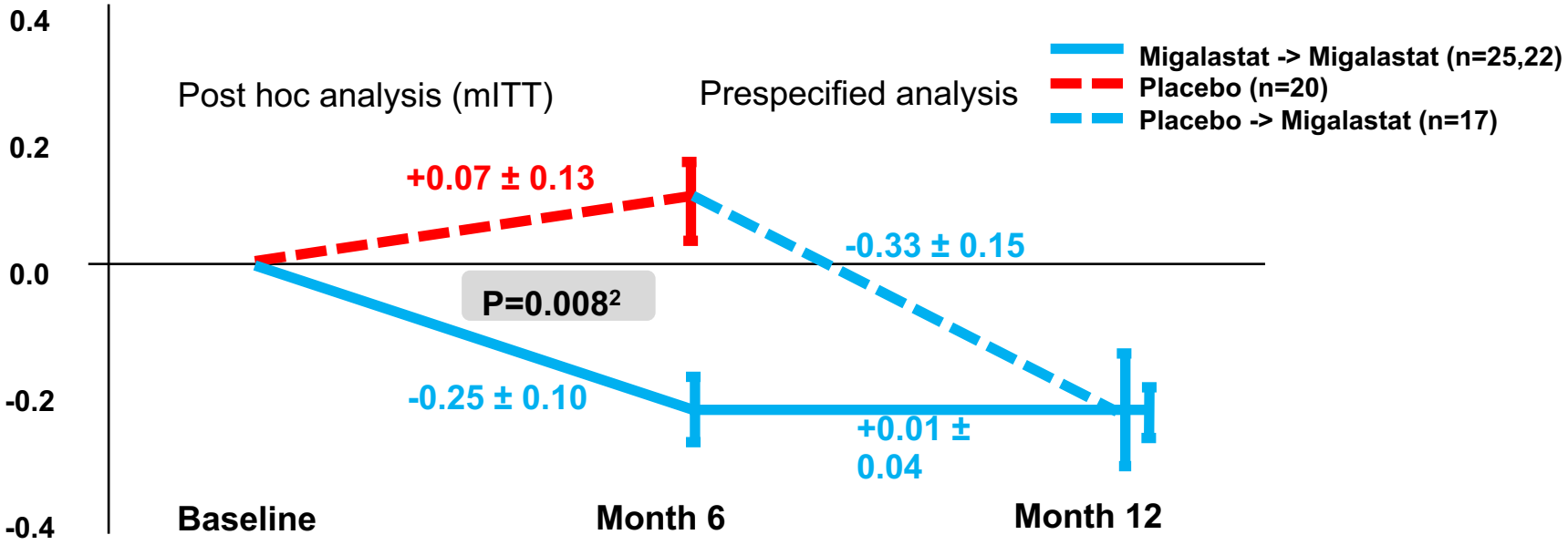
Kidney

FACETS: Kidney Interstitial Capillary GL-3

6-Month Post-Hoc Analysis and 12-Month Pre-Specified Primary Analysis

Statistically Significant Reduction in Kidney Interstitial Capillary GL-3 at Month 6 and Month 12 following Treatment with Migalastat HCl (GLP HEK Amenable)*

Mean Inclusions Per Capillary[1]



- From Baseline to 6-Month, primary endpoint analysis (ITT population): the difference in percentage of patients with a ≥50% reduction in the number of kidney IC GL-3 inclusions did not reach statistical significance

*All patients with evaluable paired biopsies and amenable GLA mutations in GLP-validated HEK assay – post hoc at month 6 and pre-specified at month 12

[1]Data points are baseline corrected; represent mean ± standard error (SEM) change from baseline in the mean number of GL-3 inclusions per capillary after 6 months of treatment with Migalastat or placebo.

[2]Analysis of covariance (ANCOVA) model with covariate adjustment for baseline value and factors for treatment group and treatment by baseline interaction. P-value corresponding to least-square mean difference between Migalastat and placebo is displayed.

[3]MMRM Pbo change M6 to M12.

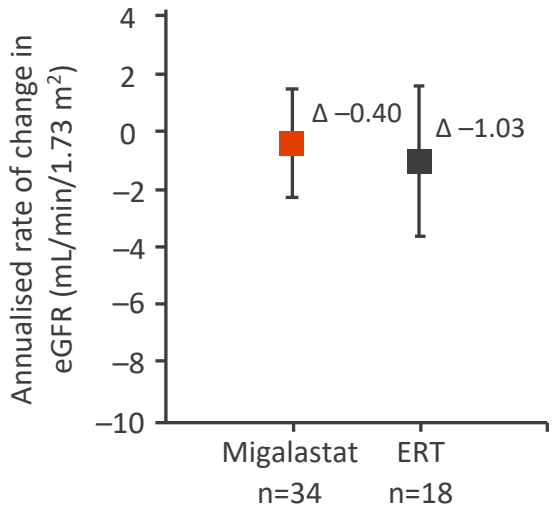
ATTRACT: Renal function remained stable on migalastat and was comparable with that achieved with ERT

Co-primary endpoints

- Change in GFR over 18 months was comparable for migalastat and ERT
  - Pre-specified criteria for comparability of treatments were met for $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$

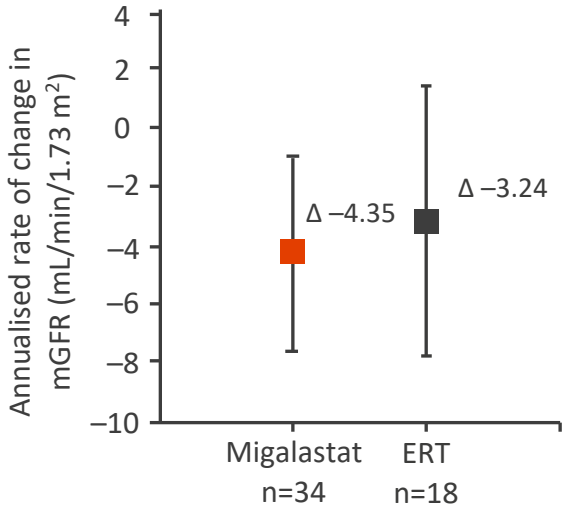
Difference of mean annualised change in $eGFR_{CKD\text{-}EPI}$ = +0.63

95% CI overlap >50% ✓ Difference means <2.2 ✓



Difference of mean annualised change in $mGFR_{iohexol}$ = −1.11

95% CI overlap >50% ✓ Difference means <2.2 ✓



CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ERT, enzyme-replacement therapy; GFR, glomerular filtration rate; eGFR, estimated GFR; mGFR, mean GFR; iohexol, iohexol clearance; LSM, least-square mean; SE, standard error

Hughes DA, Nicholls K, Shankar SP, et al. J Med Genet 2017;54(4):288-296.

Study 012 ATTRACT: Annualized GFR at 30 months in Migalastat group and ERT switchers

- eGFR annualized change was measured after 12 months of open-label migalastat treatment in patients treated with migalastat (migalastat-migalastat) or with ERT (ERT-migalastat) in the 18 month comparison period

	Migalastat - Migalastat mean ± SD 0 – 30 months (95% CI) n = 31	ERT - Migalastat mean ± SD 18 – 30 months (95% CI) n = 15
eGFR (CKD-EPI)	-1.72 ± 2.55 (-2.65, -0.78)	-2.13 ± 12.43 (-9.02, 4.75)

ANCOVA model [mITT]

GALAFOLD (migalastat hydrochloride) [Summary of product characteristics].2017;Amicus Therapeutics Data on File 012 OLE CSR.

ATTRACT : Renal Function Remained Stable Following 30 Months Migalastat Treatment using both GFR methods (patients with amenable mutations)

31 amenable patients on migalastat entered into the open label extension phase of 12 months

Treatment	Statistical Assessment	$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)	$mGFR_{Iohexol}$ (mL/min/1.73 m^2)
Migalastat	Mean annualized change from baseline to 30 months (95% CI)	–1.7 (–2.7, 0.8) n=31	–2.7 (–4.8, 0.7) n=31

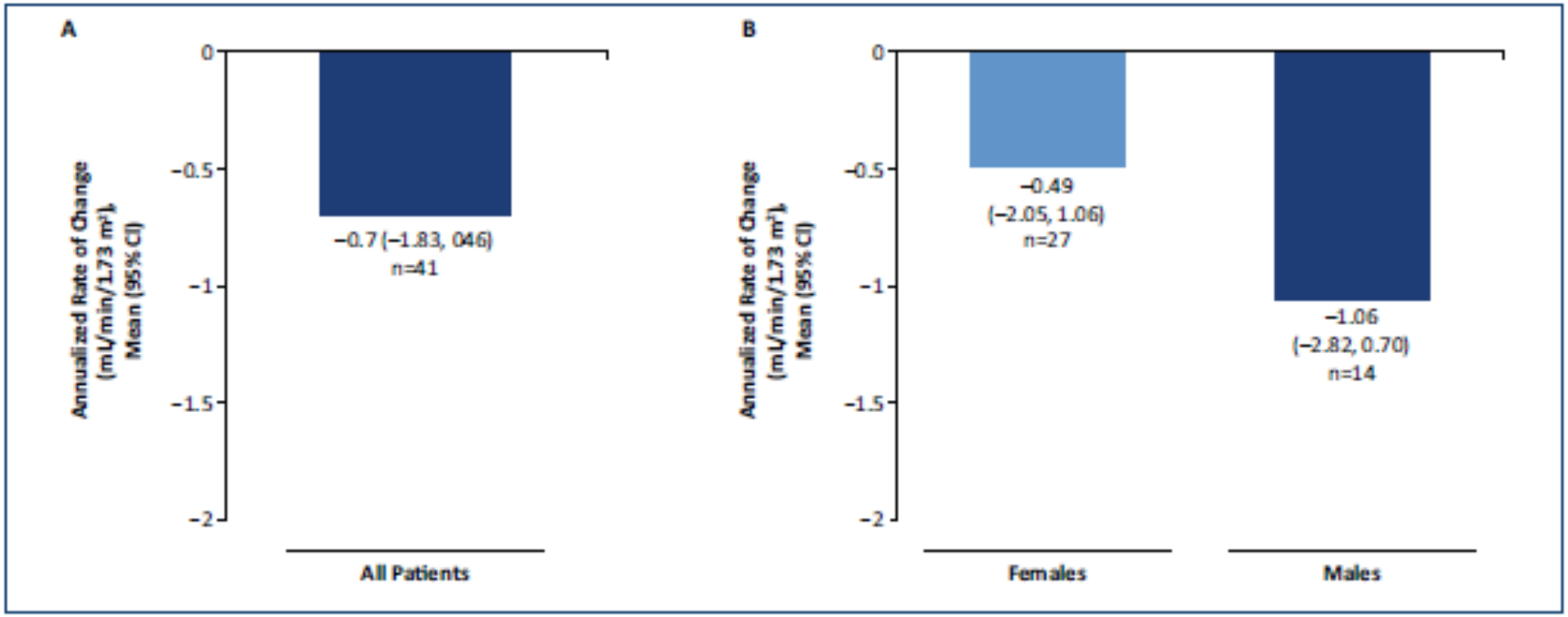
Stabilisation of the renal function on the eGFR similar to what is observed in normal healthy adults (decrease around -1 mL/min/1,73 m^2/an for a man aged > 40 ans)

Felt-Rasmussen et al. Presented at: 12th Annual WORLD Symposium™ 2017; February 13-17, 2017; San Diego, CA

FACETS: Stabilization of Renal Function with migalastat at 48 months

Annualized change of eGFR between baseline and 48 months

Figure 4. Annualized Mean Change in $eGFR_{CKD-EPI}$ From Baseline to Month 48 in (A) All Patients and (B) Patients By Sex (patients with amenable mutations)



Rate of change calculated using simple linear regression.
CI=confidence interval.

No clinically significant differences were observed during the initial 6-month placebo-controlled period.

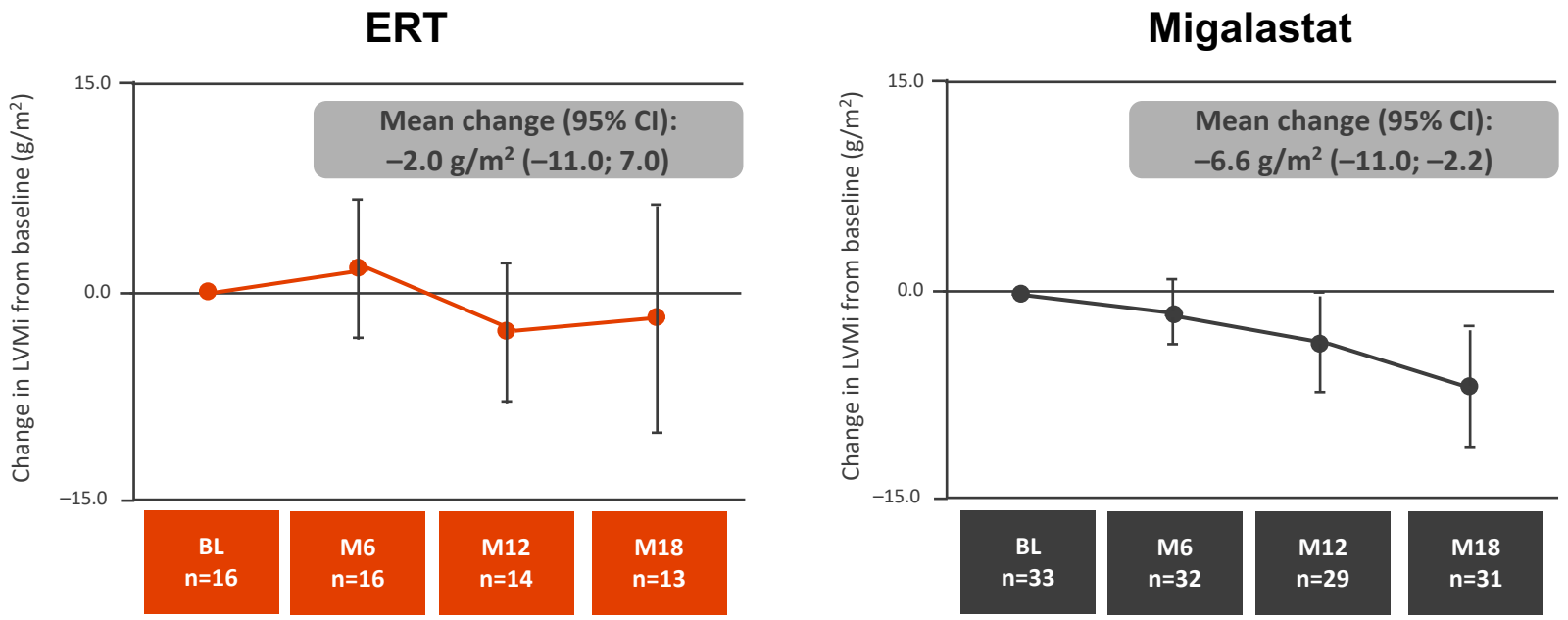
Schiffmann et al, Poster ERA-EDTA 2017

Heart

ATTRACT: LVMi was significantly decreased in amenable patients receiving migalastat

Secondary endpoint

- LVMi decreased significantly from baseline to 18 months in patients switched from ERT to migalastat

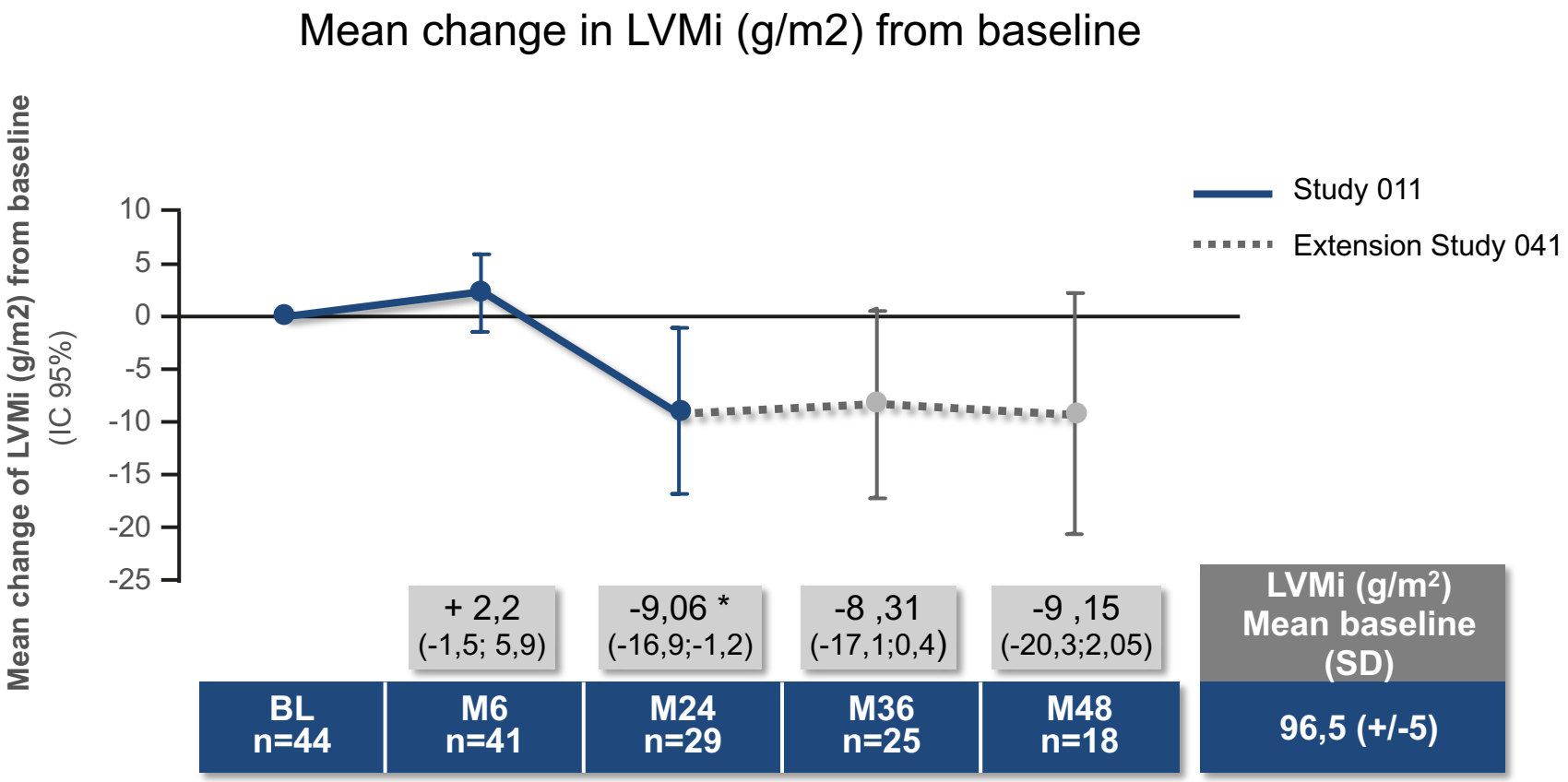


BL, baseline; CI, confidence interval; ERT, enzyme-replacement therapy; LVMi, left ventricular mass index; M, month

Hughes DA, Nicholls K, Shankar SP, et al. J Med Genet 2017;54(4):288-296.

FACETS and Open label extension Study (041)

Reduction of LVMi with migalastat is maintained at 48 months



No clinically significant differences in LVMi were observed during the initial 6-month placebo-controlled period.

*Statistically significant change from baseline based on 95% confidence interval

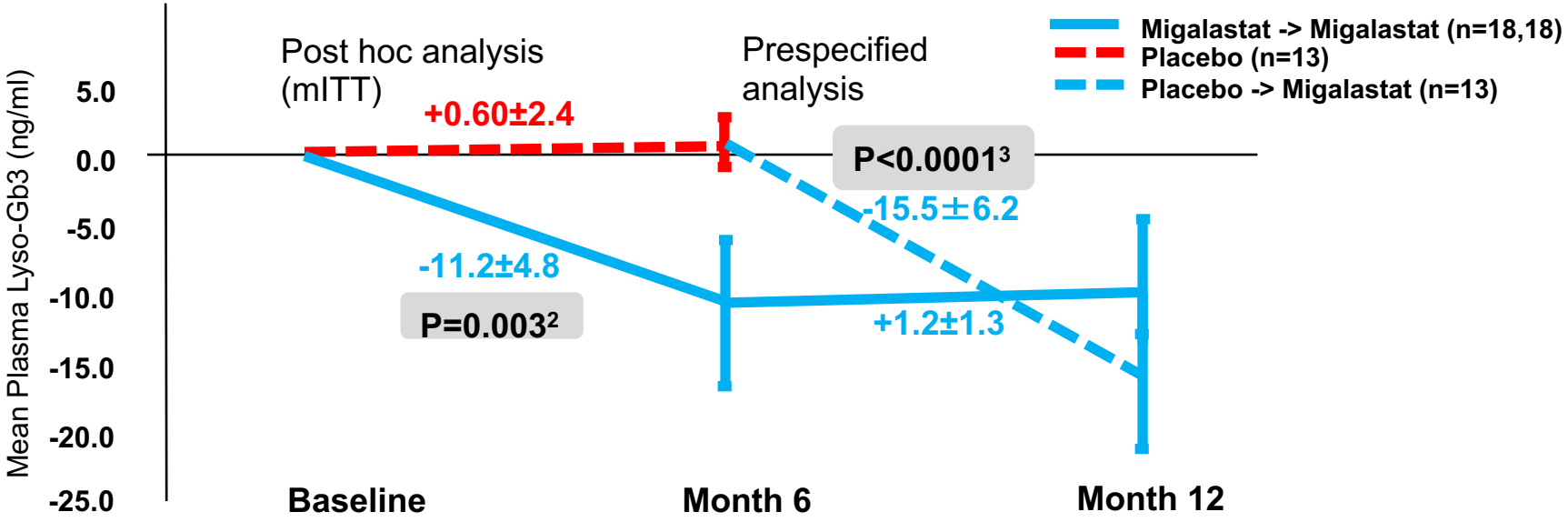
Galafold SmPC January 2018

Surrogate markers

FACETS: Plasma lyso-Gb_3

Statistically Significant Reduction in Plasma Lyso-Gb3 at Month 6 and Month 12 Following Treatment with Migalastat (GLP HEK Amenable)*

Plasma Lyso-Gb3[1]



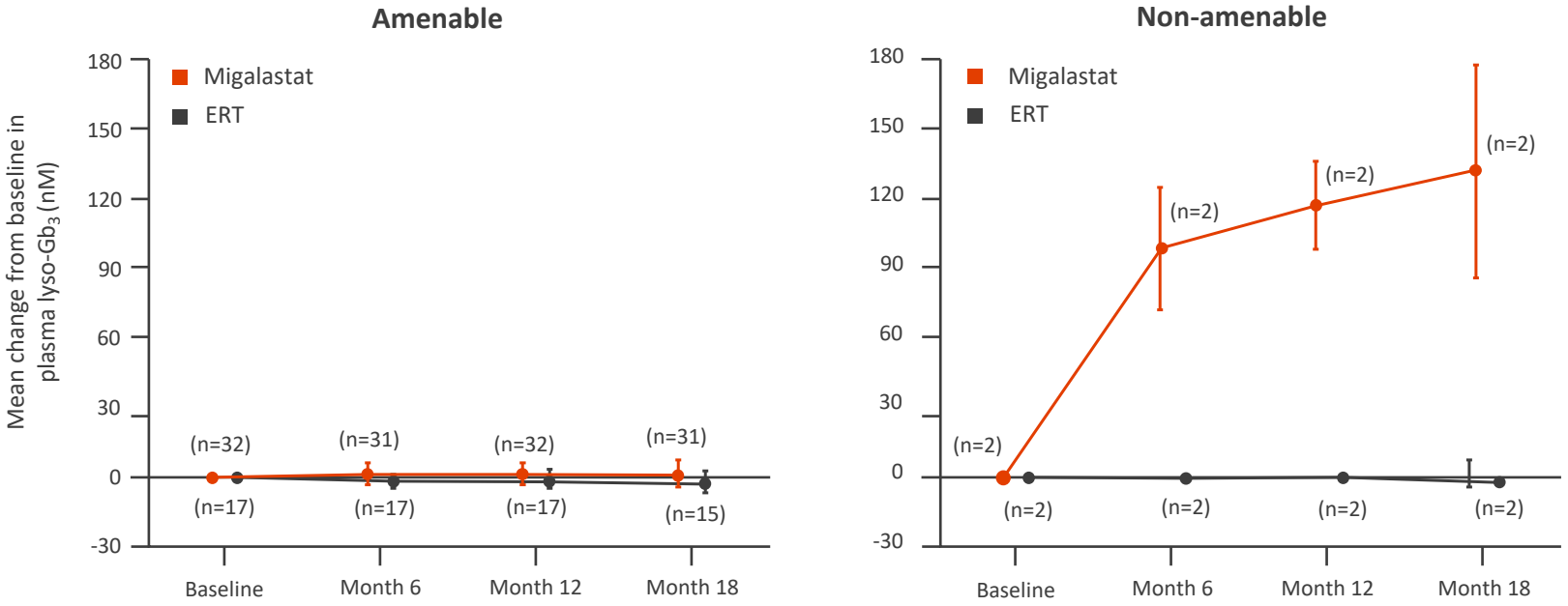
- Plasma lyso-Gb3 levels in patients with mutant α-galactosidase that was not suitable for migalastat therapy were unchanged

*Patients with amenable GLA mutations in GLP-validated HEK assay
[1]Baseline corrected. Error bars are SEM
[2]ANCOVA comparing Migalastat to placebo in Stage 1
[3]ANCOVA comparing change from month 6 to month 12 in subjects switching from placebo to Migalastat

ATTRACT: Plasma lyso-Gb_3 levels

Secondary endpoint

- Plasma lyso-Gb_3 levels slightly increased but remained low in patients with amenable mutations treated with migalastat for 30 months; levels also remained low in patients on ERT for up to 18 months*
- In patients with non-amenable mutations, plasma lyso-Gb_3 increased following treatment switch compared with patients who remained on ERT



*mITT population
ERT, enzyme-replacement therapy; lyso-Gb_3, globotriaosylsphingosine; mITT, modified intention-to-treat

Nicholls K, et al. Poster presented at: Kidney week November 2014,Philadelphia,PA; GALAFOLD (migalastat hydrochloride) [Summary of product characteristics].2017

Safety

Study AT1001-012 (ATTRACT): Safety

- Adverse events (AEs)
  - Frequency in migalastat group of treatment emergent AEs were comparable (34, 94%) to ERT group (20, 95%)
  - Most frequently reported AEs: **Nasopharyngitis** 33% (vs 33% ERT), **headache** 25% (vs 24% ERT)
- AEs mostly mild to moderate in severity
- No patient discontinued study drug due to an AE
- No deaths
- Serious adverse events (SAEs)
  - 19% in migalastat group, 33% in ERT group
  - **No reported SAE was considered to be related to study drug during the 18-month treatment period**

This study was not powered to demonstrate statistical superiority; migalastat should not be used concomitantly with enzyme replacement therapy (ERT)

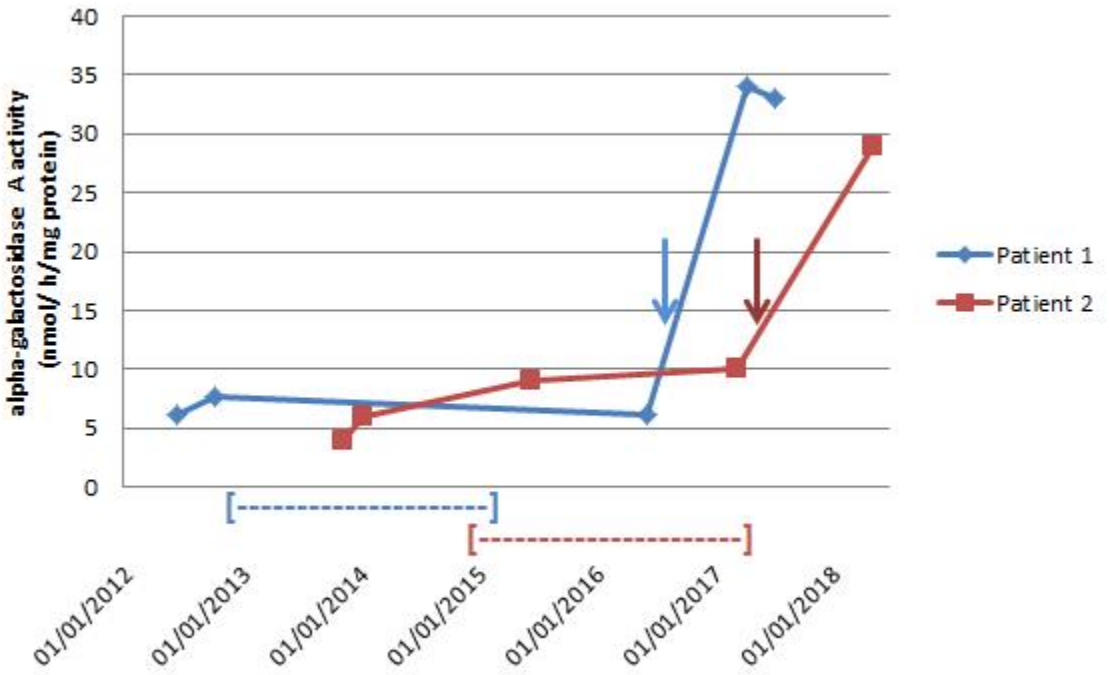
Hughes DA, Nicholls K, Shankar SP, et al. J Med Genet 2017;54(4):288-296.

Migalastat safety profile

- In Phase 3 studies, TEAEs reported with the use of migalastat were mostly mild or moderate, required no intervention or were readily managed in standard clinical practice
  - The most frequently reported TEAEs (≥10%) in the migalastat group were **headache**, **nasopharyngitis**, nausea, fatigue, pyrexia, and paresthesia
  - Compared with ERT, more patients on migalastat reported headache, upper respiratory tract infection and urinary tract infection
  - Patients switched from ERT reported higher rates of influenza, cough and sinusitis
  - No deaths or discontinuations due to TEAEs
- Due to the **limited number of patients**, the safety profile will be further characterised

ERT, enzyme-replacement therapy; TEAE, treatment-emergent adverse event
GALAFOLD [European Medicines Agency assessment report]. 2016

N215S patients-chaperon



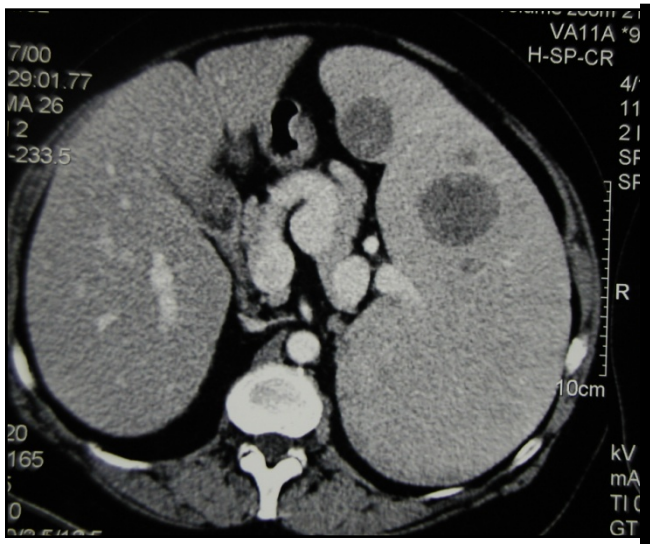
Lamari F, Mauhin W, et al.
Mol Genet Genomic Med 2019.

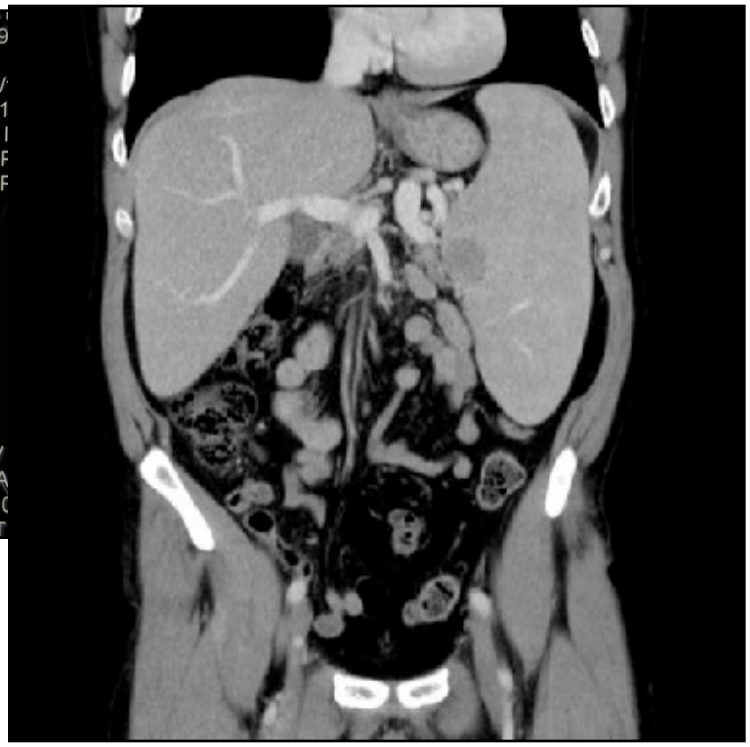
5a. Perspectives

Clinical phenotype in LSDs

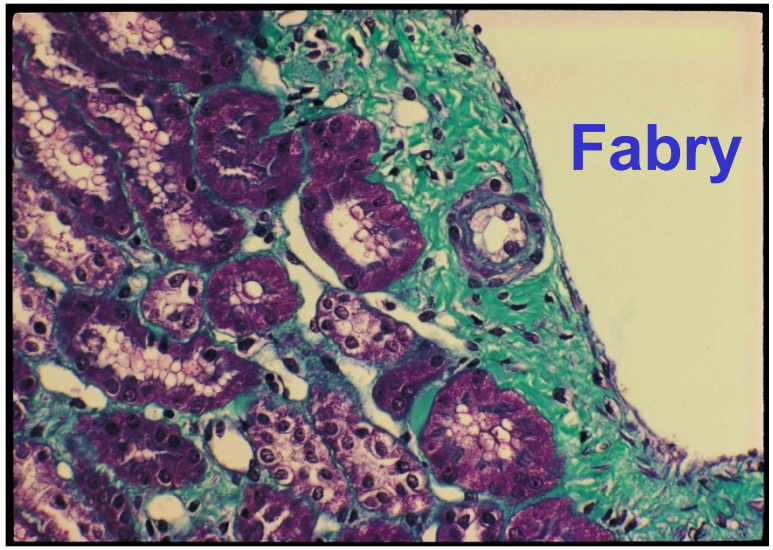
- Macrophage

Gaucher type 1



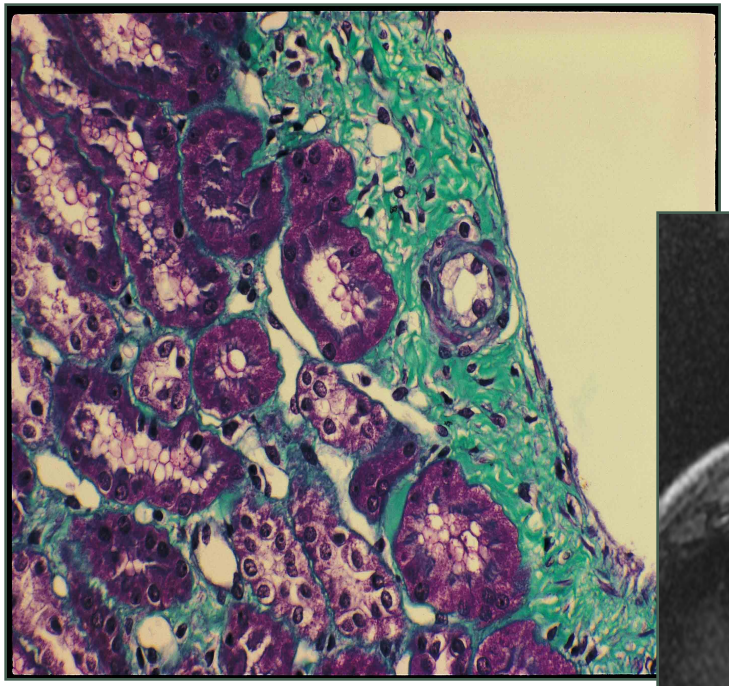


- Endothelial cell

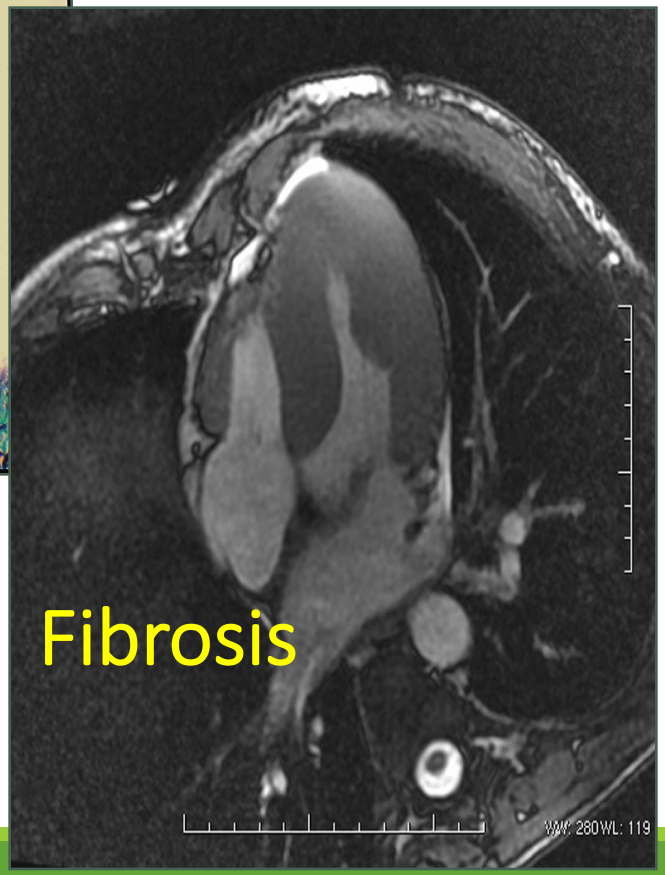


ASMD (Niemann-Pick type B)

Fabry representations



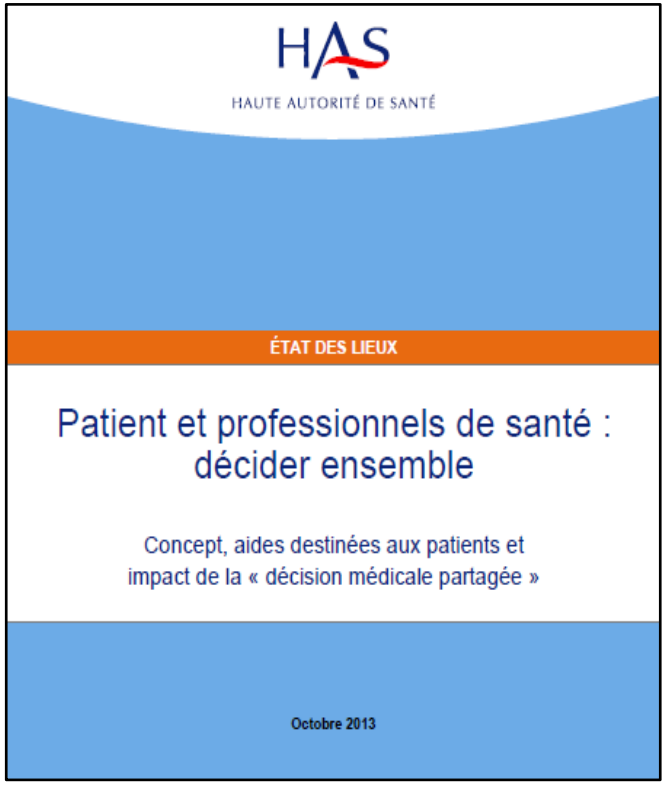
Ischemia



PNQ
Patient need Questionnaire

Patients and HCPs: Make a Decision Together–HAS October 2013

- **Shared decision-making (SDM) process is a patient-centric process**
- The principle of respect for the patient and his or her autonomy is at the heart of the SDM process, which is essentially based **on the patient's preferences and values**

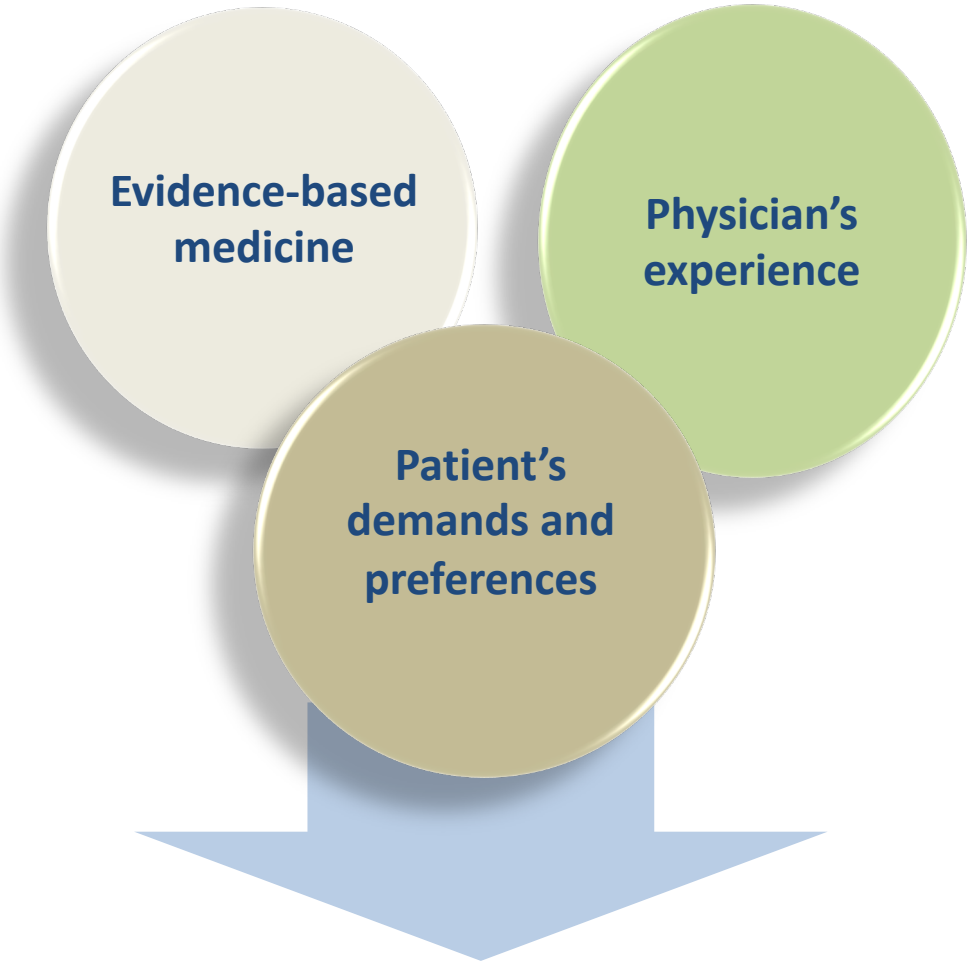


Global review about the SDM process in France published by HAS
(October 2013)

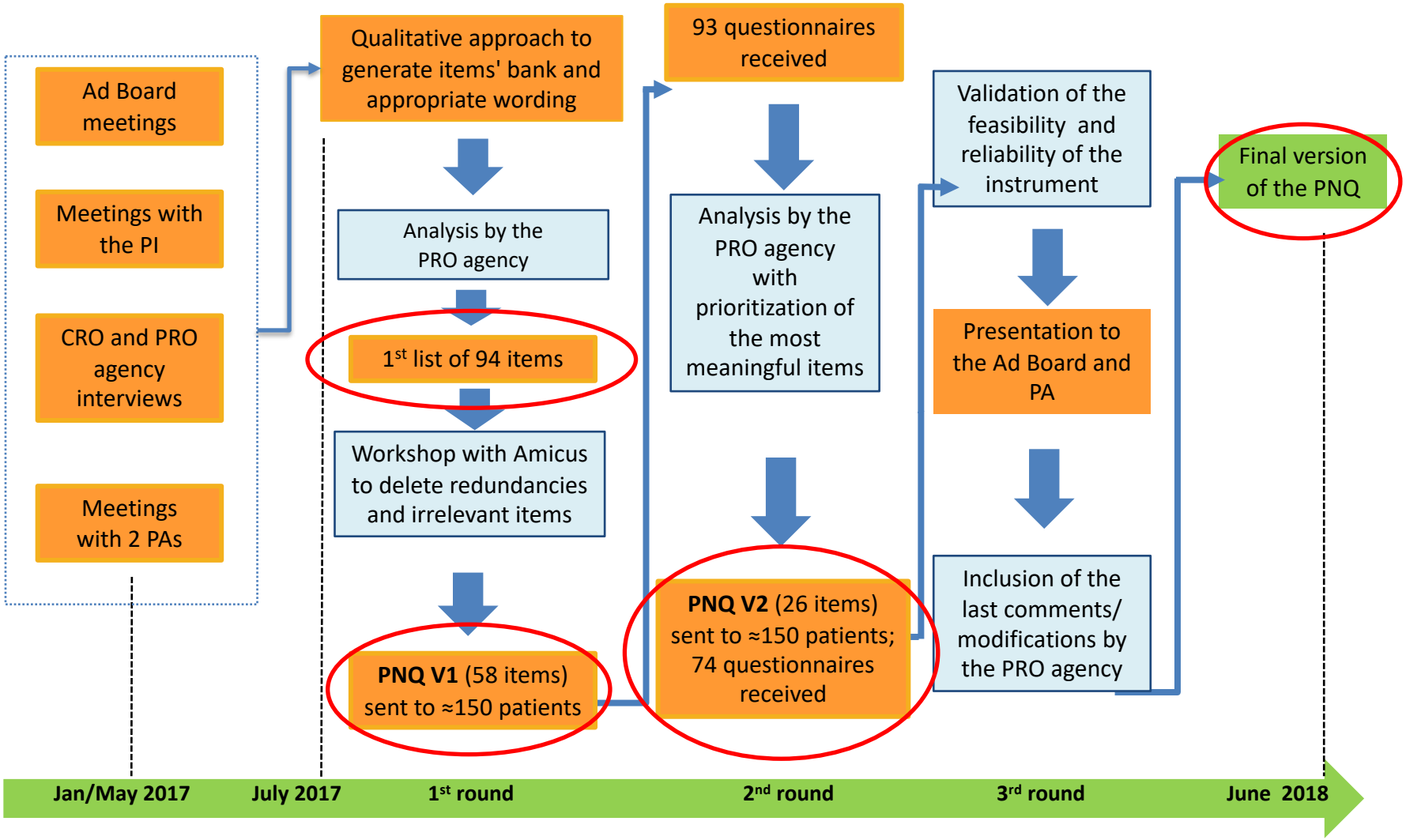
HAS=Haute Autorité de Santé; HCP=health care professional.

“SDM” or Process of Disclosing Patients’ Preferences

- **1st stage:** exchange of information between patient and physician
- **2nd stage:** deliberation
- **3rd stage:** informed and shared decision-making



PNQ: Multiple Steps for Conception and Validation



Results From 8 Initial Interviews From PNQ

A large range of clinical symptoms impact Fabry disease; however, there are 2 common themes:

- Fabry disease is a disease you can live with, you just need to adapt your lifestyle—it does not really handicap you
- It is a lifelong disease for which treatments exist, and you do not die from the disease in the short-term

It is, however, unpredictable—you never know where it will strike next.

If Fabry disease was an animal—some examples

- **Chameleon**, as it changes and is never the same, many parts are affected
- A **crocodile** but hidden under water
- An **octopus**, as it has tentacles—we have pain in our hands and extremities, and Fabry disease is all over you
- A **blood sucker** that sucks out your energy
- A **little dog** that is trained and really does no harm
- A **little animal** that slowly makes a nest inside me, but does no harm
- A **lion** that is ferocious

A Vital Role of Patient Associations

APMF and **VML**: involvement from the beginning of the project and at all stages of it, with a complementary role to that of the Scientific Committee

- At the beginning: discussion about the concept and feasibility of the project
- Progress of each step validated with both Patients Associations
- Definition of how to ensure the confidentiality of patient data
- Validation of documents for patients
- Day-to-day management of patient members of associations
  - Identification of patients likely to take part of the project
  - Contact patients to explain the project
  - Obtaining agreement from patients to participate
  - Sending of successive questionnaires, follow-up of the return of these questionnaires, and management of reminders

APMF=Association des Patients de la Maladie de Fabry; VML=Vaincre les Maladies Lysosomales.

How Patients Live With and Feel About Fabry Disease

- **How patients live with Fabry disease**
  - Principle constraints are physical: patients cannot do as they want, they are out of breath, and they suffer from a lot of pain (very often one of the most common problems cited, much more than GI)
  - Psychologically the hardest part is learning that you can transmit the illness to your offspring; that said, it does not prevent people from wanting to have children as treatments are available

- **What kind of life patients with Fabry disease wish they had**
  - Have a normal life expectancy—stop the progression of the disease (not a cure)
  - Live a normal life (such as someone without Fabry disease)
  - Fewer signs and symptoms of the disease
  - Have fewer constraints around treatment administration
  - When a diagnosis is finally made, patients seem “relieved” to know what it is; it is not a traumatic moment
  - Effective treatments exist

GI=gastrointestinal.

Final Version of the PNQ

Here is a list of statements regarding **patients' expectations about their medication** for Fabry disease.
For each of these expectations, please indicate how **important** they are to you by ticking the relevant box.
If one statement does not apply to you, for instance because you do not work, please tick the box "Does not apply to me".
If you do not know how to answer, choose the answer closest to your situation.

How important is it to you that the medication…

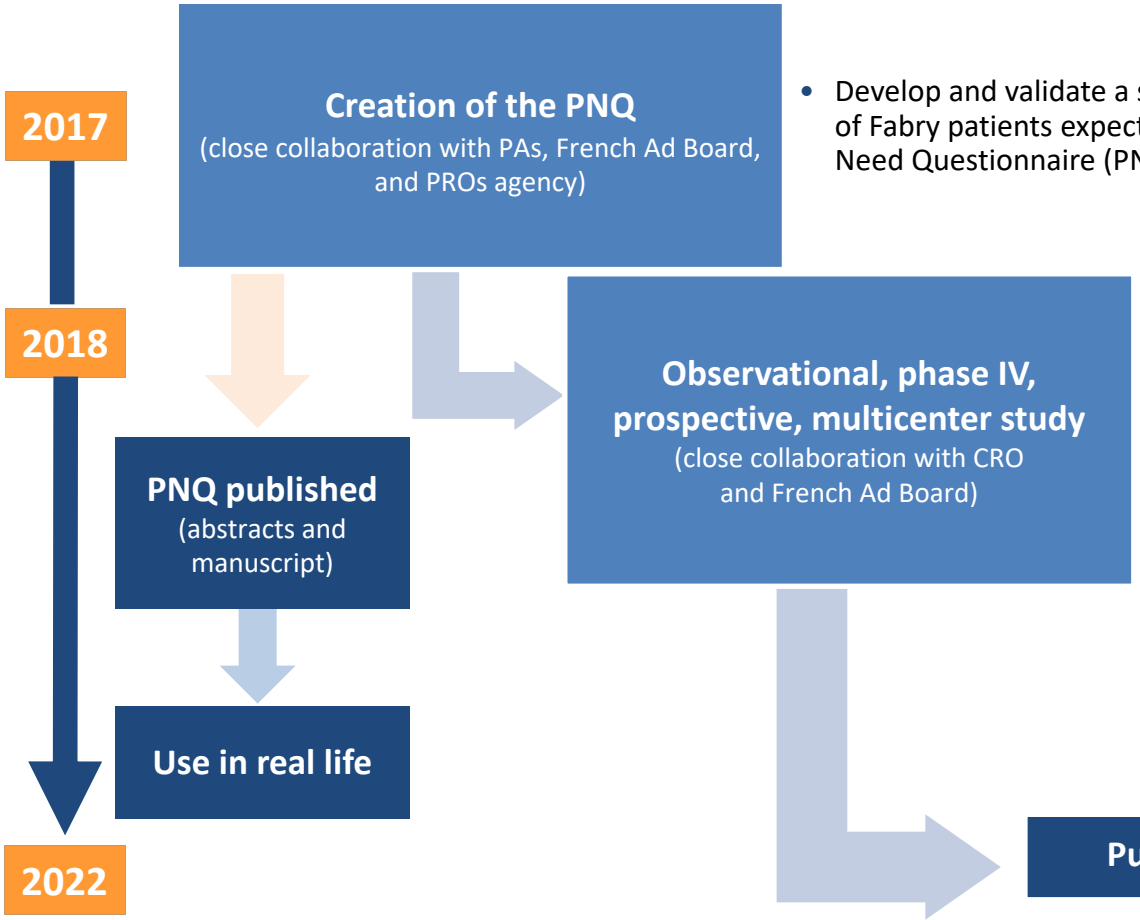
Please tick a box for each statement	Not at all important	Somewhat important	Moderately important	Fairly important	Very important	*Does not apply to me*
ensures you are less tired	1	2	3	4	5	6
reduces the pain in your hands and feet	1	2	3	4	5	6
ensures you are less breathless in your daily life or when making an effort	1	2	3	4	5	6
reduces gastrointestinal disorders (nausea, pain, diarrhoea, constipation)	1	2	3	4	5	6
enables you to tolerate heat and temperature variations better	1	2	3	4	5	
reduces the intensity, frequency, or duration of painful attacks	1	2	3	4	5	
enables you to continue working	1	2	3	4		
enables you to cope with physical exertion better	1	2	3	4		
enables you to live normally, as if you did not have Fabry disease (DIY, gardening, playing with your children/grandchildren, housework, etc.)	1					6
enables you to maintain your social life (work, school, family, friends, etc.)	1			4	5	6
enables you to travel easily	1	2	3	4	5	6
enables you to have a better quality of life	1			4	5	6
ensures you are not dependent on other people on a day-to-day basis	1		3	4	5	6
enables you to spend time with your family	1	2	3	4	5	6
enables you to stay fit for longer	1	2	3	4	5	6
prevents the onset of cardiac, renal, or neurological proble	1	2	3	4	5	6
slows down the deteriora of your org kid s, heart, .)	1	2	3	4	5	6
enables you to feel good e preceding o owing treatment administration	1	2	3	4	5	6
do rau effects o ers ects related to the medication	1	2	3	4	5	6
s yo no erience and tiredness returning on days before me ion dmi red	1	2	3	4	5	6
redu e a of medication that you are taking	1	2	3	4	5	6

How important is it for you to have a medication…

Please tick a box for each statement	Not at all important	Somewhat important	Moderately important	Fairly important	Very important	*Does not apply to me*
that easily fits into your schedule and lifestyle	1	2	3	4	5	6
that you can take or administer on your own	1	2	3	4	5	6
that is easy to administer	1	2	3	4	5	6
that is administered orally (in tablet or capsule form)	1	2	3	4	5	6
with a short duration of administration	1	2	3	4	5	6

Noël E, et al. Orphan J Rare Dis, in press.

Fabry Patients' Needs, Benefit and Satisfaction Towards Their Treatment



- Develop and validate a specific instrument for the assessment of Fabry patients expectations regarding their treatment: Patient Need Questionnaire (PNQ)

- **Primary objective:** cluster patients with Fabry disease according to their needs and expectations regarding their treatment
- Assess prospectively, in real life, patient's benefit and patient's satisfaction regarding treatment, depending on his or her initial needs (PBQ/PBI, TSQM-9)

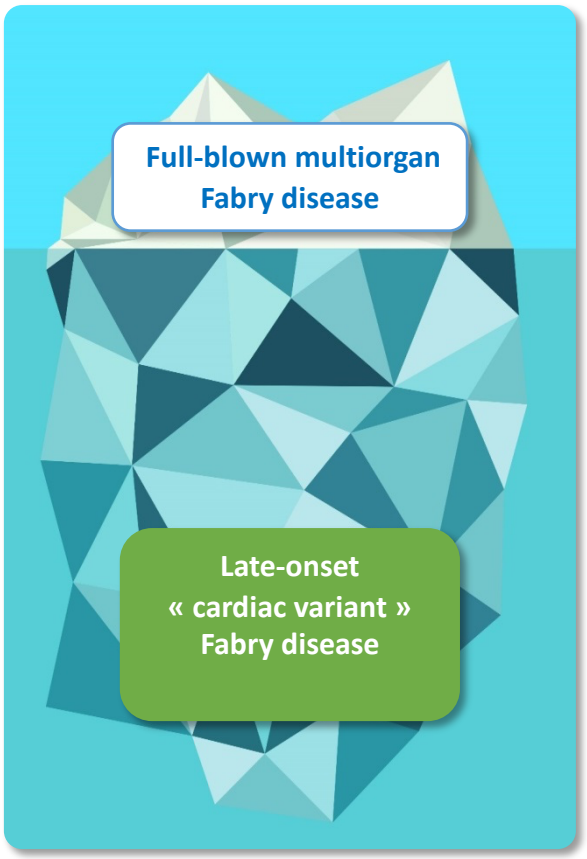
CRO=contract research organization; PA=physician assistant; PBI=patient benefit index; PBQ=patient benefit questionnaire; TSQM-9=Treatment Satisfaction Questionnaire for Medication.

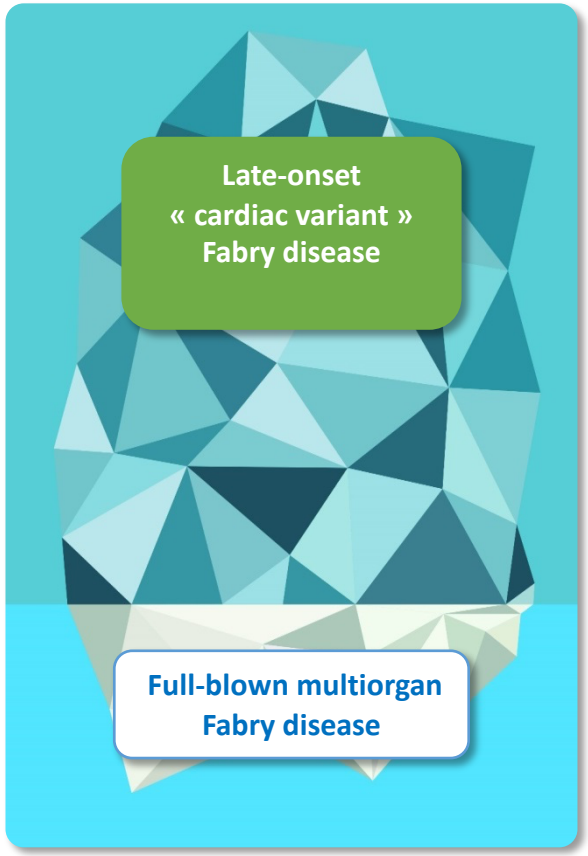
5b. Conclusion

Before

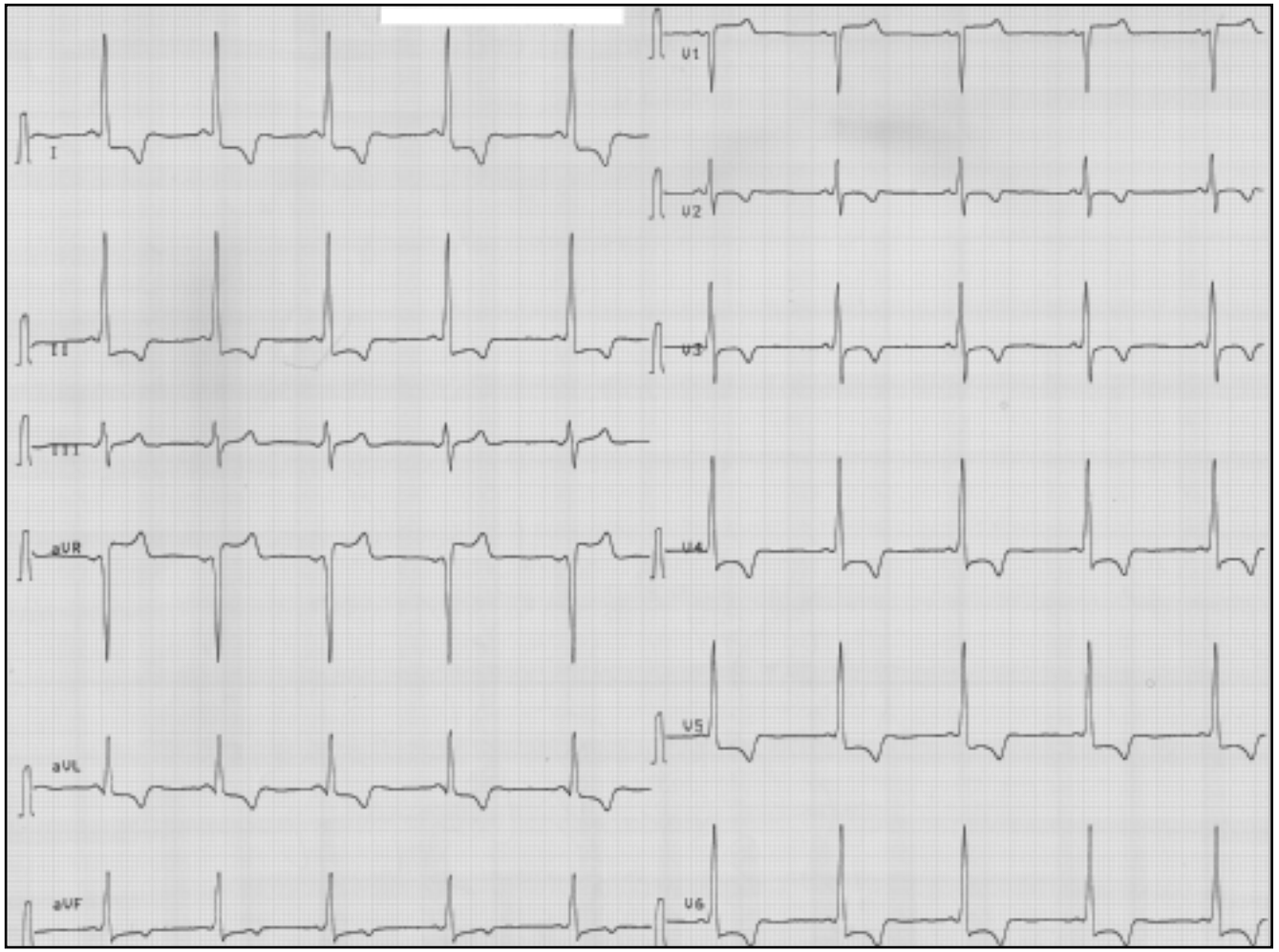
Now

Fabry disease



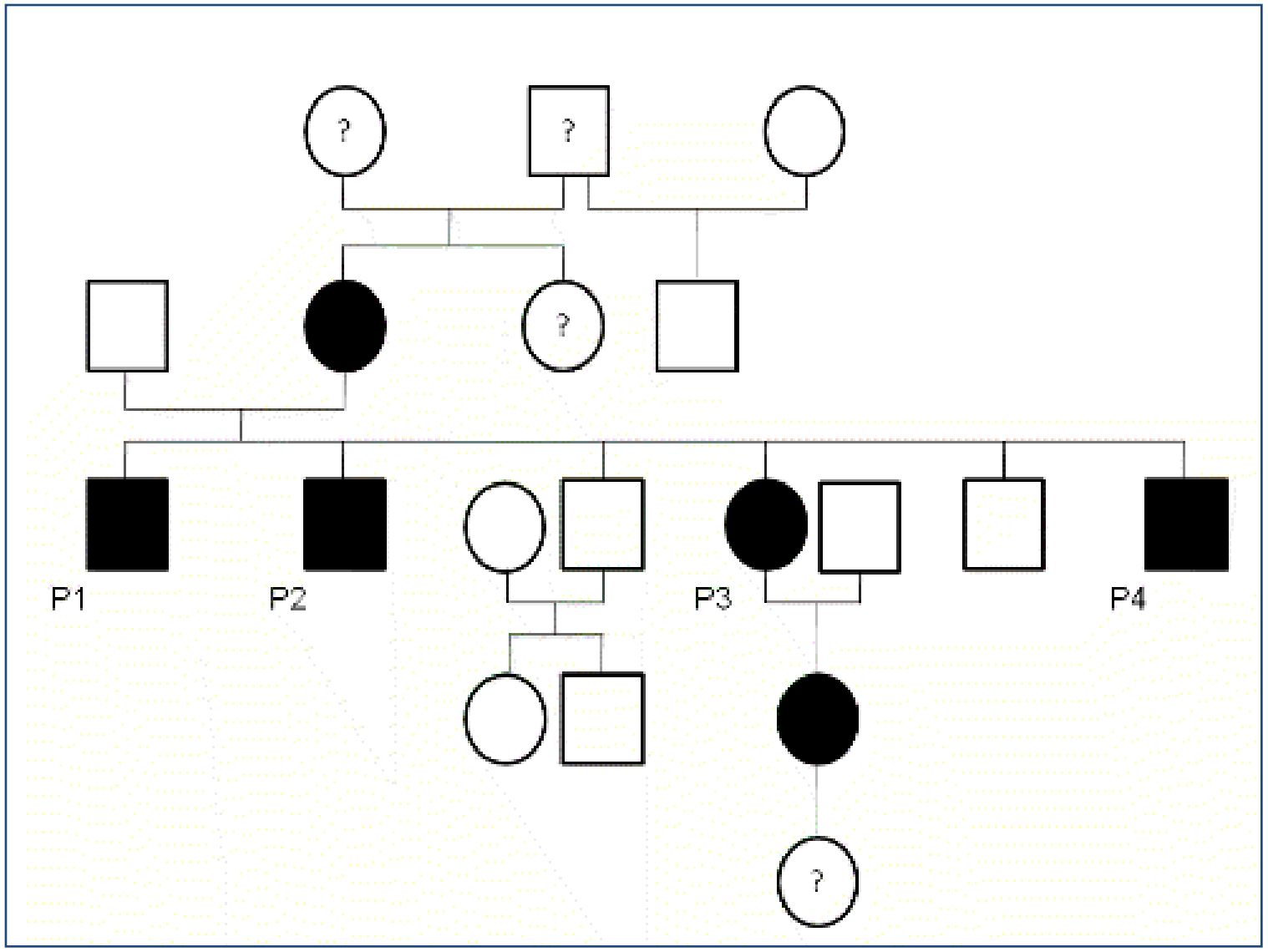


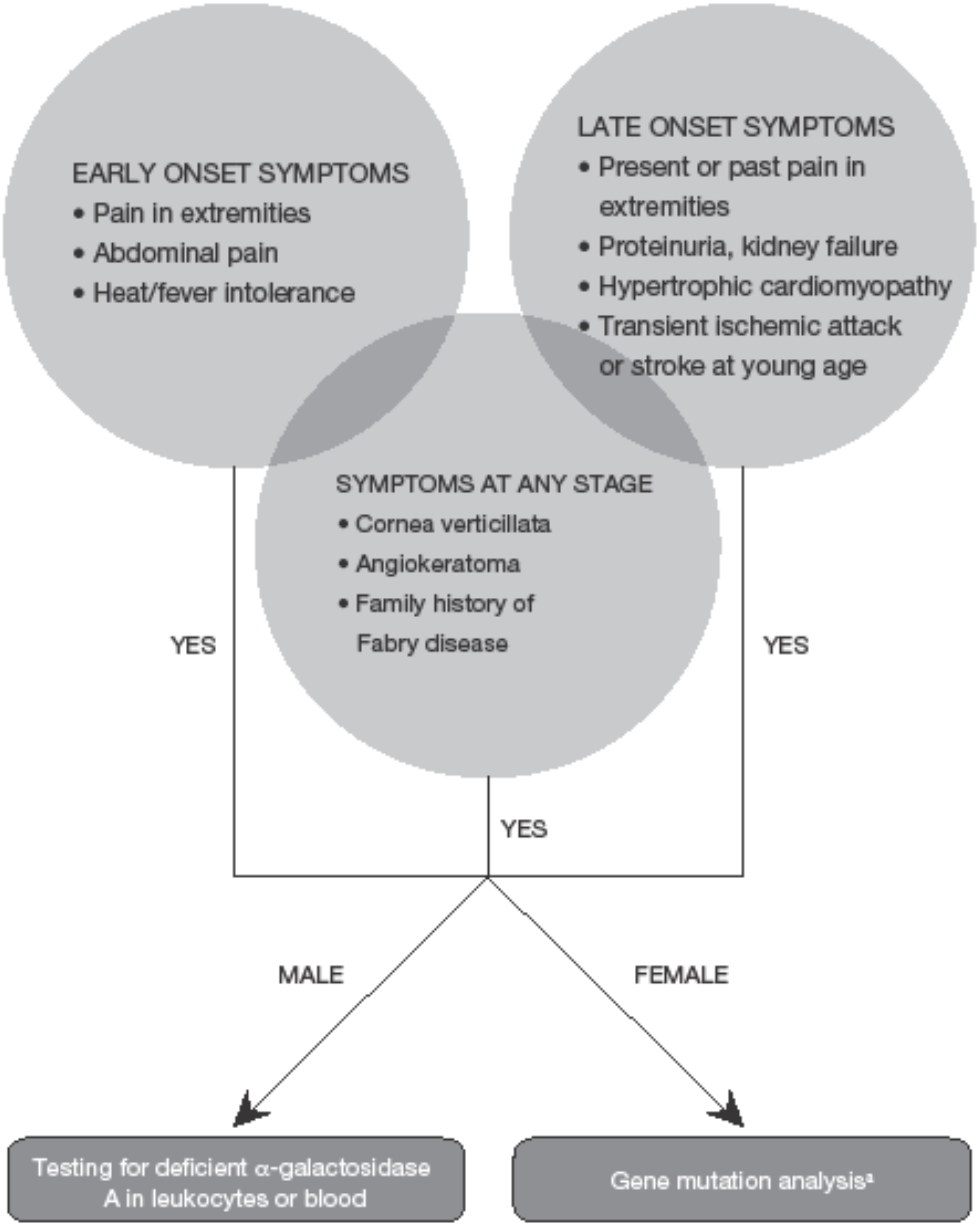
Extra-cardiac phenotype ?



An interdiciplinary team for Fabry patients

One patient = One family





Lidove O, et al. Clin Genet 2012.

Conclusion

- Early ERT is clinically efficient
- Early ERT requires **early diagnosis**
- **Early ERT is not enough**
  - Nephroprotective measures
  - Vasculoprotective therapies
- **Chaperone molecule for 30% of patients with amenable mutations?**
  - **Long-term results are needed**

Genotype/ Phenotype

- More than 100 patients included in FFABRY

- Most frequent mutation p.Asn215 Ser (n=9)

  $\Rightarrow$100% non classic phenotype

- ***Amenable*** mutation for migalastat:

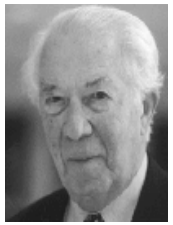
24% classic vs 68% non classic ($p<0,002$)

Mauhin W. Thesis 2018

J. Fabry

W. Anderson

C. De Duve

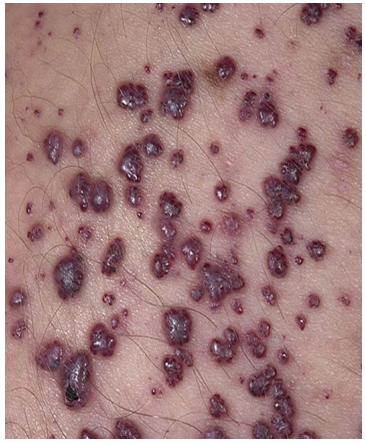


K. Hashimoto

R. Brady

1898 — **1950** — **1965** — **1967** — **2000** — **2015-16** — **……**

Angiokeratoma corporis diffusum



Lysosome

Nobel 1974

Fabry = Lysosomal disease

Defect in α- Galacto Sidase

Are female affected?

Enzyme Replacement Therapy

Fabrazyme®, Replagal®

Female are affected!

Chaperone Therapy

Galafold®

Substrate reduction therapy?

-

Gene Therapy?

-

Combination therapies?

6. Acknowledgements

Acnowledgements*

- **Patients and families**

- **Patient's associations:**
  - **APMF**
  - **VML**

- **CRML**

- **Co-workers**
  - Groupe collaboratif français
- **Collaborators**
  - **Physicians**
  - **Biochemists**
  - **Geneticists**
  - **……**

???


WHERE?
WHO?
WHAT?
WHY?
HOW?
WHEN?