La maladie de Fabry

Philippe Chevalier

Philippe Douek

Gilles Millat

Alain Fouilloux

Hospices Civils de Lyon

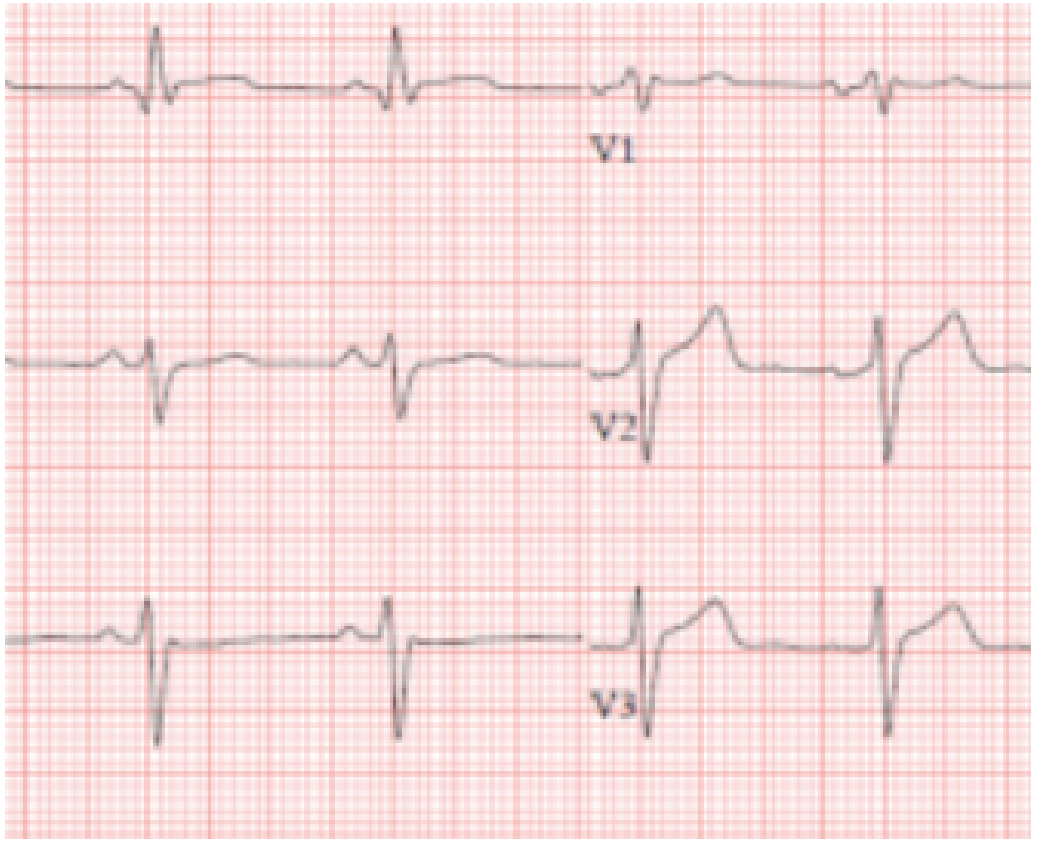
TROUBLES DU RYTHME CARDIAQUE D'ORIGINE HEREDITAIRE
CERA
CENTRE NATIONAL DE REFERENCE

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

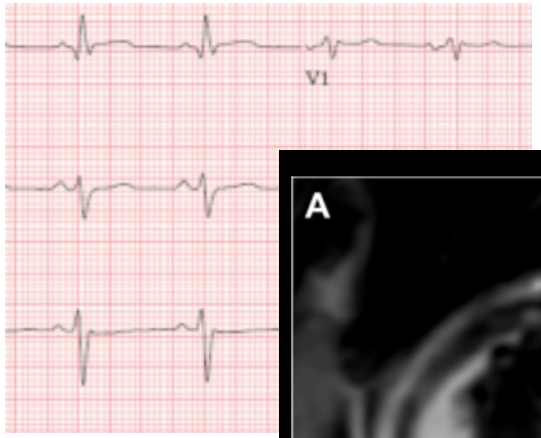
European Reference Network
for rare or low prevalence complex diseases
Network Heart Diseases
(ERN GUARD-HEART)

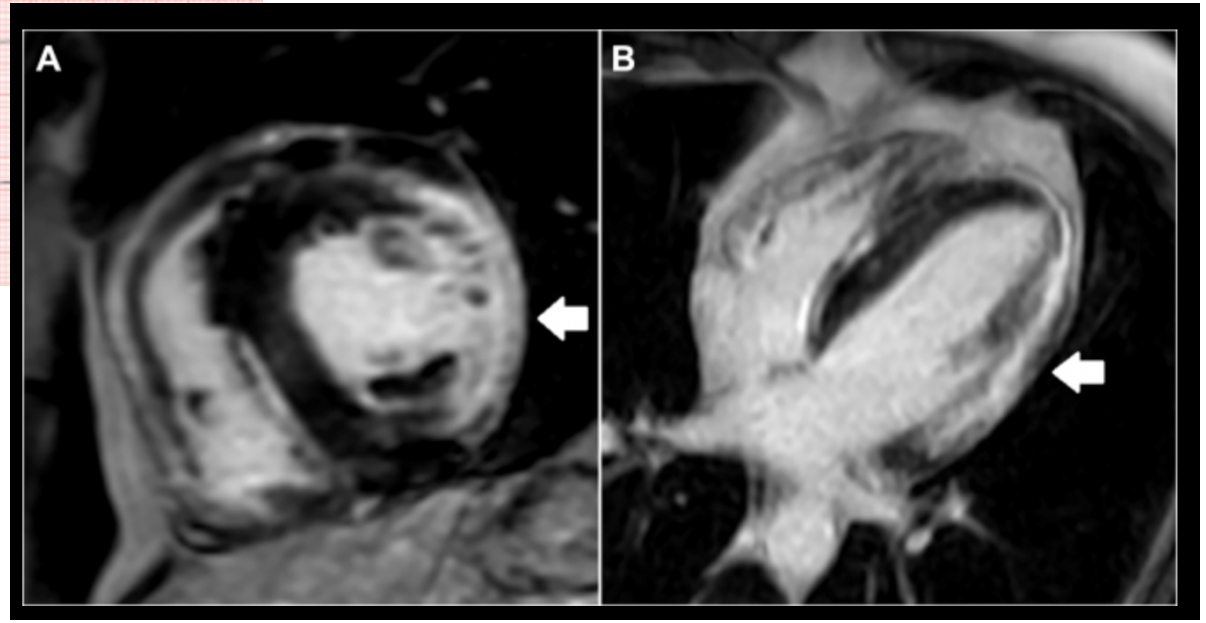
UNIVERSITÉ DE LYON

Syncope chez un homme de 58 ans, Aucun antécédent



Syncope chez un homme de 58 ans, Aucun antécédent

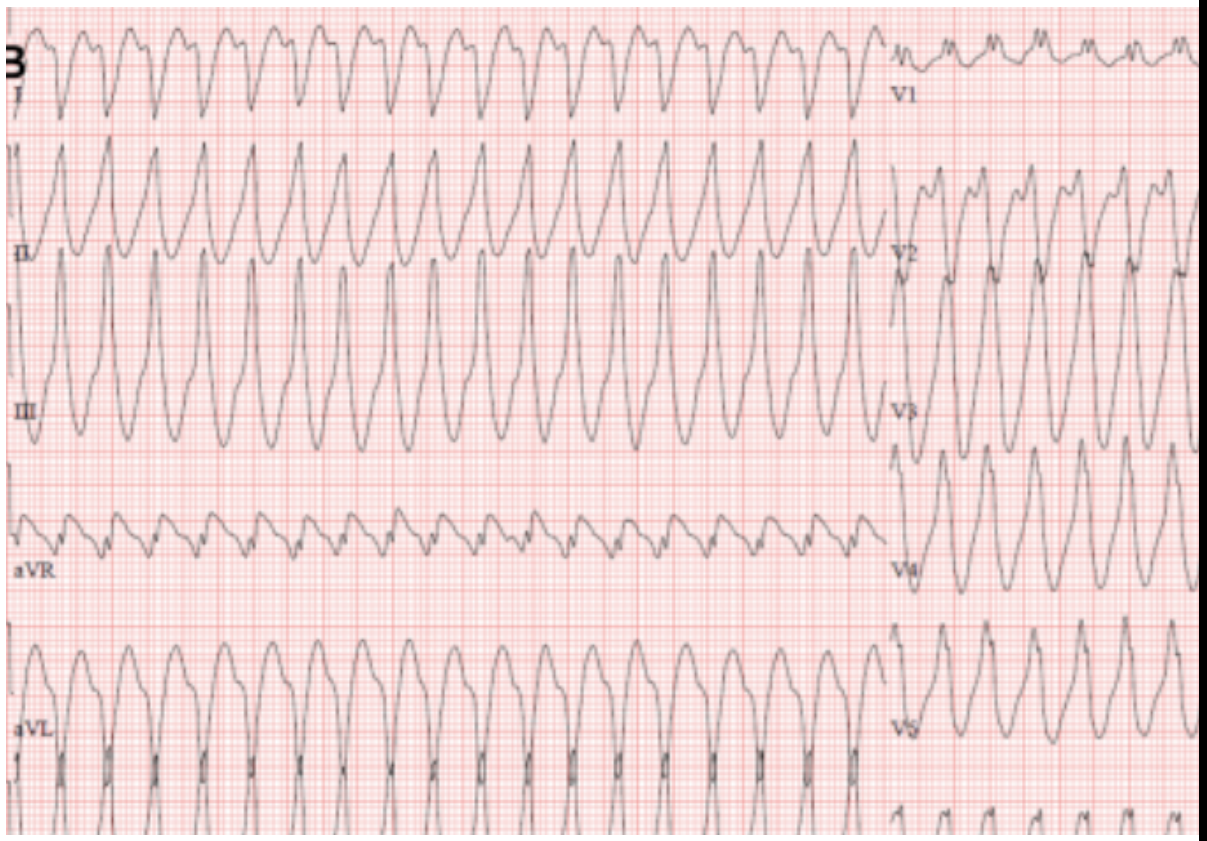


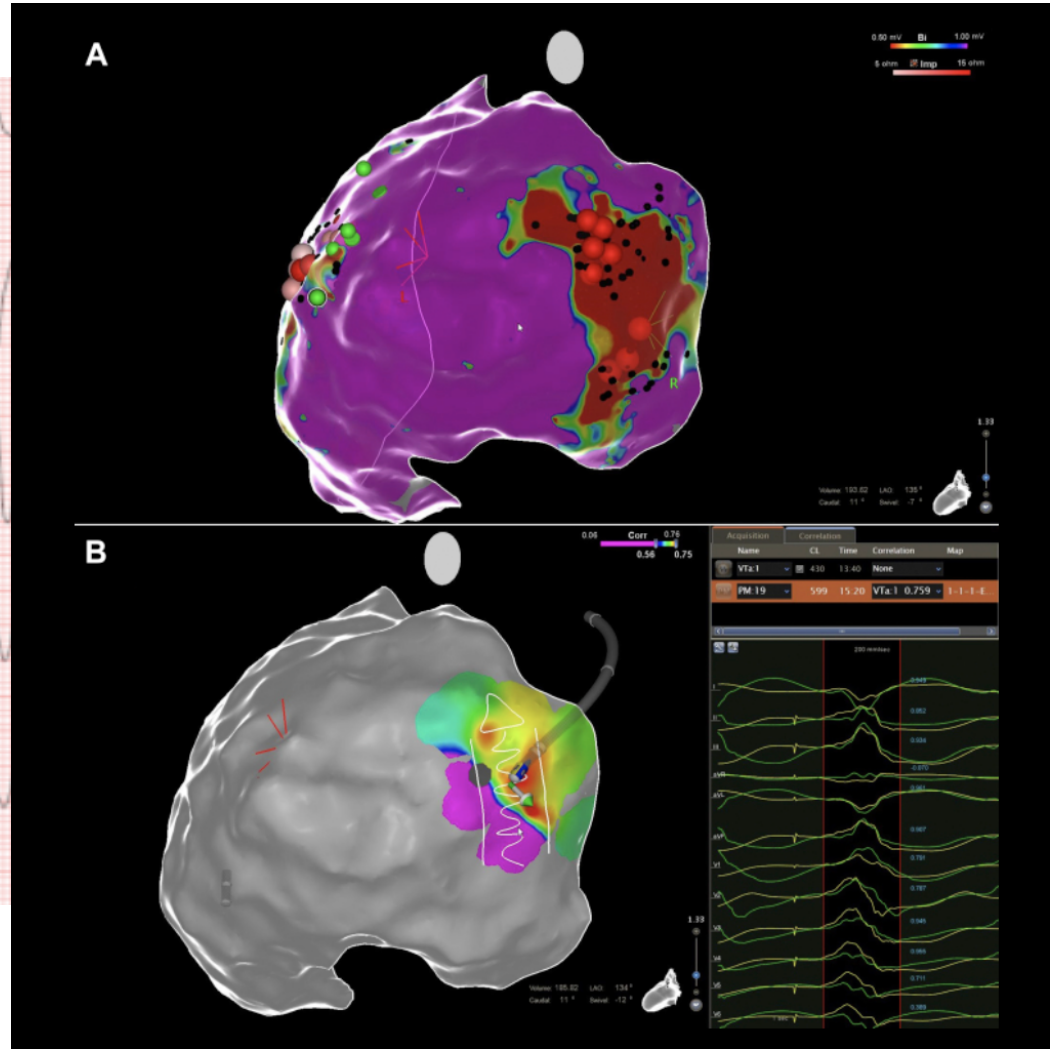


Troponine
240 ng/L

Myocardite (BB, IEC)

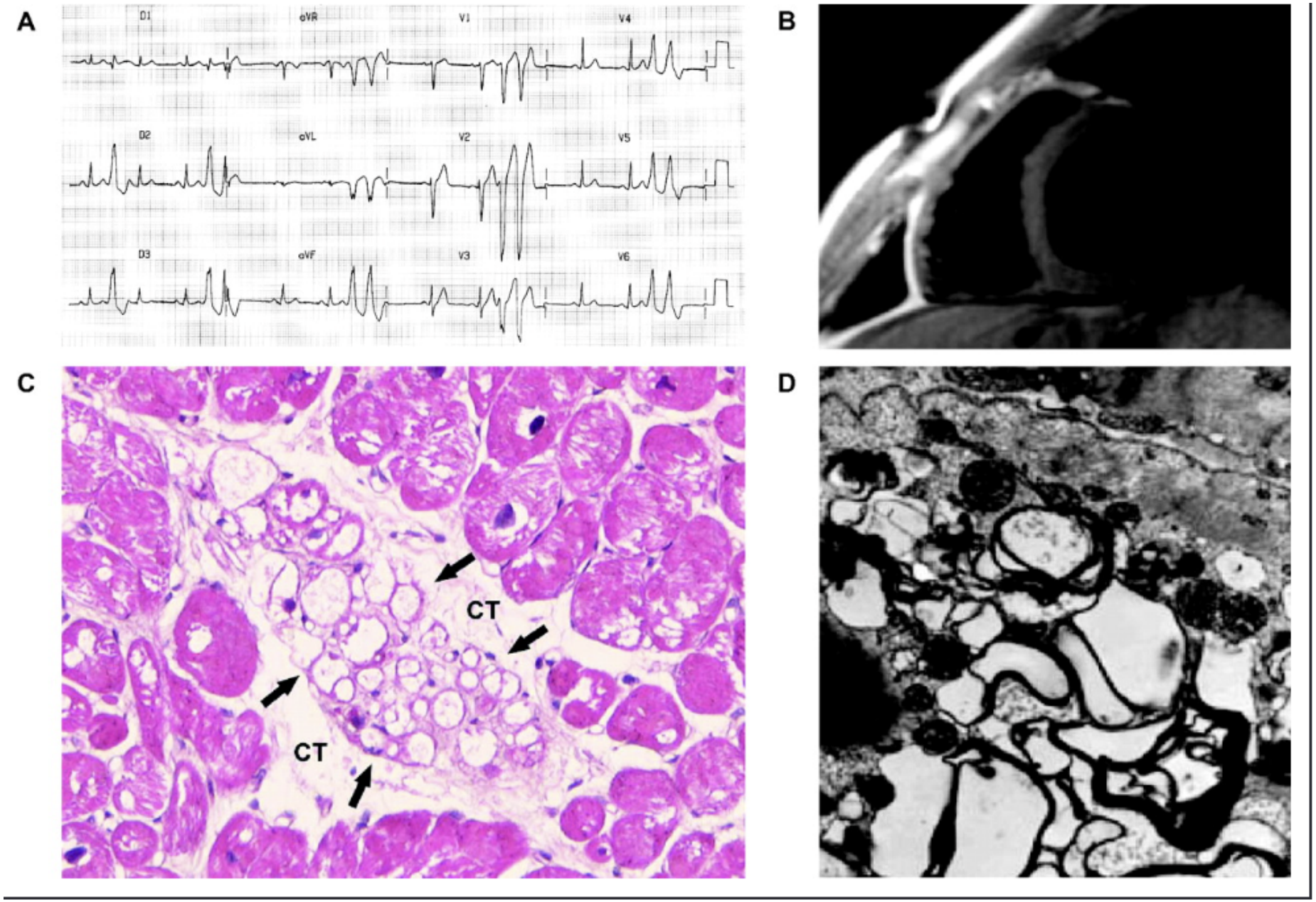
Palpitations 3 mois plus tard





Suspicion de cardiopathie arythmogène : génotypage

- Variant classe 5 sur on exon 5 du gène *GLA* : c.713G>A
- Plasma α-Gal A activity 0.30 µmol/L/h (normal : 2.66–10.20 µmol/L/h).
- Lyso-Gb3 was elevated to 14.7 nmol/L (normal <0.6 nmol/L)
- Aucun signe extracardiaque de maladie de Fabry


A
D1
aVR
V1
V4
D2
aVL
V2
V5
D3
aVF
V3
V6
B
C
CT
CT
D

Anderson–Fabry disease management: role of the cardiologist

Pieroni M, Desnick R, European Hea

Maladie de Fabry

- Comprendre
- Reconnaitre
- Traiter

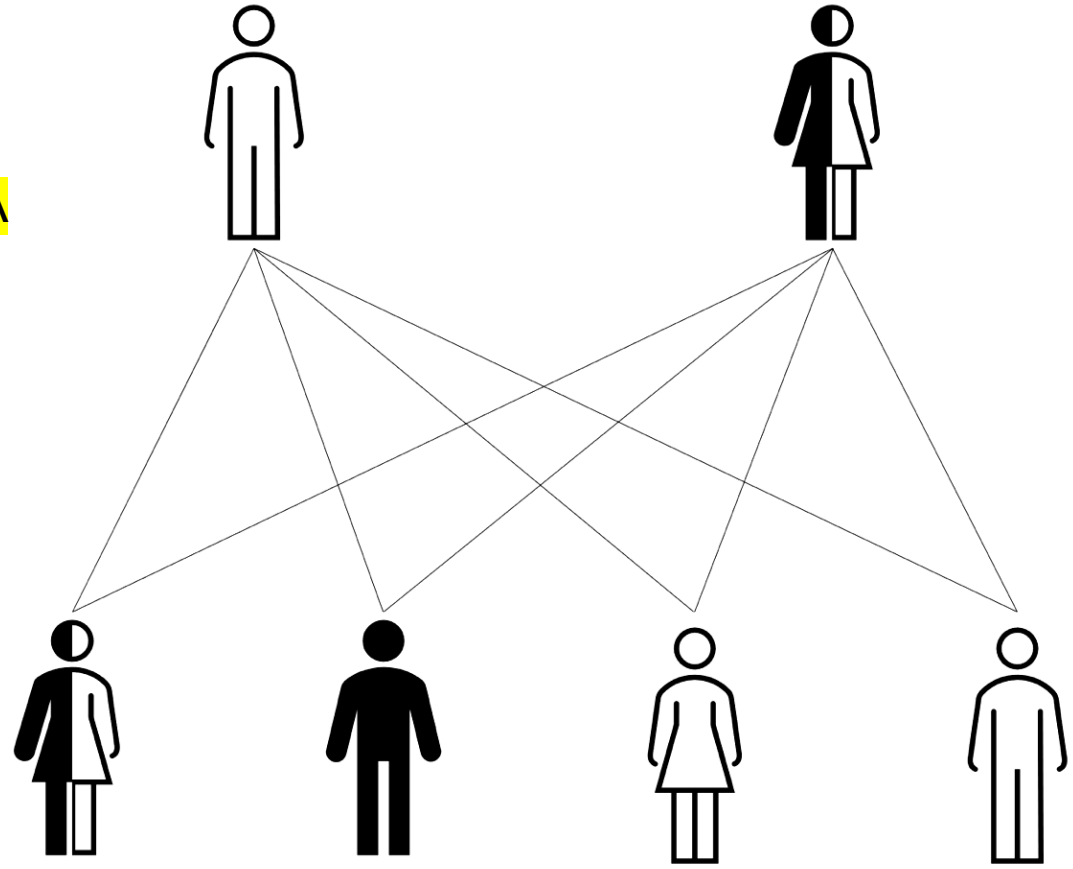
Maladie de Fabry

- Comprendre
- Reconnaitre
- Traiter

Maladie de Fabry
Maladie génétique rare liée à l'X

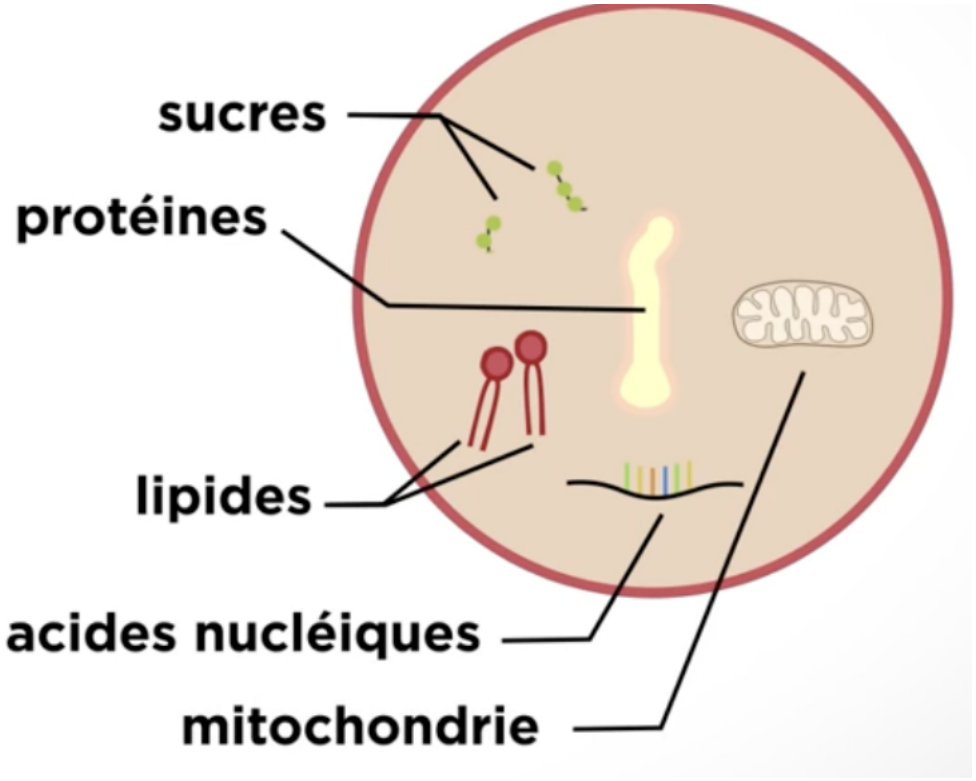
- Incidence : 1/10 000

- Mutation sur le gène GLA (1000 variants identifiés)

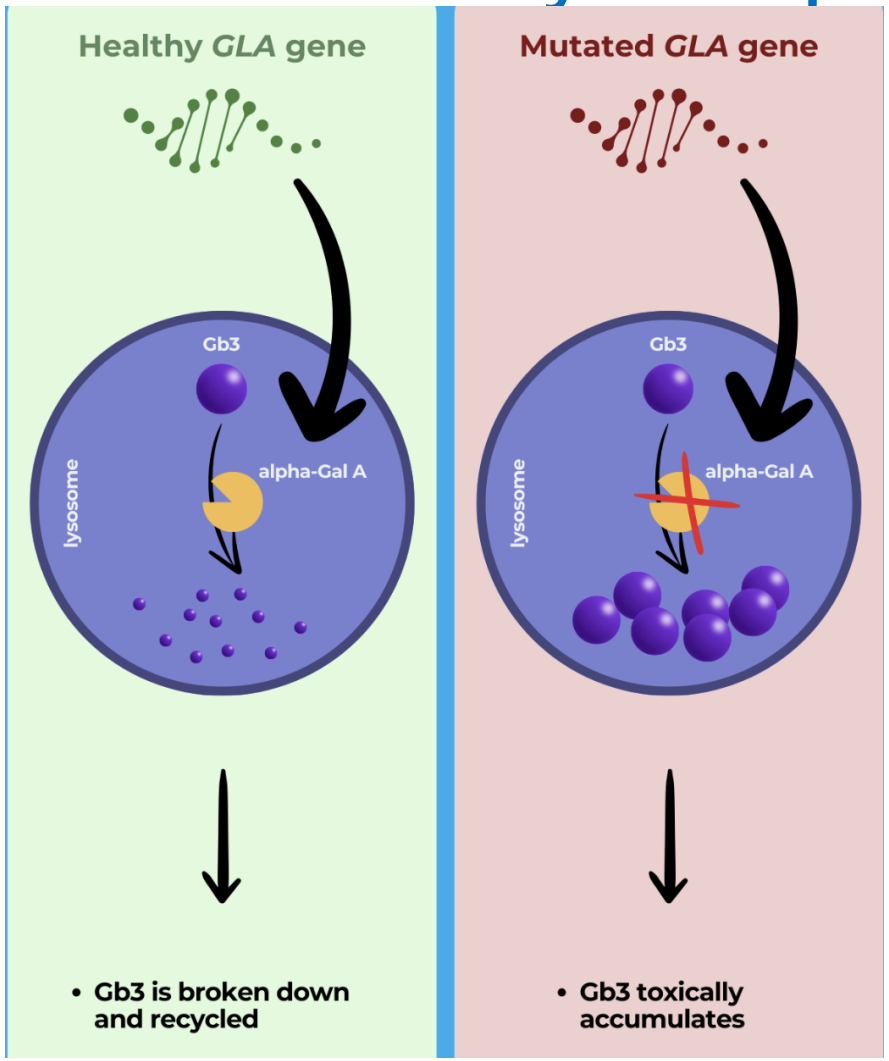


Maladie de Fabry
Un déficit enzymatique

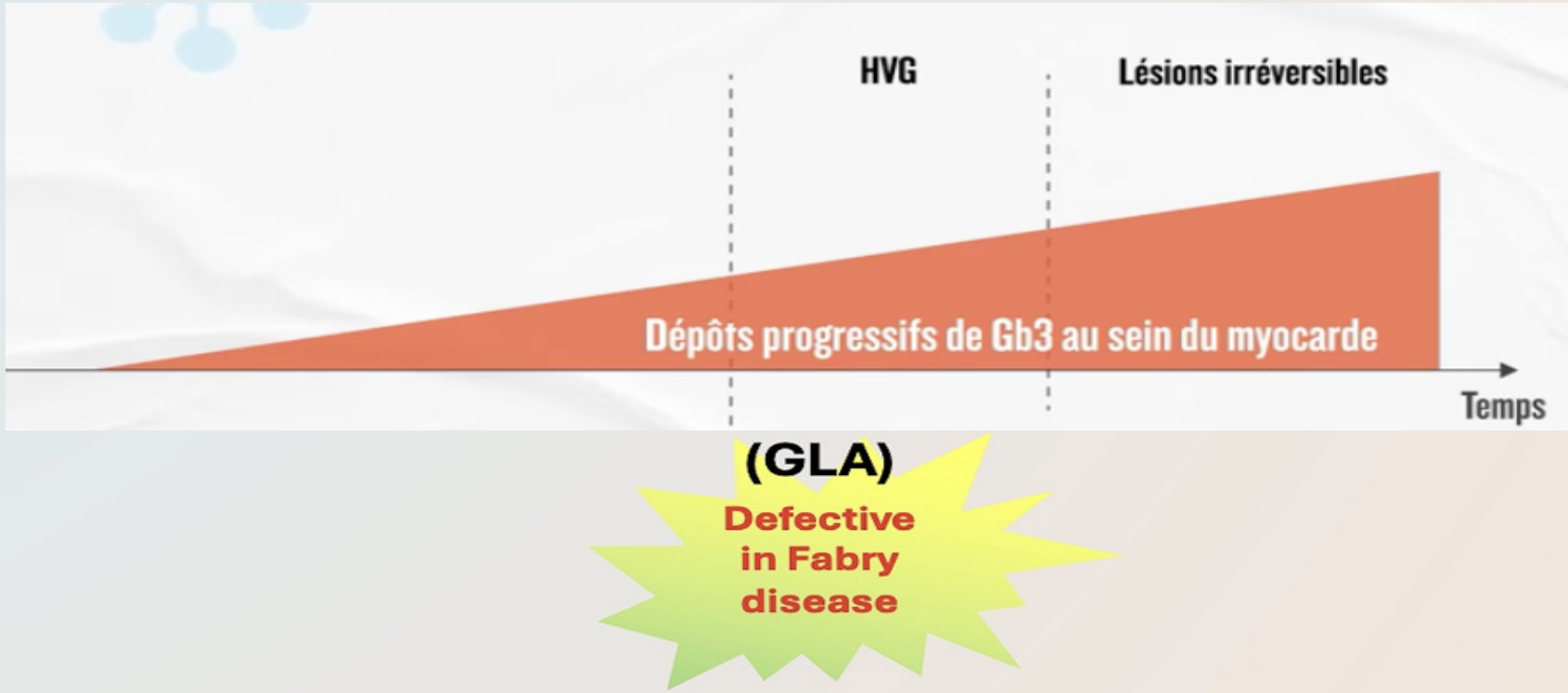
Le lysosome



Maladie de Fabry
Un déficit enzymatique

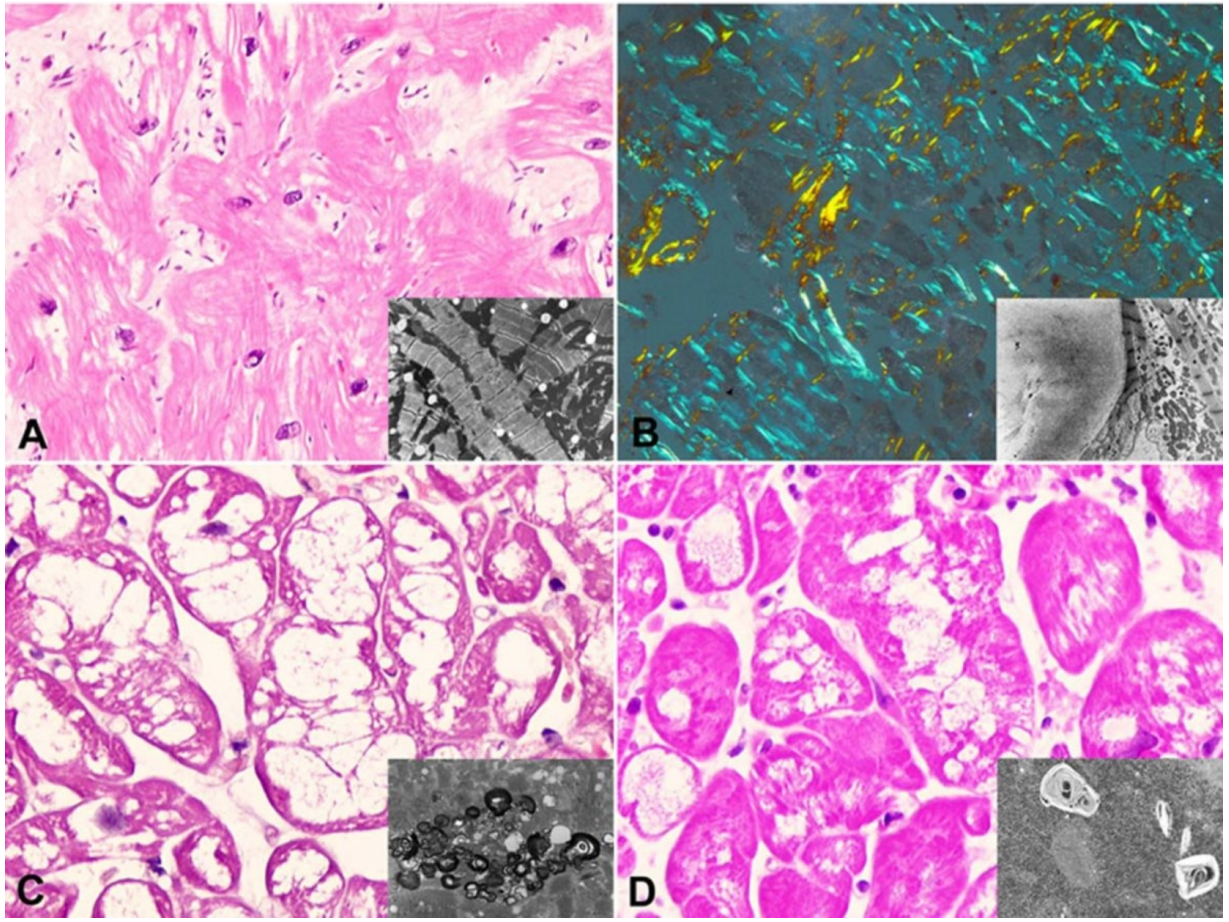


Maladie de Fabry
Une évolution longue



Maladie de Fabry
Lésions histologiques

HCM

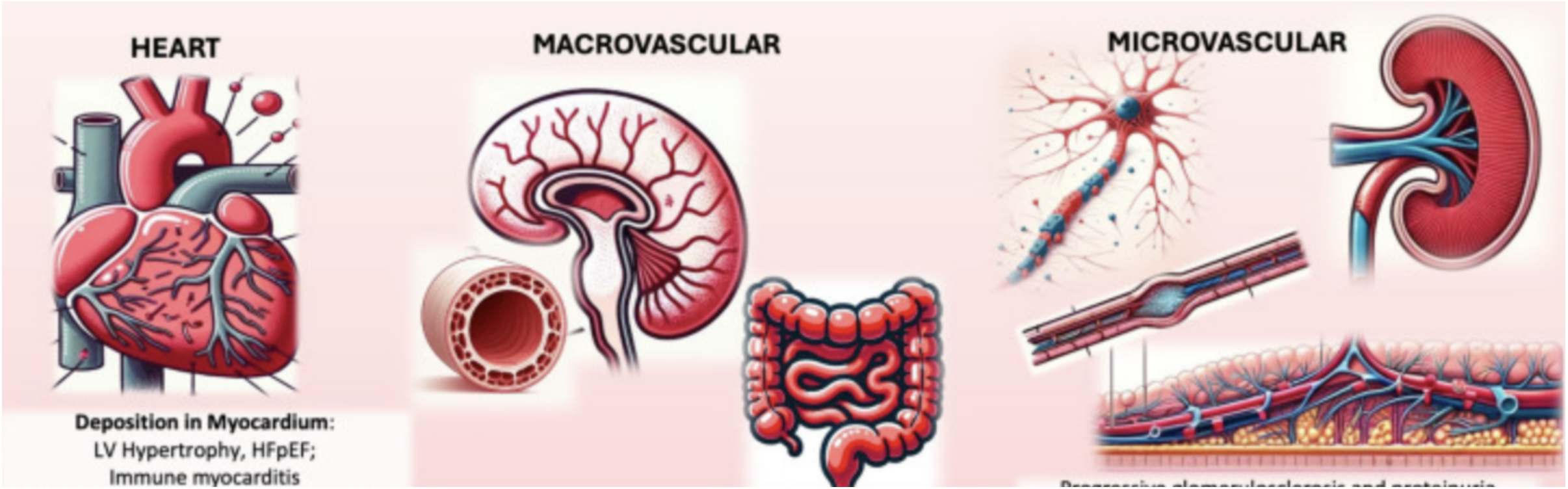


Amylose

Fabry

Glycogénose

Maladie de Fabry
Inflammation

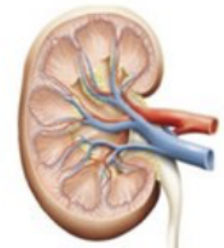


Maladie de Fabry

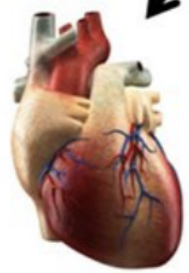
- Comprendre
- Reconnaitre
- Traiter

Fabry disease
mainly affected
organs

peripheral nervous system
neuropathic pain

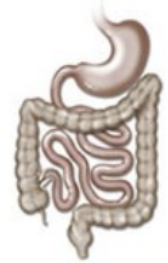


kidney
renal insufficiency



heart
cardiac arrhythmia/failure
left ventricular hypertrophy

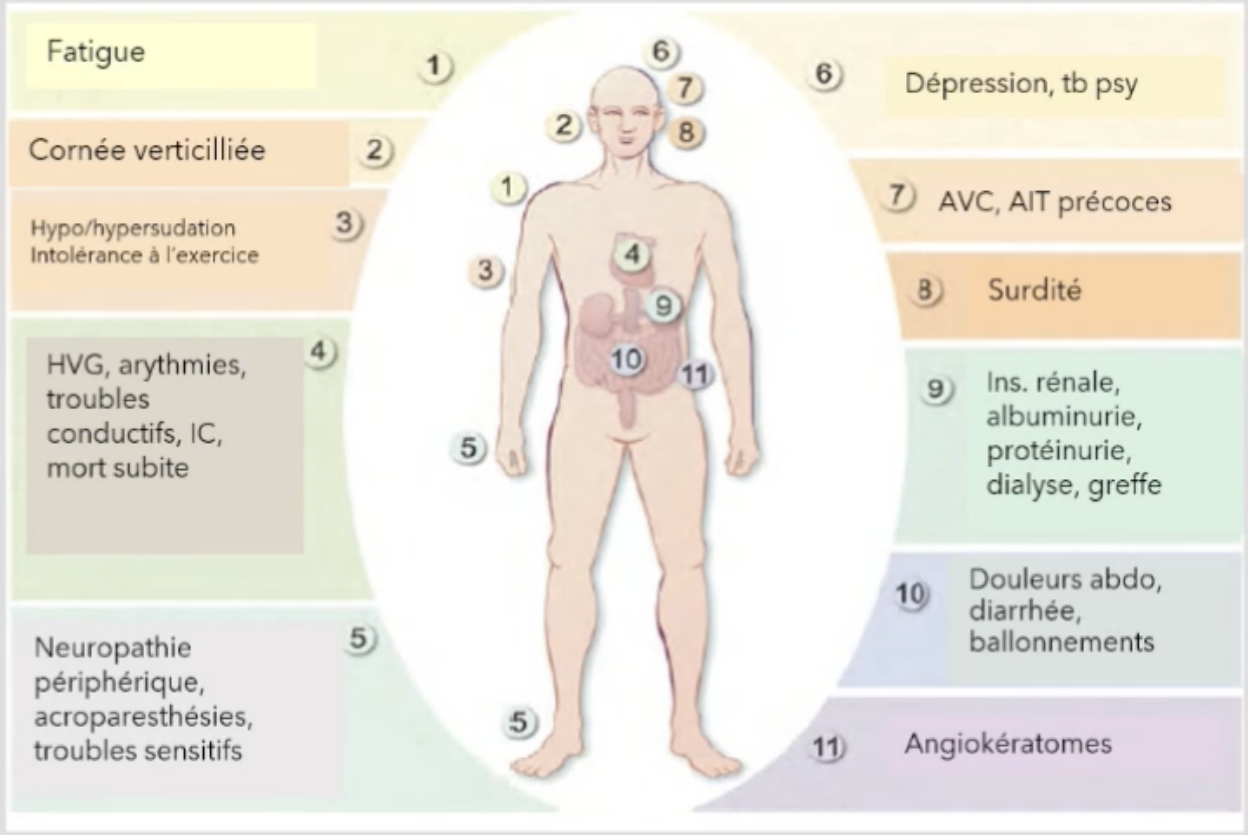
central nervous system
stroke/TIA/WML

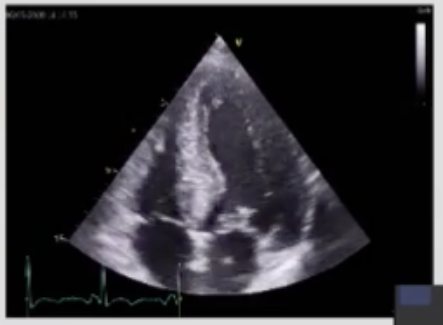


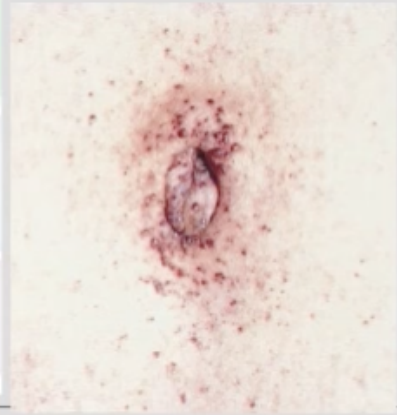
gastrointestinal tract
diarrhea, abdominal pain

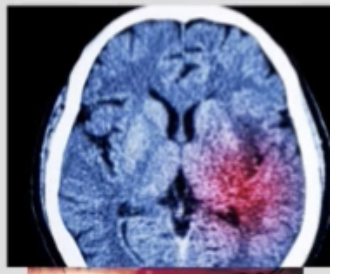
Maladie de Fabry
Les signes d'appel

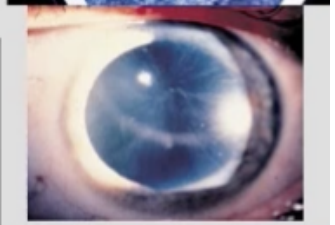
- Signes d'alerte: acroparesthésies, AIT précoce, angiokératomes, protéinurie, hypertrophie VG, PR court, ….

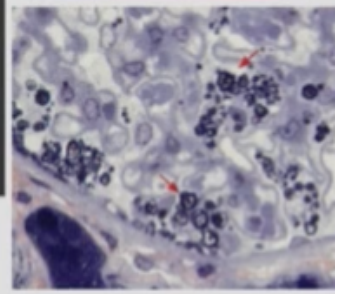




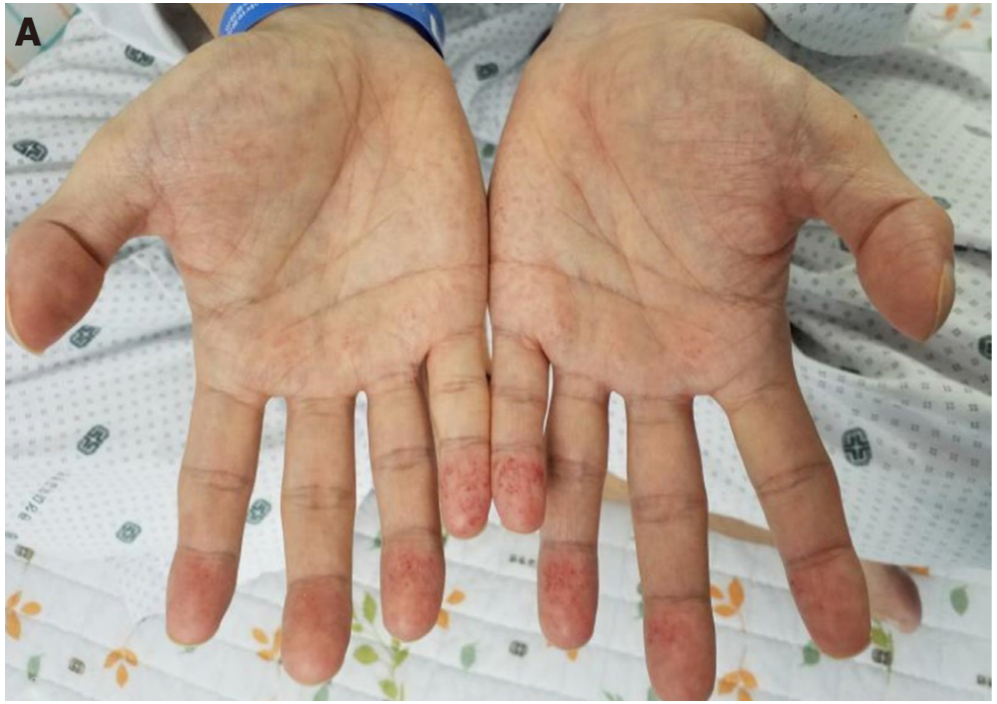




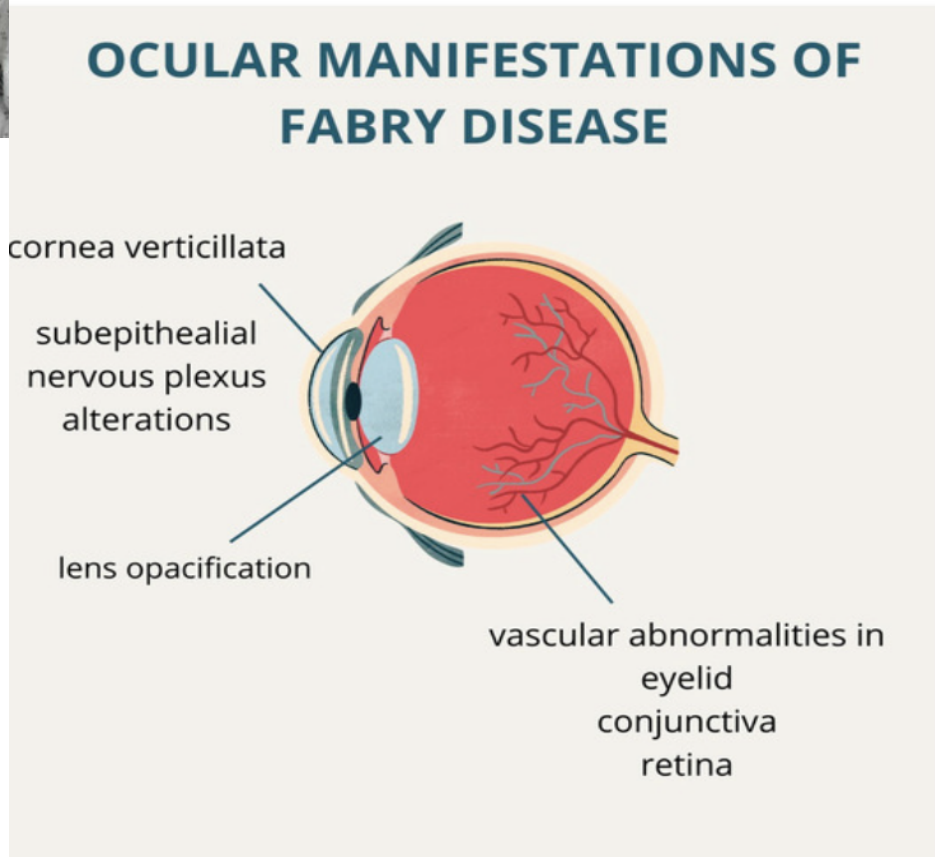




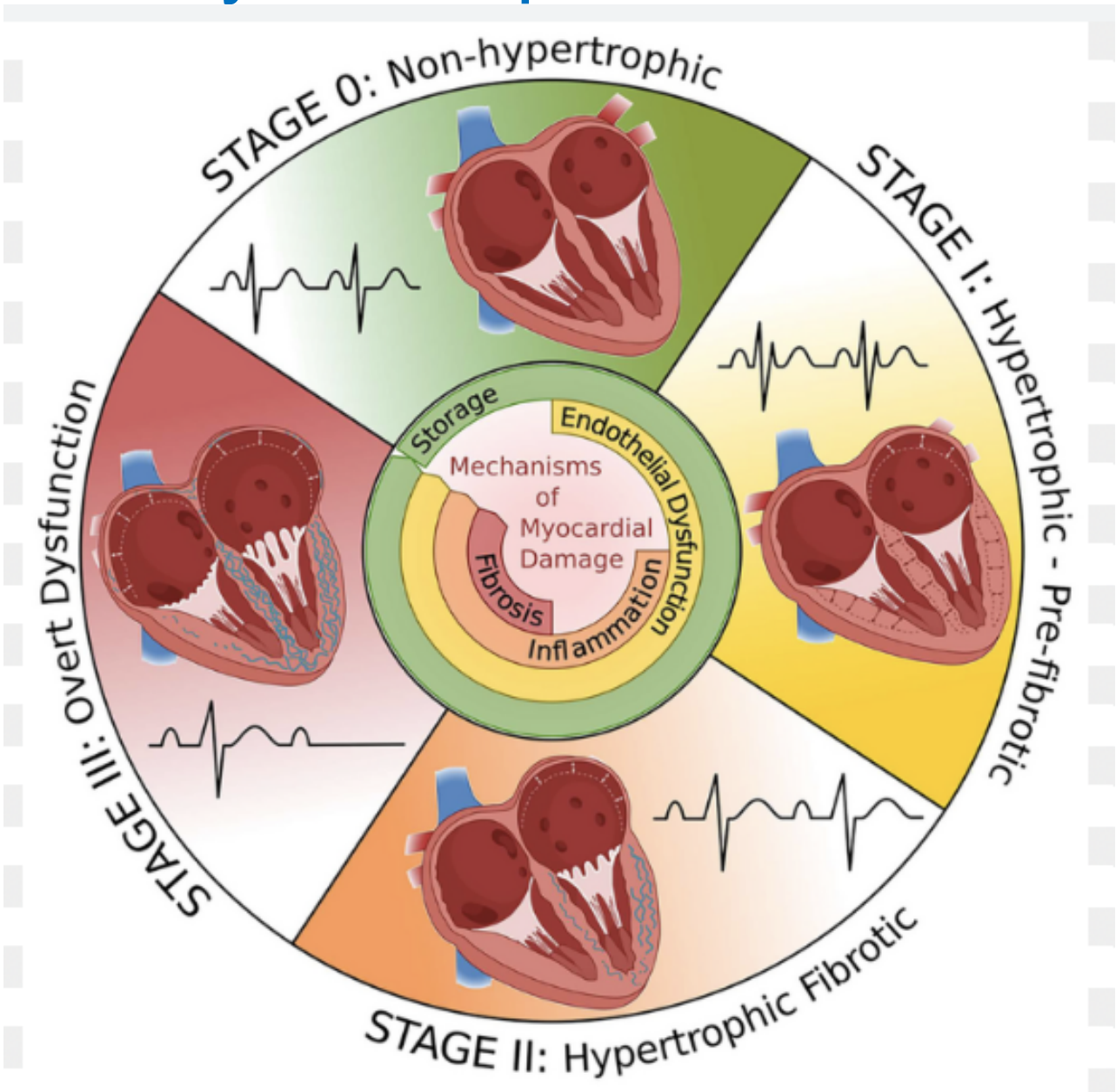
PNDS Fabry 2021



Angiokératomes



Maladie de Fabry : 4 étapes



Hypertrophie Diagnostic différentiel Phénocopies

Hypertrophic Cardiomyopathy	Hypertrophic Cardiomyopathy Phenocopy

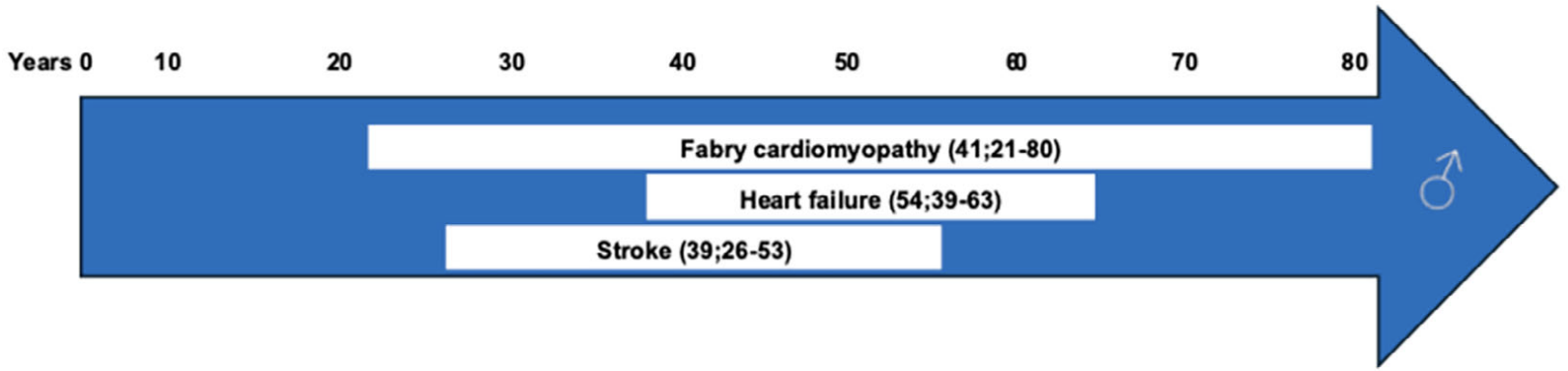
• **Non-sarcomeric**
• **Sarcomeric**
  • MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, ACTC1
	• **Infiltrative diseases**
	  • Amyloidosis
	  • Sarcoidosis
	  • Hemochromatosis
	• **Mitochondrial myopathies**
	• **RASopathies**
	• **Glycogen/Lysosomal storage**
	  • Fabry Disease
	  • Danon Disease
	  • Pompe disease
	  • PRKAG2 syndrome

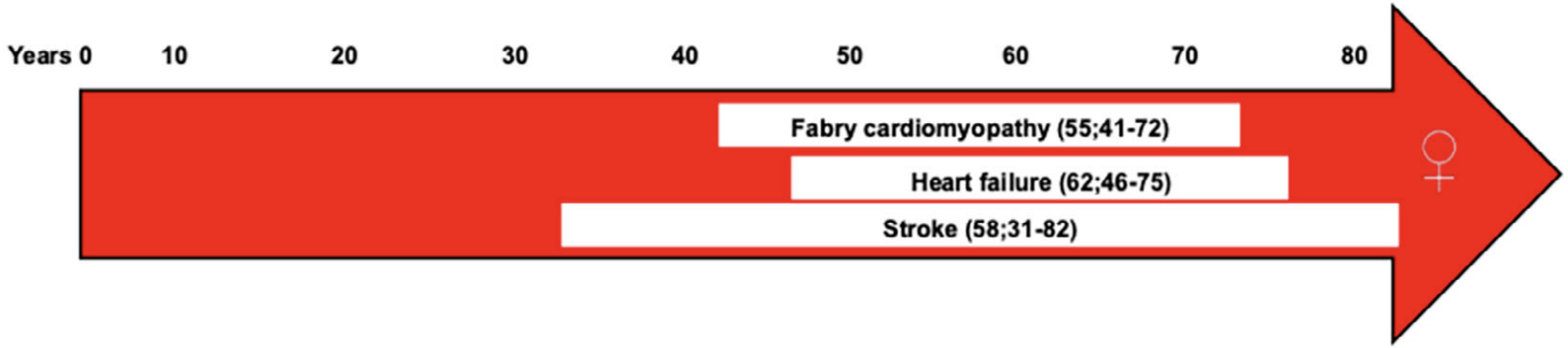
The Finnish Fabry Disease Expert Network and study patient numbers (n = 97)

Turku Fabry Disease Centre of Excellence

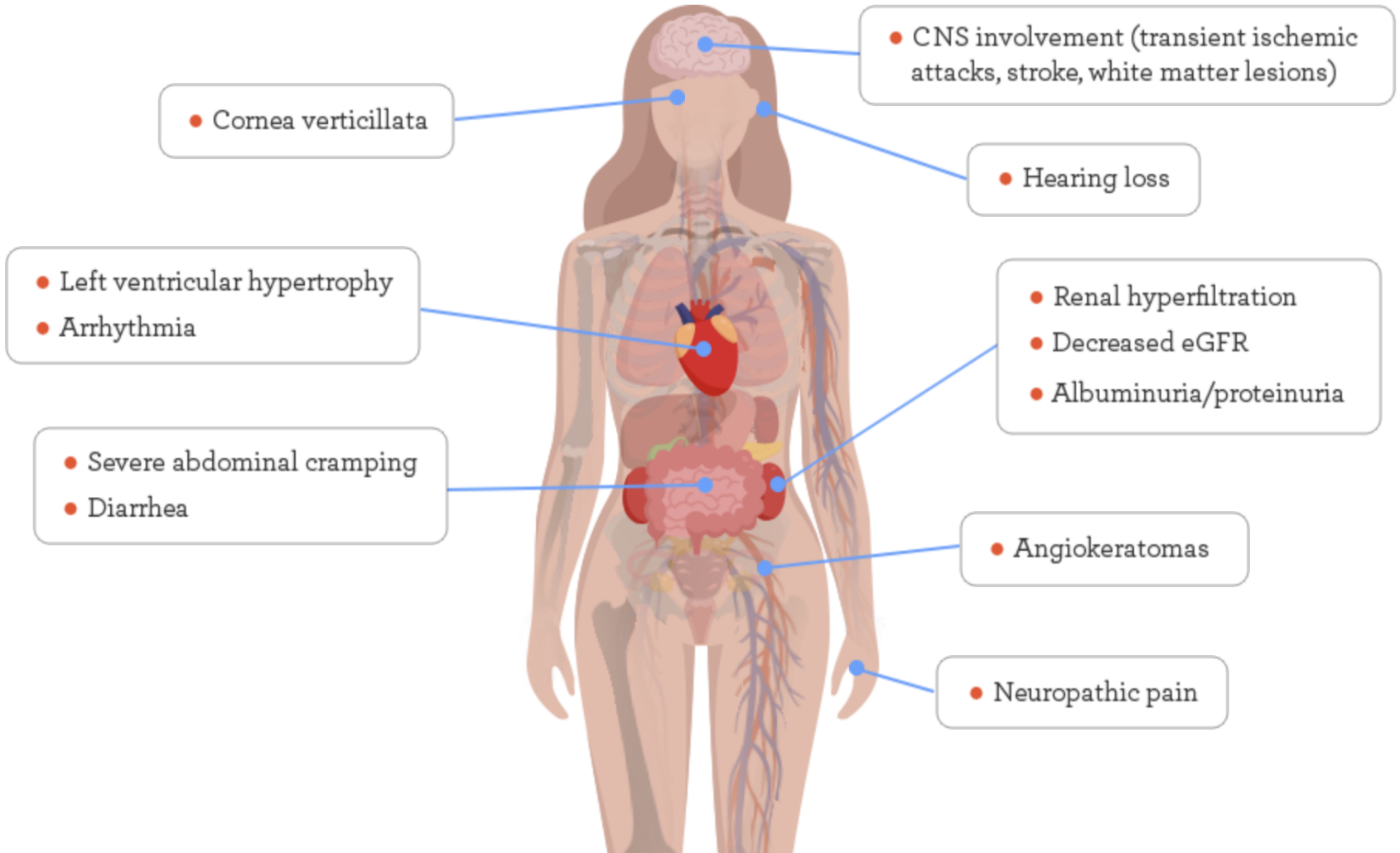
Other Fabry expert centers

Age at event by sex (y, mean;range)





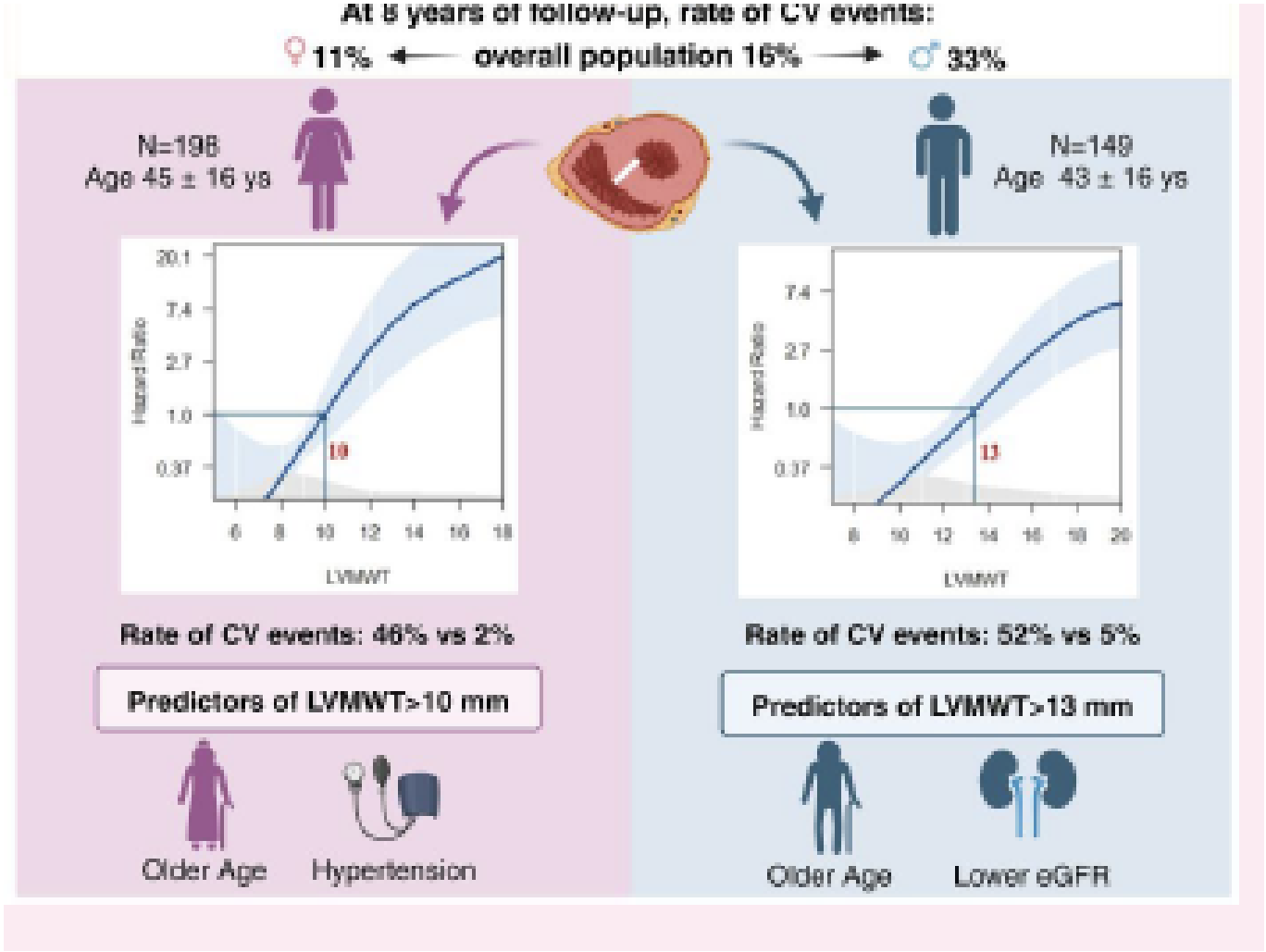
Femmes hétérozygotes ne sont pas juste « porteuses »



ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2025) **00**, 1–9
https://doi.org/10.1093/ehjci/jeaf285

ORIGINAL PAPER

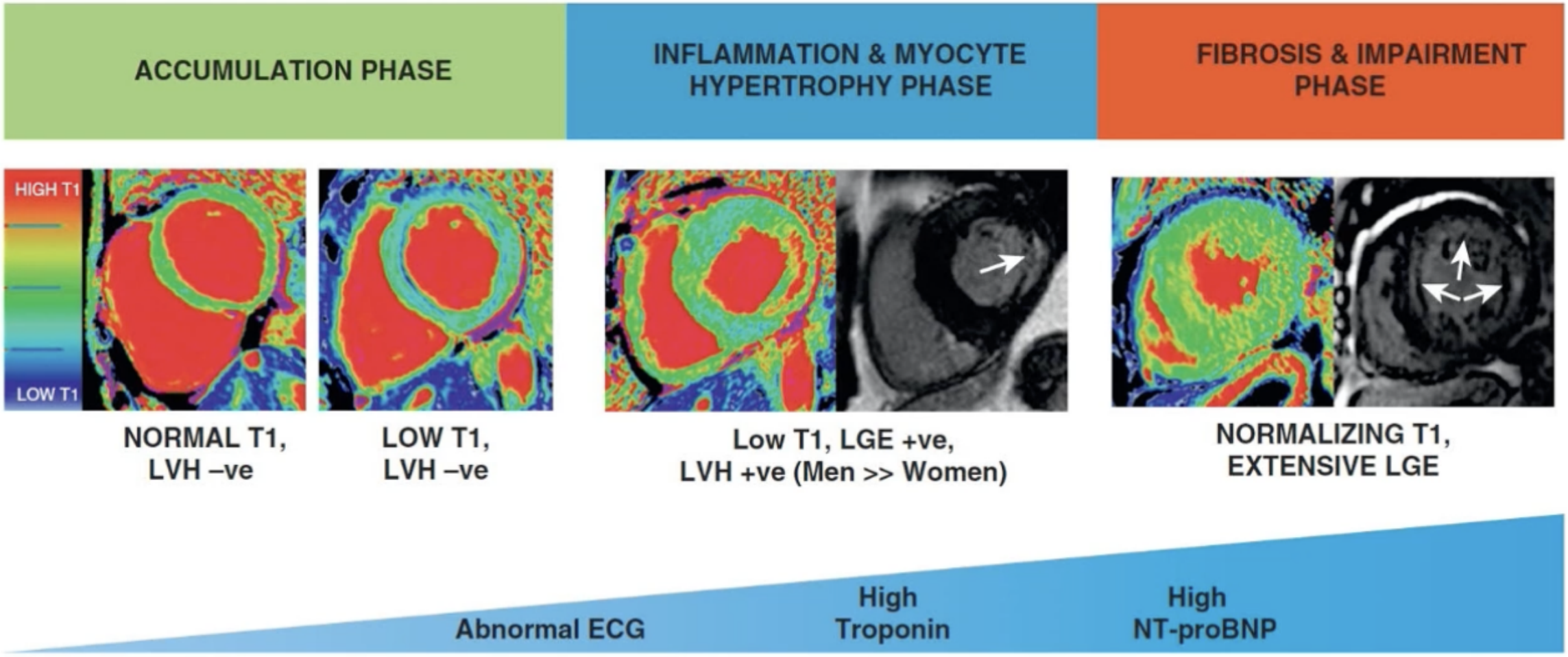
Sex-specific prognostic thresholds of left ventricular hypertrophy in fabry disease

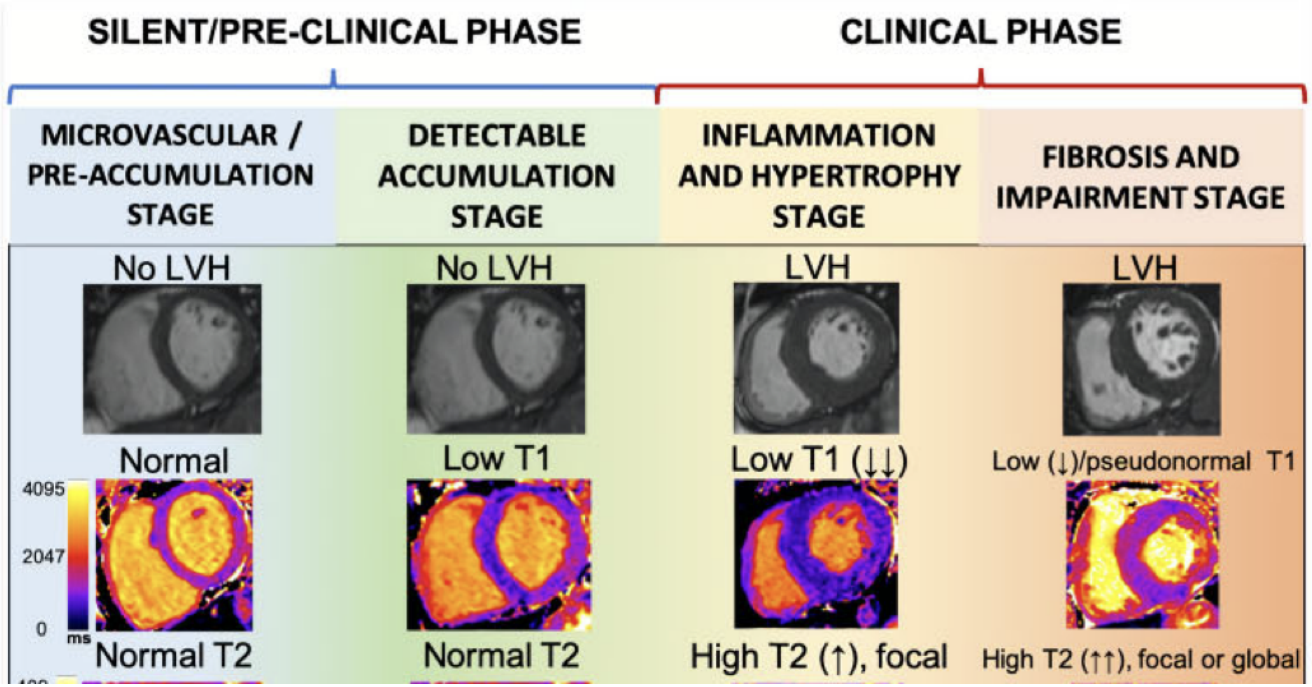


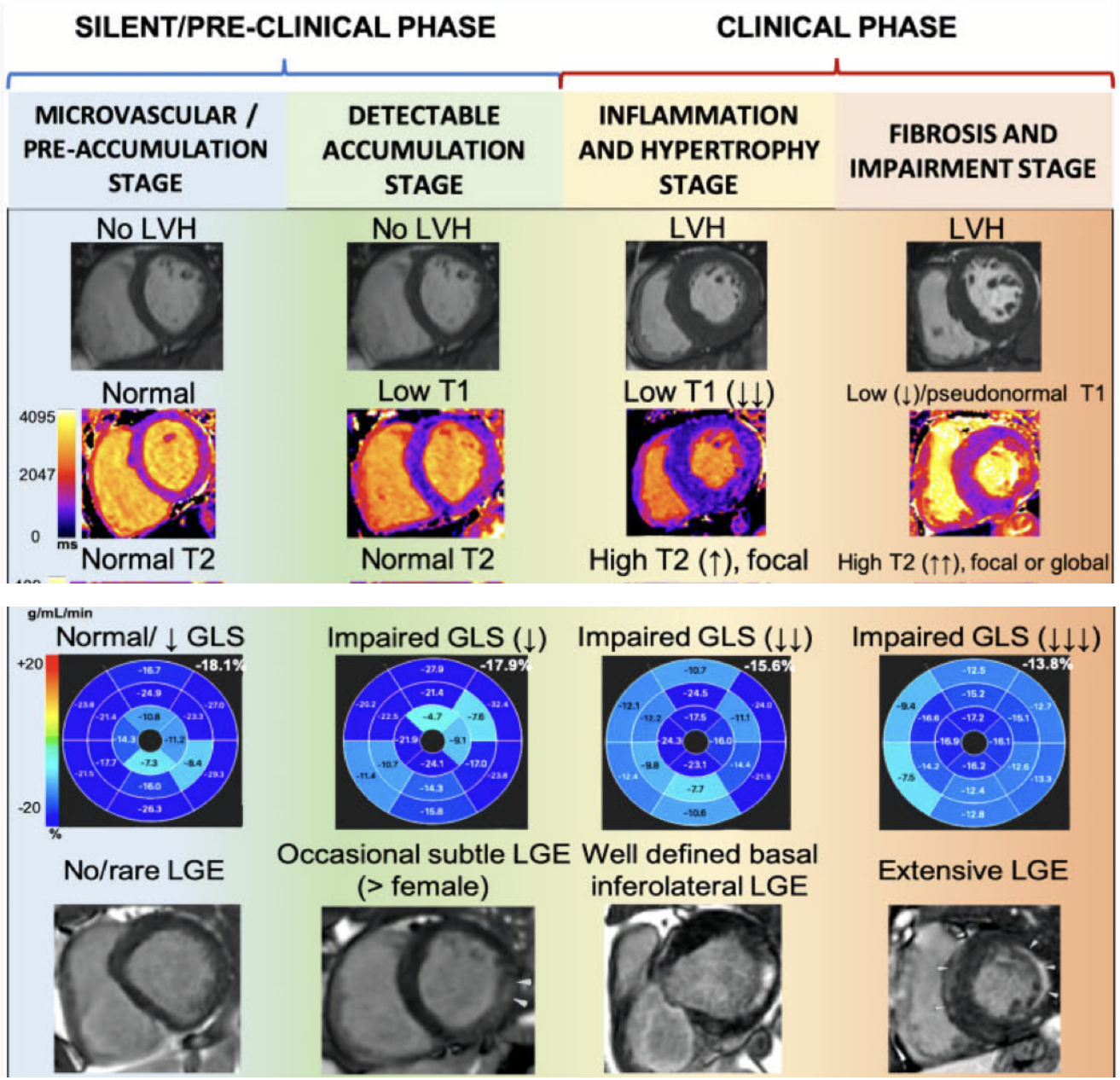
Echocardiographie transthoracique
Peu spécifique

- HVG concentrique (= sténose aortique, amylose cardiaque, cardiopathie post hypertensive)
- Gradient base à l'apex (= amylose cardiaque)
- Hypertrophie ventriculaire droite avec fonction systolique normale 30 % (10 % sarcomérique, 65 % amylose cardiaque)

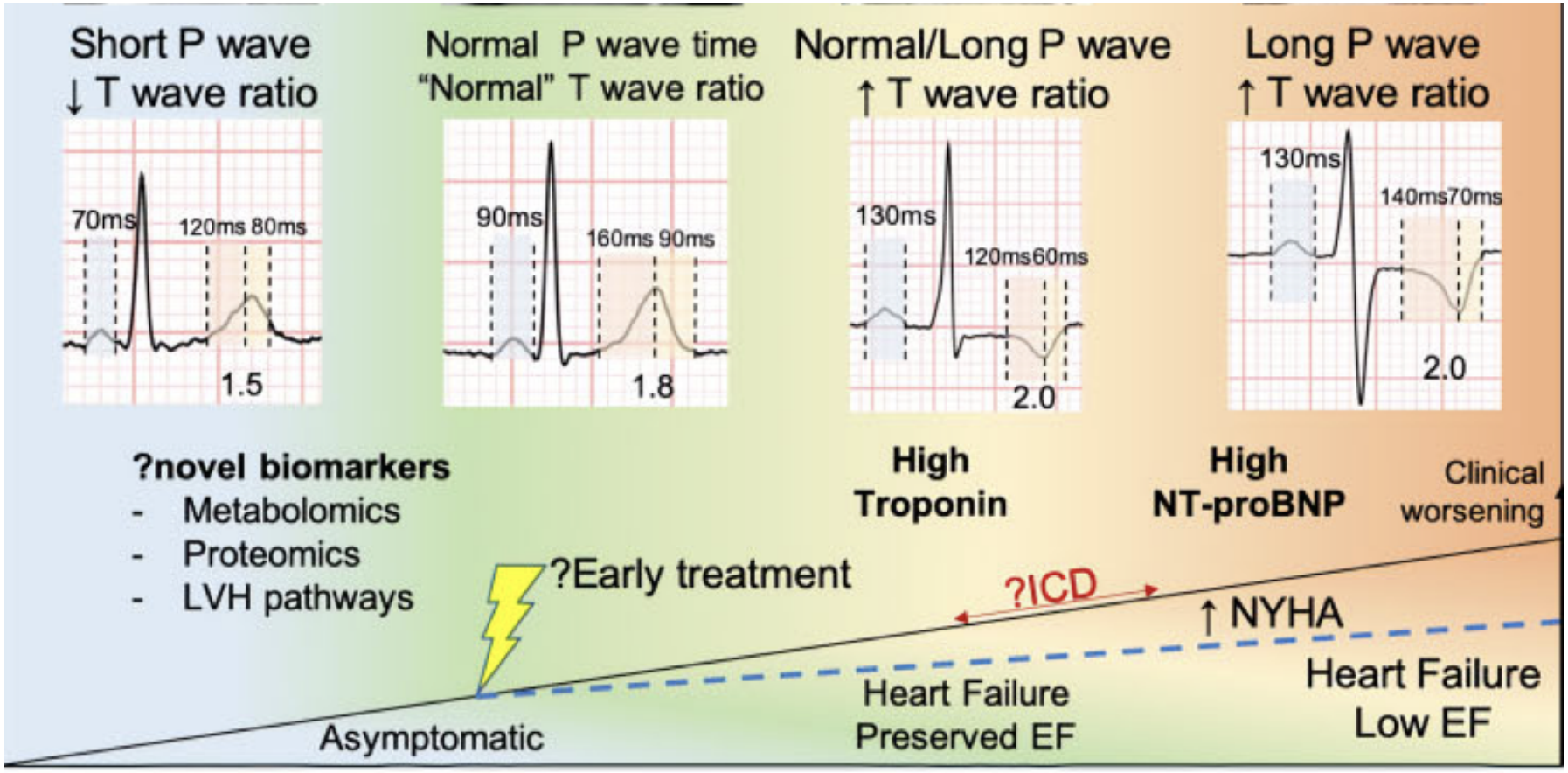
Maladie de Fabry : La cartographie T1




SILENT/PRE-CLINICAL PHASE
CLINICAL PHASE
MICROVASCULAR / PRE-ACCUMULATION STAGE
DETECTABLE ACCUMULATION STAGE
INFLAMMATION AND HYPERTROPHY STAGE
FIBROSIS AND IMPAIRMENT STAGE
No LVH
No LVH
LVH
LVH
Normal
Low T1
Low T1 (↓↓)
Low (↓)/pseudonormal T1
4095
2047
0
ms
Normal T2
Normal T2
High T2 (↑), focal
High T2 (↑↑), focal or global

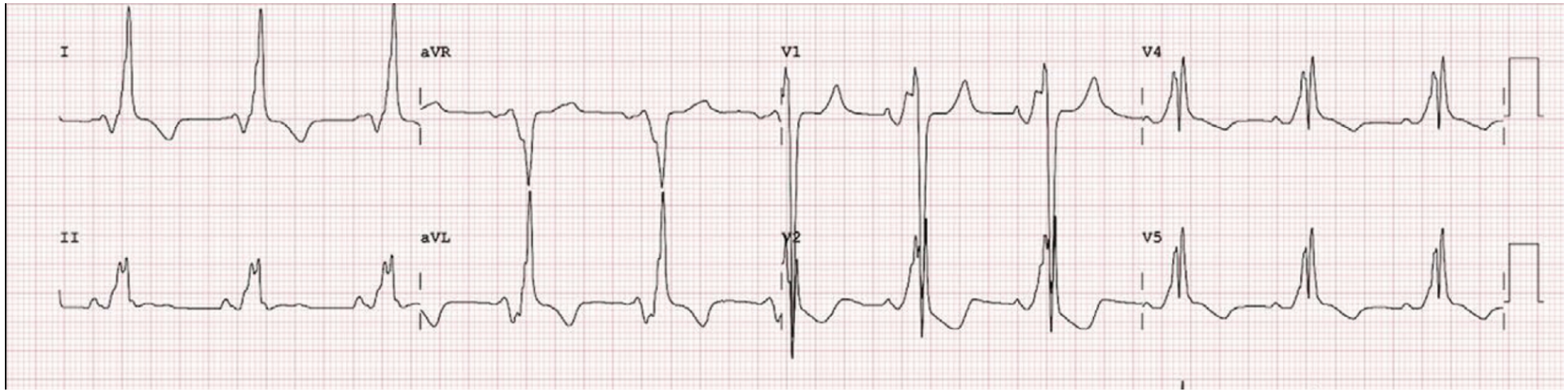

SILENT/PRE-CLINICAL PHASE
CLINICAL PHASE
MICROVASCULAR / PRE-ACCUMULATION STAGE
DETECTABLE ACCUMULATION STAGE
INFLAMMATION AND HYPERTROPHY STAGE
FIBROSIS AND IMPAIRMENT STAGE
No LVH
No LVH
LVH
LVH
Normal
Low T1
Low T1 (↓↓)
Low (↓)/pseudonormal T1
4095
2047
0
ms
Normal T2
Normal T2
High T2 (↑), focal
High T2 (↑↑), focal or global
g/mL/min
+20
-20
%
Normal/ ↓ GLS
Impaired GLS (↓)
Impaired GLS (↓↓)
Impaired GLS (↓↓↓)
-18.1%
-17.9%
-15.6%
-13.8%
No/rare LGE
Occasional subtle LGE (> female)
Well defined basal inferolateral LGE
Extensive LGE

Maladie de Fabry
Valeur de l'ECG ?



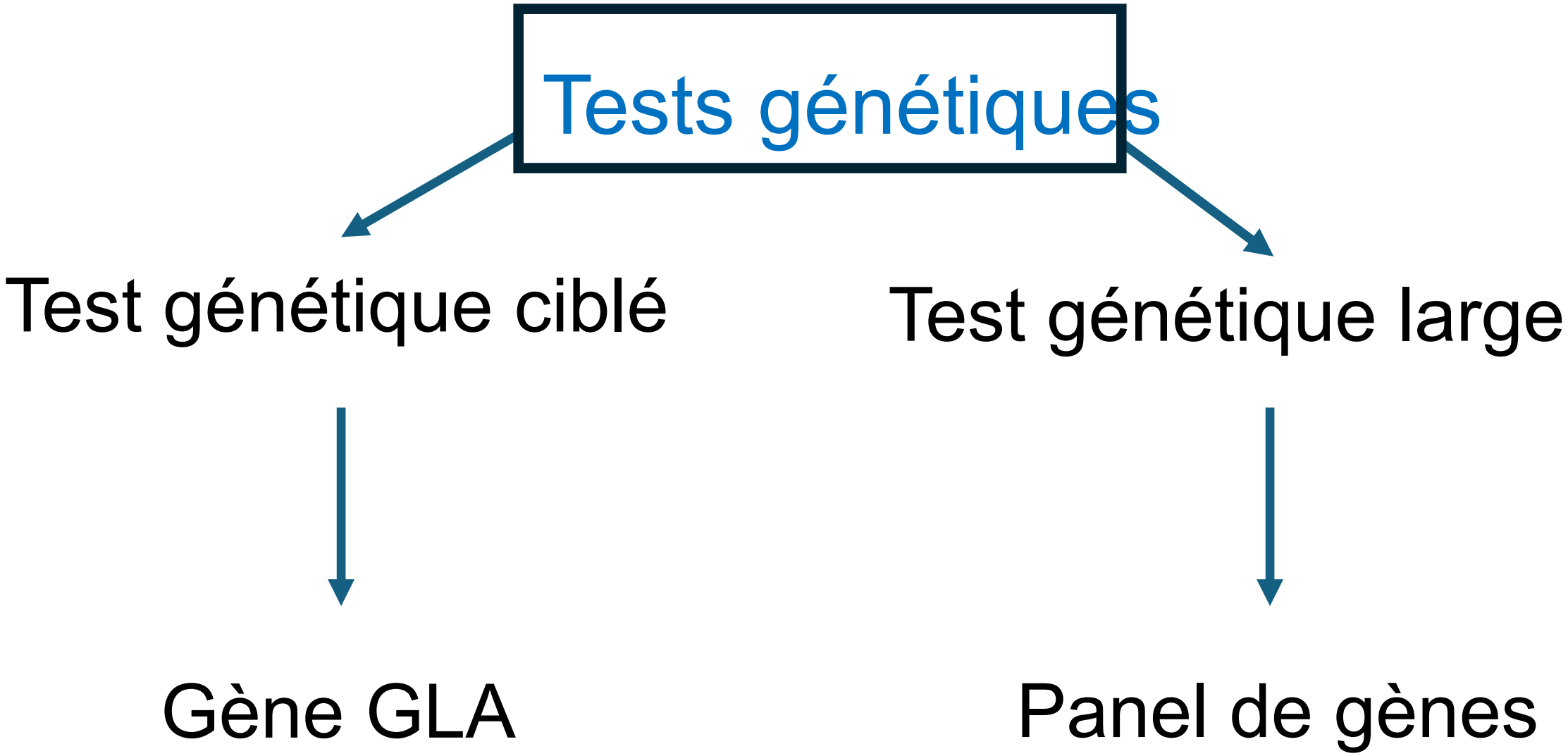
Maladie de Fabry
PR court ?

Danon, PRKAG2, Fabry ou CMH sarcomérique ?

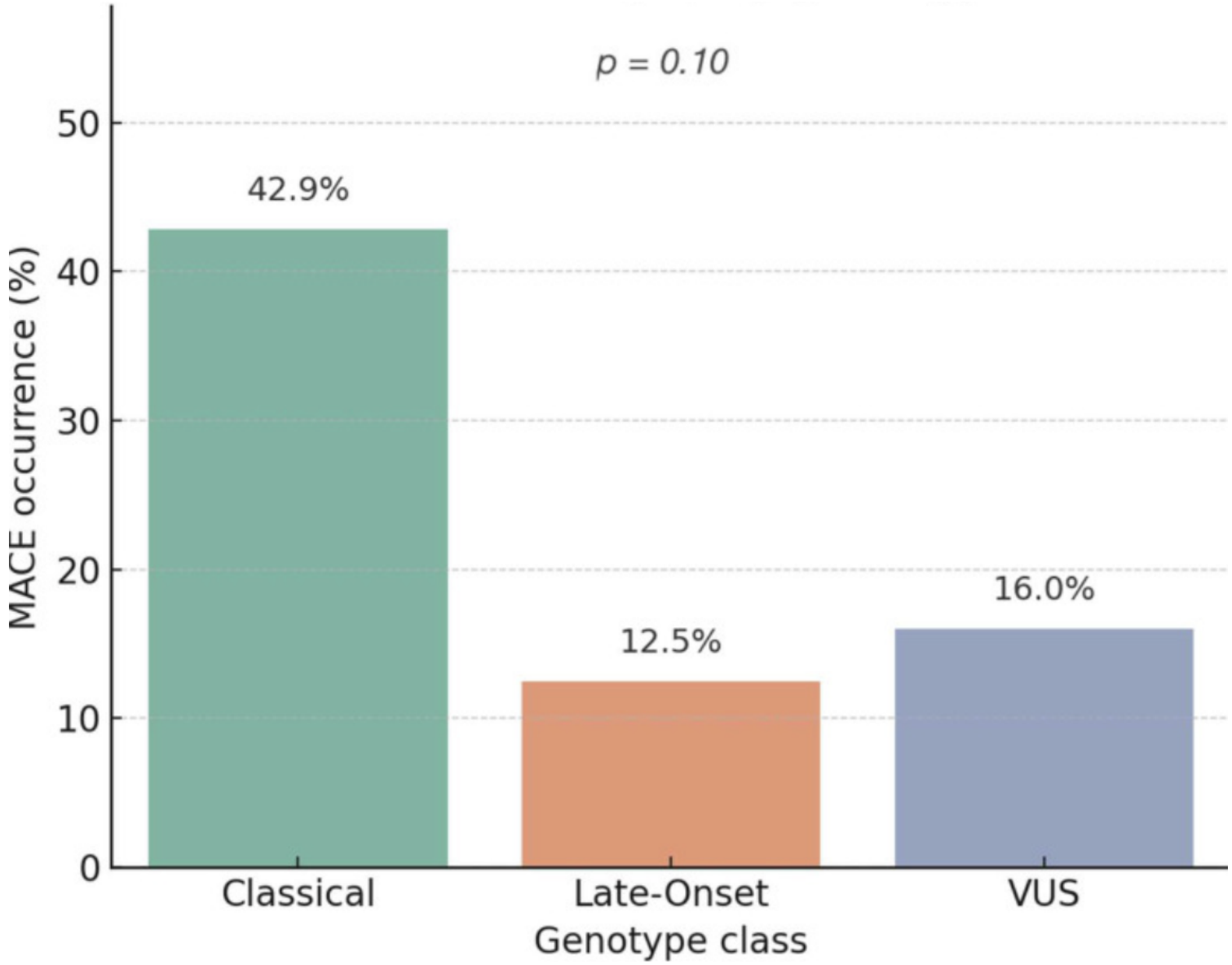


Diagnostic biologique

- Dosage de l'enzyme (normale dans 50% des cas chez la femme)
- Dosage du déchet sanguin (lyso gb3, surtout pour les femmes)
- Confirmation génétique (appartient au 1er panel CMH)


Tests génétiques
Test génétique ciblé
Test génétique large
Gène GLA
Panel de gènes

Maladie de Fabry/Génotypage



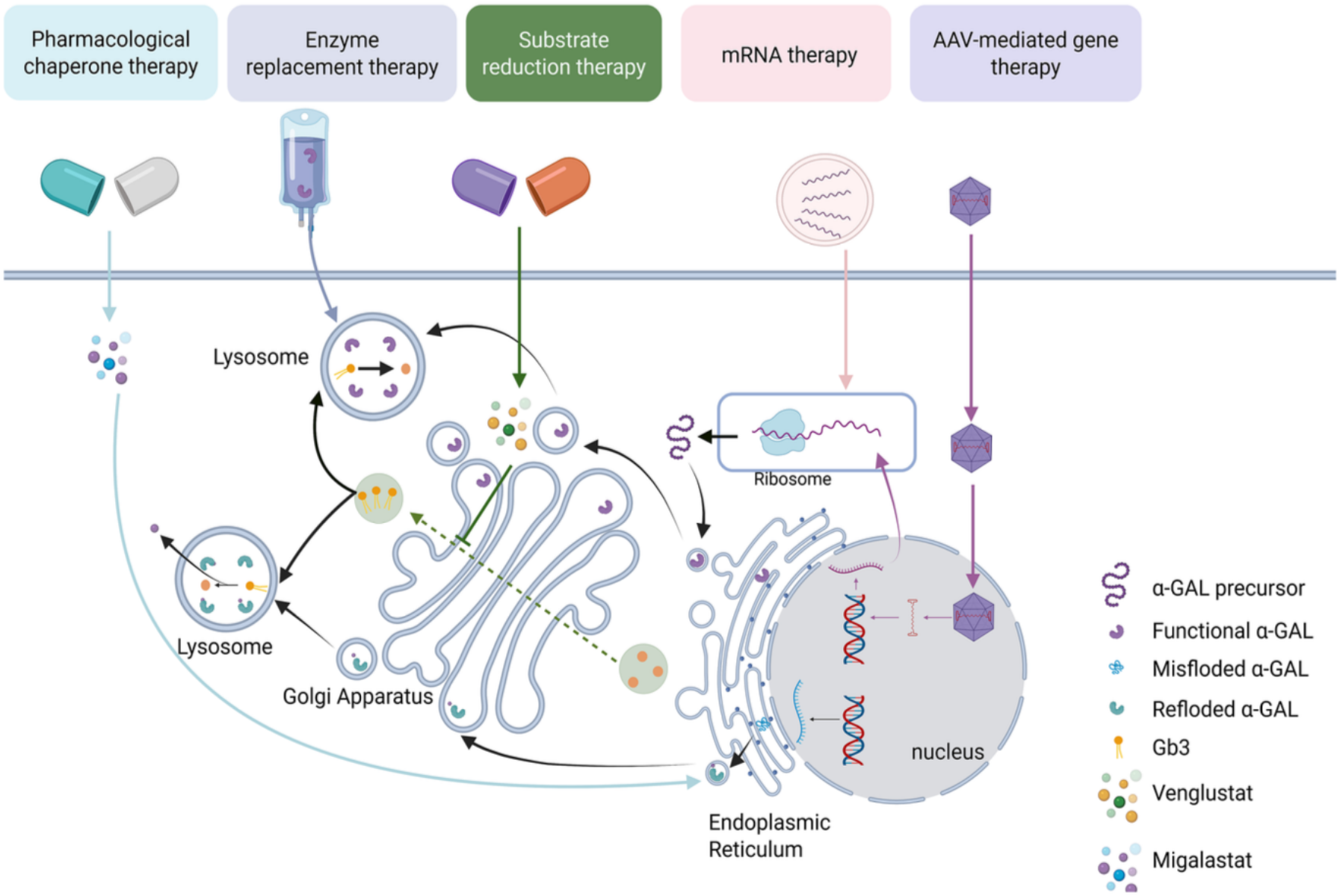
Expérience lyonnaise du génotypage (12 452 patients)

	Nombre total	Nombre de patients avec variants GLA (classe 4 ou 5)	% de patients avec variant GLA (classe 4 ou 5)
CMH	4243	15	0,35%
CMD	4145	2	0,05%
CMA	349		
CMR	107		
NCVG	292		
TTR	561	1	0,18%
SQTL	643		
BS	618		
TVPC	37		
TCC	250	1	0,40%
FVI	184		
MS	663		

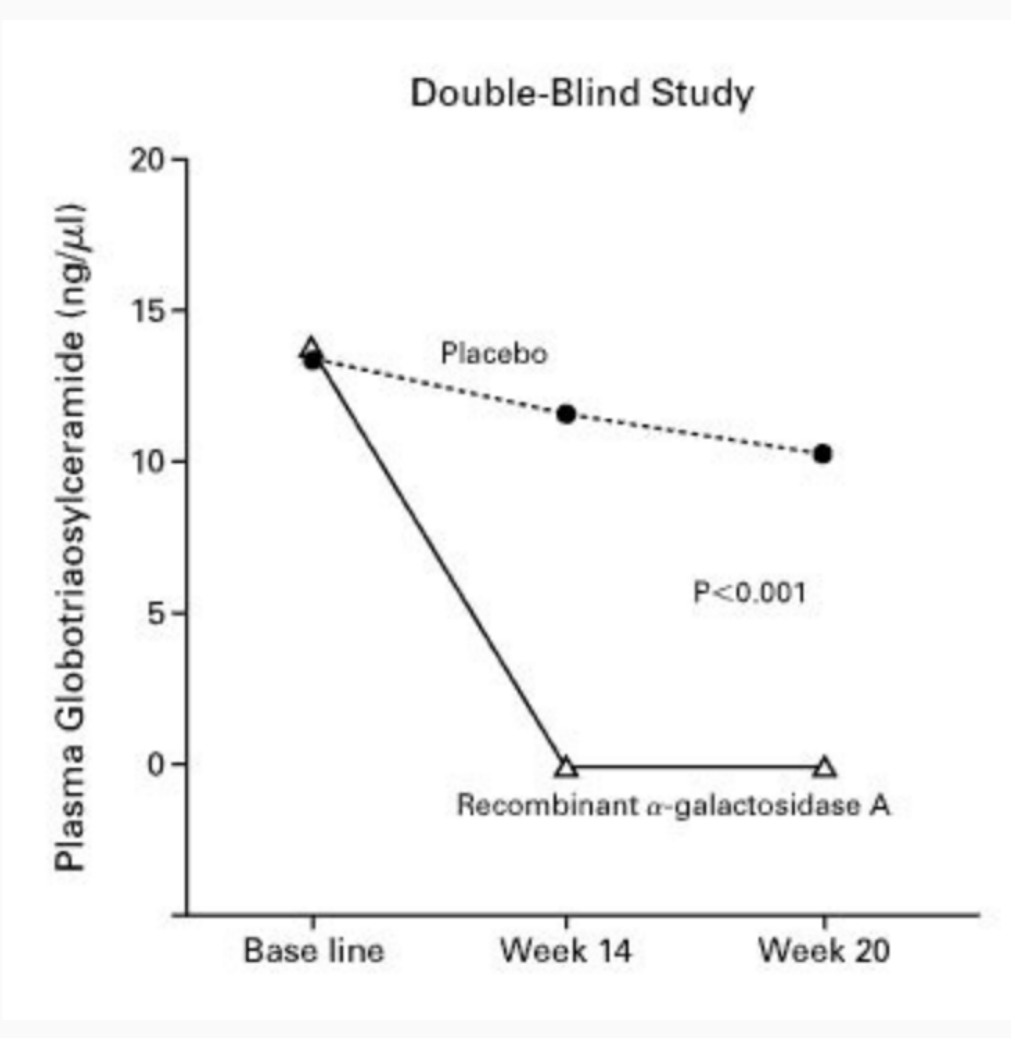
Maladie de Fabry

- Comprendre
- Reconnaitre
- Traiter

Maladie de Fabry : Traitement



Maladie de Fabry : Première étude randomisée NEJM 2001
Thérapie de substitution



20/02/2002

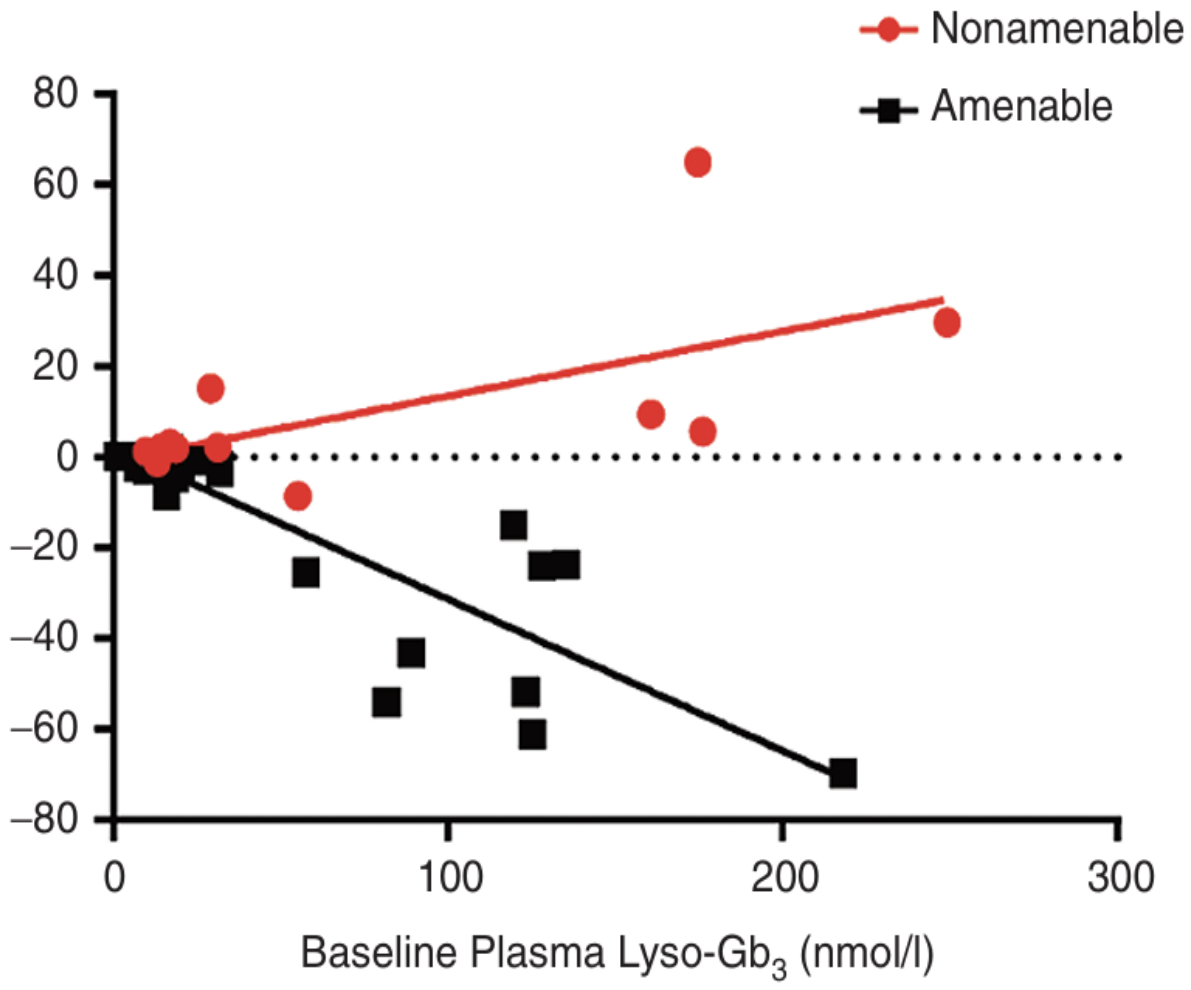
FABRAZYME 35 mg (agalsidase bêta)

Avis favorable à l'inscription de FABRAZYME 35mg sur la liste des produits agréés à l'usage des collectivités et divers serv...

ASMR : 5 | 4 | 3 | 2 | 1

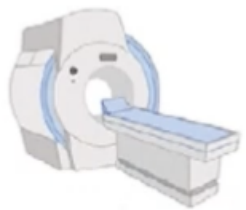
Maladie de Fabry : Pharmacogénétique (2017)

Migalasta



Effects of Enzyme Replacement Therapy on Cardiac MRI Findings in Fabry Disease: A Systematic Review and Meta-Analysis

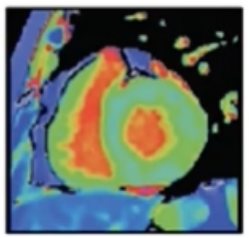
Cardiac MRI changes in Fabry Disease patients undergoing Enzyme Replacement Therapy



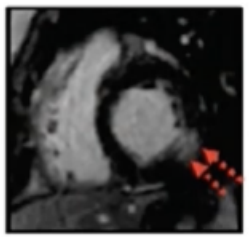
- 445 Fabry Disease patients undergoing baseline and follow-up CMR after ERT
- Evaluation of mean differences of CMR parameters

MLVWT
-1 mm (-2; -0.02)

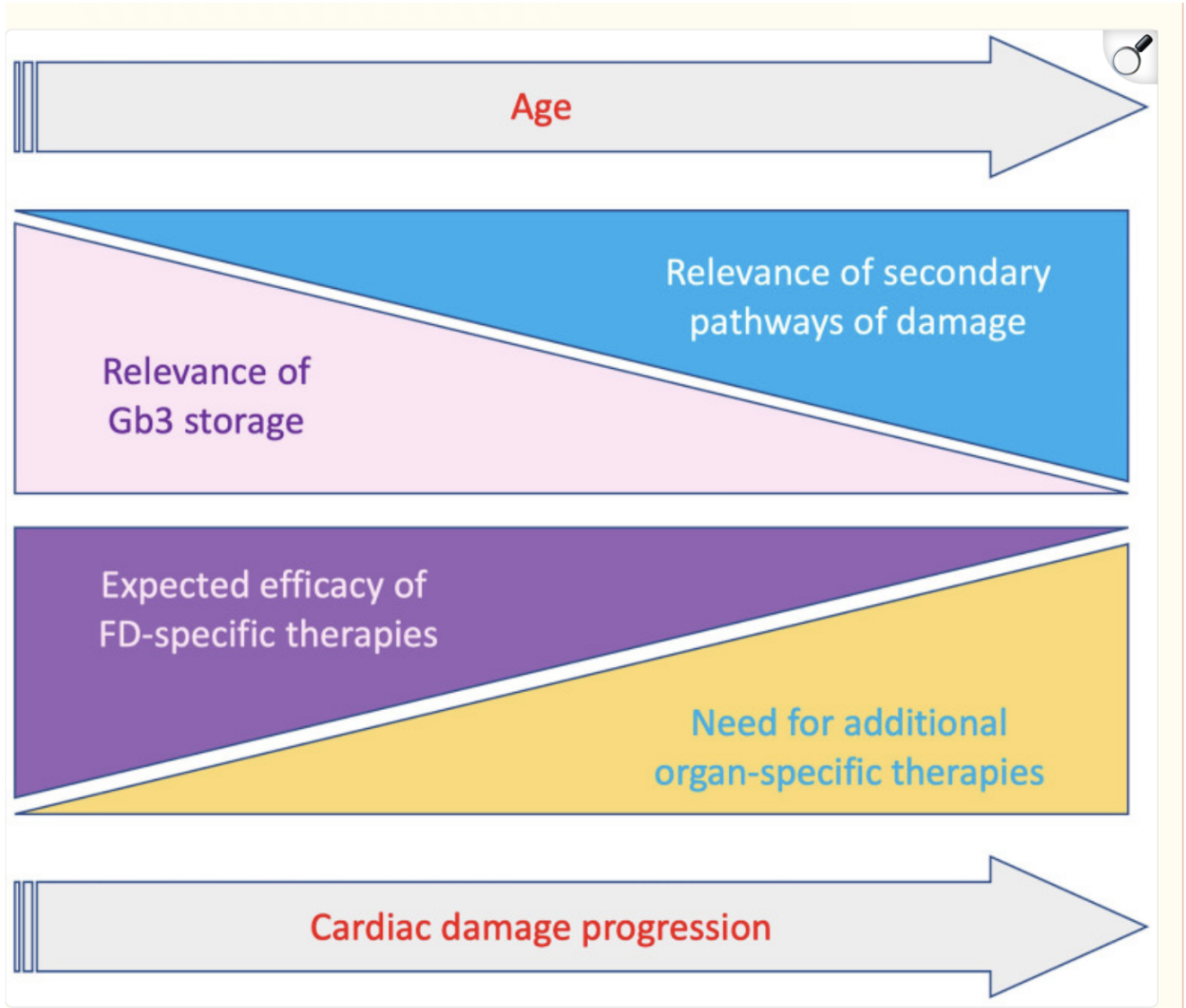
LVM
-18 g (-33; -3)



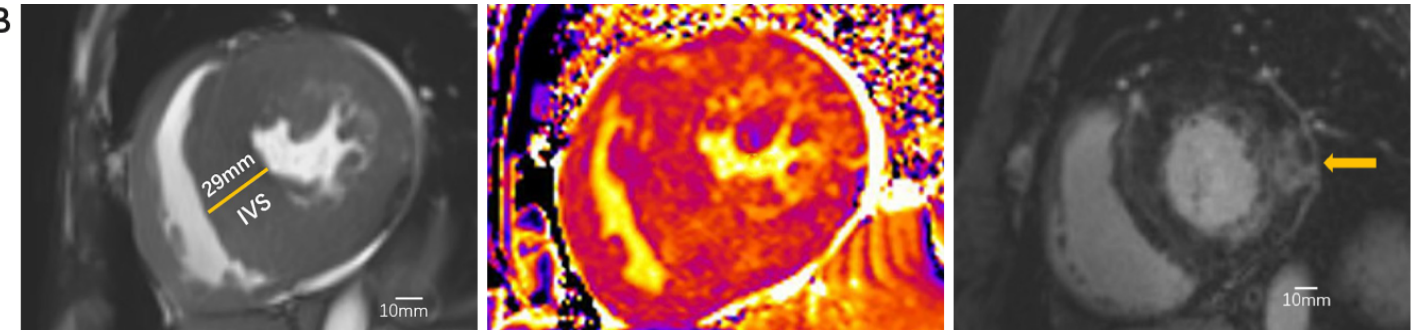
T1 mapping
6 msec (-2; 15)

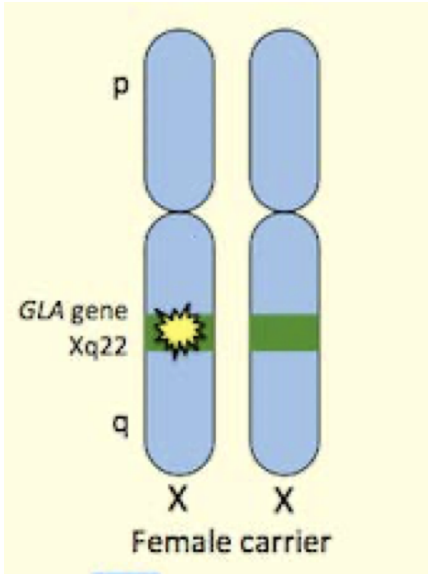


LGE extent
0.8% (0.5; 1.1)


Age
Relevance of secondary pathways of damage
Relevance of Gb3 storage
Expected efficacy of FD-specific therapies
Need for additional organ-specific therapies
Cardiac damage progression

La maladie de Fabry





Dépister précocément

- Rôles clés du génotypage et de l'IRM

- Orienter précisément

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

European Reference Network
for rare or low prevalence complex diseases
Network Heart Diseases (ERN GUARD-HEART)

The gold standard of FD diagnosis
α-Gal A activity (for males) and confirmatory genetic analysis

but identification of the broad range of variants is challenging.

Disease-specific biomarkers
such as lyso-GL3 may be valuable additions to current FD diagnostic
procedures and aid in objective monitoring of pharmacodynamic response
in patients with classic FD.

Lyso-GL3 has been shown to decline
in response to ERT but there is not a clear correlation between the
change in lyso-GL3 levelswith a reduction in clinical events.

In addition, lyso-GL3 only partially correlates with response to chaperone therapy.

the value of lyso-GL3 as a biomarker in patients with a
later-onset FD phenotype is still not well understood, nor do we have
sufficient data on changes in lyso-GL3 levels as patients age.

Nondisease-specific biomarkers are of value in assessing organ involvement
but should be used in conjunction with disease-specific biomarkers to
support their use in monitoring response to treatment.
In addition, assessment of ADAs and imaging studies, including CMR T1 mapping,
may be valuable tools tomonitor therapeutic response and disease progression

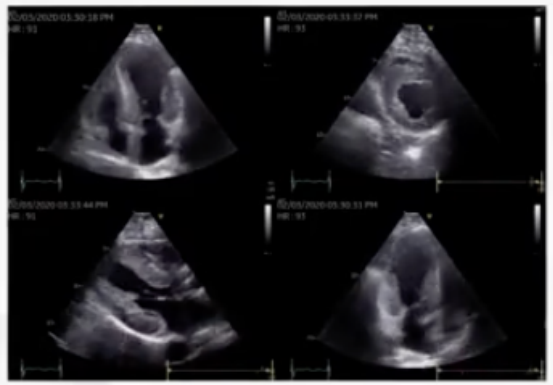
Pourquoi connaître la maladie de Fabry

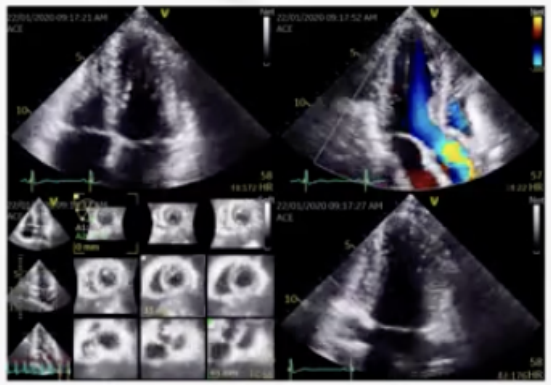
- Savoir la reconnaitre car potentiellement grave accessible à un traitement

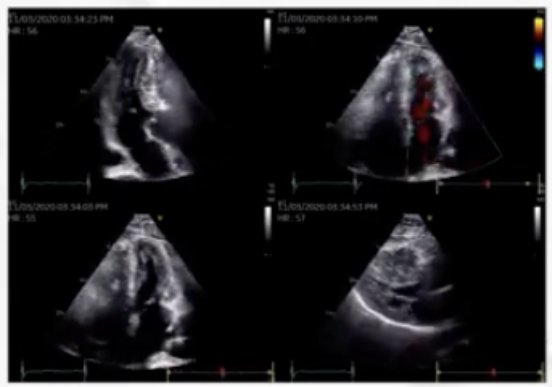
Pas d'aspect spécifique à l'échocardiographie

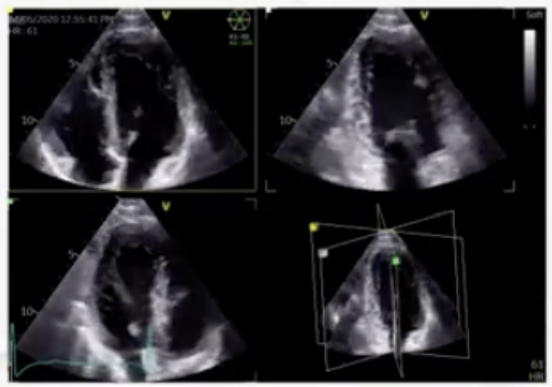
Grande hétérogénéité phénotypique

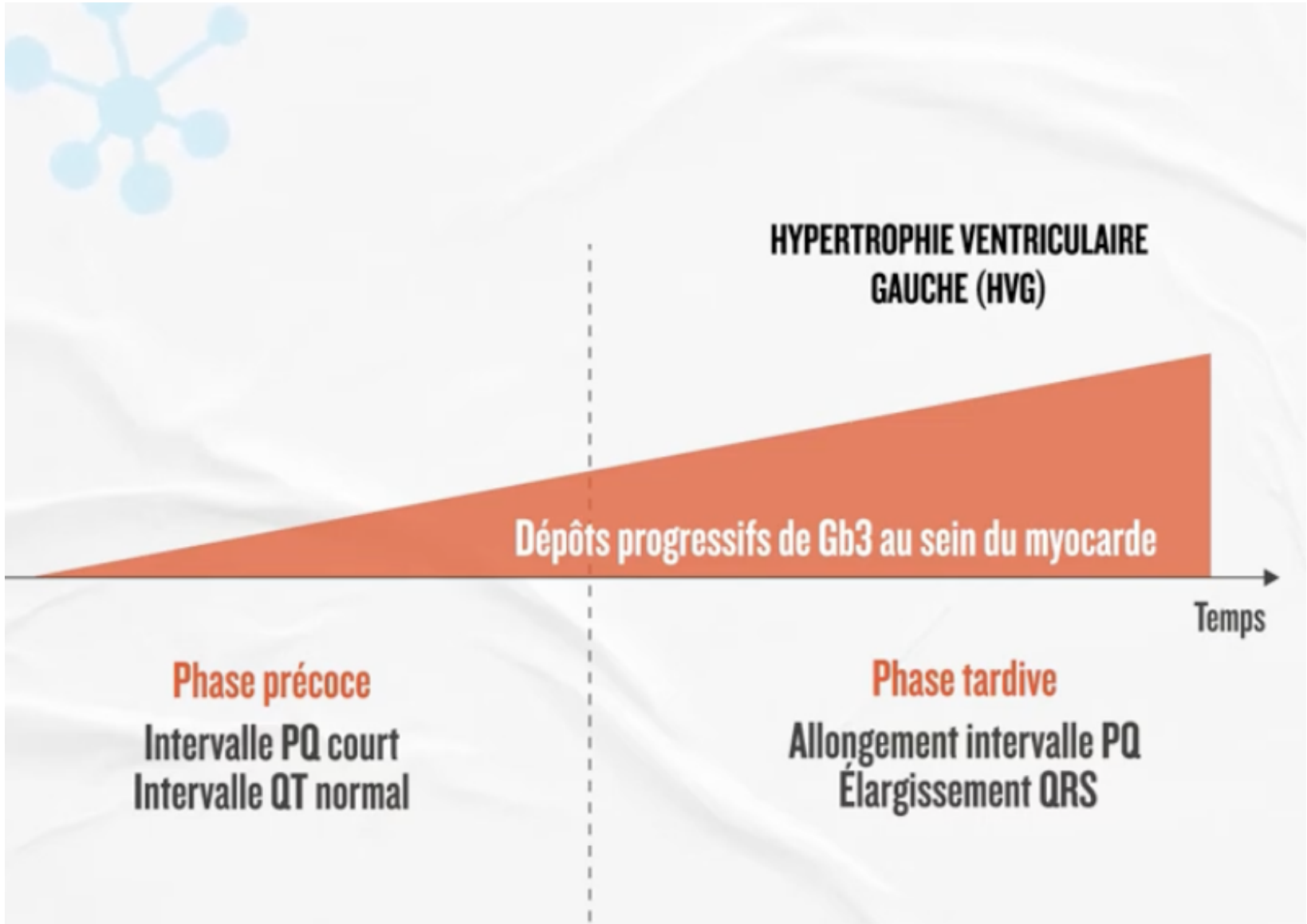
Y penser devant une HVG inexpliquée

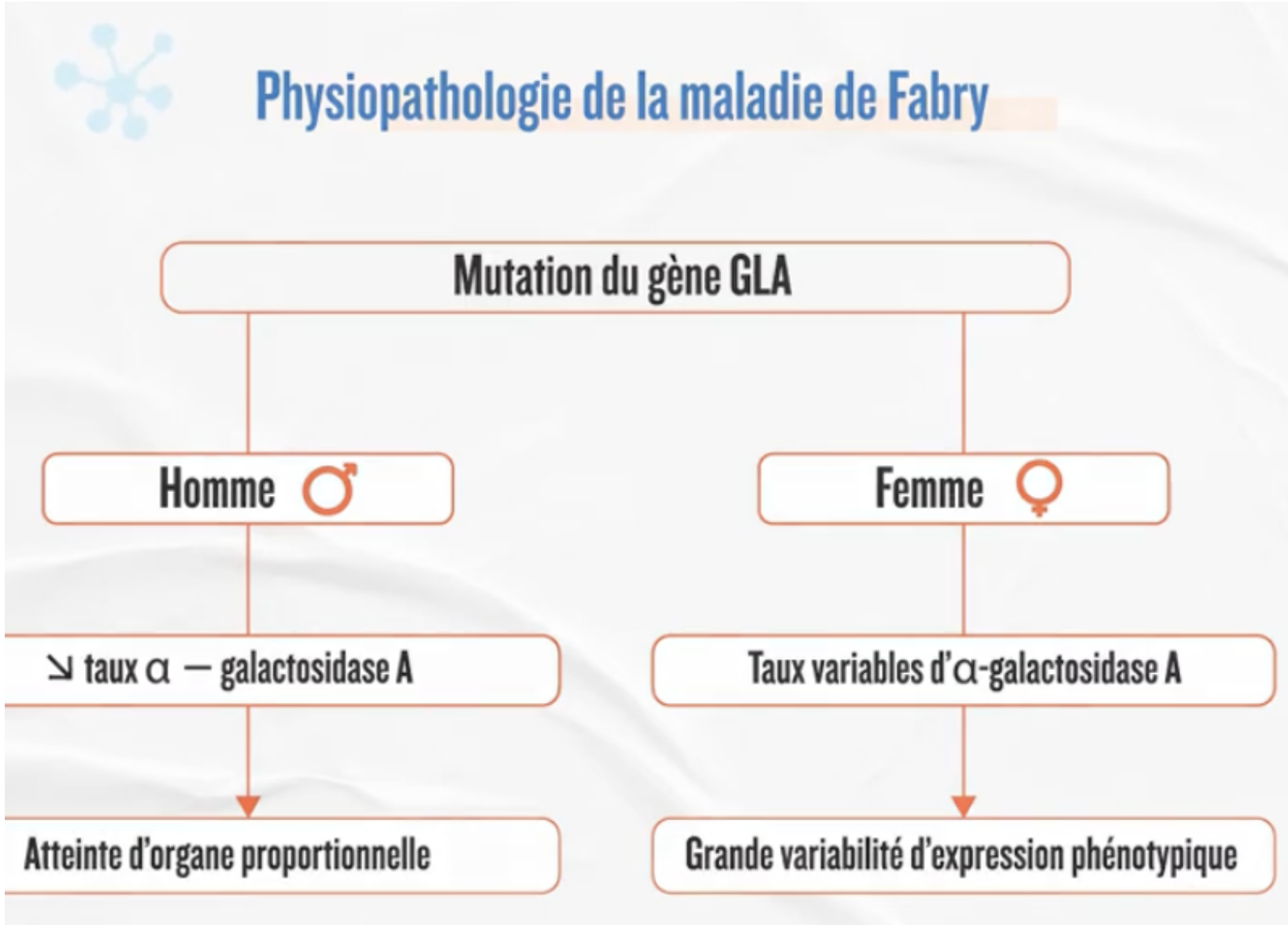


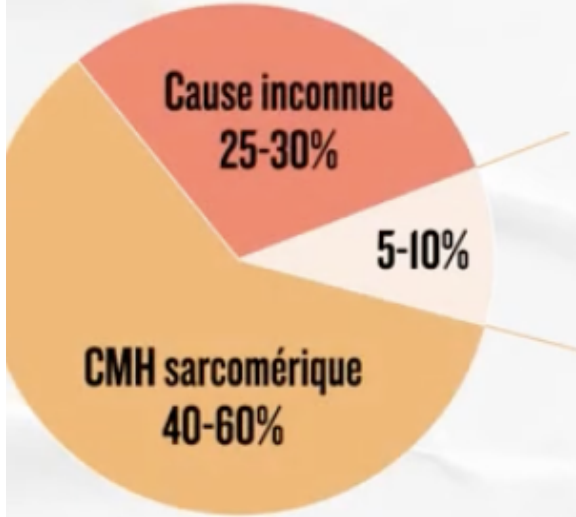







HYPERTROPHIE VENTRICULAIRE GAUCHE (HVG)
Dépôts progressifs de Gb3 au sein du myocarde
Temps
Phase précoce
Intervalle PQ court
Intervalle QT normal
Phase tardive
Allongement intervalle PQ
Élargissement QRS


Physiopathologie de la maladie de Fabry
Mutation du gène GLA
Homme ♂
Femme ♀
↘ taux α – galactosidase A
Taux variables d'α-galactosidase A
Atteinte d'organe proportionnelle
Grande variabilité d'expression phénotypique



Maladies métaboliques
Glycogénoses (Pompe, Danon), Fabry

Maladies neuro-musculaires
Friedreich, FHL I

Maladies mitochondriales
Melas Merff

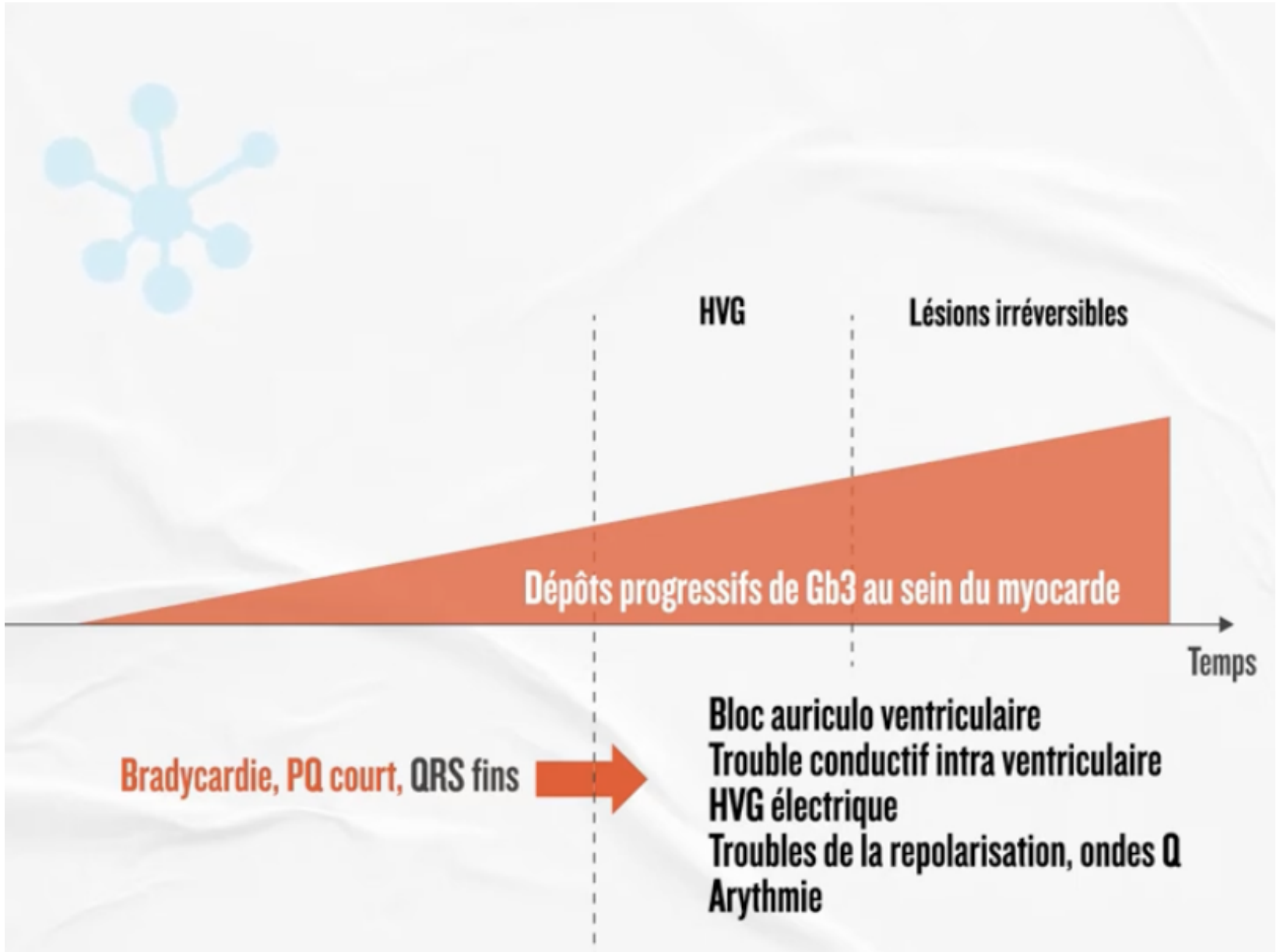
Syndromes malformatifs
Noonan, syndrome Leopard

Amylose
Amylose AL, génétique TTR, Sénile (TTR)

Nouveau-né de mère diabétique

Cause médicamenteuse
Tacrolimus, hydrochloroquine, stéroïdes

- Orienter vers de centres de compétence référence
- Lancer un bilan diagnostique simple
- Diagnostic différentiel

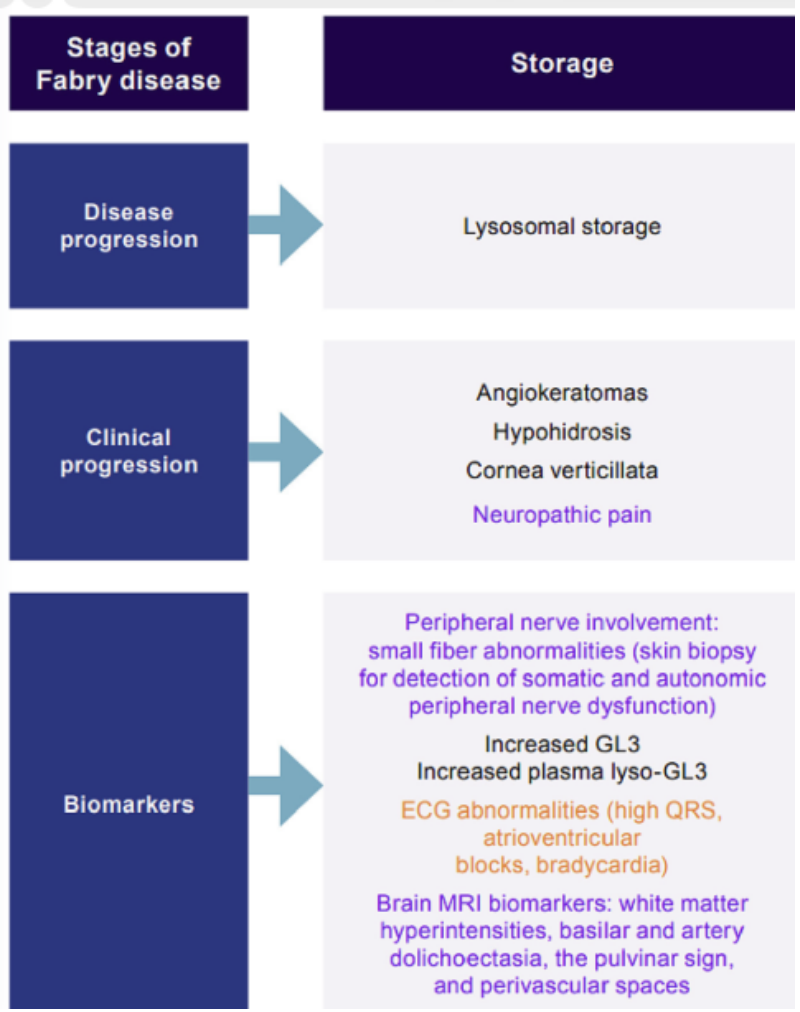

HVG
Lésions irréversibles
Dépôts progressifs de Gb3 au sein du myocarde
Temps
Bradycardie, PQ court, QRS fins
Bloc auriculo ventriculaire
Trouble conductif intra ventriculaire
HVG électrique
Troubles de la repolarisation, ondes Q
Arythmie

Maladie de Fabry

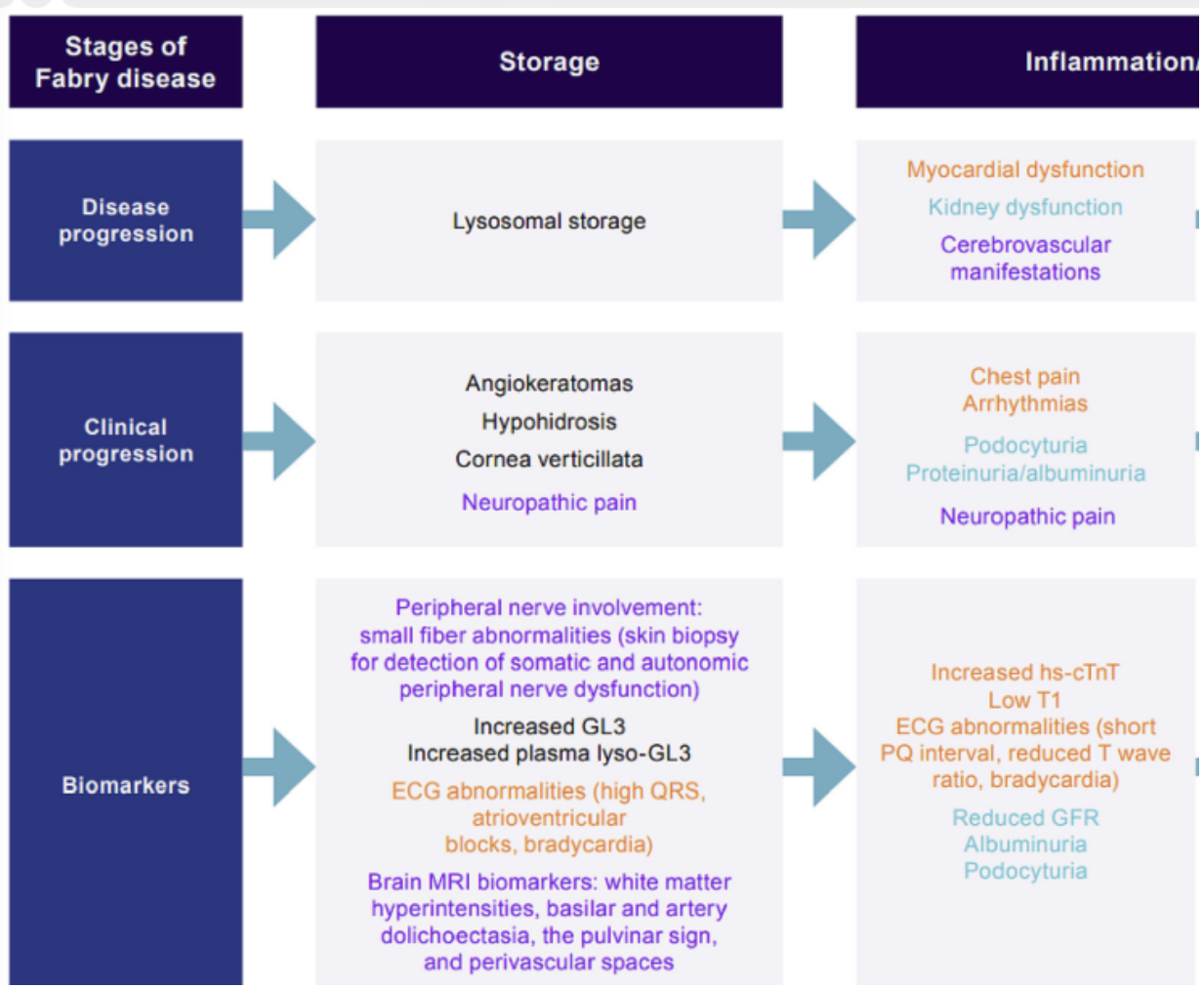
- Age moyen au diagnostic 42, 2 ans
- Membre de la famille 26 ans


1ère situation
Présence de signes d'appel
2ème situation
Absence de signes d'appel
Homme ♂
Femme ♀
Pour les 2 sexes ⚥
osage biochimique de
l' α-galactosidase
PUIS
st génétique ciblé sur
le gène GLA (si taux
d' α-galactosidase
abaissé)
Test génétique ciblé
sur le gène GLA
EN PARALLÈLE
Dosage biochimique de
l' α-galactosidase
Test génétique large par panel de gènes
EN PARALLÈLE
Chez l'homme > 30 ans : dosage biochimique
de l' α-galactosidase

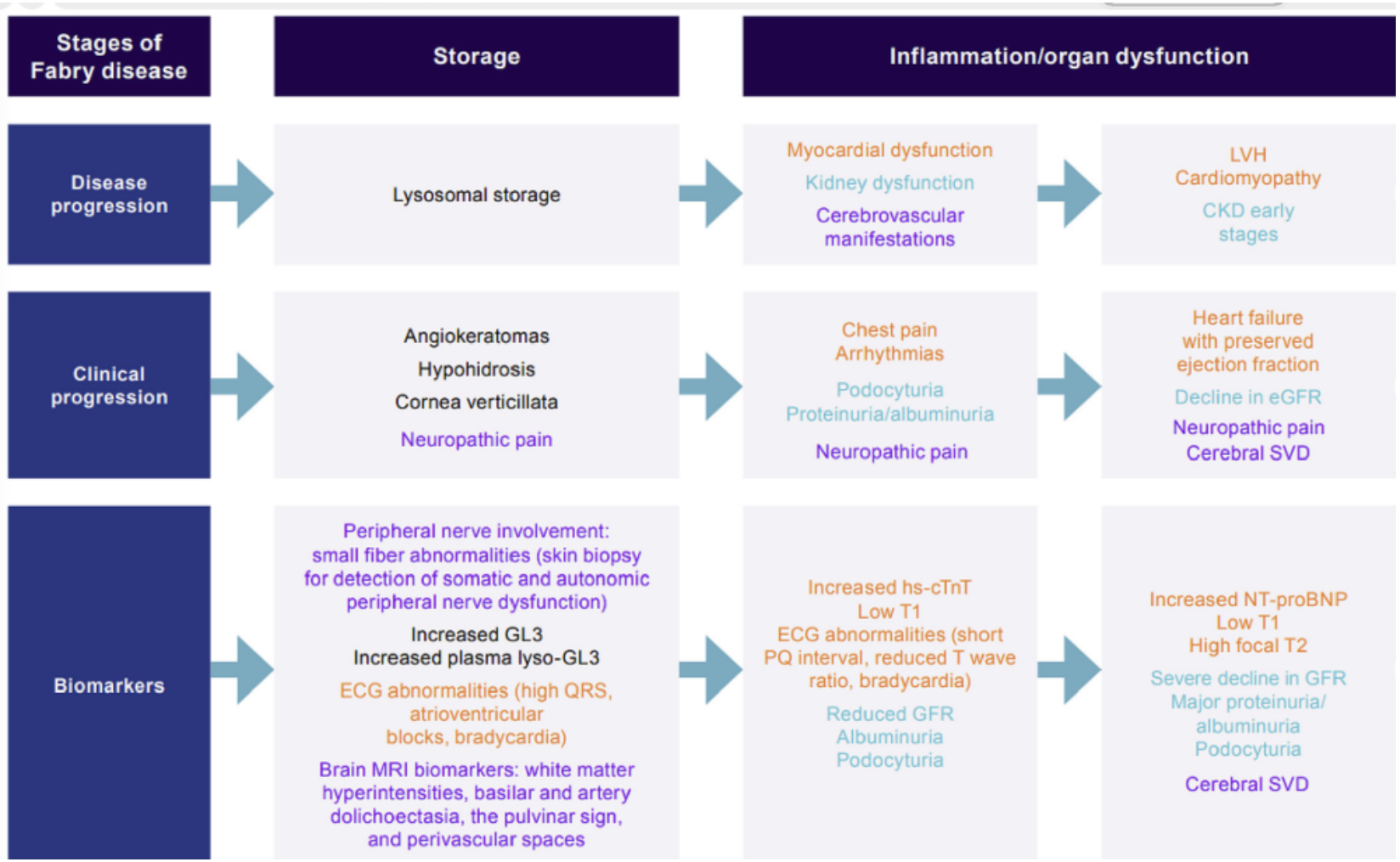
Maladie de Fabry
Diagnostic



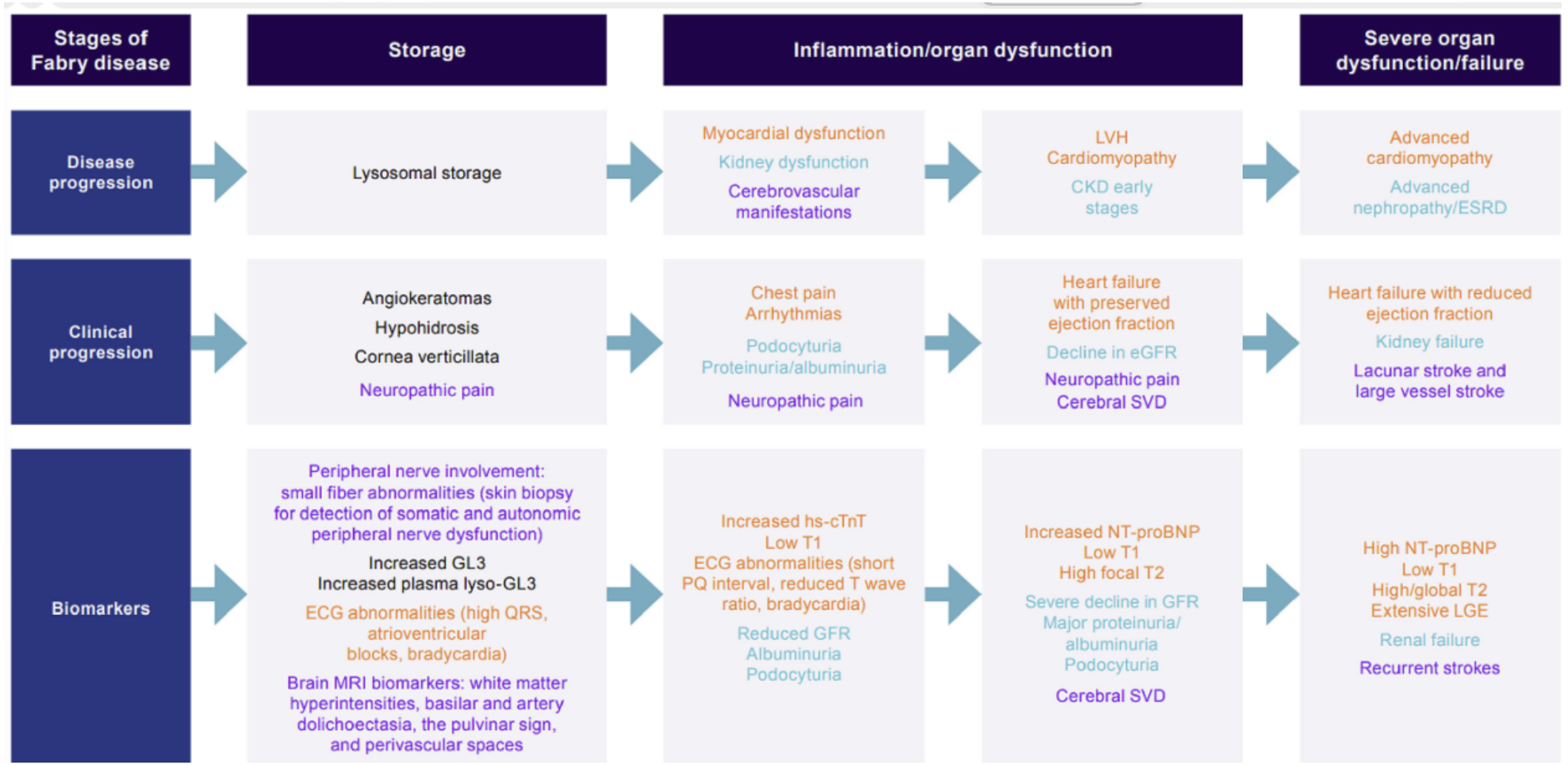
Maladie de Fabry
Diagnostic



Maladie de Fabry
Diagnostic



Maladie de Fabry
Diagnostic

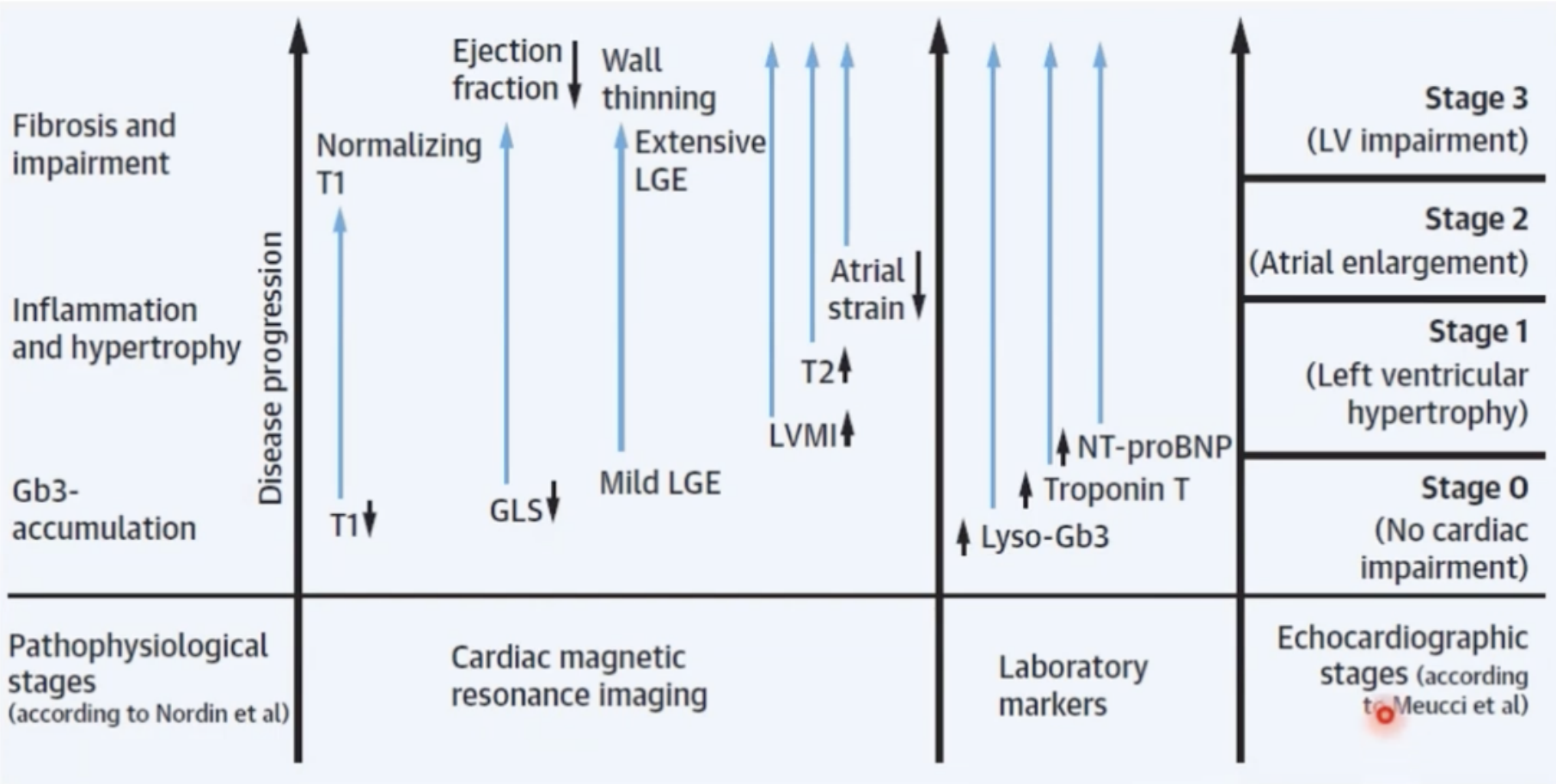


JACC JOURNALS

Staging of Fabry Cardiomyopathy by Echocardiography

Back to the Roots?*

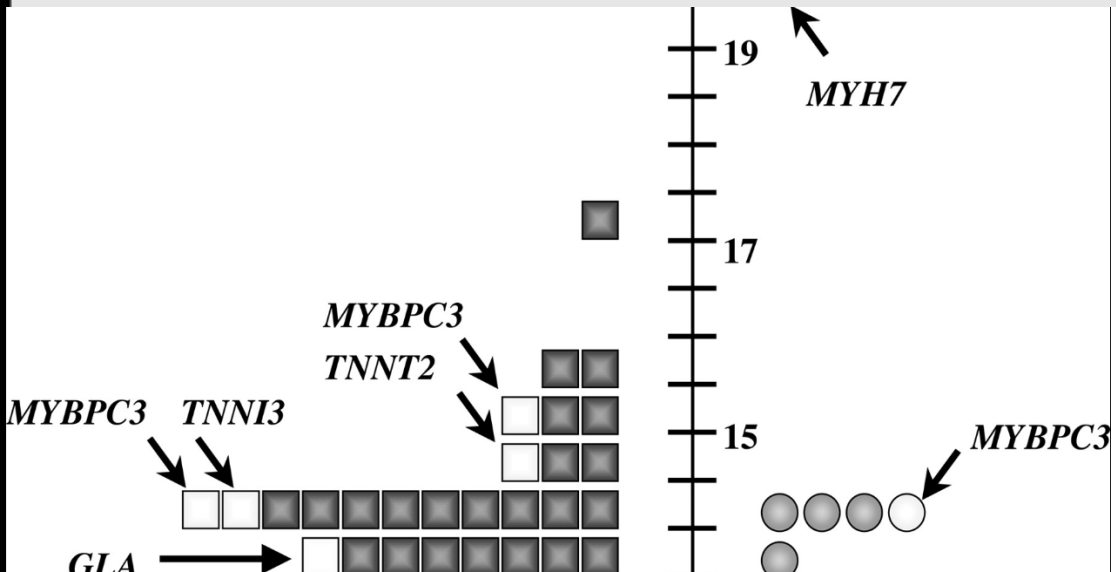
FIGURE 1 Pathophysiology, Laboratory, and Imaging Markers in Fabry Cardiomyopathy

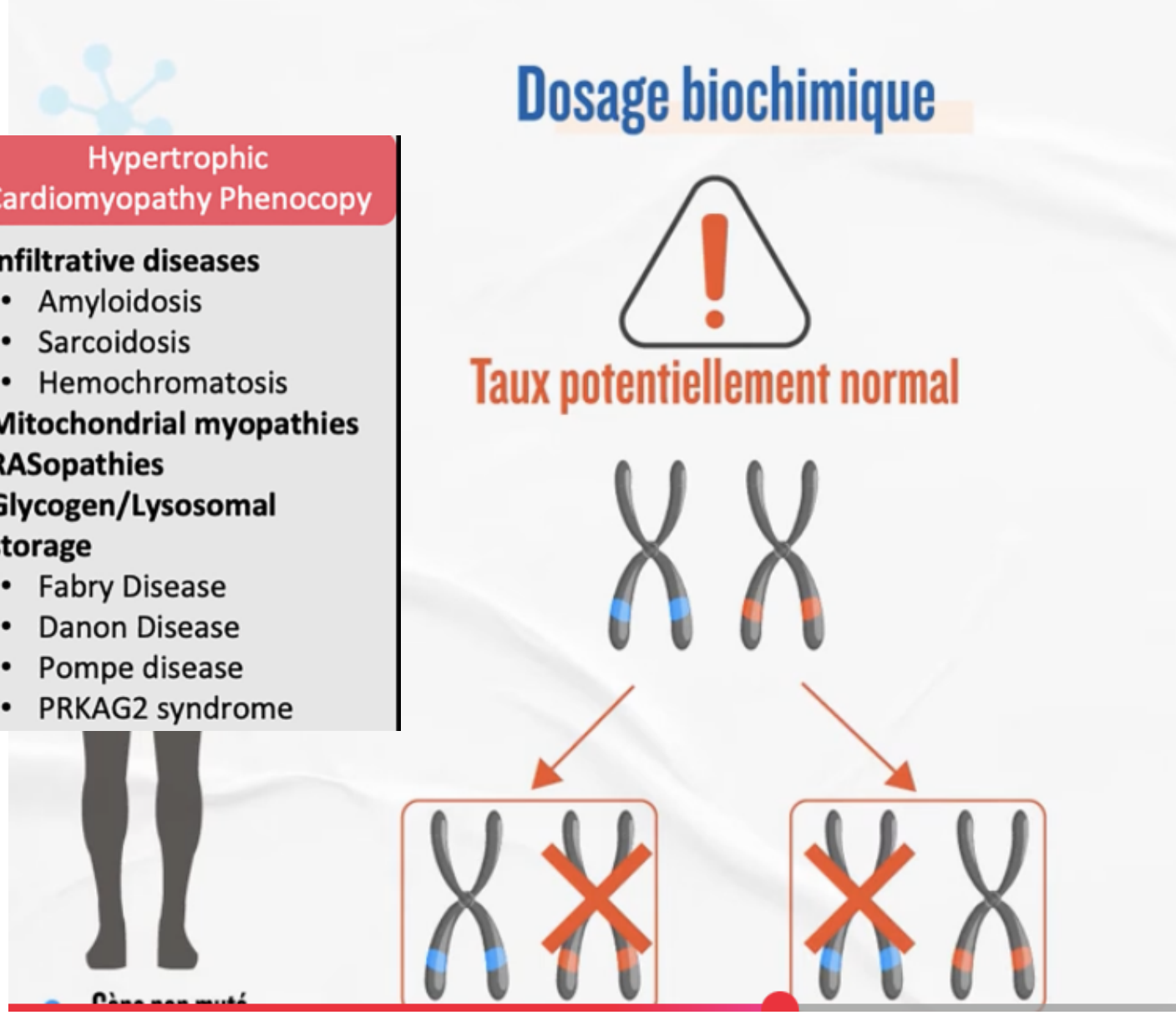


Sunder-Plassmann G , Gatterer C, MD JACC 2

Left Ventricular Hypertrophy	Hypertrophic Cardiomyopathy	Hypertrophic Cardiomyopathy Phenocopy

• **Hypertension**
• **Aortic Stenosis**
• **Subaortic stenosis**
• **Athlete's Heart**
	• **Non-sarcomeric**
	• **Sarcomeric**
	  • MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, ACTC1
		• **Infiltrative diseases**
		  • Amyloidosis
		  • Sarcoidosis
		  • Hemochromatosis
		• **Mitochondrial myopathies**
		• **RASopathies**
		• **Glycogen/Lysosomal storage**
		  • Fabry Disease
		  • Danon Disease
		  • Pompe disease
		  • PRKAG2 syndrome





Interet du test génétique

- Mutation spécifique de la maladie de Fabry
- Orientation vers une forme classique ou une forme cardiaque voire rénale ou ophtalmologique
- Aide à la stratification du risque au suivi
- Choix du traitement

Active, not recruiting

Dose-Ranging Study of ST-920, an AAV2/6 Human Alpha Galactosidase A Gene Therapy in Subjects With Fabry Disease (STAAR)

ClinicalTrials.gov ID NCT04046224

Sponsor Sangamo Therapeutics

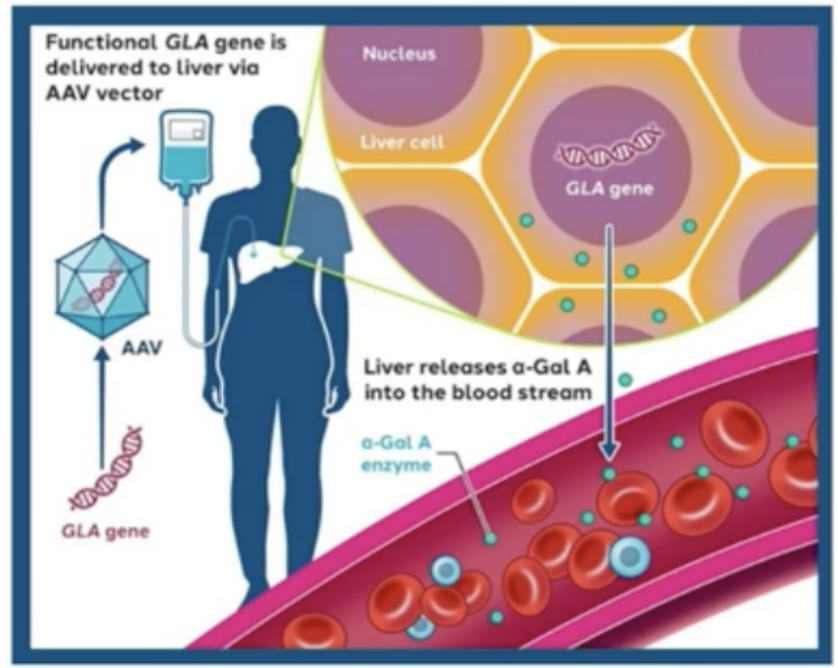
Information provided by Sangamo Therapeutics (Responsible Party)

Last Update Posted 2024-05-09

STAAR, a Phase 1/2 study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease

Robert J. Hopkin[1]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA



- Un médecin généticien
- Un médecin non généticien connaissant la maladie
- Un conseiller génétique

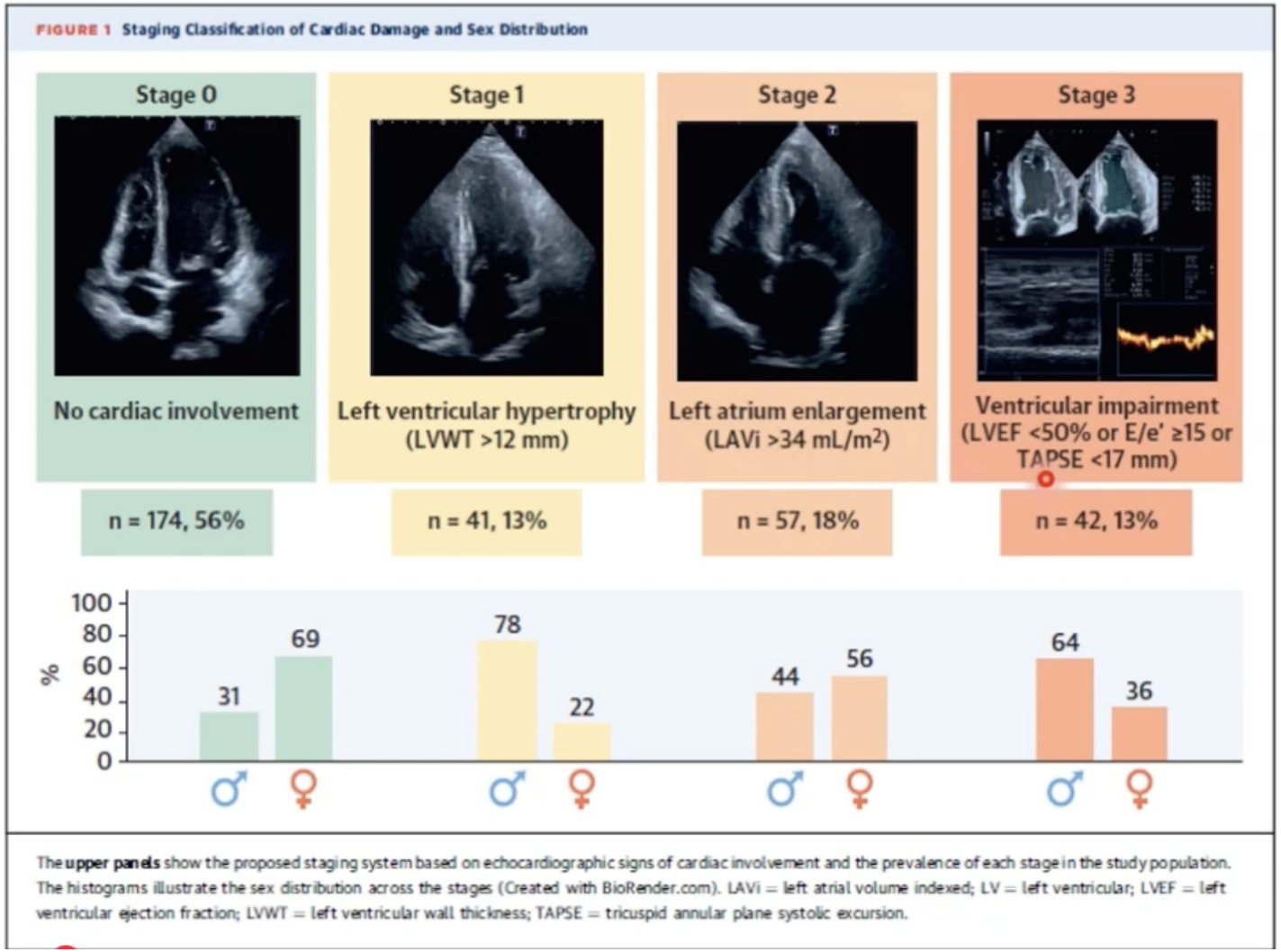
Prognostic Implications of the Extent of Cardiac Damage in Patients With Fabry Disease

Multicenter

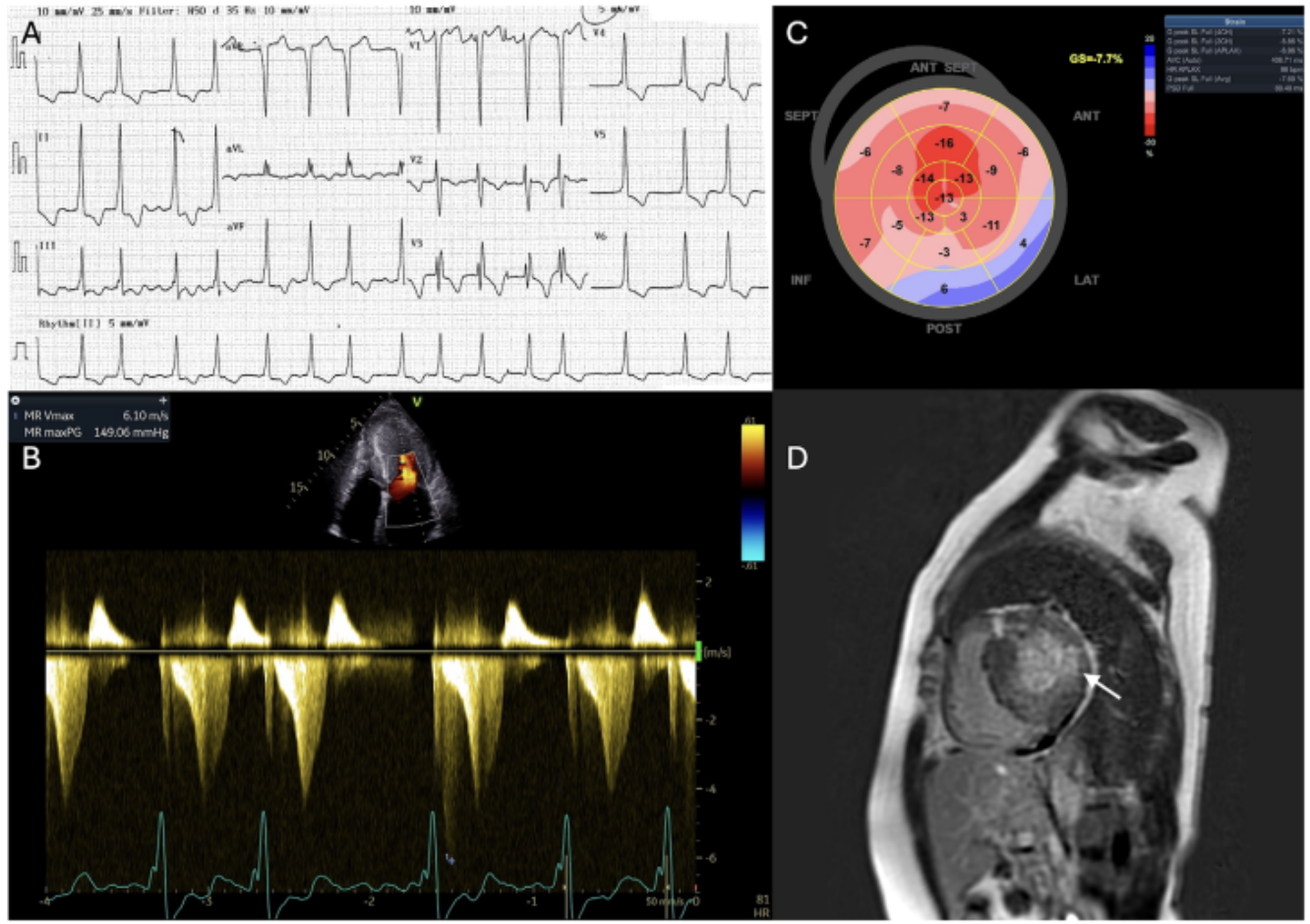
Retrospective study

314 patients

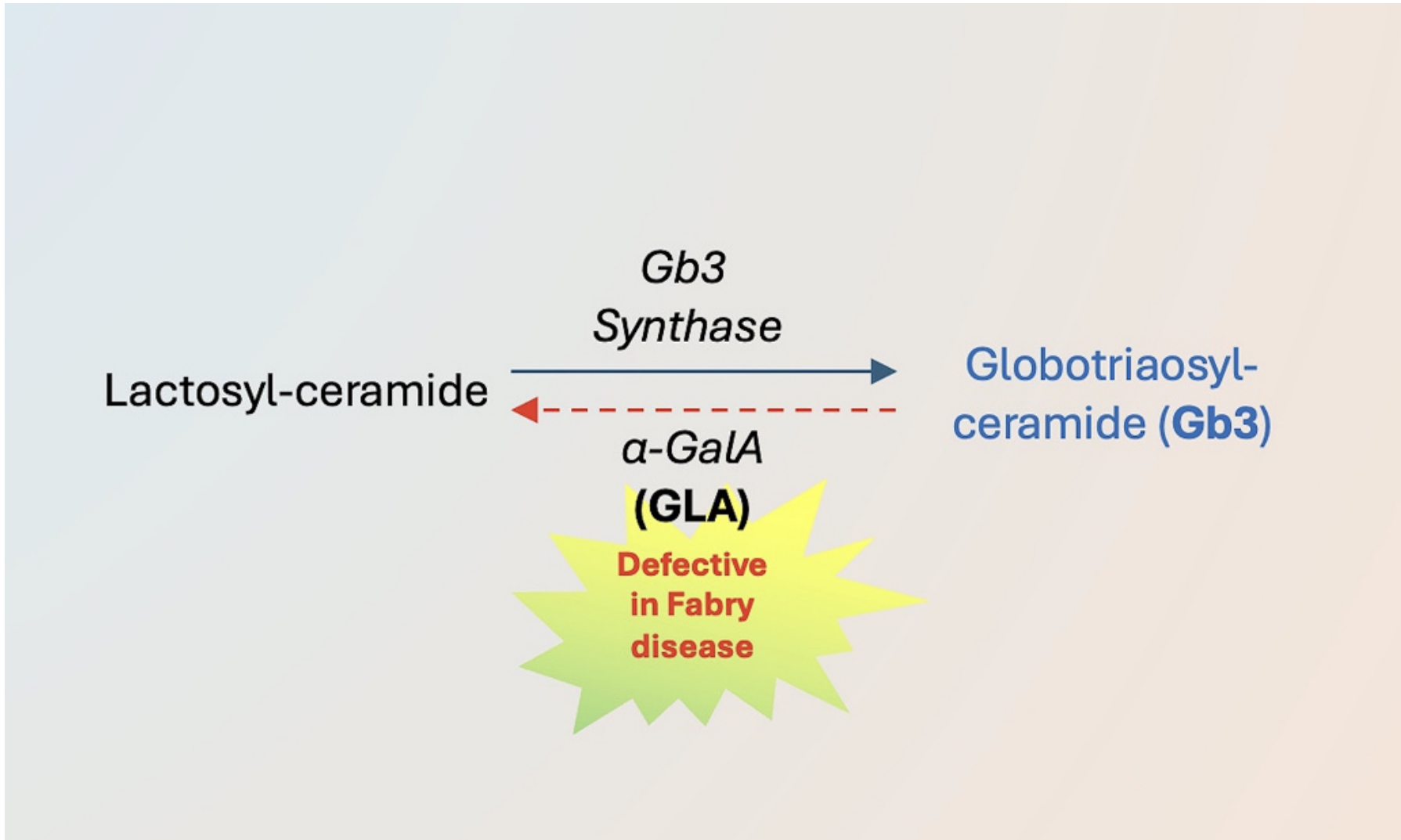
Follow up: 8 years

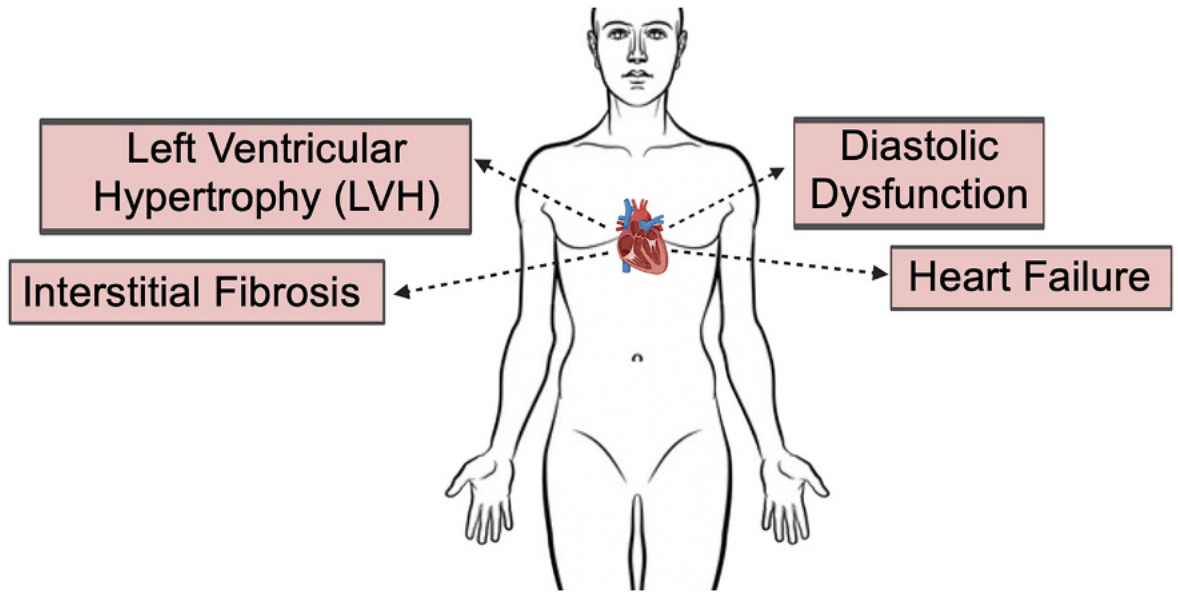


Meucci M , Graizani F J

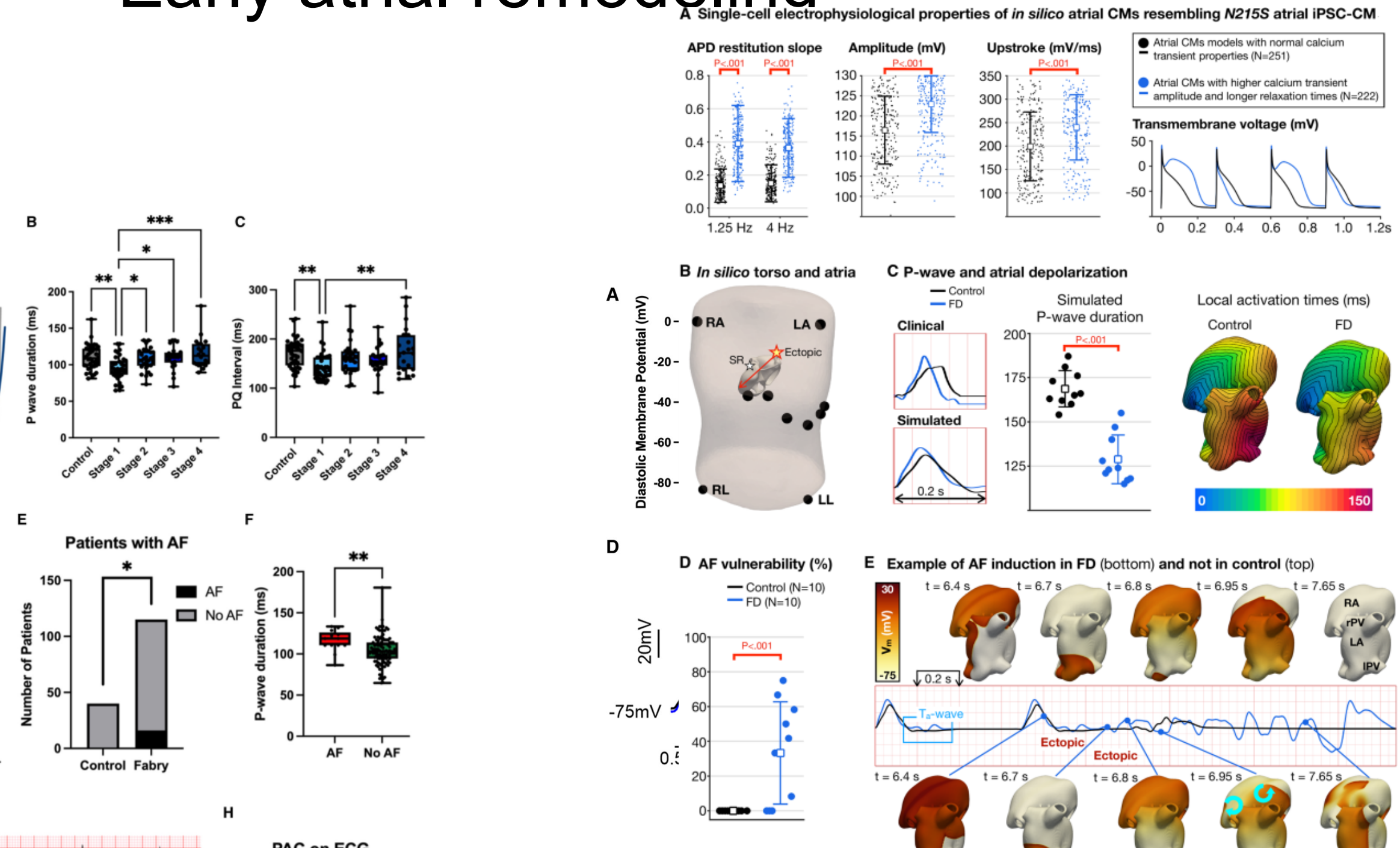

A
B
MR Vmax 6.10 m/s
MR maxPG 149,06 mmHg
C
GS=-7.7%
ANT SEPT
ANT
SEPT
INF
LAT
POST
D

	Hypertrophic Group			Dilated Group		
	Non-FD (n = 361)	FD (n = 10)	p Value	Non-FD (n = 34)	FD (n = 4)	p Value
ECG						
Heart Rate (bpm) median (IQR)	64 (58, 73)	74 (66, 77)	0.235	72 (55, 78)	59 (57, 62)	0.199
Left Atrial Anomaly	31 (10%)	1 (11%)	-	5 (20%)	0 (0%)	-
LVH–Voltage	98 (32%)	4 (44%)	0.476	5 (20%)	0 (0%)	-
LVH–Overload	87 (28%)	2 (22%)	-	7 (28%)	1 (33%)	-
NVRA	133 (43%)	4 (44%)	-	8 (32%)	1 (33%)	-
Atrioventricular Block	35 (11%)	0 (0%)	-	1 (4.0%)	1 (25%)	0.261
QRS Duration (ms) median (IQR)	103 (94, 114)	130 (110, 148)	0.029	112 (102, 136)	169 (167, 189)	0.013
QRS > 110 ms	90 (31%)	3 (60%)	0.332	13 (50%)	3 (100%)	0.232
LBBB	21 (6.8%)	0 (0%)	-	4 (16%)	0 (0%)	-
RBBB	28 (9.1%)	5 (56%)	<0.001	3 (12%)	2 (67%)	0.073
Pathological Q Waves	28 (9.1%)	0 (0%)	-	6 (24%)	0 (0%)	-
Fascicular block	24 (7.8%)	3 (33%)	0.033	2 (8.0%)	1 (33%)	0.298

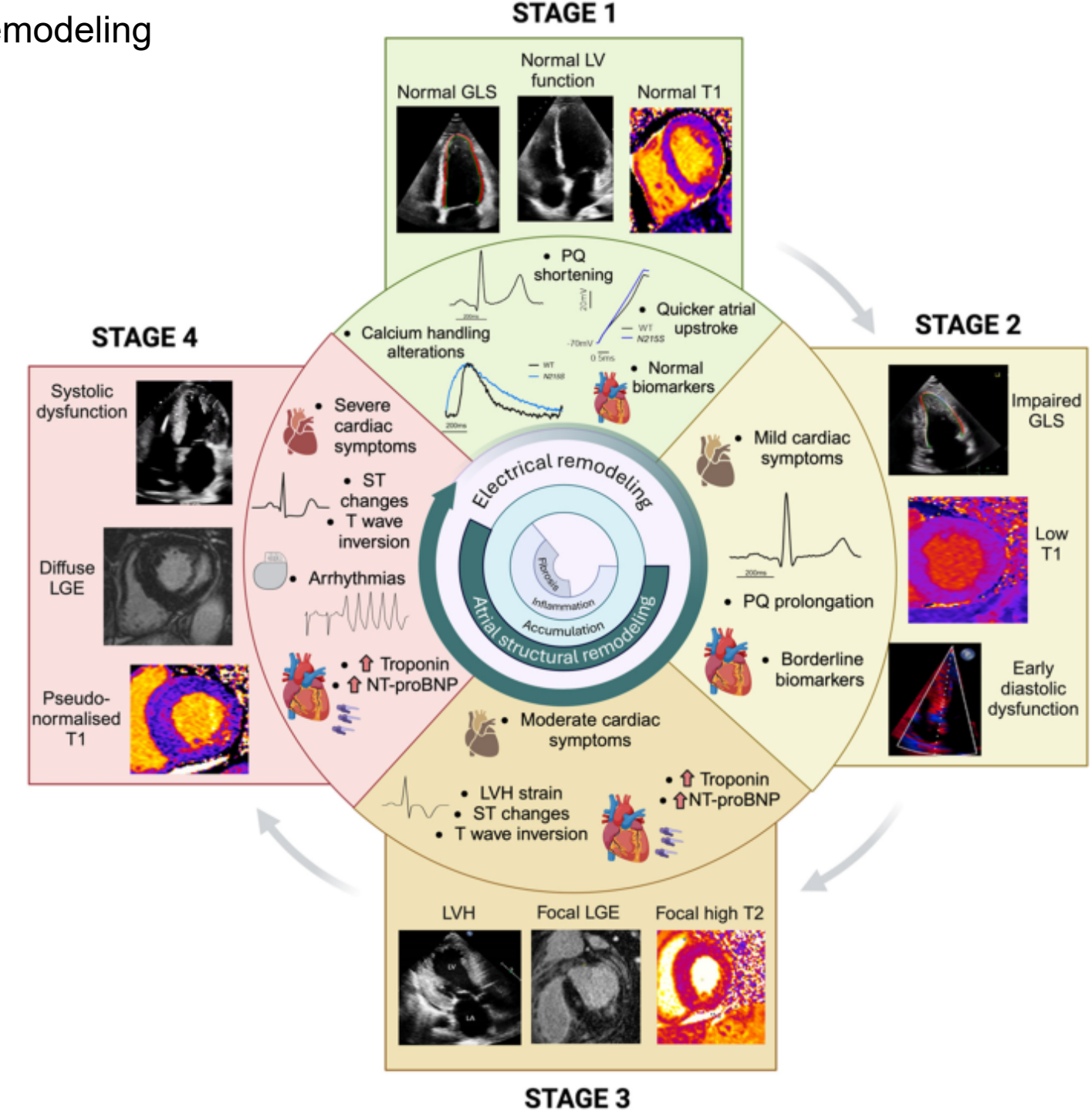

Gb3
Synthase
Lactosyl-ceramide
Globotriaosyl-ceramide (Gb3)
α-GalA
(GLA)
Defective in Fabry disease


Left Ventricular Hypertrophy (LVH)
Diastolic Dysfunction
Interstitial Fibrosis
Heart Failure

Early atrial remodelling



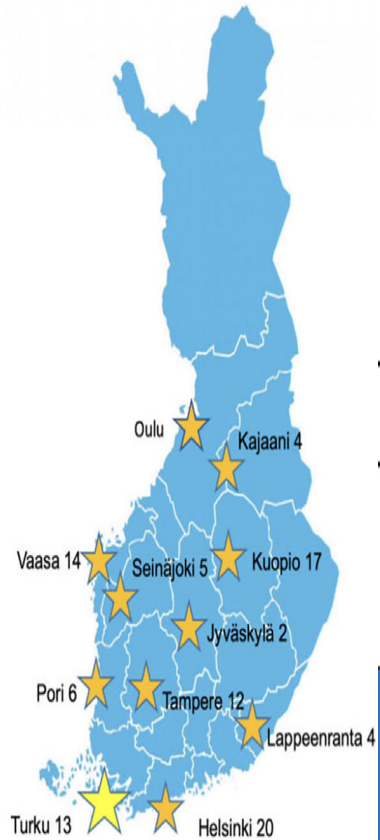
Early atrial remodeling

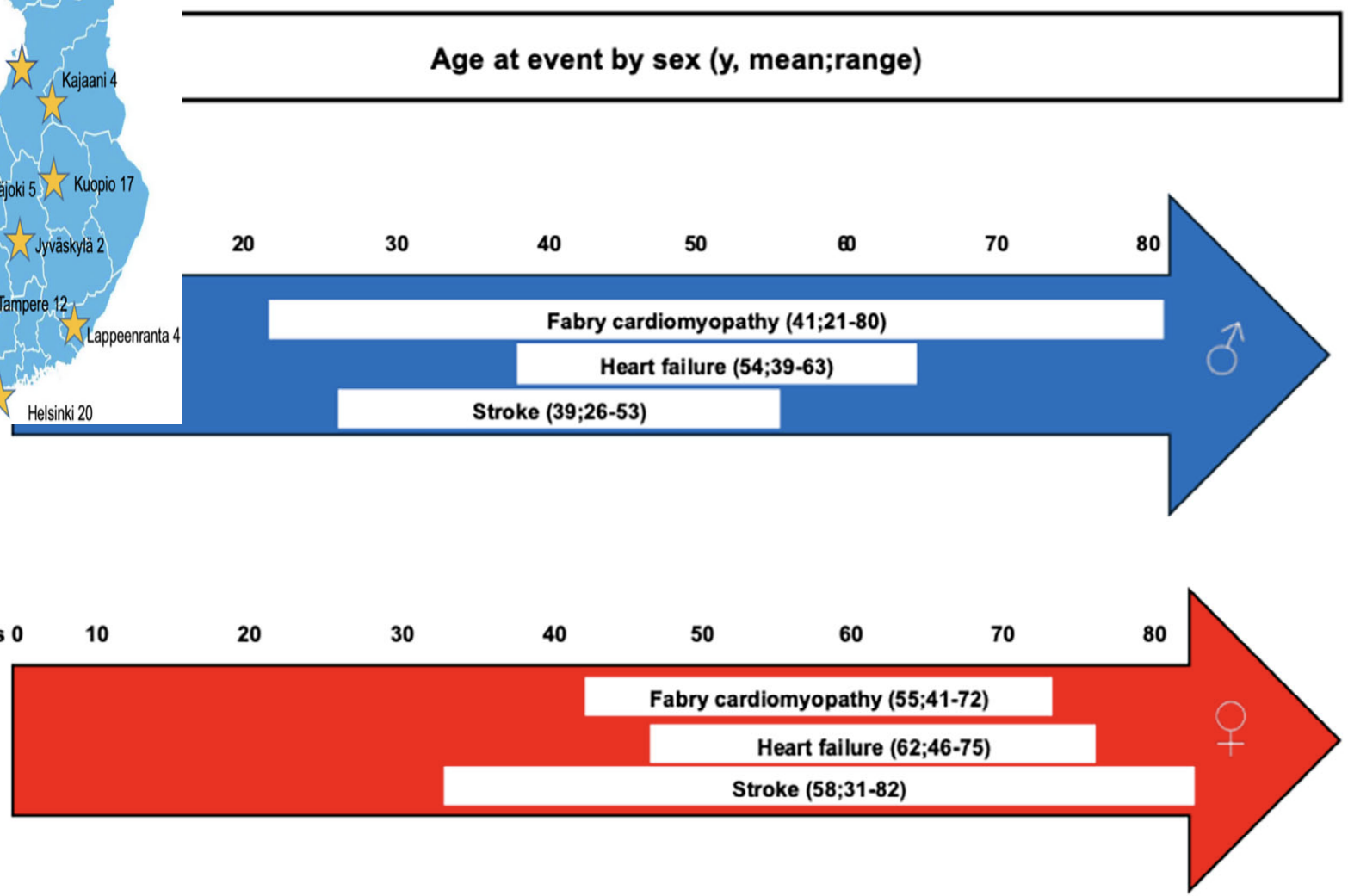


The Finnish Fabry Disease Expert Network and study patient numbers (*n* = 97)

Turku Fabry Disease Centre of Excellence

Other Fabry expert centers





Cardiac Amyloidosis Older patients; low voltage ECG with LVH; apical sparing on strain; diffuse subendocardial LGE on CMR; bone tracer scan (Tc-PYP) strongly positive (ATTR type).

Cardiac Sarcoidosis Age 30–60; often history of systemic sarcoid; arrhythmias (VT) or AV block out of proportion to LVH; patchy mid-wall or epicardial LGE in basal septum; active inflammation on FDG-PET.

Fabry Disease Age 20–50 (X-linked); multi-system involvement (neuropathy, renal failure, angiokeratomas); short PR ± WPW on ECG; low native T1 on CMR; basal inferolateral wall LGE (late stage).

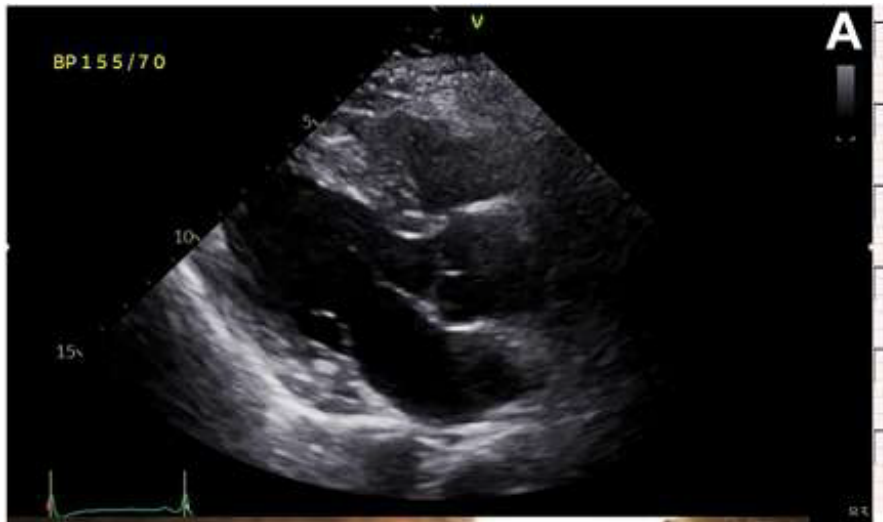
Pompe Disease Infantile onset HCM (often massive); hypotonia, feeding difficulty; very high CK; confirm by GAA enzyme assay; minimal cardiac involvement in late-onset form.

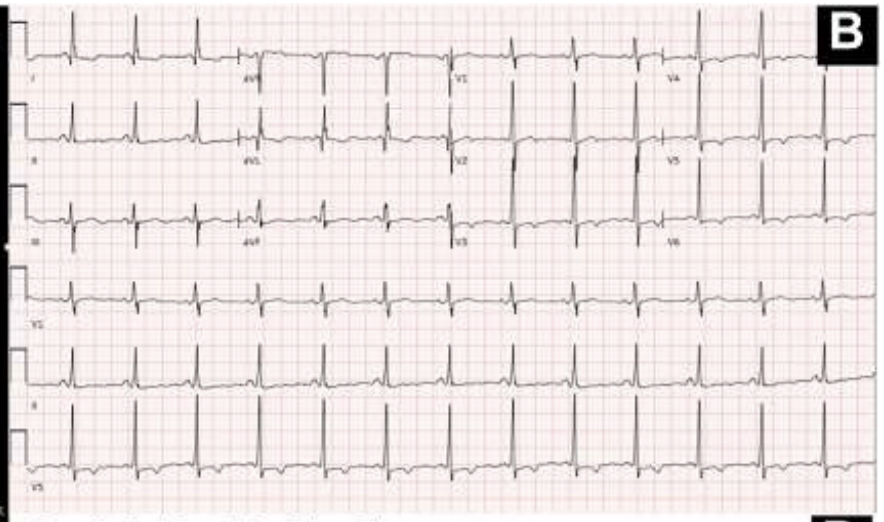
Danon Disease X-linked (boys in teens); skeletal myopathy, cognitive impairment; *pre-excitation (WPW)*; extreme LVH (septum often >20 mm); diffuse fibrosis on CMR; very high CK; rapid progression to early heart failure

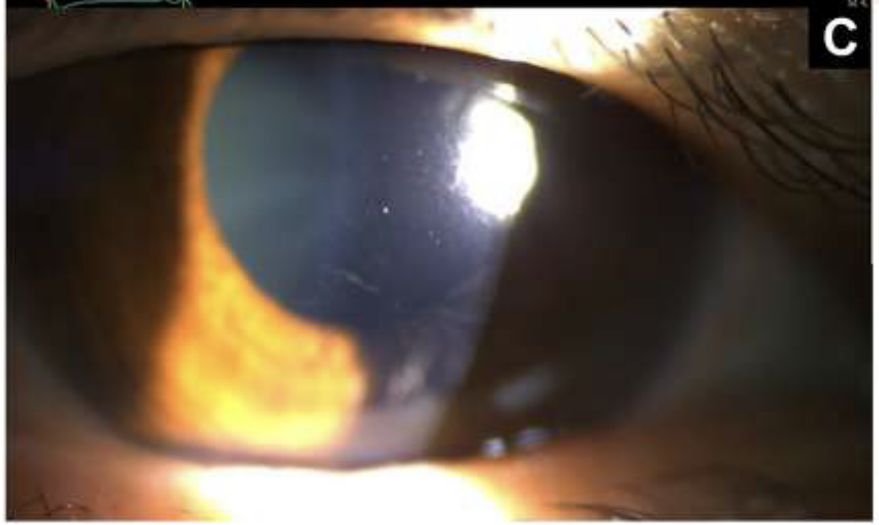
Mitochondrial CM Maternal inheritance pattern (in mtDNA diseases); multi-organ involvement (deafness, ataxia, myopathy); ± short stature or diabetes; *extensive LGE* on CMR (diffuse fibrosis); elevated lactate; confirm with genetic testing

Athlete's Heart Young competitive athletes; symmetric LVH (usually ≤15 mm) with *enlarged LV*

Femme 65 ans







Genetic Test Result for Fabry Disease

D

A heterozygous pathogenic variant was identified in the GLA gene, which is associated with X-linked Fabry disease (OMIM: 301500). Genetic testing of family members is recommended to determine segregation of the variant.

Gene	Genomic Position (GRCh37)	cDNA Change	Protein Change	Zygosity	Classification
GLA	X:100653866 C>T	c.708G>A	p.Trp236Ter	Heterozygous	Pathogenic

- Plasma Lyso-Gb3: 7.14ng/mL (<1.74)
- a-galactosidase A enzyme activity : 3.61umol/h/L (>2.35)

Of 1,077 females with FD in the Fabry Registry, **69.4%** report signs and symptoms of disease[a] [3]

Clinical events

- Percentage of females who experienced any event (cardiac, kidney, cerebral) prior to their first visit to a Fabry referral center: **19.0%** (n=28/147) in classic FD and **10.8%** (n=16/148) in non-classic FD [4]
- Age at first visit to referral center: **41.5 years** (classic FD) and **43.7 years** (non-classic FD) [4]

Health-related quality of life

- Female adolescents aged 14 to 17 years (n=26) had significantly lower scores in domains of the SF-36 compared with scores for females in general US population aged 18 to 24 years old [8]
- Quality of Life dramatically worsened among females aged 25 to 34 years (n=71). Females between the ages of 35 and 54 years exhibited significantly lower scores on SF-36 data than women in the general US population (n=181) [3]

Stroke/TIA:

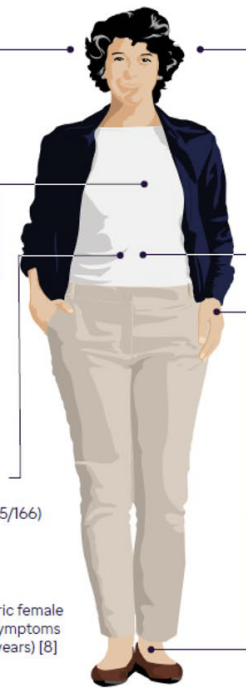
- Stroke: **7%** of females (n=18/248; mean age of onset 49.9 years) [12]
- TIA: **7%** of females (n=17/248; mean age of onset 42.9 years) [12]
- Of those women who experience stroke, **17%** (n=9/52) experience their first stroke before 30 years [16]

Cardiac involvement:

- Arrhythmias: **27%** of females (n=46/168; age first arrhythmias reported: early 20s [15]
- LVH: **18.2%** of females (n=192/1,055; mean (SD) age first reported 49.8 (12.4) years [3]
- Fibrosis (LGE on cMRI): **37%** of females (n=22/59; mean age: 45 ± 15 years) [13]
- Presence of LVH associated with **3× increased risk** of cardiac event[b] (independent of sex[c]) within 3.6 years [13]
- Presence of LGE (fibrosis) associated with **7× increased risk** of cardiac event[b] (independent of sex[c]) within 3.6 years [13]

GI disturbances:

- Abdominal pain: **45%** (n=75/166) of females [17]
- Diarrhea: **39%** (n=63/160) of females [17]
- **11.4%** (n=18/158) of pediatric female patients present with GI symptoms (median age of onset 9.5 years) [8]



Depression:

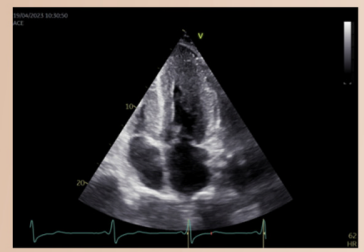
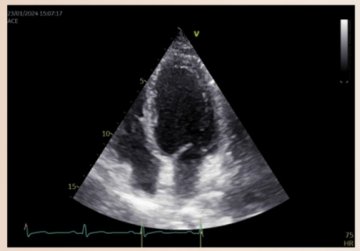
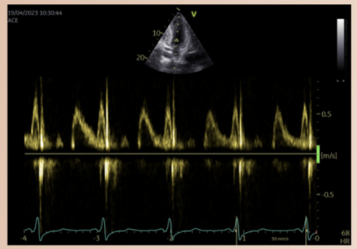
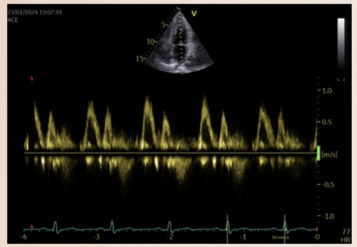
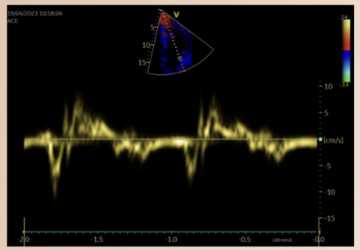
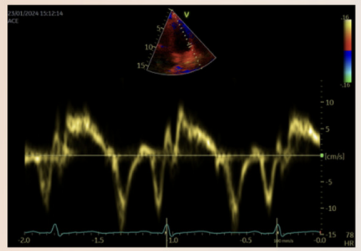
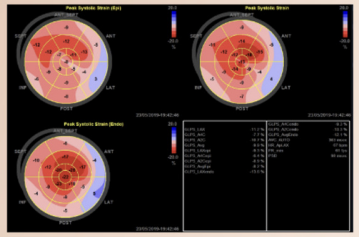
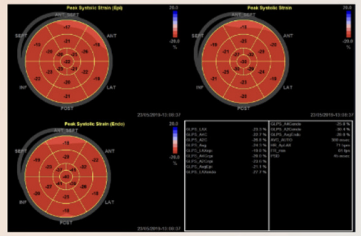
- Severe depression: **22%** (n=24/110) to **38%** (n=19/50) [10,11]

Kidney involvement:

- Proteinuria ≥300 mg/day: **39%** of females (n=135/346) [3]
- Proteinuria >3.5 g/day: **7.5%** of females (n=26/346) [3]
- ESKD: **2.2%** (n=23/1,055 at a mean age of 39.2 years) [3] to **4.8%** of females (n=8/168; median age 41.3 years) [15]

Neuropathic pain:

- **81.6%** (n=200/245) of adult females reported neuropathic pain primarily in their hands and feet [14]
- **40.5%** (n=64/158) of pediatric female patients (median age of onset 9 years) [8]

	Fabry Disease	Healthy
2D Cardiac Ultrasounds (Apex, 4 chambers)		
Trans Mitral Valve Fluximetry		
Mitral Valve Annulus Tissue Velocity		
Bull's eye Myocardial Strain Analysis		

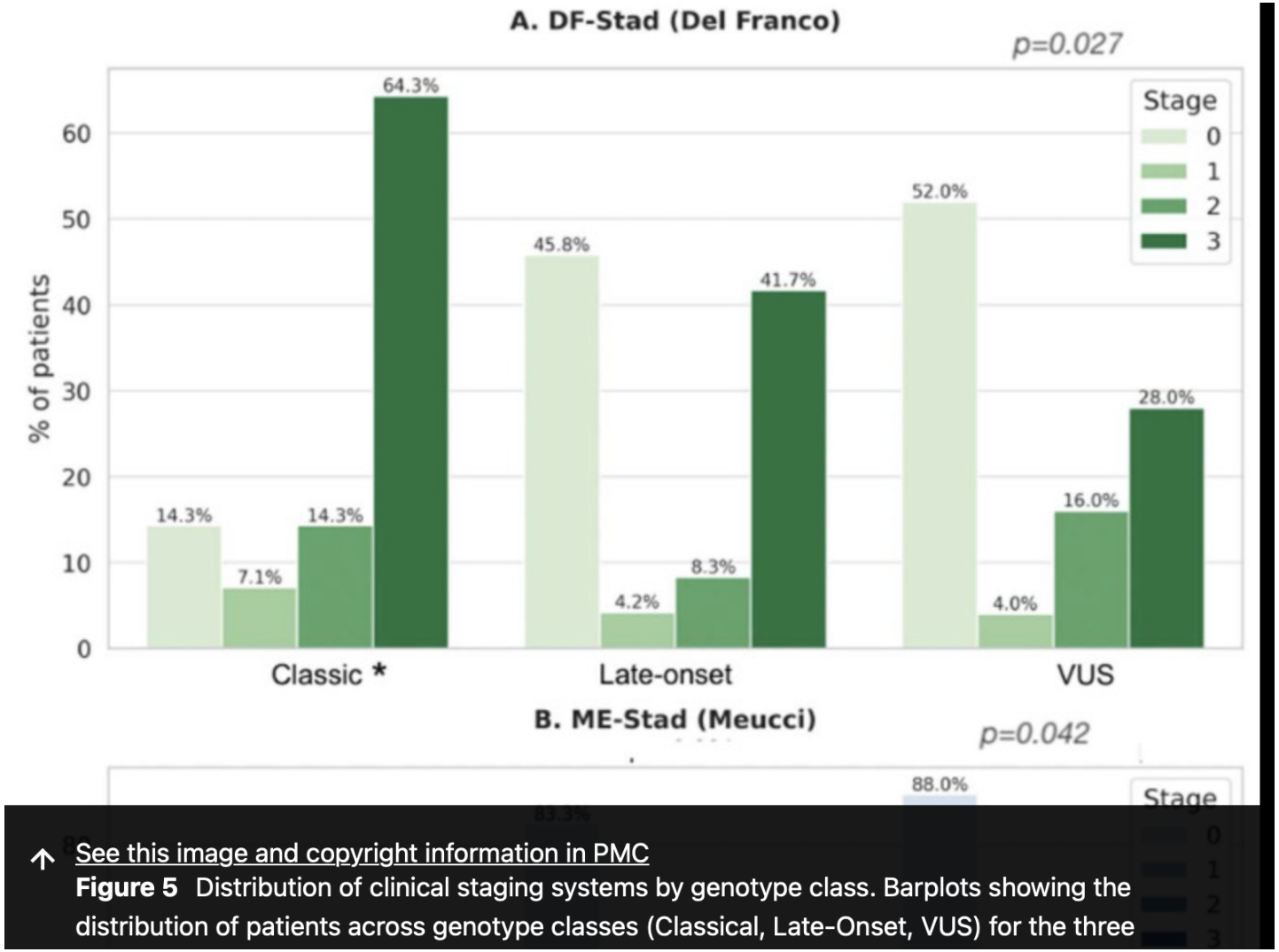
his study highlights the role of *GLA* genotype in shaping cardiovascular risk and clinical trajectory in AFD . Integrating genetic classification with clinical staging provides a powerful, multimodal approach to risk stratification and supports the move toward genotype-informed, personalized management strategies in AFD.

This study highlights the prognostic role of *GLA* genotype classification in the phenotypic expression and clinical progression of Anderson–Fabry disease. By integrating genotypic data with standardized cardiac staging systems and composite cardiovascular outcomes, we demonstrate that classical variants confer a markedly higher burden of disease and risk of major adverse cardiovascular events. These findings support the clinical utility of a comprehensive model for risk stratification that incorporates genetic variant classification into routine assessment, enabling earlier identification of high-risk patients and more tailored therapeutic strategies.

Figure 2. Boxplots show pVO_2 (% predicted), absolute pVO_2 (mL/kg/min), and VO_2/Watt with medians, interquartile ranges, and outliers (rhombus).

Figure 2. Boxplots show pVO_2 (% predicted), absolute pVO_2 (mL/kg/min), and VO_2/Watt with medians, interquartile ranges, and outliers (rhombus).

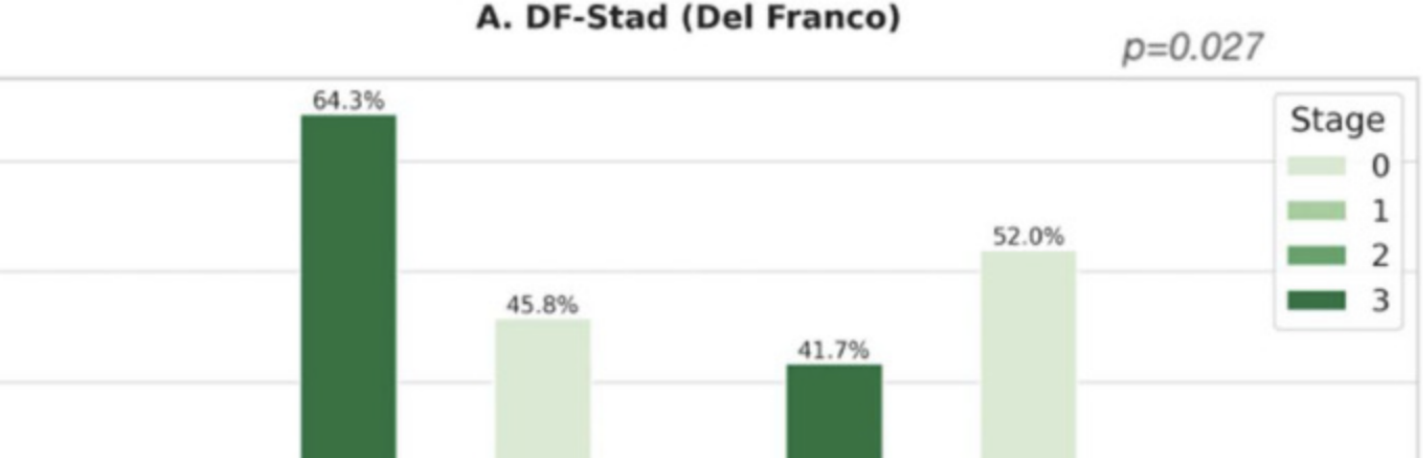
Maladie de Fabry : génétique

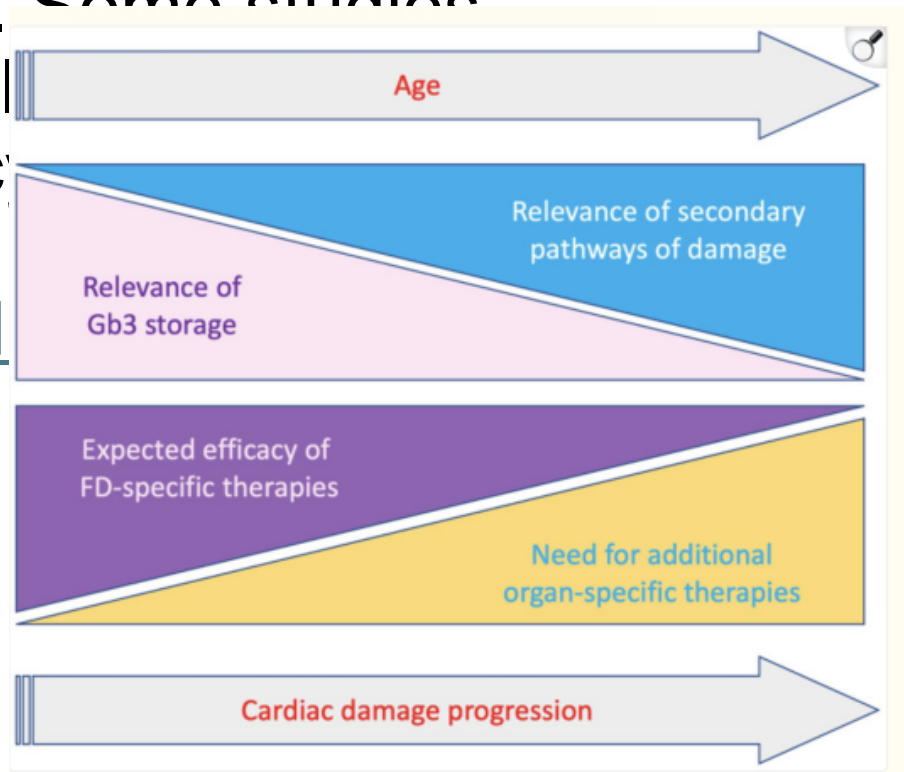


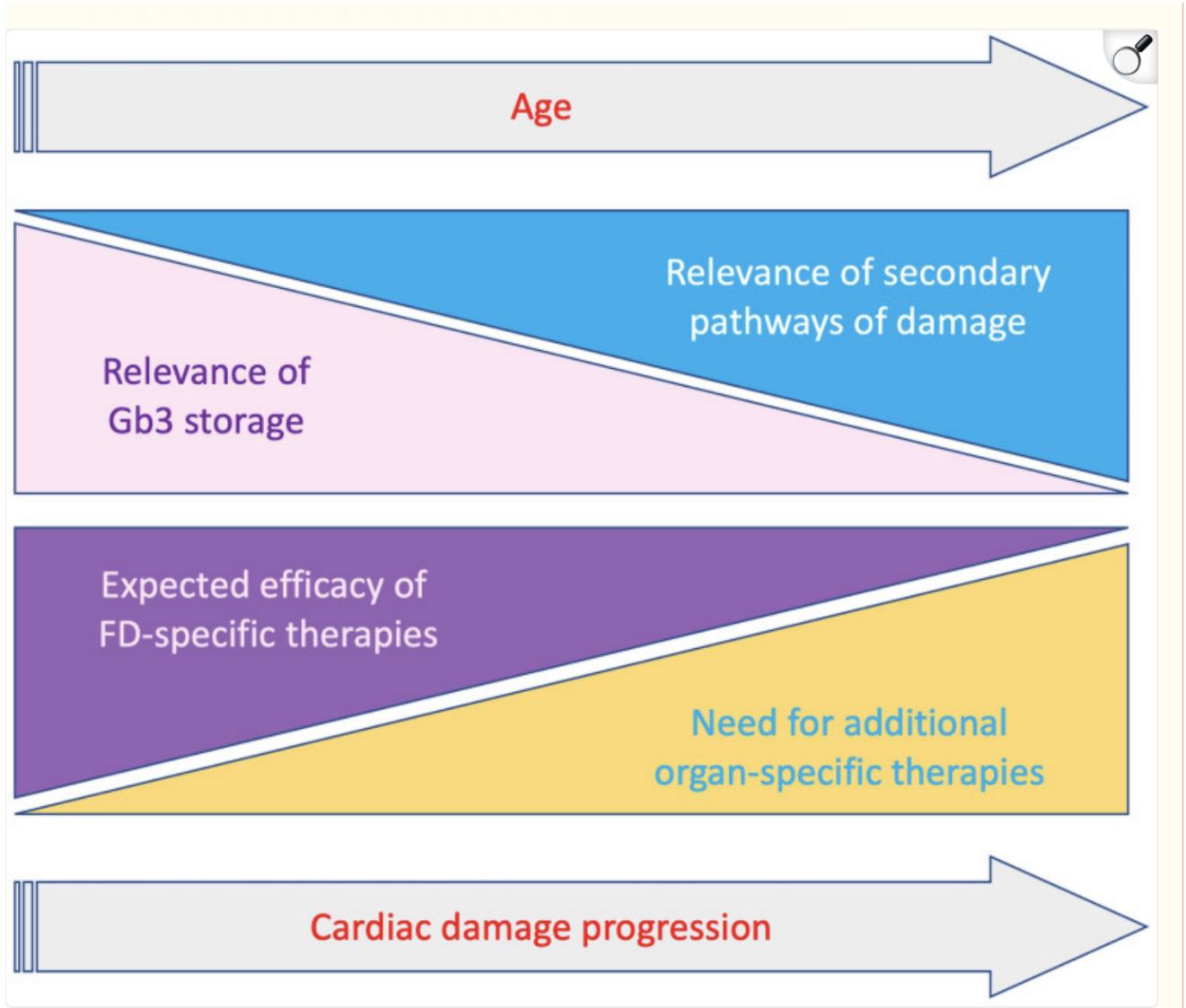
↑ See this image and copyright information in PMC

Figure 5 Distribution of clinical staging systems by genotype class. Barplots showing the distribution of patients across genotype classes (Classical, Late-Onset, VUS) for the three

- Although historically considered rare, with an incidence of 1:40,000 to 1:117,000, neonatal screening programs have revealed a much higher prevalence, especially of late-onset variants with cardiac or renal involvement. Some studies suggest a frequency as high as 1 in 3100 l in Italian reports [6,7,8,9]. This discrepanc clinical and genetic heterogeneity of AFD, [10,1 es.






Age
Relevance of secondary pathways of damage
Relevance of Gb3 storage
Expected efficacy of FD-specific therapies
Need for additional organ-specific therapies
Cardiac damage progression

Maladie de Fabry

- Maladie du stockage lysosomal lié à l'X du à une altération du gène GLA localisé dans le chromosome Xq22.1.
- lycosphingolipid deposition begins before birth and is cumulative.

- Ces mutations entraine une diminution ou une absence d'activité de l'enzyme alpha galactosidase. A (α-GLA).

- Il s'ensuit une accumulation de GB3 ou de Lyso Gb3 avec une atteinte multi organe.

Maladie de Fabry

- Pan-ethnique : incidence de 1 sur 40 000 à 1 sur 117 000

- Différentes régions géographiques : dépistage néonatal en Italie et à Taïwan prévalence jusqu'à 1 nouveau-né sur 8 800.

Maladie de Fabry

- *1 000 variants* du gène GLA identifiés (pathogènes, variants de signification incertaine (VUS) ou bénins)

- Les variants non-sens et les codons stop, absence ou faible activité de l'enzyme α-Gal A associés au phénotype « classique » de la maladie à début précoce, atteinte multi-organe.

- Les variants faux-sens : début tardif, affectant principalement le cœur. (p.N215S, p.F113L (Portugal) et IVS4+919G>A (c.936+919G>A) (Chine).

Maladie de Fabry
gène GLA

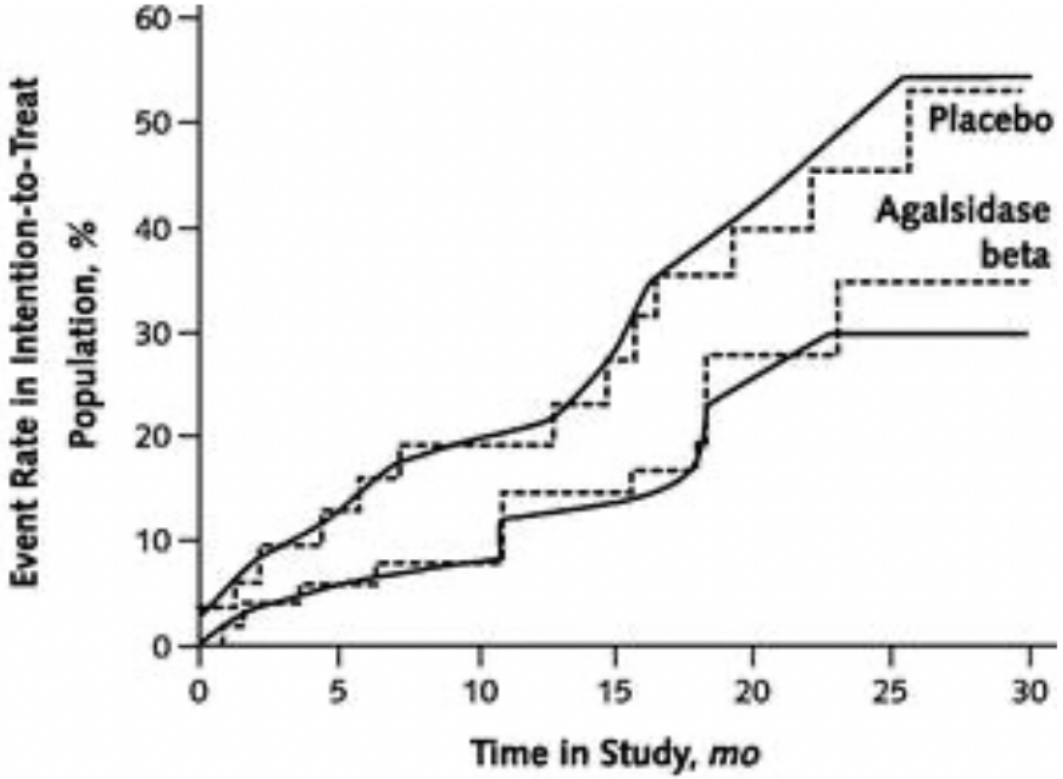
- Séquençage à haut débit de nouvelle génération pour le dépistage de cohortes de patients à haut risque a permis d'identifier de nombreux variants de signification inconnue (VSI) du gène GLA.
- Preuves cliniques, biochimiques et histopathologiques de la maladie de Fabry sont indispensables.
- Ainsi, certains variants auparavant considérés comme pathogènes ont récemment été reclassés comme polymorphismes bénins.

- Chez la plupart des patientes hétérozygotes, les manifestations cliniques vont d'un phénotype asymptomatique ou léger affectant un ou plusieurs organes et se manifestant plus tard dans la vie, à un phénotype sévère ressemblant à celui des hommes atteints de FD classique

- Agalsidase β élimination complète des dépôts de GL-3 dans les cellules endothéliales des reins, du cœur et de la peau.
- Élimination minimale ait été observée dans les cardiomyocytes et les podocytes.

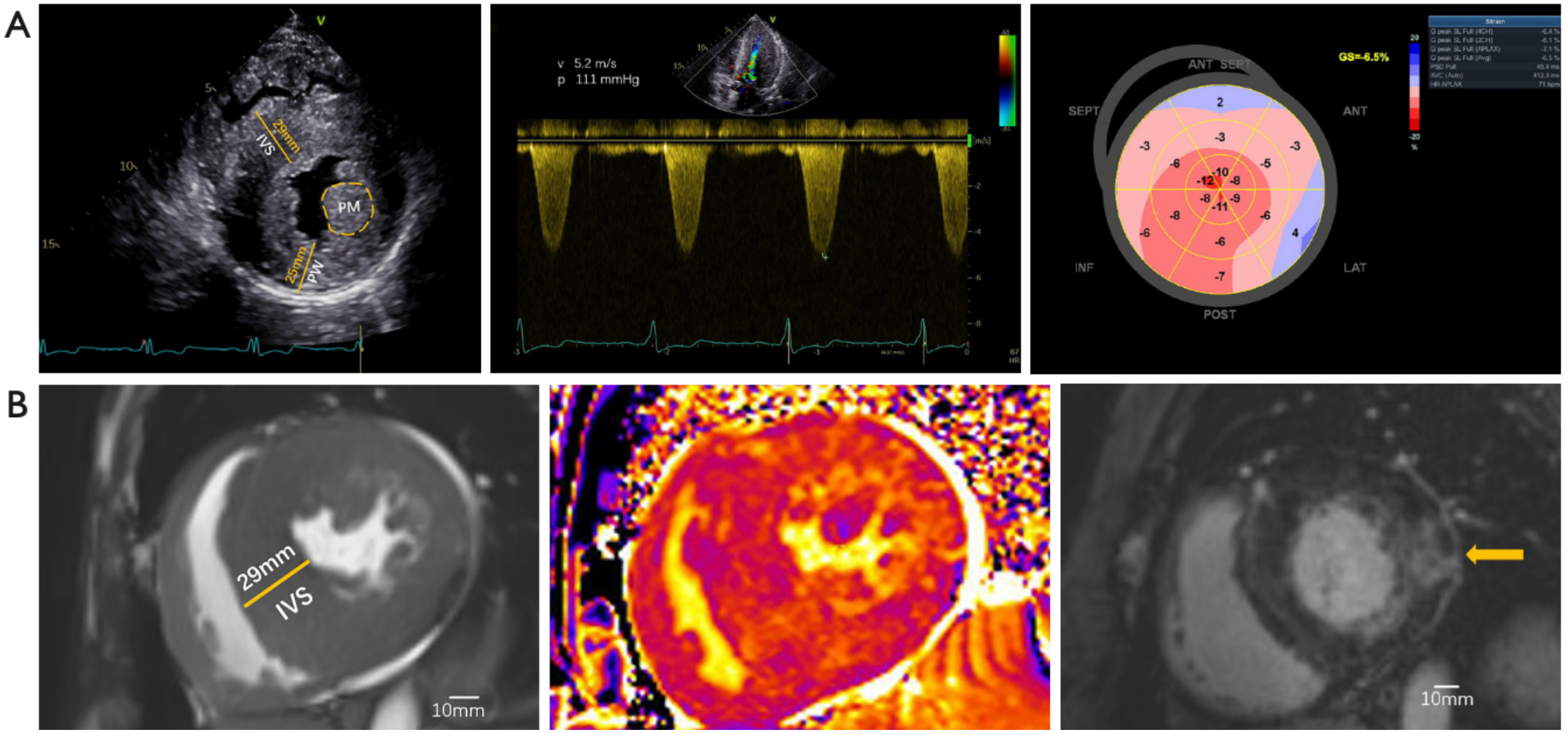
Etude randomisée 54 patients…

Primary End Point Event	Events in the Placebo Group (n = 31), n
Composite outcome	13
Renal	7
33% increase in serum c	7‡; 0
Cardiac	4
Arrhythmia; angina; MI	3; 1; 0
Cerebrovascular	2
Stroke; TIA	2; 0

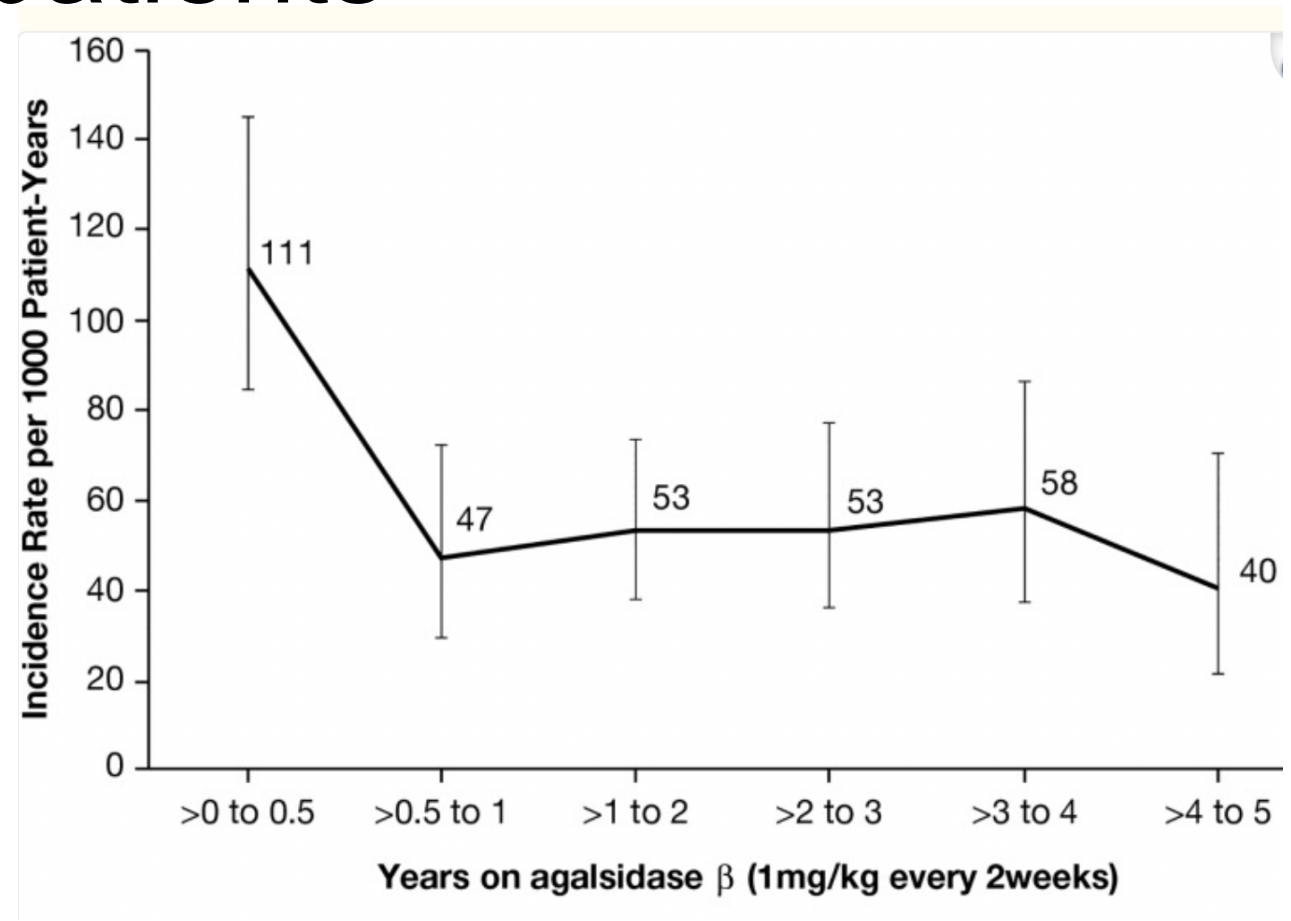


T1 mapping Contrôle qualité
Opérateur dépendant
Pixel par pixel
Biomarqueur

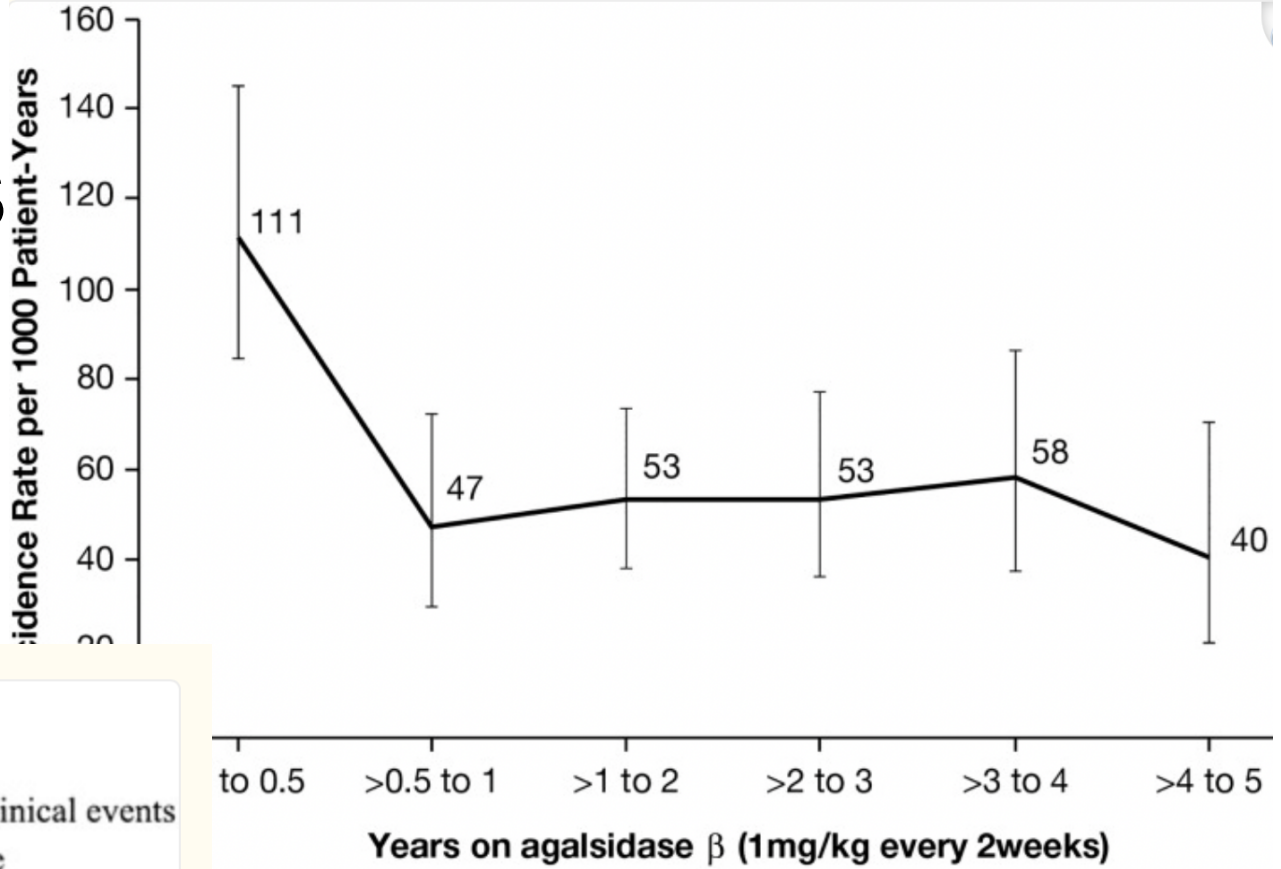
Maladie de Fabry
Imagerie cardiaque

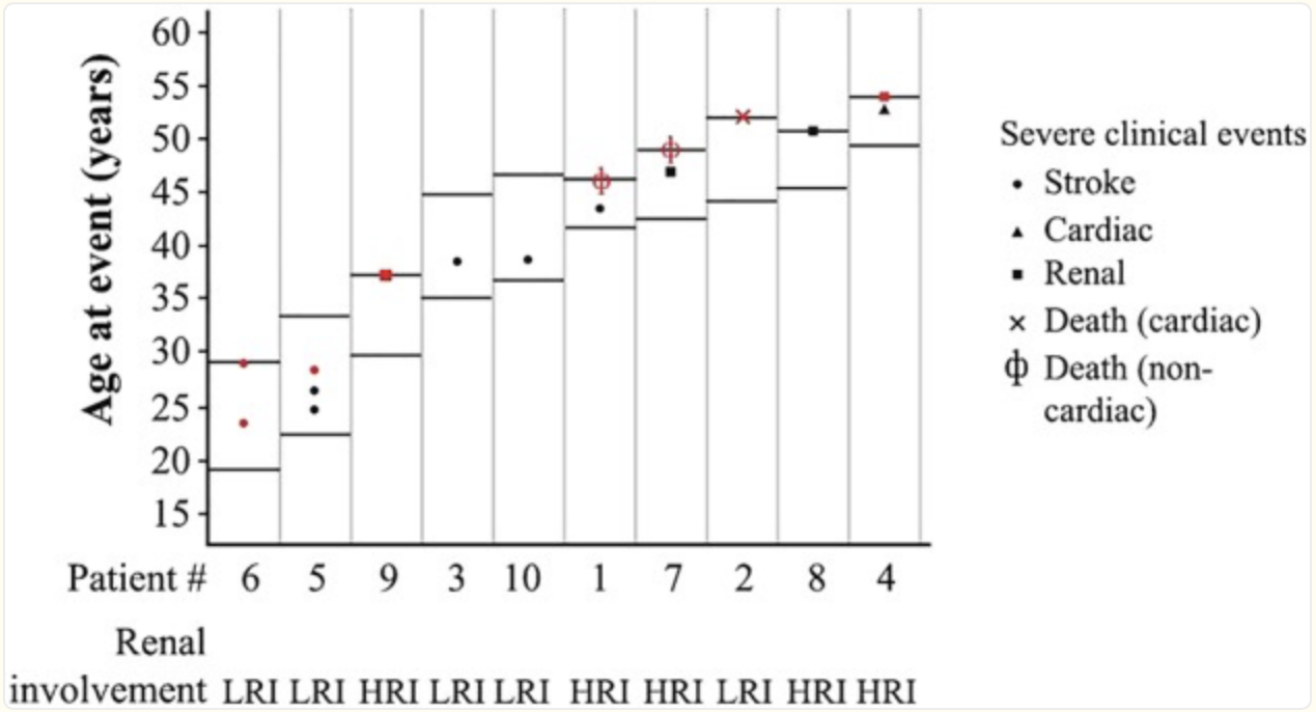


Traitement phase tardive : Résultats à 5 ans
registre 1044 patients



Résultats à 10 ans





Un IDM
5 patients avec AVC

En 2000 pas d'écho
tt enzymatique substituf
on corrige les anomalies anapathologiques
Biposie de rein de cœur

- Traitement précoce
  tardif
  Enquete familiale compléte
  Meilleure phenotypage
  Mineur asymtpto droit
  recherceh systematique tdr et CMH

- Asympto pas de traitement mais bilan des l'âge de 20 ans/ TT si T´

- Surveillance femme IRM 3 à 4 ans

- Si HVG tt pilote/

- N215F variant cardio

- Classique Lyso GB3 très élevé au dessus de 20 traité tôt

- Forme tardive atteintes précoce même dans les formes noc

  Mort subite
  dépistage précoce
  Rythmologique

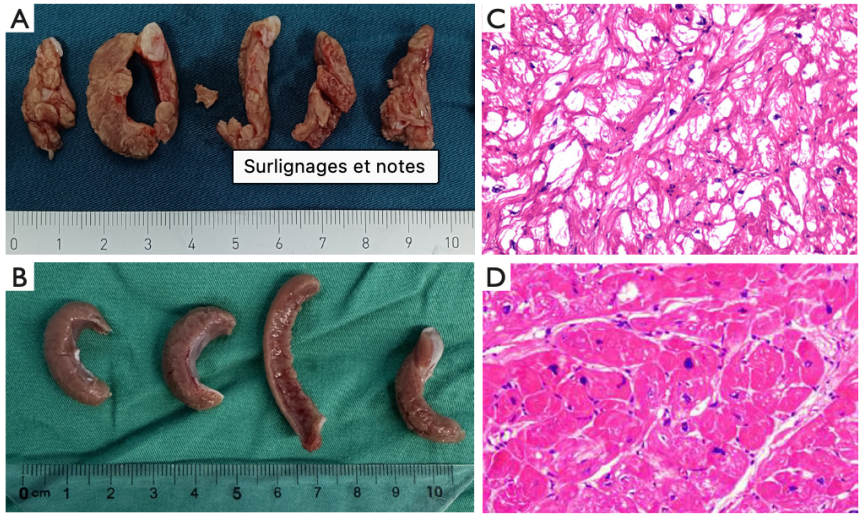
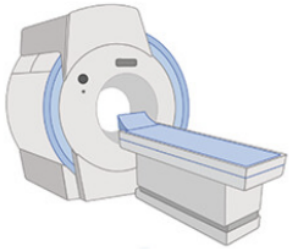
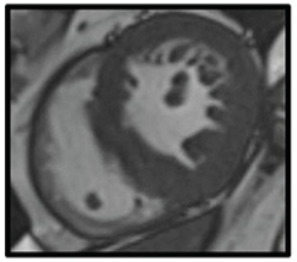


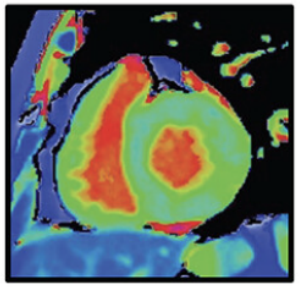
Figure 3 Resected cardiac muscle specimen and hematoxylin-eosin stain from Patient 3 (A,C) and a typical hypertrophic cardiomyopathy patient (B,D). (A) The yellowish spongy samples instead of (B) the usual reddish stony-elastic samples. (C) A typical light microscopy marker of intracellular storage with prominent vacuolization of cardiomyocytes instead of (D) a typical hypertrophy of cardiomyocytes with hyper-stained nucleus (hematoxylin-eosin, original magnification ×400).

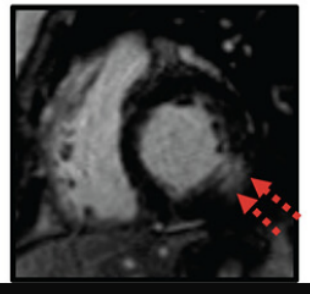
2024 Méta analyse 450 patients
41 ±11ans
45 (24–58) mois



- 445 Fabry Disease patients undergoing baseline and follow-up CMR after ERT
- Evaluation of mean differences of CMR parameters







MLVWT
-1 mm (-2; -0.02)

LVM
-18 g (-33; -3)

T1 mapping
6 msec (-2; 15)

LGE extent
0.8% (0.5; 1.1)

60

Tra

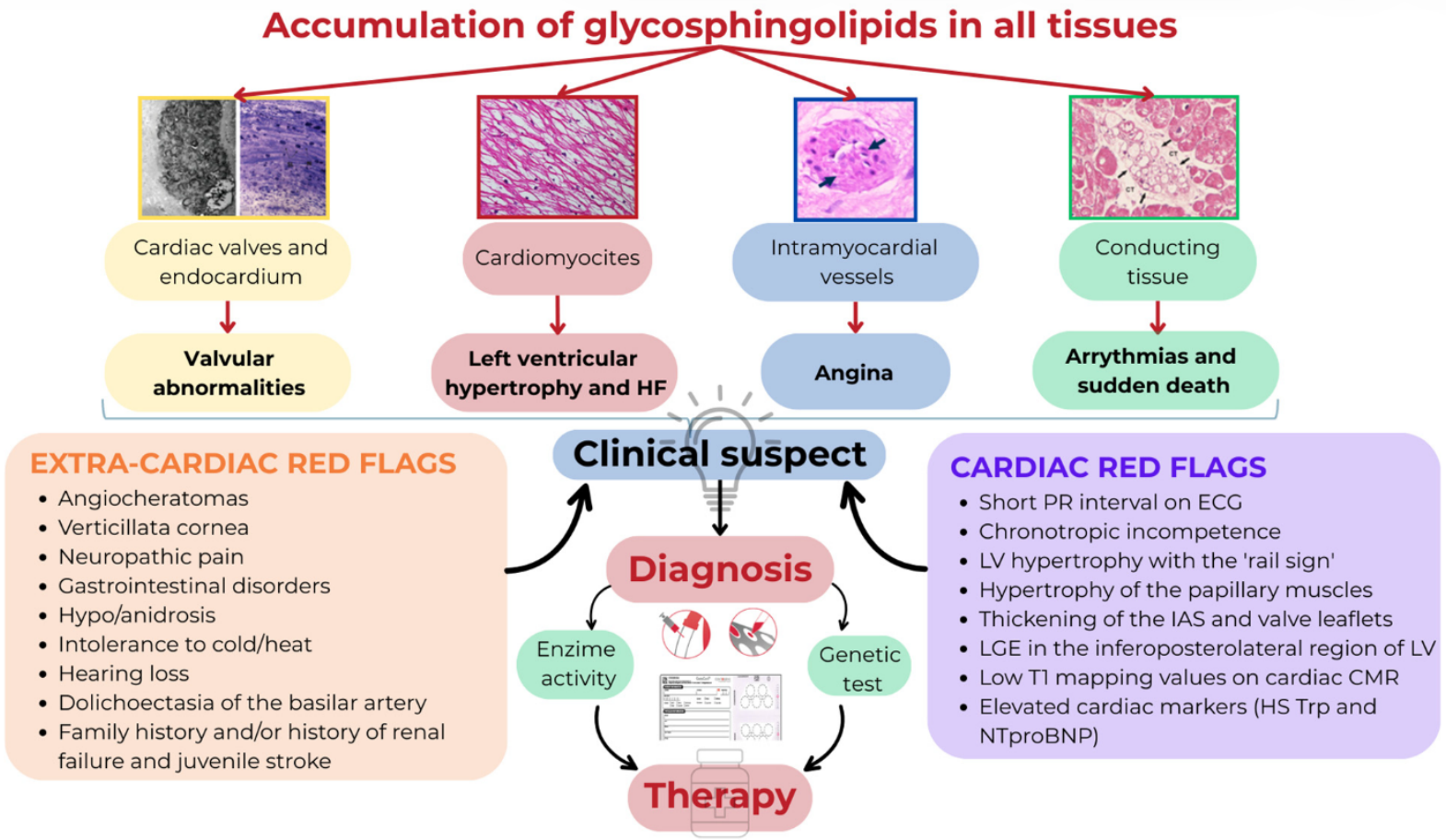
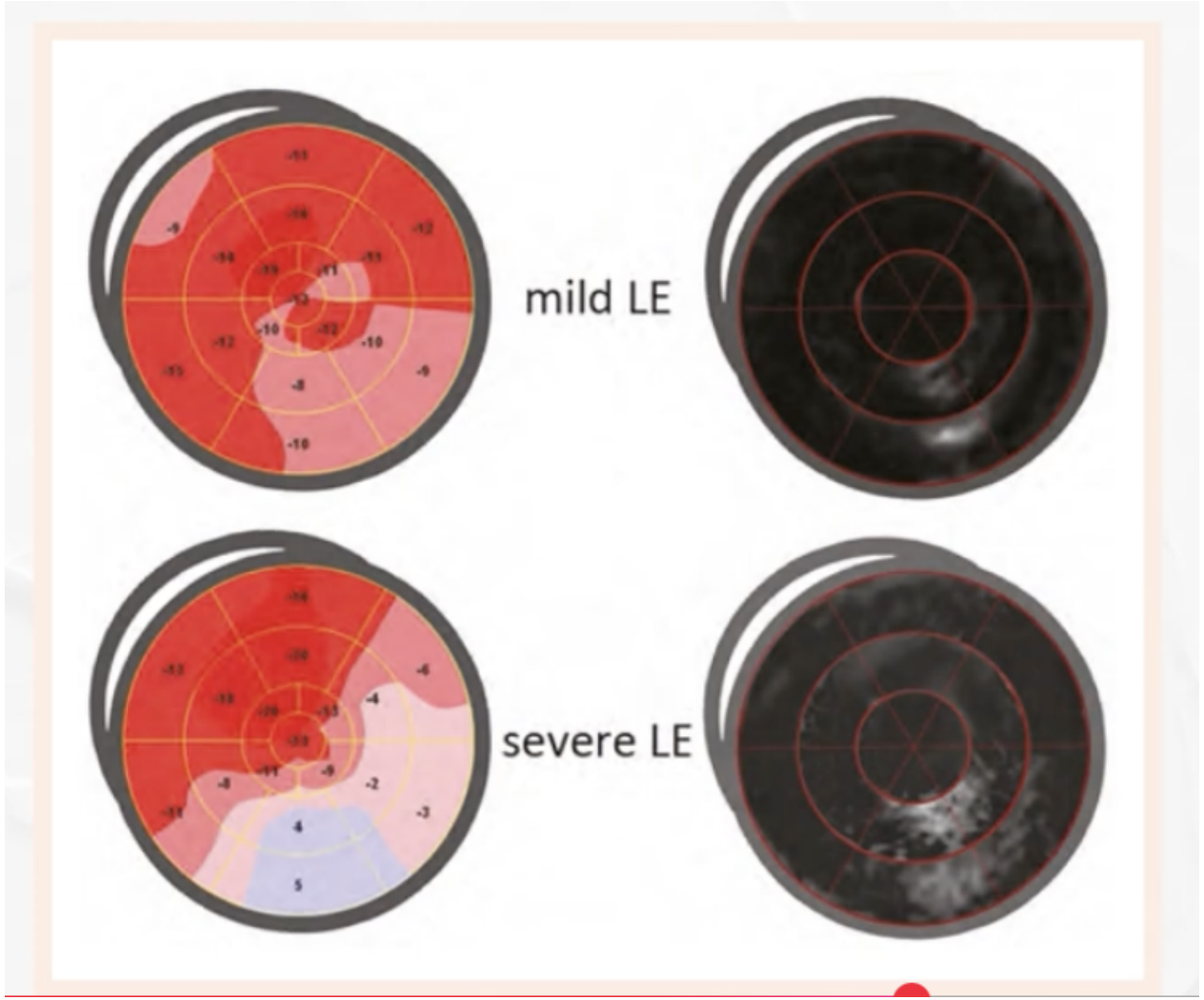


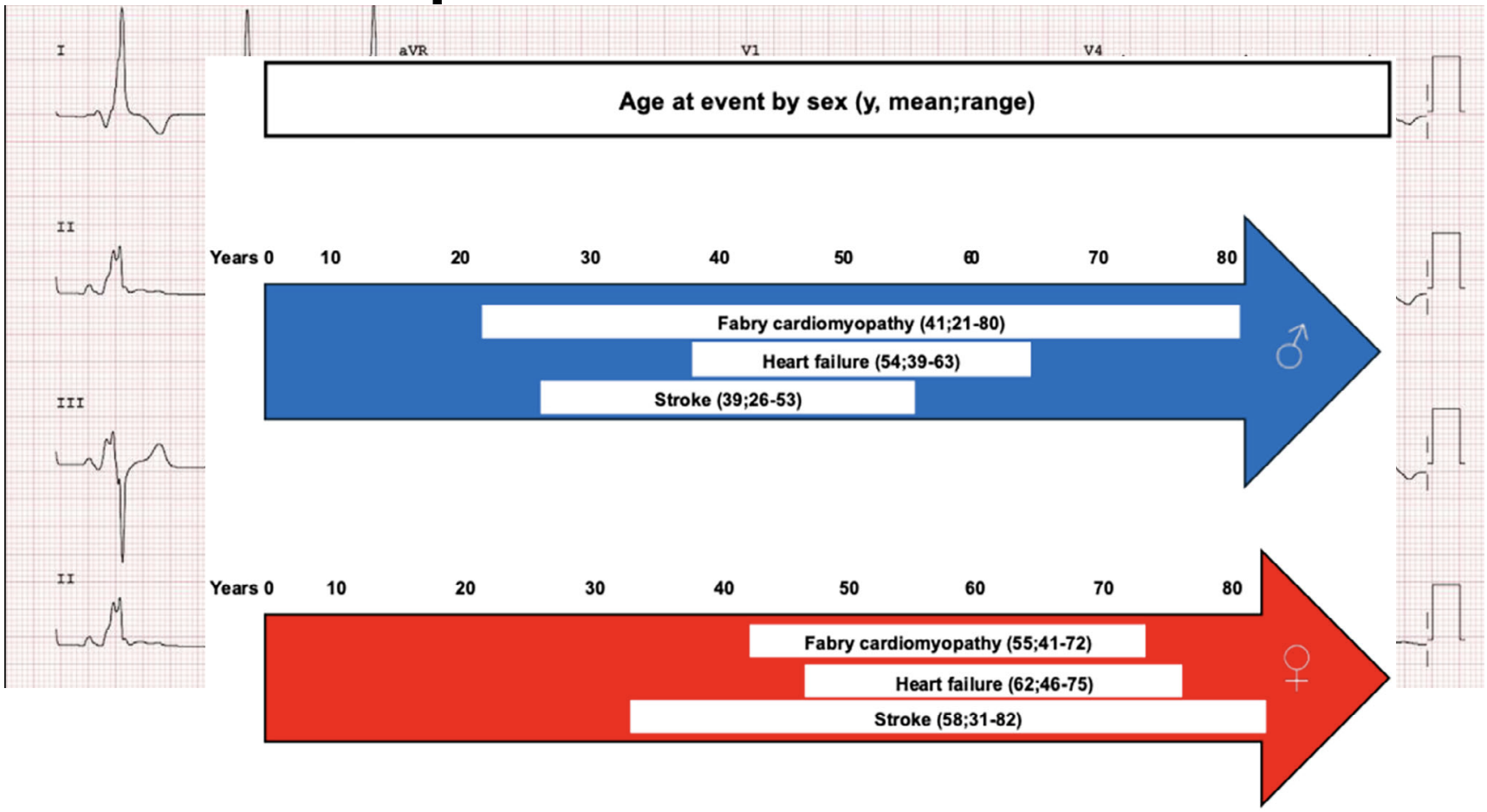
Figure 3. Diagnostic pathway in AFD.

Topographie inféro-latérale

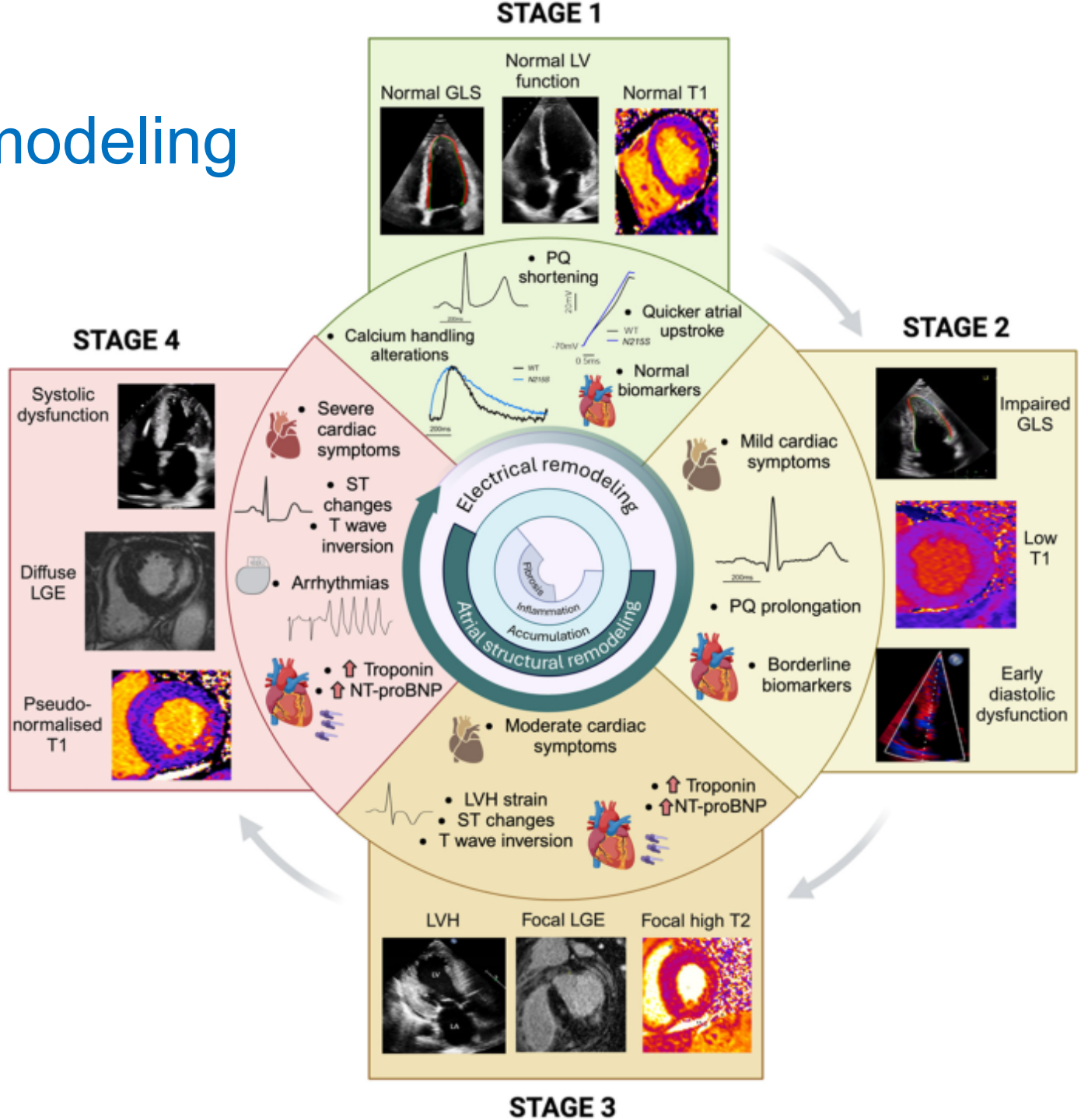


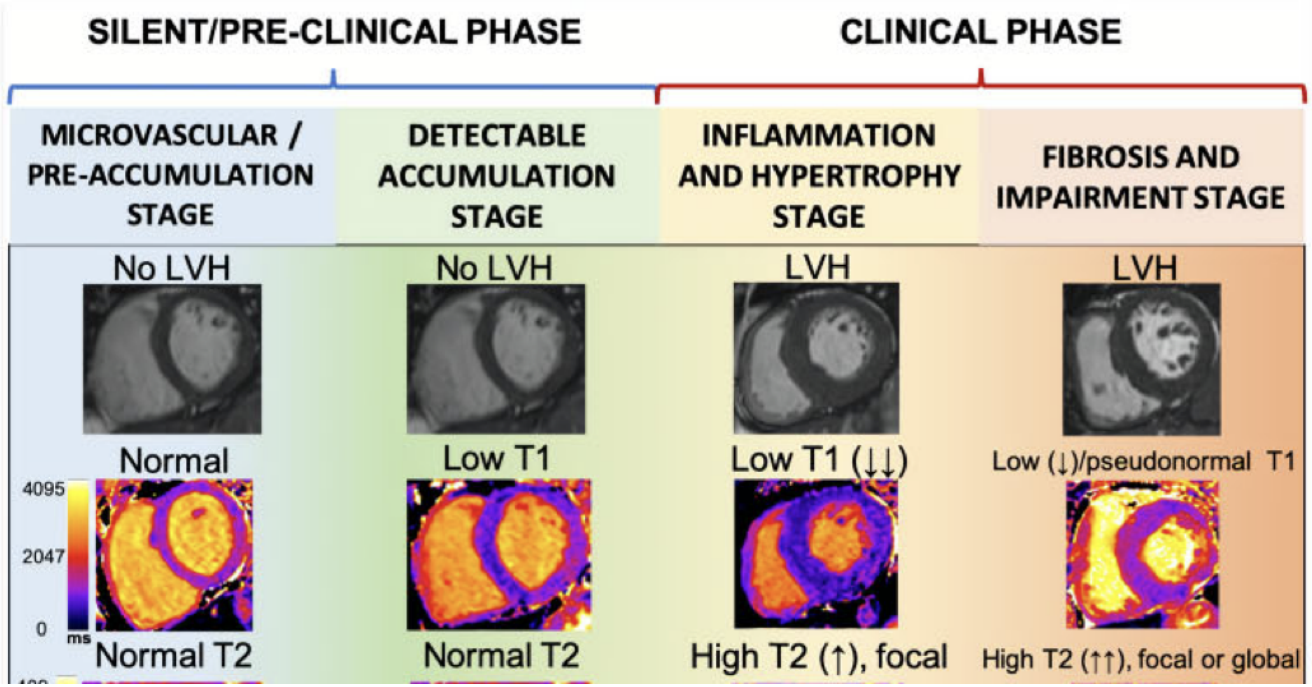
PR court

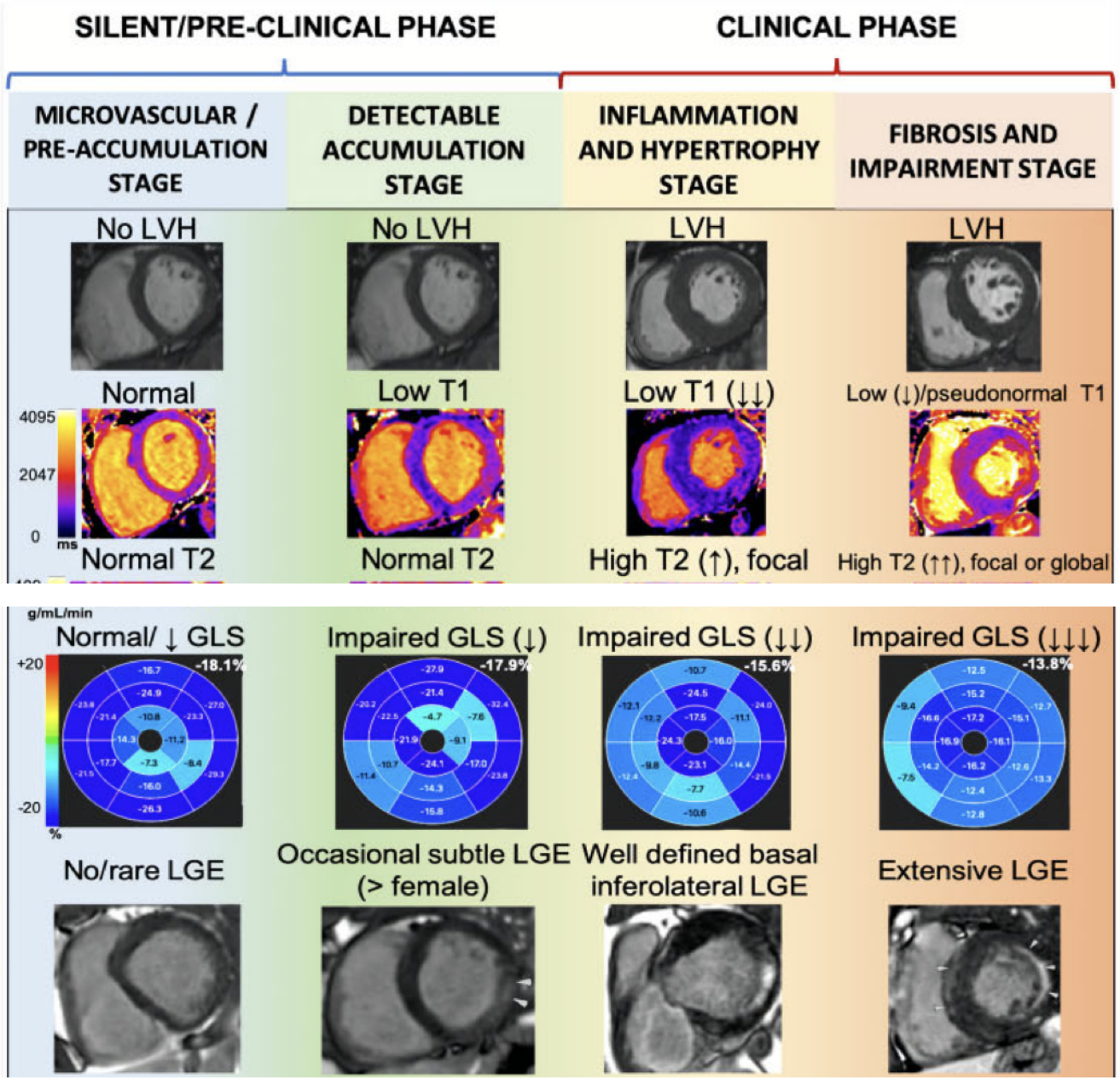
Danon disease, PRKP2 ou Fabry ou HCM sarcomérique ?



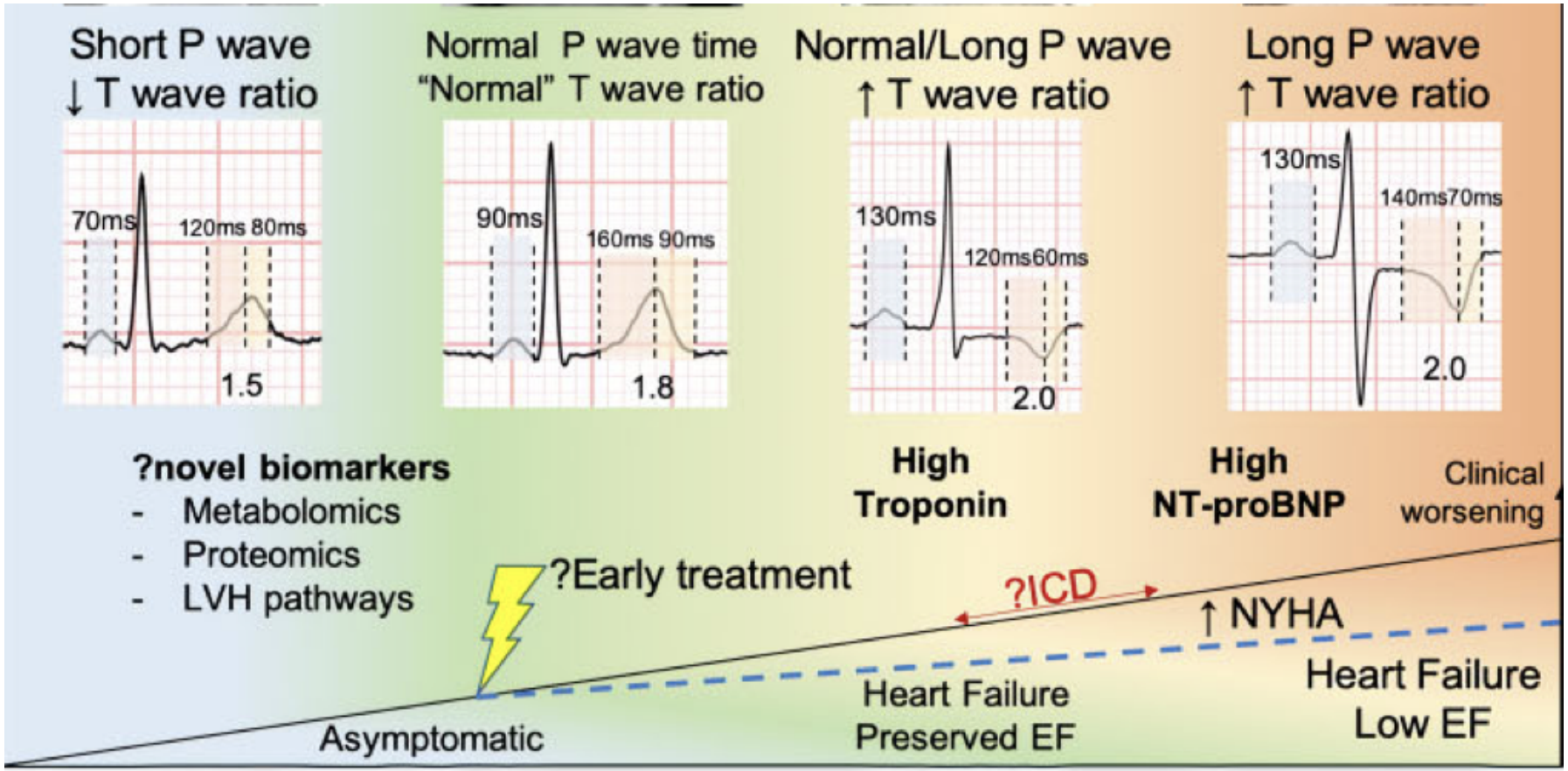
Early atrial remodeling




SILENT/PRE-CLINICAL PHASE
CLINICAL PHASE
MICROVASCULAR / PRE-ACCUMULATION STAGE
DETECTABLE ACCUMULATION STAGE
INFLAMMATION AND HYPERTROPHY STAGE
FIBROSIS AND IMPAIRMENT STAGE
No LVH
No LVH
LVH
LVH
Normal
Low T1
Low T1 (↓↓)
Low (↓)/pseudonormal T1
4095
2047
0
ms
Normal T2
Normal T2
High T2 (↑), focal
High T2 (↑↑), focal or global

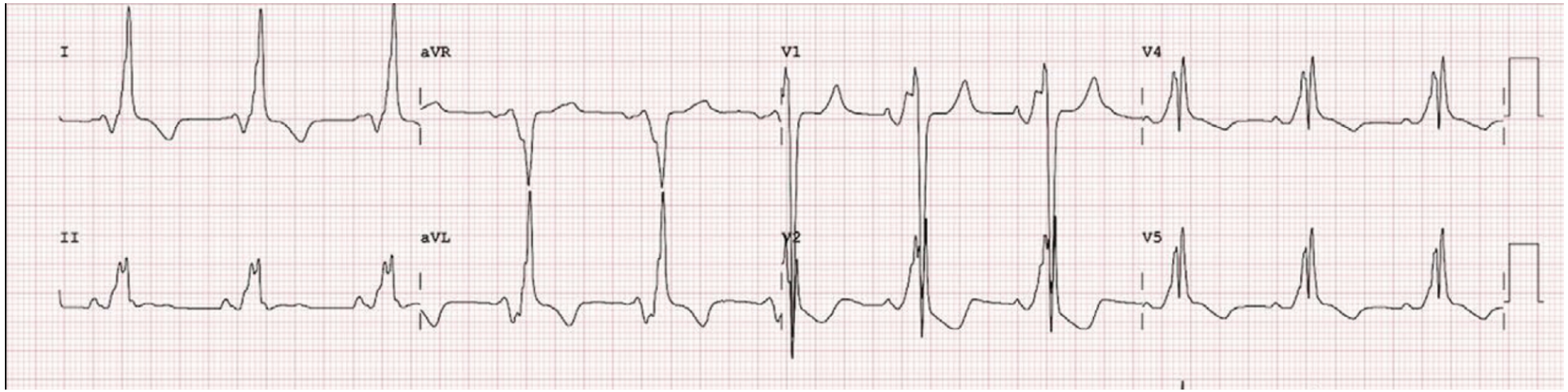

SILENT/PRE-CLINICAL PHASE
CLINICAL PHASE
MICROVASCULAR / PRE-ACCUMULATION STAGE
DETECTABLE ACCUMULATION STAGE
INFLAMMATION AND HYPERTROPHY STAGE
FIBROSIS AND IMPAIRMENT STAGE
No LVH
No LVH
LVH
LVH
Normal
Low T1
Low T1 (↓↓)
Low (↓)/pseudonormal T1
4095
2047
0
ms
Normal T2
Normal T2
High T2 (↑), focal
High T2 (↑↑), focal or global
g/mL/min
+20
-20
%
Normal/ ↓ GLS
Impaired GLS (↓)
Impaired GLS (↓↓)
Impaired GLS (↓↓↓)
-18.1%
-17.9%
-15.6%
-13.8%
No/rare LGE
Occasional subtle LGE (> female)
Well defined basal inferolateral LGE
Extensive LGE

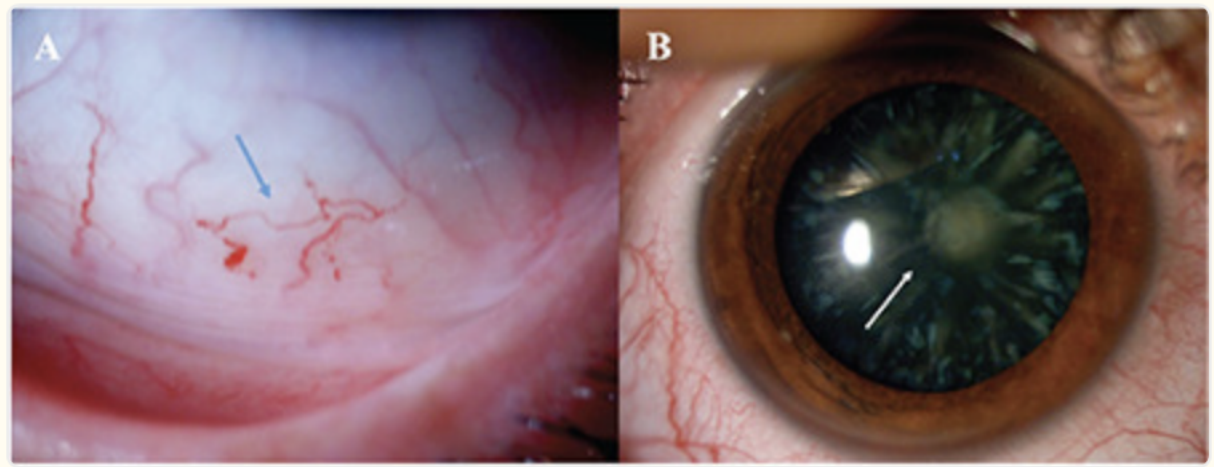
Maladie de Fabry
Valeur de l'ECG ?

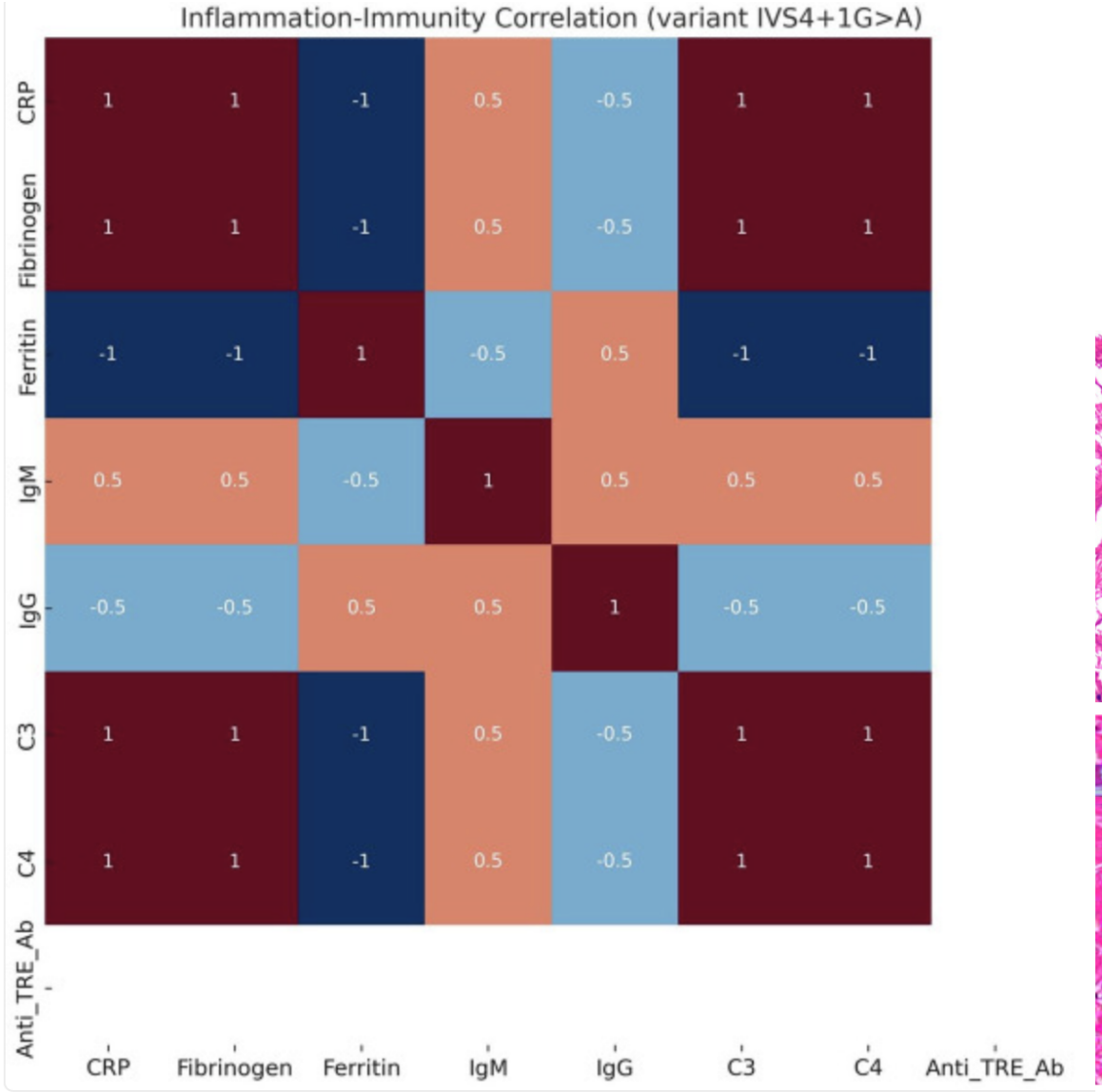


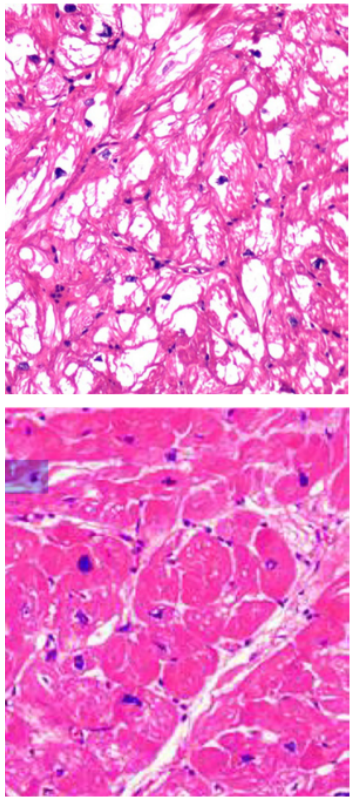
Maladie de Fabry
PR court ?

Danon, PRKAG2, Fabry ou CMH sarcomérique ?




A
B





Inflammation–Immunity Correlation Matrix (variant IVS4+1G>A). Heatmap showing pairwise correlation coef

- En 2000 pas d’écho
  tt enzymatique substituf
- Une perfusion IV tous les 14 IV jours à domicile au bout de 4 mois

- on corrige les anomalies ana-pathologiques
  Biopsie de rein de cœur

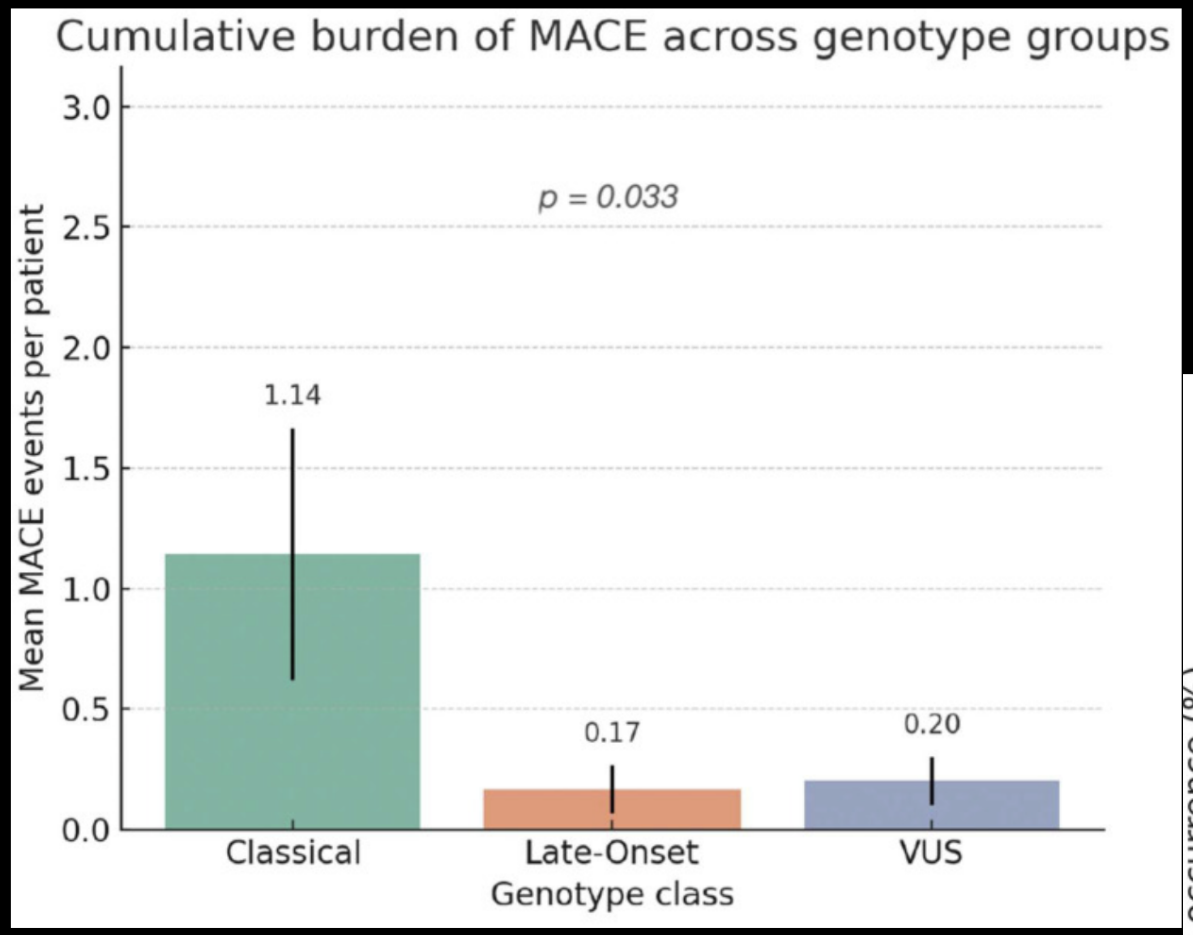
- Molécules chaperone 2015 tt oral

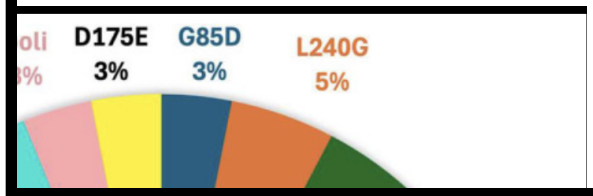
- Variants éligibles au traitement chaperon (AMICUS) variant associé au phénotypes cardiaques test in vitro restaurer l’activité enzymatique

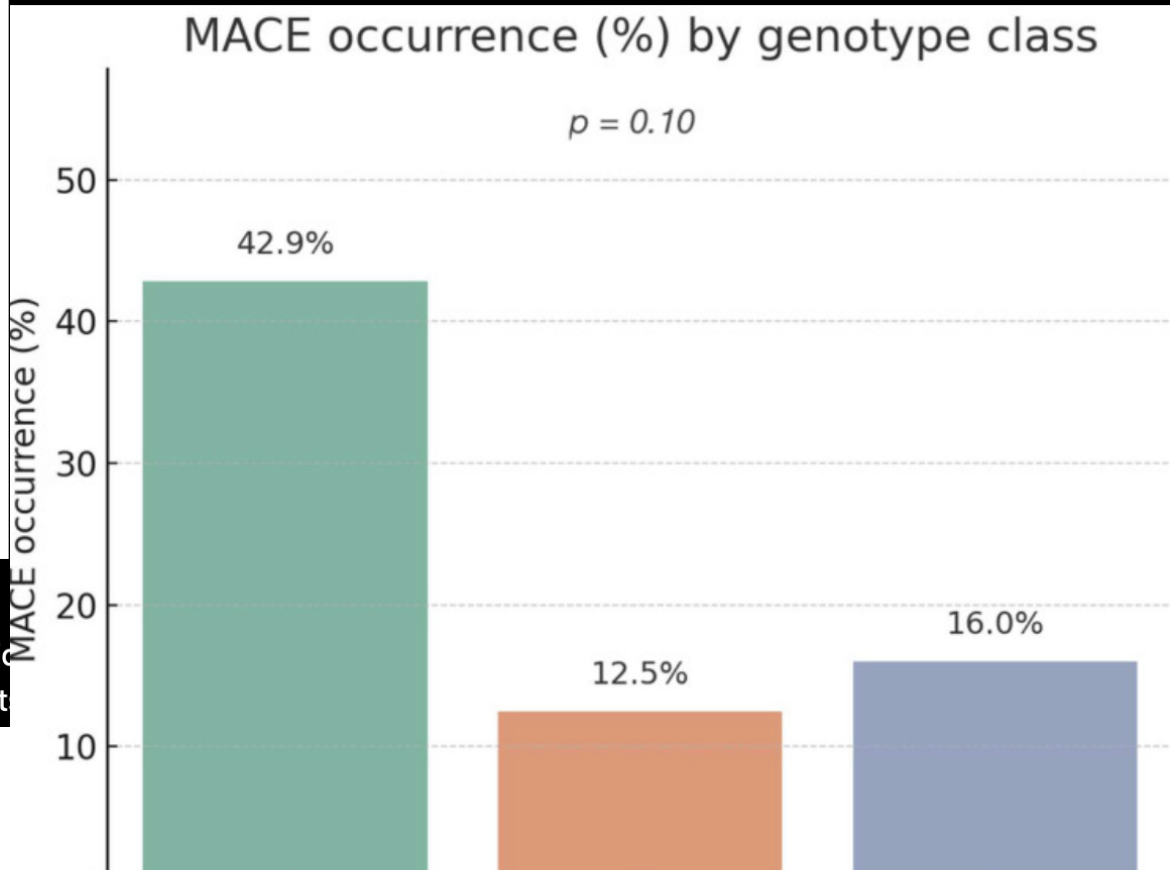
Meilleure phénotypage

Mineur asymtpto droit

recherche systematique tdr et CMH







ee this image and copyright information in PMC

igure 3 Cumulative burden of MACE across genotype groups. The mean number of majo
dverse cardiac events (MACE) per patient is shown for Classical, Late-Onset, and Variant

Fabry Disease Presenting as End-Stage Hypertrophic Cardiomyopathy: Diagnostic Pitfalls and Lessons Learned

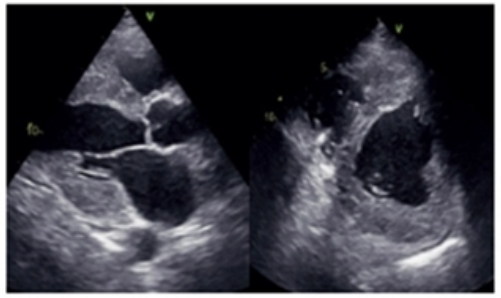
Clinical Presentation

Progressive Dyspnea

Lower Extremity Edema

↓

Class III-IV NYHA despite GDMT



Concentric hypertrophy of the interventricular septum and

Diagnostic Pitfalls

The differentiation between FD cardiomyopathy and sarcomeric HCM is challenging

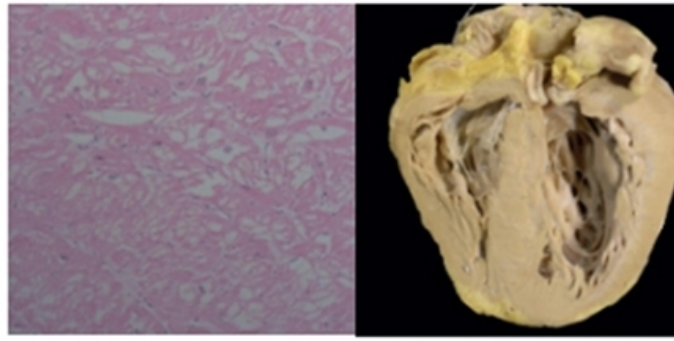
Educational Points

Consider FD in unexplained LVH

Histopathology is crucial when imaging is not revealing

Enzyme assays, genetic testing and pathology are essential

Final Diagnosis



Marked myocyte vacuolization

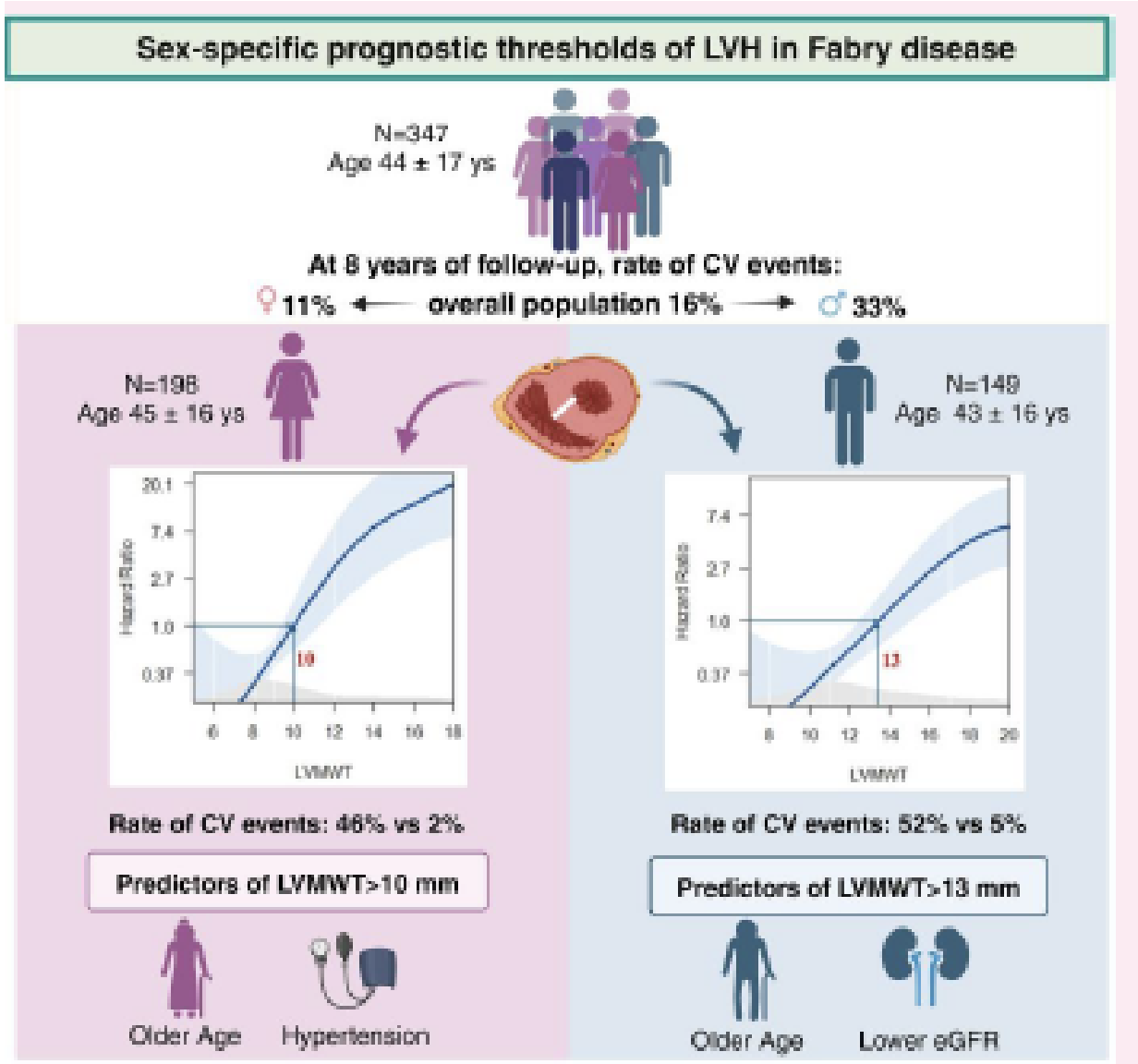
↓

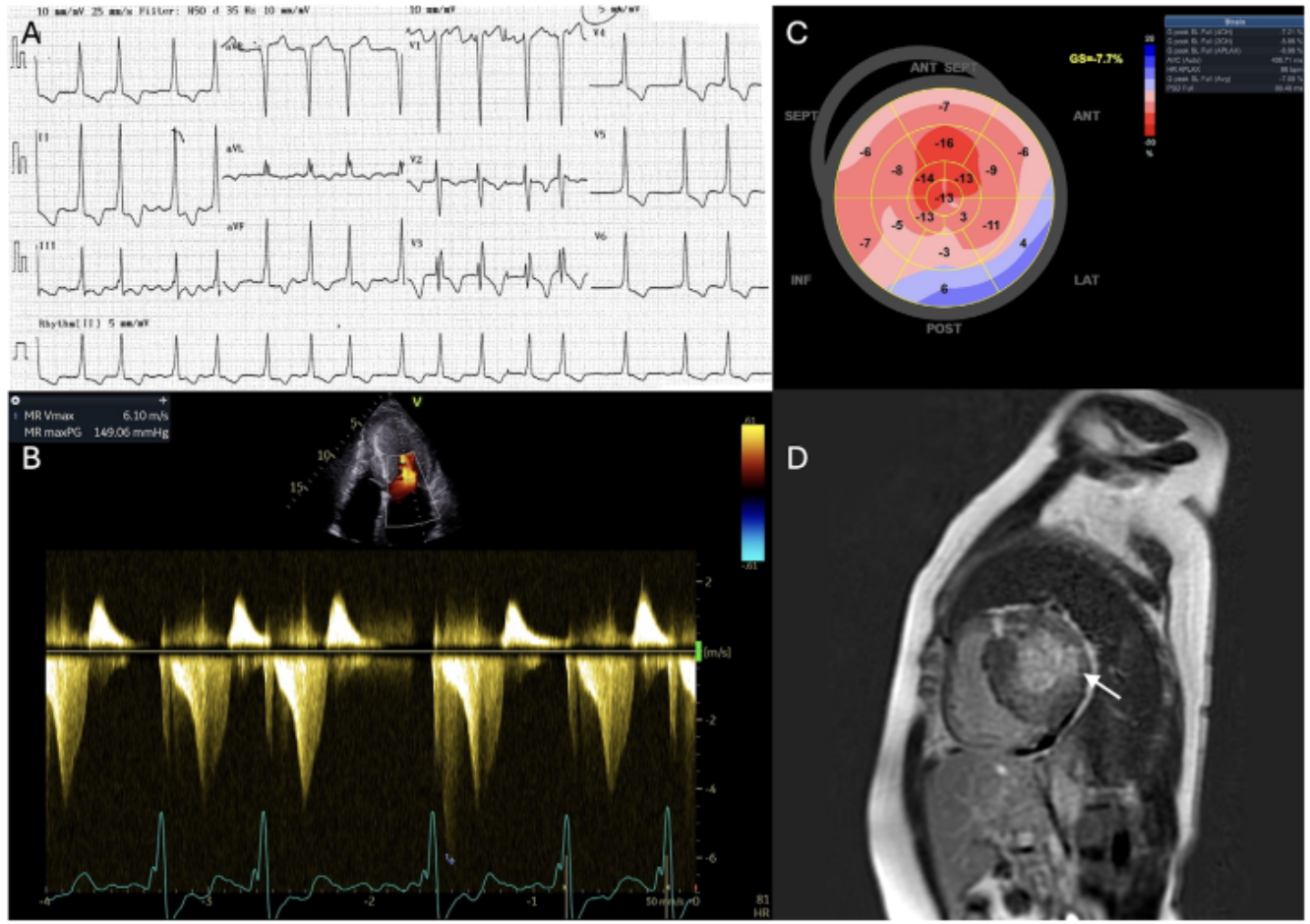
Highly suggestive of lysosomal storage disorder

↓

Targeted testing confirmed

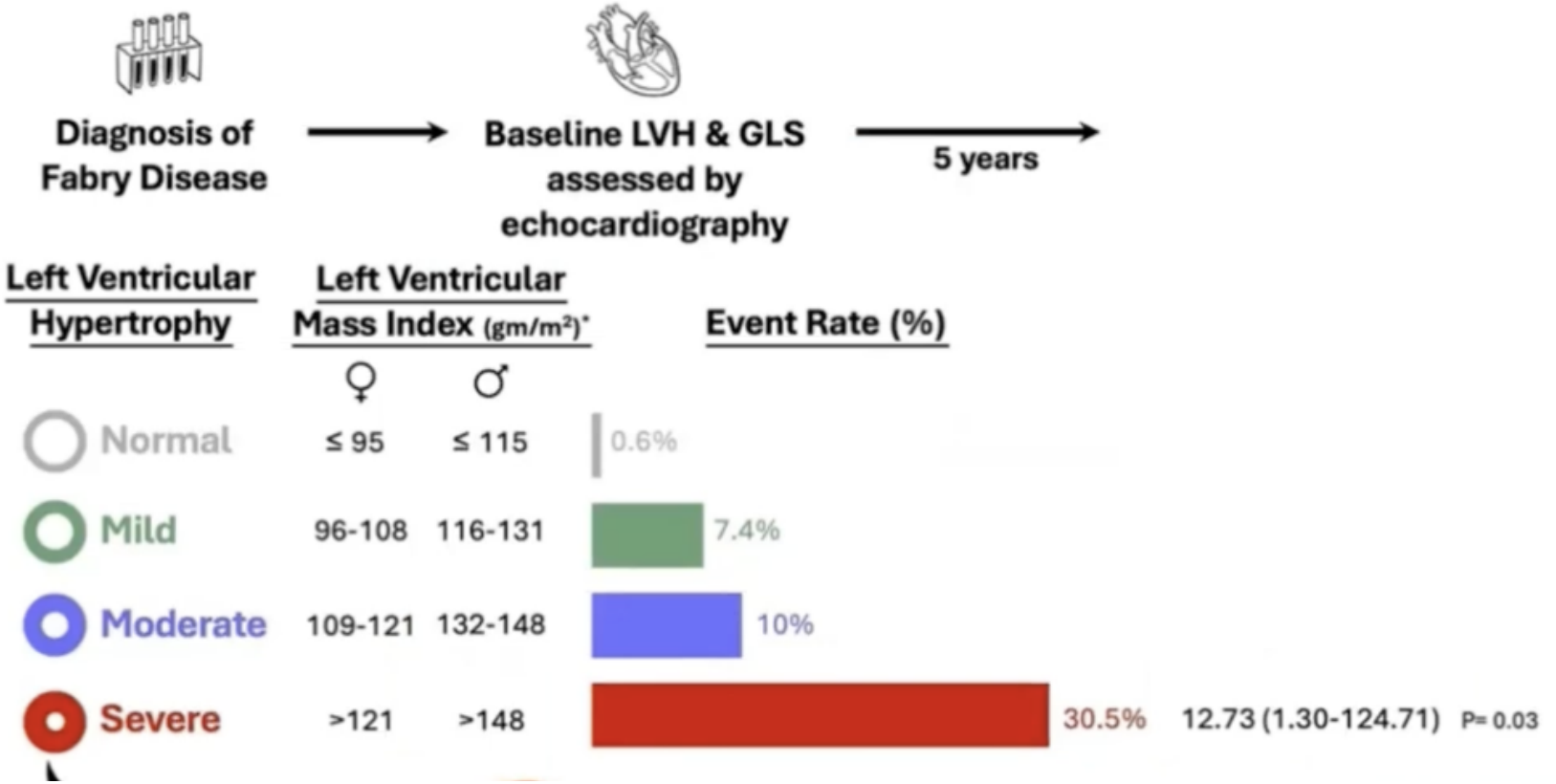
- to summarize, we believe that this case illustrates the importance of a precise etiologic diagnosis of cardiomyopathies that enabled us to initiate the appropriate treatment and the relevance. This approach is based in a fluent dialogue between primary centers who frequently assess most patients in real life and tertiary centers with further expertise.


Sex-specific prognostic thresholds of LVH in Fabry disease
N=347
Age 44 ± 17 ys
At 8 years of follow-up, rate of CV events:
♀ 11% ← overall population 16% → ♂ 33%
N=198
Age 45 ± 16 ys
N=149
Age 43 ± 16 ys
Hazard Ratio
20.1
7.4
2.7
1.0
0.37
10
6 8 10 12 14 16 18
LVMWT
Hazard Ratio
7.4
2.7
1.0
0.37
13
8 10 12 14 16 18 20
LVMWT
Rate of CV events: 46% vs 2%
Rate of CV events: 52% vs 5%
Predictors of LVMWT>10 mm
Predictors of LVMWT>13 mm
Older Age
Hypertension
Older Age
Lower eGFR


A
B
MR Vmax 6.10 m/s
MR maxPG 149,06 mmHg
C
GS=-7.7%
ANT SEPT
ANT
SEPT
INF
LAT
POST
D

	Hypertrophic Group			Dilated Group		
	Non-FD (n = 361)	FD (n = 10)	p Value	Non-FD (n = 34)	FD (n = 4)	p Value
ECG						
Heart Rate (bpm) median (IQR)	64 (58, 73)	74 (66, 77)	0.235	72 (55, 78)	59 (57, 62)	0.199
Left Atrial Anomaly	31 (10%)	1 (11%)	-	5 (20%)	0 (0%)	-
LVH–Voltage	98 (32%)	4 (44%)	0.476	5 (20%)	0 (0%)	-
LVH–Overload	87 (28%)	2 (22%)	-	7 (28%)	1 (33%)	-
NVRA	133 (43%)	4 (44%)	-	8 (32%)	1 (33%)	-
Atrioventricular Block	35 (11%)	0 (0%)	-	1 (4.0%)	1 (25%)	0.261
QRS Duration (ms) median (IQR)	103 (94, 114)	130 (110, 148)	0.029	112 (102, 136)	169 (167, 189)	0.013
QRS > 110 ms	90 (31%)	3 (60%)	0.332	13 (50%)	3 (100%)	0.232
LBBB	21 (6.8%)	0 (0%)	-	4 (16%)	0 (0%)	-
RBBB	28 (9.1%)	5 (56%)	<0.001	3 (12%)	2 (67%)	0.073
Pathological Q Waves	28 (9.1%)	0 (0%)	-	6 (24%)	0 (0%)	-
Fascicular block	24 (7.8%)	3 (33%)	0.033	2 (8.0%)	1 (33%)	0.298

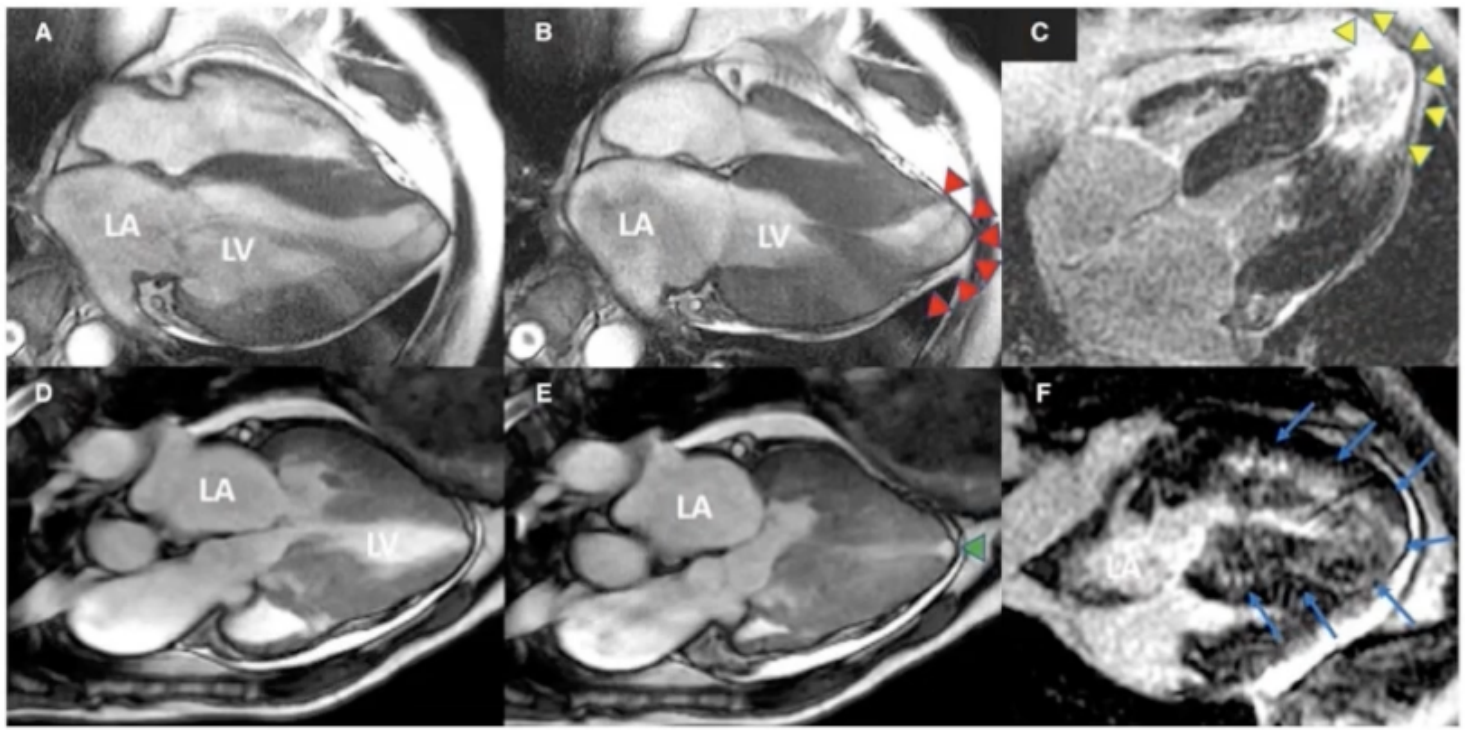
Prognostic Implications of Left Ventricular Hypertrophy and Mechanical Function in Fabry Disease: A Longitudinal Cohort Study



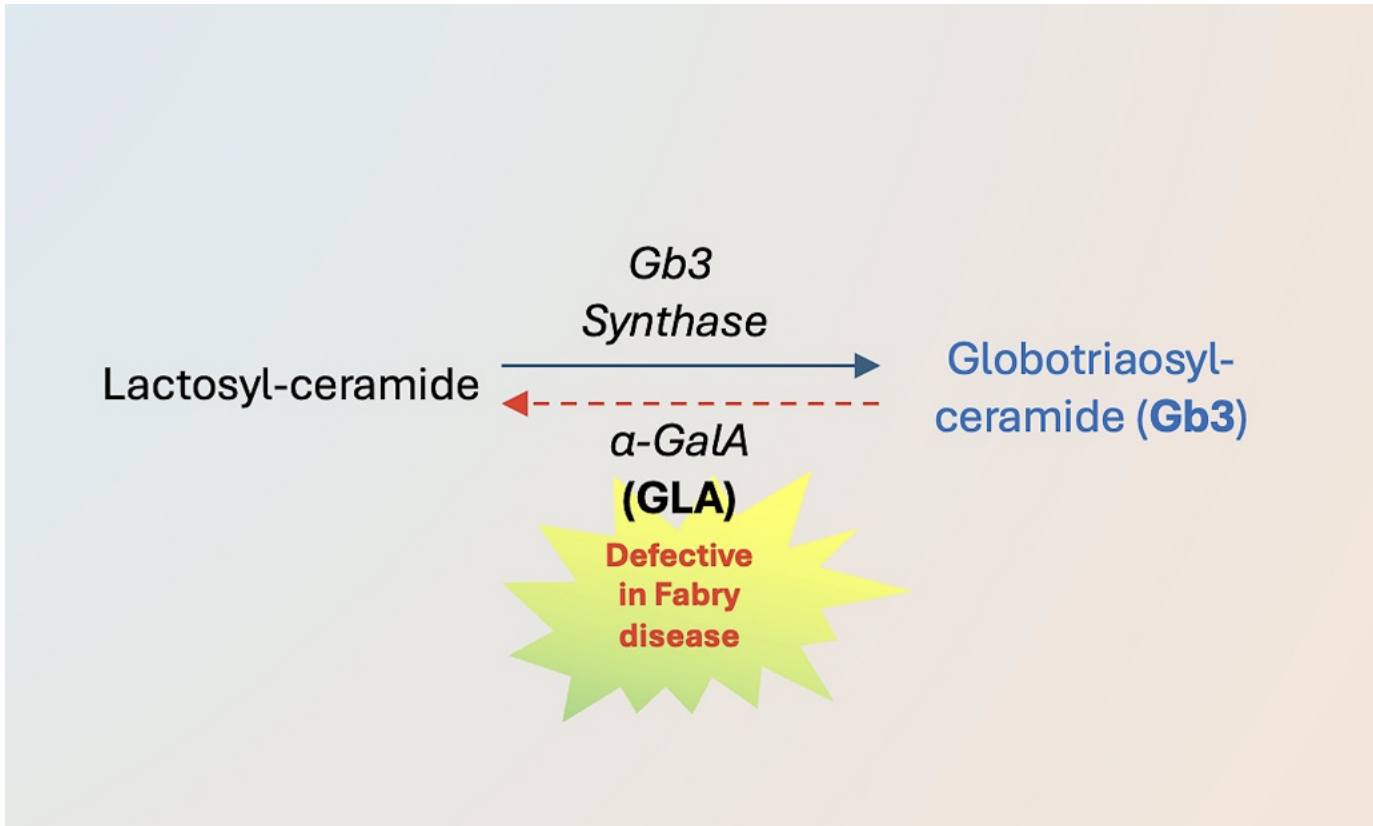
Chang HC, Yu WC JASE 2

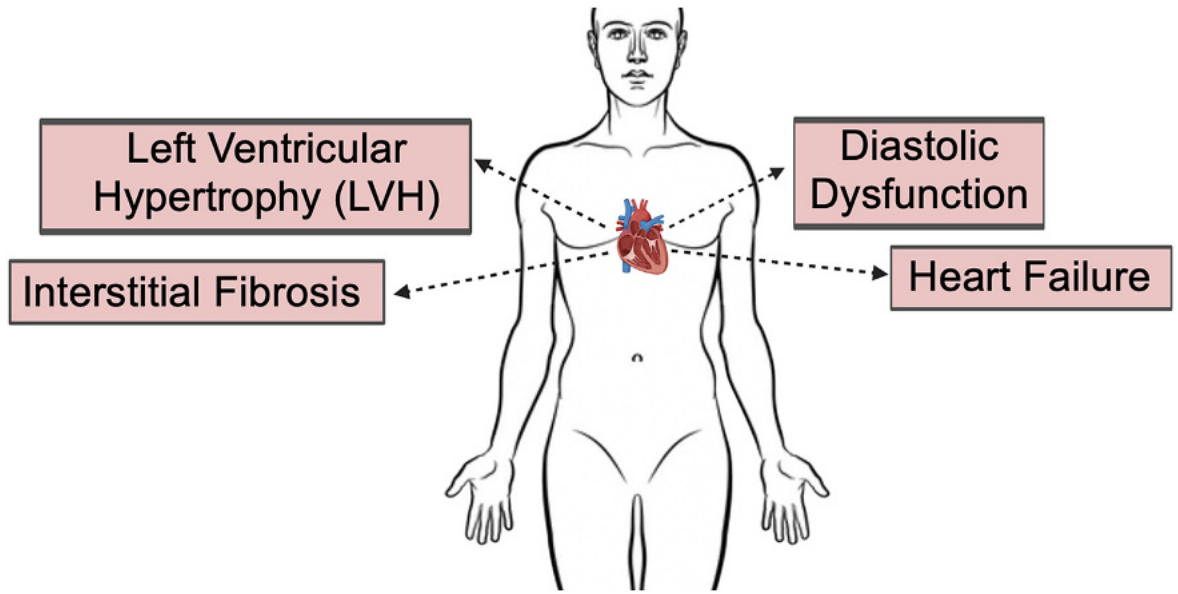
Left Ventricular Apical Aneurysm in Fabry Disease: Implications for Clinical Significance and Risk Stratification

Retrospective study 266 patients Fabry with LVH – single center - Taiwan

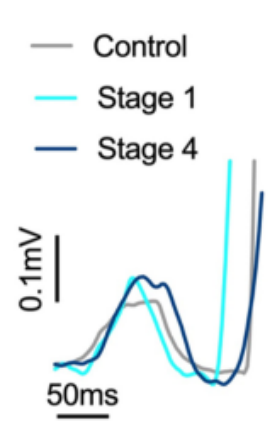


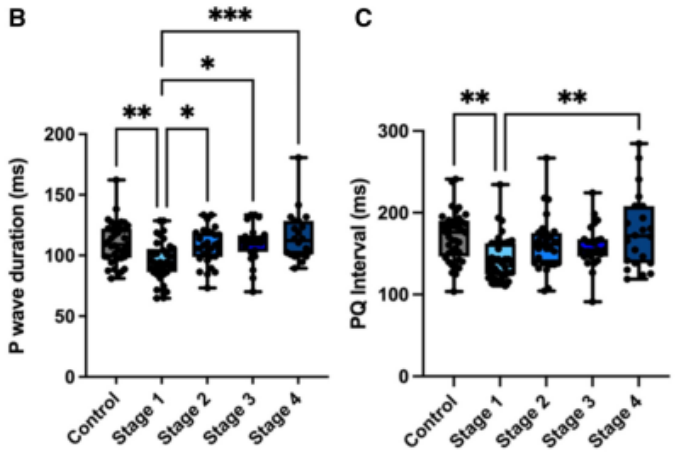
10% of patients with Fabry disease with left ventricular hypertrophy

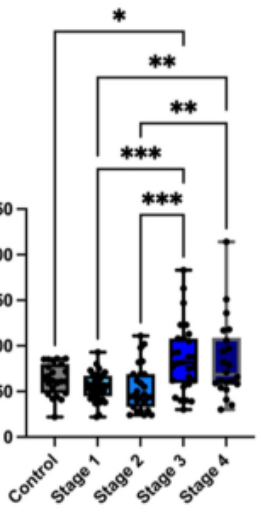

Gb3
Synthase
Lactosyl-ceramide
Globotriaosyl-
ceramide (Gb3)
α-GalA
(GLA)
Defective
in Fabry
disease

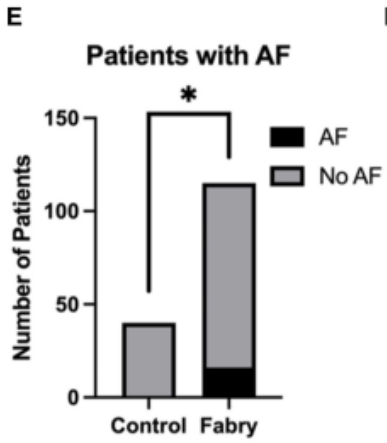

Left Ventricular Hypertrophy (LVH)
Diastolic Dysfunction
Interstitial Fibrosis
Heart Failure

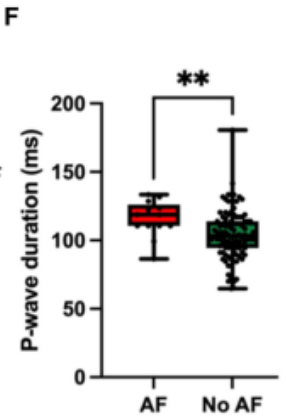
Early atrial remodeling

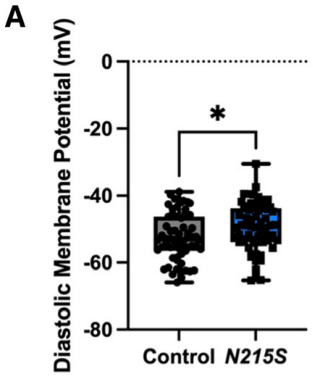


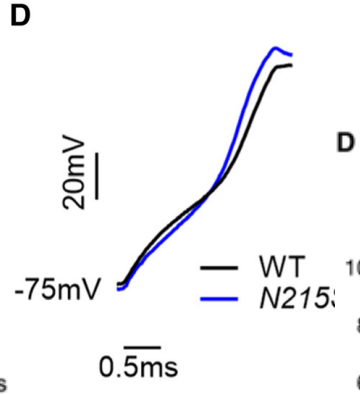


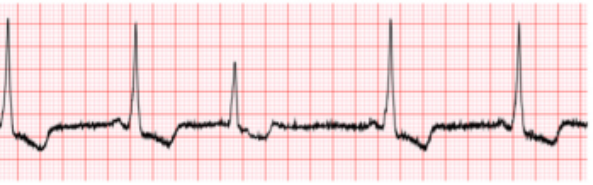


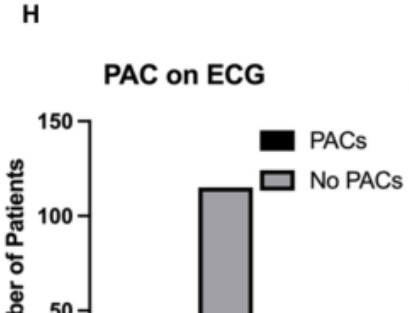


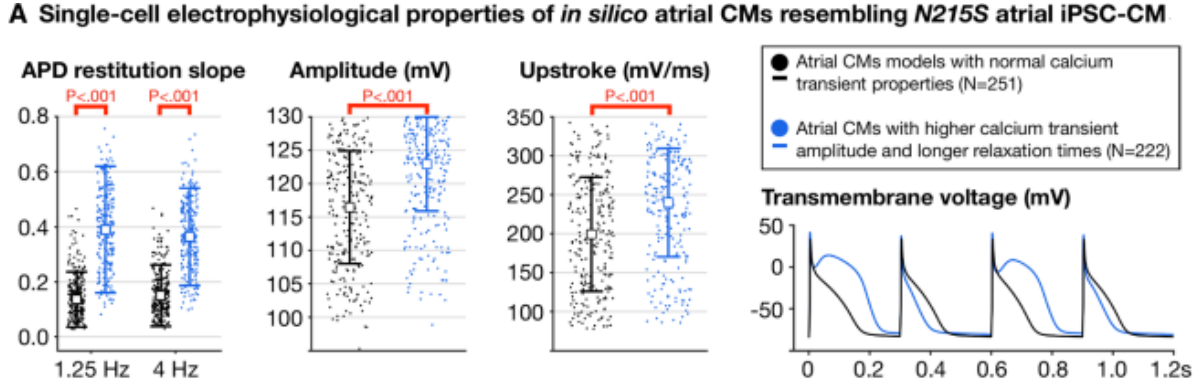


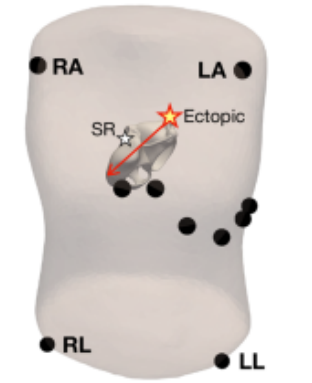


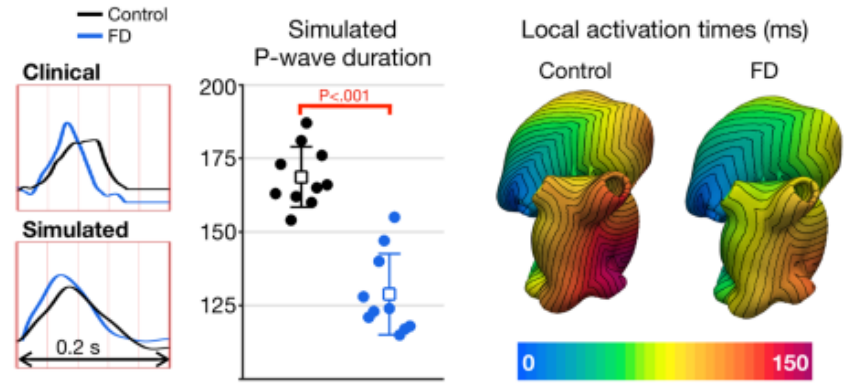


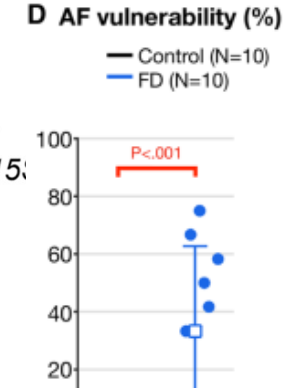


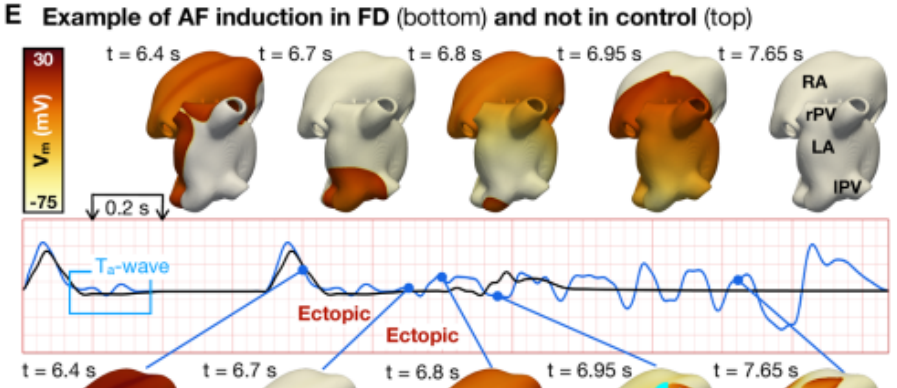




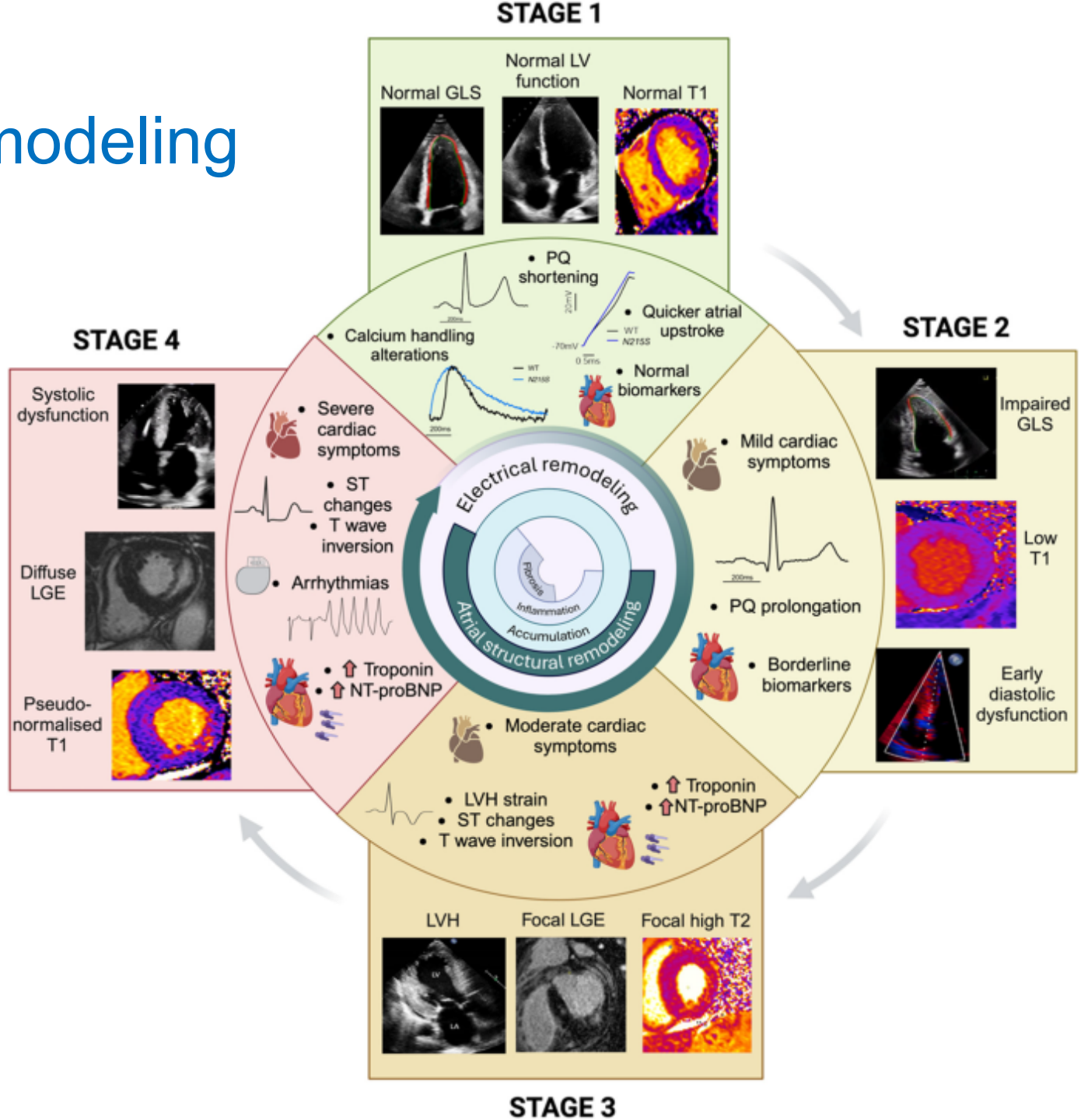


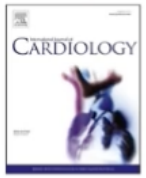






Early atrial remodeling



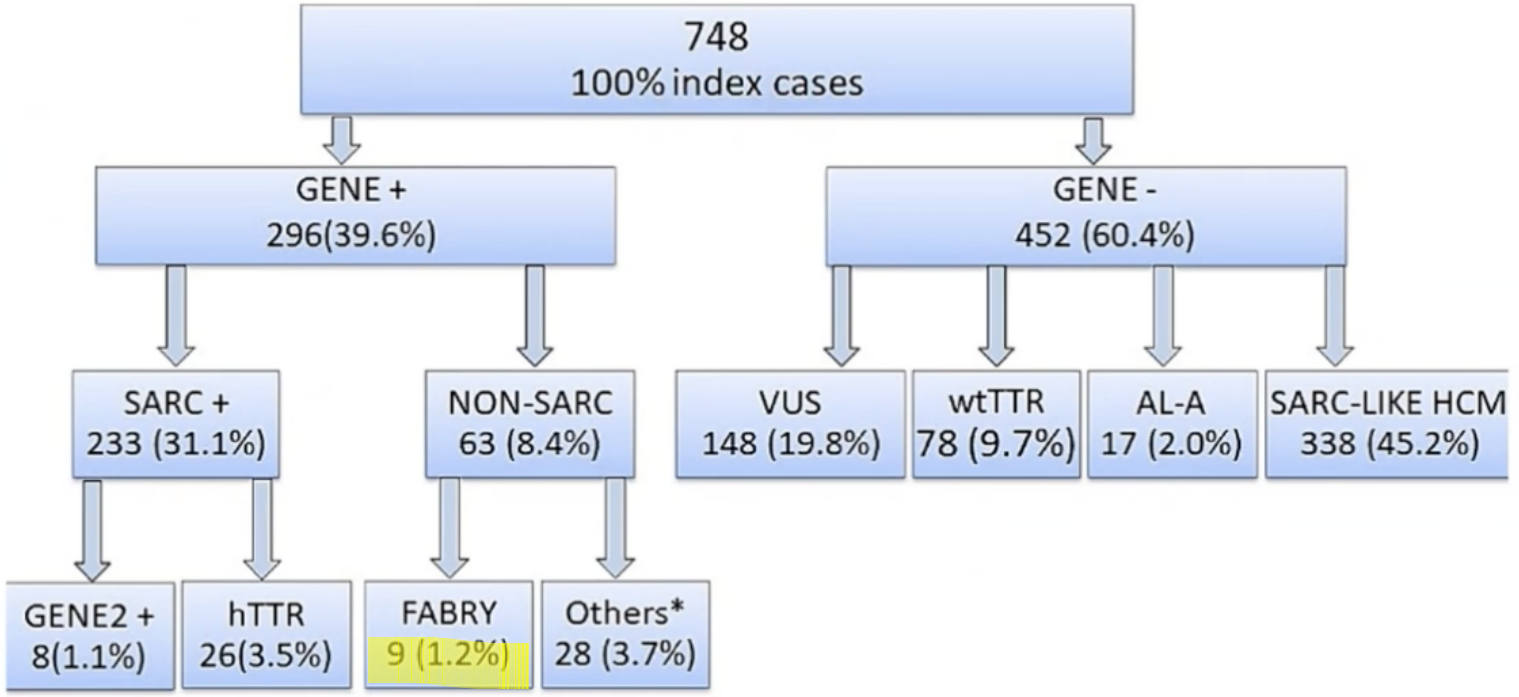


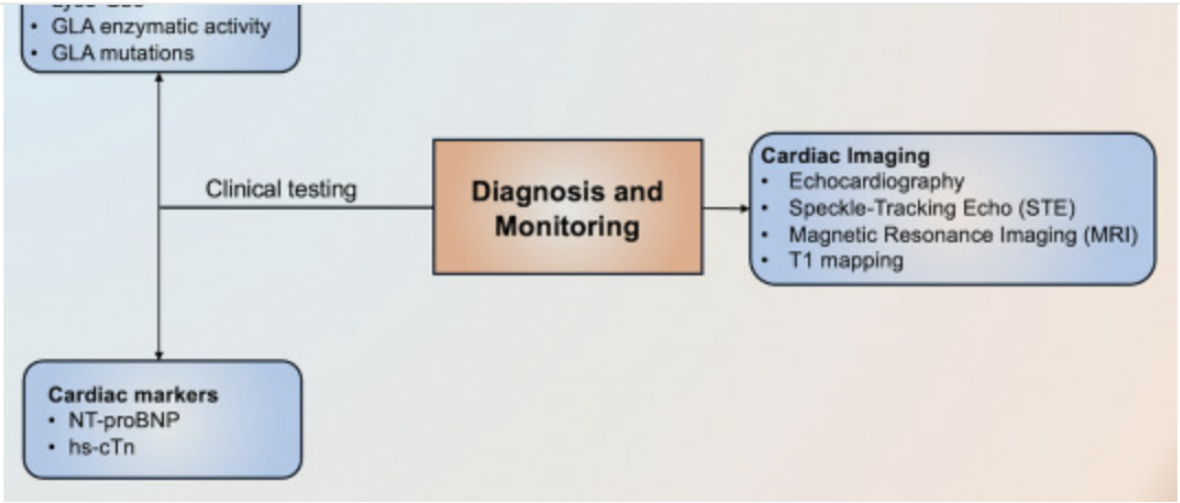
The French hypertrophic cardiomyopathy gene register: A systematic large gene screening for hypertrophic cardiomyopathy

NGS 12 genes

ACTC1, CSRP3, GLA, LMNA, MYBPC3, MYH7, MYL2, MYL3, TNNI3, TNNT2, TPM1, TTR

(First step 12 genes → panel 17, 58, 80 genes)




• GLA enzymatic activity
• GLA mutations
Clinical testing
Diagnosis and Monitoring
Cardiac Imaging
• Echocardiography
• Speckle-Tracking Echo (STE)
• Magnetic Resonance Imaging (MRI)
• T1 mapping
Cardiac markers
• NT-proBNP
• hs-cTn

nephropathy, suggesting a potential therapeutic target (Figure 4).

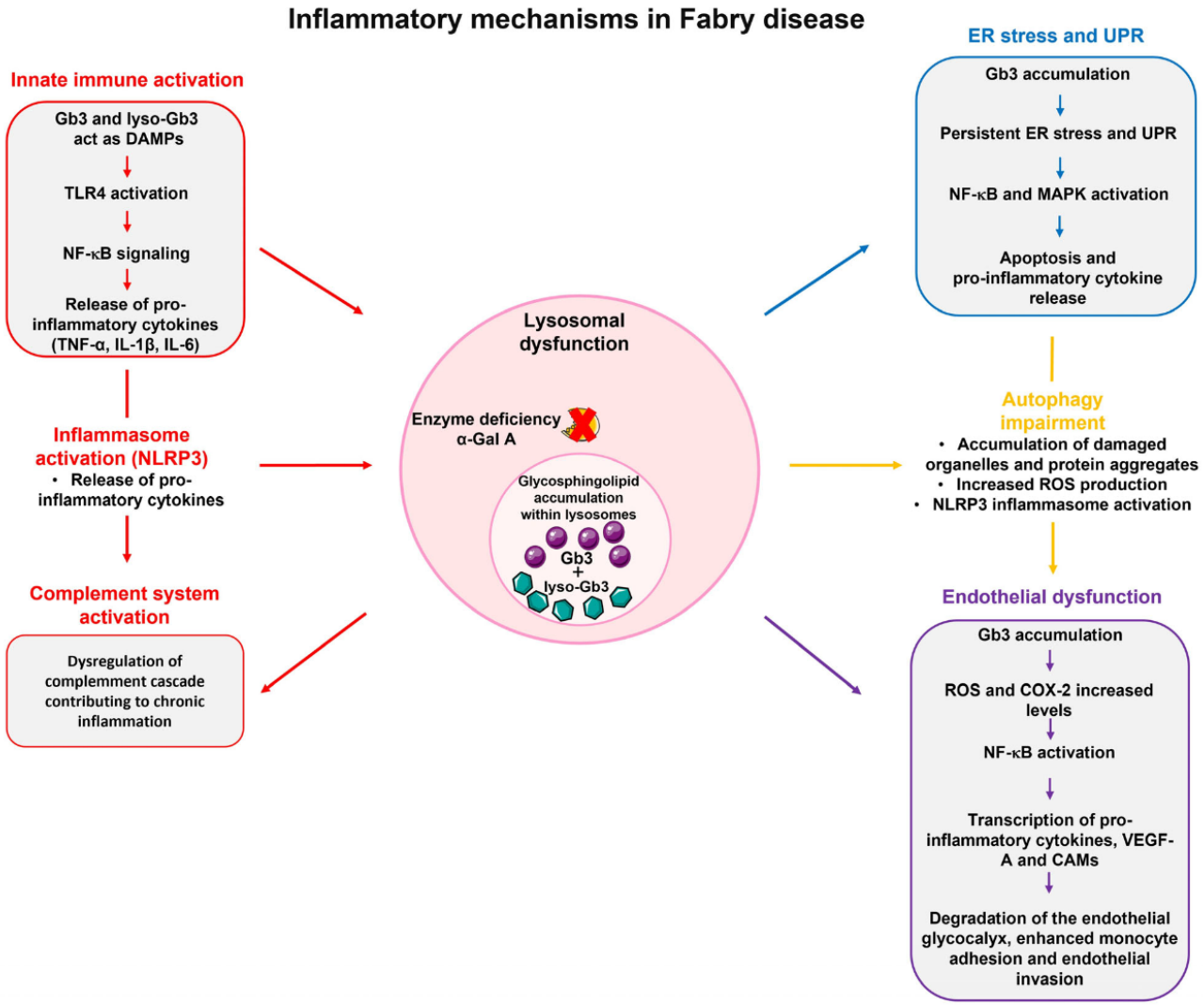
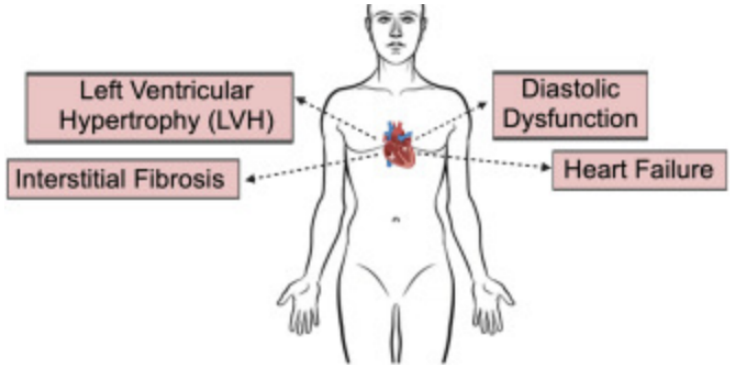


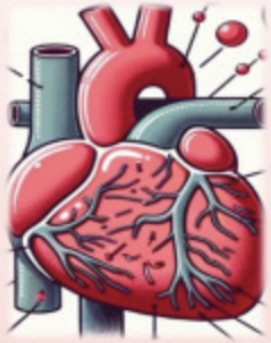
Figure 4. Inflammatory mechanisms involved in Fabry disease. Lysosomal dysfunction resul



INFLAMMATION-related Cardiovascular complications in AFD: a systemic vasculopathy

Pathological basis: Lysosomal inclusions or lipid deposits in various cell types, prominently in vascular endothelial and smooth muscle cells, cardiac cells, renal epithelial cells, and nerve cells including dorsal root ganglia and some central nervous system neurons

HEART

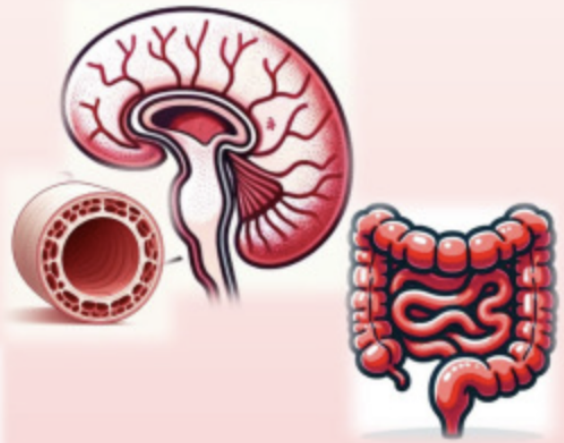


Deposition in Myocardium:
LV Hypertrophy, HFpEF;
Immune myocarditis
(macrophage/lymphocyte infiltrates)

Deposition in intramyocardial vessels:
ischemia (coronary MVD), angina and AMI;
Fibrosis→ arrhythmias

Deposition in conduction tissue:

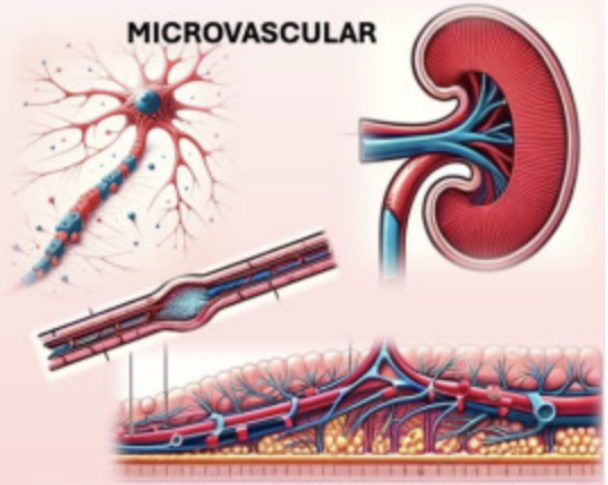
MACROVASCULAR



Increased vessel thickness (carotid IMT)
Small vessel cerebral disease
TIA/Stroke of undetermined origin (young age)

Gastrointestinal disturbances

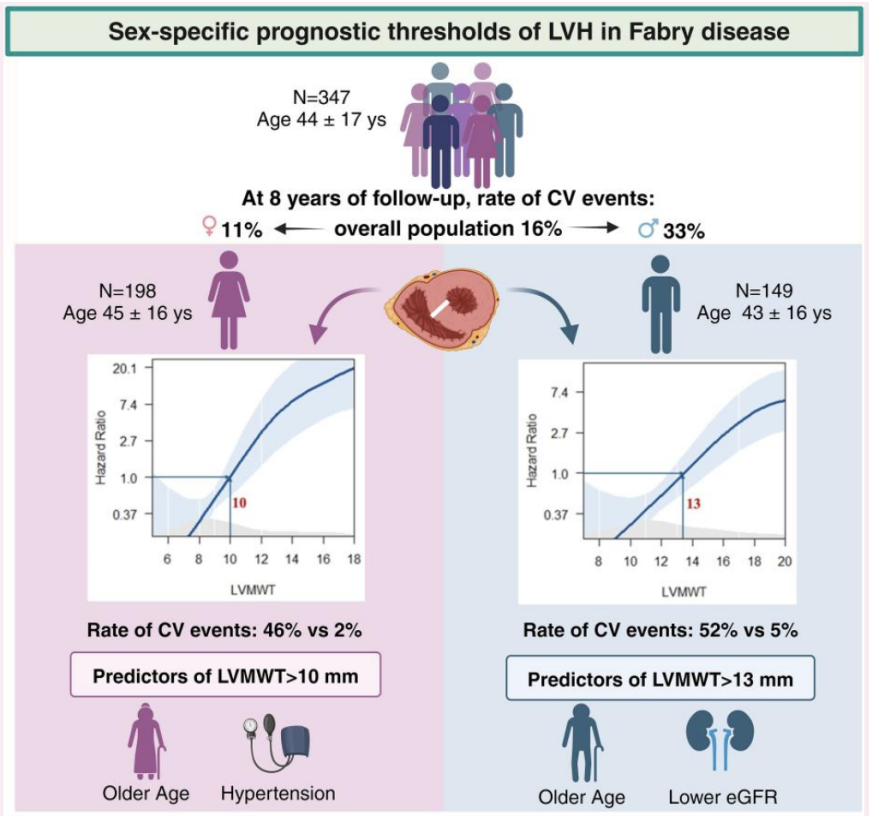
MICROVASCULAR



Progressive glomerulosclerosis and proteinuria
Renal failure

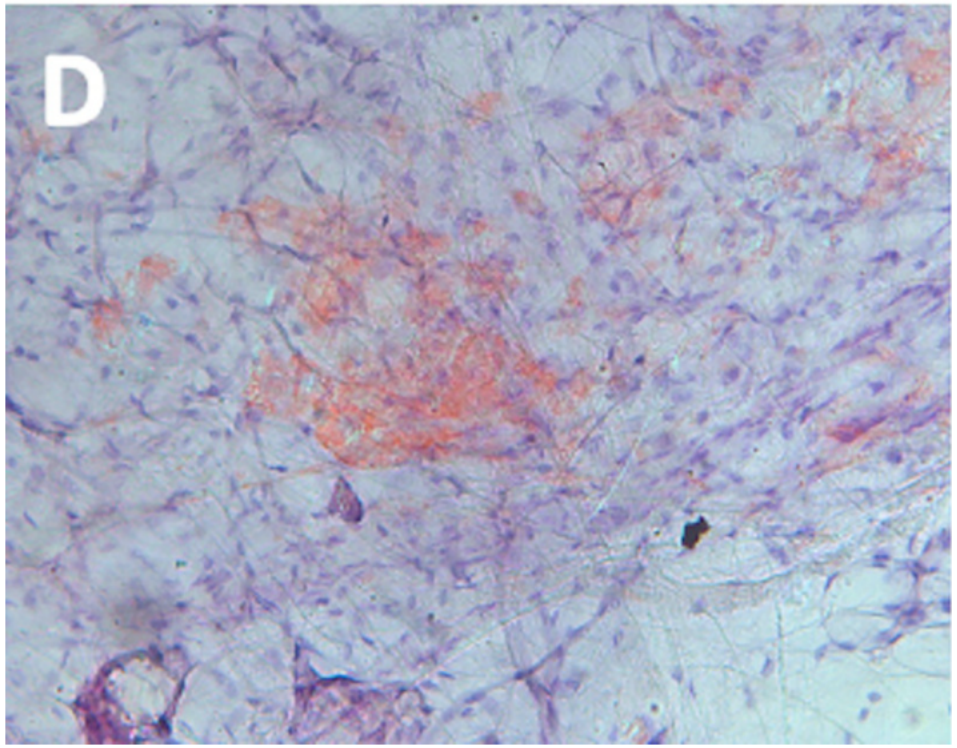
Acroparesthesias, pain (Fabry crises)
Early peripheral (autonomic) neuropathy

Hypohidrosis, angiokeratomas; retinal vascular tortuosity.
Tinnitus, dizziness, and sensori-neural hearing loss
Raynaud phenomenon

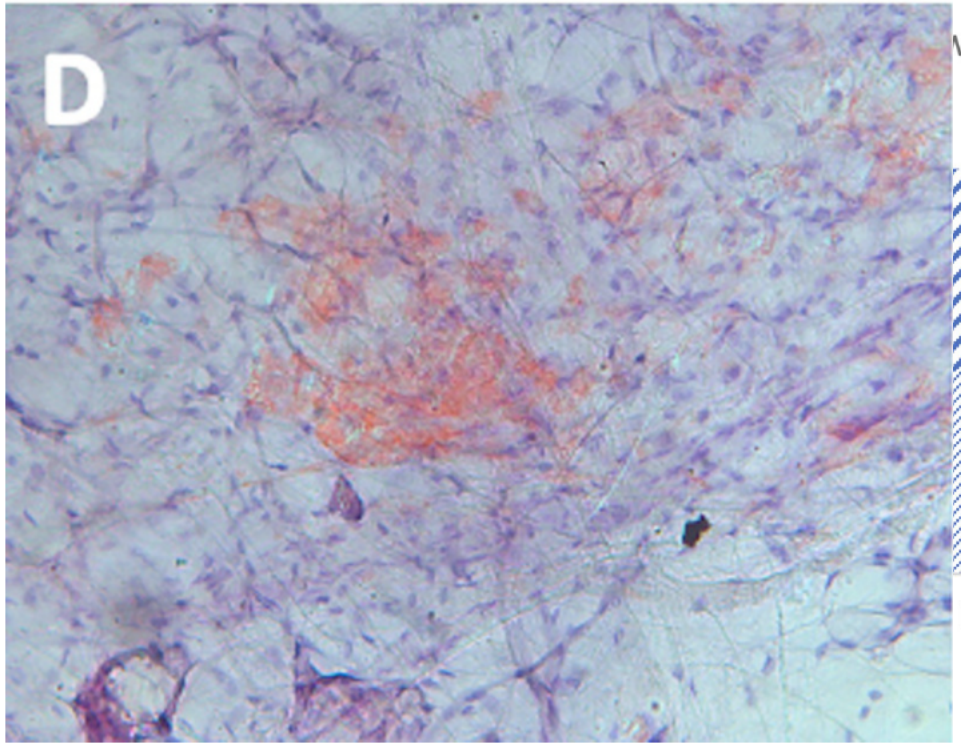


CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVMWT, left ventricular maximal wall thickness; LVH, le
ypertrophy.

Rouge congo



Chronologie



with elevated

50%

50%

Female

Ajouter un é

Écrire une descri
signification de c

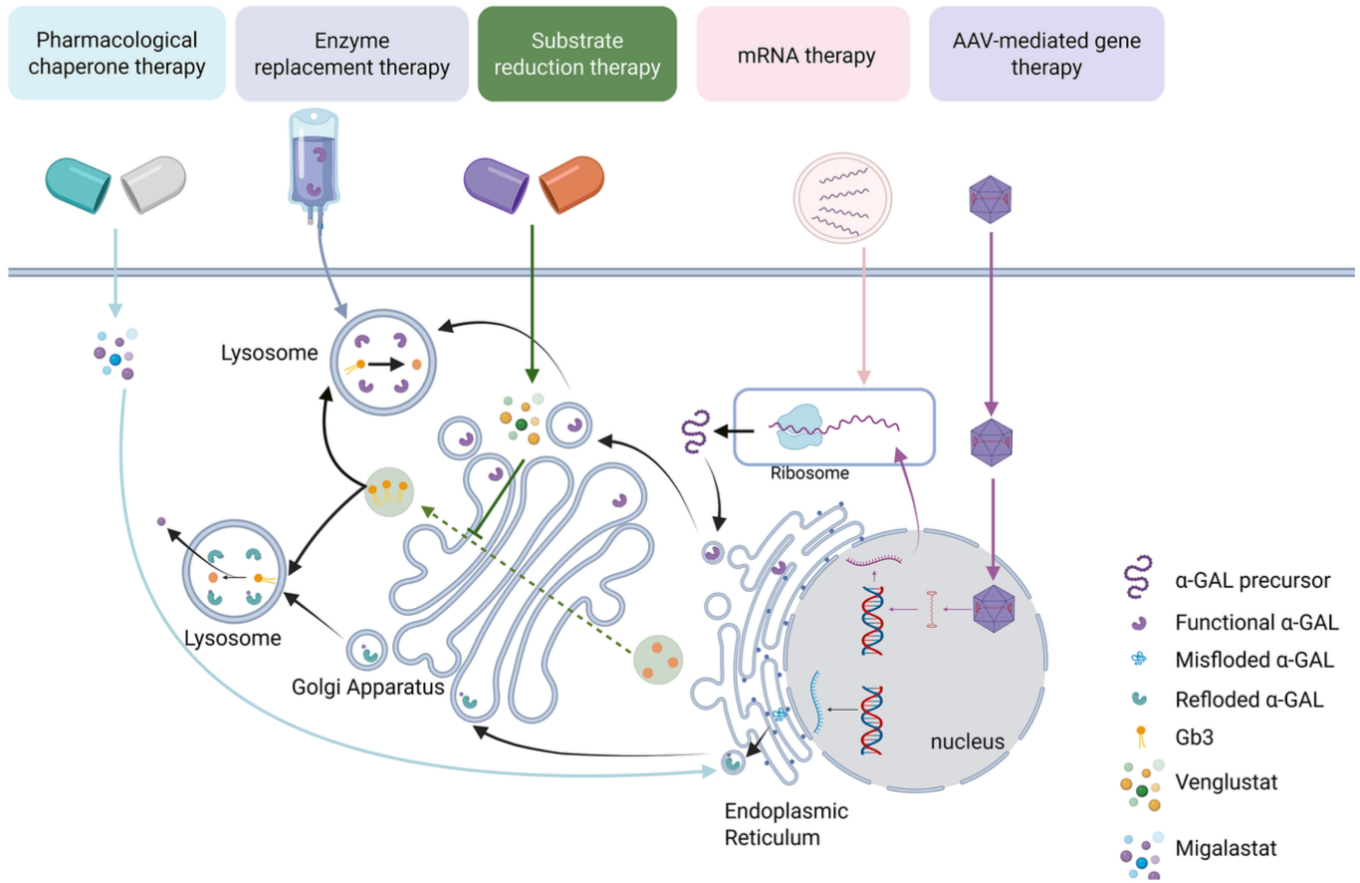
n événement

cription de la
e cet événement

gure 1 Genotype distribution in patients with elevated troponin based on sex.

signification de cet evenement

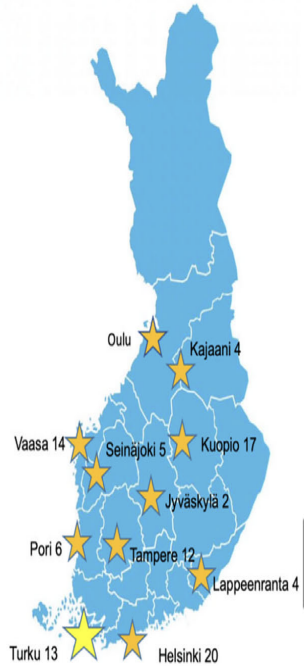
signification de cet evenement


Pharmacological chaperone therapy
Enzyme replacement therapy
Substrate reduction therapy
mRNA therapy
AAV-mediated gene therapy
Lysosome
Ribosome
Lysosome
Golgi Apparatus
nucleus
Endoplasmic Reticulum
α-GAL precursor
Functional α-GAL
Misfloded α-GAL
Refloded α-GAL
Gb3
Venglustat
Migalastat

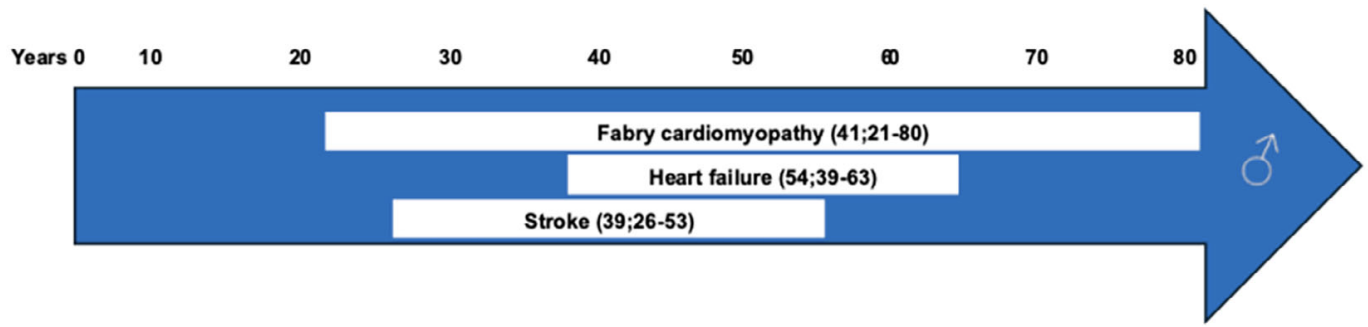
The Finnish Fabry Disease Expert Network and study patient numbers (*n* = 97)

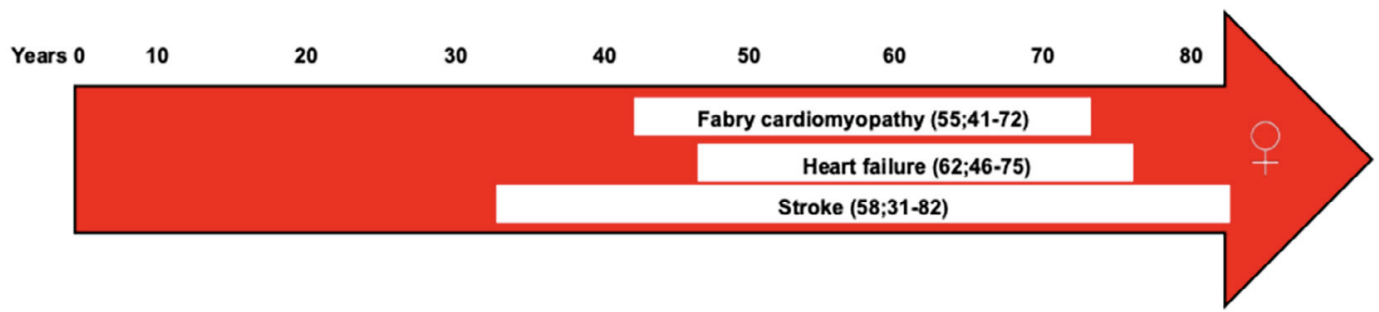
Turku Fabry Disease Centre of Excellence

Other Fabry expert centers



Age at event by sex (y, mean;range)

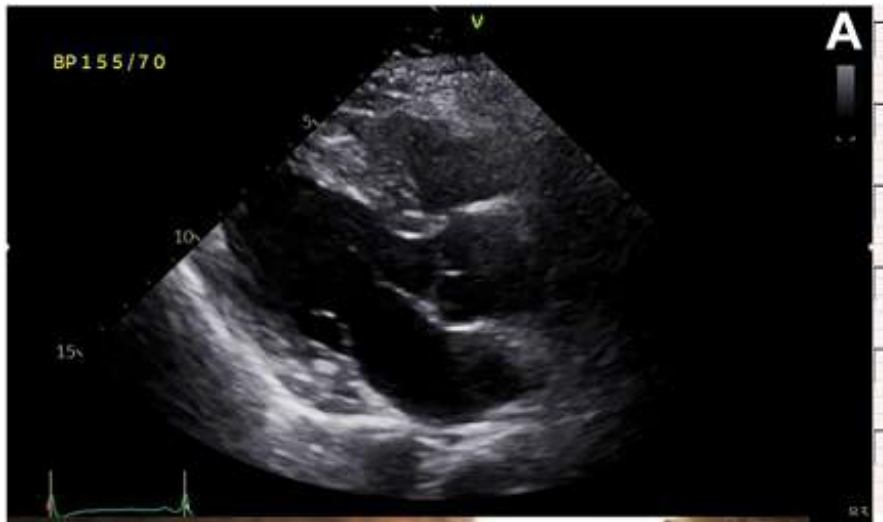


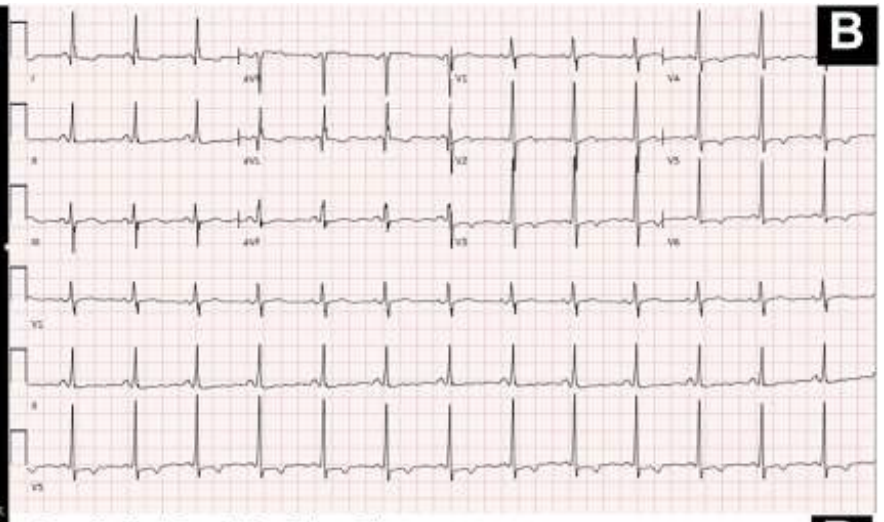


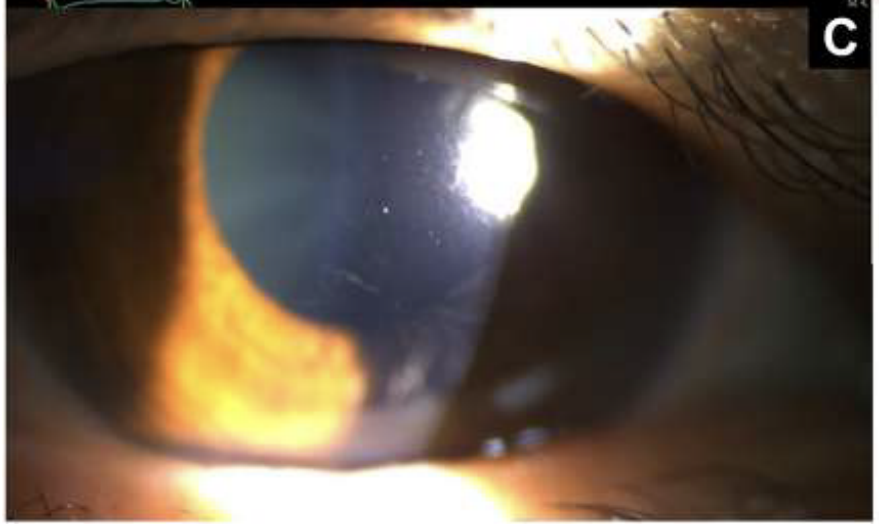
CMH sarcomérique
Phénocopies

-Cardiac Amyloidosis
-Cardiac Sarcoidosis
-Fabry
-Pompe Disease
-Danon Disease
-Mitochondrial CM
-Athlete’s Heart
-Hypertension .

Femme 65 ans







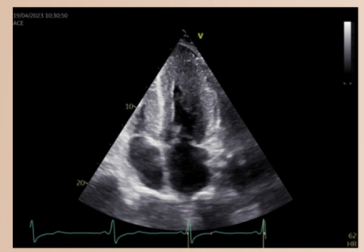
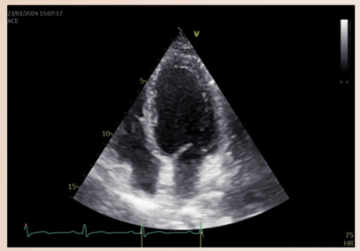
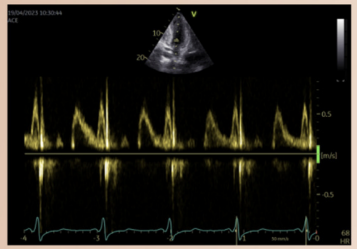
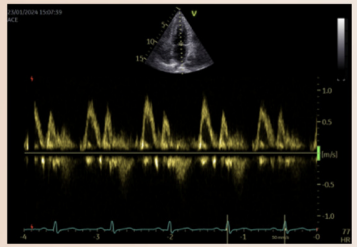
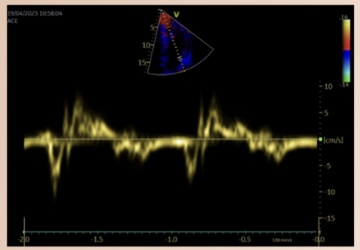
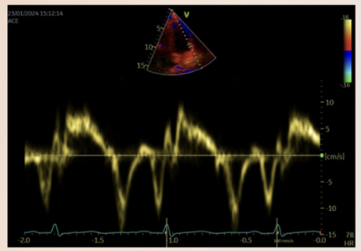
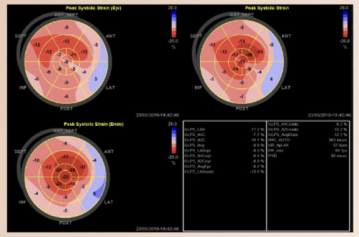
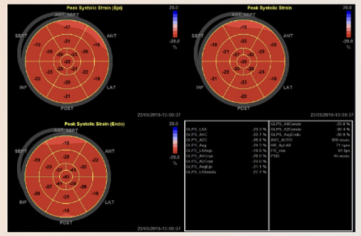
Genetic Test Result for Fabry Disease

D

A heterozygous pathogenic variant was identified in the GLA gene, which is associated with X-linked Fabry disease (OMIM: 301500). Genetic testing of family members is recommended to determine segregation of the variant.

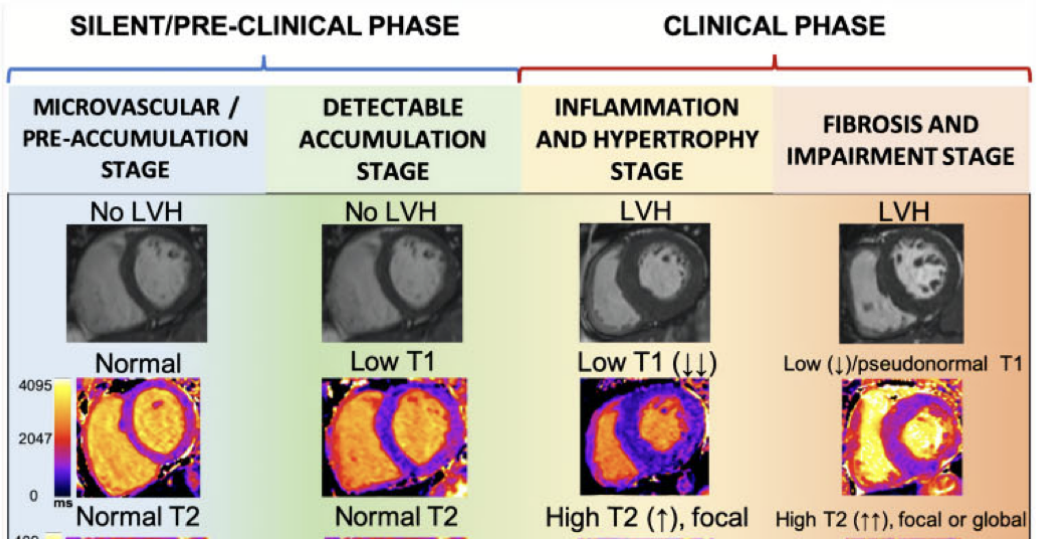
Gene	Genomic Position (GRCh37)	cDNA Change	Protein Change	Zygosity	Classification
GLA	X:100653866 C>T	c.708G>A	p.Trp236Ter	Heterozygous	Pathogenic

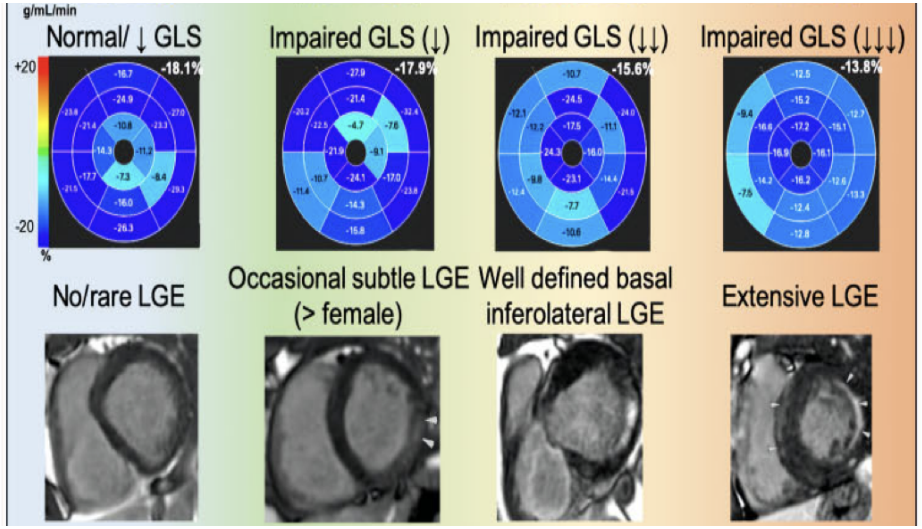
- Plasma Lyso-Gb3: 7.14ng/mL (<1.74)
- a-galactosidase A enzyme activity : 3.61umol/h/L (>2.35)

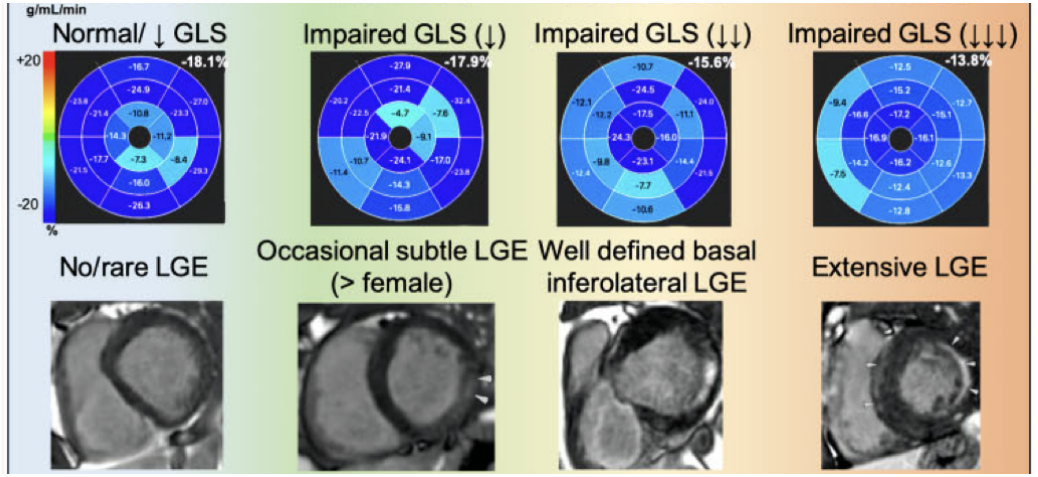
	Fabry Disease	Healthy
2D Cardiac Ultrasounds (Apex, 4 chambers)		
Trans Mitral Valve Fluximetry		
Mitral Valve Annulus Tissue Velocity		
Bull's eye Myocardial Strain Analysis		

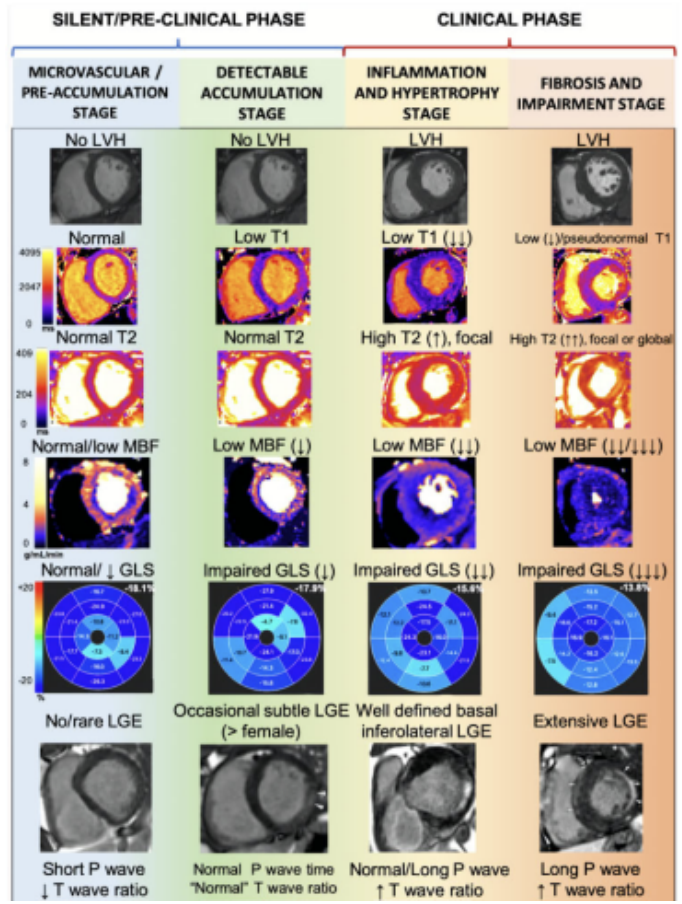
- Although historically considered rare, with an incidence of 1:40,000 to 1:117,000, neonatal screening programs have revealed a much higher prevalence, especially of late-onset variants with cardiac or renal involvement.
- Some studies suggest a frequency as high as 1 in 3100 live births and 1:8882 in Italian reports [6,7,8,9]. `

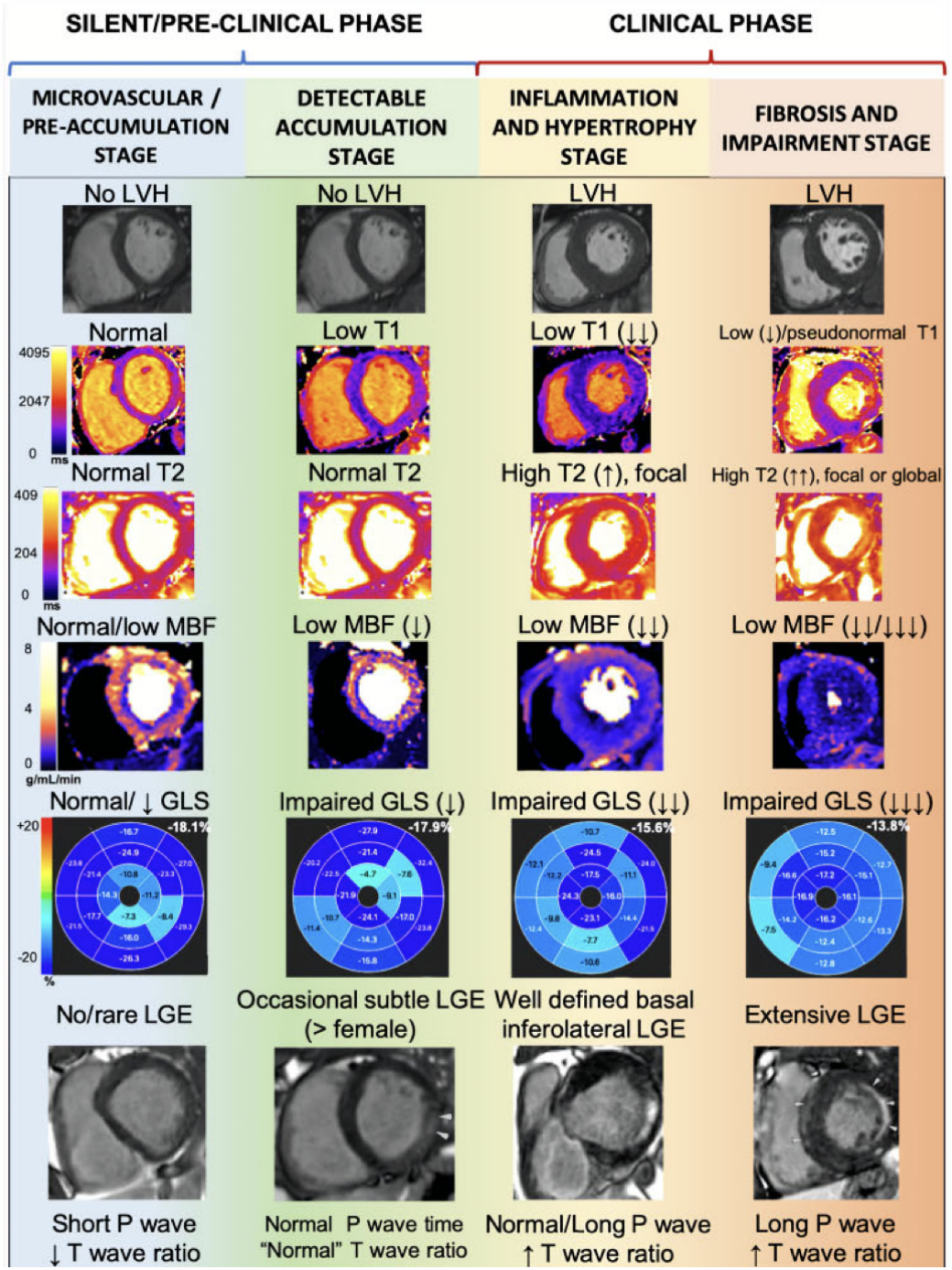
- This discrepancy highlights both the clinical and genetic heterogeneity of AFD, and the need for careful classification of *GLA*-variants [10,11], especially

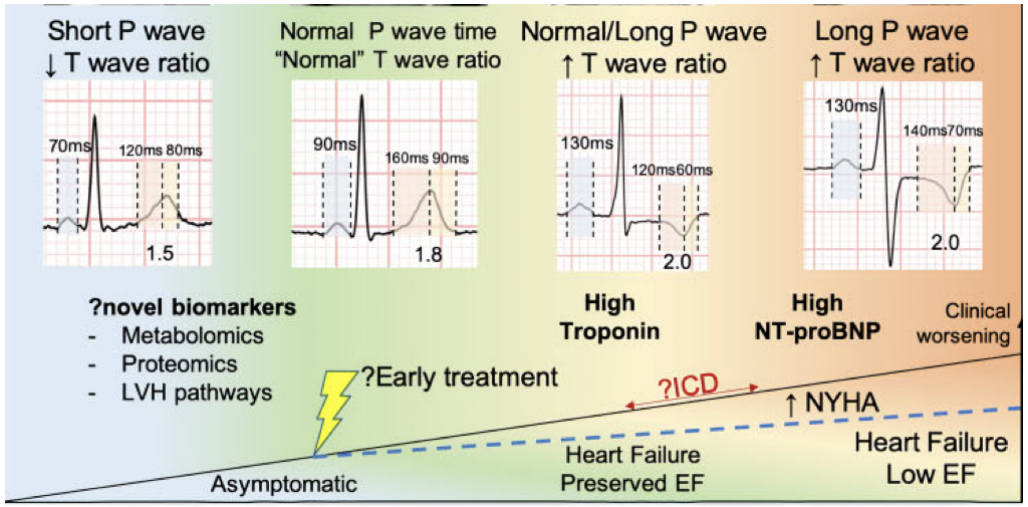

SILENT/PRE-CLINICAL PHASE
CLINICAL PHASE
MICROVASCULAR / PRE-ACCUMULATION STAGE
DETECTABLE ACCUMULATION STAGE
INFLAMMATION AND HYPERTROPHY STAGE
FIBROSIS AND IMPAIRMENT STAGE
No LVH
No LVH
LVH
LVH
Normal
Low T1
Low T1 (↓↓)
Low (↓)/pseudonormal T1
4095
2047
0
ms
Normal T2
Normal T2
High T2 (↑), focal
High T2 (↑↑), focal or global


g/mL/min
Normal/ ↓ GLS
Impaired GLS (↓)
Impaired GLS (↓↓)
Impaired GLS (↓↓↓)
+20
-20
%
-18.1%
-17.9%
-15.6%
-13.8%
No/rare LGE
Occasional subtle LGE (> female)
Well defined basal inferolateral LGE
Extensive LGE


g/mL/min
Normal/ ↓ GLS
+20
-20
%
-18.1%
Impaired GLS (↓)
-17.9%
Impaired GLS (↓↓)
-15.6%
Impaired GLS (↓↓↓)
-13.8%
No/rare LGE
Occasional subtle LGE
(> female)
Well defined basal
inferolateral LGE
Extensive LGE


SILENT/PRE-CLINICAL PHASE
CLINICAL PHASE
MICROVASCULAR / PRE-ACCUMULATION STAGE
DETECTABLE ACCUMULATION STAGE
INFLAMMATION AND HYPERTROPHY STAGE
FIBROSIS AND IMPAIRMENT STAGE
No LVH
No LVH
LVH
LVH
Normal
Low T1
Low T1 (↓↓)
Low (↓)/pseudonormal T1
Normal T2
Normal T2
High T2 (↑), focal
High T2 (↑↑), focal or global
Normal/low MBF
Low MBF (↓)
Low MBF (↓↓)
Low MBF (↓↓/↓↓↓)
Normal/ ↓ GLS
Impaired GLS (↓)
Impaired GLS (↓↓)
Impaired GLS (↓↓↓)
No/rare LGE
Occasional subtle LGE (> female)
Well defined basal inferolateral LGE
Extensive LGE
Short P wave
↓ T wave ratio
Normal P wave time
"Normal" T wave ratio
Normal/Long P wave
↑ T wave ratio
Long P wave
↑ T wave ratio


SILENT/PRE-CLINICAL PHASE
CLINICAL PHASE
MICROVASCULAR / PRE-ACCUMULATION STAGE
DETECTABLE ACCUMULATION STAGE
INFLAMMATION AND HYPERTROPHY STAGE
FIBROSIS AND IMPAIRMENT STAGE
No LVH
No LVH
LVH
LVH
Normal
Low T1
Low T1 (↓↓)
Low (↓)/pseudonormal T1
4095
2047
0
ms
Normal T2
Normal T2
High T2 (↑), focal
High T2 (↑↑), focal or global
409
204
0
ms
Normal/low MBF
Low MBF (↓)
Low MBF (↓↓)
Low MBF (↓↓/↓↓↓)
8
4
0
g/mL/min
Normal/ ↓ GLS
Impaired GLS (↓)
Impaired GLS (↓↓)
Impaired GLS (↓↓↓)
+20
-20
%
-18.1%
-17.9%
-15.6%
-13.8%
No/rare LGE
Occasional subtle LGE (> female)
Well defined basal inferolateral LGE
Extensive LGE
Short P wave
↓ T wave ratio
Normal P wave time
"Normal" T wave ratio
Normal/Long P wave
↑ T wave ratio
Long P wave
↑ T wave ratio


Short P wave
↓ T wave ratio
70ms
120ms 80ms
1.5
Normal P wave time
"Normal" T wave ratio
90ms
160ms 90ms
1.8
Normal/Long P wave
↑ T wave ratio
130ms
120ms60ms
2.0
Long P wave
↑ T wave ratio
130ms
140ms70ms
2.0
?novel biomarkers
- Metabolomics
- Proteomics
- LVH pathways
High
Troponin
High
NT-proBNP
Clinical
worsening
?Early treatment
?ICD
↑ NYHA
Asymptomatic
Heart Failure
Preserved EF
Heart Failure
Low EF


Systemic
• Enzyme Replacement Therapy (ERT)
• Chaperone Therapy
• Substrate Reduction Therapy (SRT)
• CRISPR and gene therapy
Therapeutic strategies
Cardiovascular
• Angiotensin-converting enzyme (ACE) inhibitors
• Angiotensin receptor blockers (ARB)
• β-blockers
• Diuretics

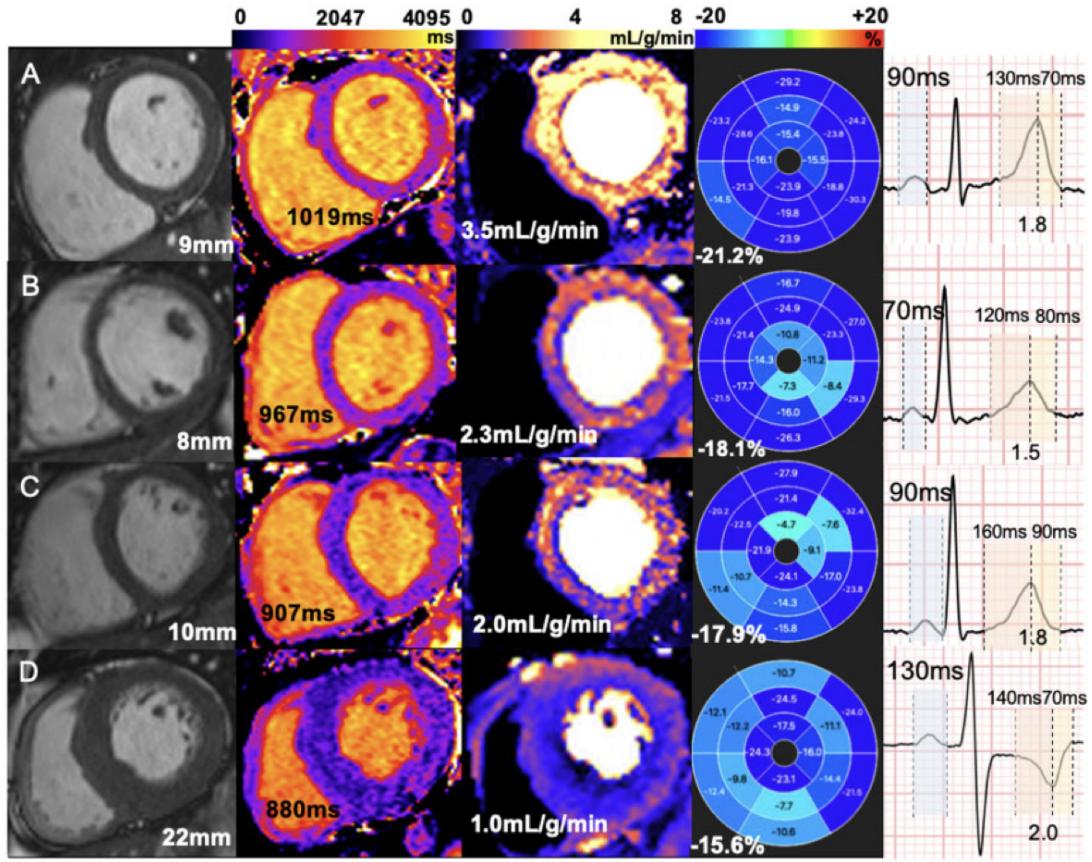
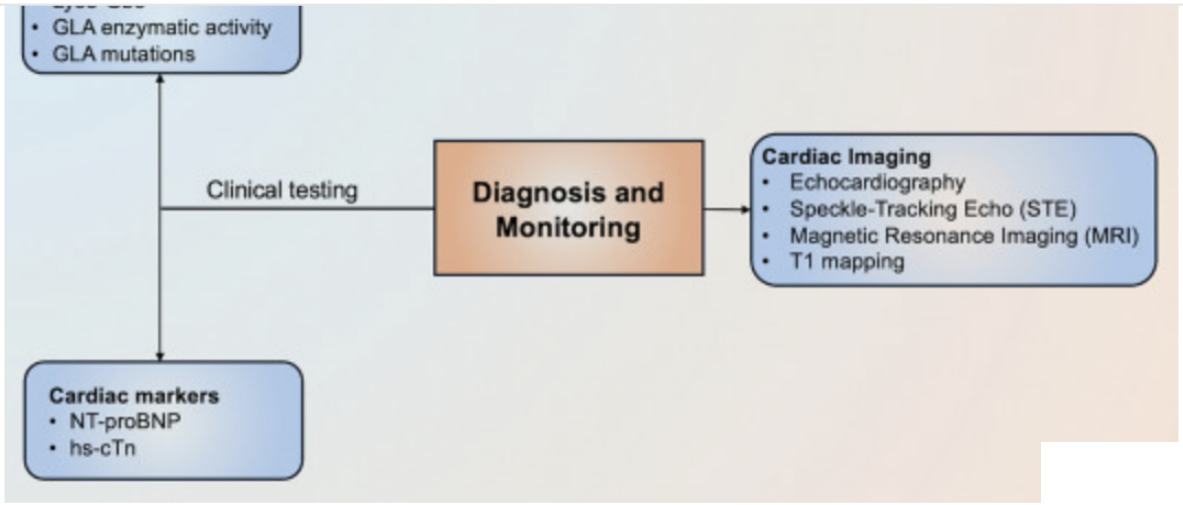
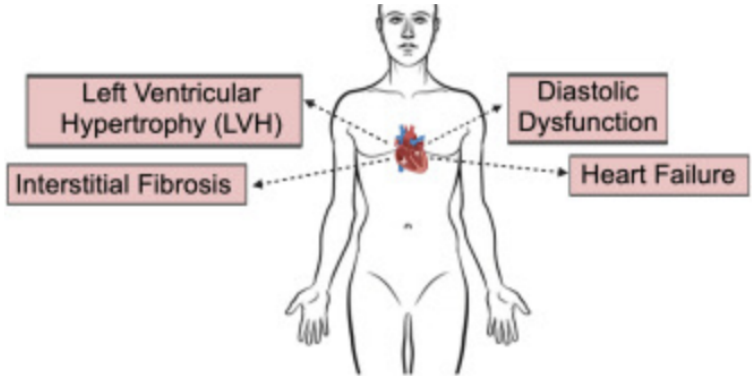


Figure 4 Multiparametric cardiovascular magnetic resonance and electrocardiographic assessment in patients with FD and healthy controls. Left to right—steady-state free precession cines, native T1 mapping, stress MBF mapping, GLS, P-wave duration, and T-wave ratio. (*A*) Healthy control, no


GLA enzymatic activity
GLA mutations
Clinical testing
Diagnosis and Monitoring
Cardiac Imaging
Echocardiography
Speckle-Tracking Echo (STE)
Magnetic Resonance Imaging (MRI)
T1 mapping
Cardiac markers
NT-proBNP
hs-cTn


Left Ventricular Hypertrophy (LVH)
Diastolic Dysfunction
Interstitial Fibrosis
Heart Failure

Circulation

LETTER | Originally Published 22 July 2019 |

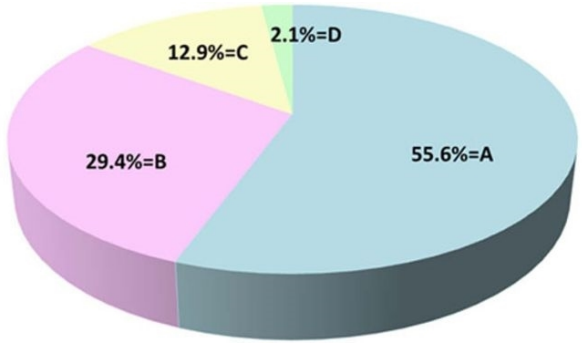
Check for updates

Different Histopathologic Diagnoses in Patients With Clinically Diagnosed Hypertrophic Cardiomyopathy After Surgical Myectomy

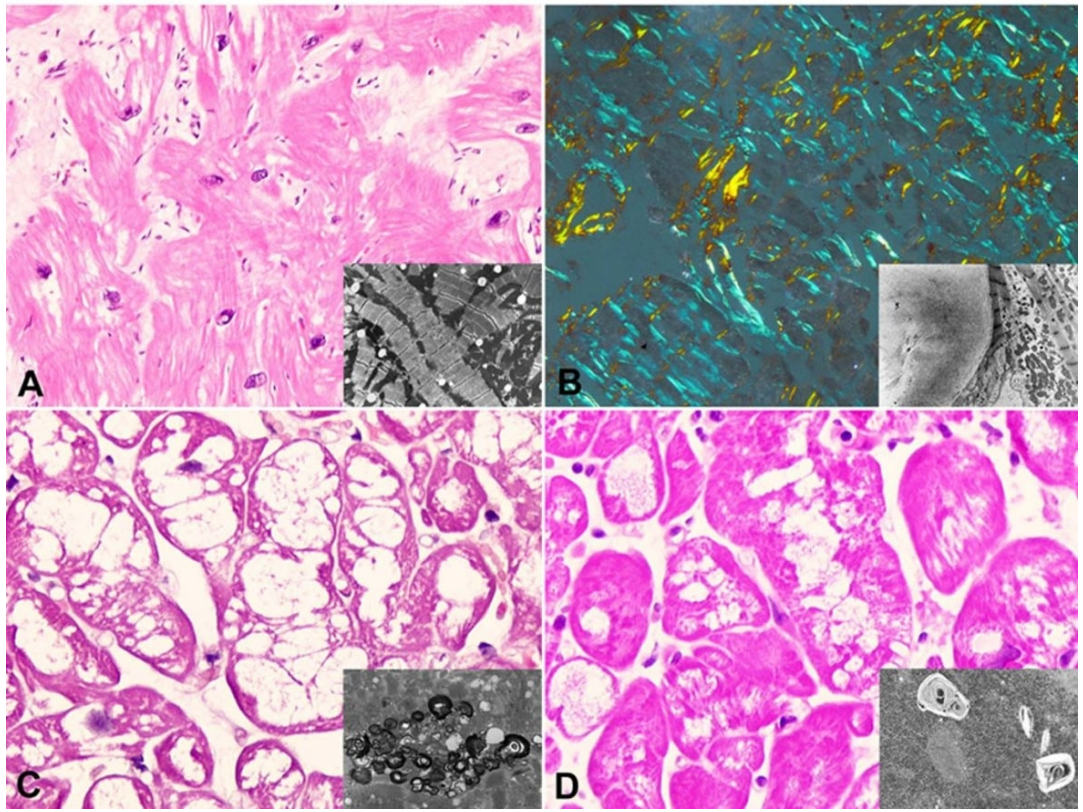
Alaa Alashi, MD, Ria M. Desai, Tamanna Khullar, MD, Kevin Hodges, MD, E. Rene Rodriguez, MD, Carmela Tan, MD, Zoran B. Popovic, MD, PhD,

esai, MD | AUTHOR INFO &

Variable	HCM (n=2018)	Hypertensive Heart Disease (n=280)	Storage Diseases (n=33)	Amyloidosis (n=18)	HCM With Concomitant Myocarditis (n=123)
Age, y	252±14	67±13	51±17	73±9	51±14
Male sex, n (%)	1114 (55)	148 (53)	15 (46)	13 (72)	53 (43)
Hypertension, n (%)	746 (37)	280 (100)	11 (33)	13 (72)	54 (44)
CAD, n (%)	324 (16)	154 (55)	3 (9)	5 (28)	18 (15)
Family history of HCM, n (%)	286 (14)	0	0	0	0
Family history of SCD, n (%)	263 (13)	12 (4)	3 (9)	0	11 (9)
Atrial fibrillation, n (%)	478 (24)	56 (20)	10 (30)	2 (11)	37 (30)
Pacemaker, n (%)	57 (3)	7 (3)	3 (9)	2 (11)	3 (2)
ICD, n (%)	250 (12)	19 (7)	5 (35)	0	22 (18)
β-Blockers, n (%)	1428 (71)	223 (80)	24 (73)	12 (67)	81 (66)
Calcium blockers, n (%)	448 (22)	58 (21)	5 (15)	4 (22)	26 (21)
LVEF, %	62±7	63±7	60±4	63±6	60±6



HCM



Amylose

Glycogenose

Fabry


Systemic
• Enzyme Replacement Therapy (ERT)
• Chaperone Therapy
• Substrate Reduction Therapy (SRT)
• CRISPR and gene therapy
Therapeutic strategies
Cardiovascular
• Angiotensin-converting enzyme (ACE) inhibitors
• Angiotensin receptor blockers (ARB)
• β-blockers
• Diuretics

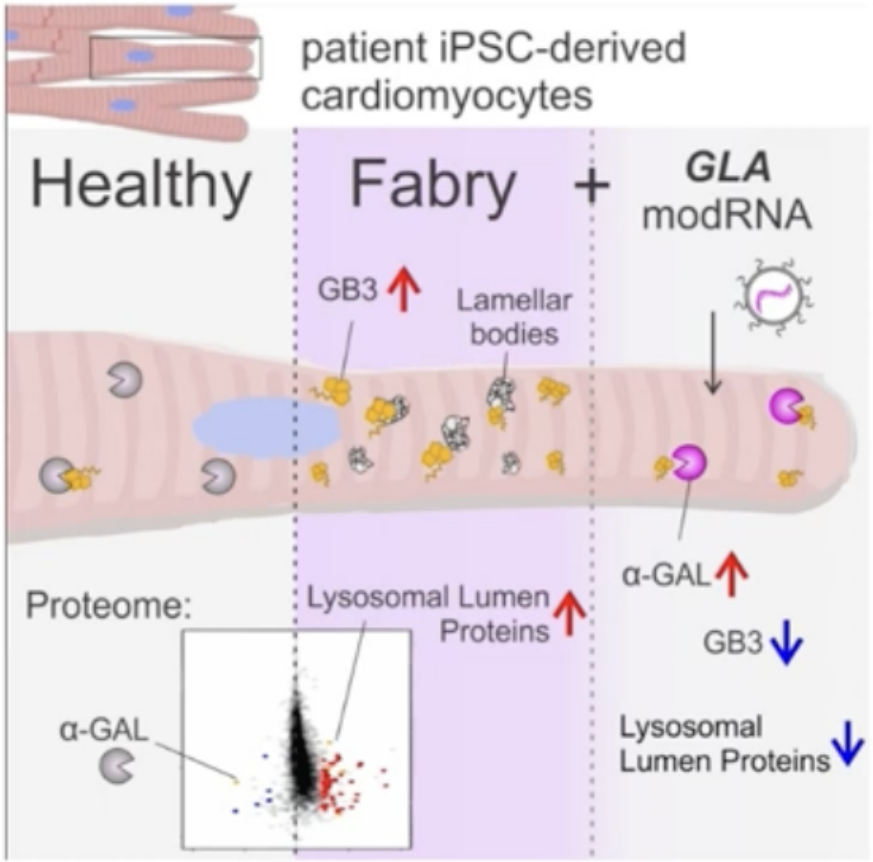
Le futur..

REPORT · Volume 110, Issue 9, P1600-1605, September 07, 2023 · *Open Access* Download Full Issue

GLA-modified RNA treatment lowers GB3 levels in iPSC-derived cardiomyocytes from Fabry-affected individuals

Menno ter Huurne [1,2,13] · Benjamin L. Parker [3,4] · Ning Qing Liu [5] · … · Kathy M. Nicholls [9] · Enzo R. Porrello [1,2,3]
David A. Elliott [1,2,12,13,14,15] … Show more

A — Cardiac diff



Efficacité du traitement ?

Circulation

CURRENT ISSUE

RESEARCH ARTICLE | Originally Published 8 October 2013 |

Check for updates

Progression of Fabry Cardiomyopathy Despite Enzyme Replacement Therapy

Maurizio Pieroni, MD, PhD, Antonia Camporeale, MD, Roberta Della Bona, MD, PhD, Alessandra Sabini, MD, Deborah Cosmi, MD, Annalisa Magnolfi, MD, and Leonardo Bolognese, MD | AUTHOR INFO & AFFILIATIONS

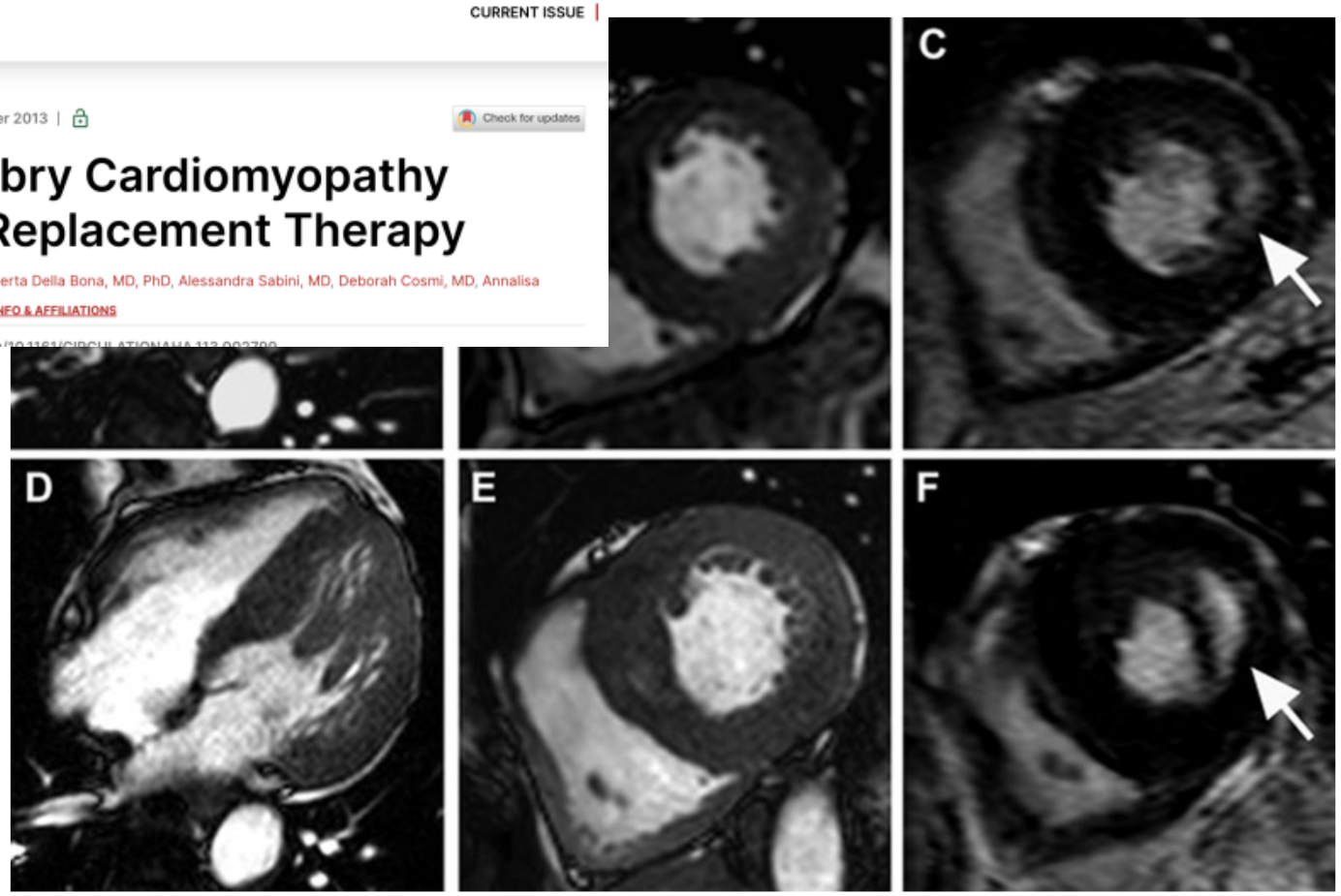
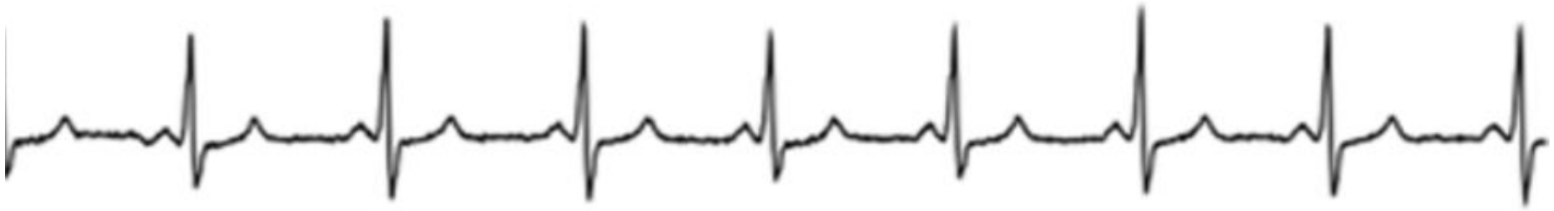
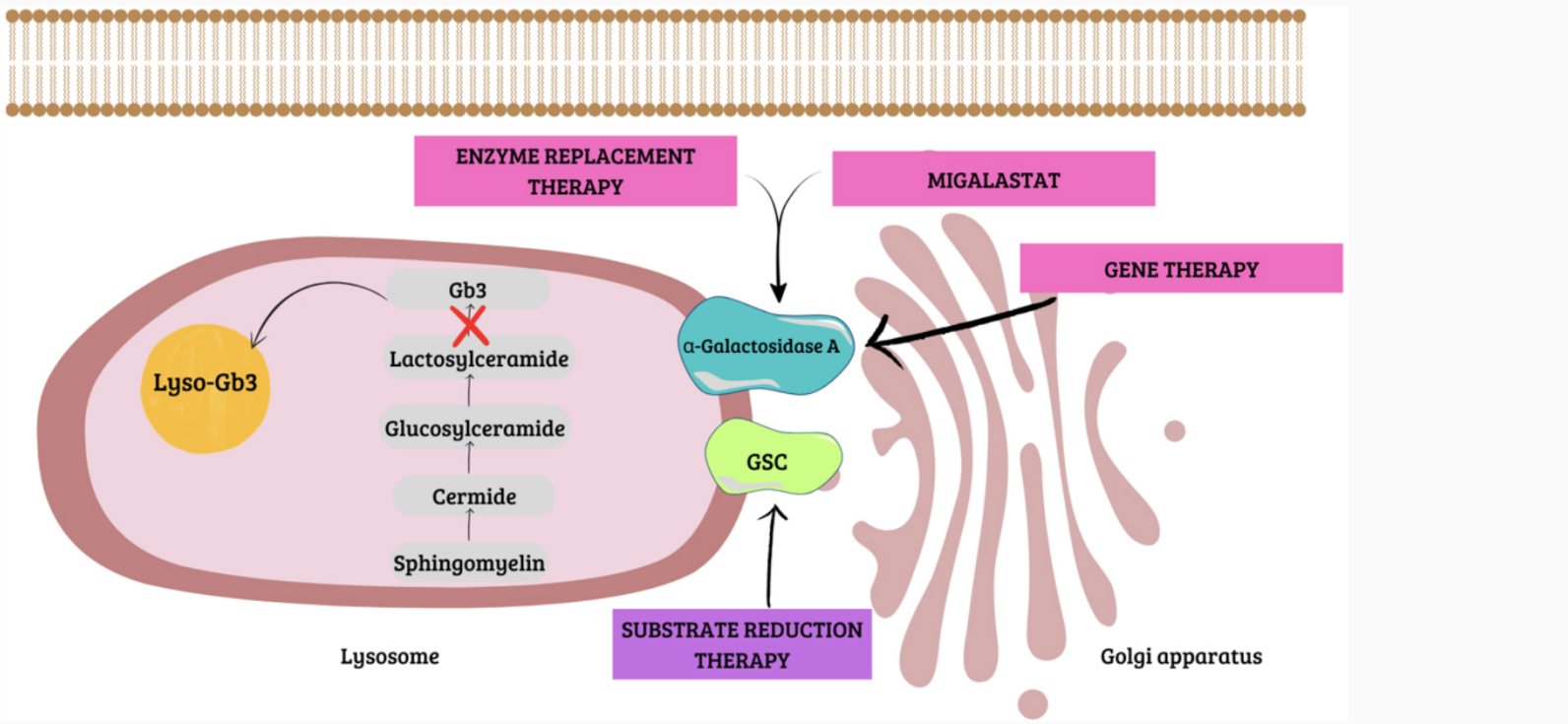


Figure 2. Cardiac magnetic resonance progression of cardiac involvement in Fabry disease. **A** through **C**, Baseline evaluation before enzyme replacement therapy (2005). **D** through **F**, Follow-up evaluation





B, Cardiac magnetic resonance imaging showing normal thickness of the ventricular walls and the absence of late-enhancement signals after gadolinium infusion. C, Left ventricular endomyocardial

Maladie de Fabry : Pharmacogénétique 2017

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE Official journal of the American College of Medical Genetics and Genomics

Open

The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat

Elfrida R. Benjamin, PhD[1], Maria Cecilia Della Valle, PhD[1], Xiaoyang Wu, PhD[1], Evan Katz, MSc[1],

- ith the most severe, classic phenotype have minimal or undetectable levels of α-Gal A activity and early, continuous accumulation of glycosphingolipids, most notably globotriaosylceramide (GL-3 or Gb_3), in lysosomes.
- This occurs in a wide range of cell types, including vascular endothelial and smooth muscle cells, neural cells, cardiomyocytes, all kidney cell types, as well as in plasma and urine [[1], [2], [3]]. Progressive accumulation of GL-3 in multiple cell types within vital organs leads to potentially life-threatening complications including strokes, cardiac arrhythmias, cardiomyopathy, and renal failure [4]. I
- In addition, globotriaosylsphingosine (lyso-GL-3 or lyso-Gb_3), the deacylated form of GL-3, accumulates in plasma, and is a useful biomarker for diagnosis and staging of Fabry disease [3,5].

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE Official journal of the American College of Medical Genetics and Genomics

Open

The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat

Elfrida R. Benjamin, PhD[1], Maria Cecilia Della Valle, PhD[1], Xiaoyang Wu, PhD[1], Evan Katz, MSc[1],

- Galafold®, Amicus Therapeutics), is available for enzyme enhancement therapy [21,22] and is suitable for patients with amenable pathogenic *GLA* variants as determined by an *in vitro* assay [23]

Traitement de la maladi de Fabry

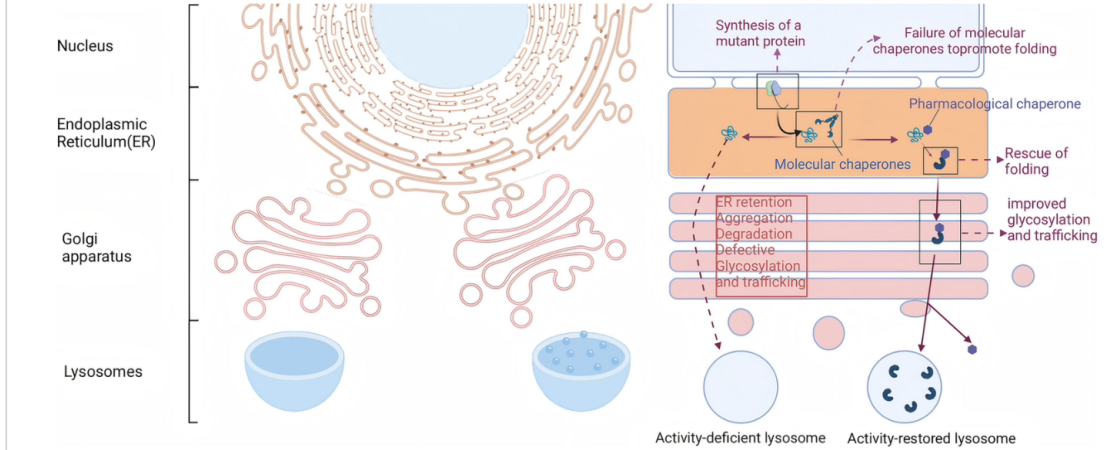


FIGURE 2
Migalastat stabilizes mutated α-Gal A enzymes to enhance enzymatic activity.

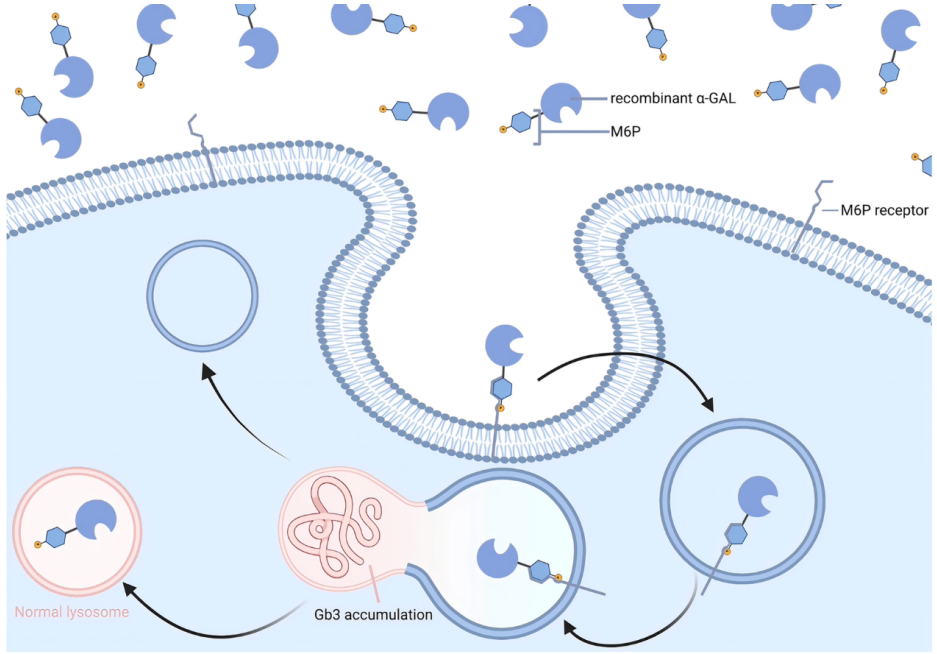


FIGURE 1

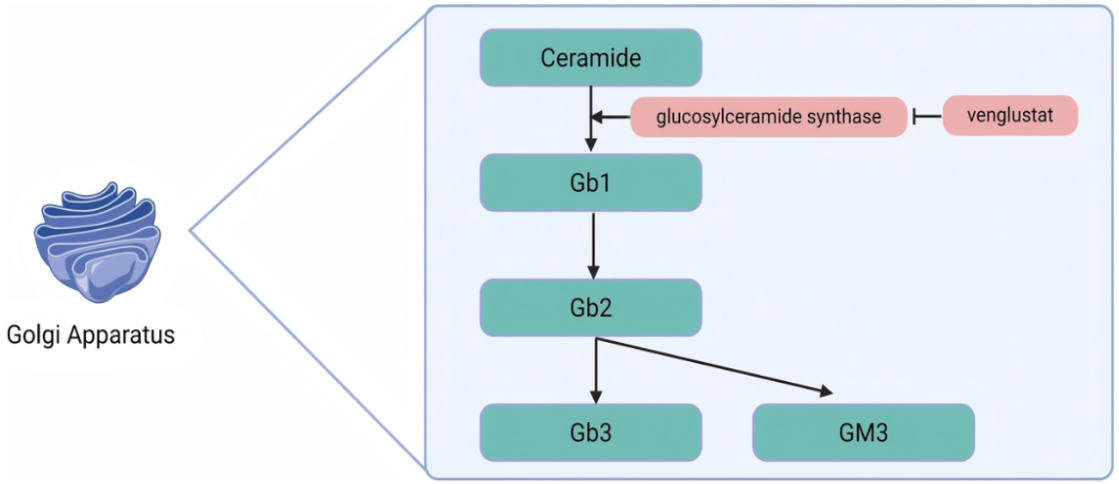


FIGURE 3
Venglustat inhibits glucose ceramide synthase to reduce Gb3 production.

Molecular Genetics and Metabolism
Volume 143, Issues 1–2, September–October 2024, 108545

Restoration of peripheral neuropathy in Fabry mice via intrathecal administration of an adeno-associated virus vector encoding mGLA cDNA

Takashi Higuchi [a], Yohta Shimada [a], Yukari Takahashi [b], Fusao Kato [b], Toya Ohashi [a,c], Hiroshi Kobayashi [a]

20/02/2002

FABRAZYME 35 mg (agalsidase bêta)

Avis favorable à l'inscription de FABRAZYME 35mg sur la liste des produits agréés à l'usage des collectivités et divers serv...

ASMR : 5 | 4 | 3 | 2 | 1

Stages of Fabry disease	Storage	Inflammation/organ dysfunction		Severe organ dysfunction/failure
Disease progression	Lysosomal storage	Myocardial dysfunction Kidney dysfunction Cerebrovascular manifestations	LVH Cardiomyopathy CKD early stages	Advanced cardiomyopathy Advanced nephropathy/ESRD
Clinical progression	Angiokeratomas Hypohidrosis Cornea verticillata Neuropathic pain	Chest pain Arrhythmias Podocyturia Proteinuria/albuminuria Neuropathic pain	Heart failure with preserved ejection fraction Decline in eGFR Neuropathic pain Cerebral SVD	Heart failure with reduced ejection fraction Kidney failure Lacunar stroke and large vessel stroke
Biomarkers	Peripheral nerve involvement: small fiber abnormalities (skin biopsy for detection of somatic and autonomic peripheral nerve dysfunction) Increased GL3 Increased plasma lyso-GL3 ECG abnormalities (high QRS, atrioventricular blocks, bradycardia) Brain MRI biomarkers: white matter hyperintensities, basilar and artery dolichoectasia, the pulvinar sign, and perivascular spaces	Increased hs-cTnT Low T1 ECG abnormalities (short PQ interval, reduced T wave ratio, bradycardia) Reduced GFR Albuminuria Podocyturia	Increased NT-proBNP Low T1 High focal T2 Severe decline in GFR Major proteinuria/ albuminuria Podocyturia Cerebral SVD	High NT-proBNP Low T1 High/global T2 Extensive LGE Renal failure Recurrent strokes

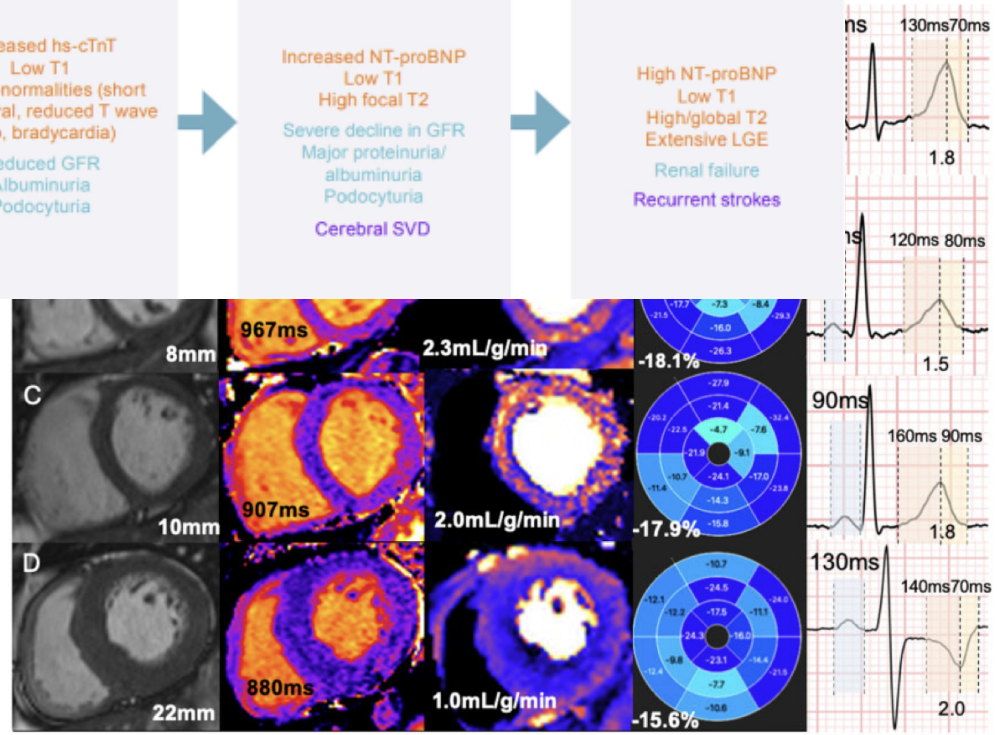
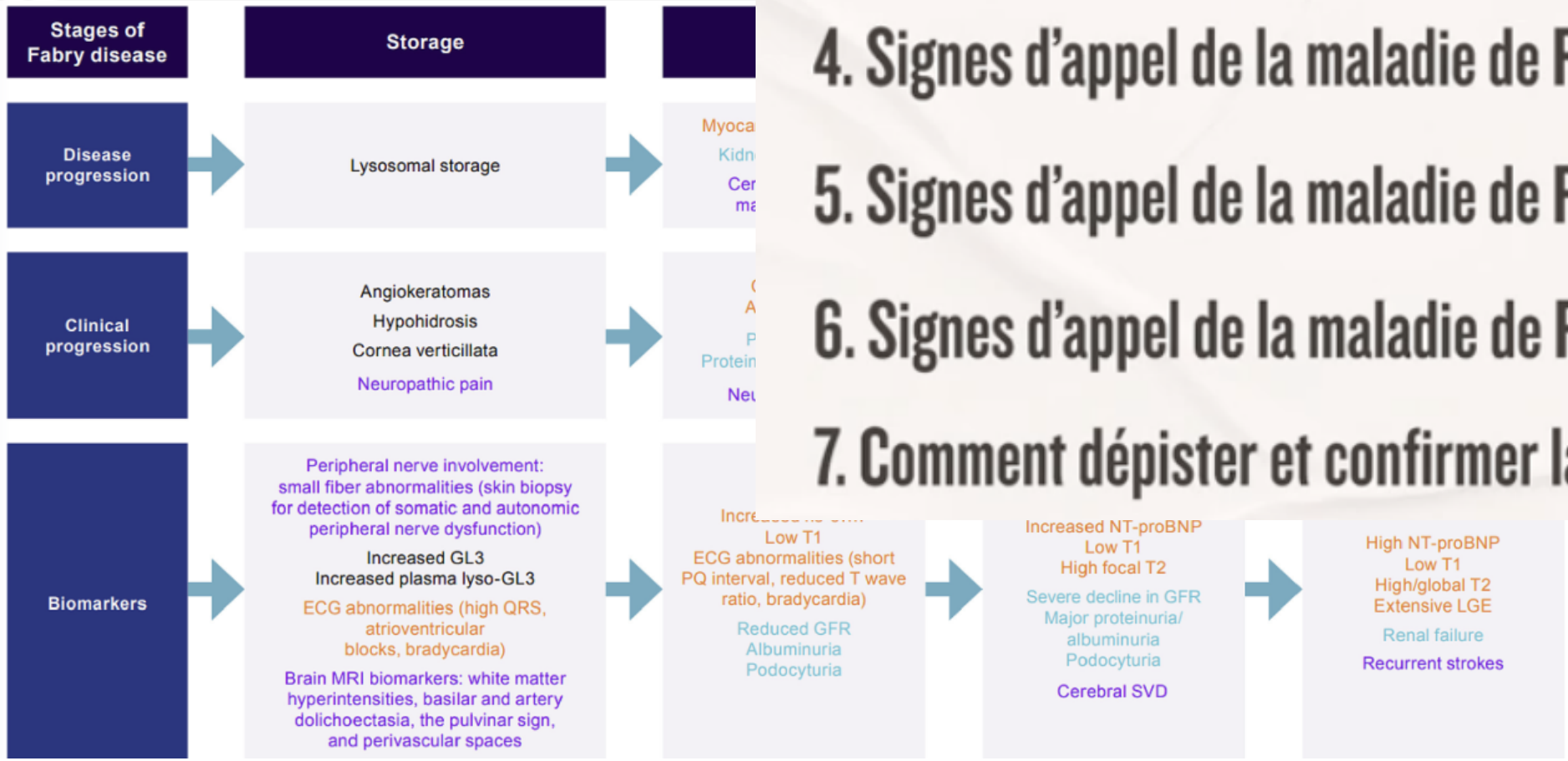


Figure 4 Multiparametric cardiovascular magnetic resonance and electrocardiographic assessment in patients with FD and healthy controls. Left to right—steady-state free precession cines, native T1 mapping, stress MBF mapping, GLS, P-wave duration, and T-wave ratio. (*A*) Healthy control, no

1. Bilan étiologique général d'une CMH
2. Qu'est-ce que la maladie de Fabry et pourquoi en parler ?
3. Quand penser à la maladie de Fabry en cardiologie ?
4. Signes d'appel de la maladie de Fabry à l'ECG
5. Signes d'appel de la maladie de Fabry à l'écho
6. Signes d'appel de la maladie de Fabry à l'IRM
7. Comment dépister et confirmer la maladie de Fabry ?



1. Bilan étiologique général d'une CMH

2. Qu'est-ce que la maladie de Fabry et pourquoi en parler ?

3. Quand penser à la maladie de Fabry en cardiologie ?

4. Signes d'appel de la maladie de Fabry à l'ECG

5. Signes d'appel de la maladie de Fabry à l'écho

6. Signes d'appel de la maladie de Fabry à l'IRM

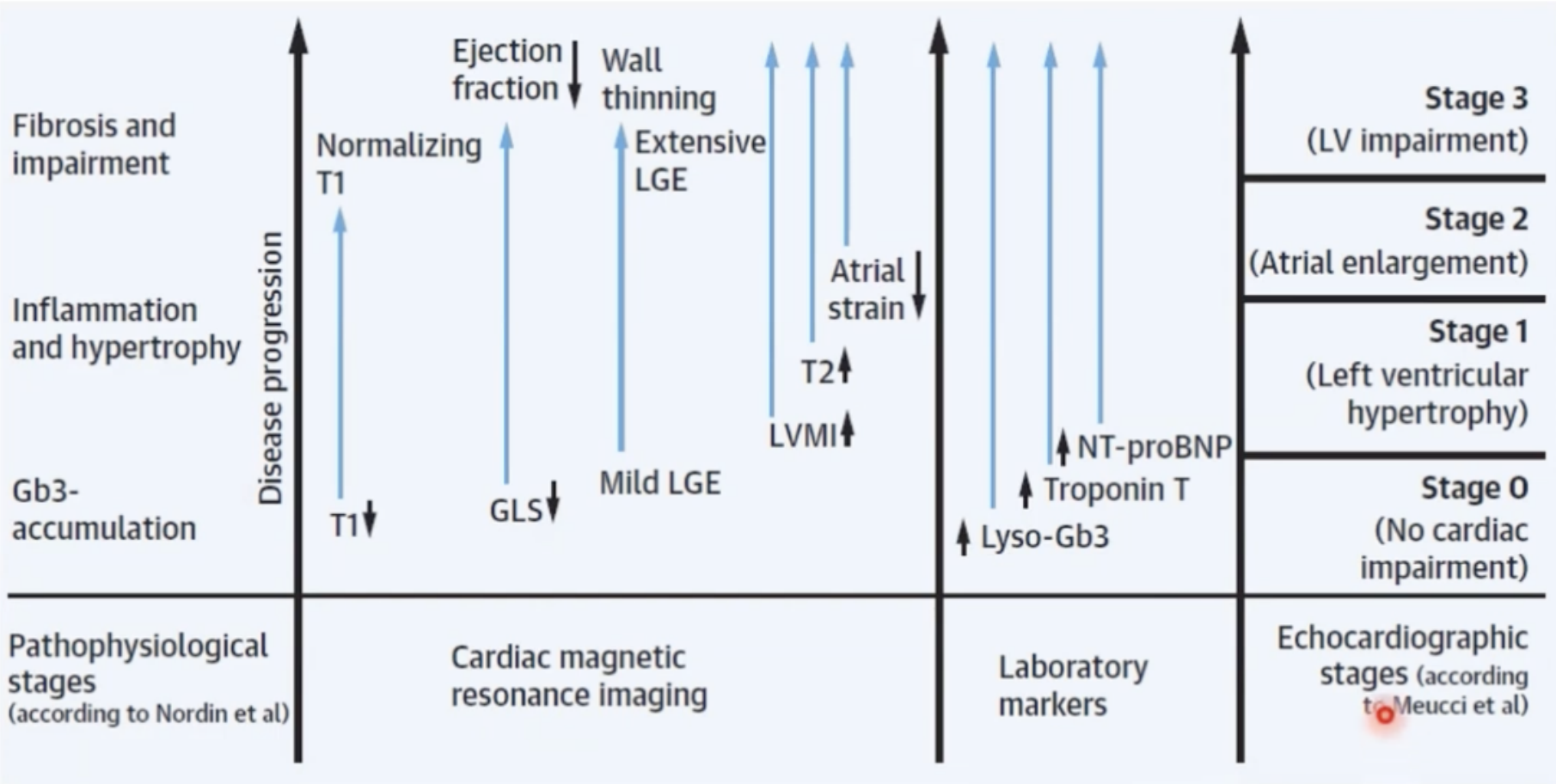
7. Comment dépister et confirmer la maladie de Fabry ?

JACC JOURNALS

Staging of Fabry Cardiomyopathy by Echocardiography

Back to the Roots?*

FIGURE 1 Pathophysiology, Laboratory, and Imaging Markers in Fabry Cardiomyopathy



Sunder-Plassmann G , Gatterer C, MD JACC 2

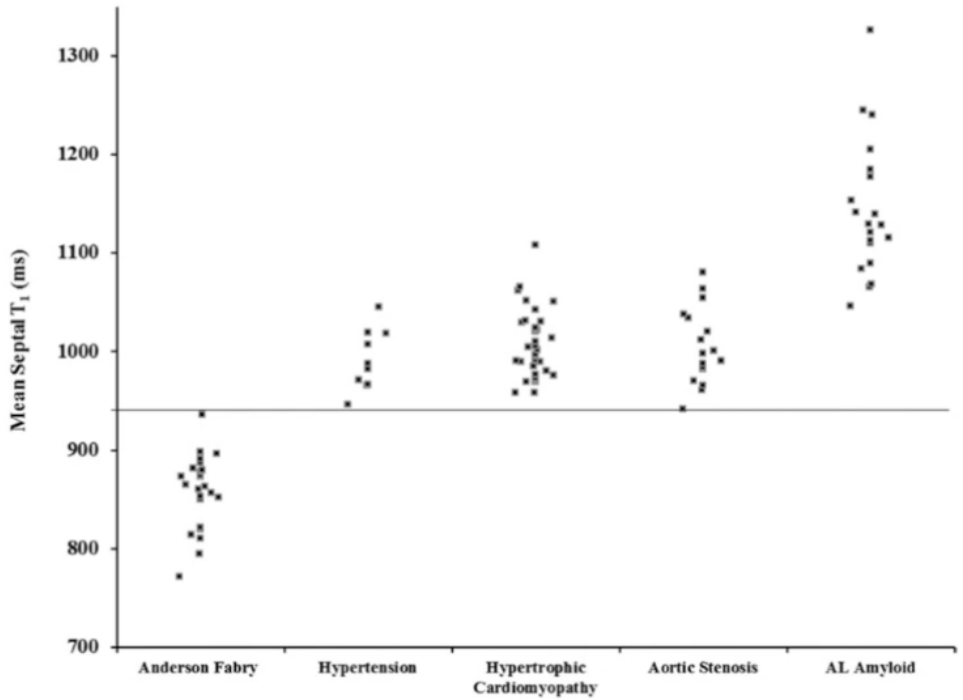
- Although historically considered rare, with an incidence of 1:40,000 to 1:117,000, neonatal screening programs have revealed a much higher prevalence, especially of late-onset variants with cardiac or renal involvement.
- Some studies suggest a frequency as high as 1 in 3100 live births and 1:8882 in Italian reports [6,7,8,9]. `

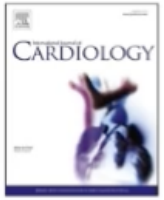
- This discrepancy highlights both the clinical and genetic heterogeneity of AFD, and the need for careful classification of *GLA*-variants [10,11], especially

IRM cardiaque essentielle dans le Fabry

- T1 mapping abaissé ou T1 pseudo normal
- T2 marqueur d'inflammation +/- pronostic
- +/- prise de contraste au gadolinium (inféro latéral)

médipôle





Sudden cardiac death risk prediction in Fabry disease: How many strings do we have on our bow?

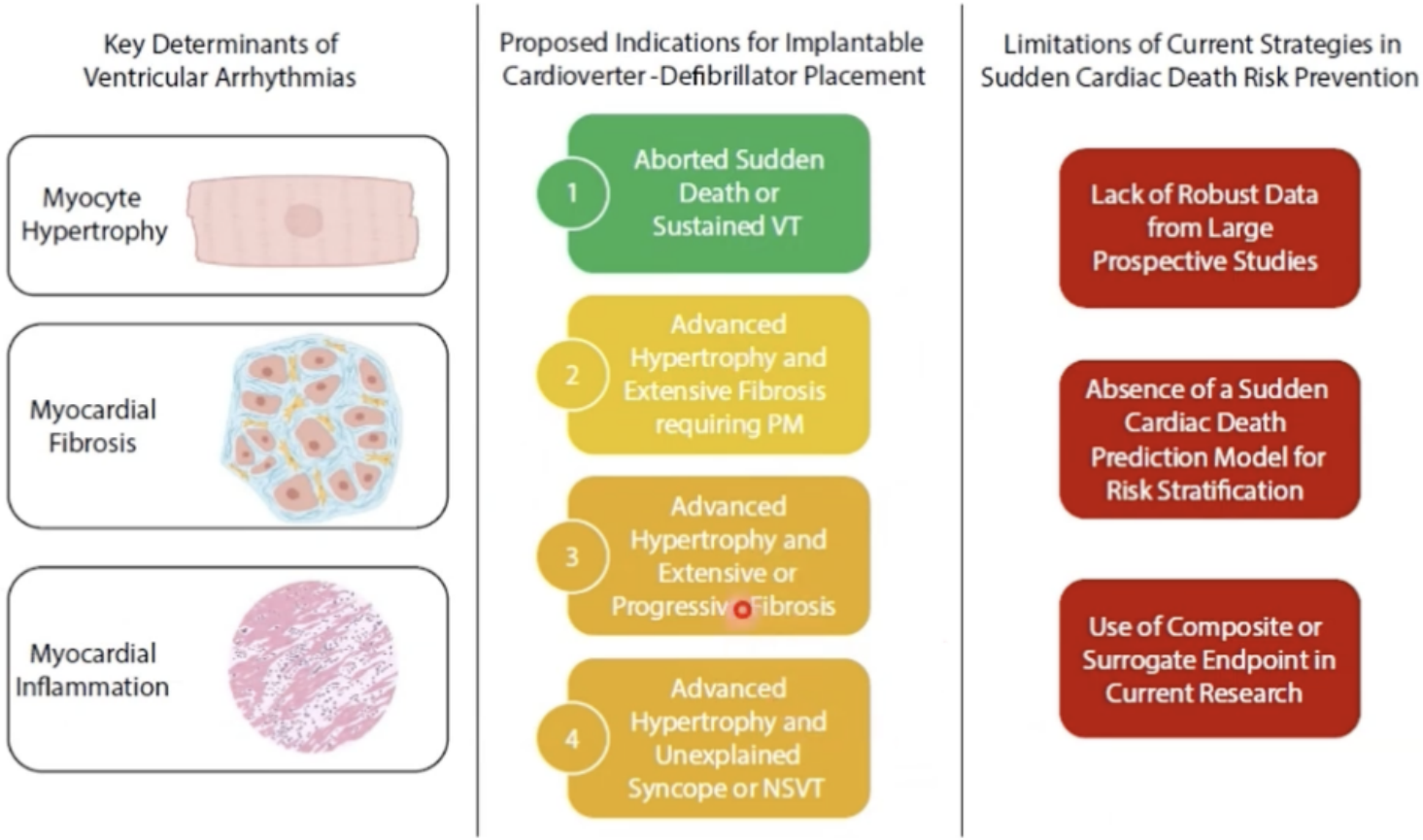


Fig. 1. Sudden cardiac death in Fabry disease: key determinants of ventricular arrhythmias, proposed indications for implantable cardioverter-defibrillator placement, and limitations of current strategies for sudden cardiac death risk prevention.