Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

EVENTO FORMATIVO INTERREGIONALE SIIA
PIEMONTE | LIGURIA | VALLE D'AOSTA
Torino, 12 ottobre 2024

Update 2

Quando sospettare la malattia di Fabry nell'iperteso adulto

Presenta: *Franco Rabbia – Torino*

Federico Pieruzzi MD, PhD

School of Medicine and Surgery, University of Milano-Bicocca

Clinical Nephrology, Fondazione IRCCS San Gerardo dei Tintori

Monza, Italy

Quocumque modo faciemus
Fondazione IRCCS San Gerardo dei Tintori

Sistema Socio Sanitario
Regione Lombardia

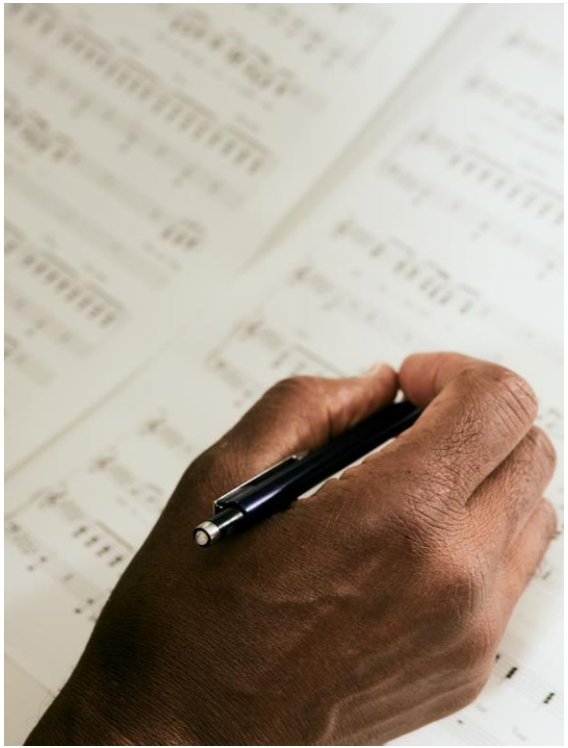
Università degli Studi di Milano Bicocca

Dichiarazione Autocertificazione Docente /Relatore
ASSENZA CONFLITTO D'INTERESSE

- Il Sottoscritto **Federico Pieruzzi** in qualità di relatore ai sensi *ai sensi dell'art. 76, comma 4 dell'Accordo Stato- Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM,*

dichiara,

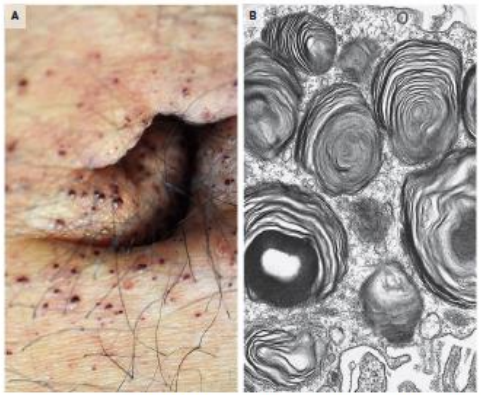
- che negli ultimi due anni ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
- Sanofi
- Takeda
- Chiesi
- Amicus



IMAGES IN CLINICAL MEDICINE

Stephanie V. Sherman, M.D., *Editor*

Fabry's Disease



Stephen Soloway, M.D.
Denise Lister, C.M.A.

Arthritis and Rheumatology Associates of South Jersey
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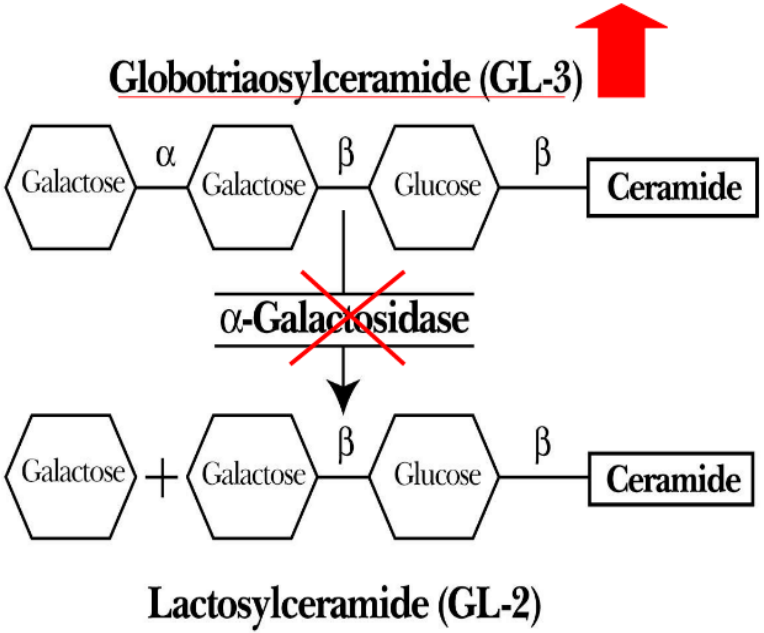
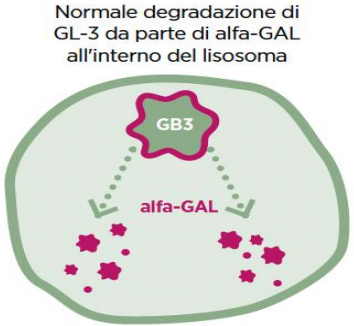
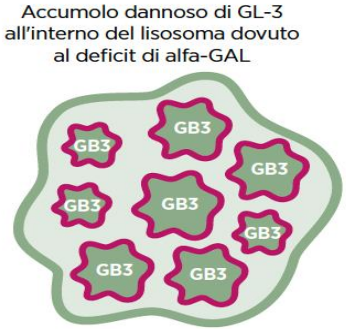
A 44-YEAR-OLD MAN PRESENTED TO THE RHEUMATOLOGY CLINIC WITH A 5-year history of heat intolerance and burning pain in his hands and feet. He also had exertional dyspnea, decreased perspiration, sinus tachycardia, and proteinuria of unclear cause. On physical examination, there were periumbilical vascular skin lesions that had been present for the previous 20 years (Panel A), a finding consistent with angiokeratomas. A sample from a 24-hour urine collection showed nonnephrotic proteinuria. Light microscopy of a sample of kidney tissue was notable for focally swollen podocytes with vacuolated cytoplasm. Electron microscopy showed lamellated deposits typical of globotriaosylceramide in podocytes, a finding known as zebra bodies that is characteristic of Fabry's disease (Panel B). A leukocyte assay showed that α-galactosidase A activity was less than 1.0 nmol per hour per milligram of protein (reference range, 45 to 85). Genetic testing identified a variant in *GLA*. A diagnosis of Fabry's disease was made. Fabry's disease is an X-linked lysosomal storage disease characterized by a deficiency in α-galactosidase A, a lysosomal hydrolase enzyme. The resulting accumulation of glycosphingolipids within cells leads to various symptoms, including neuropathy, autonomic dysfunction, hypohidrosis, skin lesions, and proteinuria (as seen in this patient). Genetic testing of the patient's family identified the *GLA* variant in his mother and brother. Treatment with enzyme-replacement therapy was started, and referral was made to neurology, nephrology, and cardiology specialists for cardiac evaluation and long-term management of the condition.

DOI: 10.1056/NEJMicm2402990

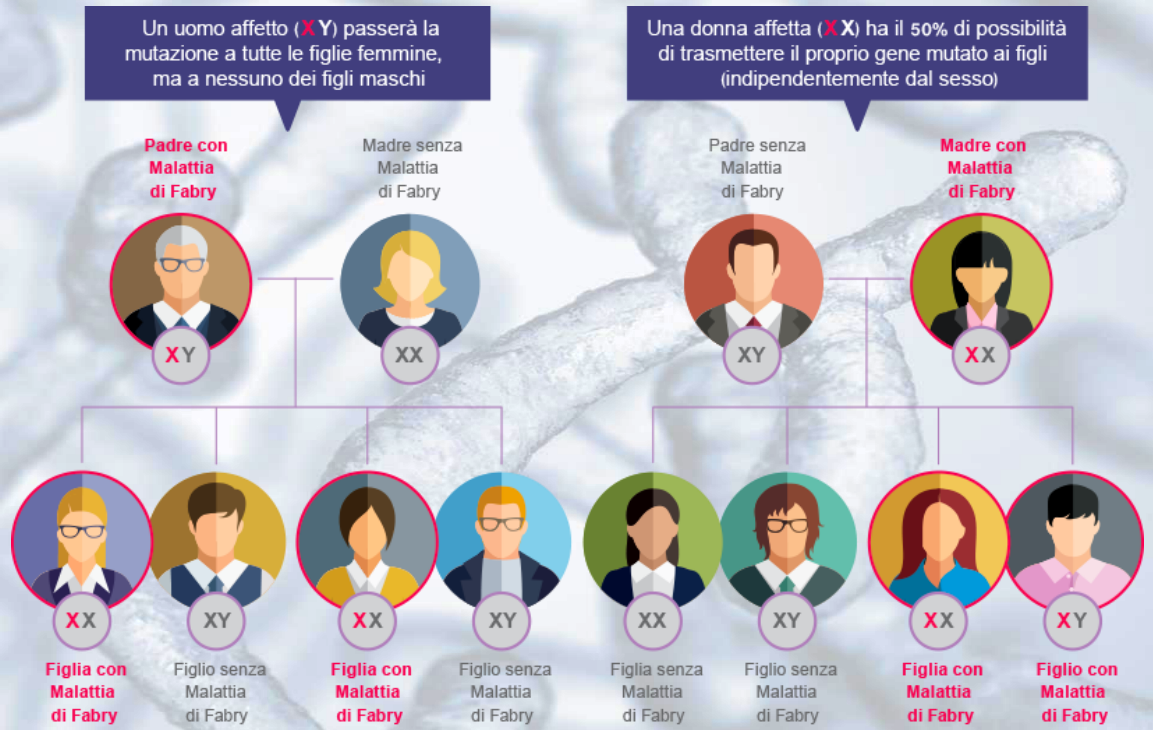
MALATTIA METABOLICA DA ACCUMULO LISOSOMIALE
DEFICIT ENZIMATICO DI ALFA GALATTOSIDASI-A



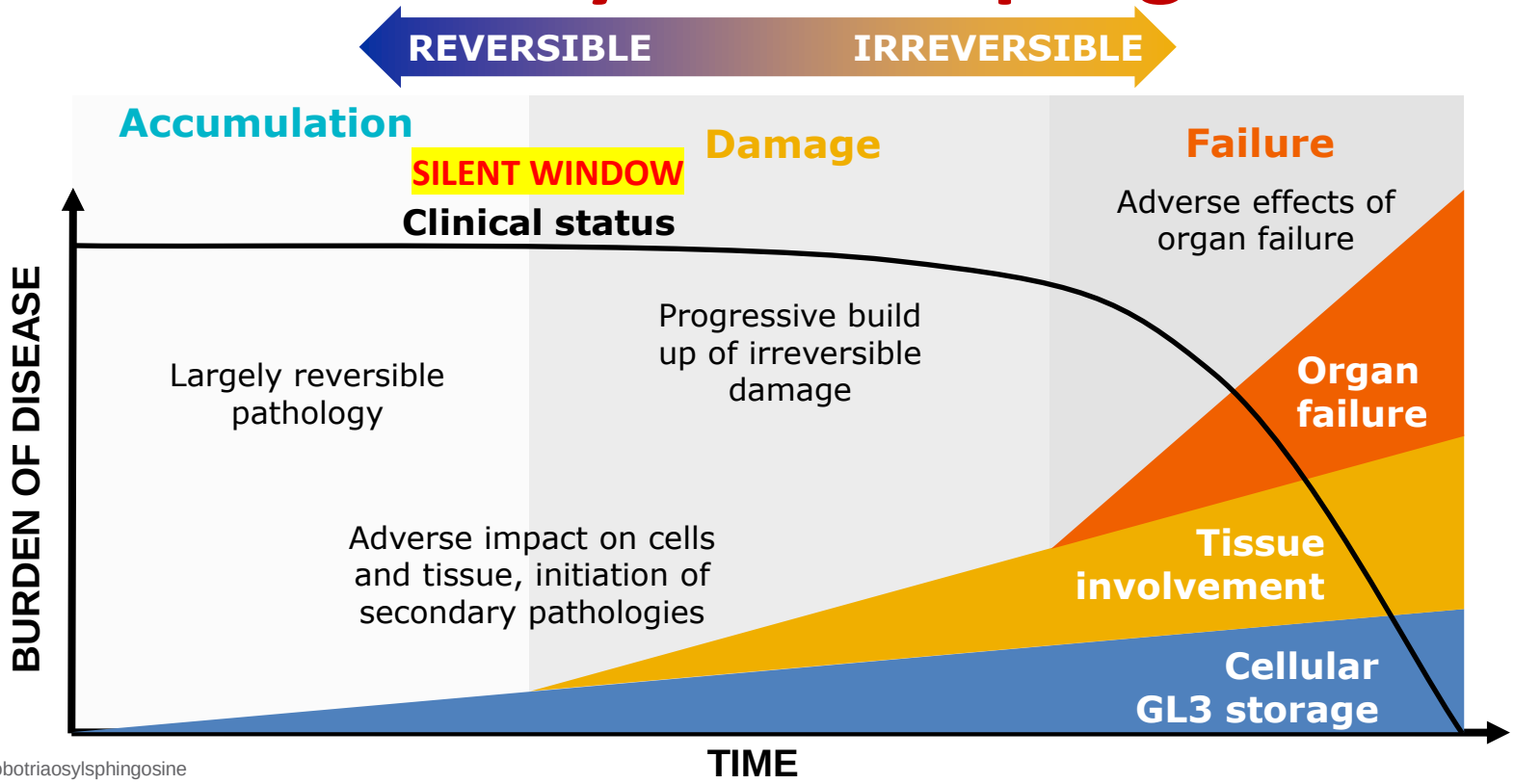




X-LINKED DISEASE

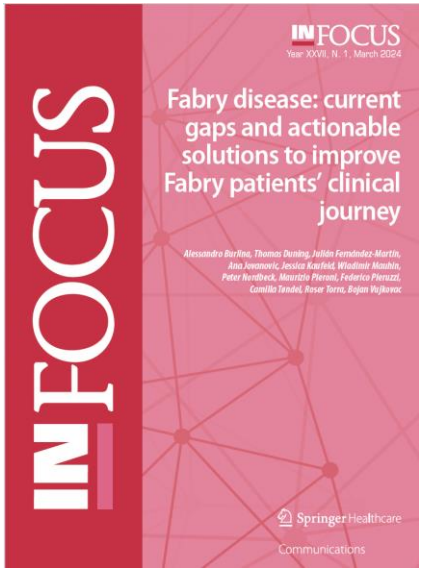


Fabry disease progression



GL3, globotriaosylsphingosine

Eng CM, et al. *J Inherit Metab Dis*. 2007;30:184–92. ©2007 SSIEM & Springer, with permission



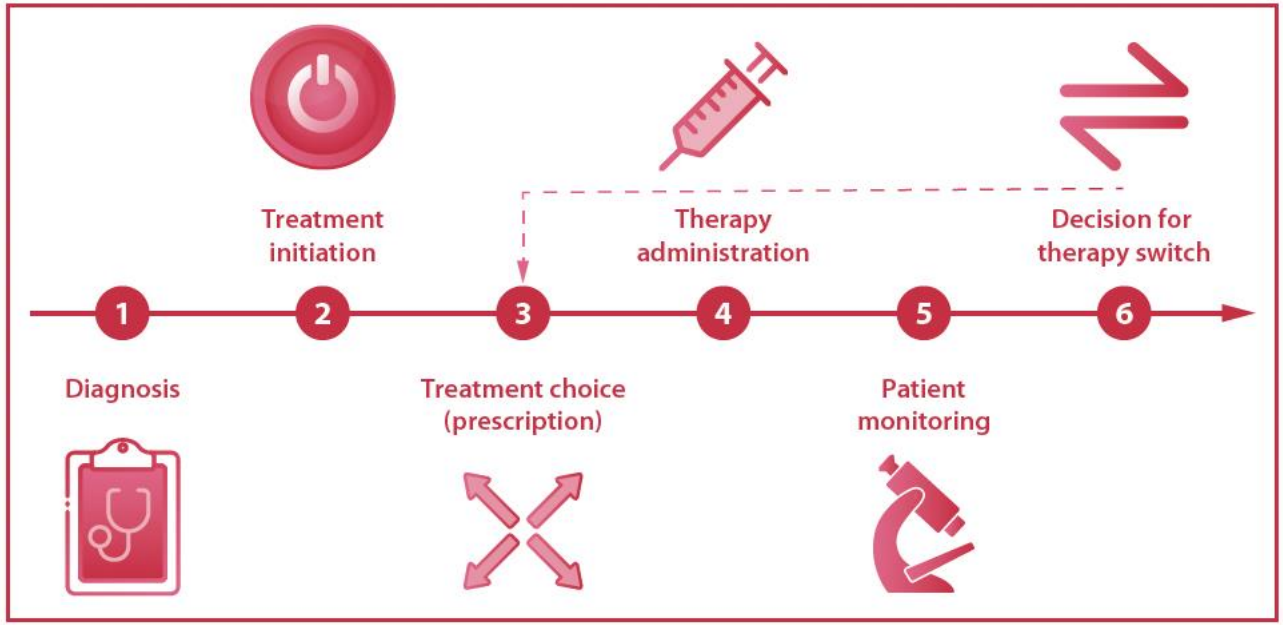
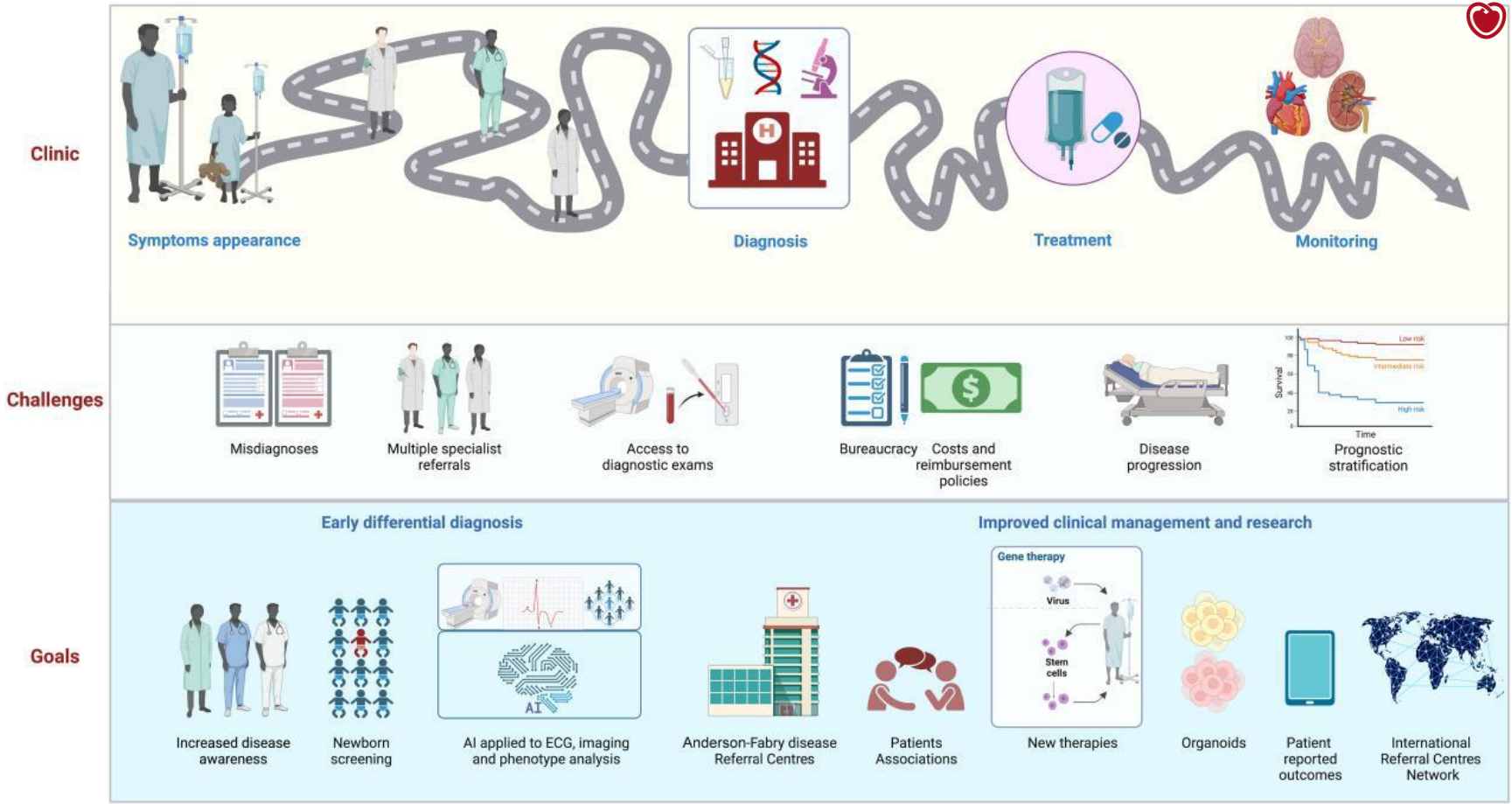
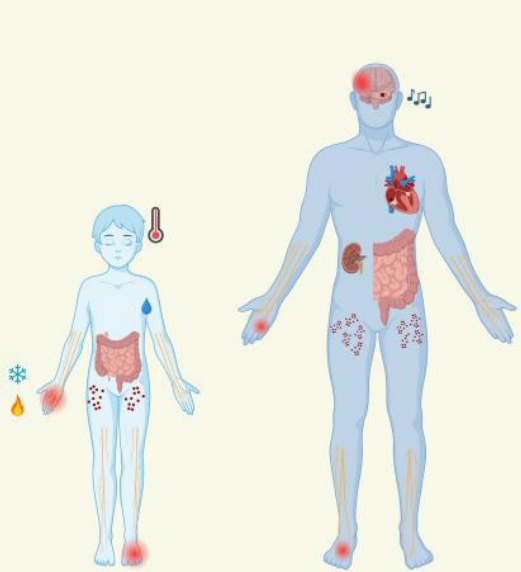


Figure 1. The six main steps in the specialists' journey in FD (Fabry Disease)

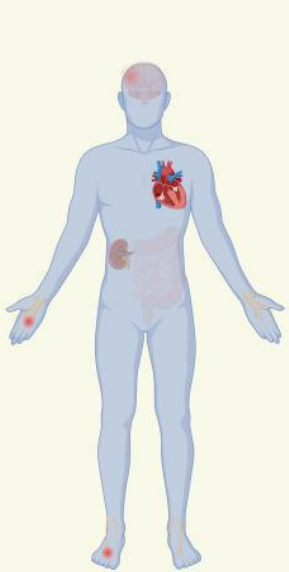


Eur Heart J, ehae148, https://doi.org/10.1093/eurheartj/ehae148



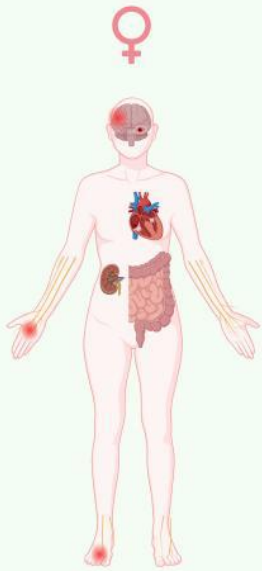
Classic phenotype

- Absent-very low (<5% of normal) alpha-Gal A activity
- High LysoGb3 plasma levels
- Childhood onset with GI symptoms, neuropathic pain, fever, hypohidrosis, angiokeratomas, hearing loss, corneal opacities (cornea verticillata)
- Development of multi-organ (heart, kidneys, CNS) involvement during adolescence and early adulthood



Non-Classic phenotype

- Low (but >5% of normal) alpha-Gal A activity
- Moderately increased LysoGb3 plasma levels
- 3rd-4th decade onset
- Main cardiac phenotype
- Mild involvement of other tissues possible
  - Proteinuria and eGFR reduction
  - GI symptoms
  - Neuropathic pain



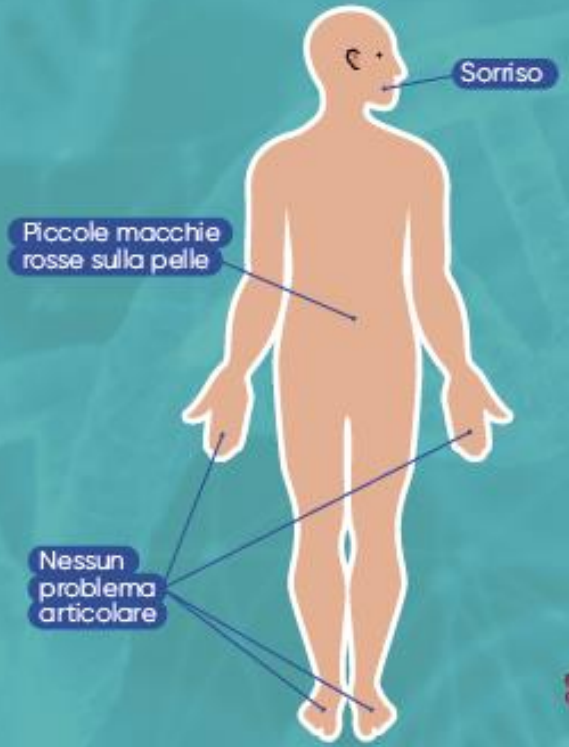
Female heterozygotes

- Variable (low to normal) alpha-Gal A activity
- Normal-moderately increased LysoGb3 plasma levels
- Usually 3rd-4th decade onset
- Phenotype ranging from asymptomatic to severe as in affected male relatives due to random X-inactivation, DNA methylation, other epigenetic factors
- Prevalent cardiac phenotype with wide range of other organs involvement

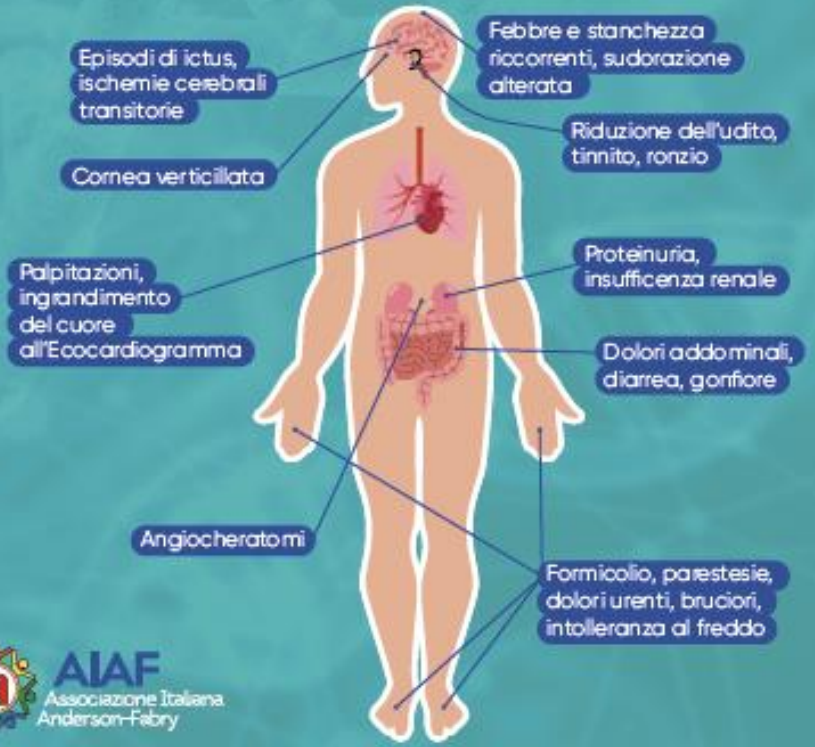
Eur Heart J, ehae148, https://doi.org/10.1093/eurheartj/ehae148

I SINTOMI DELLA MALATTIA DI ANDERSON-FABRY

COSA SI VEDE



COME SI MANIFESTA

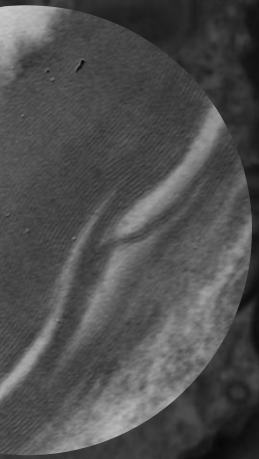
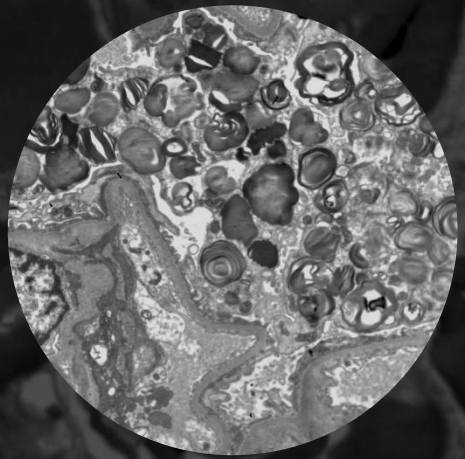
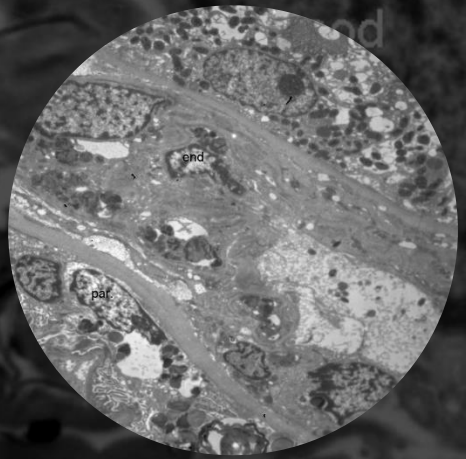


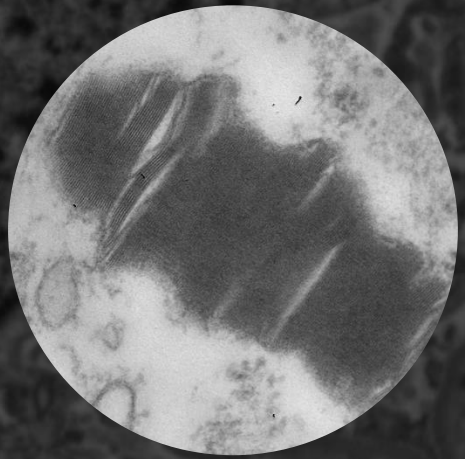
AIAF
Associazione Italiana Anderson-Fabry

"How is Fabry kidney Disease diagnosed?"

CLINICAL SYMPTOMS/SIGNS
RELATED TO FABRY DISEASE

SCREENINGS



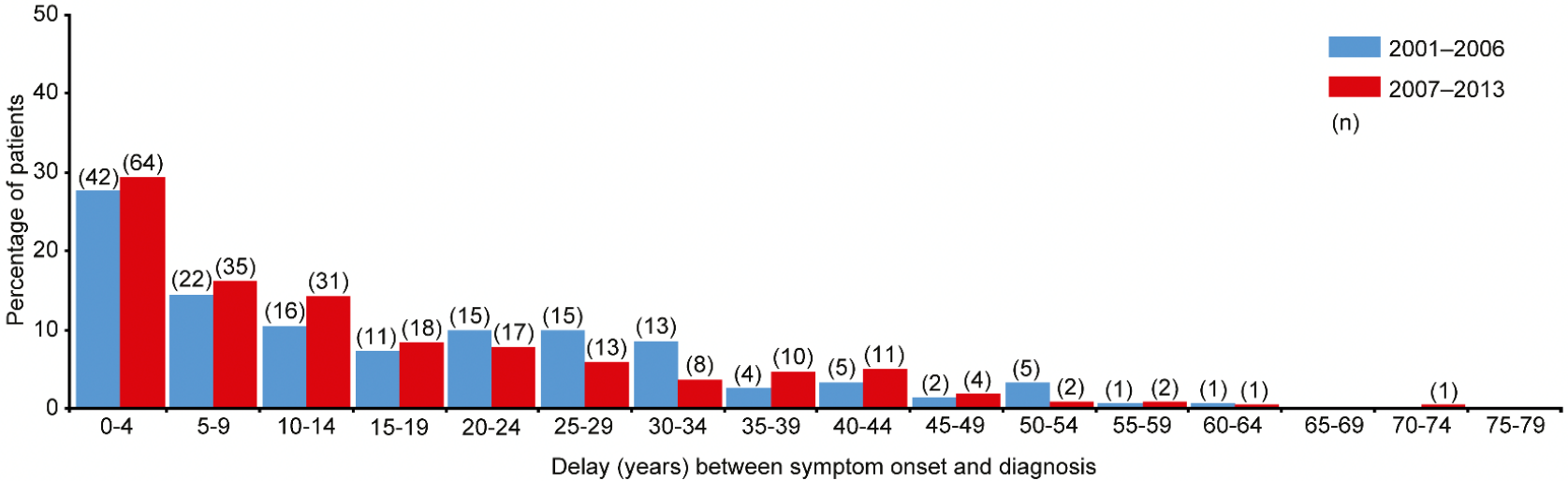
IDENTIFICAZIONE DI ACCUMULO LISOSOMIALE DI SFIGOLIPIDI

“..il paziente che sto visitando potrebbe avere la malattia di Fabry…?"

Type of specialist FD first suspected by	All patients Year of diagnosis		
	Before 2006 *n* (%)	2007–2013 *n* (%)	Overall* *n* (%)
Overall	270	202	472
Nephrologist	59 (21.9)	26 (12.9)	85 (18.0)
Cardiologist	32 (11.9)	43 (21.3)	75 (15.9)
Ophthalmologist	44 (16.3)	19 (9.4)	63 (13.4)
Geneticist	8 (3.0)	45 (22.3)	53 (11.2)
Dermatologist	39 (14.4)	6 (3.0)	45 (9.5)
Neurologist	20 (7.4)	15 (7.4)	35 (7.4)
Other	22 (8.2)	9 (4.5)	31 (6.6)
General practitioner	16 (5.9)	13 (6.4)	29 (6.1)
Pediatrician	22 (8.2)	6 (3.0)	28 (5.9)
Internist	5 (1.9)	16 (7.9)	21 (4.5)
Rheumatologist	2 (0.7)	3 (1.5)	5 (1.1)
Gastroenterologist	1 (0.4)	1 (0.5)	2 (0.4)

Resin et al. Int J Clin Pract 2017

IL RITARDO DIAGNOSTICO E TERAPEUTICO NEI PAZIENTI CON MALATTIA DI FABRY

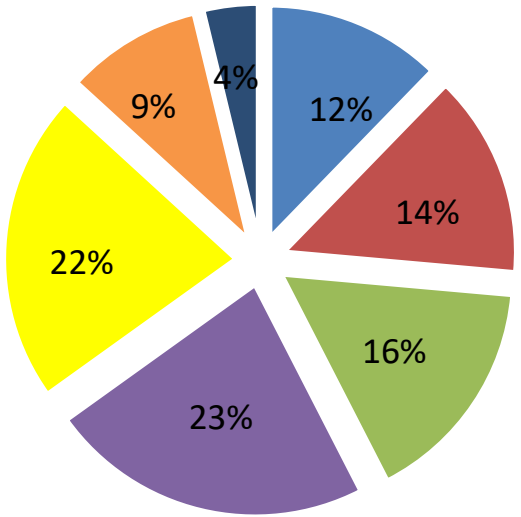


Resin et al. Int J Clin Pract 2017 Jan;71(1). doi: 10.1111/ijcp.12914

Età alla diagnosi della malattia di Fabry *(in classi)*

- ✓ Il **25%** dei pazienti attende 15-30 anni per ottenere la diagnosi
- ✓ il **40%** dei pazienti riceve inizialmente una diagnosi sbagliata

N =106



Tra 0 e 9 anni
Tra 10 e 19 anni
Tra 20 e 29 anni
Tra 30 e 39 anni
Tra 40 e 49 anni
Tra 50 e 59 anni
Tra 60 e 69 anni

DIAGNOSI IN ETA' ADULTA

- IRC senza diagnosi, anche allo stadio terminale, proteinuria dndd;
- Cardiomiopatia inspiegabile, specialmente ipertrofia del ventricolo sinistro;
- Aritmie, anomalie valvolari, scompenso, cardiopatia ischemica;
- Ictus, TIA;
- Astenia, intolleranza al calore e al freddo;
- Perdita di udito;
- Caratteristica opacità corneale; angiocheratomi cutanei

Desnick et al. *Ann Intern Med.* 2003; 138: 338-346

Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:8-17
https://doi.org/10.5049/EBP.2023.21.1.8

Management of Hypertension in Fabry Disease

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Fabry disease (FD), a rare X-linked lysosomal storage disorder that depletes alpha-galactosidase A (α-GalA), is caused by mutations in the GLA gene. Diminished α-GalA enzyme activity results in the accumulation of Gb3 and lyso-Gb3. The pathophysiology of hypertension in FD is complex and unclear. The storage of Gb3 in arterial endothelial cells and smooth muscle cells is known to produce vascular injury by increasing oxidative stress and inflammatory cytokines as a primary pathophysiological mechanism. In addition, Fabry nephropathy developed, resulting in a decrease in kidney function and contributing to hypertension.

The prevalence of hypertension in patients with FD was between 28.4% and 56%, whereas hypertension in patients with chronic kidney disease ranged between 33% and 79%. A study using 24-hour ambulatory blood pressure monitoring (ABPM) to measure blood pressure (BP) indicated a high prevalence of uncontrolled hypertension in FD. Thus, 24-hour ABPM ought to be considered for FD hypertension assessments.

Appropriate treatment of hypertension is believed to reduce mortality in patients with FD caused by kidney disease, cardiovascular disease, and cerebrovascular disease because hypertension significantly impacts organ damage. Up to 70% of FD patients have been reported to have kidney involvement, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prescribed for proteinuria are recommended as first-line therapy with antihypertensive drugs. In conclusion, hypertension should be controlled appropriately, given the different morbidity and mortality caused by significant organ involvement in FD patients.

Key Words: Fabry disease, Hypertension, Enzyme replacement therapy, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers

Table 1. Prevalence of hypertension in Fabry patients

Author, year	Region	N	Male (%)	Age (year)	Diagnosis of HTN	eGFR	eGFR<60, n (%)	HTN, n (%)	HTN in CKD, n (%)	Kidney involvement, %	CNS involvement, %	Cardiac involvement, %	ERT/Chaperon therapy, %	ACEI/ARBs, %
Dincer, 2022	Turkey	30	53.3	38.1±13.4		91.7±40.8	9 (30%)	12 (40%)	5 (55.6%)	71	35.4	32.3	96.8	35.5
Ferrari, 2021	Argentina	93	44.0	32±16.6	History of HTN	-	38 (41%)	26 (28%)	-	41	-	47	100	-
Rossi, 2021	Europe	32	25.0	50.3±12.4	SBP ≥130 or DBP≥80 mmHg vis ABPM	-	6 (19%)	10 (31%)	2 (33%)	32.3	65.6	90.6	59.4	21.9
Lenders, 2020	Germany	59	53.0	49±13	History of HTN	-	1 (5%)	33 (63.5%)	-	70.8	-	68	57.6	72.1
Wang, 2020	Taiwan	22	72.7	47 [32.8–56.3]	History of HTN	83.6 (59.8–112.2)	2 (9.1%)	9 (40.9%)	-	-	-	24.7	-	-
Lidove, 2016 (FOS)	Global	2,044	56.0	≥18	History of HTN	-	-	599 (29%)	-	48.9	19.7	66.3	67.2	35.6
Schiffmann, 2009	Global	395	61.0	41.0 (5.0–77.1)	History of HTN	-	77 (19%)	221 (56%)	61 (79%)	26.3	17	58.7	100	16.7
Ortiz, 2008	Global	1,262	46.0	-	SBP ≥130 or DBP≥80 mmHg vis office BP	81/82 for male and female	255 (20%)	554 (44%)	-	-	-	-	-	-
Kleinert, 2006 (FOS)	Global	391	54.0	40 (24, 58)	SBP ≥130 or DBP≥80 mmHg vis office BP	79 (53, 109)	104 (27%)	205 (52.4%)	70 (67%)	-	-	-	-	24.9
Branton, 2002	USA	105	100.0	38±11	History of HTN	-	-	31 (30%)	-	74.3	-	-	-	19

ABPM, Ambulatory blood pressure monitoring; ACEI, Angiotensin-Converting Enzyme Inhibitors; ARBs, Angiotensin II receptor blockers; FOS, Fabry Outcome Survey registry; HTN, hypertension; CKD, chronic kidney disease

High Blood Pressure & Cardiovascular Prevention (2021) 28:309–319
https://doi.org/10.1007/s40292-021-00450-0

ORIGINAL ARTICLE

Elevated Ambulatory Blood Pressure Measurements are Associated with a Progressive Form of Fabry Disease

Federica Rossi[1] · Einar Svarstad[2] · Hassan Elsaid[3] · Agnese Binaggia[4] · Letizia Roggero[1] · Sara Auricchio[4] · Hans-Peter Marti[2,3] · Federico Pieruzzi[1,4]

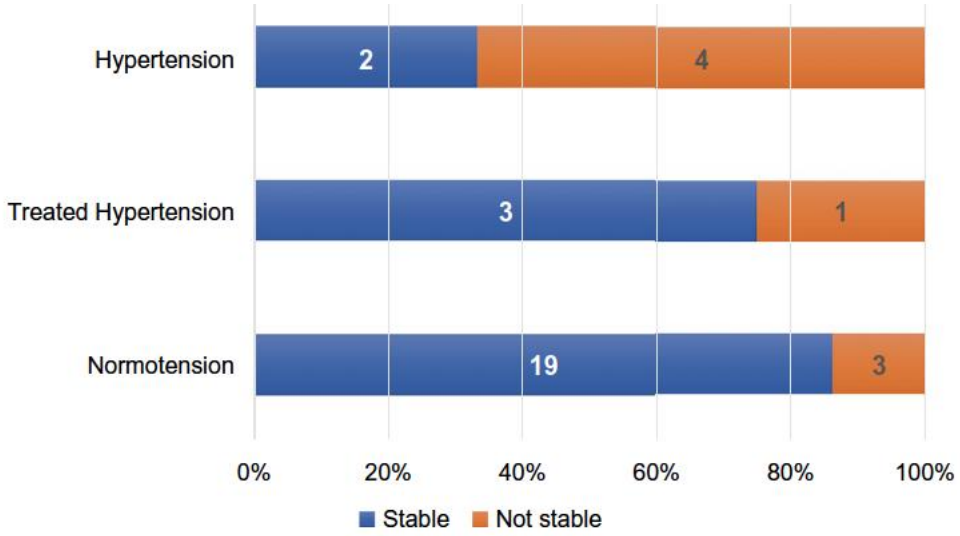
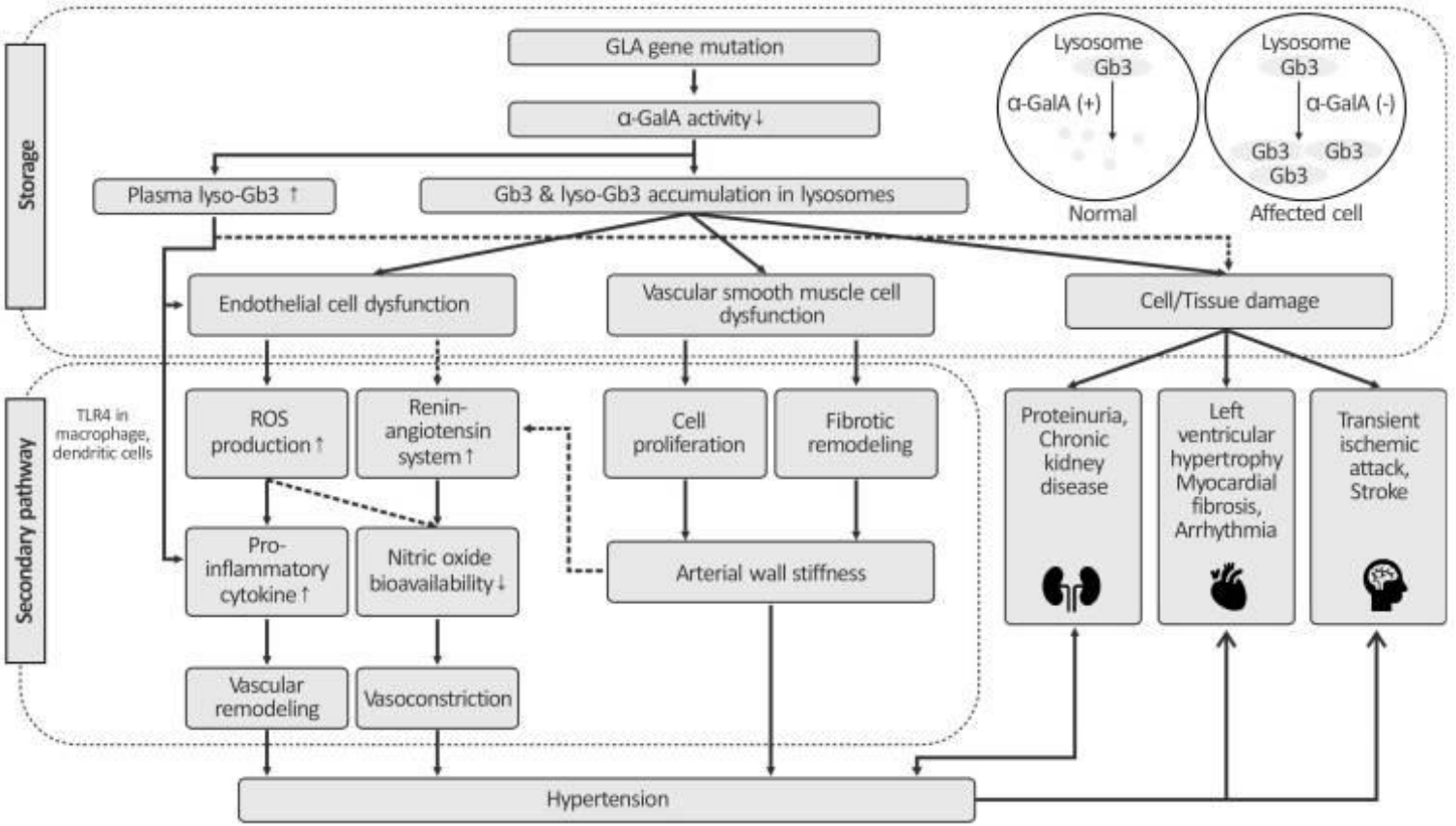


Fig. 1 Fabry Stabilization Index (FASTEX) score

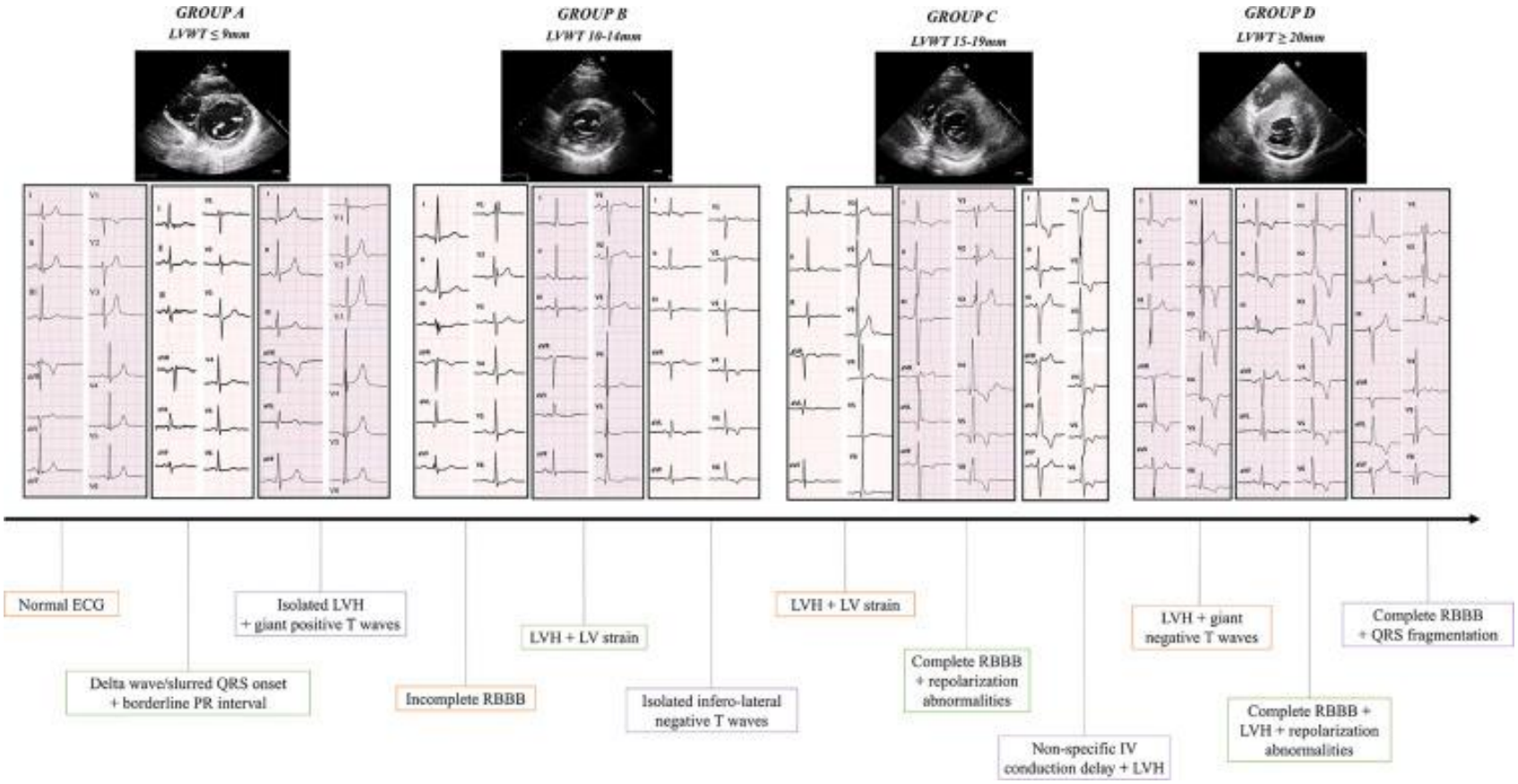
The proposed pathophysiology of hypertension in Fabry disease

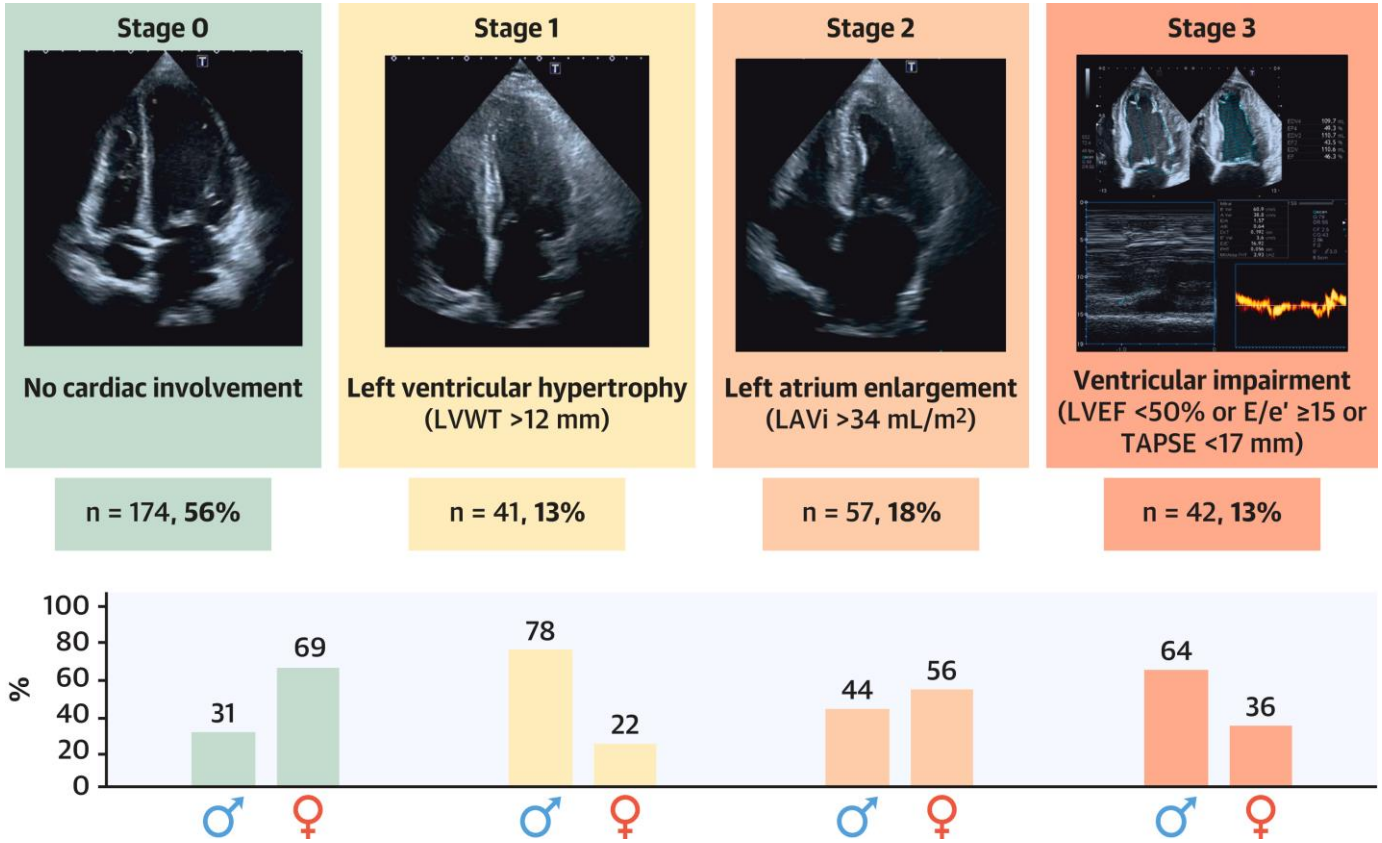


Electrocardiogram analysis in Anderson-Fabry disease: a valuable tool for progressive phenotypic expression tracking

V. Parisi[1,2†], R. Baldassarre[1,2†], V. Ferrara[3], R. Ditaranto[1,2], F. Barlocco[3], R. Lillo[3], F. Re[3], G. Marchi[3], C. Chiti[3], F. Di Nicola[1,2], C. Catalano[1,2], L. Barile[1,2], M. A. Schiavo[1,2], A. Ponziani[1,2], G. Saturi[1,2], A. G. Caponetti[1,2], A. Berardini[1,2], M. Graziosi[1,2], F. Pasquale[1,2], I. Salamon[3], M. Ferracin[3], E. Nardi[3], I. Capelli[1,2,3], D. Girelli[3], J. R. Gimeno Blanes[4], M. Biffi[1,2], N. Galiè[1,2,3], I. Olivotto[1,2], F. Graziani[1,2] and E. Biagini[1,2*]

Front Cardiovasc Med. 2023; 10: 1184361. Published online 2023 Jun 21. doi: 10.3389/fcvm.2023.1184361


GROUP A
LVWT ≤ 9mm
GROUP B
LVWT 10-14mm
GROUP C
LVWT 15-19mm
GROUP D
LVWT ≥ 20mm
Normal ECG
Delta wave/slurred QRS onset + borderline PR interval
Isolated LVH + giant positive T waves
Incomplete RBBB
LVH + LV strain
Isolated infero-lateral negative T waves
LVH + LV strain
Complete RBBB + repolarization abnormalities
Non-specific IV conduction delay + LVH
LVH + giant negative T waves
Complete RBBB + LVH + repolarization abnormalities
Complete RBBB + QRS fragmentation



Meucci et al JACC VOL. 82, NO. 15, 2023

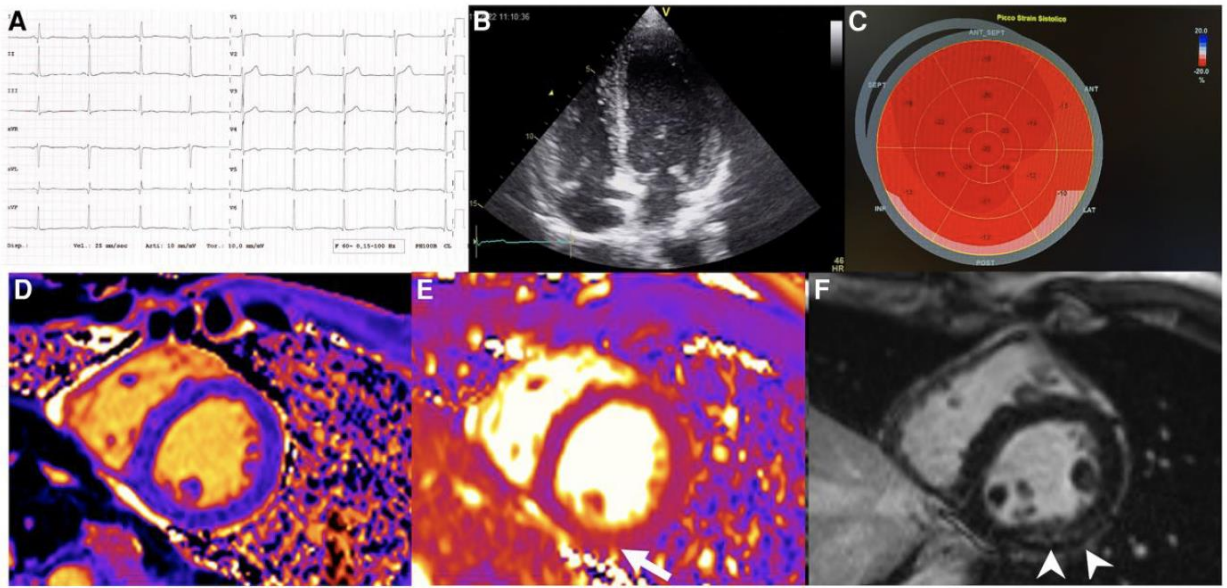
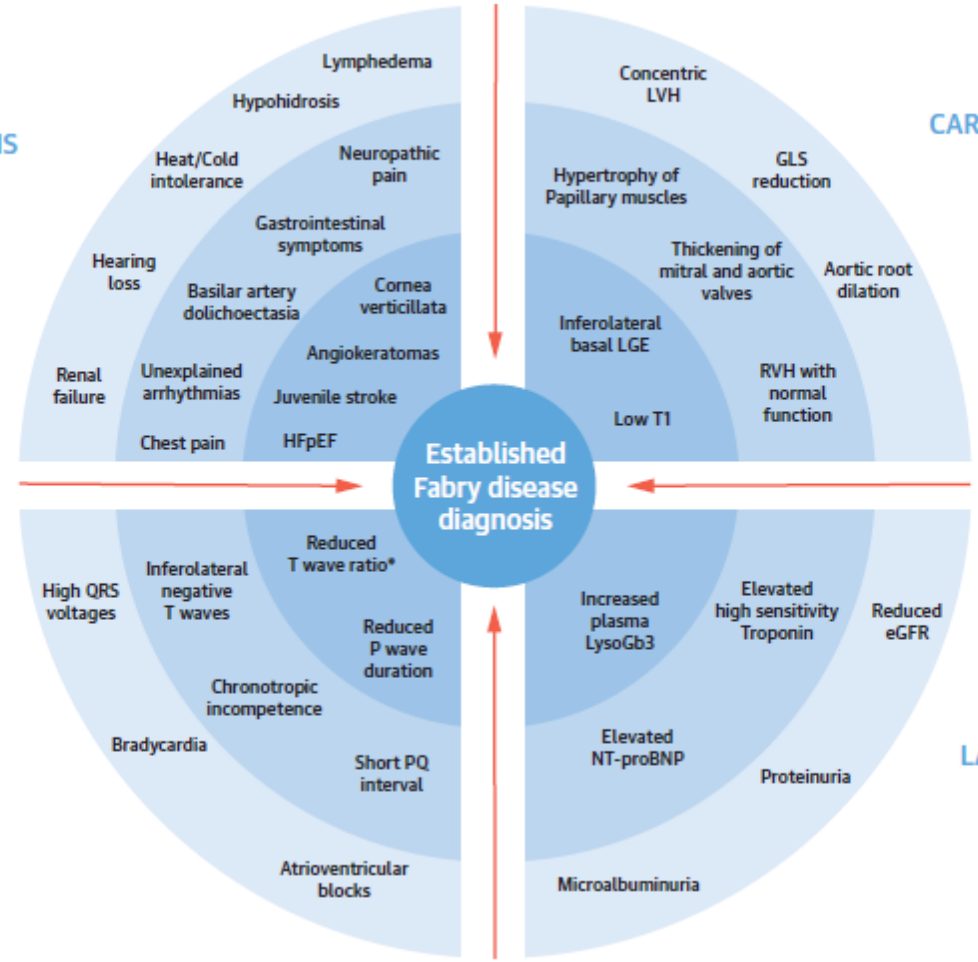
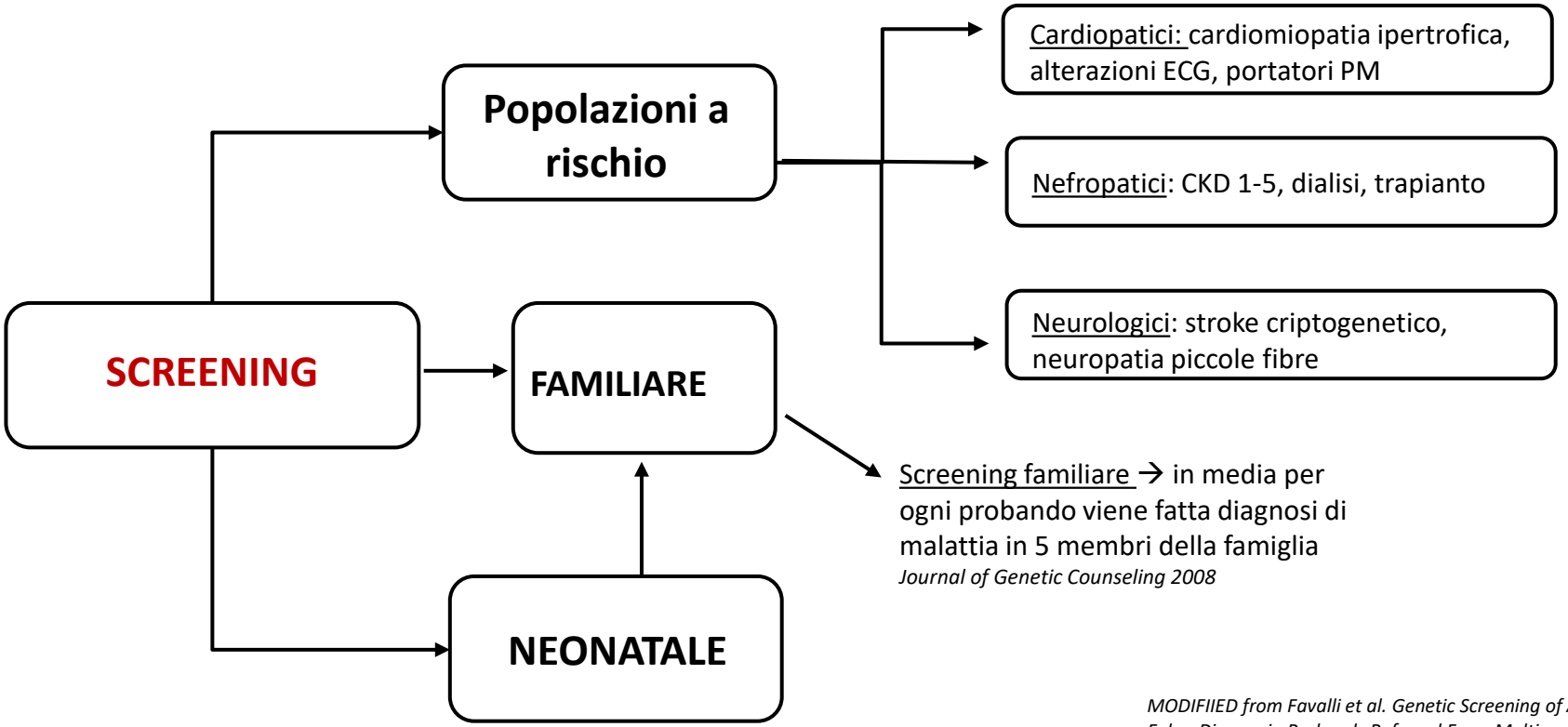


Figure 6 A representative case of a male patient with classic Anderson–Fabry disease and pre-left ventricular hypertrophy cardiac involvement. A 29-year-old male patient carrier of the variant c.859T>C associated with a classic phenotype. Electrocardiogram (*A*) shows sinus rhythm with no signs of left ventricular hypertrophy but repolarization abnormalities in lateral and inferior leads. Transthoracic echocardiogram in apical four-chamber view (*B*) shows normal wall thickness and volume of the left ventricle with initial reduction of longitudinal strain velocities in the inferolateral segments (*C*). Cardiac magnetic resonance shows (*D*) diffusely reduced native T_1 values (905 ± 18 ms, normal reference value 984 ± 18 ms). At T_2 mapping sequences (*E*), a very focal area of high T_2 values in the inferior wall (arrow) can be appreciated, corresponding in post-contrast sequences (*F*) to a thin midwall stria of late gadolinium enhancement (arrowheads)


CLINICAL MANIFESTATIONS
Lymphedema
Hypohidrosis
Heat/Cold intolerance
Neuropathic pain
Gastrointestinal symptoms
Hearing loss
Basilar artery dolichoectasia
Cornea verticillata
Angiokeratomas
Renal failure
Unexplained arrhythmias
Juvenile stroke
Chest pain
HFpEF
CARDIAC IMAGING
Concentric LVH
Hypertrophy of Papillary muscles
GLS reduction
Thickening of mitral and aortic valves
Aortic root dilation
Inferolateral basal LGE
RVH with normal function
Low T1
Established Fabry disease diagnosis
ECG
Reduced T wave ratio*
Inferolateral negative T waves
High QRS voltages
Reduced P wave duration
Chronotropic incompetence
Bradycardia
Short PQ interval
Atrioventricular blocks
LABORATORY FINDINGS
Increased plasma LysoGb3
Elevated high sensitivity Troponin
Reduced eGFR
Elevated NT-proBNP
Proteinuria
Microalbuminuria



MODIFIIED from Favalli et al. Genetic Screening of Anderson-Fabry Disease in Probands Referred From Multispecialty Clinics JACC VOL. 68, NO. 10, 2016: 1037–50

International Journal of Cardiology 167 (2013) 2555–2560

Contents lists available at ScienceDirect

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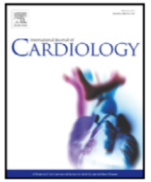
journal homepage: www.elsevier.com/locate/ijcard



Prevalence of Fabry disease in a predominantly hypertensive population with left ventricular hypertrophy☆,☆☆

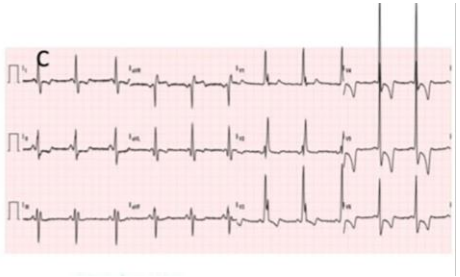
Wim Terryn [a,*], Gert Deschoenmakere [b], Jan De Keyser [c], Wouter Meersseman [d], Wim Van Biesen [e], Brigitte Wuyts [f], Dimitri Hemelsoet [g], Hilbert Pascale [h], Julie De Backer [i], An De Paepe [j], Bruce Poppe [j], Raymond Vanholder [a,e]

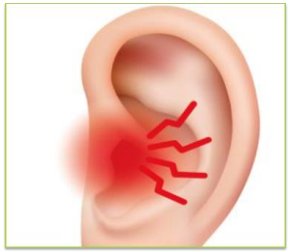
Aim: determine the prevalence of FD in an unselected population of everyday clinical practice presenting LVH, defined as a maximal end-diastolic septal or posterior wall thickness ≥13 mm, without exclusion of patients with arterial hypertension or valvular pathology, and using optimal screening methods.

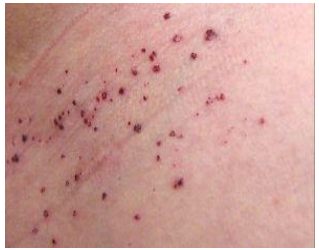
Results: 362 men and 178 women were screened. Six patients were diagnosed with a genetic sequence alteration of the GLA gene.

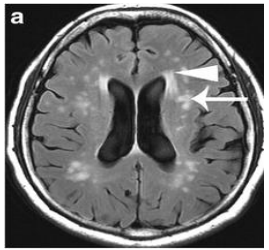
Conclusions: In a group of unselected patients with LVH, we found a prevalence of Fabry disease of 0.9%. AHT or type of hypertrophy should not be an exclusion criterion for screening for FD.

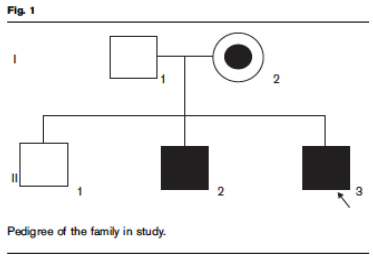
SOSPETTO DIAGNOSTICO

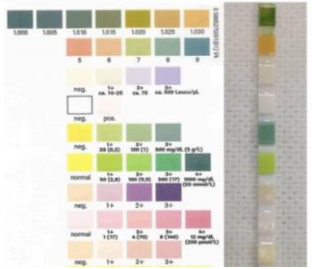


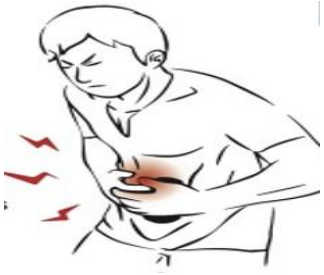


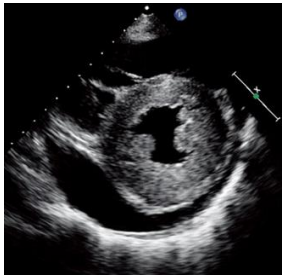


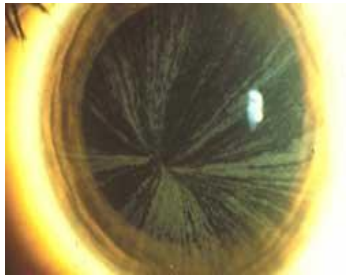










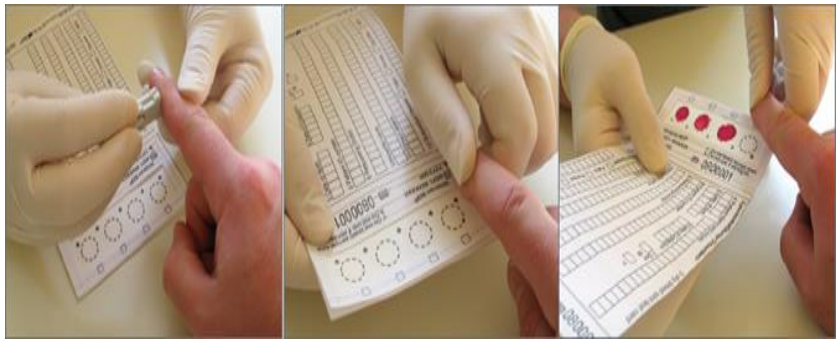


MINDSET METABOLICO
CLINICO- ANAMNESTICO

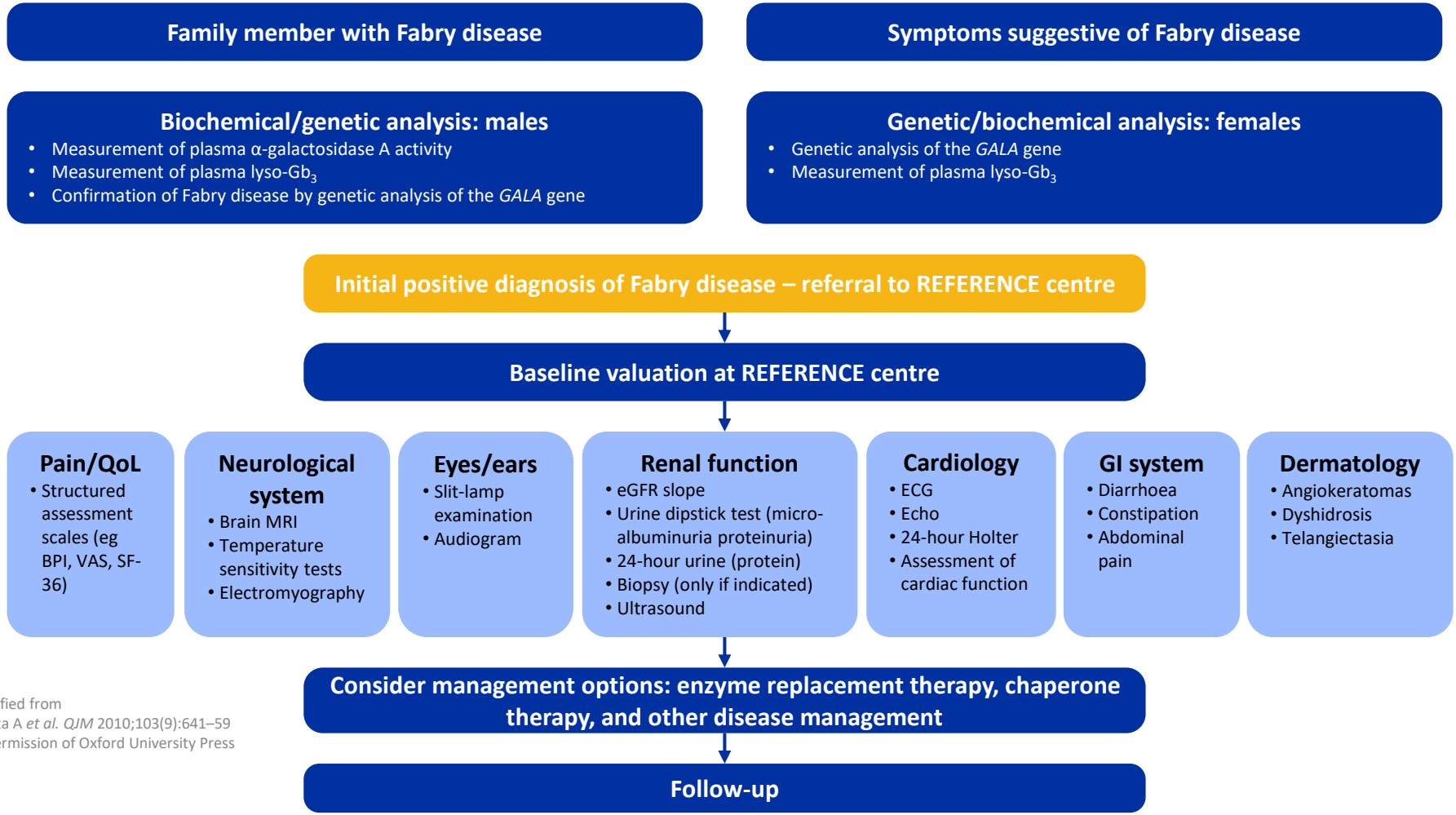
…dal SOSPETTO alla DIAGNOSI…

ATTIVITA’ ENZIMATICA - ANALISI MOLECOLARE - Lyso-Gb

A) Eseguire DBS



B) Contattare il centro di riferimento



Modified from
Mehta A *et al. QJM* 2010;103(9):641–59
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Unknown genotype-phenotype relationship

Received: 22 September 2021 | Revised: 13 December 2021 | Accepted: 16 December 2021
DOI: 10.1111/cge.14102

REVIEW

CLINICAL GENETICS WILEY

Challenging the traditional approach for interpreting genetic variants: Lessons from Fabry disease

Dominique P. Germain[1,2] | Thierry Levade[3,4] | Eric Hachulla[5] | Bertrand Knebelmann[6] | Didier Lacombe[7,8] | Vanessa Leguy Seguin[9] | Karine Nguyen[10] | Esther Noël[11] | Jean-Pierre Rabès[2,12]

TABLE 4 Practical recommendations for a more accurate diagnosis of Fabry disease

- Combine insights from disease specific databases and in vitro prediction tools with expert clinical opinion, defining the relative weight of each ACMG criterion.
- Consider the genetic variant as probably benign if its allele total or subpopulation frequency is:
  - Higher than the overall prevalence of FD (0.0125%),
  - Higher than the frequency of the most common pathogenic allele.
- Perform segregation analysis when additional information is required.
- Review the literature and databases periodically to check whether the variant has been reclassified.

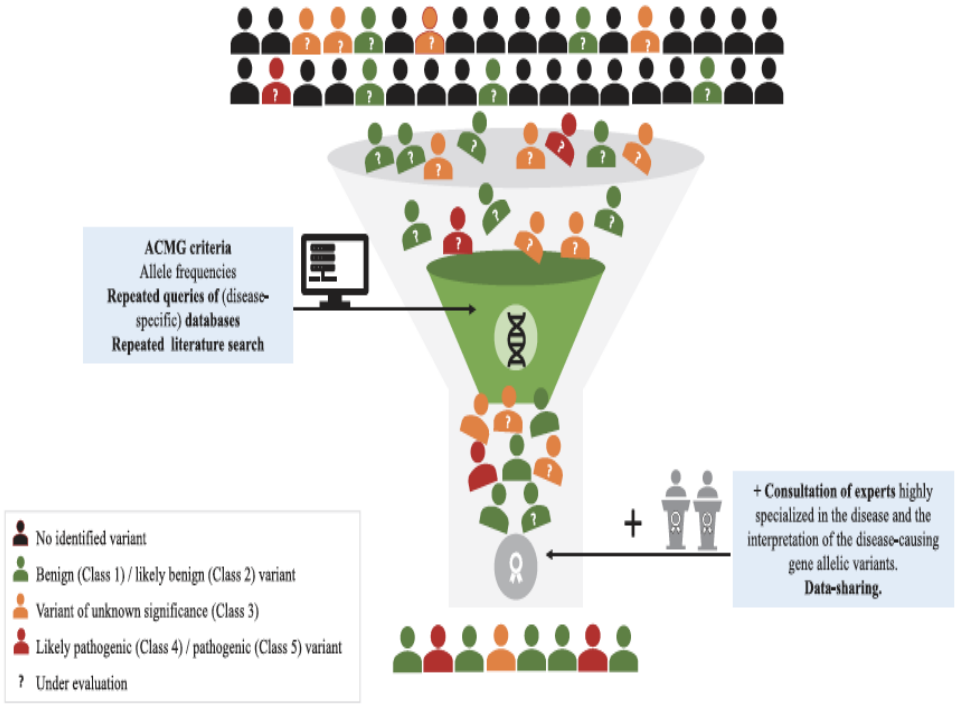


FIGURE 3 Interpreting pathogenicity of genetic variants when facing uncertainty: lessons from Fabry disease (FD) [Colour figure can be viewed at wileyonlinelibrary.com]

Clinical Genetics. 2021;100:239–247.

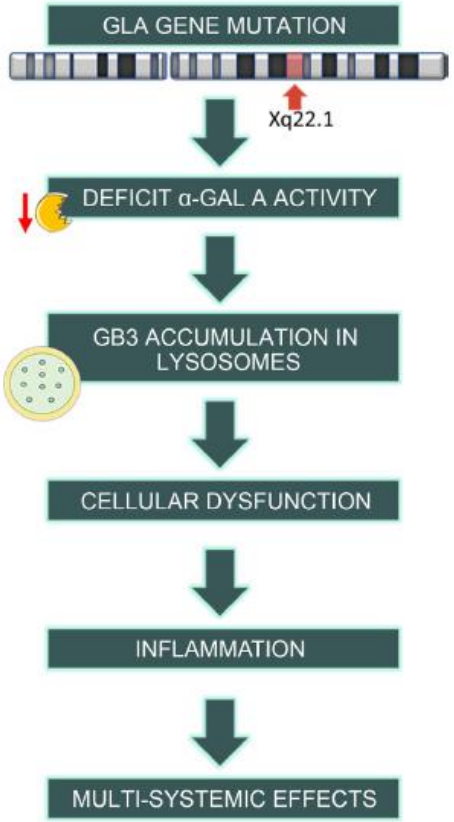
Received: 8 February 2021 | Revised: 22 April 2021 | Accepted: 14 May 2021

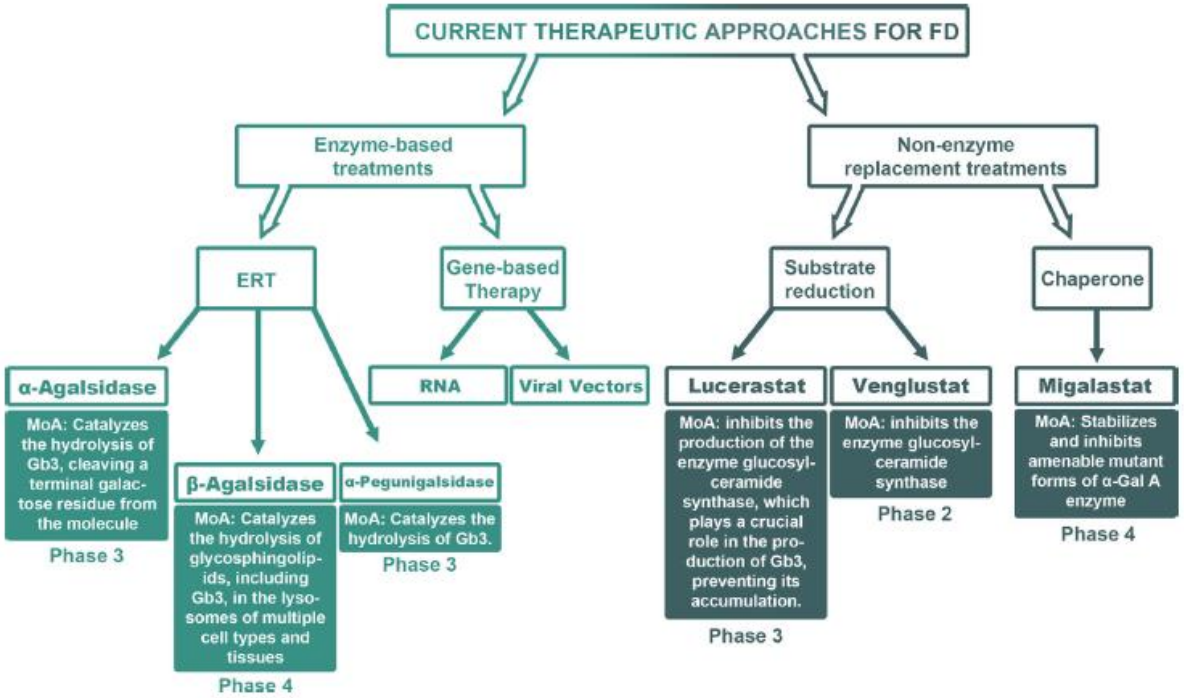
DOI: 10.1111/cge.13999

REVIEW

CLINICAL GENETICS WILEY

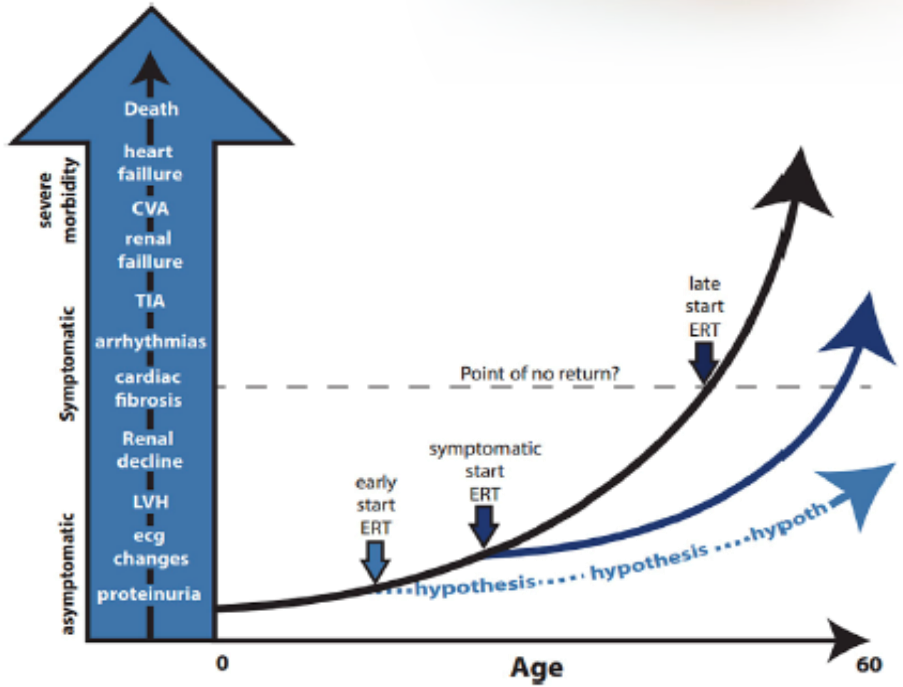
Current and experimental therapeutics for Fabry disease





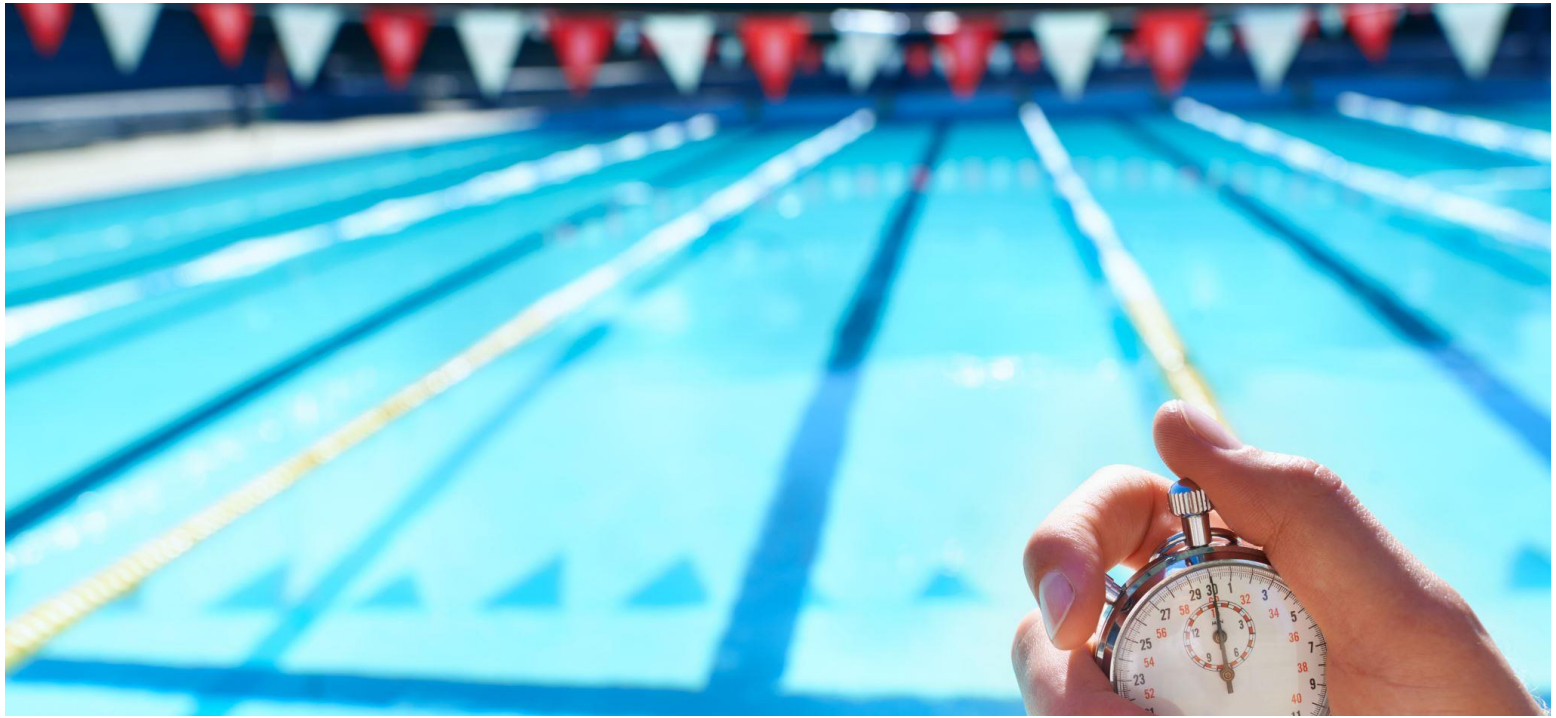
Early ERT Initiation in Pediatric Male Patients With Classical Fabry Disease May Be Associated With Attenuated Disease Progression[1]

- **Delay** the need of renal replacement therapies
- **Slow down** progression
- **Stabilize** signs/symptoms



[a]who started treatment with agalsidase-β in childhood.
CVA, cerebrovascular accident; ECG, electrocardiogram; ERT, enzyme replacement therapy; LVH, left ventricular hypertrophy; TIA, transient ischemic attack.
1. van der Veen SJ, et al. Mol Genet Metab. 2022;135(2):163–9.

OPTIMIZED THERAPEUTIC TIMING



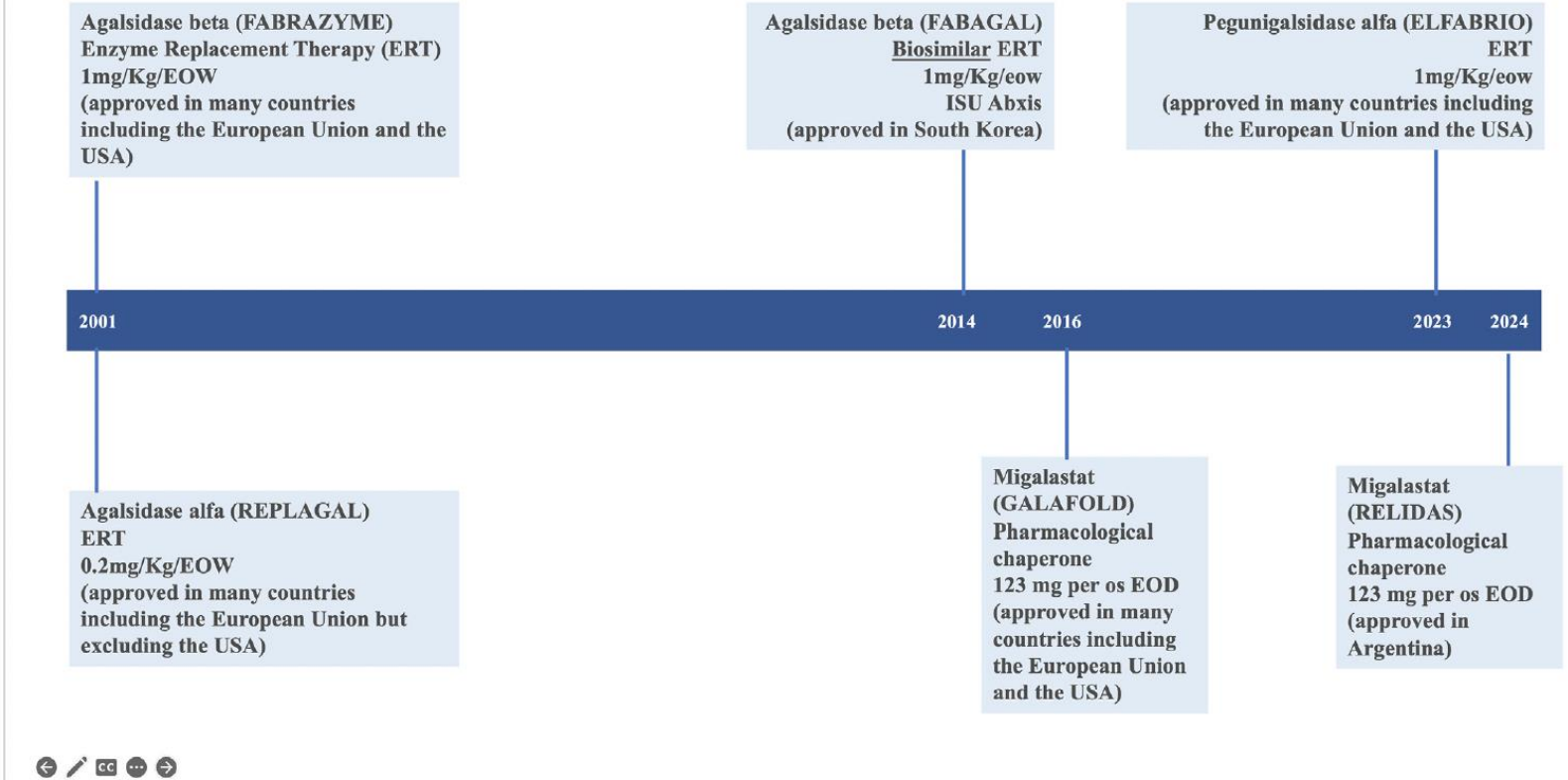
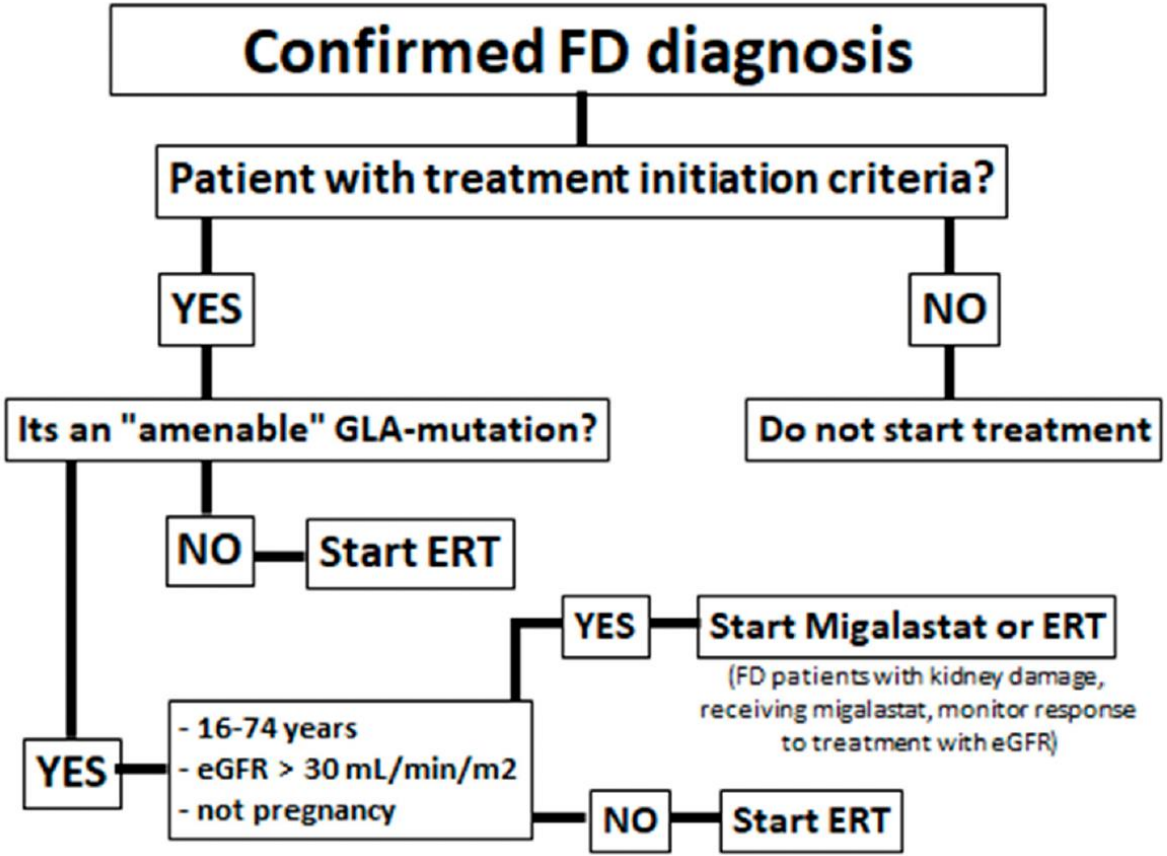
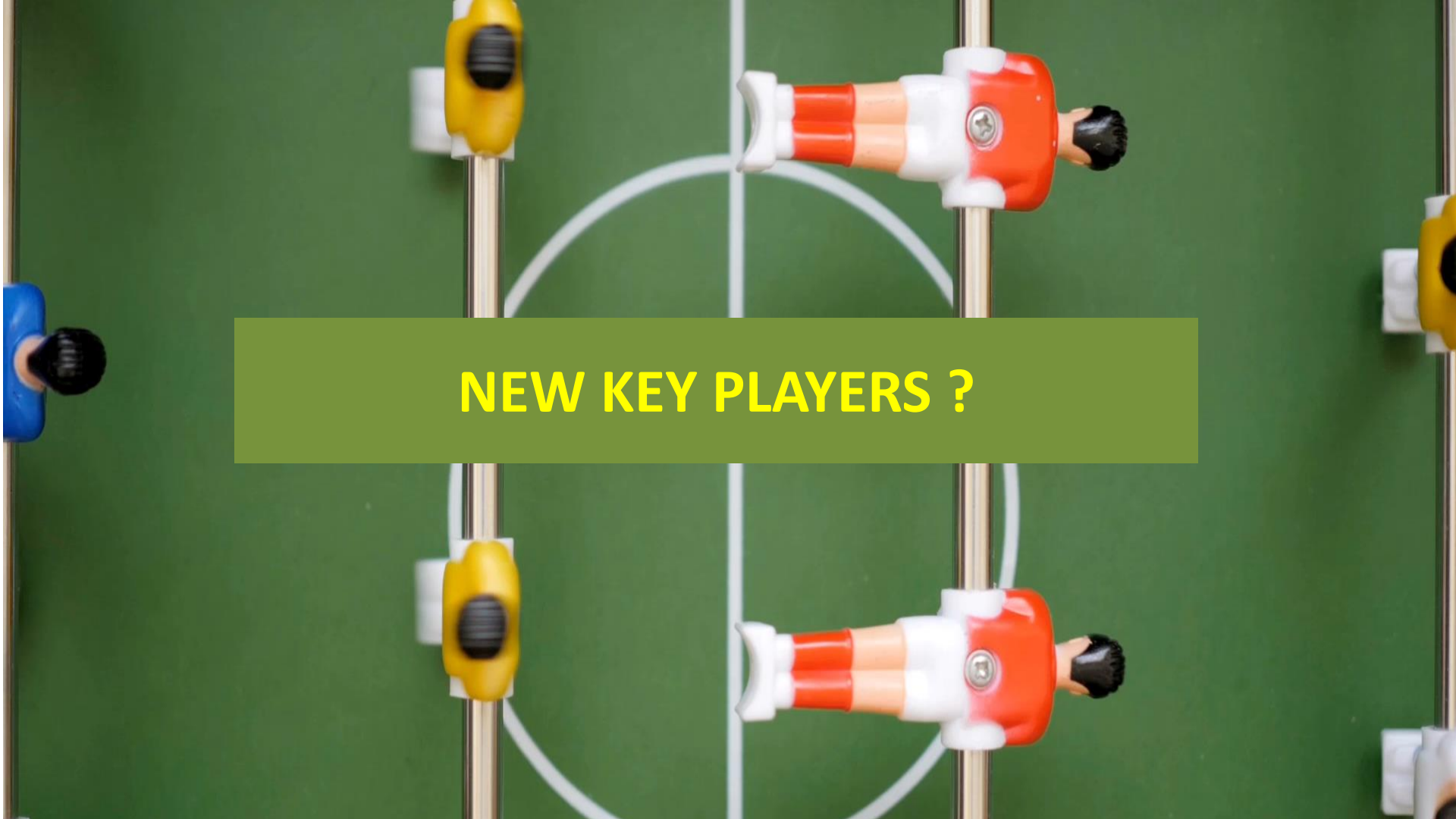


FIGURE 1
Current therapeutic landscape in Fabry disease.

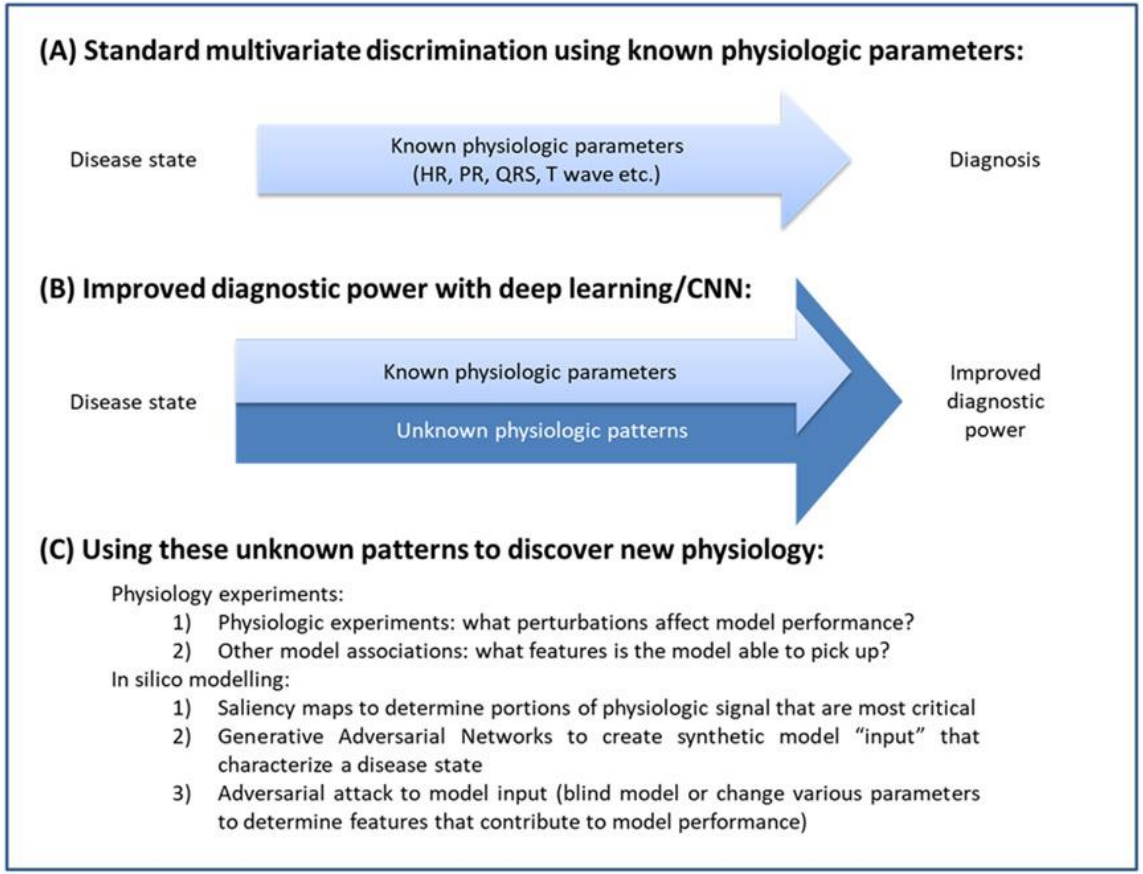
Germain DP and Linhart A (2024), Pegunigalsidase alfa: a novel, pegylated recombinant alpha-galactosidase enzyme for the treatment of Fabry disease. Front. Genet. 15:1395287.



Genes 2022, 13, 1751


NEW KEY PLAYERS ?

Artificial Intelligence-Enabled ECG: Physiologic and Pathophysiologic Insights and Implications



Compr Physiol. Author manuscript; available in PMC 2022 December 28.

Journal of
Clinical Medicine

MDPI

Article

Supporting the Diagnosis of Fabry Disease Using a Natural Language Processing-Based Approach

Adrian A. Michalski [1,2,†], Karol Lis [1,3,*,†], Joanna Stankiewicz [1,4], Sylwester M. Kloska [1,5], Arkadiusz Sycz [1,6], Marek Dudziński [1,7], Katarzyna Muras-Szwedziak [8,9], Michał Nowicki [8,9], Stanisława Bazan-Socha [8,10], Michal J. Dabrowski [1,11,‡] and Grzegorz W. Basak [1,3,‡]

This work aimed to create a risk factor scoring system to support physicians in FD diagnosis using real-life data. The authors used a machine learning original approach facilitated by the NLP tool evaluating patients' EHR which can can highlight seemingly imperceptible facts or symptoms that typically elude physicians, preventing proper FD detection.

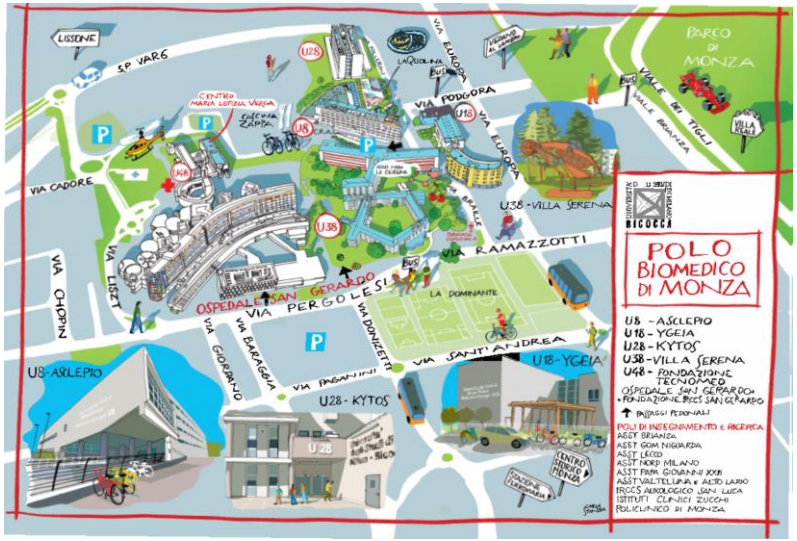
J. Clin. Med. 2023, 12, 3599. https://doi.org/10.3390/jcm12103599

Key points

- Fabry disease is a multisystemic disease that can affect several organs, resulting in cardiac, neurologic, and renal manifestations.
- Fabry disease is an underestimated disease mainly because of the aspecific phenotipyc variability (HIDDEN DISEASE)
- Suspect Fabry Disease: think metabolic
- Differential diagnosis is crucial in patients with similar clinical-instrumental features
- Several red flags, defined as clinical or instrumental features that help for the diagnosis of a specific disorder, have been proposed to suspect FD.
- New AI diagnostic tools and machine learning algorithms might increase the awareness of FD
- Early diagnosis is linked to early treatment aiming at preventing the disease progression to irreversible organ damage and organ failure.

Grazie!

Multidisciplinary Clinical and Research Unit of Adult Fabry Disease



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Quocumque modo faciemus

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Sistema Socio Sanitario
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European Reference Network
for rare or low prevalence complex diseases
Network Hereditary Metabolic Disorders (MetabERN)

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