

MALATTIA DI ANDERSON-FABRY

Tra sospetto clinico, diagnosi e terapia

PLACE 2026

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Sospetto clinico

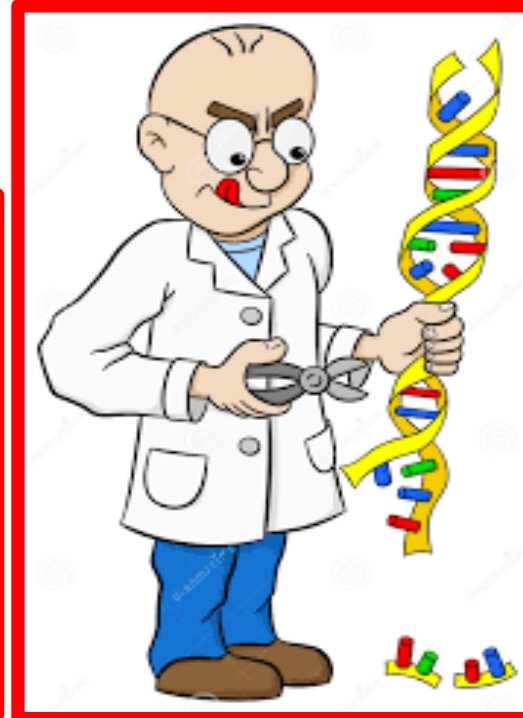
A cardiomyopathy mindset

- Competenze specifiche
- Mentalità
- Organizzazione

MRI



Genetic



Diagnosi della malattia di Fabry in una popolazione ad alto rischio cardiologico

- Lo *screening* per la malattia di Fabry dovrebbe essere condotto in tutti i pazienti con diagnosi confermata di HCM o LVH senza spiegazione $\geq 13\text{mm}$ e oltre i 30 anni di età¹

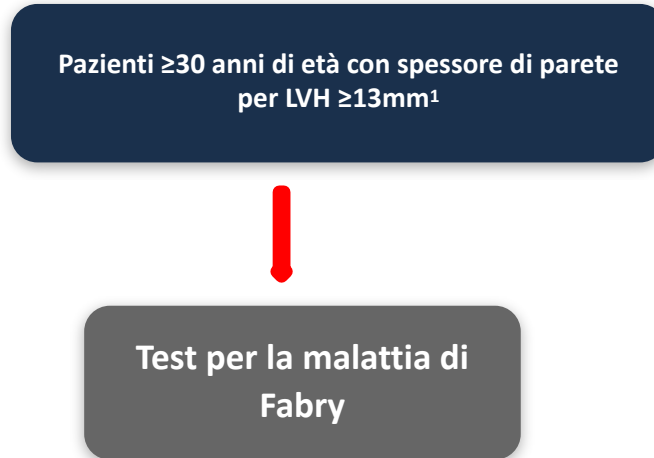


HCM, hypertrophic cardiomyopathy (cardiomiopatia ipertrofica); LVH, left ventricular hypertrophy (ipertrofia ventricolare sinistra)

1. Elliott, et al. *Eur Heart J*. 2014;35: 2733-2779

Diagnosi della malattia di Fabry

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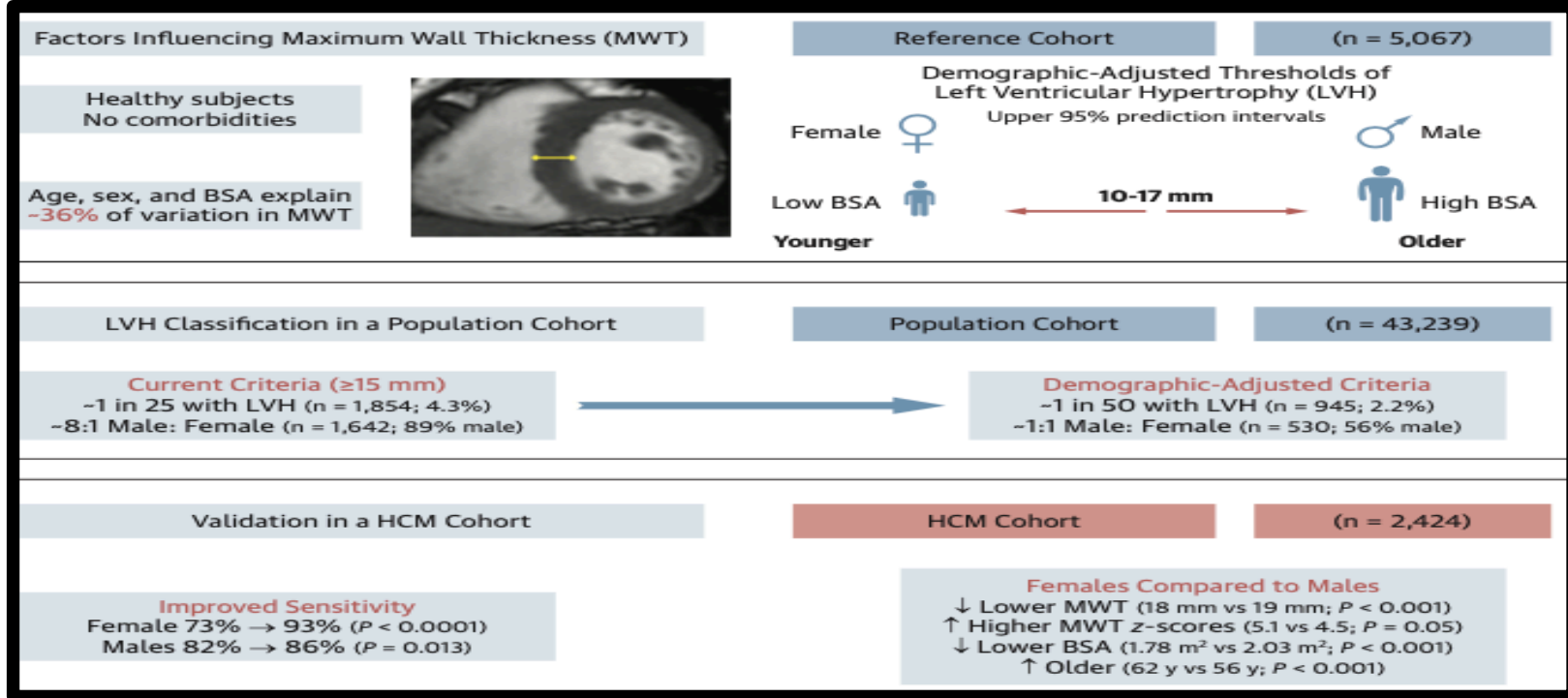
HCM, hypertrophic cardiomyopathy (cardiomiopatia ipertrofica); LVH, left ventricular hypertrophy (ipertrofia ventricolare sinistra)

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Finding	Specific diseases to be considered
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson-Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders
Mild to moderate pericardial effusion	Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium on 2D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations
Extreme concentric LVH (wall thickness $\geq 30\text{ mm}$)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease
Right ventricular outflow tract obstruction	Noonan syndrome and associated disorders

Is time to change the cut off mindset

Demographic-Adjusted Left Ventricular Hypertrophy Thresholds for Hypertrophic Cardiomyopathy Diagnosis



Age, sex, and body size influence the normal heart MWT.

Using a fixed LVH threshold **15 mm** biases LVH ascertainment in both population and HCM cohorts.

A demographic-adjusted approach for LVH improves ascertainment and diagnostic accuracy

HCM – Definition.... One Size does not fit all

Sex: ☐ Male ☒ Female

Age (Years):

BSA (m2):

Measured MWT (mm):

(optional)

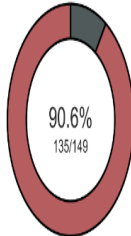
Predicted MWT: **8 mm**
7.90 mm (2sf)

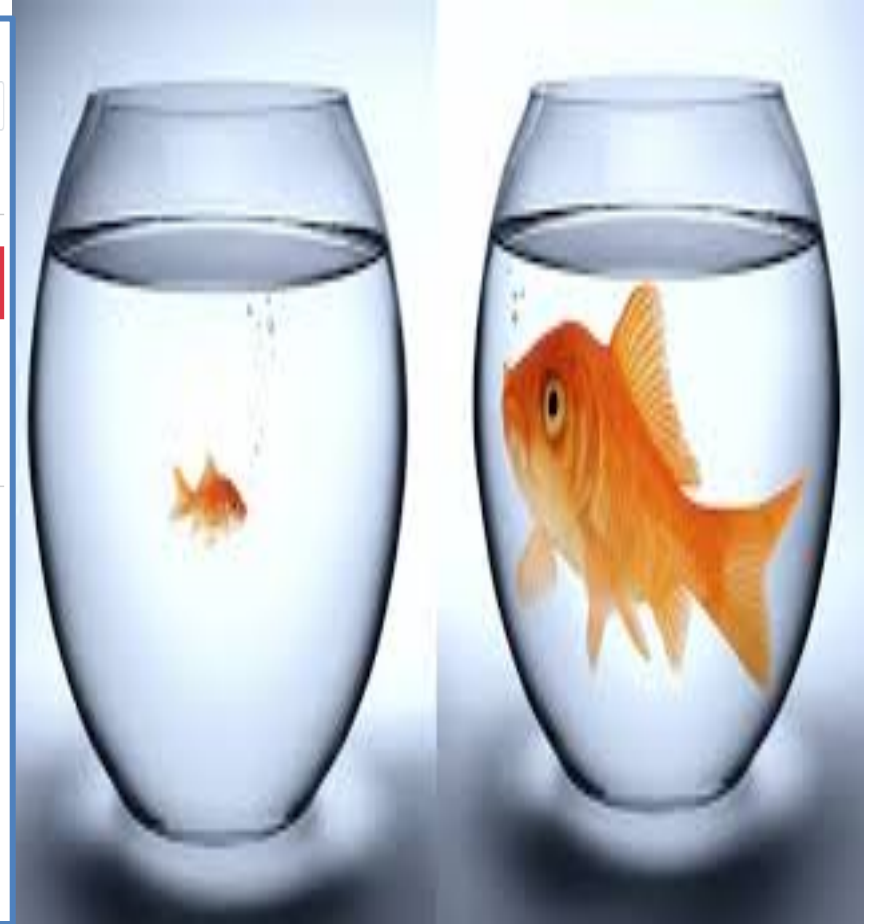
Upper Limit MWT (Inappropriate hypertrophy): **10 mm**
10.27 mm (2sf)

High sensitivity and specificity of distinguishing healthy from HCM

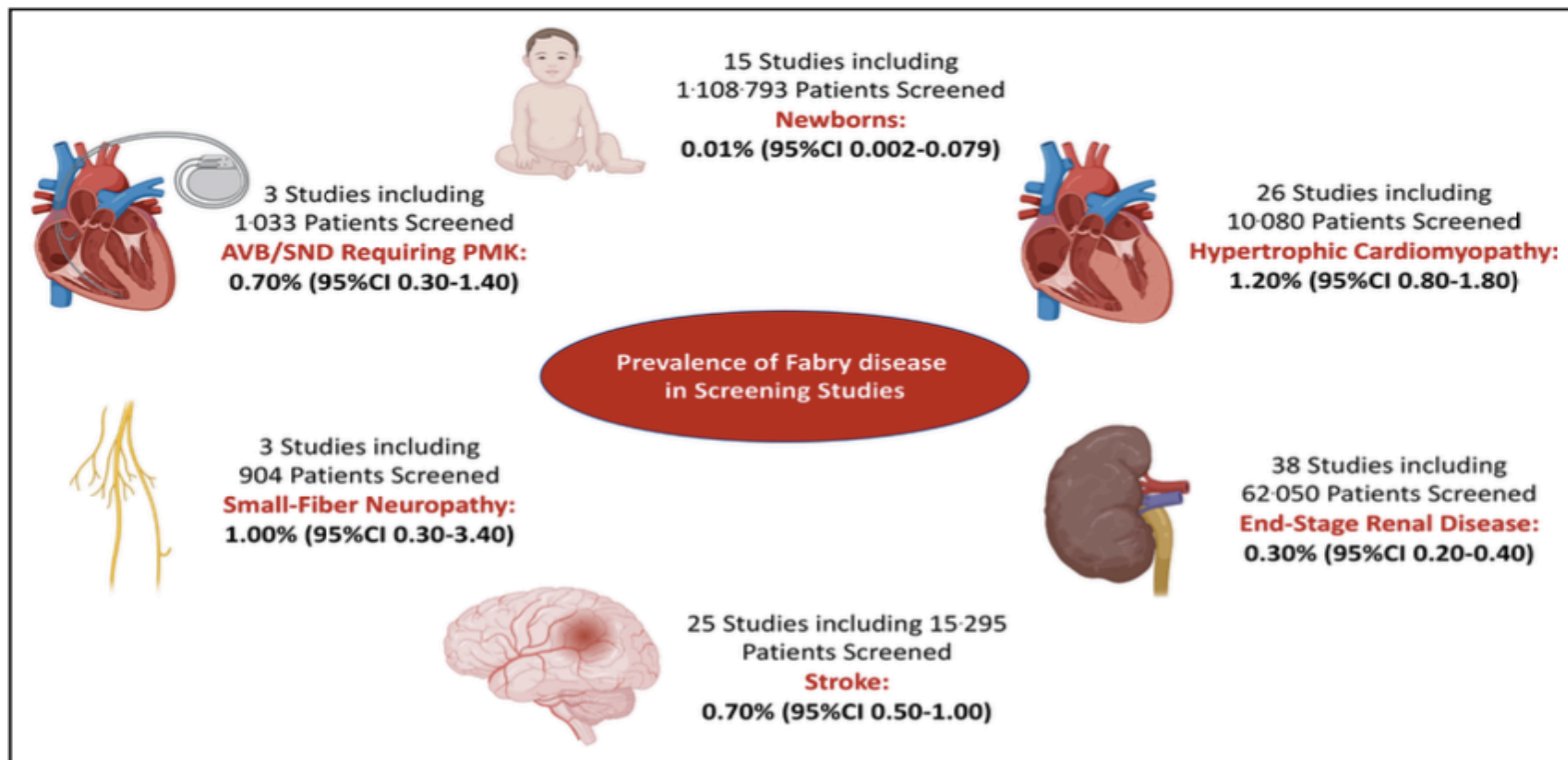


Age
Sex
BSA

UK Biobank	Healthy Volunteers	Hypertrophic Cardiomyopathy
		



Anderson Fabry Disease e Studi di Screening

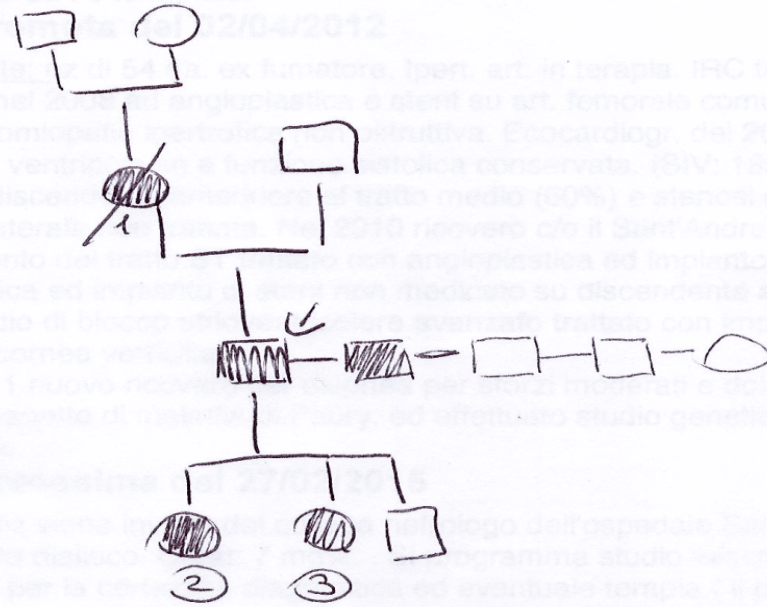


Impatto della classificazione delle varianti *GLA* sulla prevalenza stimata della malattia di Fabry: una revisione sistematica e una meta-analisi degli studi di screening

Monda et al. Genom Precis Med 2023

Diagnosi
1898-2026

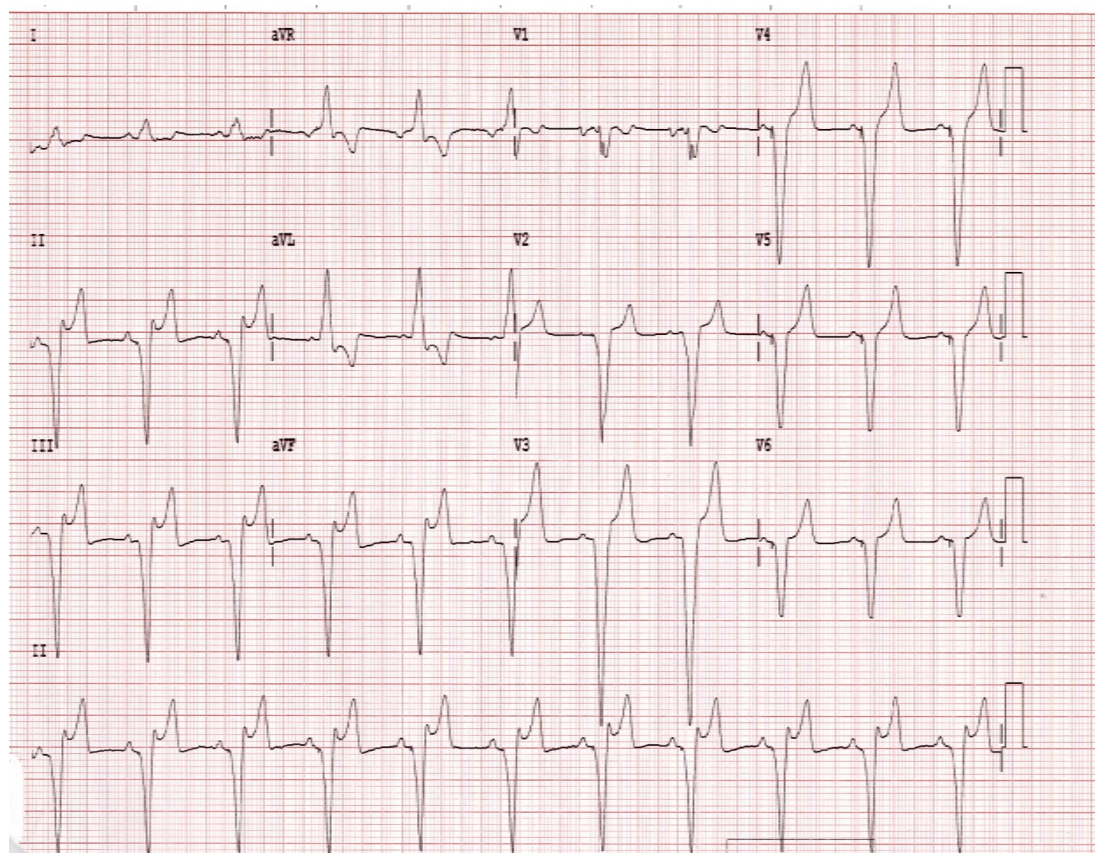
- M
- 1957
- Madre deceduta a 58 aa per ictus cerebri affetta da IRC terminale
- Ex fumatore, iperteso, AOA con IRC terminale
- CMI non ostruttiva diagnosticata nel 2002
- 2008 aterosclerosi critica su DA trattata con PTCA e stent, 2010 NSTEMI PTCA con stent su CDX



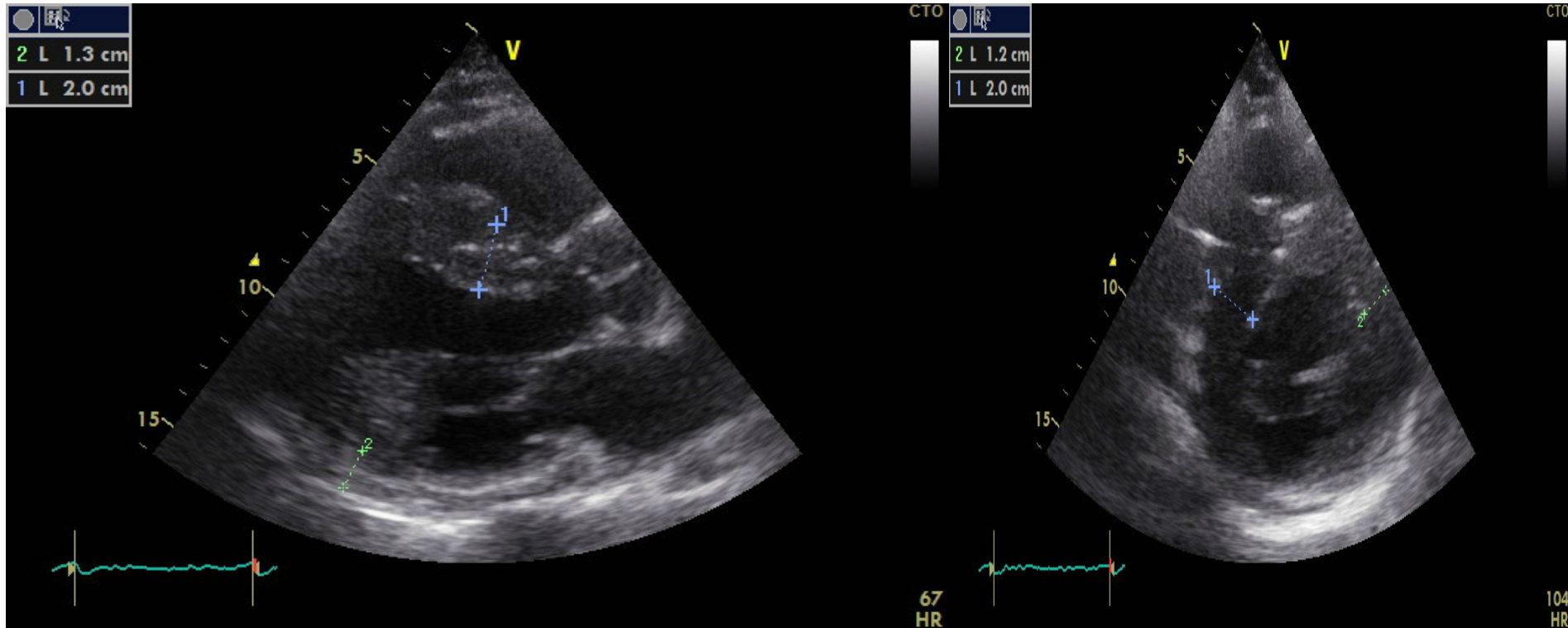
① Decesso a 58 per IRA

2-3 Terapia dialitica

2010 BAV avanzato sottoposto a PMK bicamerale
2015 analisi genetica (mutazione 9249K gene alfa
GAL) ed inizio ERT 2015 impianto di AICD
sottocutaneo



ECOCARDIOGRAMMA



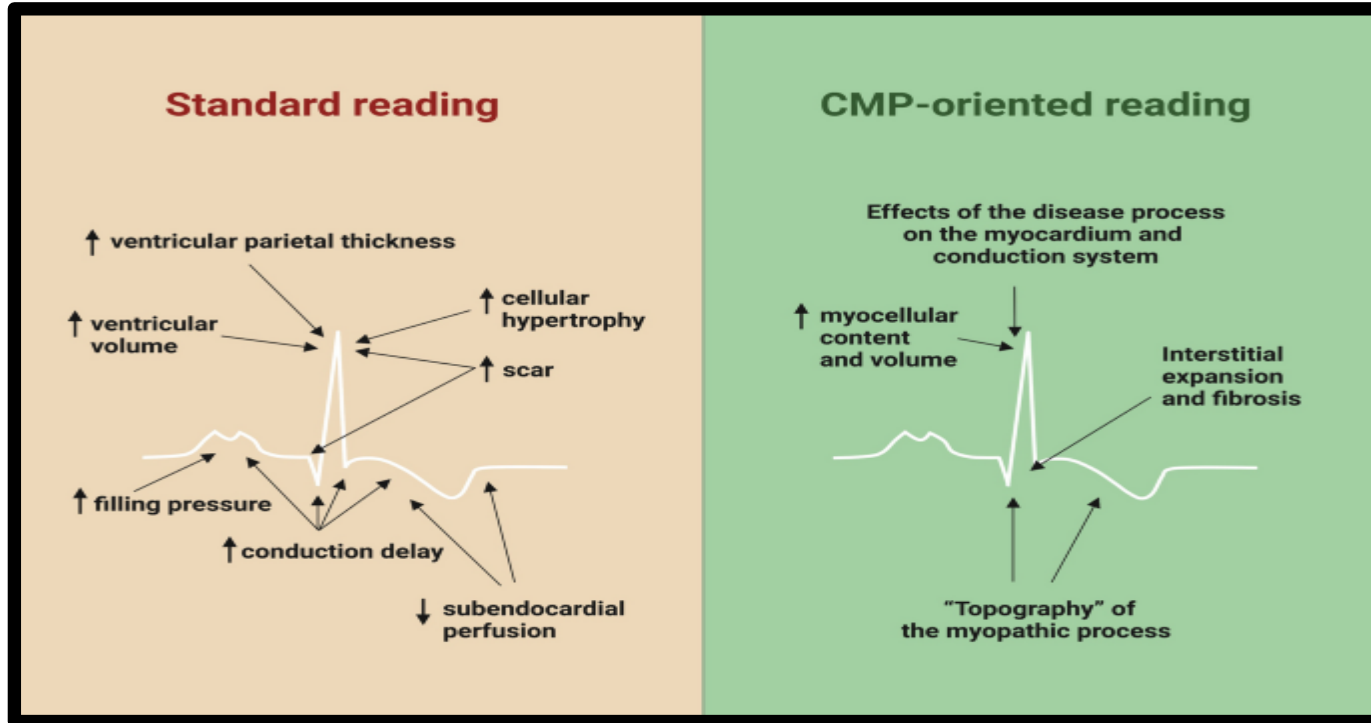
A cardiomyopathy mindset



ECG

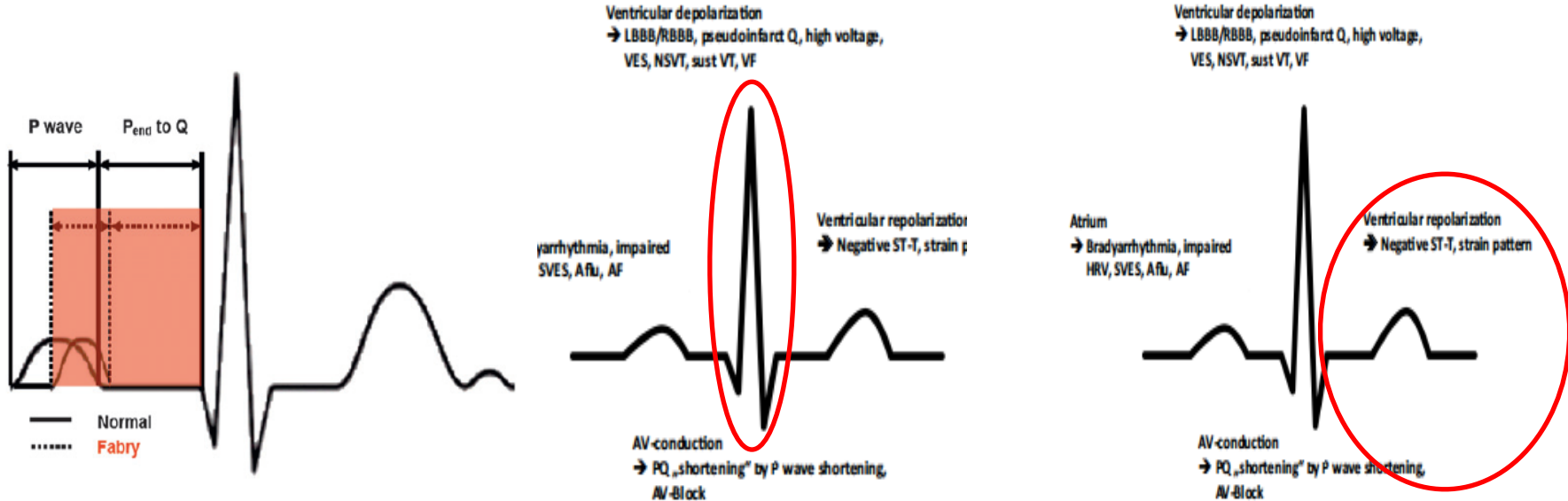
A cardiomyopathy mindset: ECG

ECG is the most accessible, cost-effective, and noninvasive means to assess cardiac activity and function



ECG-conduction abnormalities and arrhythmia

Low prevalence (14%) of atrioventricular conduction abnormalities without Accessory pathway

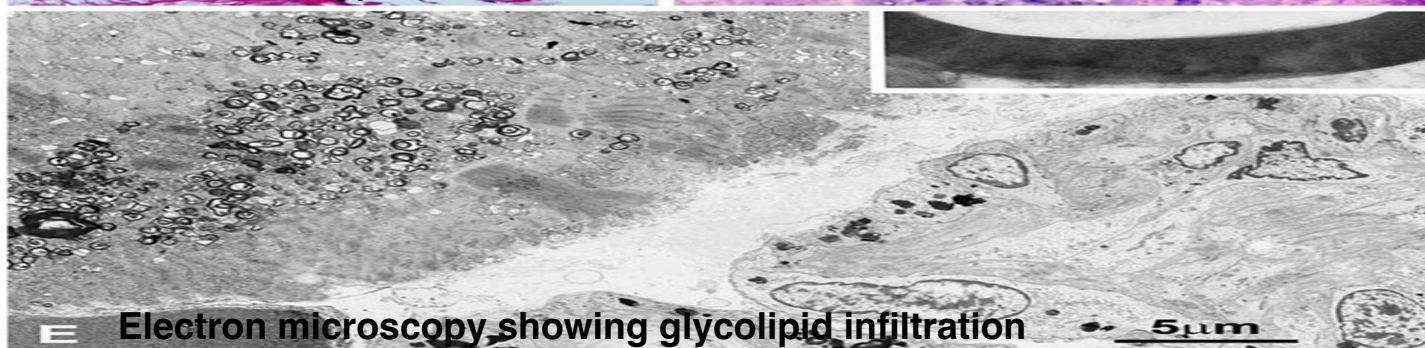
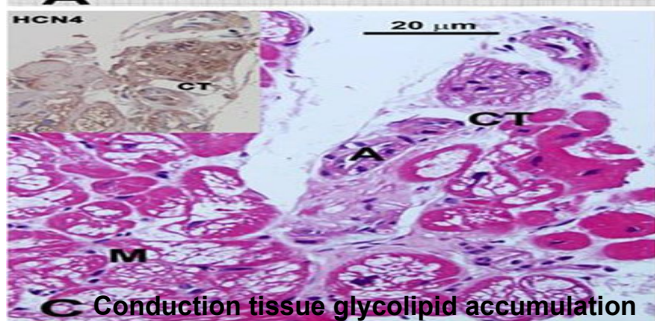
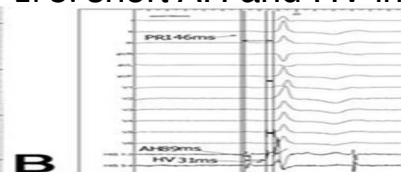


Conduction Tissue in Fabry Disease

ECG: short PR with ST/T-wave changes



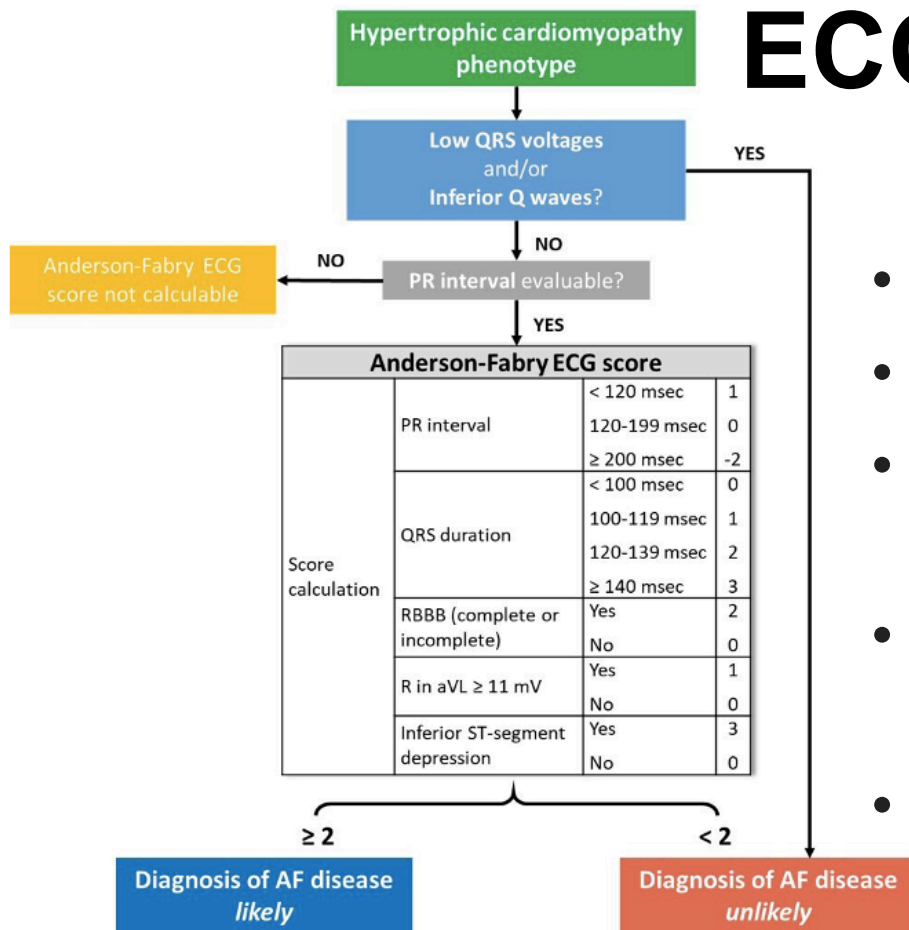
EPS: short AH and HV intervals



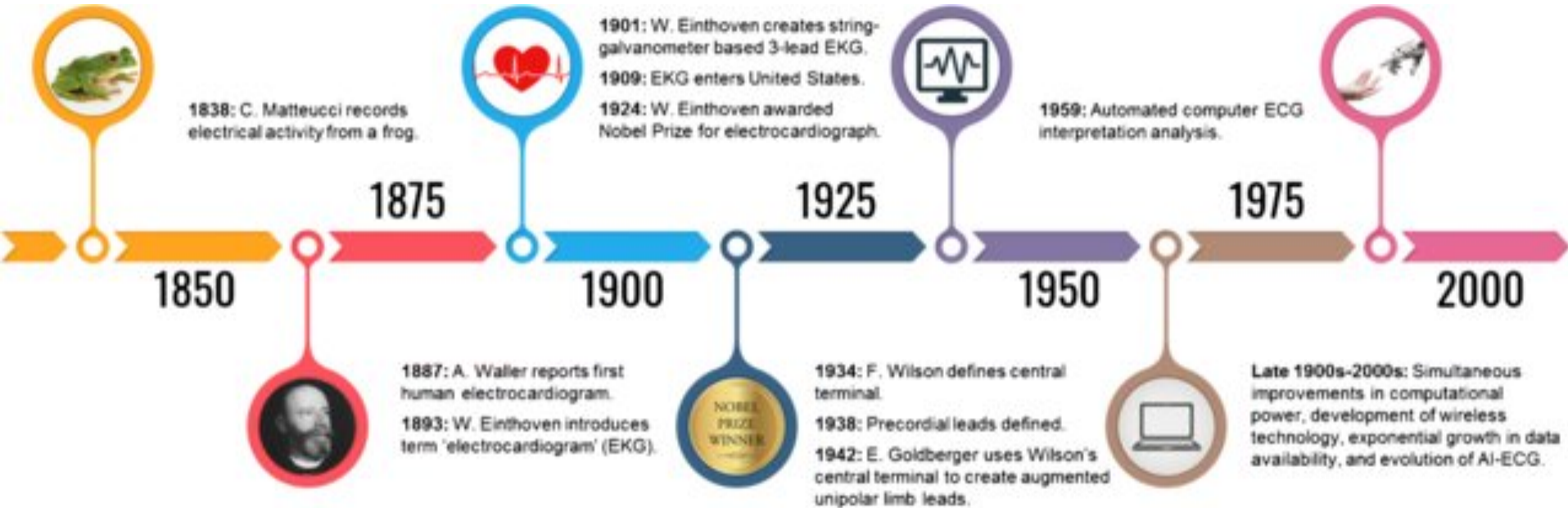
ECG

Predictor of AFD

- Short PR interval
- Prolonged QRS duration
- Right bundle branch block (RBBB)
- R in augmented vector left (aVL) ≥ 1.1 mV
- inferior ST depression



Key achievements in the development of and advances in the ECG over time

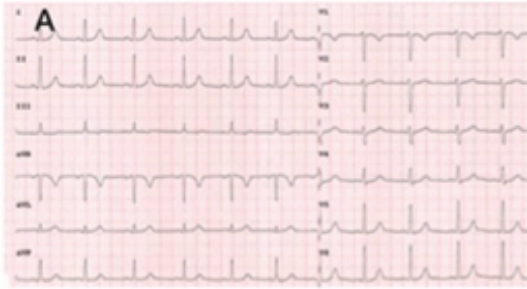


Wearable technologies

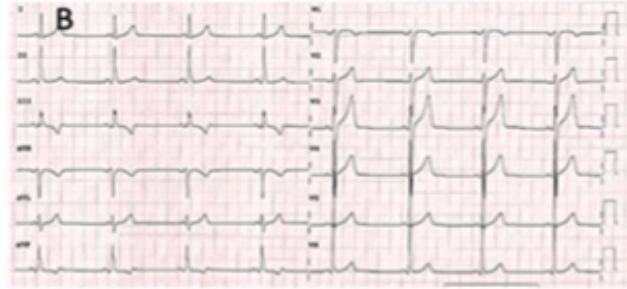
AI driven ECG interpretation software

ECG

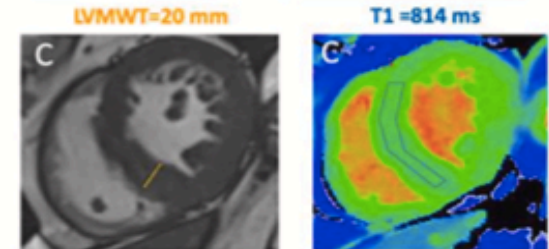
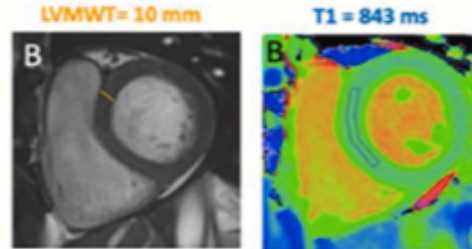
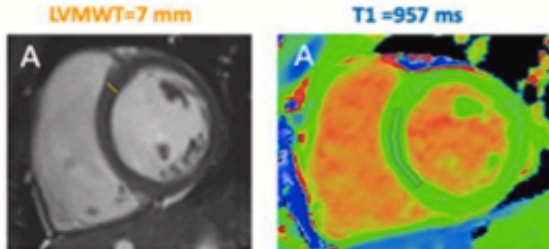
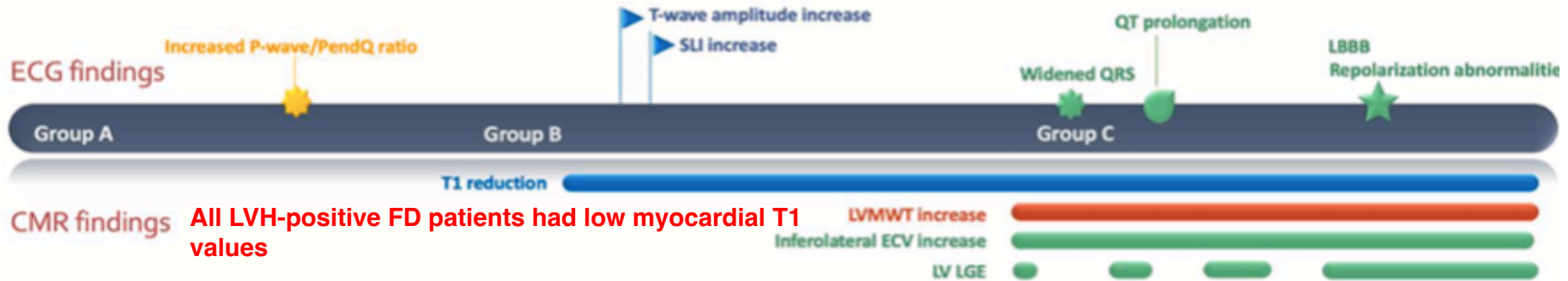
A Normal T1 no LVH



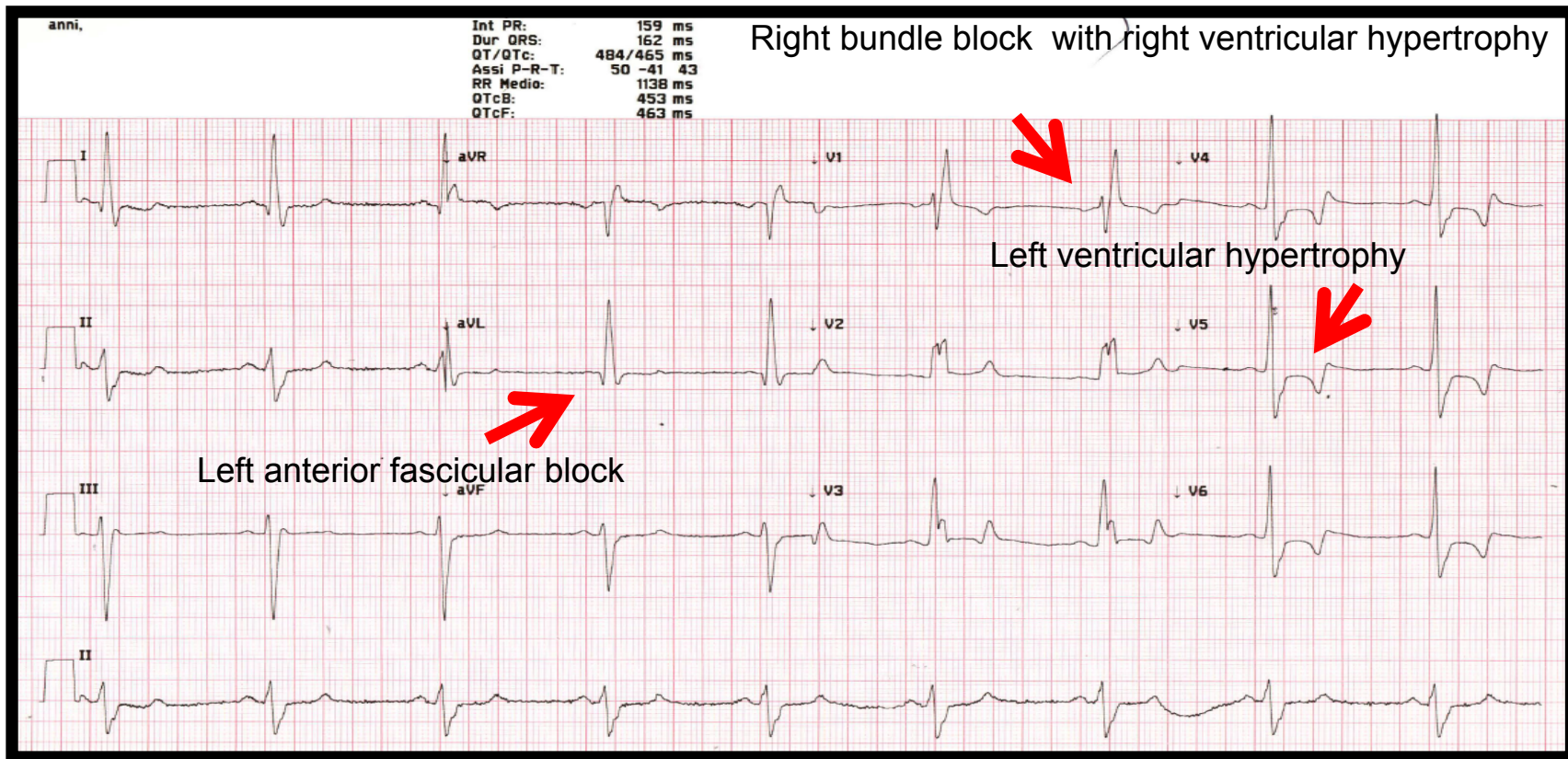
B Low T1 no LVH



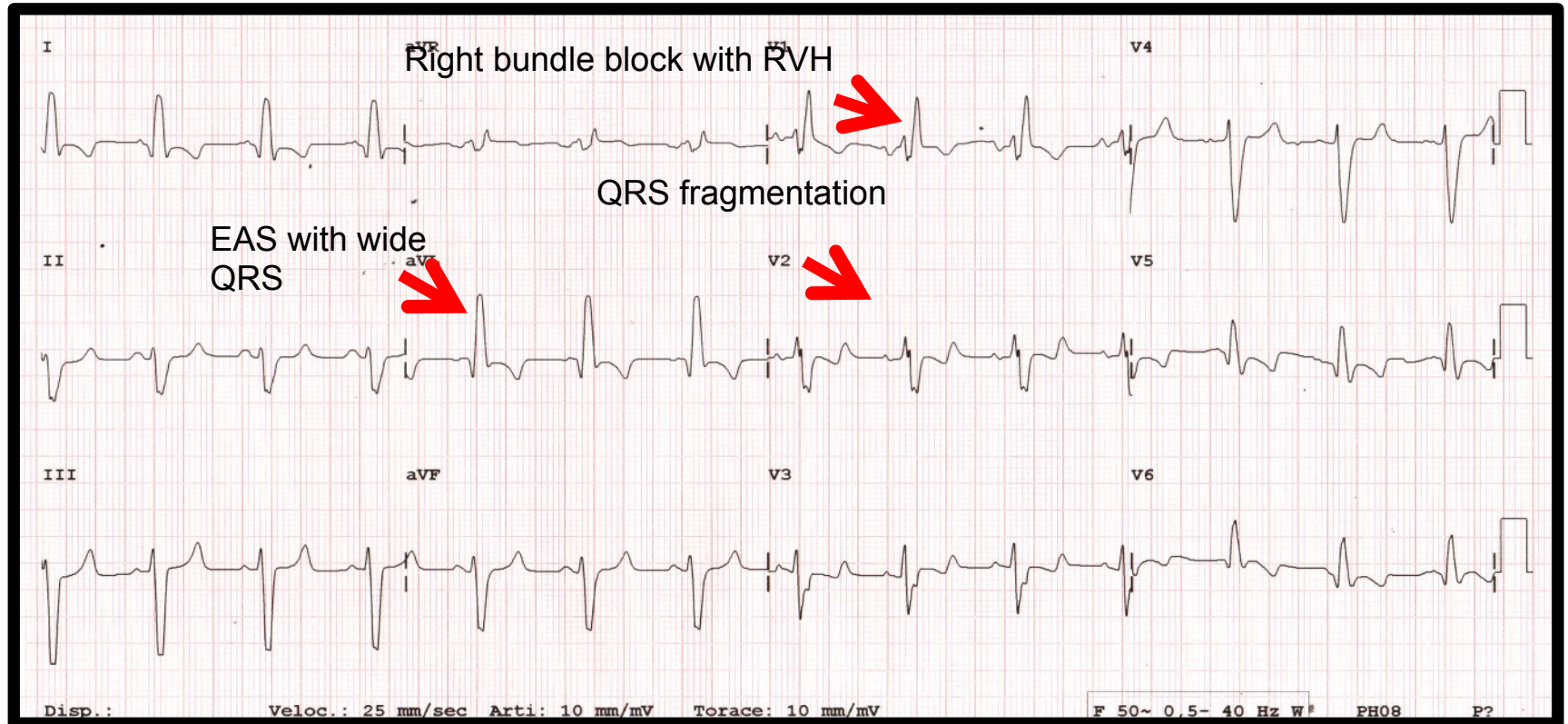
C Low T1 + LVH



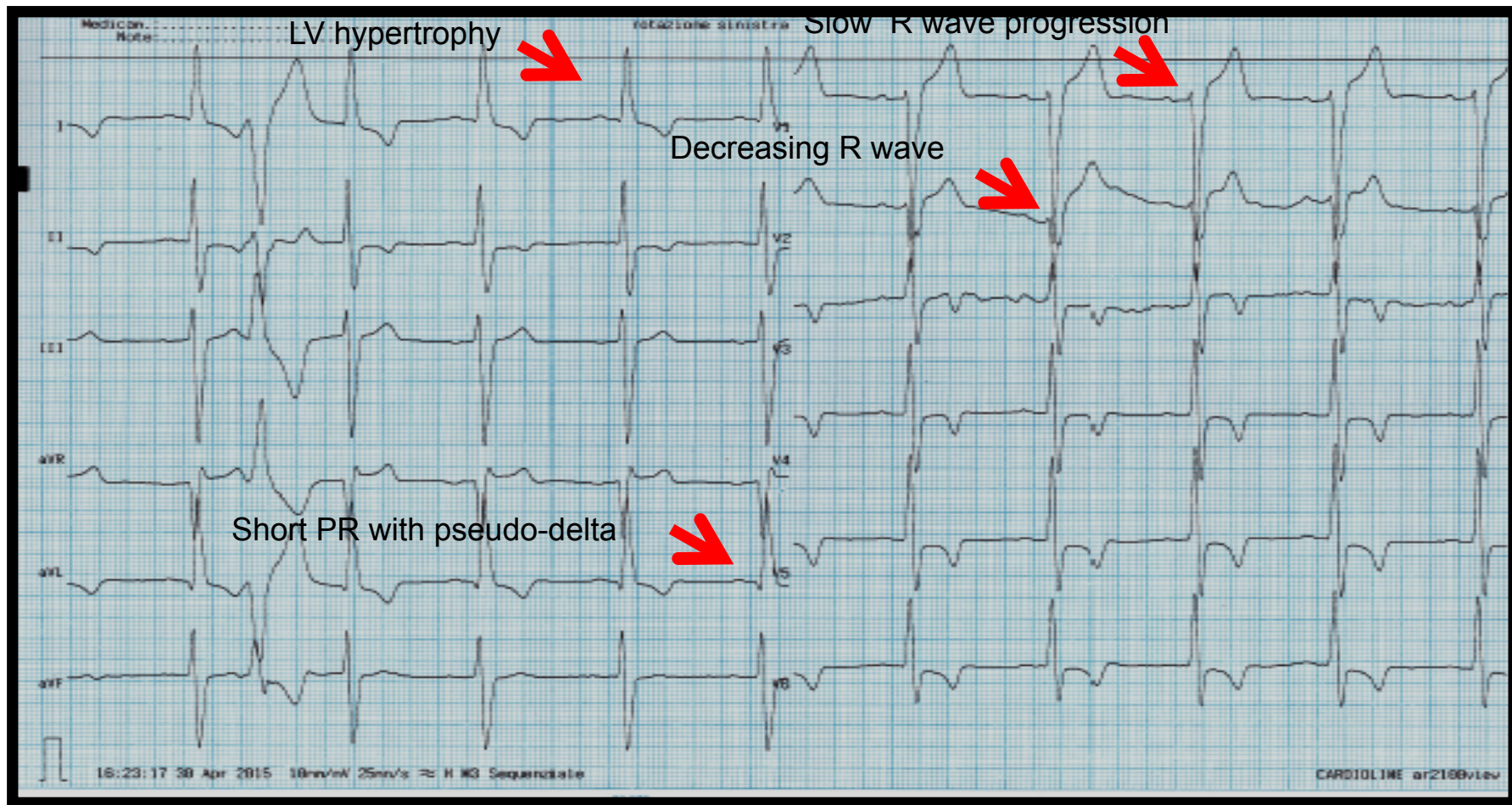
ECG



ECG

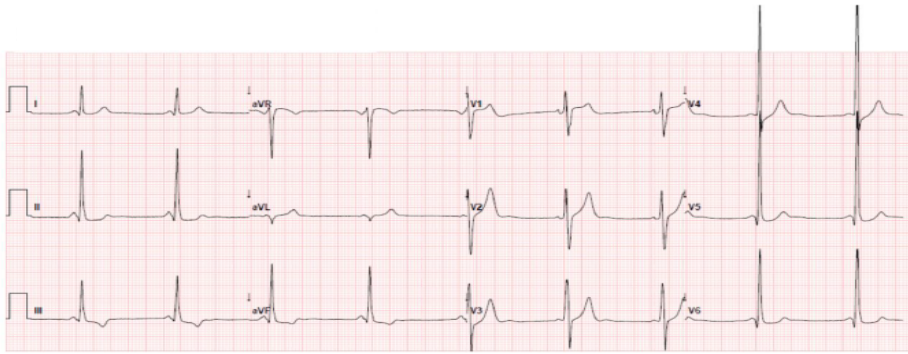


ECG

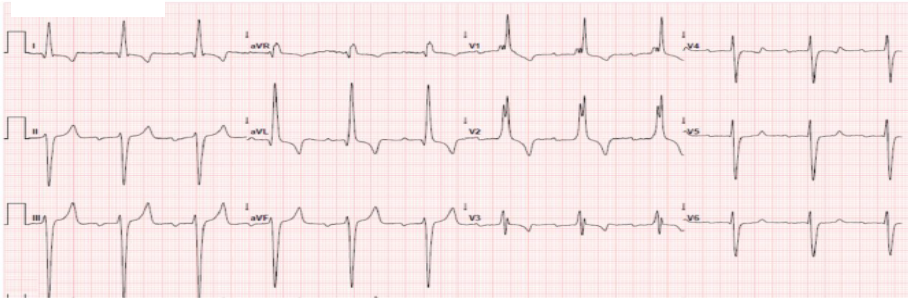


ECG

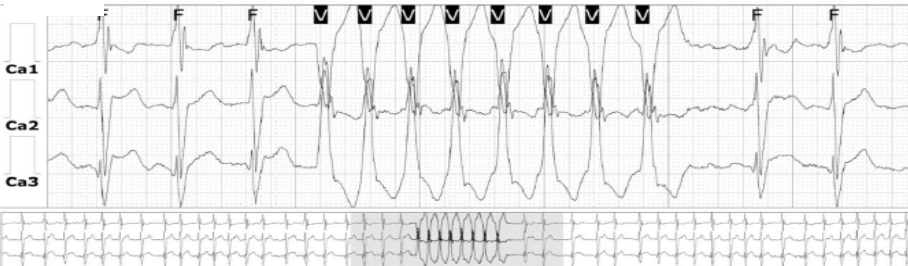
- Early Phase



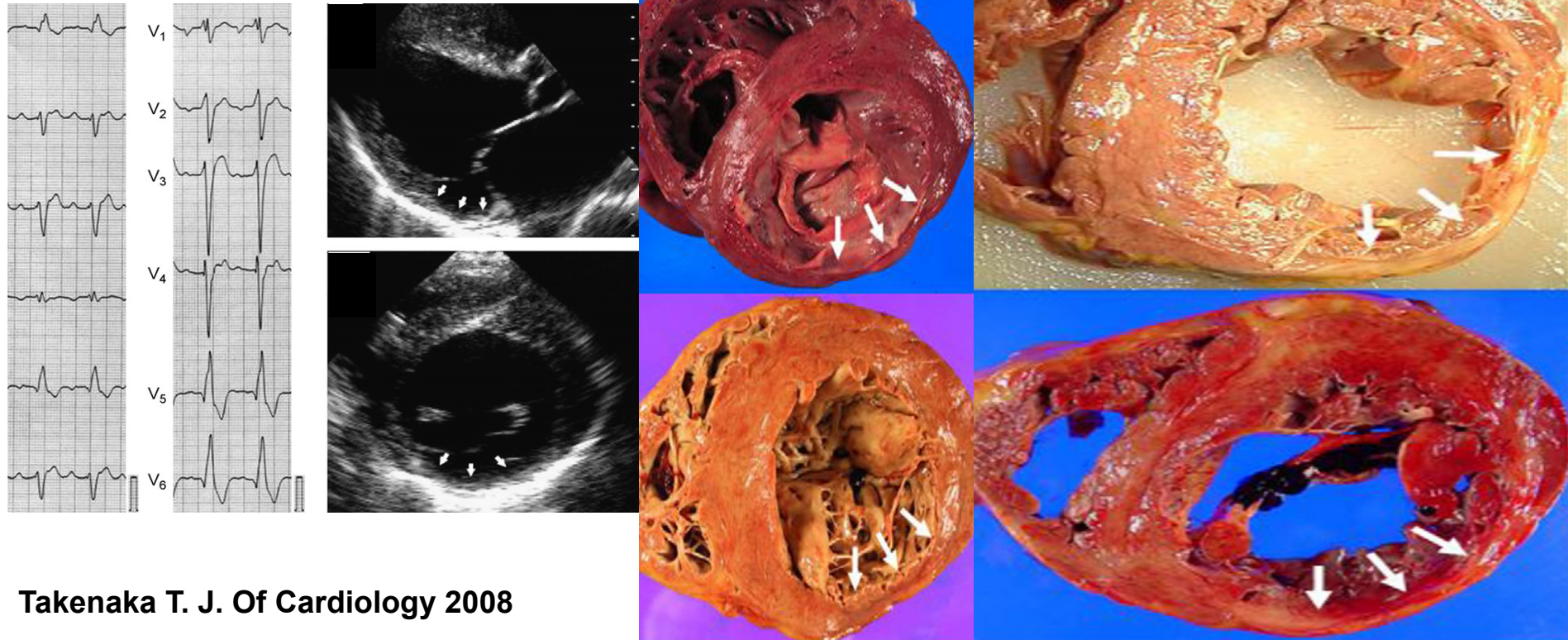
- Mid Term



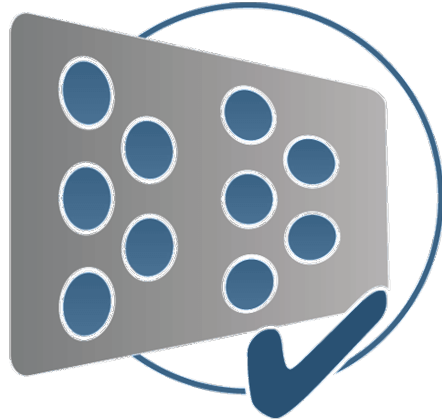
- Late Stage



Terminal stage cardiac findings in patients with cardiac Fabry disease: An electrocardiographic, echocardiographic, and autopsy study



Fase Diagnostica: DBS



- Semplicità
- Rapidità risposta
- Completezza
- Follow up



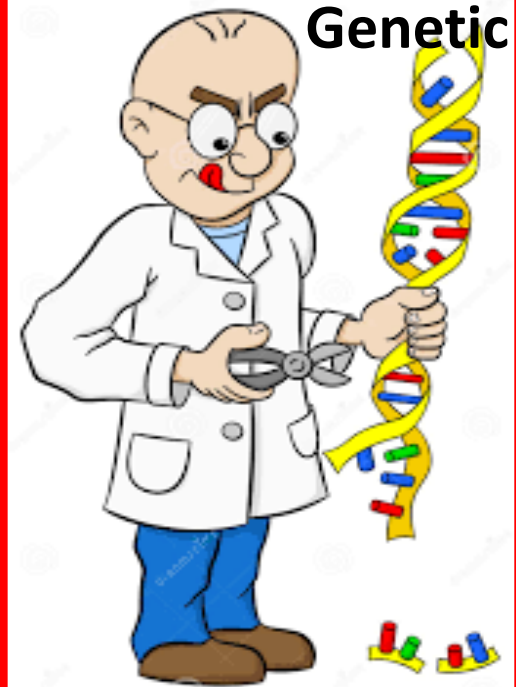
A cardiomyopathy mindset

- Competenze specifiche
- Mentalità
- Organizzazione

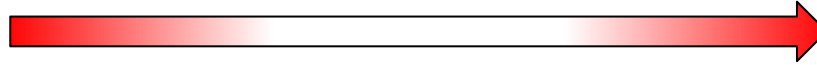
MRI



Genetic



Pazienti affetti da M. di A. Fabry



Popolazione di pazienti con nuova diagnosi

- 38 pazienti
- 21 M
- 17 F
- ERT 13
- Terapia Chaperonica 8
- Attualmente non in terapia 13



● N215S. ● Del es 3-4 ● 118C ● 313T ● Ile303Phe ● pR301G

Genetica

- N215S: 11 pazienti
- Del es 3-4: 3 pazienti
- 118C: 2 pazienti
- 313T: 4 pazienti
- Ile 303Phe: 1 paziente
- pR301G: 6 pazienti

Diagnosi e diagnosi differenziale in ambulatorio cardiomiopatie con personale dedicato: RM cardiaca e genetica

Ambulatorio dedicato cardiomiopatia ipertrofica

Screening pazienti in dialisi e CMI

Consulenza genetista

Progetto analisi albero genealogico

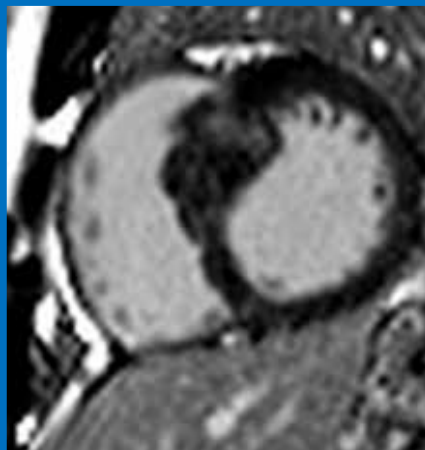
Gruppo di lavoro dedicato alle cardiopatie di origine genetica

Radiologi con esperienza nell'imaging cardiaco

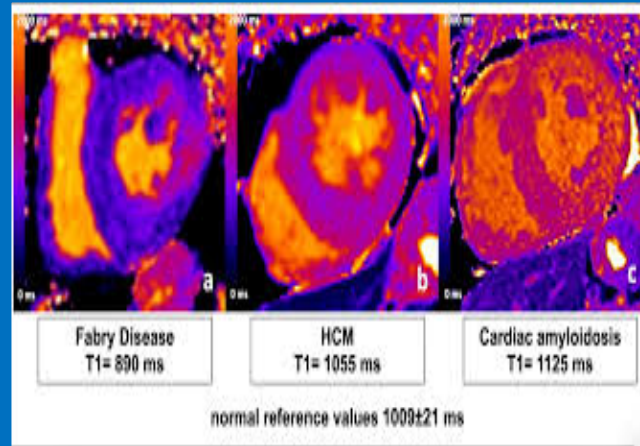
Infermieri dedicati

Tecnici specializzati nella programmazione dei device e monitoraggio remoto

Fenotipo ipertrofico



Diagnosi differenziale



A cardiomyopathy mindset



MRI

Uomo, 56 anni

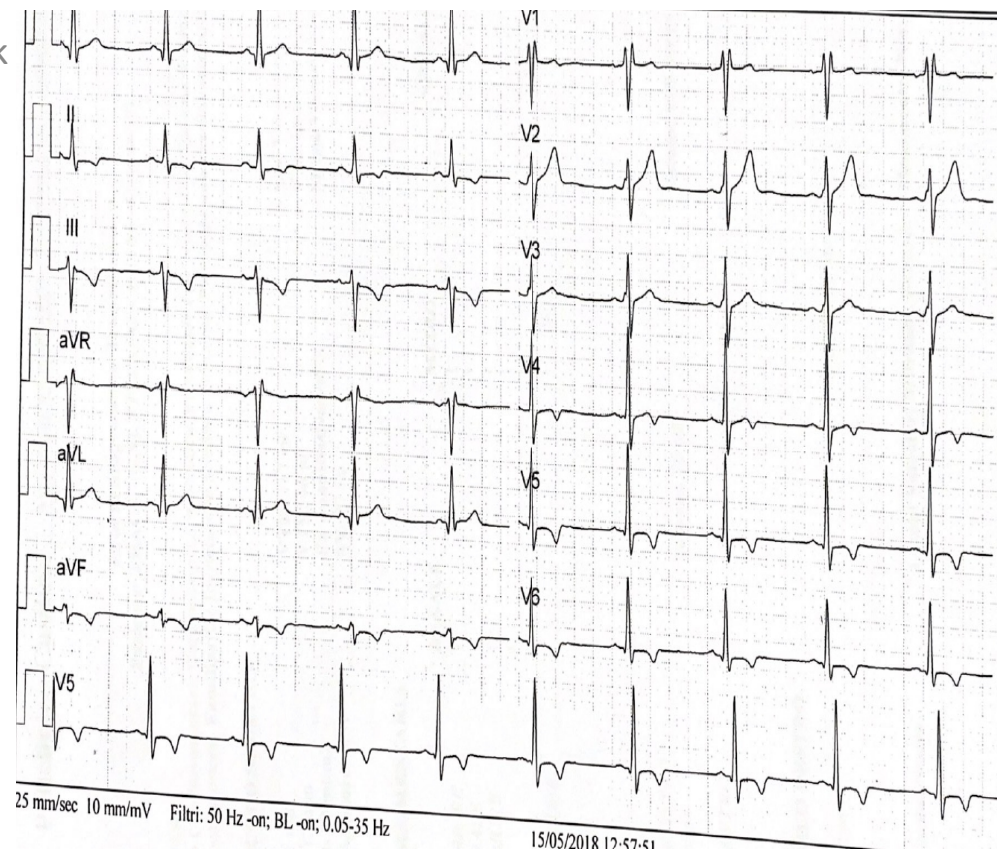
FRCV: ipertensione arteriosa, OSAS in CPAP

Anamnesi familiare: madre in vita, ipertesa con cardiopatia non meglio precisata; padre deceduto per k polmone, portatore di PMK. Una figlia.

Anamnesi patologica remota: ECG eseguito durante visita in medicina del lavoro con alterazioni della RV in sede infero-laterale (2018).

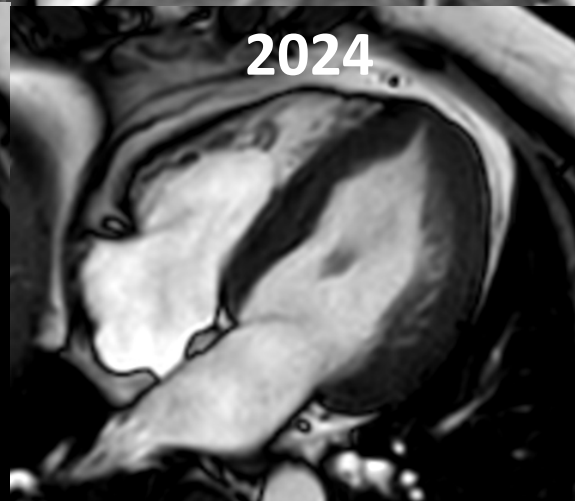
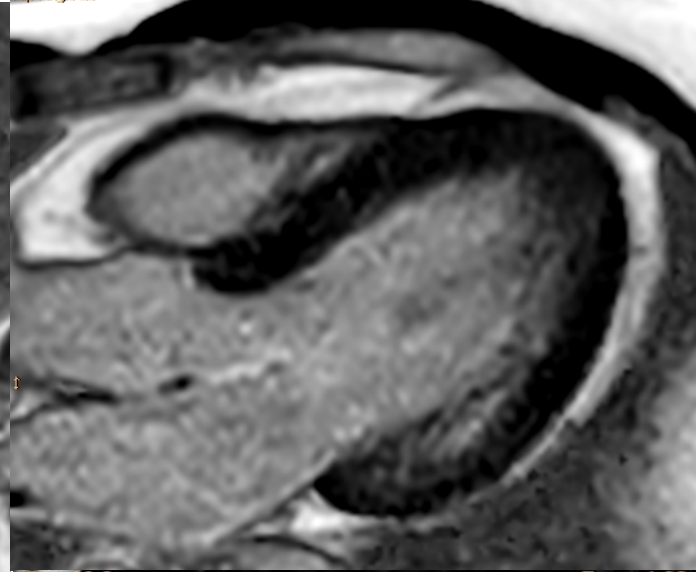
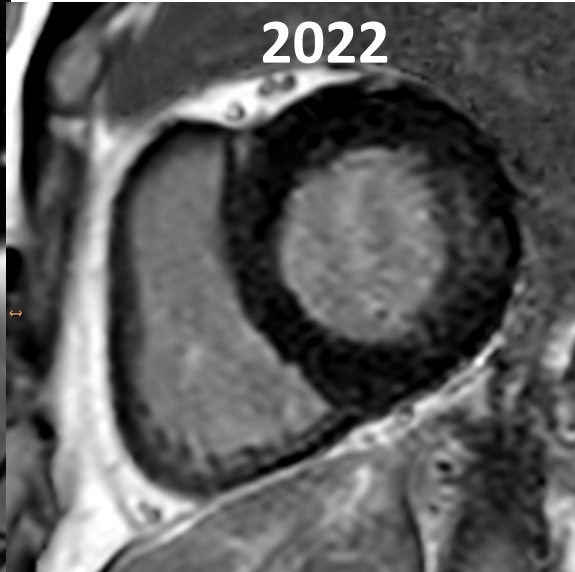
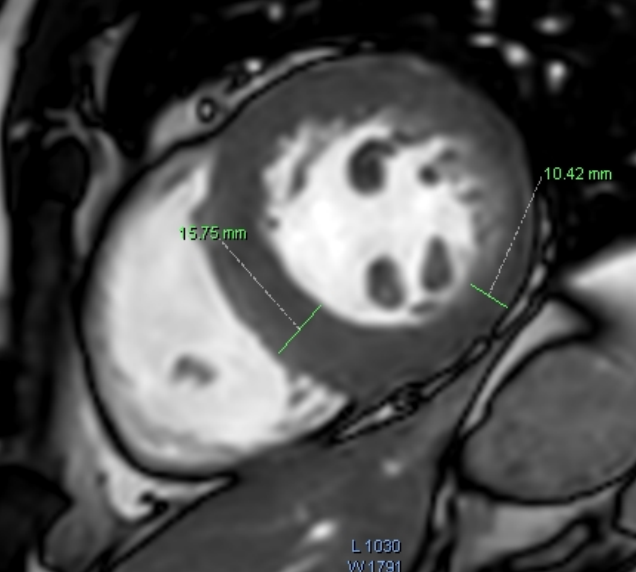
Anamnesi patologica prossima: saltuari episodi di cardiopalmo

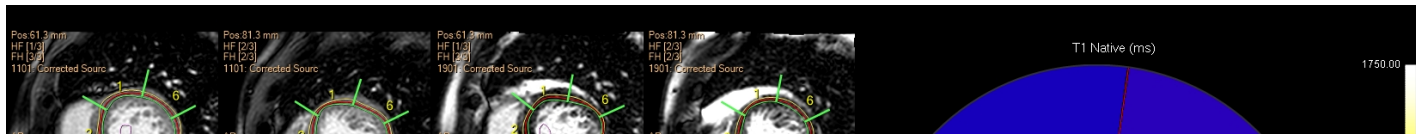
Terapia: Bisoprololo 2,5 mg/bid
Triatec 10 mg/die
Folina 5 mg/die



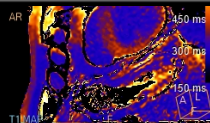
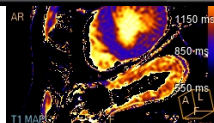
Esami diagnostici 2022

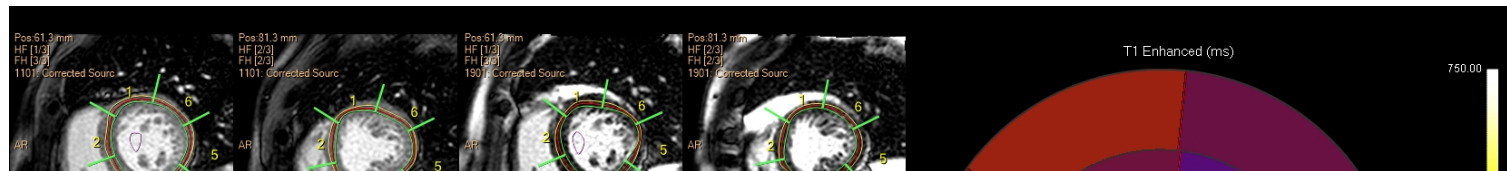
- **Ecocardiogramma c/D:** SIV 16 mm non gradiente LVOT o medio-ventricolare.
- **ECG Holter** in carvedilolo 25 mg ½ cp/die: RS alla FCm di 57 bpm. Non aritmie. Non pause.
- **Eco TSA:** IMT 1 cm.
- **TC coronarica:** coronarie esenti da stenosi emodinamicamente significative.
- **RMN cardiaca (01/2022):** SIV basale 16 mm, apice 13 mm, ipertrofia papillari; non DE, T1 mapping normale.





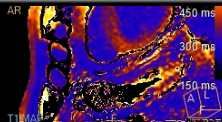
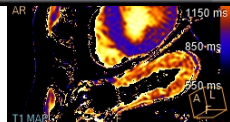
	T1 Native: Regional Result-1101, Slice No.: 1						
	Segment 1	Segment 2	Segment 3	Segment 4	Segment 5	Segment 6	Summary
T1 Native	822±60.9 ...	862±44.5 ...	860±49.9 ...	901±76.7 ...	937±74.5 ...	881±84.8 ...	876±76.0 ...
R1 Native	1.22±0.09...	1.16±0.06...	1.17±0.07...	1.12±0.10...	1.07±0.09...	1.15±0.11...	1.15±0.10...
T1 Enhanced	404±26.0 ...	410±22.3 ...	411±22.6 ...	395±45.9 ...	356±35.9 ...	374±27.0 ...	395±36.5 ...
R1 Enhanced	2.48±0.16...	2.45±0.14...	2.44±0.14...	2.57±0.31...	2.84±0.28...	2.69±0.20...	2.56±0.25...
ϵ	25.5 %	26.0 %	25.8 %	28.8 %	35.3 %	31.2 %	28.2 %
ROI Area Native	205 mm ²	182 mm ²	197 mm ²	136 mm ²	207 mm ²	168 mm ²	1095 mm ²
ROI Area Enhanced	163 mm ²	161 mm ²	181 mm ²	186 mm ²	119 mm ²	114 mm ²	924 mm ²
Hematocrit	45.2 %	45.2 %	45.2 %	45.2 %	45.2 %	45.2 %	45.2 %
Field Strength	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T





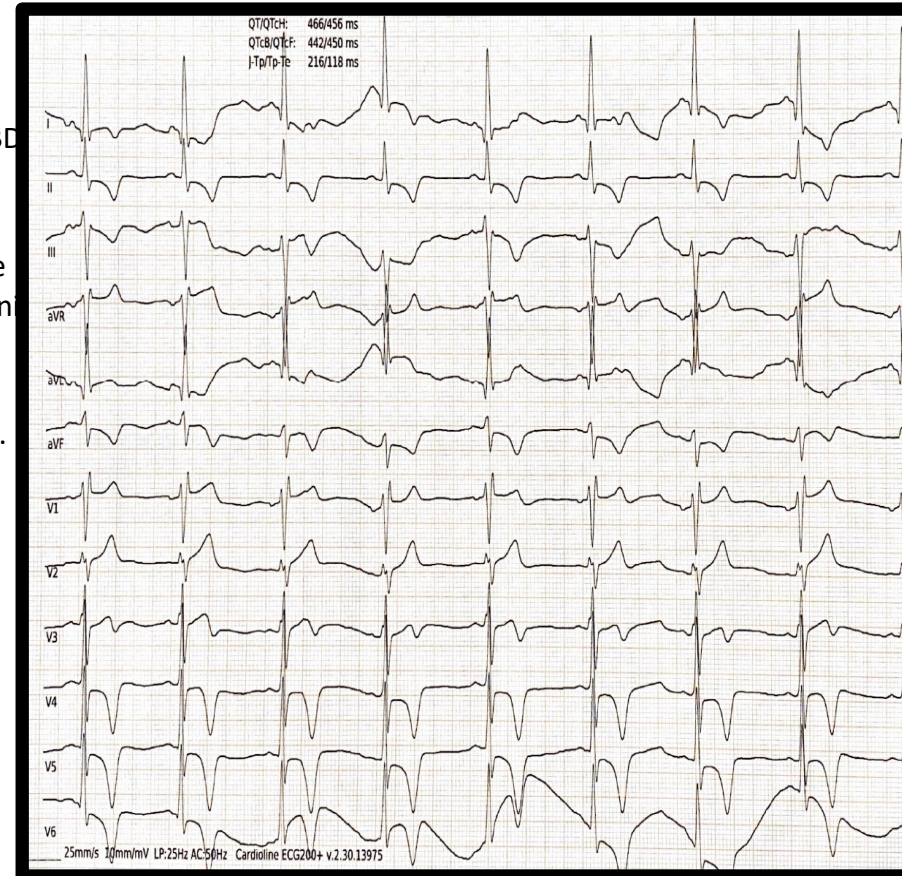
T1 Enhanced: Regional Result-1901, Slice No.: 2

	Segment 1	Segment 2	Segment 3	Segment 4	Segment 5	Segment 6	Summ
T1 Native	843±56.7	857±47.2 ...	918±50.9 ...	1007±438	1129±467...	906±68.6 ...	939±273
R1 Native	1.19±0.08...	1.17±0.07...	1.09±0.06...	1.07±0.19...	0.99±0.35...	1.11±0.08...	1.11±0.1
T1 Enhanced	375±26.7 ...	372±19.4 ...	380±19.6 ...	402±33.0 ...	355±32.2 ...	360±33.8 ...	373±32.3
R1 Enhanced	2.68±0.19...	2.70±0.14...	2.64±0.14...	2.51±0.21...	2.84±0.24...	2.81±0.27...	2.70±0.2
ϵ	30.0 %	30.9 %	31.3 %	30.4 %	39.1 %	34.0 %	32.8 %
ROI Area Native	138 mm ²	184 mm ²	133 mm ²	117 mm ²	146 mm ²	151 mm ²	869 mm ²
ROI Area Enhanced	115 mm ²	153 mm ²	117 mm ²	145 mm ²	179 mm ²	154 mm ²	862 mm ²
Hematocrit	45.2 %	45.2 %	45.2 %	45.2 %	45.2 %	45.2 %	45.2 %
Field Strength	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T	1.5 T



Esami diagnostici (2023)

- **TDS (04/2023):** 87% FCT max, 175 W. Nel recupero 2 BEV isolati tipo BBD asse inferior (wash-out da betabloccante).
- **Ecocardiogramma c/D (04/2023):** CMP ipertrofica concentrica a localizzazione prevalentemente medio-apicale, non ostruttiva (spessore max medio-apicale 16 mm). Normali dimensioni endocavitarie e funzioni di pompa (FE 66%). DD II grado. Lieve dilatazione atriale sn. IM lieve.
- **ECG Holter (04/2023)** [in Bisoprololo 5 mg/die]: RS alla FCm di 56 bpm (min 40 bpm, max 100 bpm). 5 BEV. 31 BESV e una tripletta. Non pause.
- **Microalbuminuria:** 106 mg/l (09/2023), 28.8 mg/l (10/2023).
- **ECG (09/2023):** RS alla FC 54 bpm. Anomalie della RV in sede infero-laterale.
- **Visita oculistica (2/10/2023):** IC astigmatismo



Esami ematochimici:

	Maggio 2023	Settembre 2023
Emoglobina (g/dl)	15.4	14.3
Piastrine (cell/mq)	271000	267000
Creatinina (mg/dl)	1.11	0.97
Sodio (mEq/l)	138	139
Potassio (mEq/l)	4.59	4.75
Colesterolo totale (mg/dl)	185	157
Colesterolo LDL (mg/dl)	121	110
Colesterolo HDL (mg/dl)	48	45
Trigliceridi (mg/dl)	78	69
TSH (μ UI/ml)	0.54	0.5

EEC (09/2023): Nt-pro-BNP 137 pg/ml, TnI hs 18.2 pg/ml, Ferritina 162 ng/ml

Test genetico:

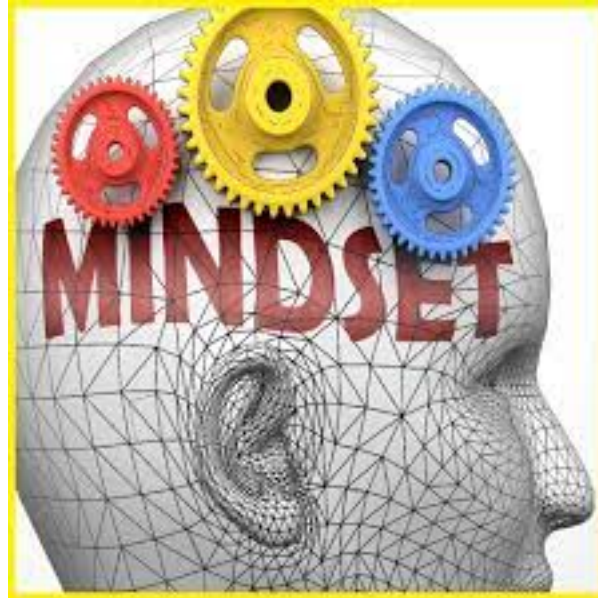
Esequito a Gennaio 2023 – Risultati a Luglio 2023

Mutazione in emizigosi della variante c.644A>G:p.Asn215Ser nell'esone 5 del gene GLA.

Tale variante è classificabile secondo i criteri ACMG come variante patogenetica (Classe 5, ovvero causativa di patologia). La variante è presente nel database gnomAD v2.1.1 con una bassissima frequenza allelica (0.0005%), è presente nel database ClinVar (ID 10730) con 18 sottomissioni come variante patogenetica per malattia di Fabry senza conflitti di interpretazione, ed è ampiamente descritta in letteratura in individui con malattia di Fabry con prevalente fenotipo cardiaco e ad esordio tardivo. In particolare è stato effettuato uno studio (PMID: 29649853) che ha confrontato 125 pazienti con questa variante (66 femmine eterozigoti e 59 maschi emizigoti) rispetto a pazienti con Malattia di Fabry Classica (401 pazienti). I pazienti con questa variante sono risultati con un rischio aumentato per complicanze cardiache, anche severe, rispetto ai pazienti con altre varianti associate a Malattia di Fabry Classica e un rischio minore per complicanze renali e cerebrovascolari, per le quali si consiglia di instaurare un follow-up. Sono poi stati effettuati studi funzionali su questa variante che hanno evidenziato una diminuzione della funzione dell'enzima prodotto dal gene, che tuttavia mostrava un'attività enzimatica residua che rimaneva superiore all'1% (PMID: 16773563, 17555407, 21598360).

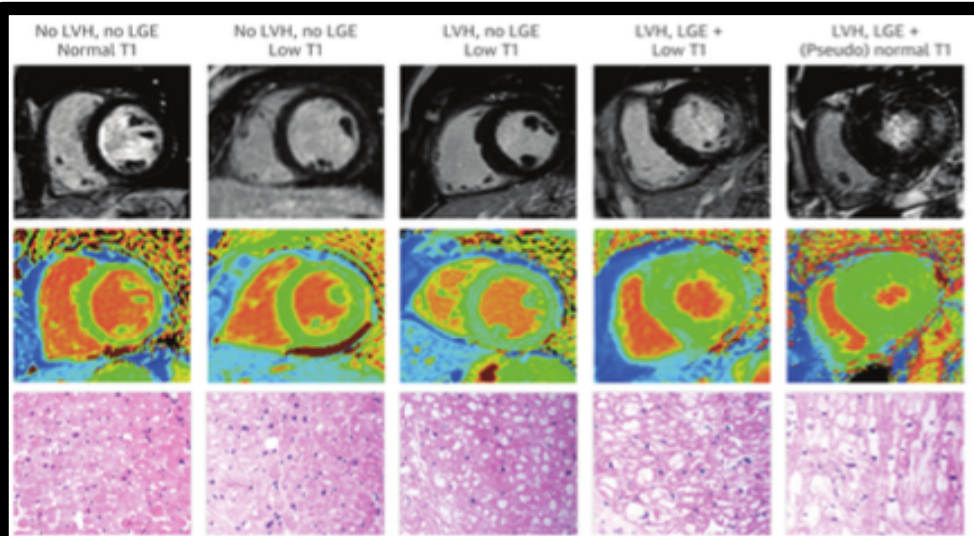
Pertanto sulla base della patogenicità della variante presente in emizigosi (sulla singola copia del cromosoma X) nel Sig. Fragomeni è possibile porre una diagnosi di Malattia di Fabry (OMIM # 301500), una malattia causata dalla funzionalità ridotta dell'enzima alfa-galattosidasi con accumulo di uno glicosfingolipide, il globotriaosilceramide, in vari tessuti causando problematiche multisistemiche.

A cardiomyopathy mindset



MRI

Correlations Between Cardiac Magnetic Resonance and Myocardial Histologic Findings in Fabry Disease



Correlations Between Cardiac Magnetic Resonance and Myocardial Histologic Findings in Fabry Disease JACCi 2023

COMMENTO A:

Correlations Between Cardiac Magnetic Resonance and Myocardial Histologic Findings in Fabry Disease

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A CURA DI:

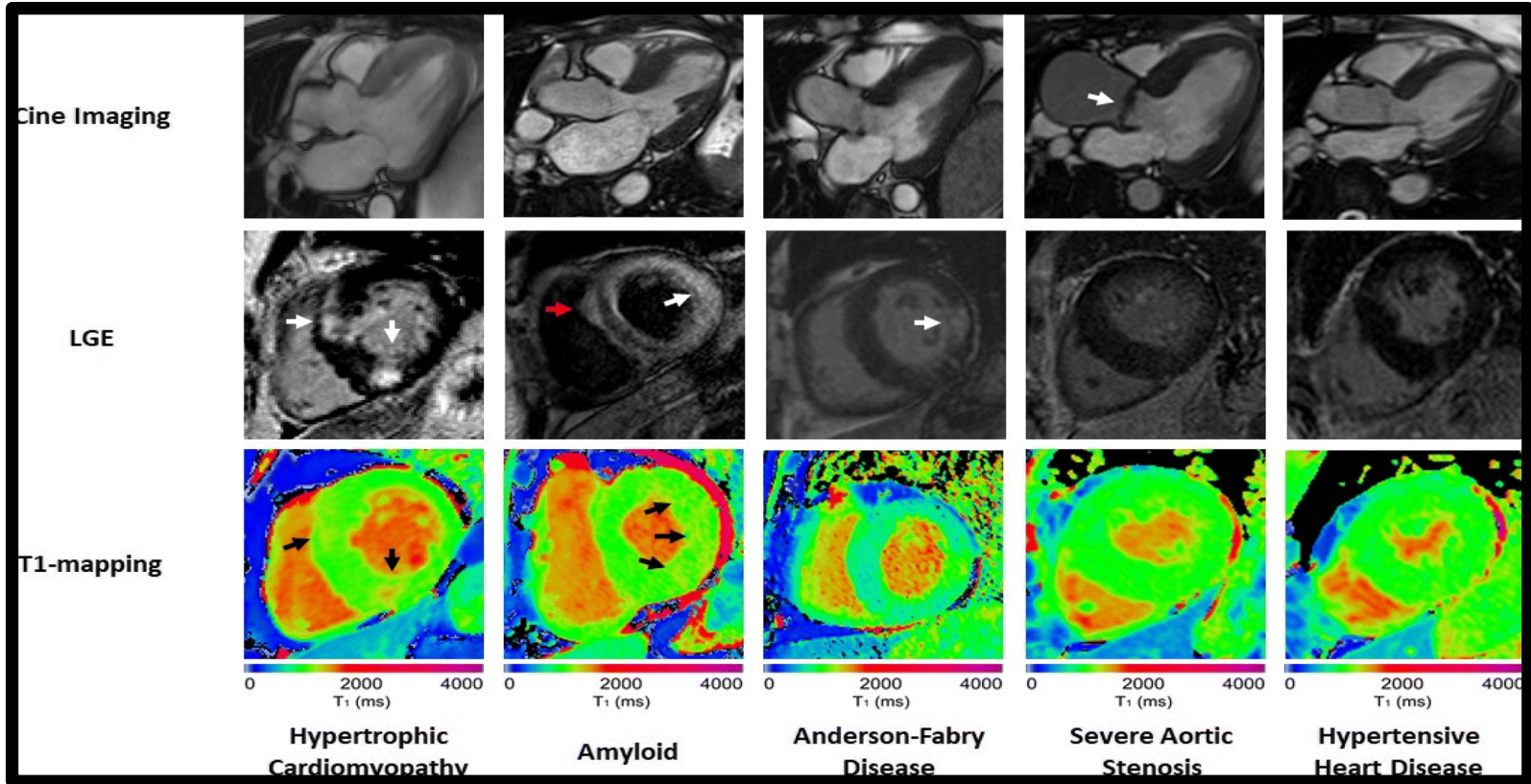
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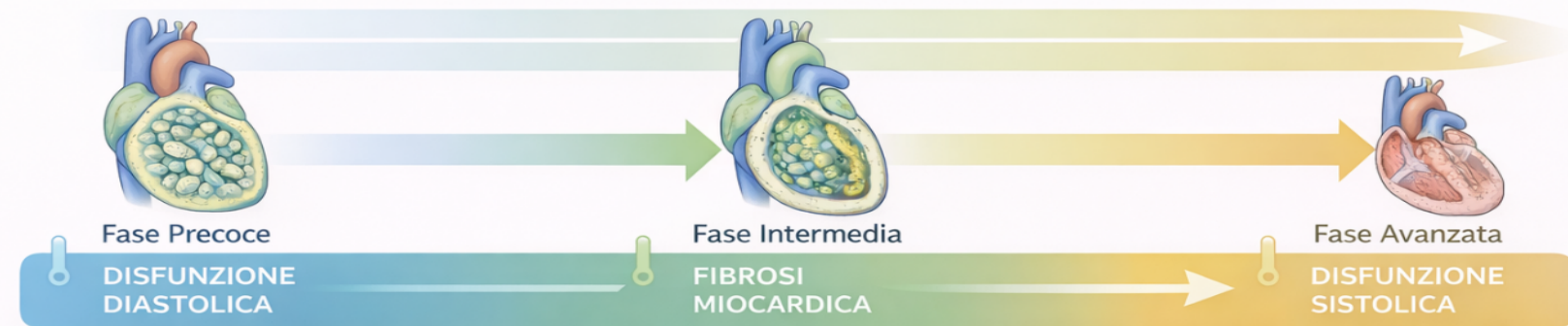
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Cardiopatia a fenotipo ipertrofico: RM cardiaca: first look, fast diagnosis



Progressione cardiaca nella malattia di Fabry verso lo scompenso cardiaco



Meccanismi:

- Accumulo di Gb3 nei miociti
- ↑ rigidità parietale
- Alterato rilasciamento attivo
- ↑ Pressioni di riempimento

Ecocardiografiche:

↑ E/Ee' ↑ Massa ventricolare ↓ GLS



Funzione sistolica preservata

Meccanismi:

- LGE alla CMR
- Punto di non ritorno fisiopatologico

Meccanismi:

- Attivazione Infiammatoria
- Stress ossidativo
- Rimodellamento extracellulare
- Deposizione fibroelastica

Fibrosi:

- ↓ ↑ Compliance ventricolare
- Alterata sincronizzazione contrattile
- ↑ ↑ Rischio aritmico



Meccanismi:

- Fibrosi estesa
- Morte cellulare
- Rimodellamento ventricolare

↓ Frazione di eiezione

- Dilatazione ventricolare
- Scompenso avanzato

Gb3: globotriaosilceramide

GLS: Global Longitudinal Strain

LGE: Late Gadolinium Enhancement

CMR: Risonanza magnetica cardiaca

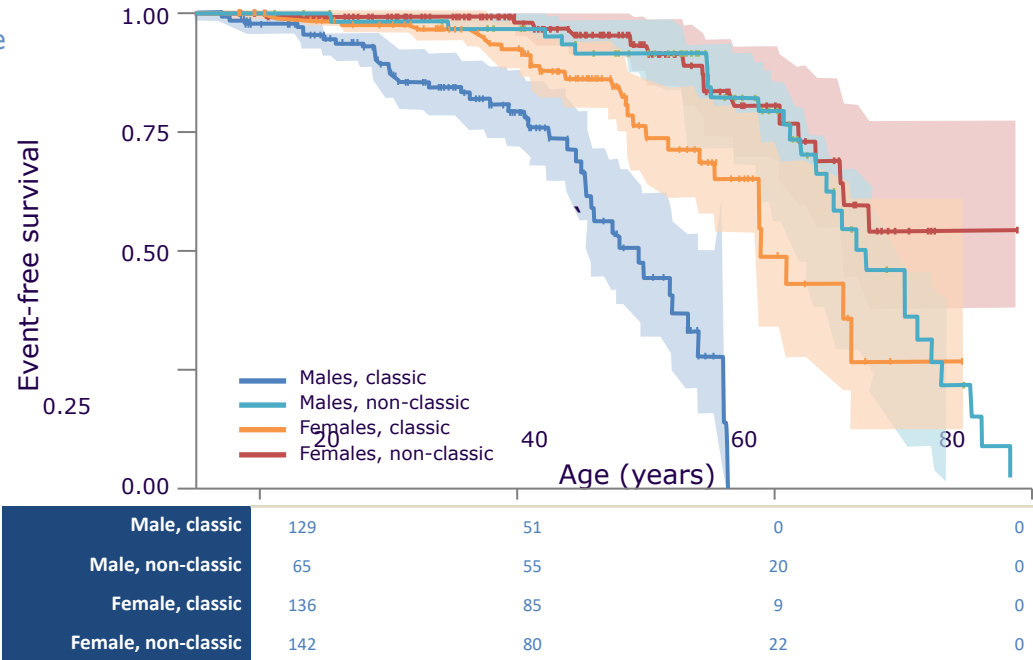
FE: Frazione di eiezione

HFpEF: Heart Failure con frazione eiezione preservata

M. Di Fabry e outcome

Event-free survival (any event) stratified for sex and phenotype

Retrospective assessment of event-free survival from birth to the first clinical visit (before ERT) in 499 adult patients (mean age 43 years old; 41% men; 57% with the classic phenotype) from three international centers of excellence

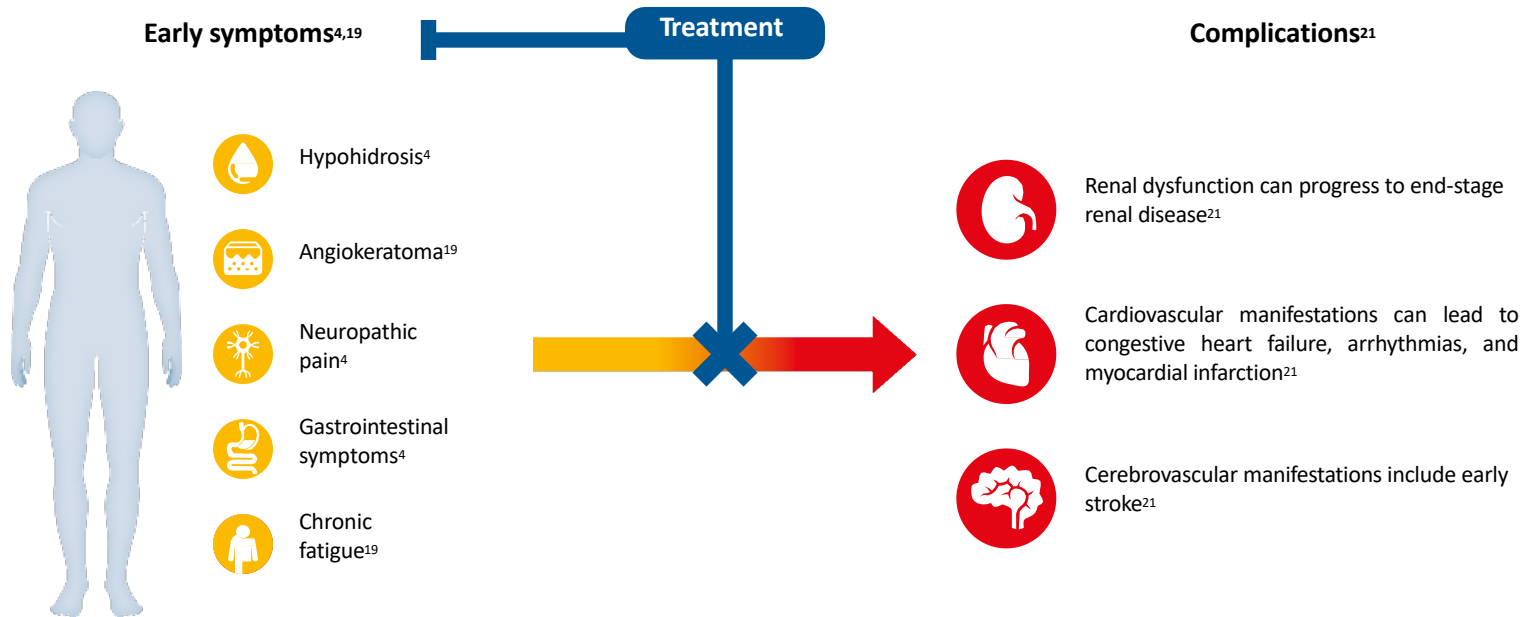


1. Arends M, et al. J Am Soc Nephrol 2017;28:1631-41.
2. Germain DP. Orphanet J Rare Dis. 2010;22;5:30;
3. Eng et al. Genet Med 2006;8:539-48; Germain. Orphanet J Rare Dis 2010;5:30;
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NEED FOR EARLY INTERVENTION

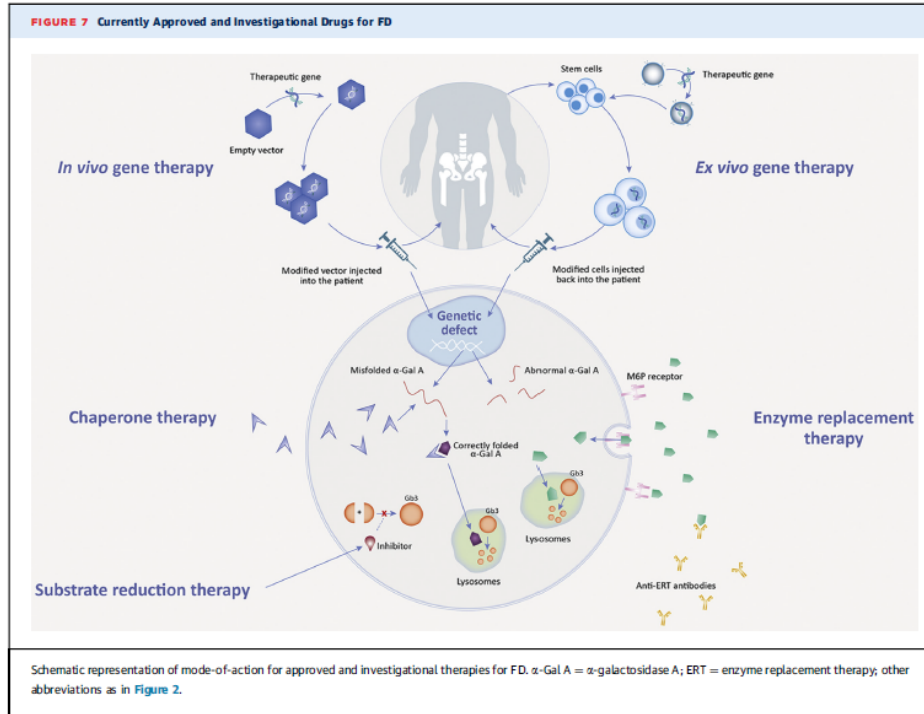
Clinical variability of different mutations, variable disease severity and symptom onset make the Fabry disease notoriously difficult to diagnose.²⁰ The need for prompt and accurate diagnosis of this devastating, progressive disease became paramount so that patients could be identified and treated before incurring irreversible organ damage.²¹

Ideally, treatment would alleviate the early symptoms as well as reduce or eliminate the risk of developing life-threatening complications later in life.²²



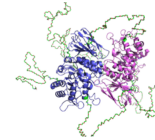
	agalsidasi beta	agalsidasi alfa	migalastat	pegunigalsidasi alfa
Indicazione terapeutica	 > 7 years old	 > 6 years old	 ≥ 12 years old	 ≥ 18 years old
Posologia e modalità di somministrazione	 15mg/h initial infusion, reduced as tolerance increases.	 40 min infusion	 Every other day oral tablet (4h fasting [2 pre and 2 post-]) administration	 3h initial infusion, reduced to 1,5h according to patient tolerability
Proprietà di farmacocinetica	 Mean half life 45-100 min.	 ~108 minutes in males. ~89 minutes in females	 Mean half life 3-5h.	 Mean half life 80 h.

Currently approved and Investigational drugs for Fabry Disease



ERT ev

Agalsidase Alfa	Agalsidase Beta
Recombinant α -galactosidase A produced from human fibroblasts [11]	Recombinant α -galactosidase A produced from Chinese hamster ovary (CHO) cells [11]
Intravenous [45]	Intravenous [46]
0.2 mg/Kg every other week [45] over 40 minutes	1 mg/Kg every other week [46] ≤ 0.25 mg/min for initial infusion or 15 mg/hr, rate can be gradually increased after initial infusion



Pegunigalsidase alfa is PEGylated

Chaperone orale

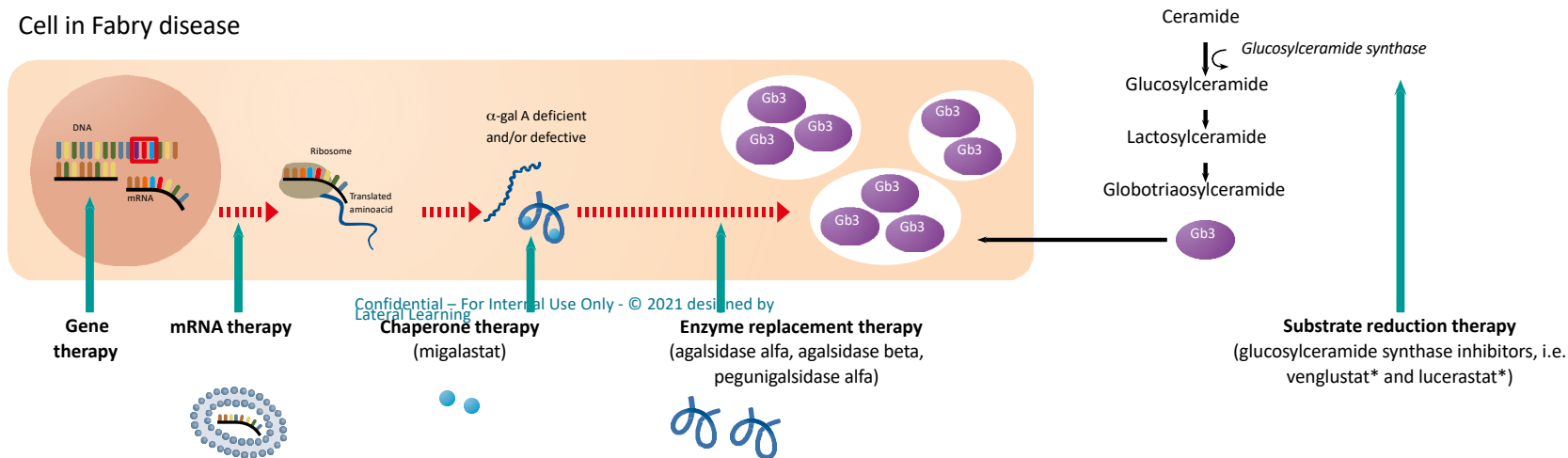
Pieroni M, Moon JC, Arbustini E, Barriales-Villa R, Camporeale A, Vujkovic AC, Elliott PM, Hagege A, Kuusisto J, Linhart A, Nordbeck P, Olivotto I, Pietilä-Effati P, Namdar M. Cardiac Involvement in Fabry Disease: JACC Review Topic of the Week. J Am Coll Cardiol. 2021 Feb 23;77(7):922-936.

TREATMENTS FOR FABRY DISEASE

Therapies for Fabry disease are directed at either replacing or generating deficient enzyme, or blocking the accumulation of substrate.⁷

For over 15 years, two recombinant enzyme preparations which aim to reconstitute defective α -galactosidase A, have been available to treat patients. In the past years, several new treatment modalities for Fabry disease have been developed, but only chaperone therapy which binds to the unstable α -galactosidase A to aid proper folding in patients with amenable variants of the GLA gene, is currently approved. Several other new approaches are being explored in clinical and preclinical studies. Amongst these are substrate reduction therapy and gene- and mRNA based therapy.^{6,7}

Cell in Fabry disease



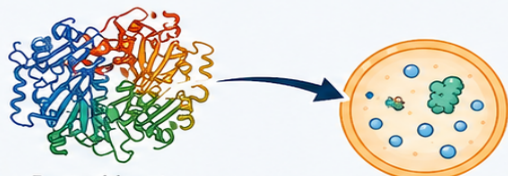
Fabry Disease – Pipeline Analysis

Sponsor	Asset	Stage	Mechanism of Action	Route of Administration	Modality	Submission	Regulatory
 sanofi	Venglustat	Phase III	GCS inhibitor	Oral	Small Molecule	2026	US/EU/JP Orphan US FTD
 idorsia	Lucerastat	Phase III	Glucosylceramide synthase (GCS) inhibitor	Oral	Small Molecule	2026?	
 BIOSIDUS	AGA BETA Biosimilar	Phase III	Recombinant human alpha galactosidase A (agalsidase beta)	IV	ERT		
 AccL Where Science and Medicine Meet	AL1211 (AL01211)	Phase II	Glucosylceramide synthase (GCS) inhibitor	Oral	Small Molecule		FDA Orphan
 Sangamo	isargalgene civaparvec	Phase I/II	AAV2/6_GLA cDNA	IV	Gene Therapy	H2 2025 (Accelerated approval)	US/EU Orphan; US FTD
 uniQure	AMT-191	Phase I/II	AAV5_GLA	IV	Gene Therapy	Precedent for an Accelerated Approval pathway	US Orphan/FTD
 4DMT	4D-310	Phase I/II	C102 vector-GLA gene	IV	Gene Therapy		FTD
 EXEGENESIS BIO	EXG110	Phase I/II (Planned)	AAV_GLA	IV	Gene Therapy	US Phase I Plan, China first patient dosed	FDA Orphan
 GC Biopharma 	HM15421/GC1134A	Phase I/II	Long-acting GLA	SC	ERT		FDA Orphan

CURRENTLY AVAILABLE THERAPIES FOR FABRY DISEASE

1. ENZYME REPLACEMENT THERAPY (ERT)

Replaces the deficient α -Gal A enzyme



Recombinant human α -galactosidase A

Lysosome



REPLAGAL®
(agalsidase alfa)

Intravenous infusion
every 2 weeks



FABRAZYME®
(agalsidase beta)

Intravenous infusion
every 2 weeks



ELFABRIO®
(pegunigalsidase alfa-iwxj)
PRX-102

Intravenous infusion
every 2 weeks

2. PHARMACOLOGICAL CHAPERONES

Stabilize the mutant enzyme, indicated only for specific mutations



Mechanism:
Correct protein folding

Lysosome



GALAFOLD®
(migalastat)



Oral
administration

3. SUPPORTIVE THERAPY AND SYMPTOM MANAGEMENT

To manage organ complications



Renal management,
transplantation



Cardiac management,
pacemaker



Stroke prevention,
neurological support



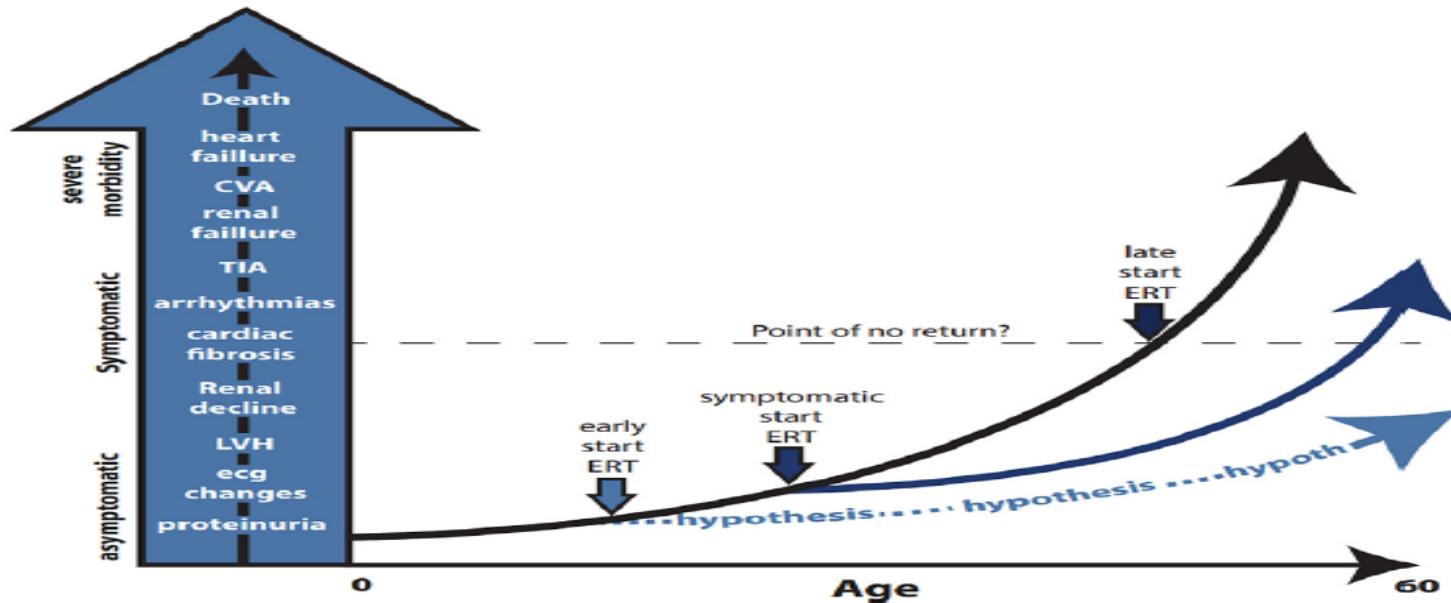
Pain management,
specific medications



Therapeutic choice should be individualized based on phenotype, mutation, organ involvement, and disease stage. Regular follow-up with a multidisciplinary team is essential to optimize outcomes.

**Always consult a specialist physician for diagnosis and treatment.*

Treatment of Male classic FD Patients Before the Age of 16 has a Beneficial Impact on Progression of Clinical Renal and Cardiac Manifestations of FD



Start of treatment with ERT as soon as possible (before age 16), in male cFD patients is associated with reduced occurrence of renal and cardiac manifestations of FD, as assessed by intermediate endpoints. Confirmation that this approach delays or even prevents renal failure and cardiac events requires another decade of follow-up

PRIMO ANNUNCIO

ROMA CARDIOMIOPATIE

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