

FENOTIPO IPERTROFICO: UPDATE 2026

Red Flags nella Cardiopatia a Fenotipo Ipertrofico: Tempo di un Aggiornamento?

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Hypertrophic Cardiomyopathy

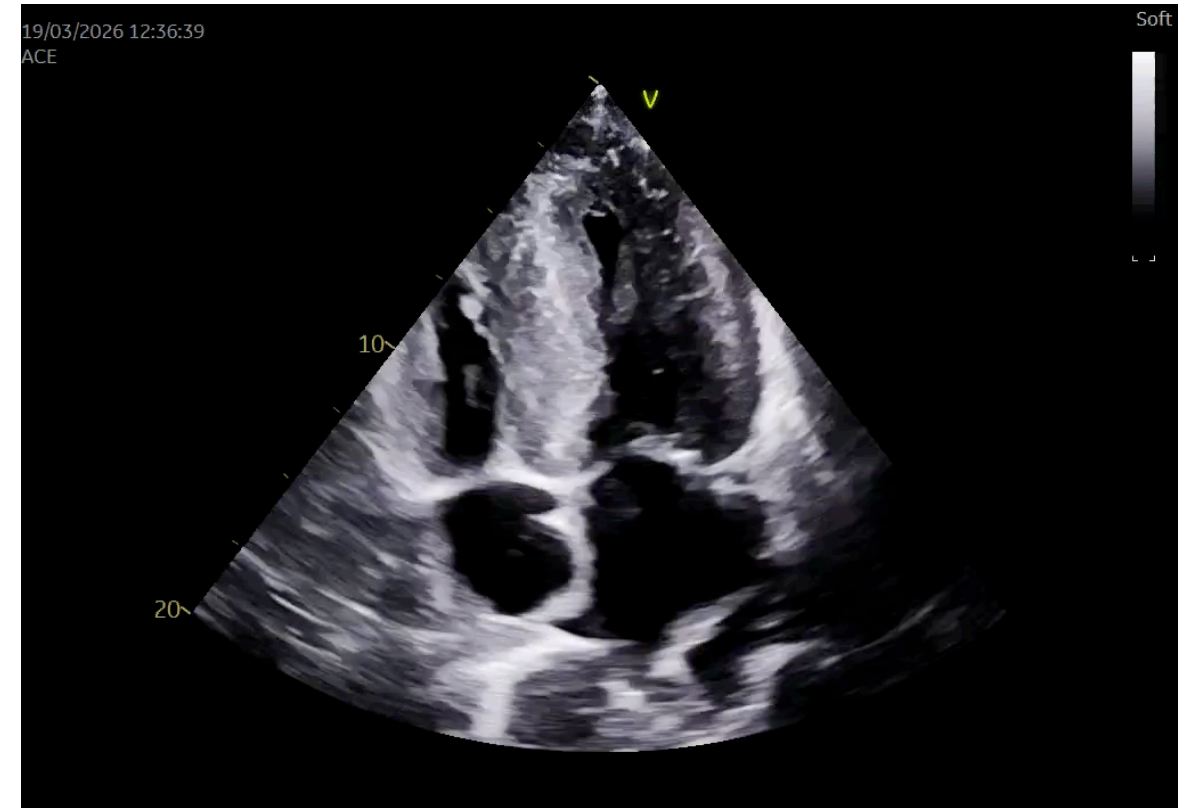
Increased LV Wall Thickness or Mass Not Solely Explained By Abnormal Loading Conditions

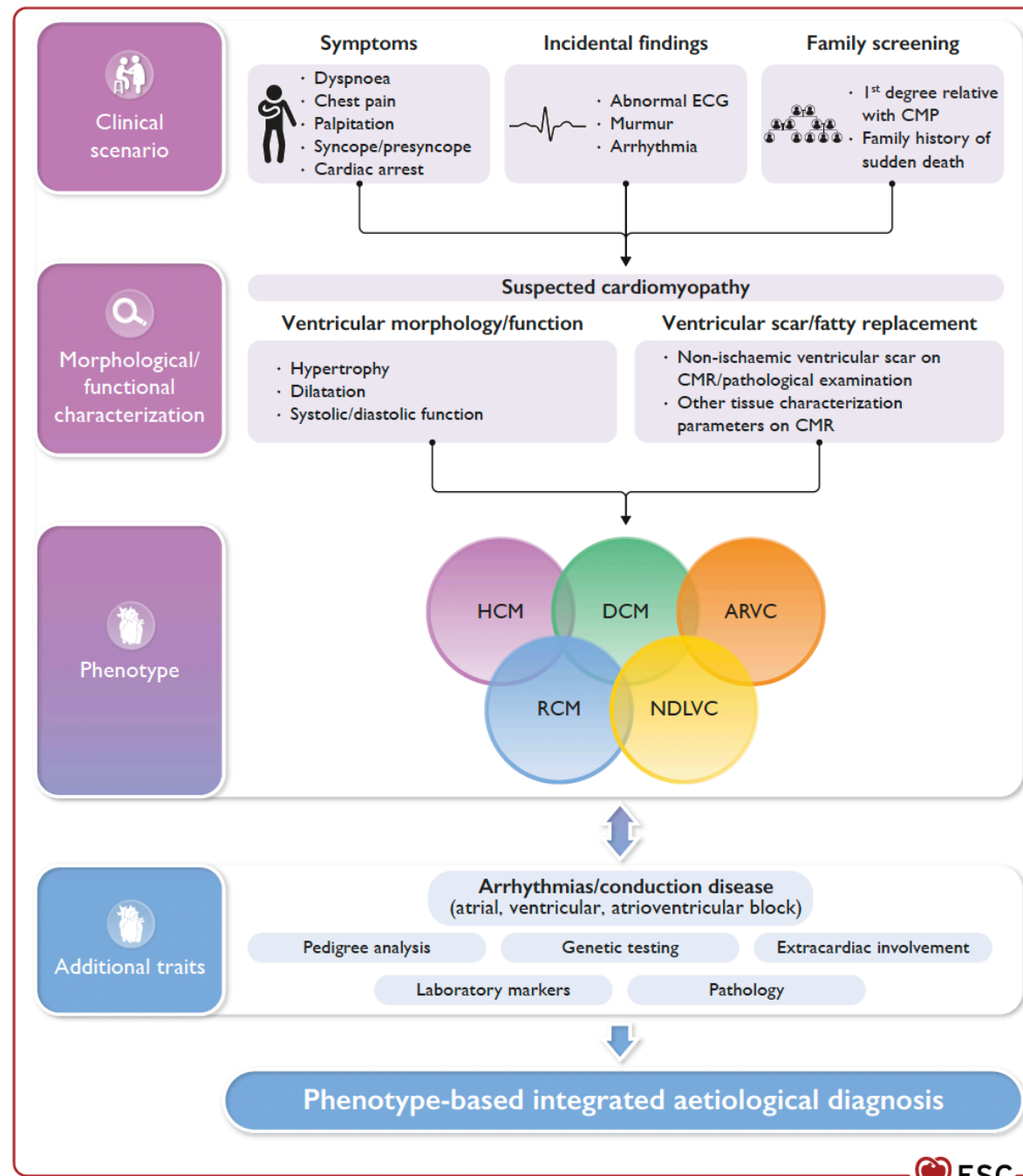
Diagnostic Criteria

Adults: *LV wall thickness ≥ 15 mm in any myocardial segment not solely explained by loading conditions*

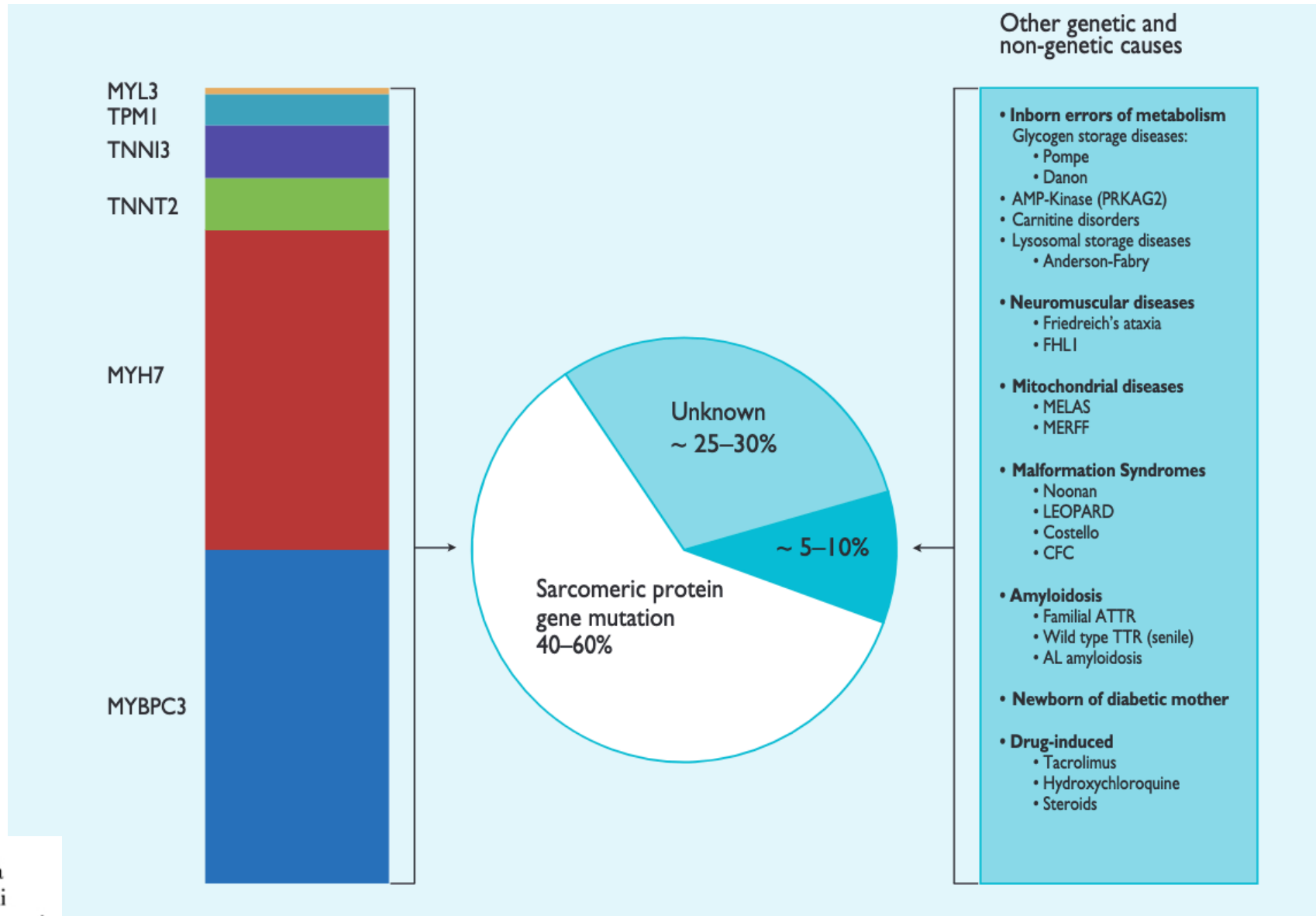
Relative: *LV wall thickness ≥ 13 mm*

Children: *LV wall thickness > 2 SD from the predicted mean (z-score > 2)*

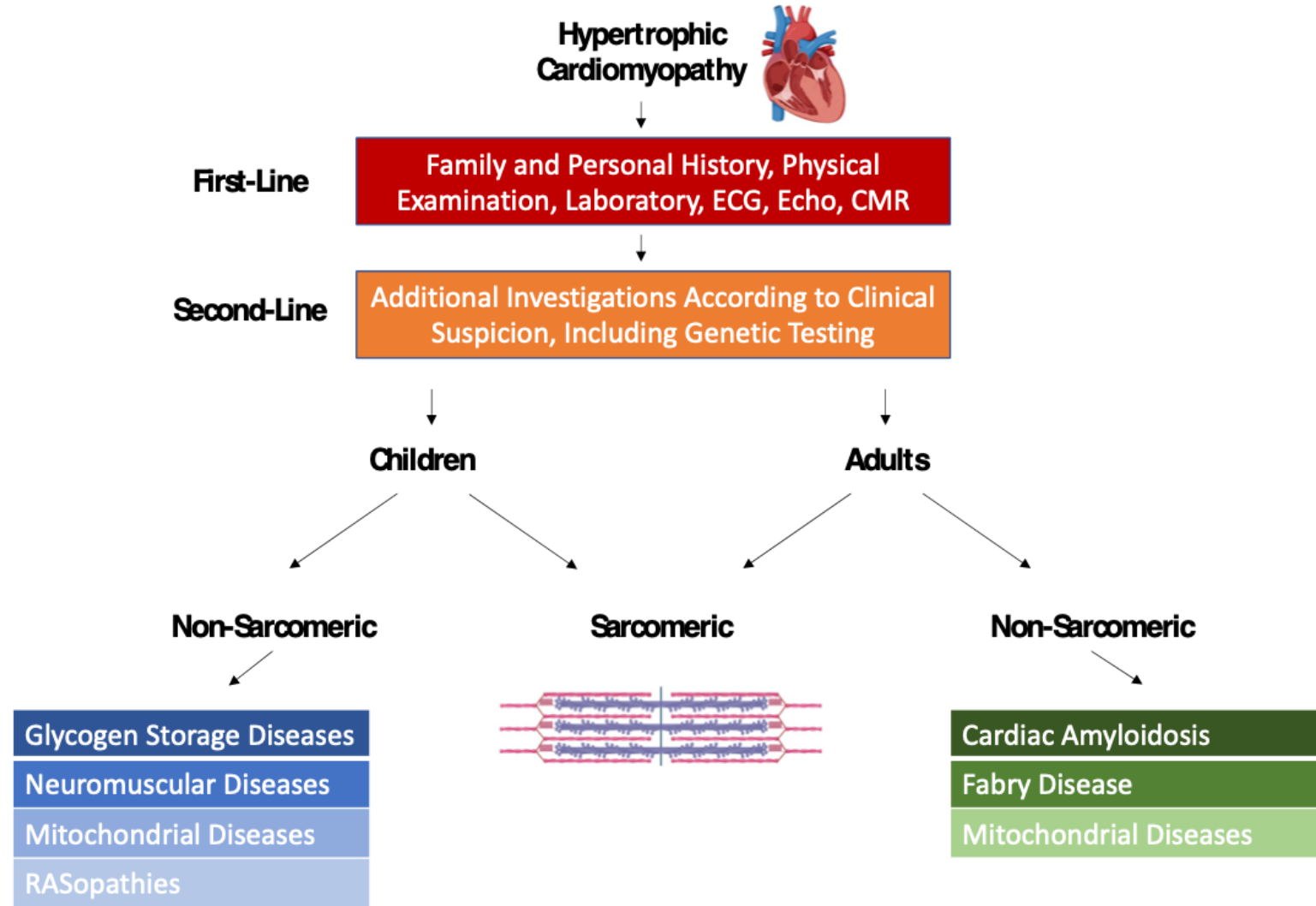




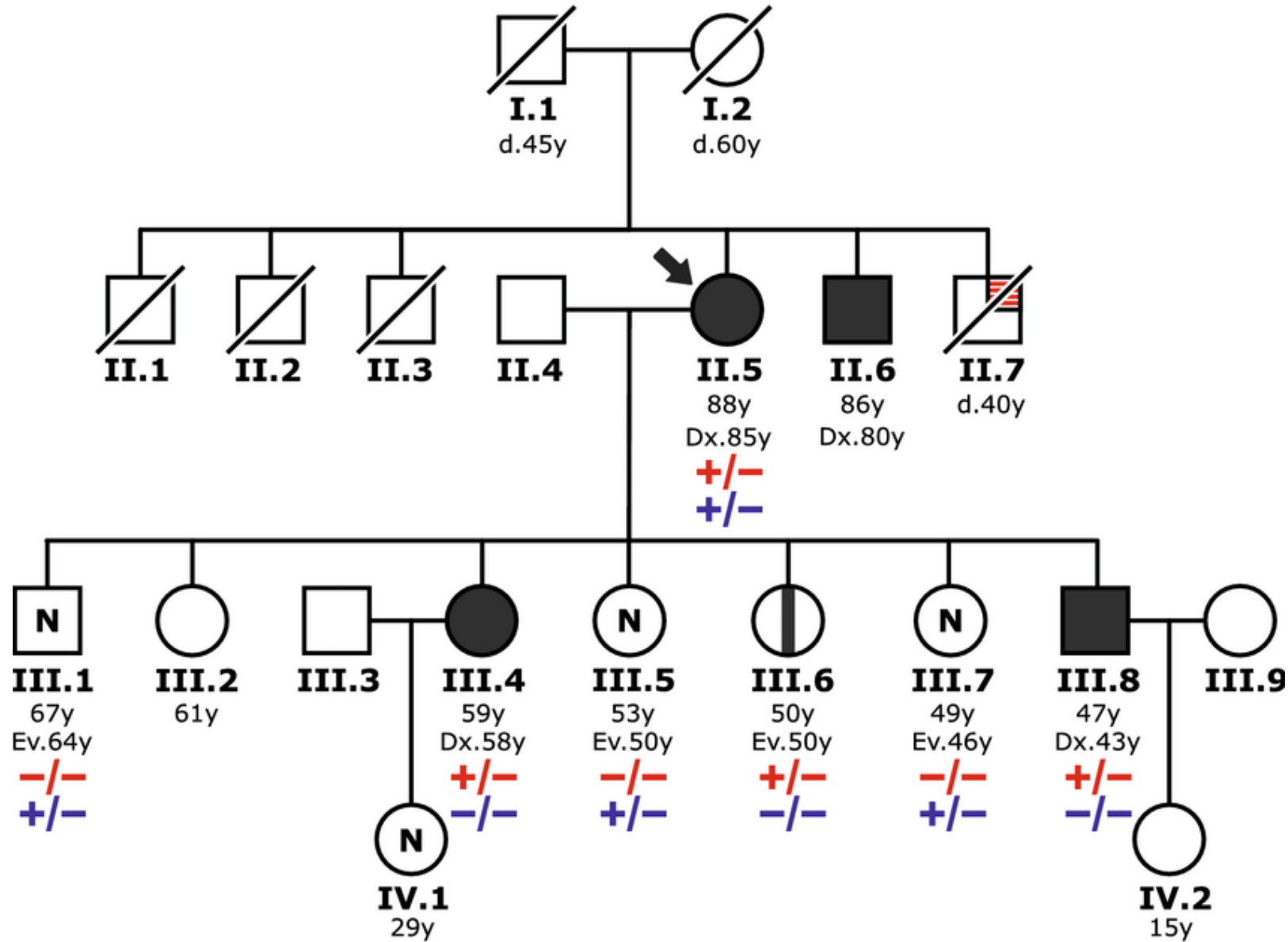
Aetiological Diagnosis



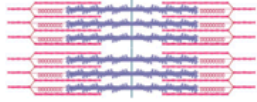
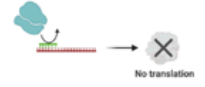
Diagnostic Work



Family Screening



Targeted Treatment

	Etiology	Novel Therapies	
Sarcomeric HCM	Mutations in Sarcomeric Genes Responsible for an Hypercontractility Phenotype	Myosin Inhibitors Gene Therapy	→ Mavacamten Aficamten 
Fabry Disease	Mutations in <i>GLA</i> Gene Responsible for Gb3 and LysoGb3 Accumulation	Enzyme Replacement Therapy Chaperone Therapy Substrate Reduction Therapy	→ Agalsidase Alpha Agalsidase Beta Pegunigalsidase → Migalastat → Lucerastat Venglustat   
Cardiac Amyloidosis	Abnormal Amyloid Fibrils Formation and Deposition	Antisense Oligonucleotides Small Interfering RNA Tetramer Stabilizers Clearance of Amyloid Deposits	→ Inotersen Eplotersen → Patisiran Vutrisiran → Tafamidis Acoramidis → Antibodies    

Cardiomyopathy Mindset

Red Flags Approach

“A fundamental tenet of this approach is that the systematic search for diagnostic clues or ‘red flags’ can identify particular disorders and guide rational selection of diagnostic tests [...]”

“This approach does not necessarily involve the use of novel or particularly sophisticated tests, but it does require deliberate analysis of every aspect of the individual and their family as well as an integrated probabilistic interpretation of cardiac investigations.”

Age



Red-Flags

Spec

Disease(s)

<20 years

81%

Syndromic

20 - 60 years

80%

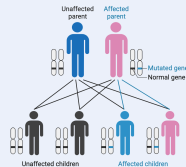
Sarcomeric

>60 years

85%

Infiltrative

Family History



X-linked

81%

AFD

Autosomal recessive

80%

Friedreich's Ataxia

Matrilinear

85%

Mitochondrial

Physical Exam



Ophtalmoplegia,
wide-spaced eyes

100%
100%

Noonan

Short stature,
café-au-lait spots

80%
100%

Leopard

Ataxia

100%

Friedreich's Ataxia

Angiokeratomas
Neuropathic pain
Cornea verticillata

100%
100%
100%

AFD

Carpal tunnel syndrome

94%

TTR Amyloidosis

Laboratory tests



Increased Transaminases

83%

Pompe disease

Electrocardiogram



Pseudo-STEMI pattern

80%

Sarcomeric

Advanced AV Blocks
Low QRS voltages

79%

Amyloidosis

Echocardiography



SAM
LVOTO
Asymmetric LVH
Apical LVH

86%
91%
82%
100%

Sarcomeric

Granular sparkling myocardium
thickened interatrial septum
Pericardial effusion

88%
100%
80%

Amyloidosis

Concentric LVH

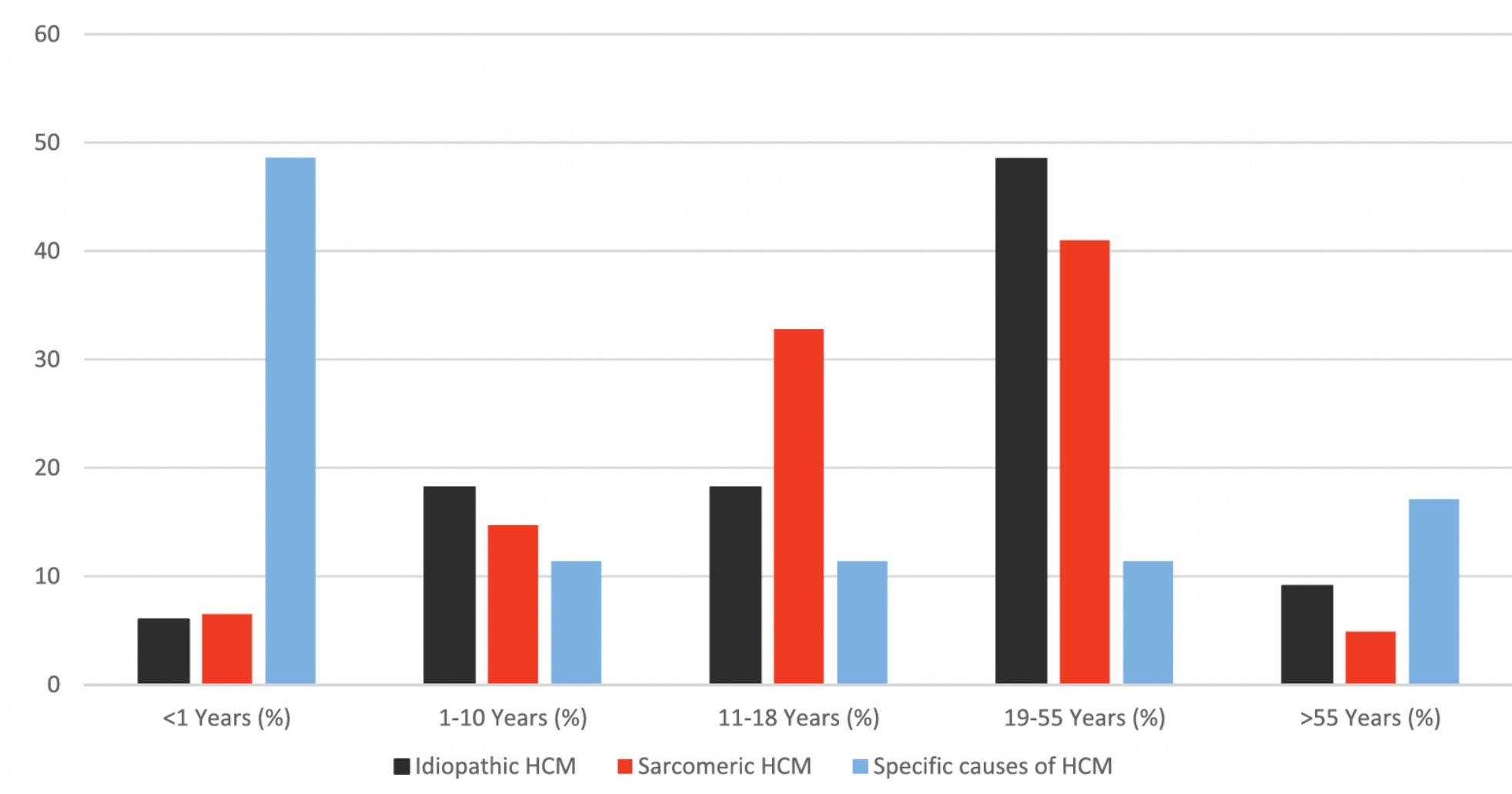
78%

AFD, Mitochondrial,
Noonan, TTR Amyloidosis,
Pompe, Danon

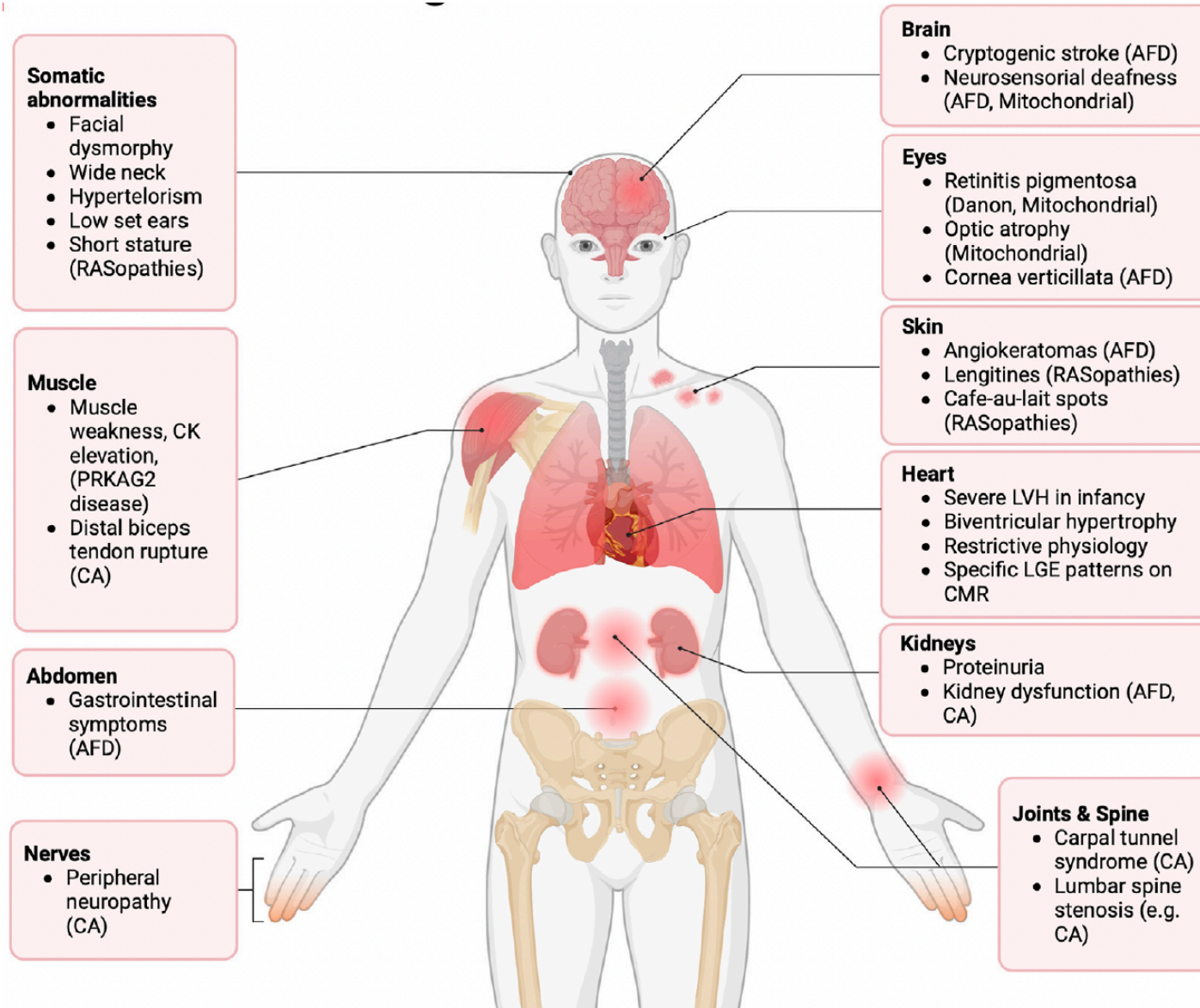


European
Reference
Network

for rare or low prevalence
complex diseases

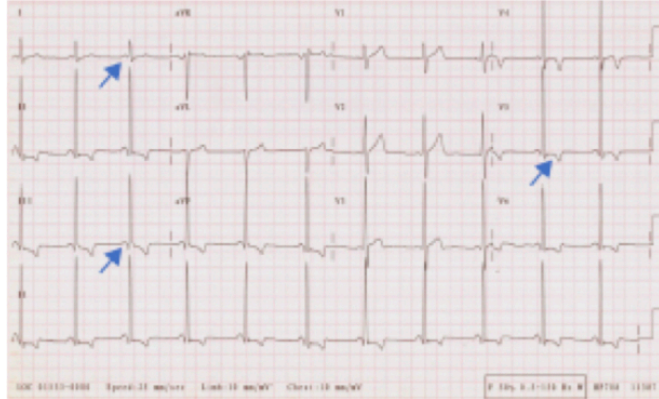


Clinical History and Laboratory



Bakalacos A, Monda E et al. *Can J Cardiol*

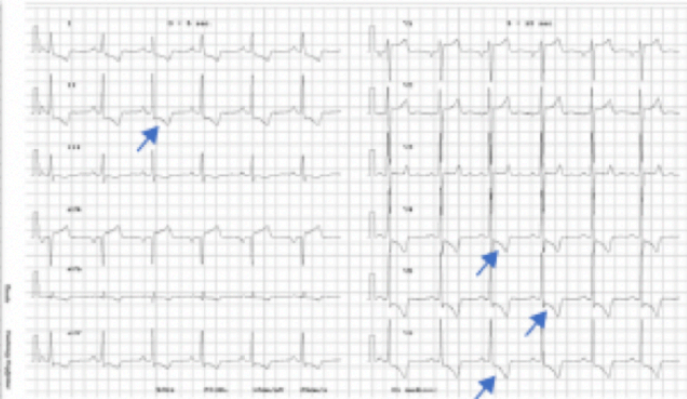
A Short PR without delta wave



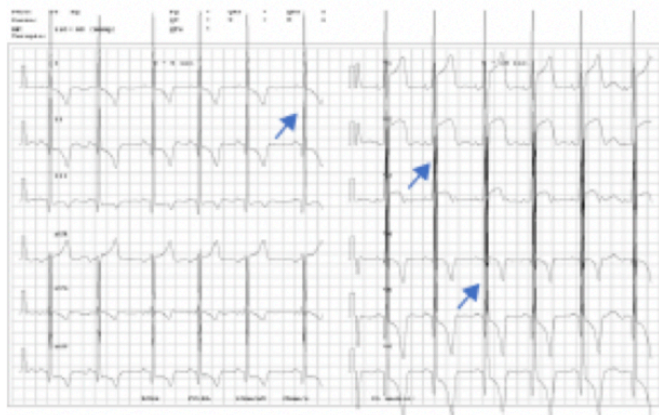
B Extreme Right QRS Axis Deviation



C Deep Infero-lateral T wave inversion



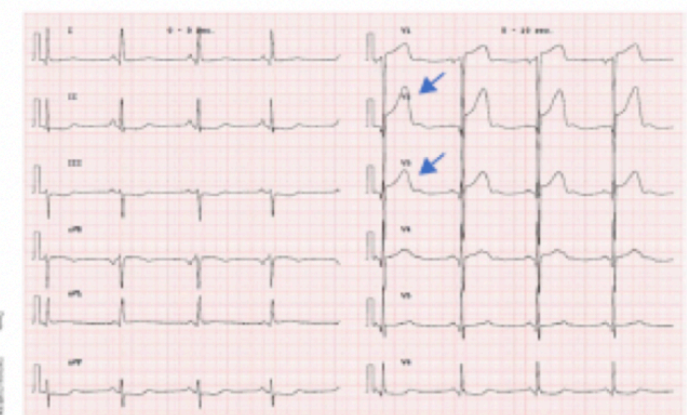
D Extreme LVH (Sokolow > 45)



E Low QRS Voltages

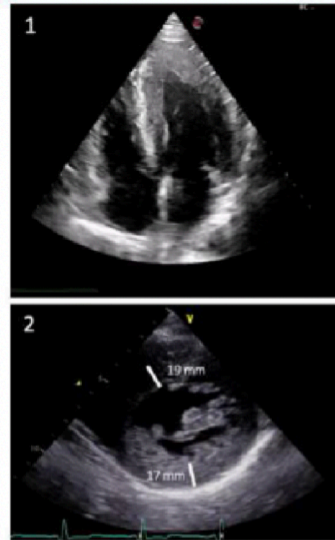


F Pseudo STEMI Pattern

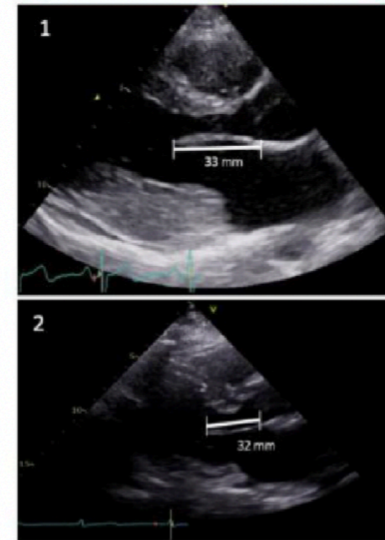


Echocardiography

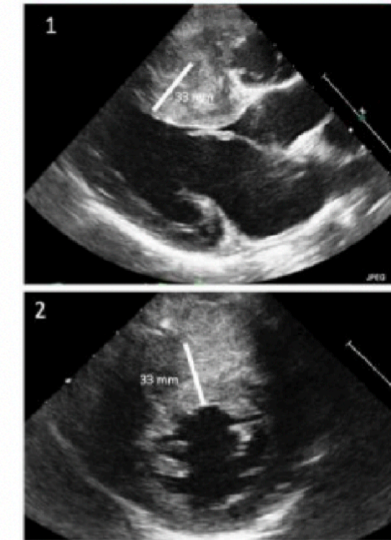
A CONCENTRIC HYPERTROPHY



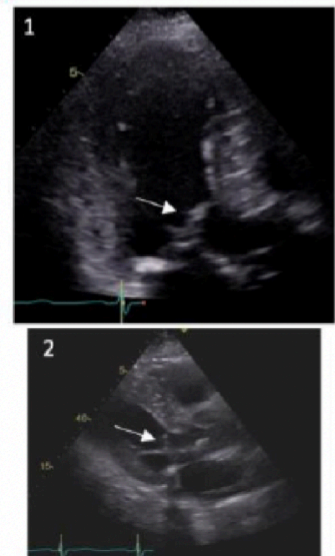
B AML > 30 mm



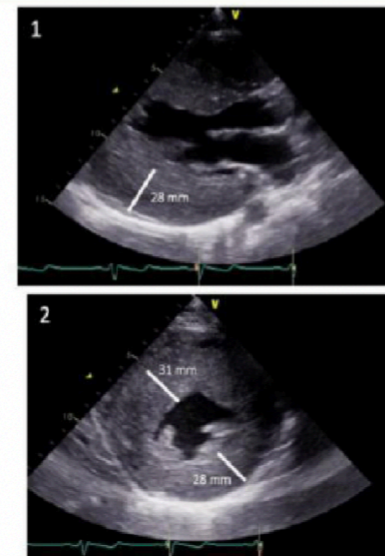
C ASYMMETRIC SEPTAL LVH



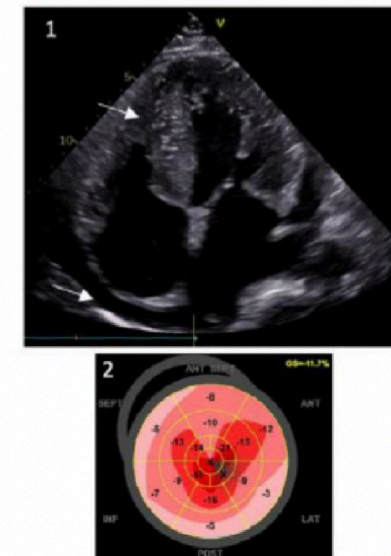
D SAM OF MITRAL VALVE



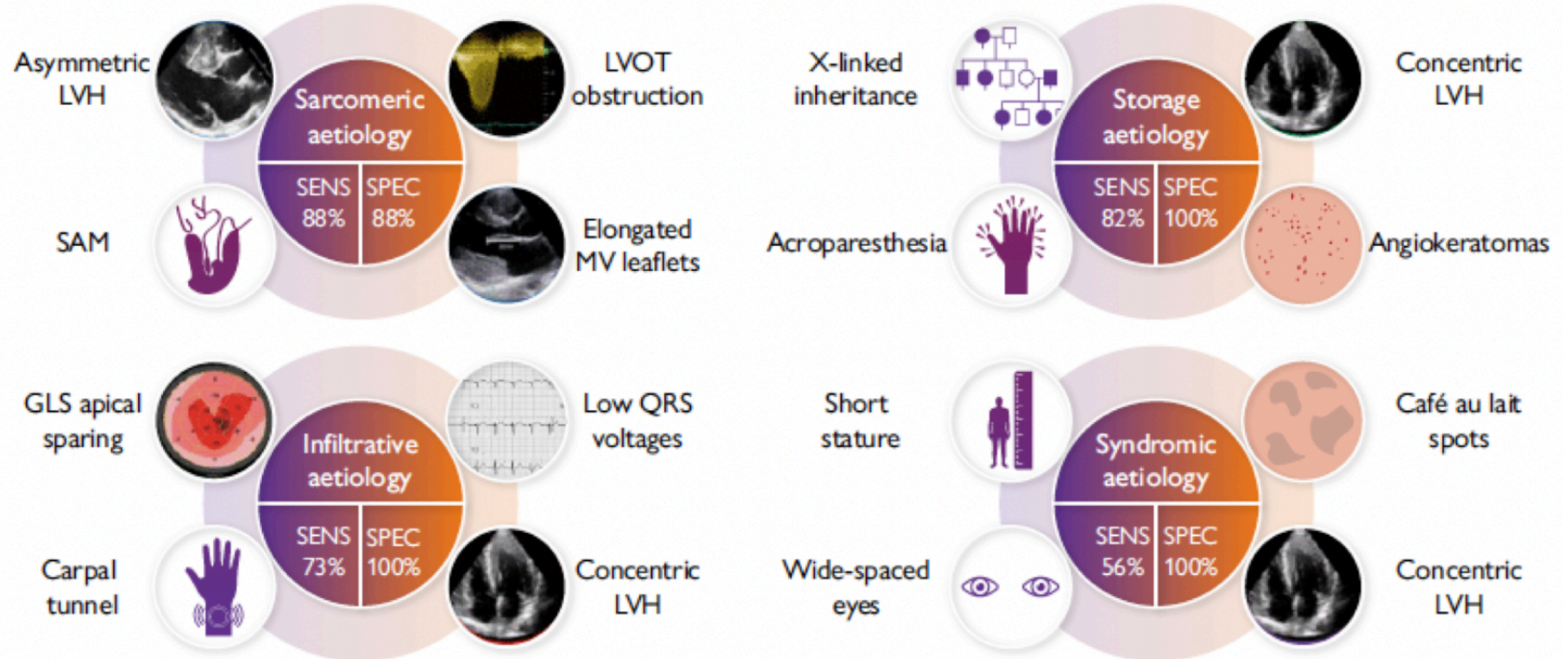
E SEVERE LEFT POSTERIOR WALL HYPERTROPHY



F APICAL SPARING



Red Flags Cluster



Cardiomyopathy phenotype

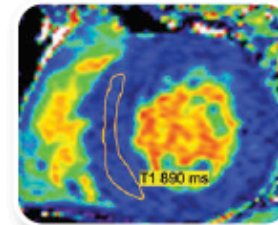
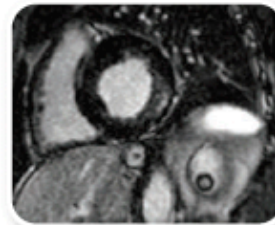
Finding

Cardiac CMR examples

Specific diseases to be considered

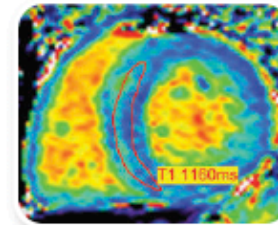
HCM

Posterolateral LGE and concentric LVH
Low native T1



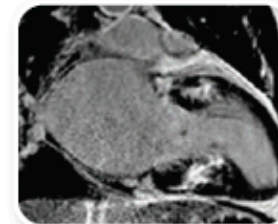
Anderson–Fabry disease

Diffuse subendocardial LGE,
high native T1



Amyloidosis

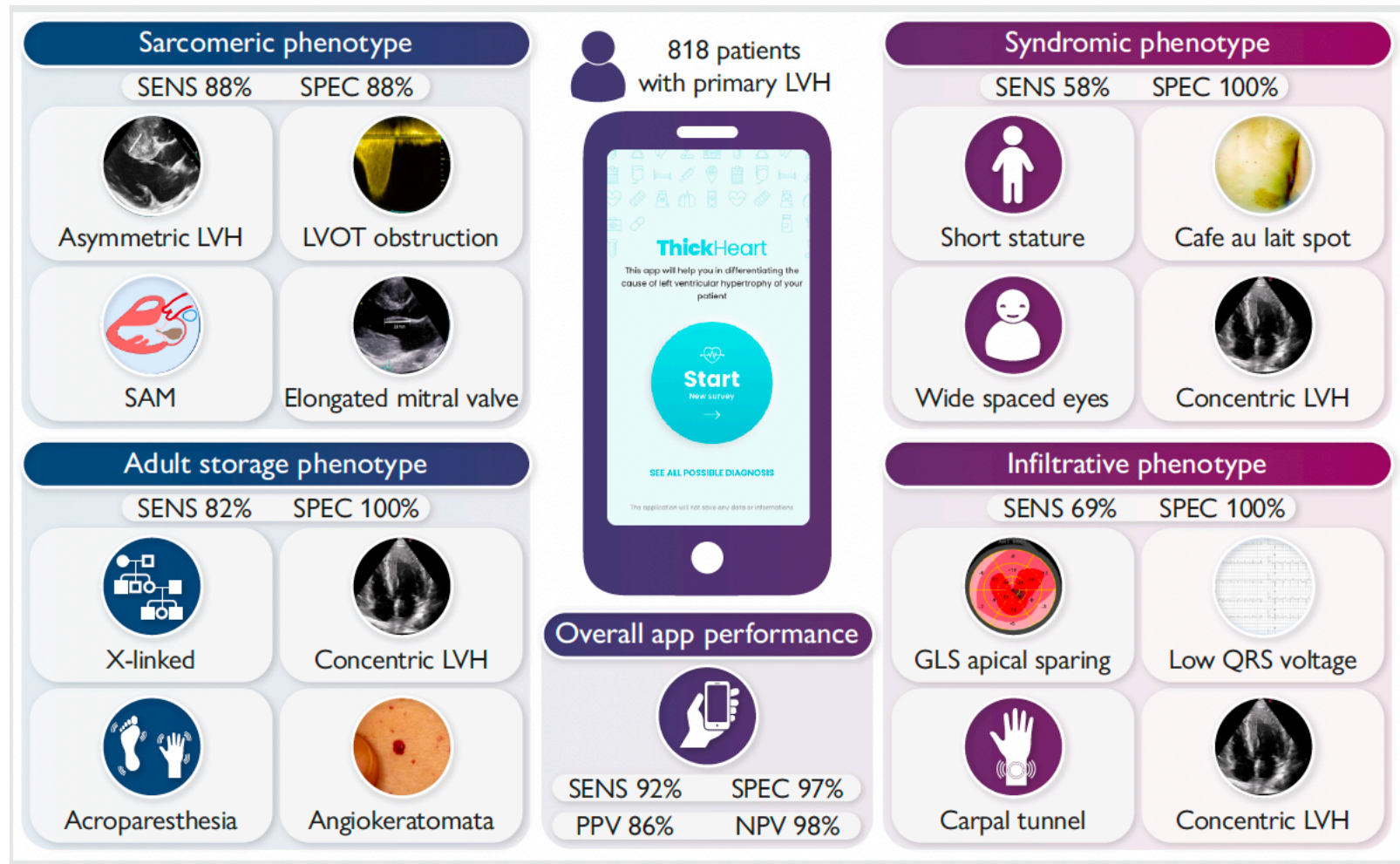
Patchy mid-wall in hypertrophied areas



Sarcomeric HCM

Development of a smartphone-based app to support the differential diagnosis in patients with primary left ventricular hypertrophy

Niccolò Maurizi ^{1,2,*}, Emanuele Monda ³, Maurizio Pieroni ¹, Elena Biagini ⁴, Ella Field ^{5,6}, Silvia Passantino ⁷, Gabriella Dallaglio ¹, Carlo Fumagalli ¹, Panagiotis Antiochos ², Ioannis Skolidis ⁸, Henri Lu ², Ioannis Kachrimanidis ⁹, Alessia Argirò ¹, Francesca Girolami ⁷, Franco Cecchi ^{1,10}, Francesco Cappelli ¹, Perry M. Elliott ¹¹, Juan Pablo Kaski ^{5,6}, Giuseppe Limongelli ³, and Iacopo Olivetto ^{1,7}



ThickHeart

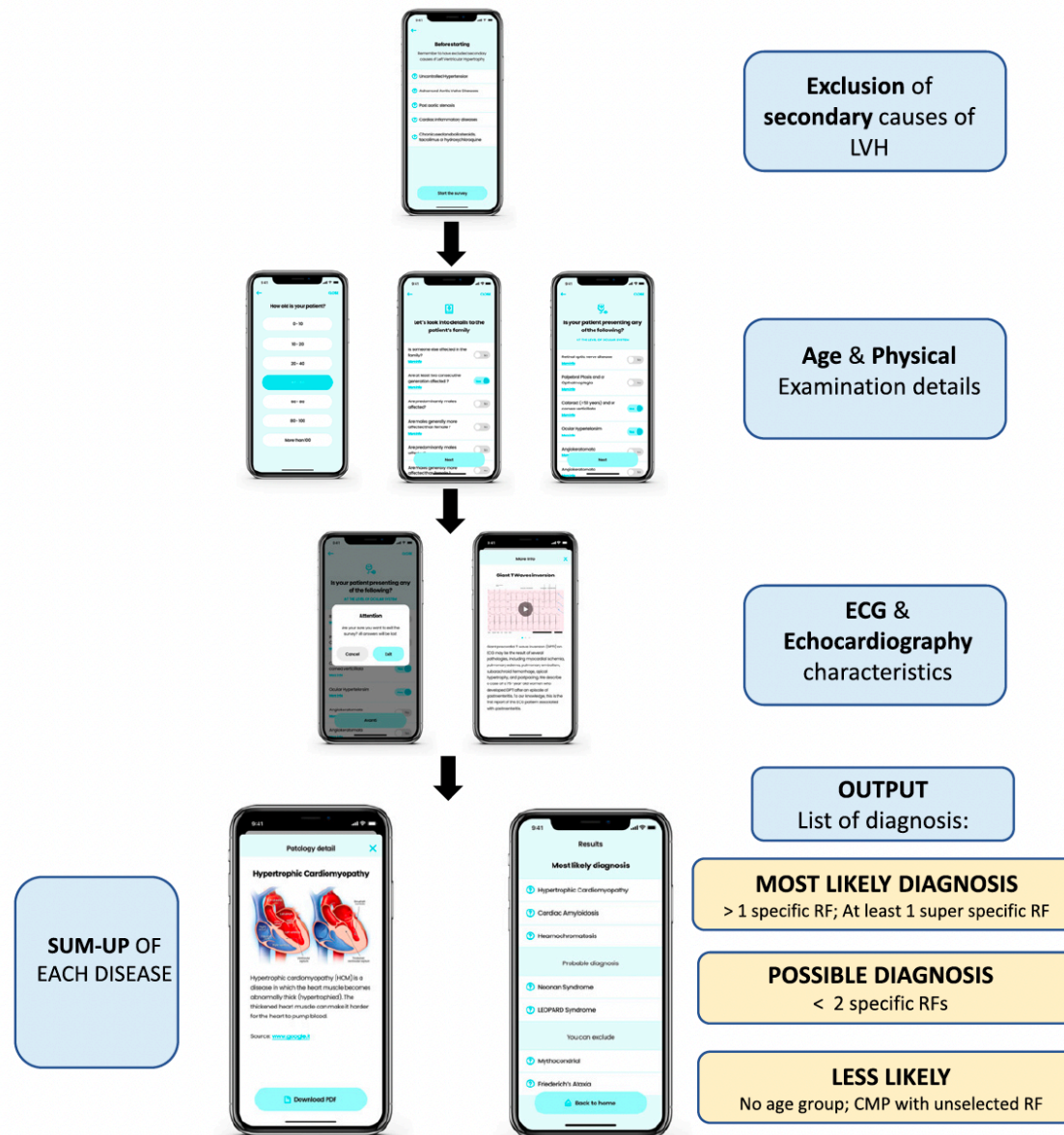
This app is designed to help physician in the differential diagnosis of patients presenting with primary left ventricular hypertrophy.

Start
New survey

SEE ALL POSSIBLE DIAGNOSIS

Tap to know more about this app
The application will not save any data or informations

<https://thickheart.com>

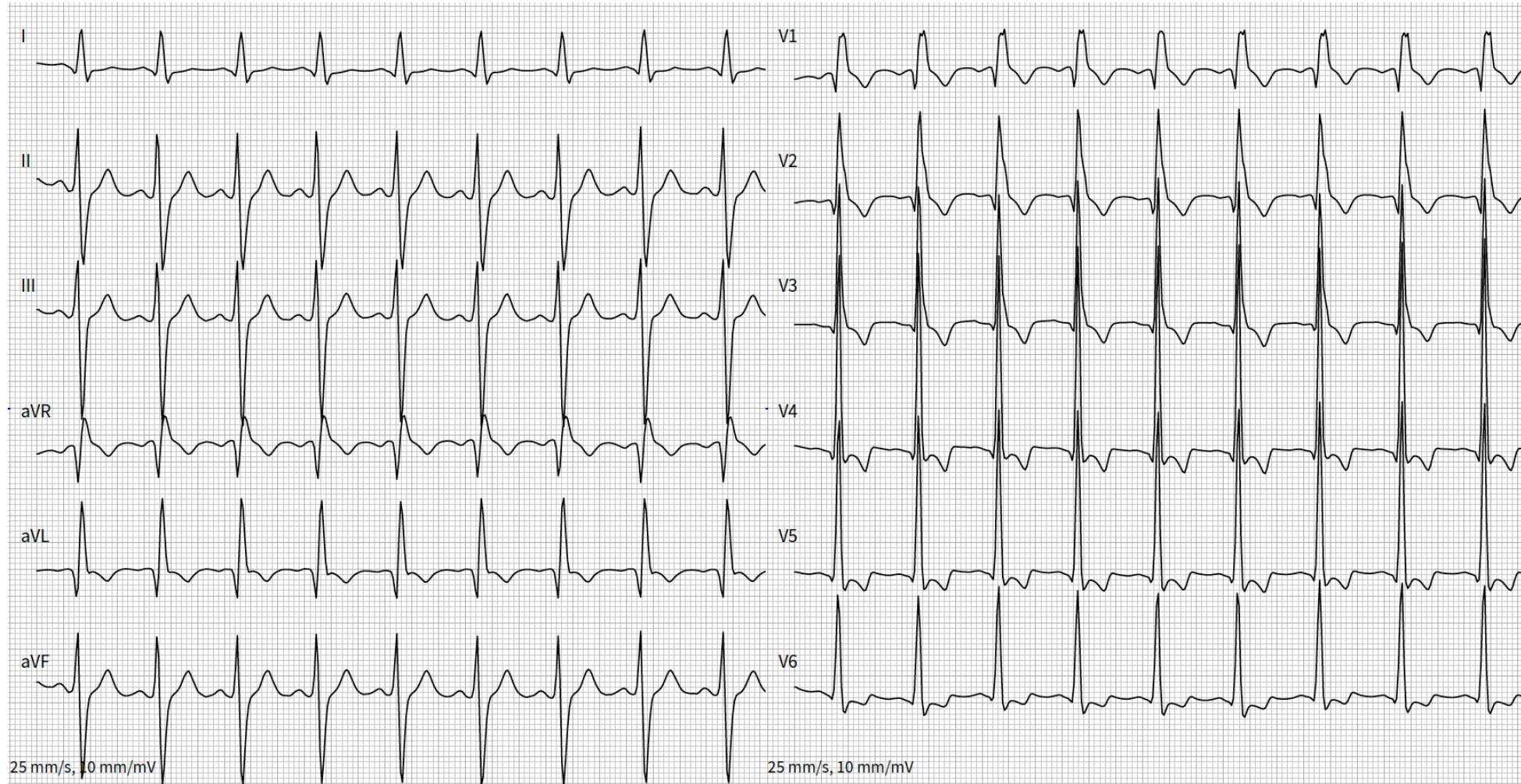


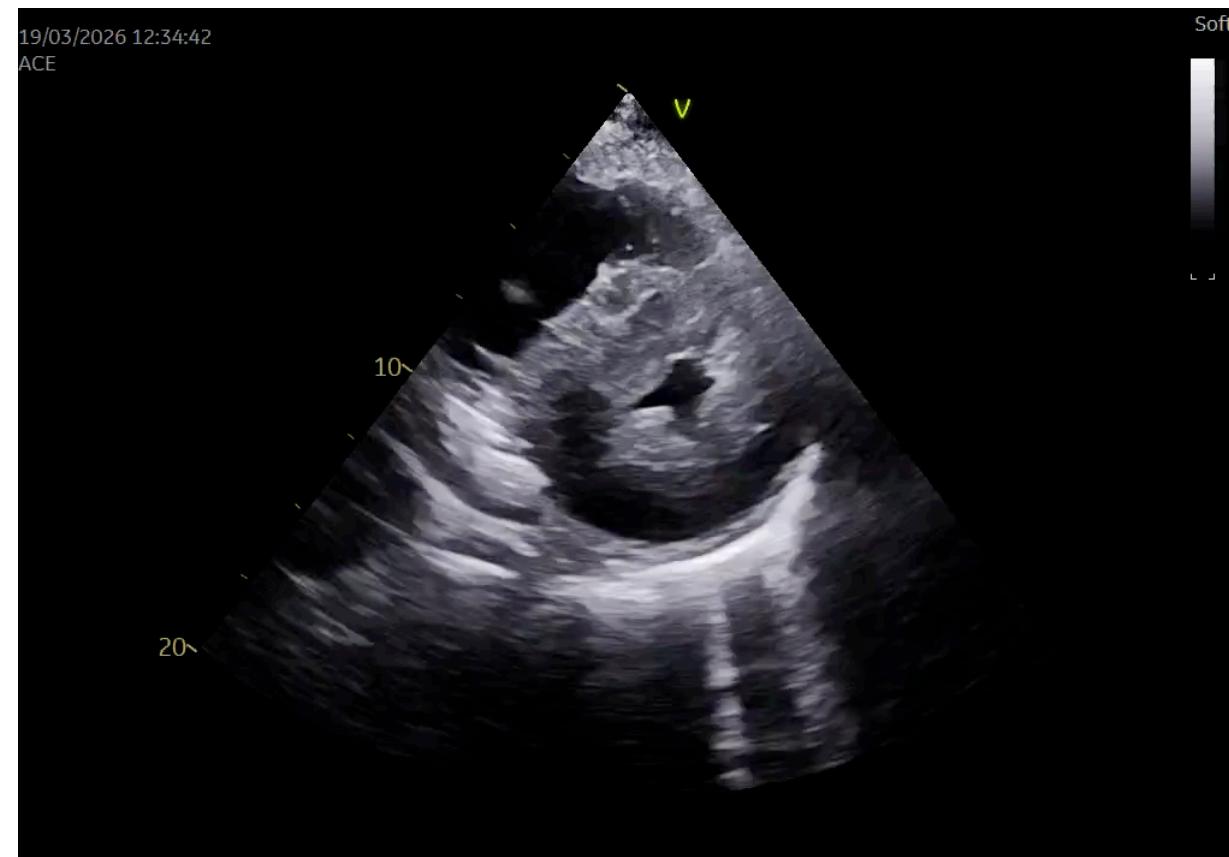
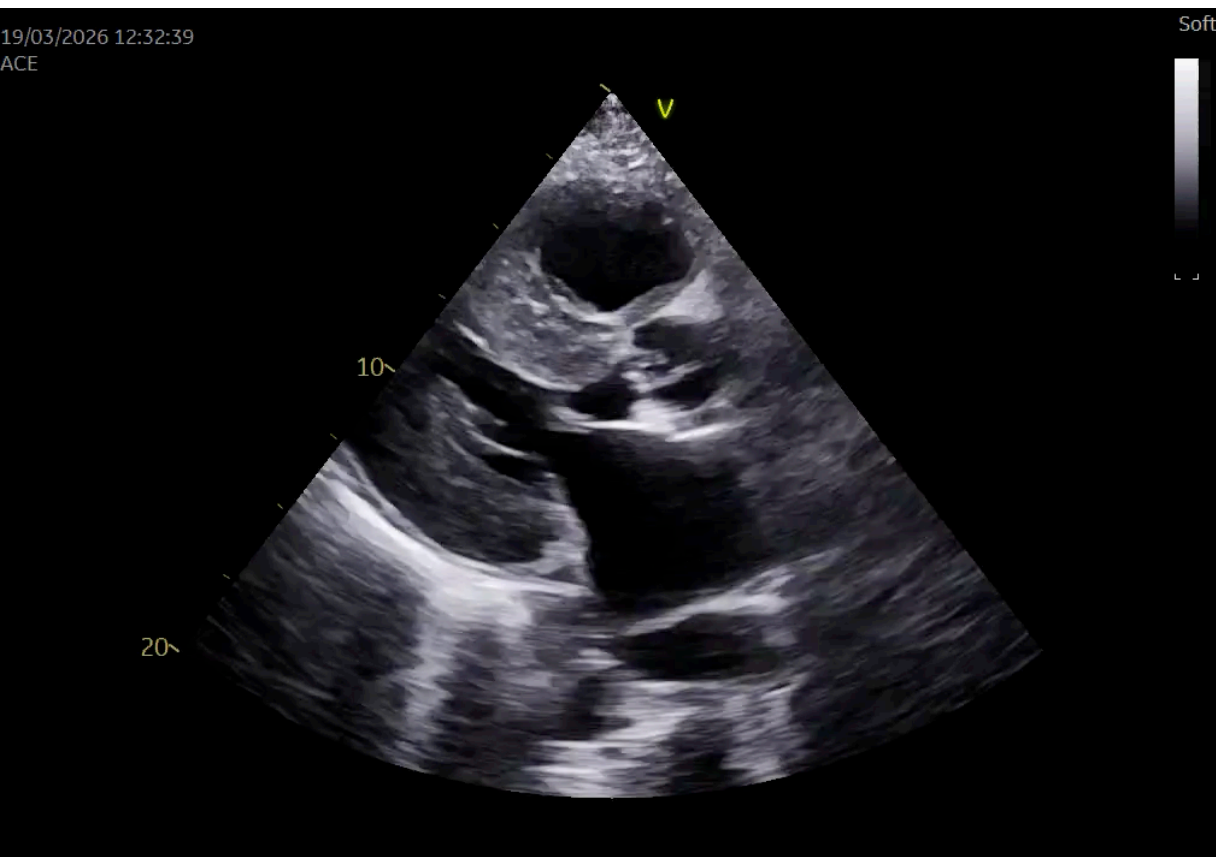
50-year-old male was referred to our clinic after the detection of LVH

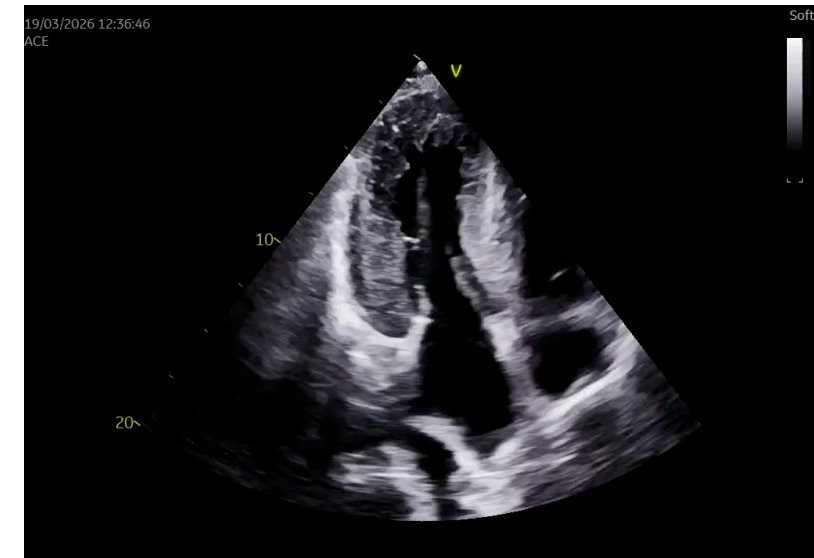
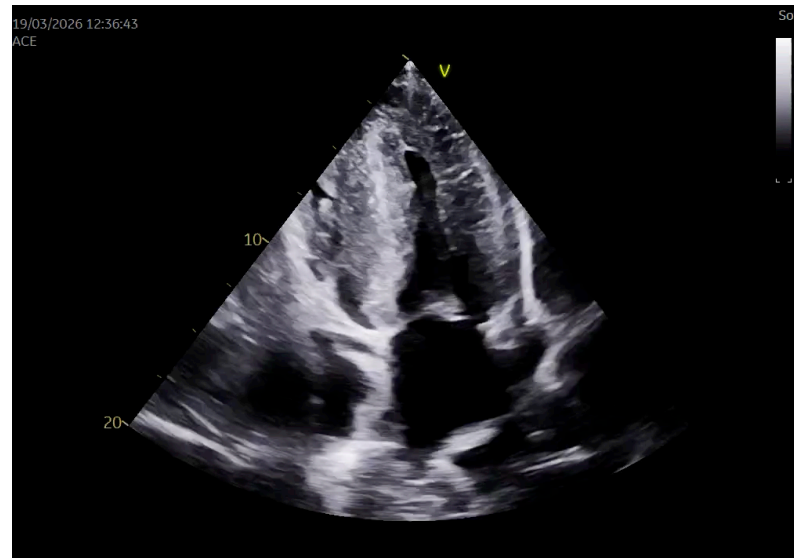
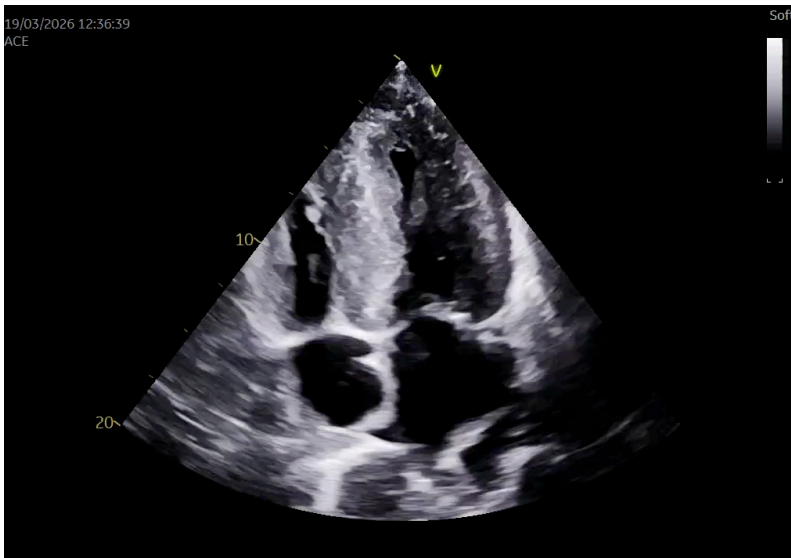
No FH for CMP or SCD

Unsuccessful catheter ablation for ventricular pre-excitation at 20 years old

Diagnosis of Hypertension and Microalbuminuria at 45 years old







More Likely Diagnosis?

Sarcomeric HCM

LVH due to Hypertension

Fabry Disease

Cardiac Amylodosis

More Likely Diagnosis?

Sarcomeric HCM

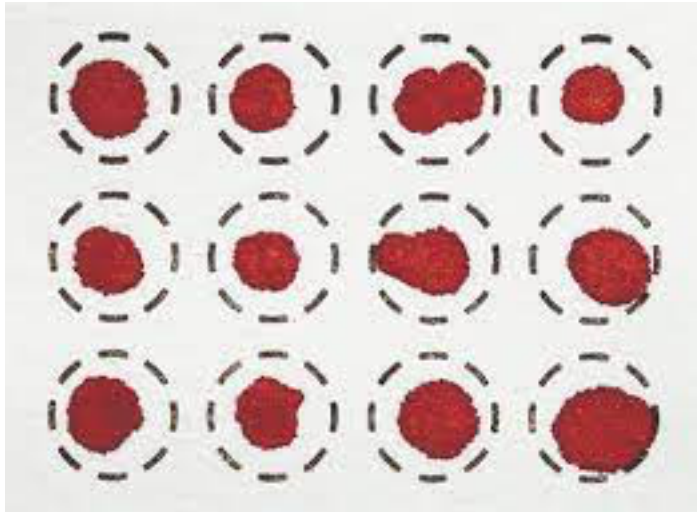
LVH due to Hypertension

Fabry Disease

Cardiac Amylodosis

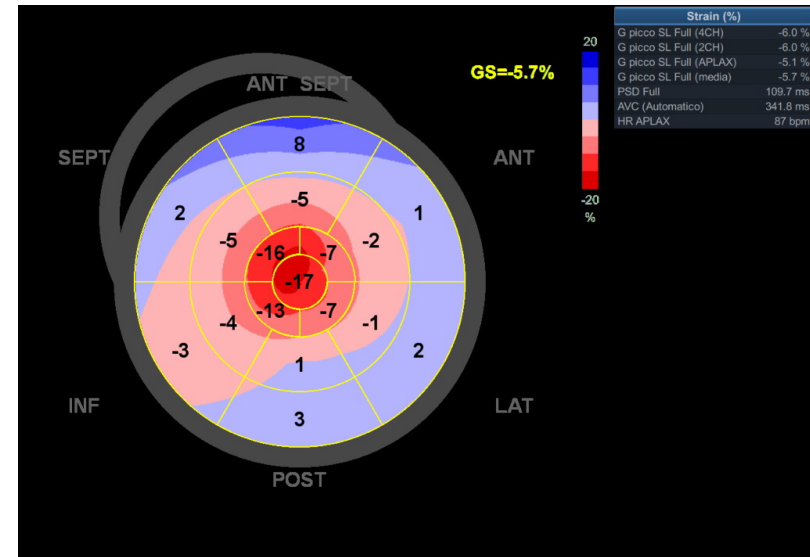
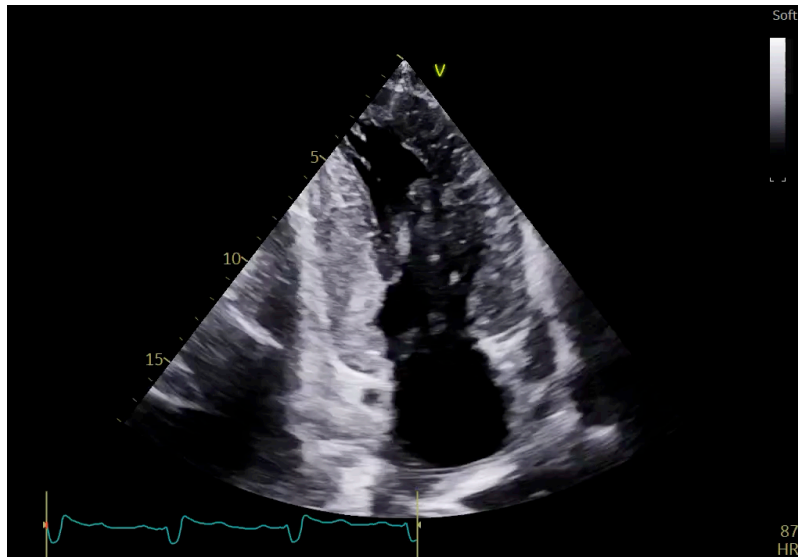
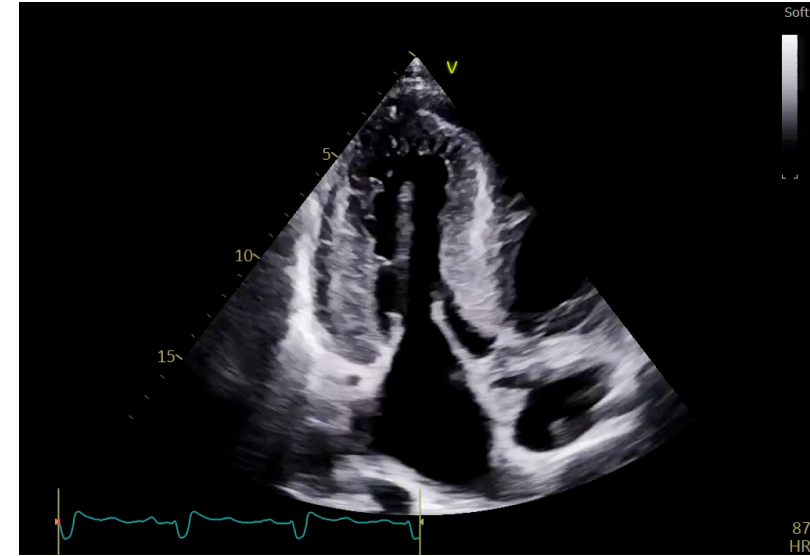
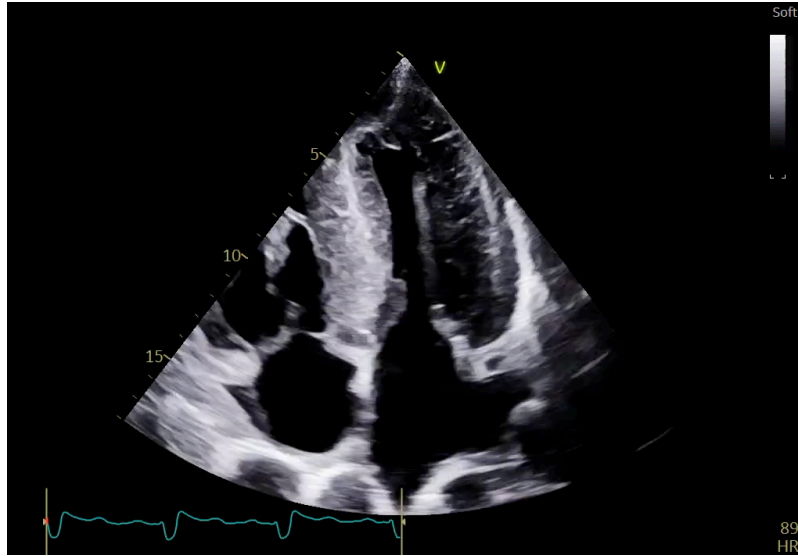
Red Flags

Extra-Cardiac Red Flags				Cardiac Red Flags	
Presenting Decades of Age	Any time	Family history of renal failure and/or stroke	Family history of LVH, particularly if no evidence of male-to-male transmission	History	Diagnostic Tool
	1-2	Neuropathic pain			
	1-2	Gastrointestinal symptoms	Short PQ interval [†]	Electrocardiography	
	1-2	Angiokeratomas	Bradycardia		
	1-2	Cornea verticillata*	Chronotropic incompetence		
	1-2	Hypohidrosis, heat/cold, and exercise intolerance	Atrioventricular blocks [†]		
	1-2	Albuminuria	LVH with normal systolic function	2D-echocardiography	
	3-4	Juvenile and/or cryptogenic TIA/stroke	Reduced global longitudinal strain		
	3-4	Hearing loss (either progressive or sudden)	Mild-to-moderate aortic root dilation		
	3-4	Dolichoectrasia of the basilar artery, chronic white matter hyperintensities at brain MRI	Mitral and aortic valve thickening with mild-to-moderate regurgitation		
	3-4	Proteinuria	Hypertrophy of papillary muscles	Cardiac Magnetic Resonance	
	3-4	Renal failure	Mid-layer posterolateral late gadolinium enhancement		
	3-4	Lymphedema	Low native T1		



No Pathogenic Variant
In GLA

DBS



More Likely Diagnosis?

Sarcomeric HCM

LVH due to Hypertension

~~Fabry Disease~~

Cardiac Amylodosis

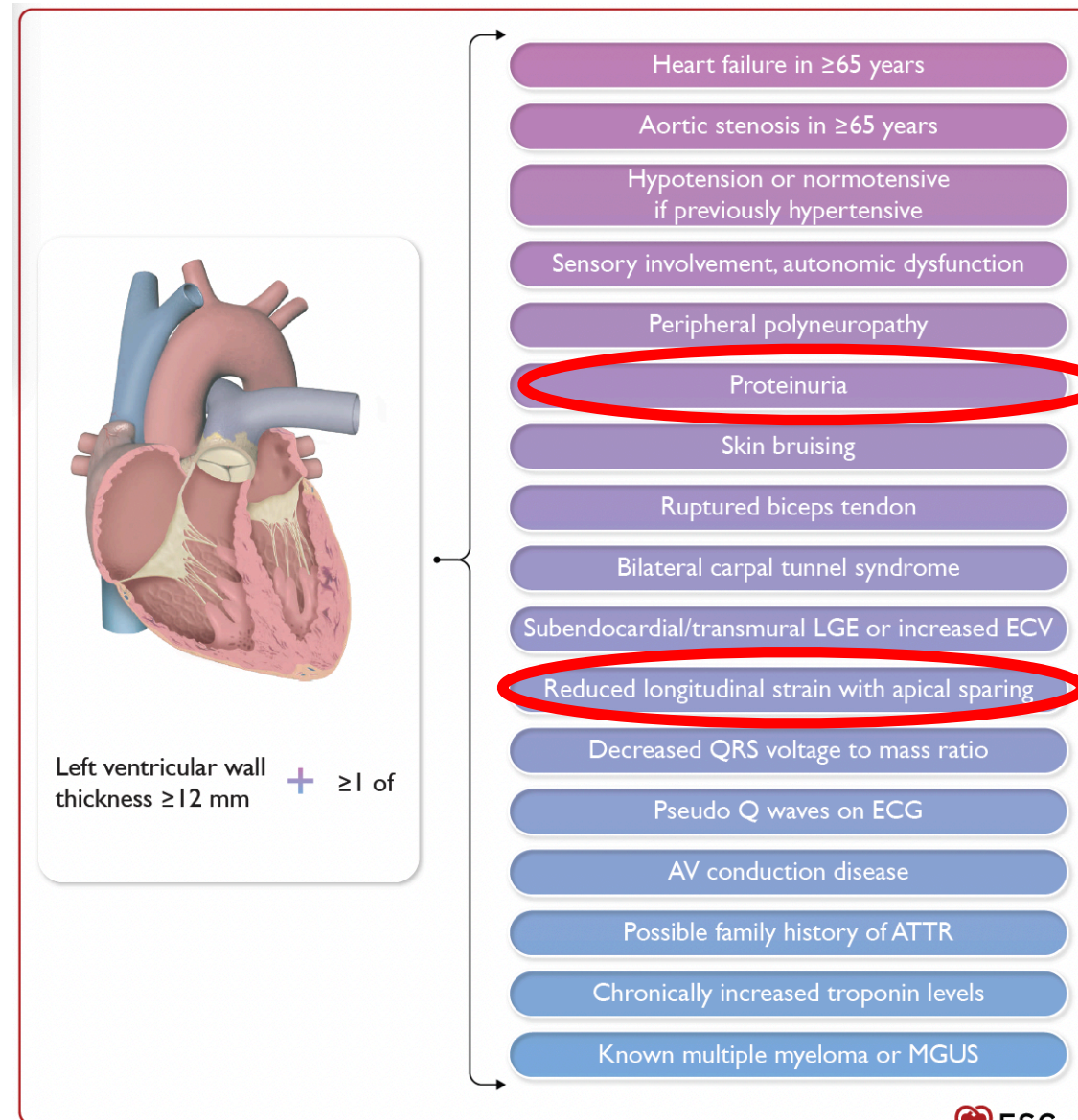
More Likely Diagnosis?

Sarcomeric HCM

LVH due to Hypertension

~~Fabry Disease~~

Cardiac Amylodosis



Signs and symptoms, ECG, ECHO, or CMR suggestive of cardiac amyloidosis

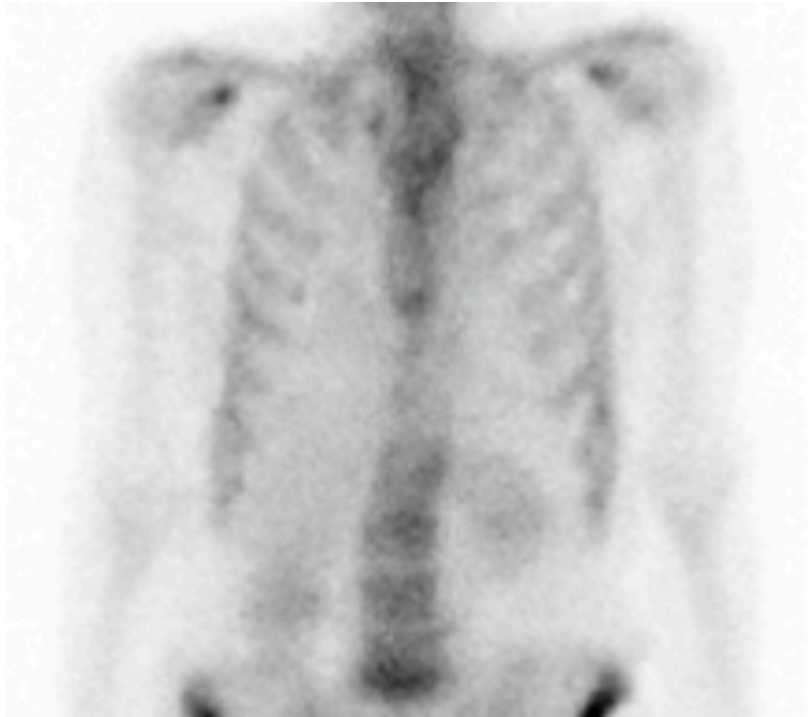


^{99m}Tc -DPD/PYP/HMDP
scintigraphy with SPECT



Haematologic tests
(serum free light chain quantification
and serum and urine immunofixation)

**^{99m}Tc -DPD/PYP/HMDP
Scintigraphy with SPECT** &



Haematologic tests
(serum free-light chain
quantification & serum and
urine immunofixation)

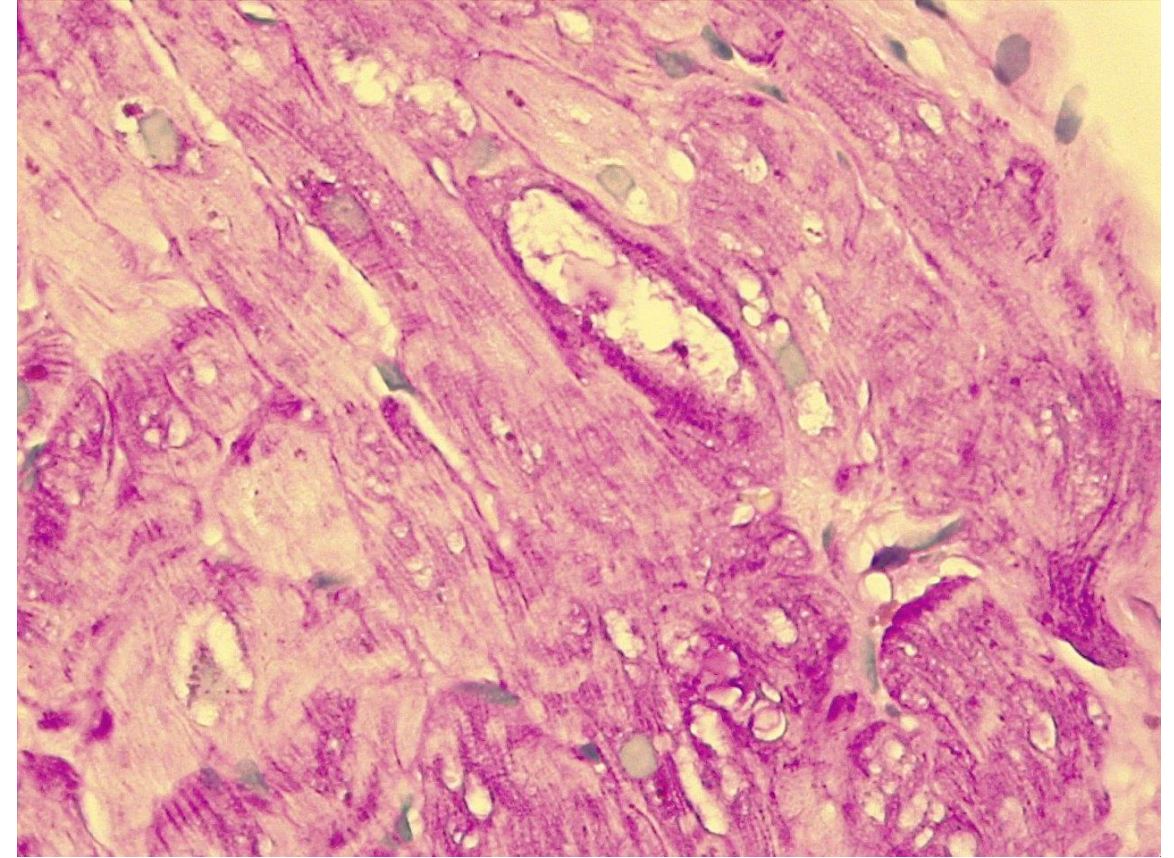
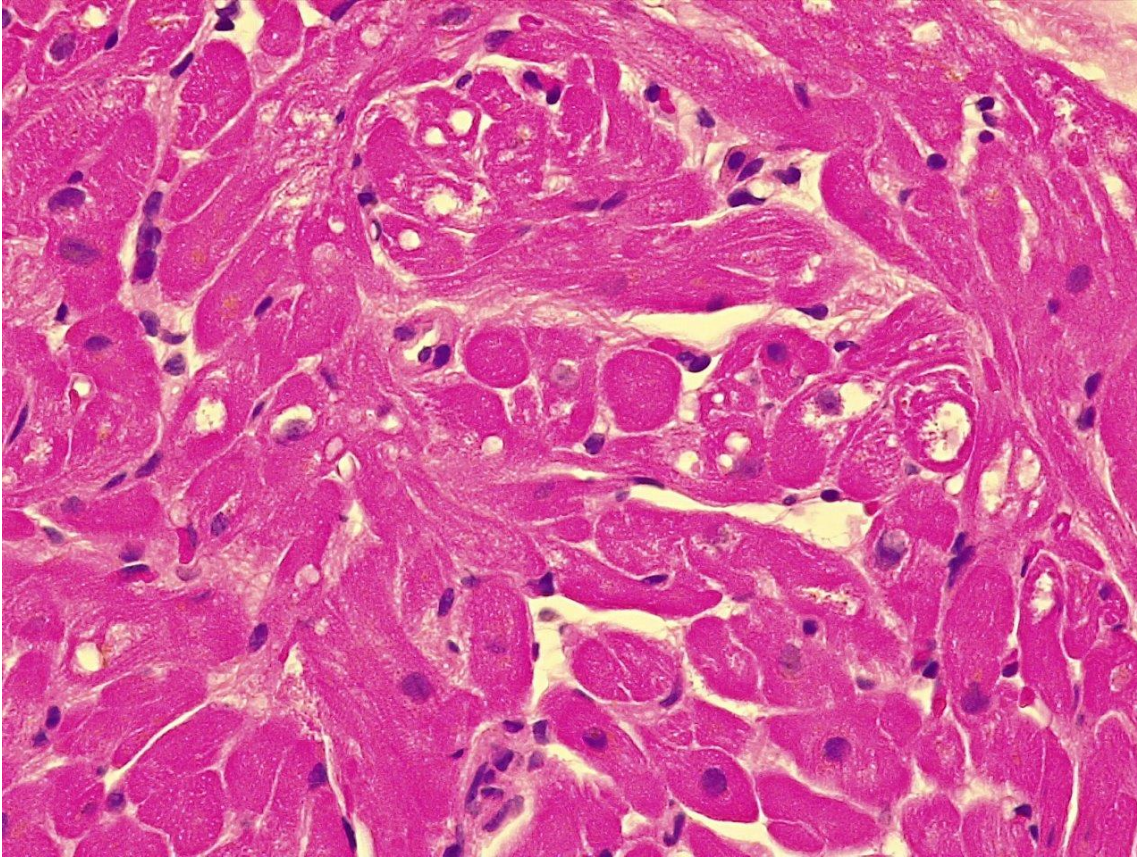


Positive

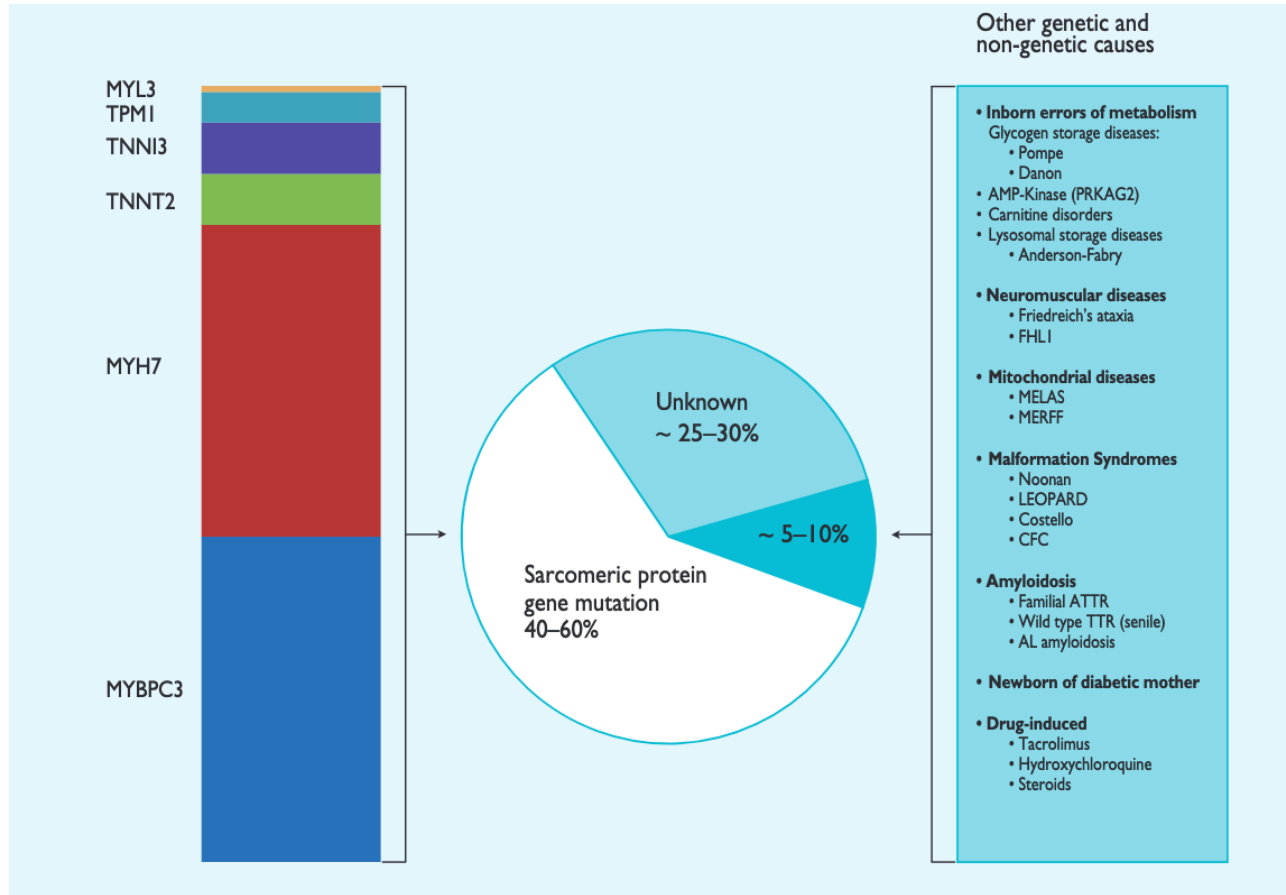


EMB

No Amyloid but Glycogen Accumulation Within Cardiomyocyte Vacuoles



Genetic Testing Results



NGS Panel:
Pathogenic Variant in
PRKAG2

- **Red flags provide a structured framework to guide the diagnostic work-up of patients with unexplained left ventricular hypertrophy.**
- **No single red flag is diagnostic; the integration of clinical, electrocardiographic, imaging, laboratory, and family data is essential.**
- **A systematic search for red flags enables a cost-effective and phenotype-driven selection of advanced investigations, including genetic testing and disease-specific biomarkers.**
- **Establishing the correct aetiological diagnosis has major implications for prognosis, family screening, and the implementation of targeted therapies.**



Grazie per l'Attenzione

Emanuele Monda, MD, PhD, FESC
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