ΜΕΤΑΒΟΛΙΚΕΣ ΜΥΟΚΑΡΔΙΟΠΑΘΕΙΕΣ

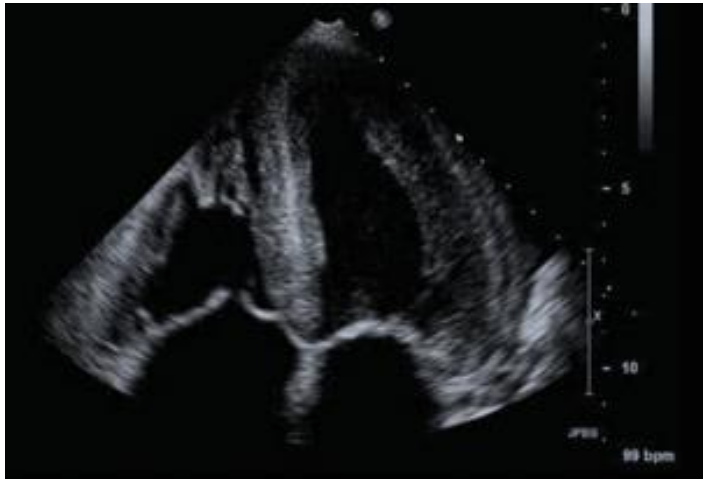
Alexios Antonopoulos

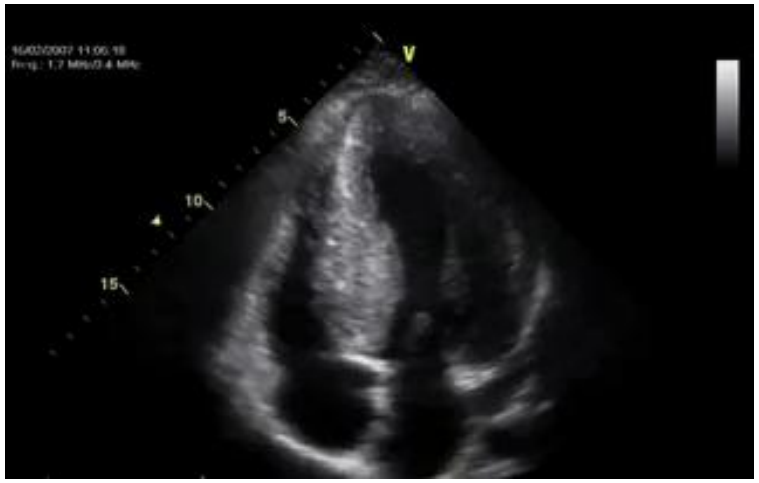
Assistant Professor of Cardiology

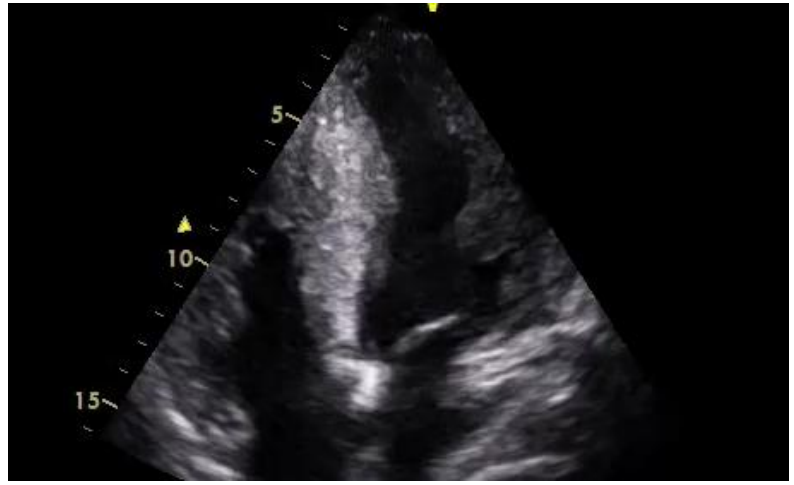
Cardiogenetics and Sports Cardiology Unit, 1st Cardiology Dpt,

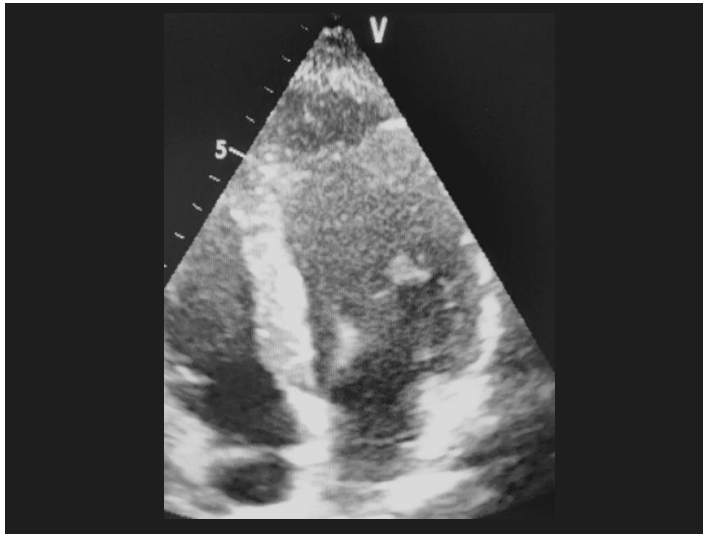
National and Kapodistrian University of Athens

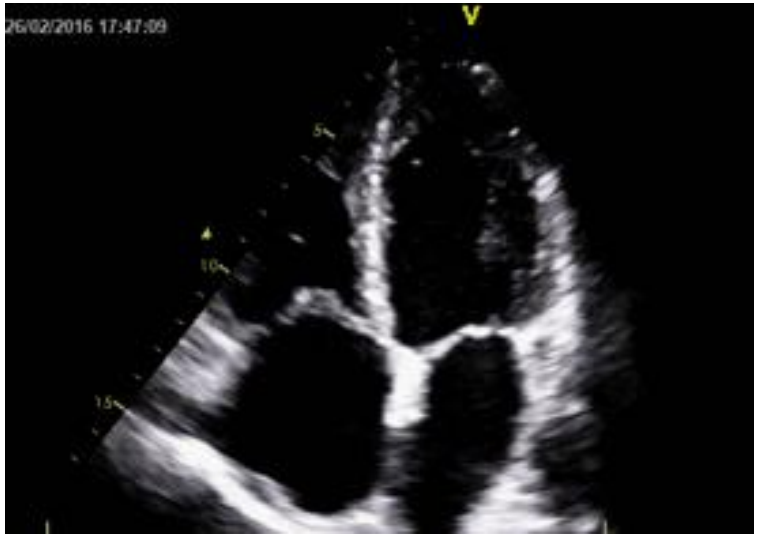
“HFpEF”

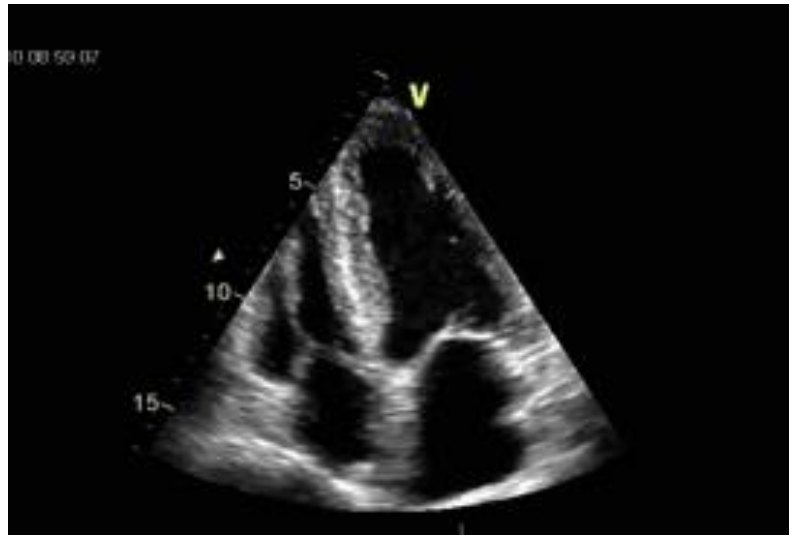




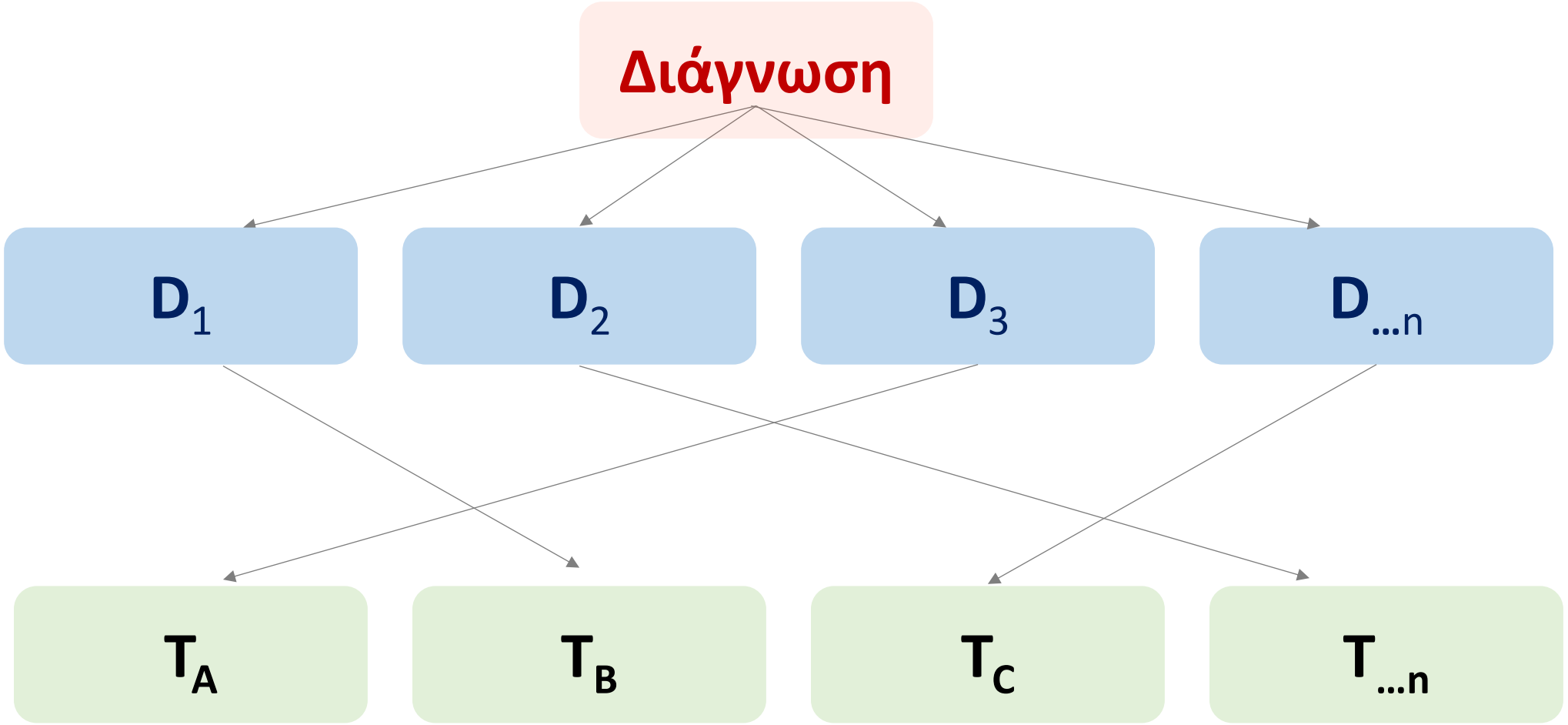








Ορθή διάγνωση → Ορθή & αποτελεσματική θεραπεία



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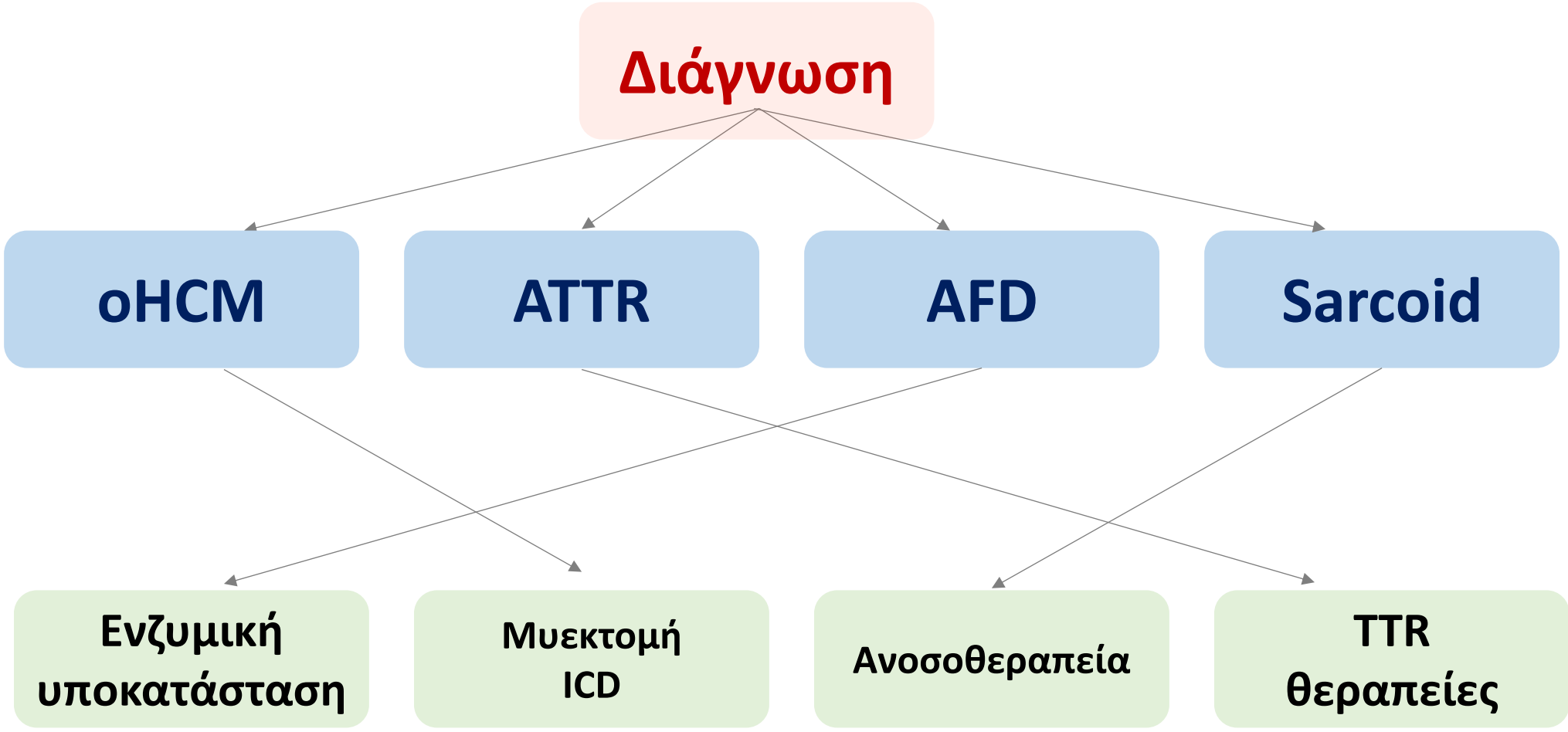
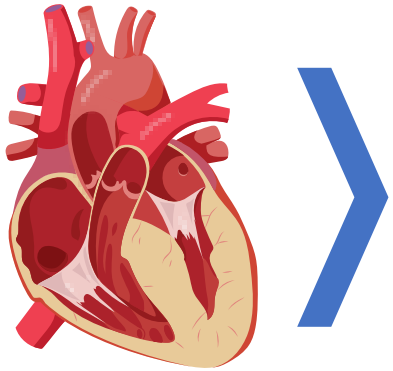


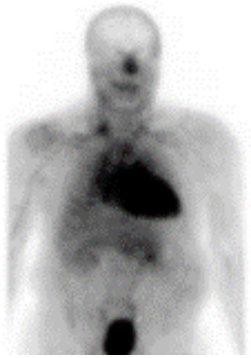
Θεραπείες

Imaging has transformed the diagnosis of cardiac amyloidosis

Diagnosis of ATTR-CM can be achieved non-invasively[1,2]



Invasive heart biopsies



Non-invasive cardiac scintigraphy

Incidence of ATTR-CM in the UK[3]

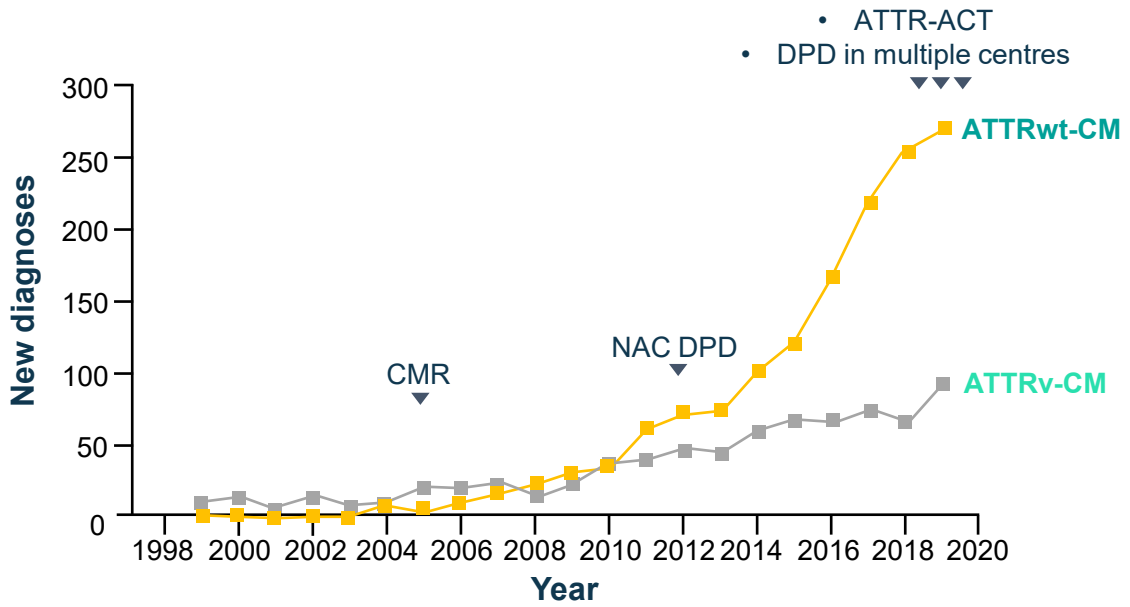
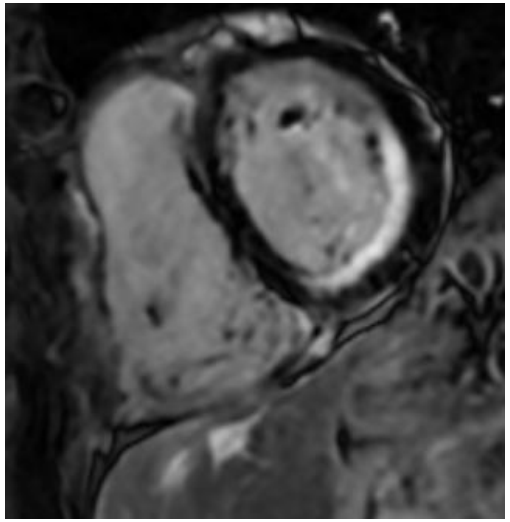


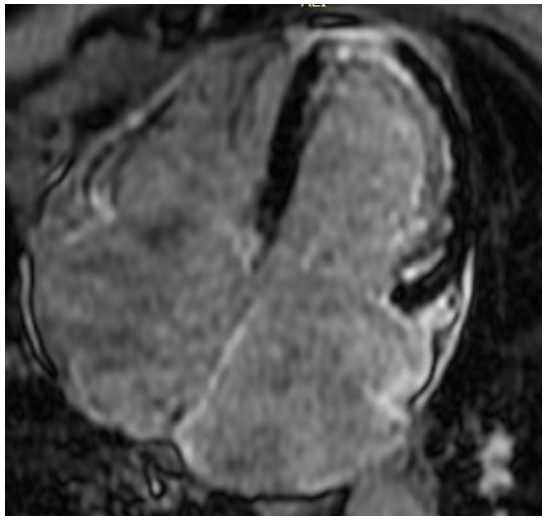
Figure adapted from Fontana M, et al. 2023.[3]

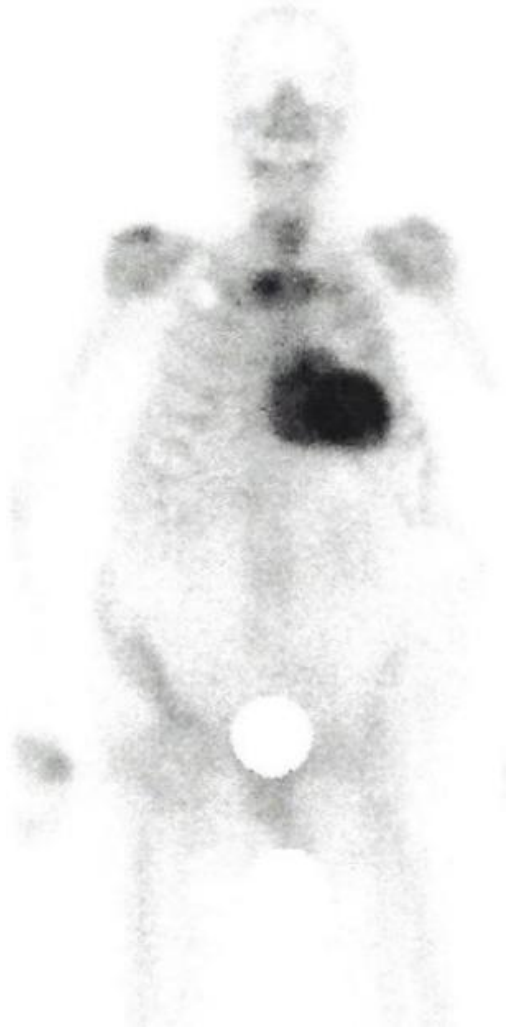
The number of patients diagnosed with ATTR-CM, especially ATTRwt-CM, has risen in recent years due to non-invasive diagnostic methods and increased awareness

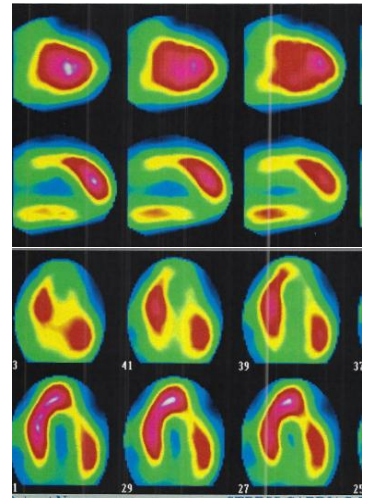
Diagnosis of Amyloidosis made easy (CMR + Bone scans)

Male 76 years old
Hypertension
Shortness of breath
LVEF 51%m mild LVH

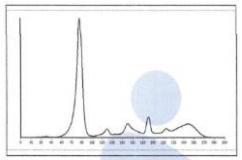








SPE: normal
UPE: normal



FLC
κ normal
λ normal
κ/λ ratio 1.01

ATTR
No TTR variant
tafamidis tx

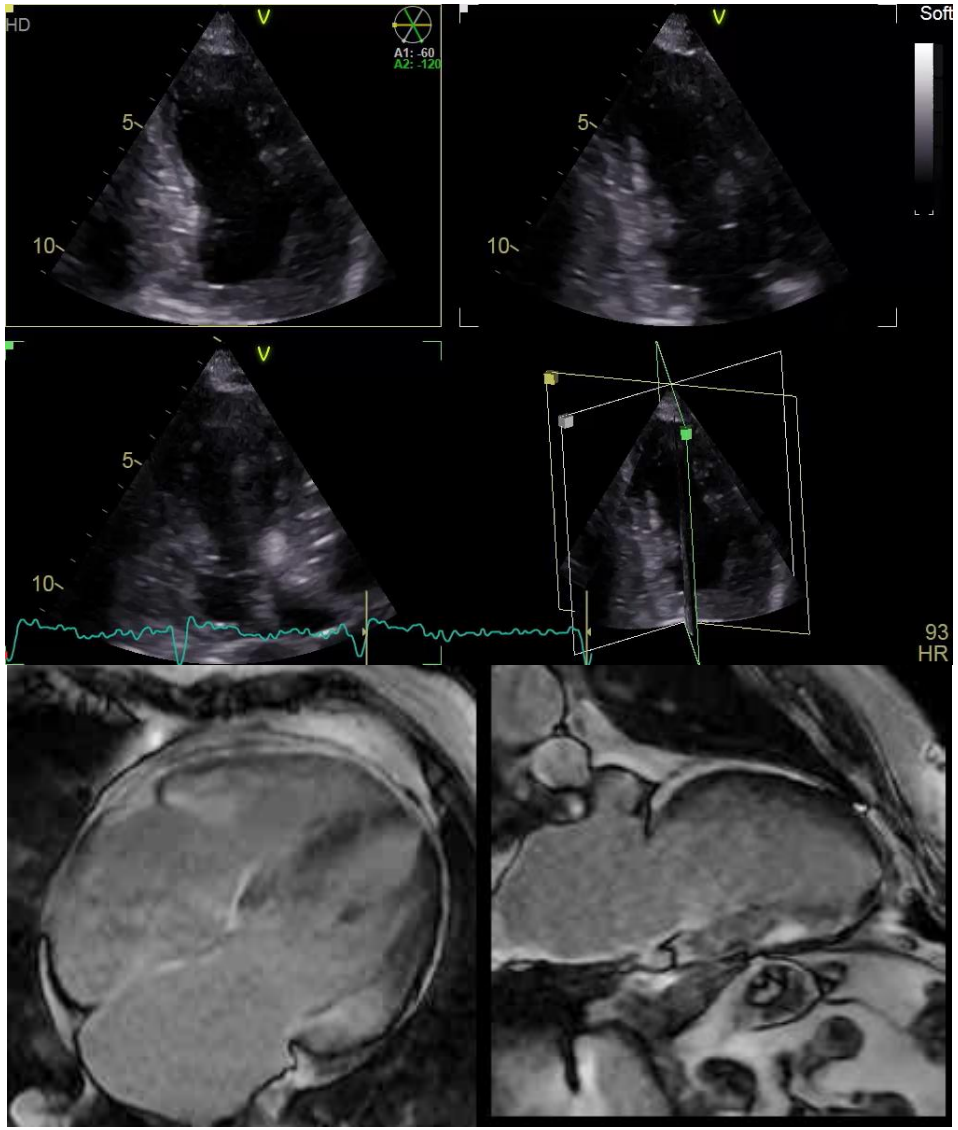
But… not every cardiac amyloidosis diagnosis is easy

- Male 72 years old
- Fit but easy fatigue
- LVH
- Referred for amyloidosis work-up

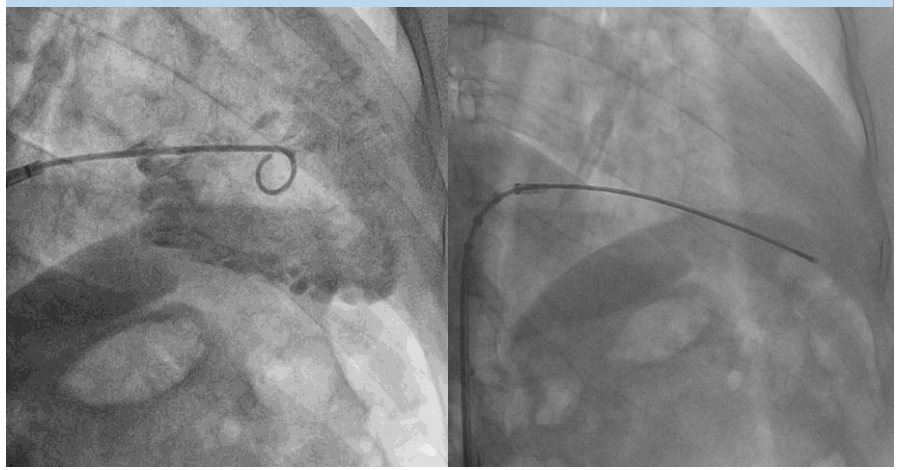
ATTR?

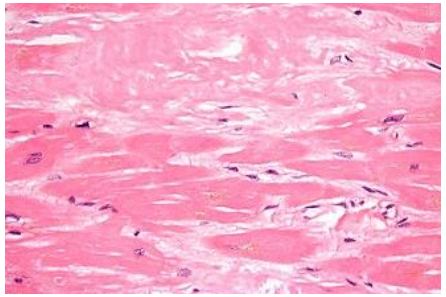
- NTproBNP 2400pg/mL
- cTnI 32pg/mL
- **IgG λ band**

- Bone marrow (-)
- Fat pad (-)



Endomyocardial Biopsy to the rescue





- Amyloid (+) on Congo red
- Immunohistochemistry for κ/λ IgG & TTR
  - κ (-), λ (-)
  - TTR (+++)

ATTR-CM diagnosis
Treatment with vutrisiran

Metabolic cardiomyopathies

Disorders of Amino Acid and Organic Acid Metabolism
- Propionic acidemia – DCM
- Methylmalonic aciduria
- Malonic academia
- β-ketothiolase deficiency – DCM
- Mevalonic academia
- Tyrosinemia - HCM
- Oxalosis - HCM, RCM*

Disorders of Fatty Acid Metabolism
Carnitine Transport Defects
- Systemic primary carnitine deficiency – HCM, DCM
- Muscle carnitine deficiency – HCM, DCM
- Carnitine-palmitoyl transferase type II deficiency
- Carnitine acylcarnitine translocase deficiency

Fatty Acid Oxidation Defects
- Very long-chain acyl-CoA dehydrogenase deficiency – HCM
- Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency – HCM, DCM
- Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
- Multiple acyl-CoA dehydrogenase deficiency (glutaric academic type II) – HCM

Disorders of Glycogen Metabolism
- GSD II (Pompe disease, acid α-glucosidase/acid maltase) – HCM
- GSD III (Cori disease; debranching enzyme) – HCM
- GSD IV (Anderson disease; branching enzyme) – DCM
- GSD IX (cardiac phosphorylase kinase) – HCM
- PRKAG2 Deficiency – HCM with WPW
- Danon Disease (Pseudo-Pompe disease with normal acid maltase; LAMP2) – HCM

Disorder of Glycoprotein Metabolism
- Congenital disorders of Glycosylation – HCM

Lysosomal Storage Disorders
Disorders of Mucopolysaccharide Metabolism
- MPS I (Hurler, Hurler-Scheie, and Scheie syndromes) – HCM, DCM
- MPS II (Hunter syndrome) – HCM
- MPS III (Sanfilippo syndrome) – HCM
- MPS IV (Morquio syndrome) – HCM
- MPS VI (Maroteaux-Lamy syndrome) – DCM
- MPS VII (Sly syndrome) – HCM

Disorder of Glycogen Metabolism
- GSD II (Pompe disease, acid α-glucosidase/acid maltase) – HCM
- Danon Disease (Pseudo-Pompe disease with normal acid maltase; LAMP2) – HCM, DCM
- Gaucher disease (glucocerebrosidase) - HCM*
- Fabry disease (α-galactosidase) – HCM*

Disorders of Combined Ganglioside, Mucopolysaccharide, and Oligosaccharide Metabolism
- GM1 Gangliosidosis (HCM, DCM)
- GM2 Gangliosidosis (Sandhoff disease) – HCM, DCM

Mitochondrial Disorders
- Pyruvate dehydrogenase deficiency (Leigh disease) – HCM
- Complex I Deficiency – DCM
- Complex II Deficiency –
- Complex III Deficiency (Histiocytoid Cardiomyopathy) – HCM
- Complex IV Deficiency (muscle and Leigh disease forms) – HCM
- Complex V Deficiency – HCM
- MELAS (Mitochondrial transfer RNA mutation) – HCM
- MERFF (Mitochondrial transfer RNA mutation) – HCM, DCM
- Kearns-Sayre syndrome (mitochondrial DNA deletions/duplications) – HCM
- Barth syndrome (3-methylglutaconic aciduria type II) – HCM, DCM, Mixed
- Sengers syndrome – HCM

Peroxisomal Disorder
- Refsum disease (phytanic a4cid oxidase) – HCM, DCM

Cox et al. Prog Pediatr Cardiol. 2007 ; 24(1): 15–25

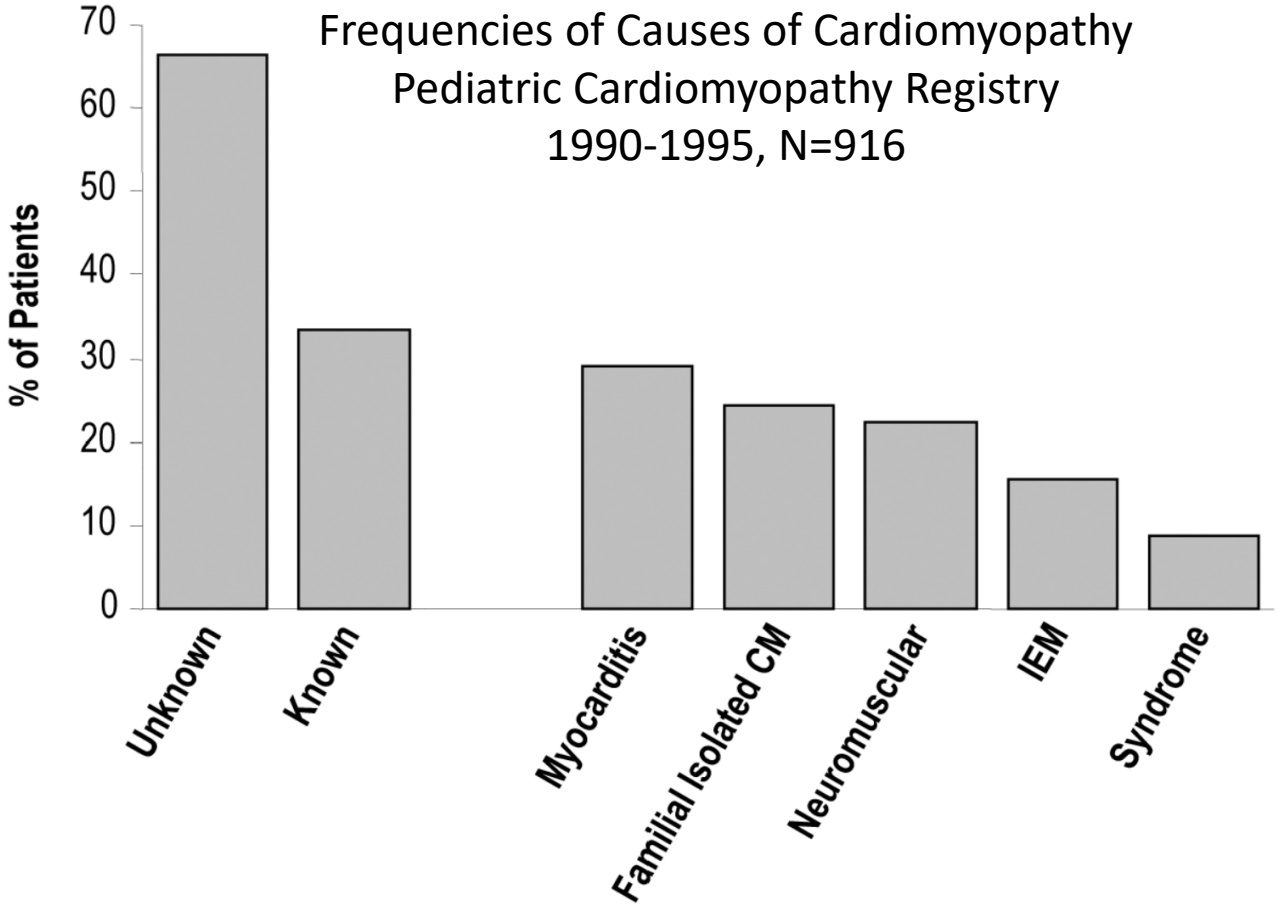
INTERNATIONAL CLASSIFICATION OF INHERITED METABOLIC DISORDERS (ICIMD)

http://www.icimd.org/

Metabolic cardiomyopathies

1. **Genetic / inherited (Inborn Errors of Metabolism)**
    a. Disorders of Amino Acid and Organic Acid Metabolism
    b. Disorders of Fatty Acid Metabolism
    c. Lysosomal Storage Diseases (LSD) - *AFD, MPS*
    d. Glycogen Storage Diseases (GSD)
    Pompe, Danon, PRAKG2
    e. Mitochondrial cytopathies
    MELAS, MERFF,
    Kearns-Sayre syndrome, Barth syndrome
2. **Acquired ?**
    - Diabetes / obesity-related cardiomyopathy

Metabolic Cardiomyopathies

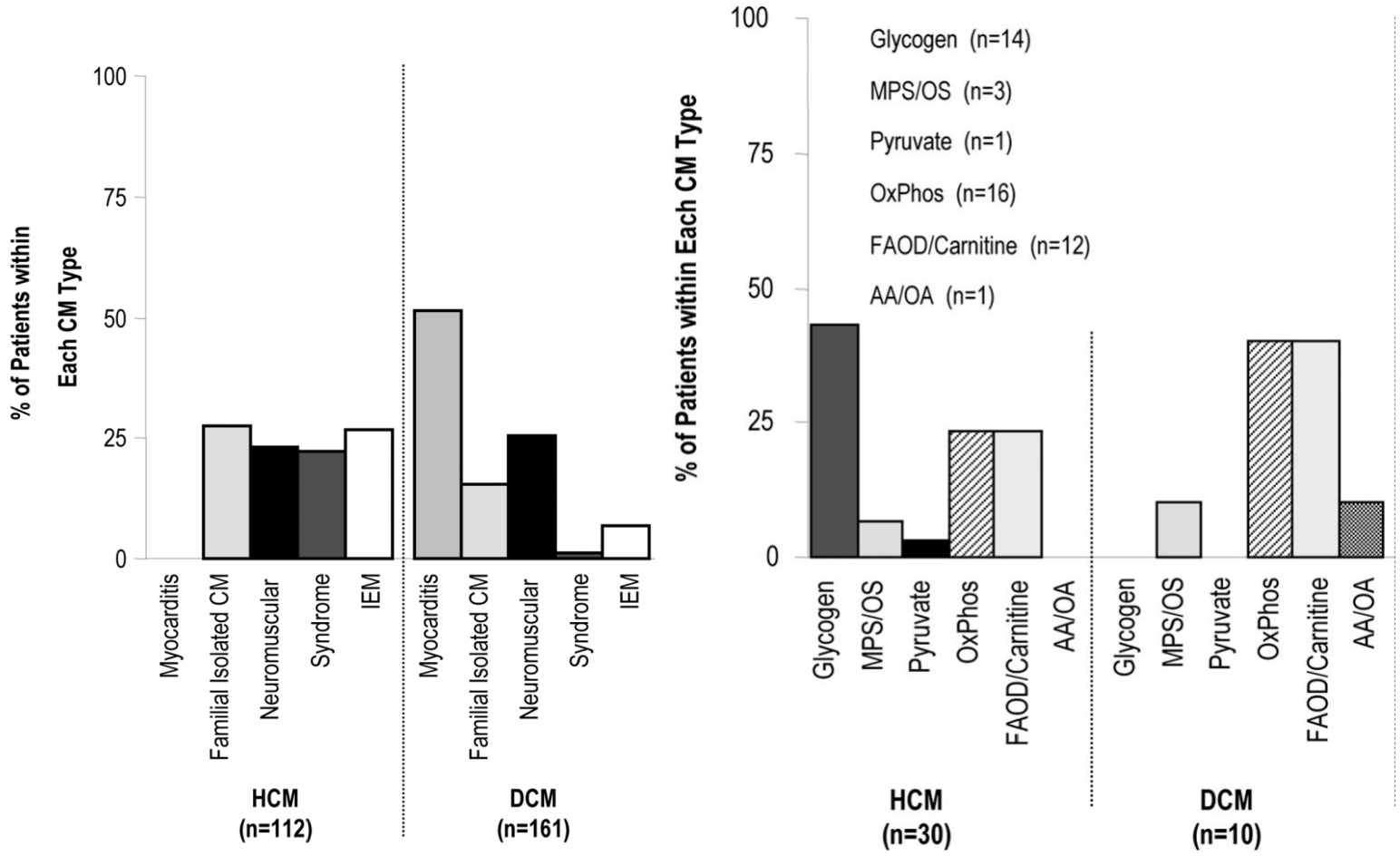


~15-20% of all cases of pediatric cardiomyopathy

- 4-16% of pediatric DCM
  - mitochondrial disorders
  - Barth syndrome
  - primary carnitine deficiency
- ~14% of pediatric HCM

Cox G. Prog Pediatr Cardiol. 2007 ; 24(1): 15–25.

Metabolic Cardiomyopathies



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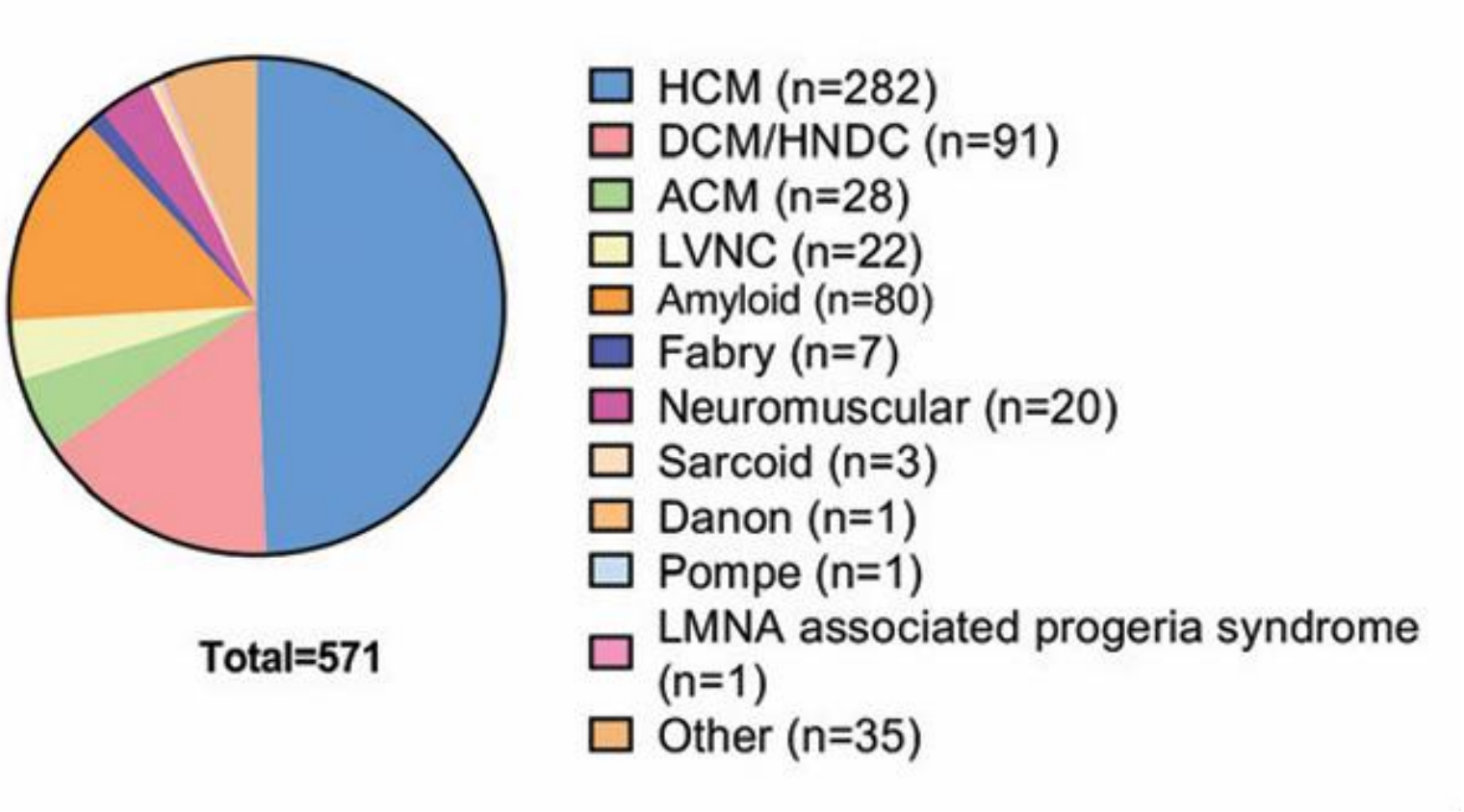
Metabolic Cardiomyopathies

The Rarest of the Rare

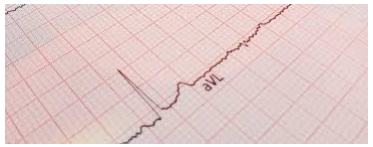
2018-2025

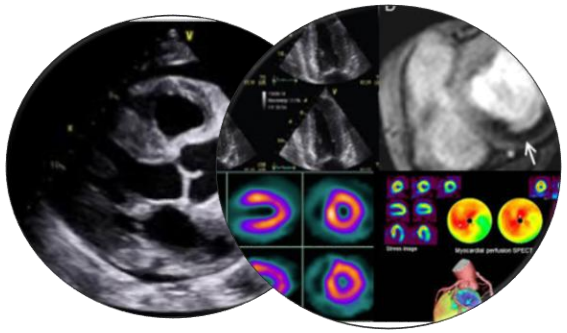


The clinical puzzle of cardiomyopathies

Patient referrals

Clinical work-up





Disease classification

Disease subgroups

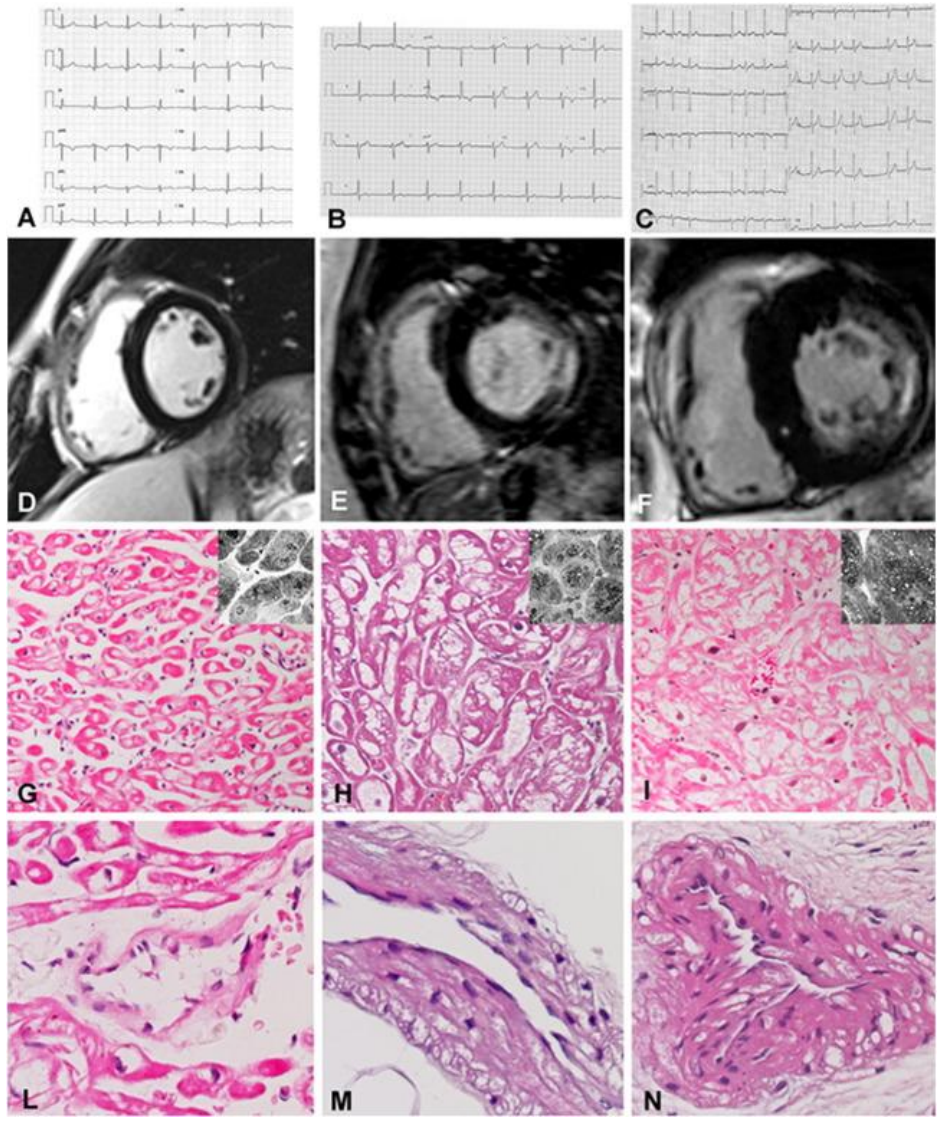
DCM	idiopathic infective inflammatory autoimmune familial / genetic arrhythmic HNDC **metabolic**
HCM	sarcomeric / non-sarcomeric HCM obstructive / non-obstructive HCM rasopathy, **mitochondrial** **storage / metabolic disease**
ACM	Desmosomal non-desmosomal ARVC - ALVC Biventricular
Infiltr.	Amyloid AL htATTR, wtATTR Sarcoid Hemochromatosis
Other	

Genetic basis

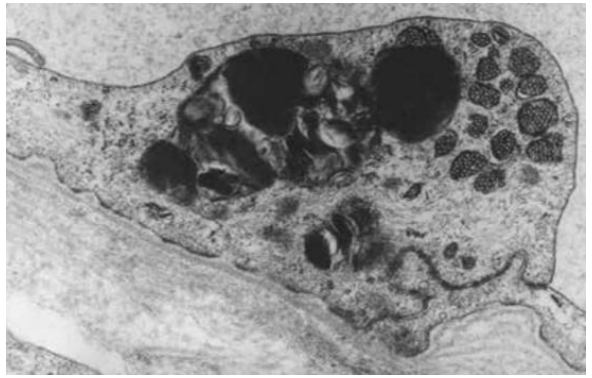
Prognosis
Treatment

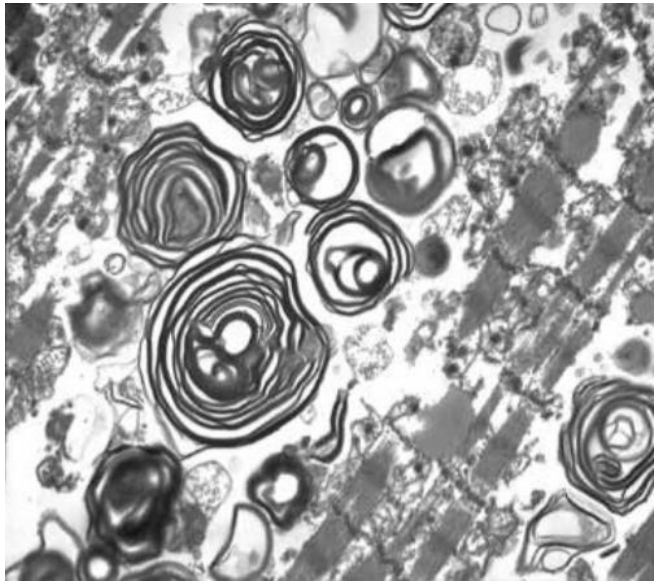
Anderson – Fabry Disease

Anderson Fabry Disease

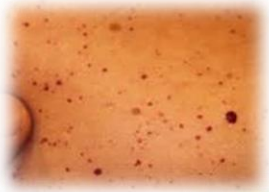


- mutations in the α-galactosidase A gene (GLA)
- X-linked (Xq22) / >900 mutations described
- Reduced/undetectable α-galactosidase A (AGAL) enzyme levels.
- progressive accumulation of GLA substrates
- glycolipids–primarily globotriaosylceramide (Gb3) & lyso-Gb3
- ‘Zebra’ bodies





Cardiac and extracardiac findings in AFD

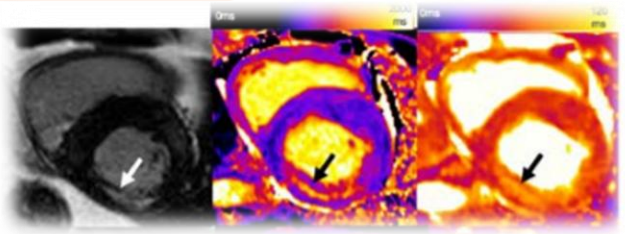


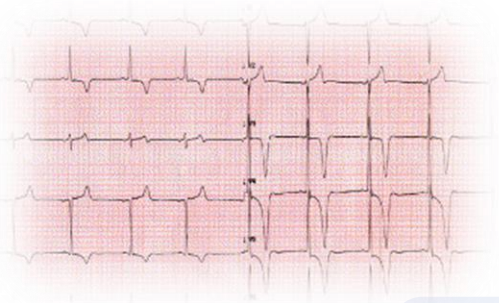
CLINICAL MANIFESTATIONS

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

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

CARDIAC IMAGING





Established Fabry disease diagnosis

High QRS voltages
Inferolateral negative T waves
Reduced T wave ratio*
Reduced P wave duration
Chronotropic incompetence
Bradycardia
Short PQ interval
Atrioventricular blocks

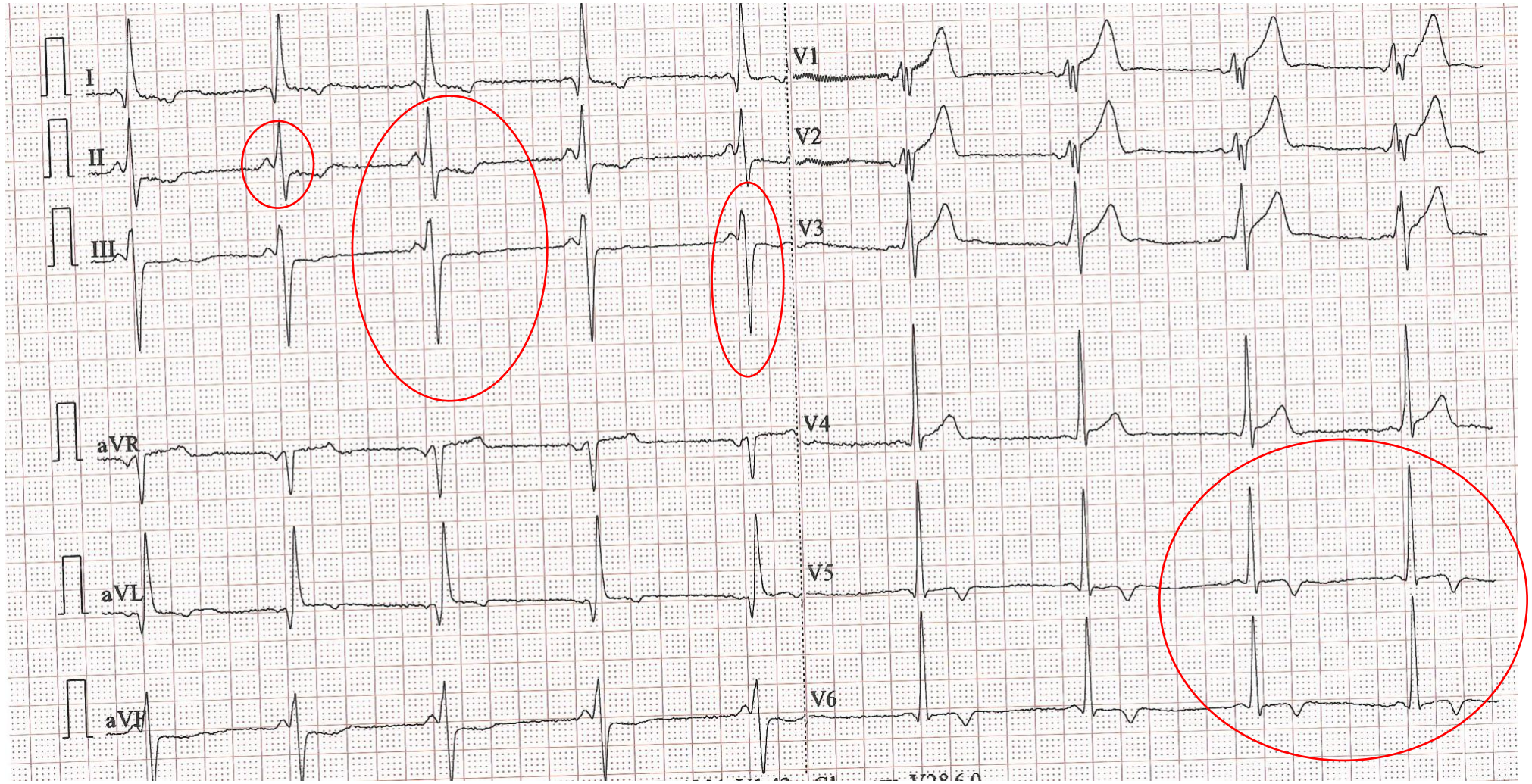
ECG

Increased plasma LysoGb3
Elevated high sensitivity Troponin
Reduced eGFR
Elevated NT-proBNP
Proteinuria
Microalbuminuria

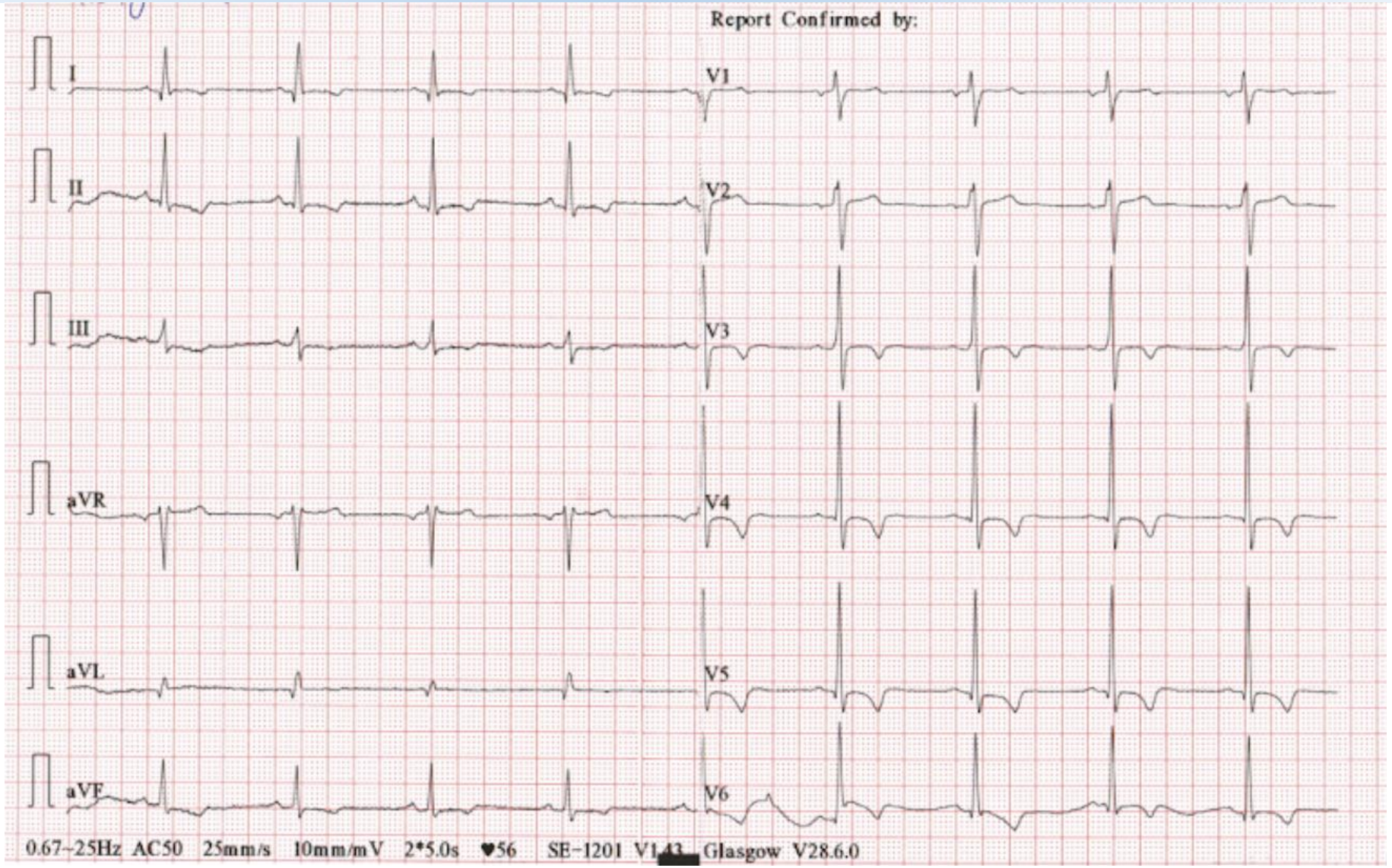
LABORATORY FINDINGS

Pieroni et al, JACC 2021

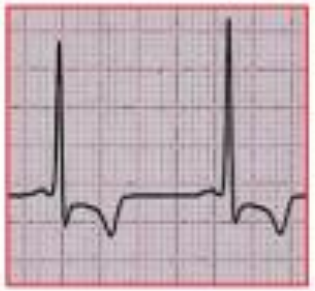
ECG findings in Anderson - Fabry Disease



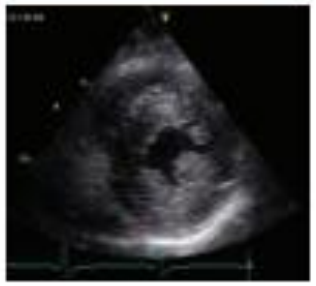
ECG findings in Anderson - Fabry Disease



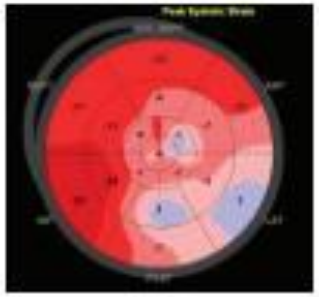
Imaging findings in Anderson - Fabry Disease



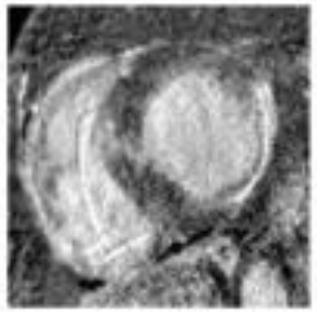
Short PR
Conduction disease



Concentric LVH
RVH
Papillary muscle hypertrophy



Reduced GLS in posterior wall



Posterior wall scar

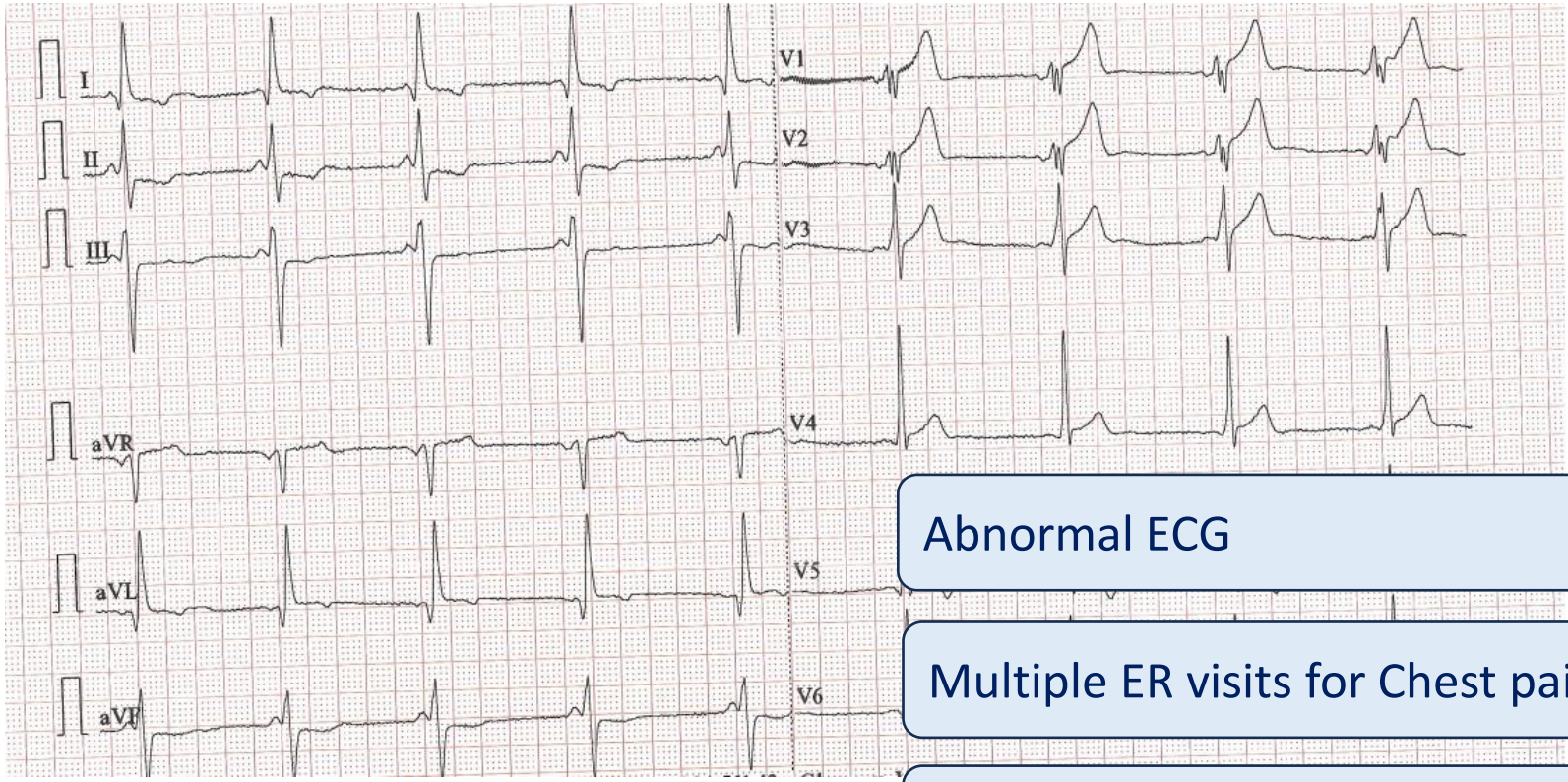
Low T1

T1 may be pseudonormal in the presence of fibrosis

Male with LVH & abnormal ECG for 15 years

Male athlete
56 years old
Hypertension

LVH
Microalbuminuria 52mg/24h
Sweating
Palpitations
Short PR
Deep S wave III
TWI I, aVL, V5-V6



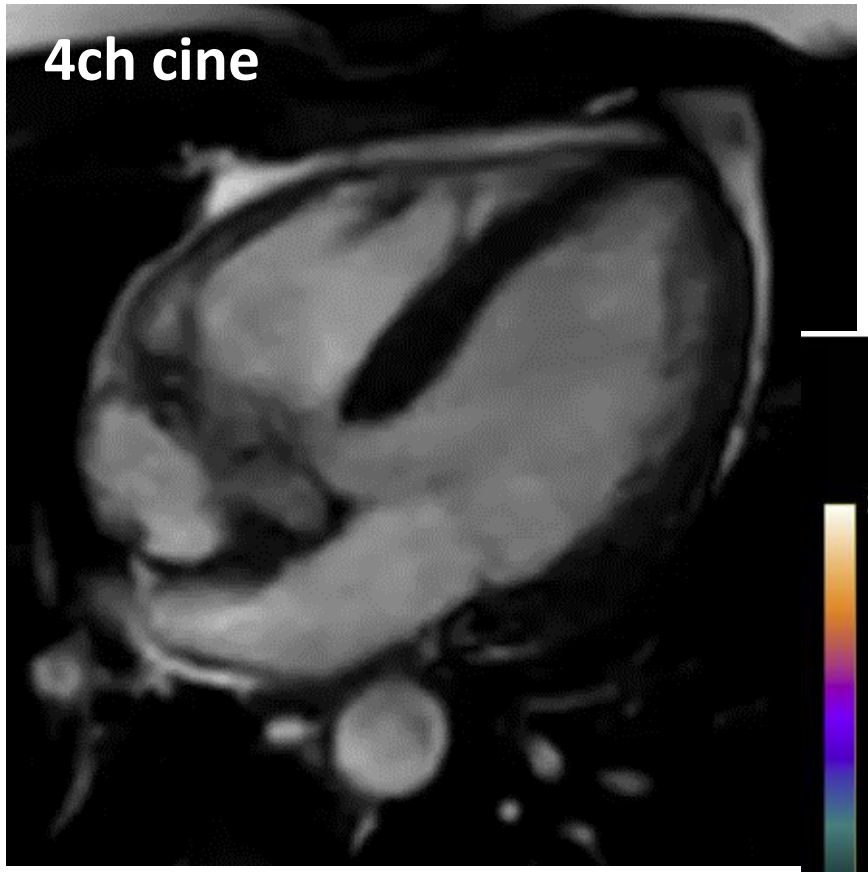
Abnormal ECG

Multiple ER visits for Chest pain (x6)

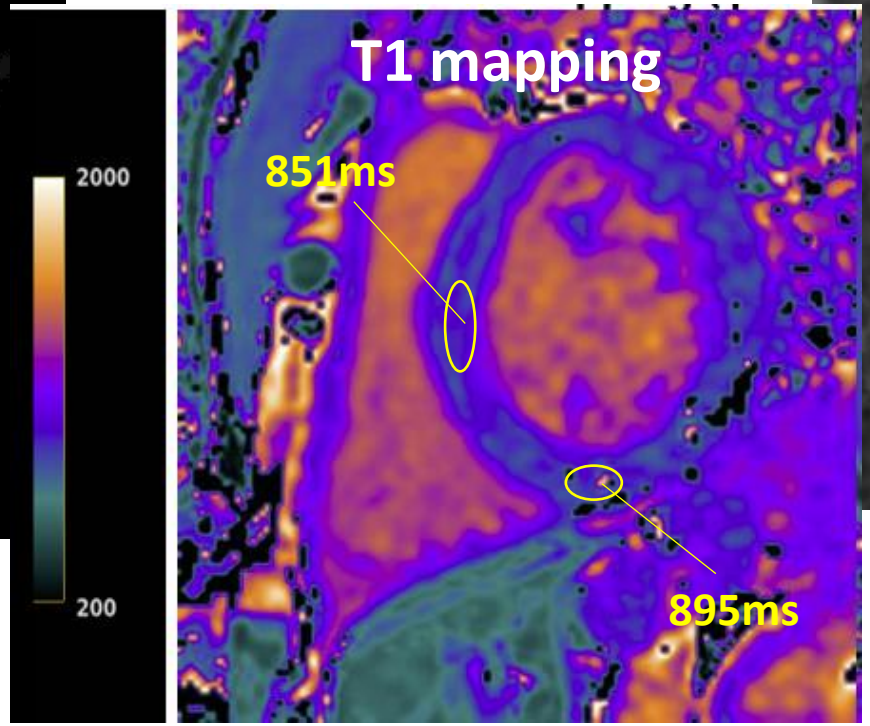
Mild troponin rise

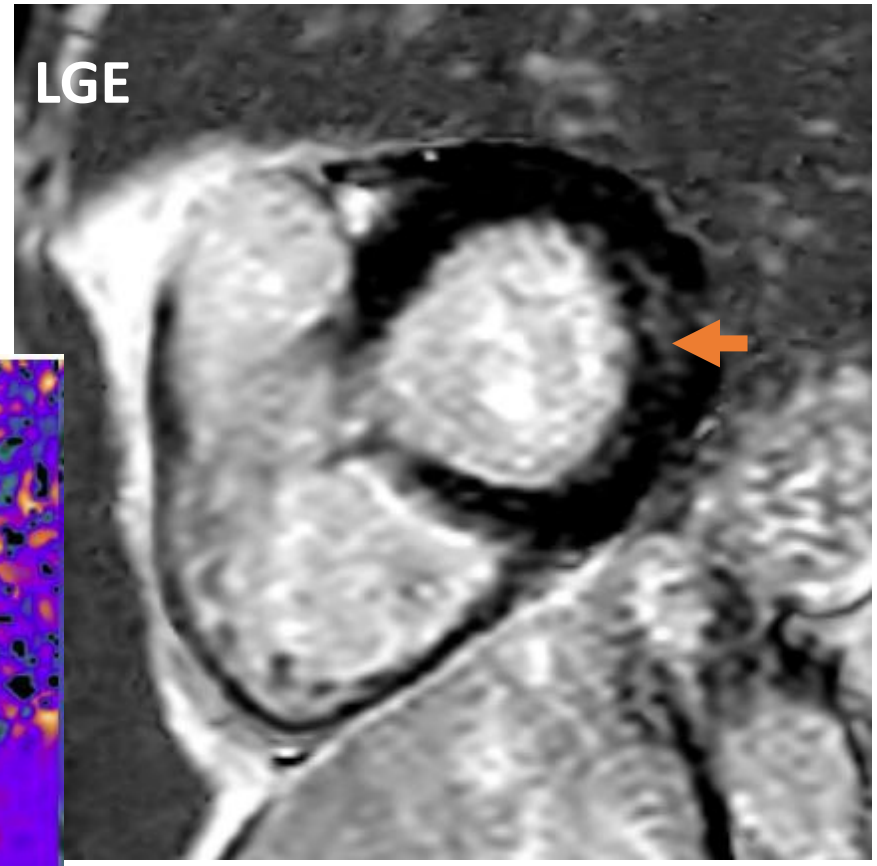
Several (x3) coronary angiograms

Male with LVH & abnormal ECG for 15 years



Normal LV/RV volumes
Normal LV/RF function
Mild LVH (13mm)
Low T1 mapping
Midwall LGE basal lateral wall

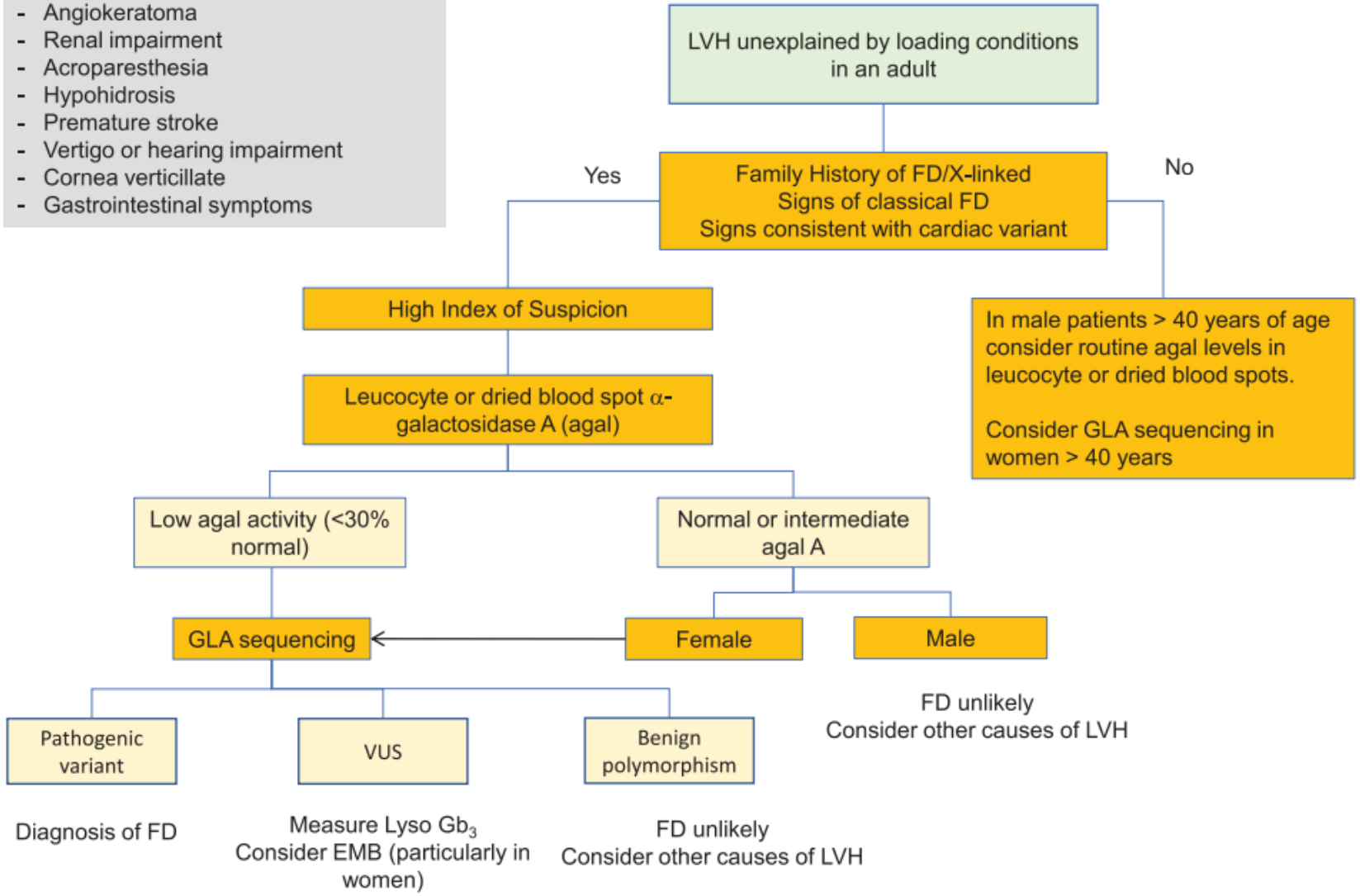




alpha-galactosidase-A (low)
Genetic testing: Variant **GLA**
Migalastat treatment

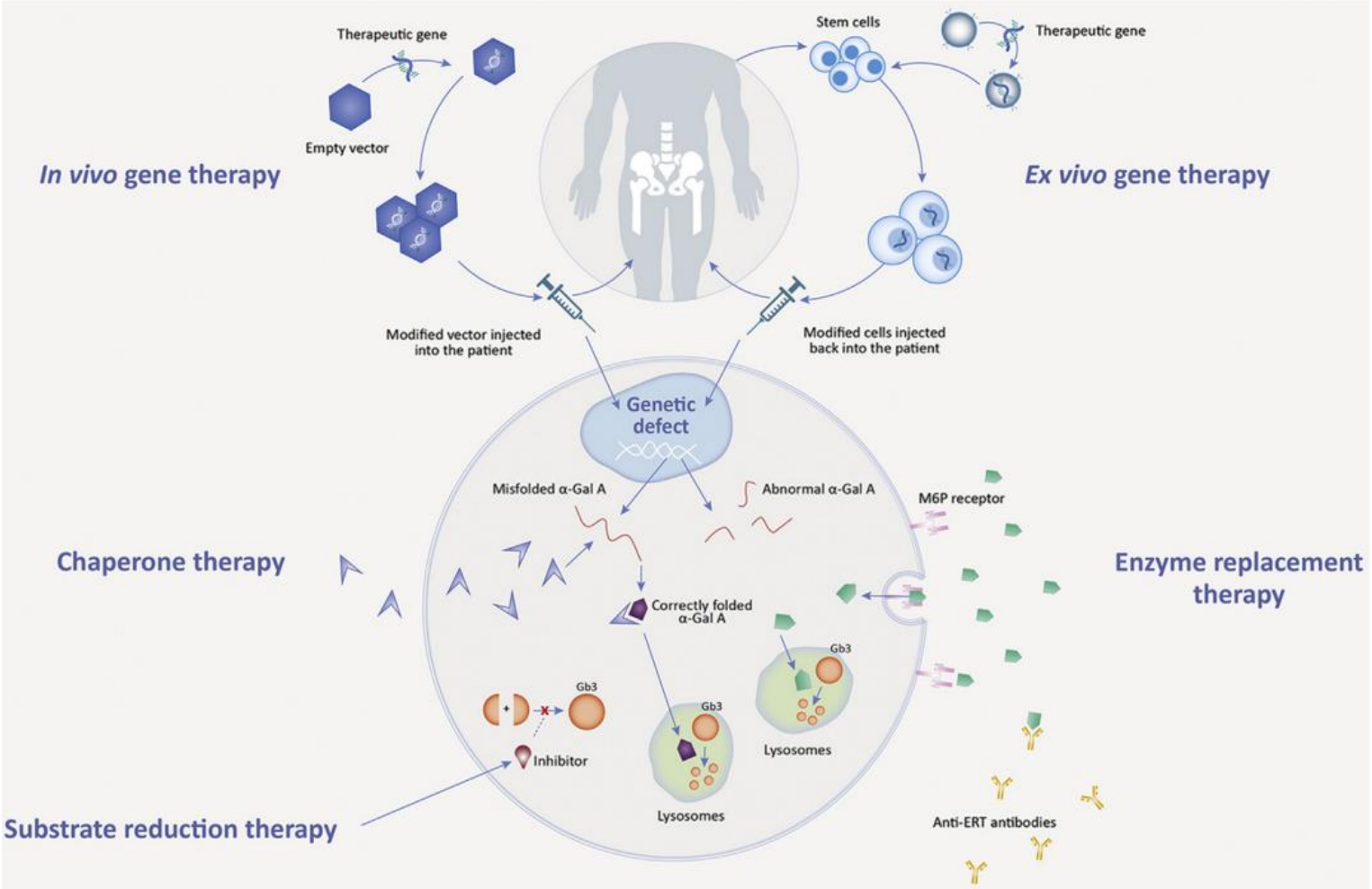
Diagnosis of AFD

Signs and symptoms of classical FD:
- Angiokeratoma
- Renal impairment
- Acroparesthesia
- Hypohidrosis
- Premature stroke
- Vertigo or hearing impairment
- Cornea verticillate
- Gastrointestinal symptoms



Linhart et al. EJHF 2020

Treatment of AFD

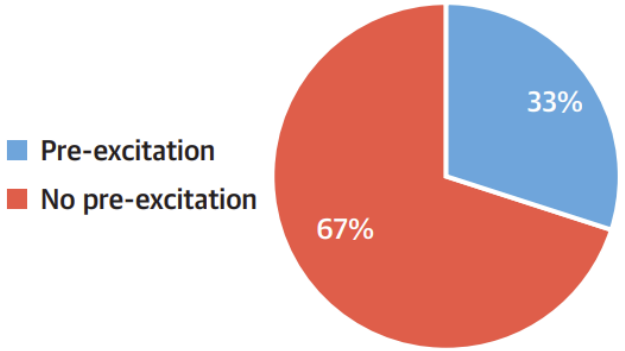


Pieroni et al JACC 2021

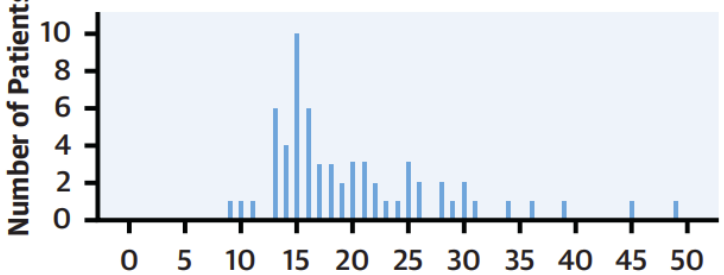
ECG findings in metabolic cardiomyopathies

HCM + WPW +/- conduction disease

CLASSICAL FEATURES
Pre-excitation in Electrocardiography

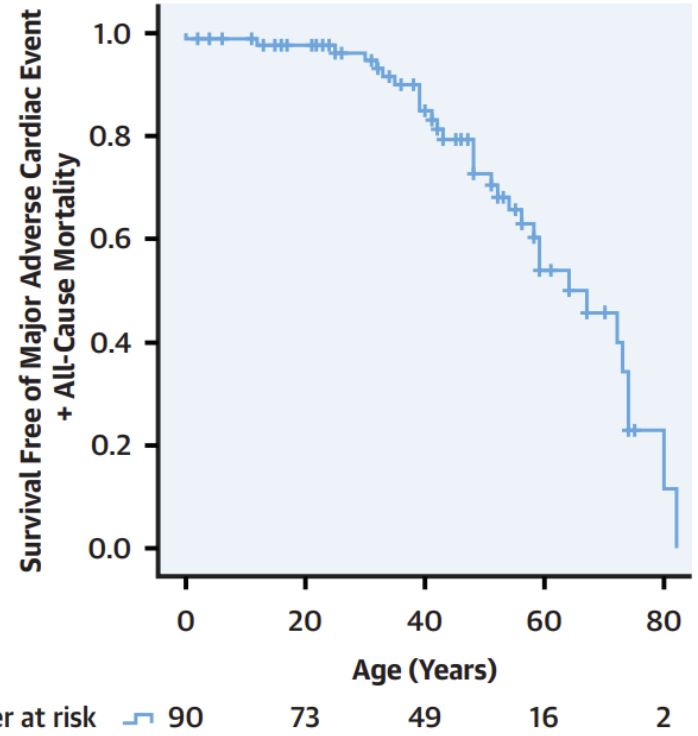


Maximal Left Ventricular Wall Thickness in Affected Patients (mm)

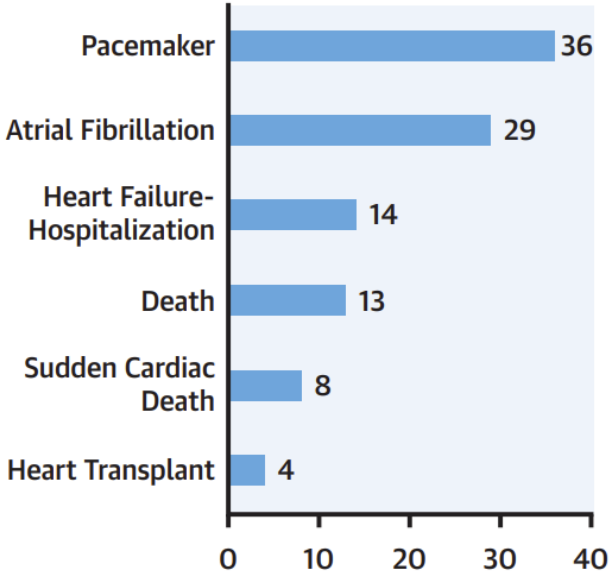


✓ 63% of patients with left ventricular wall thickness <20 mm

SURVIVAL FREE OF EVENTS

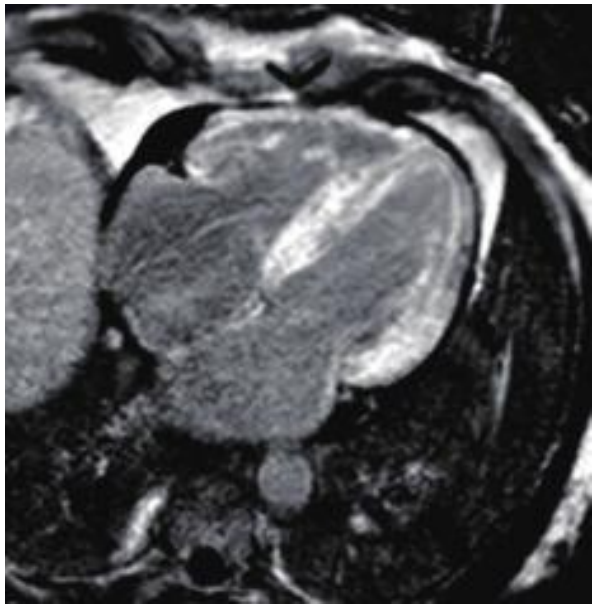


EVENTS AT END OF FOLLOW-UP (%)

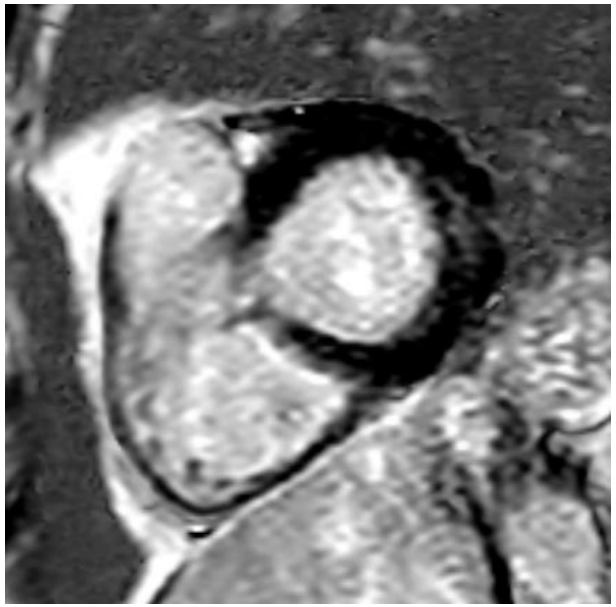


Unusual imaging appearances in metabolic cardiomyopathies

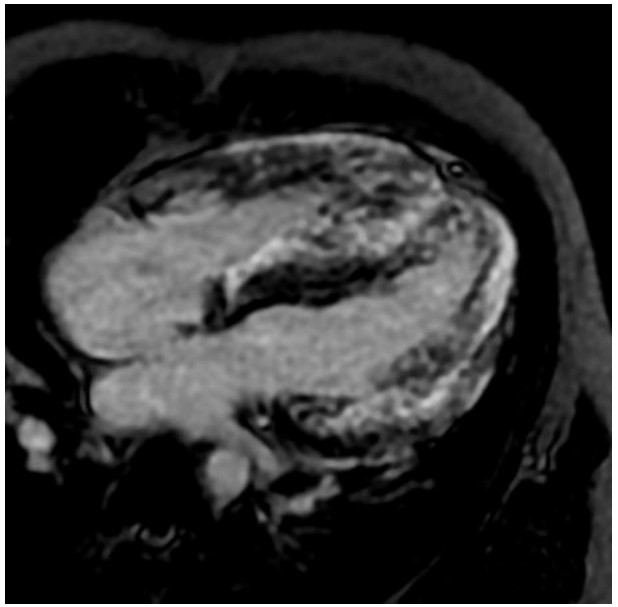
LGE in “Hypertrophic Cardiomyopathy”



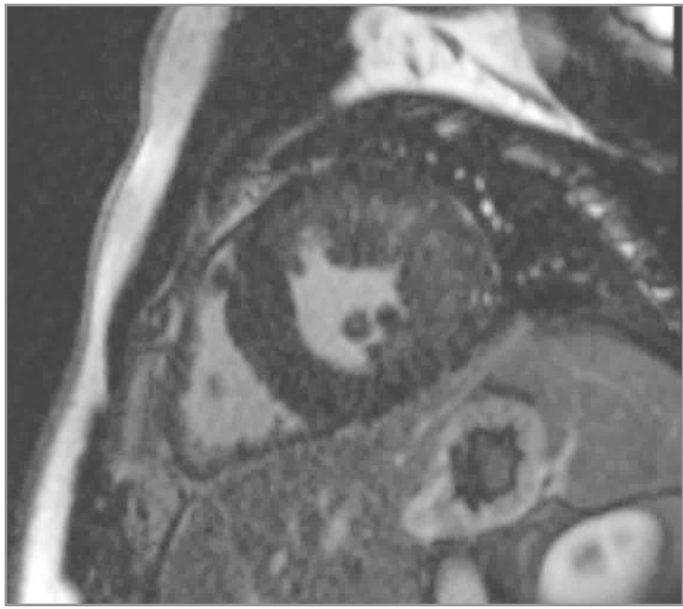
Amyloidosis



Anderson-Fabry



Danon Disease



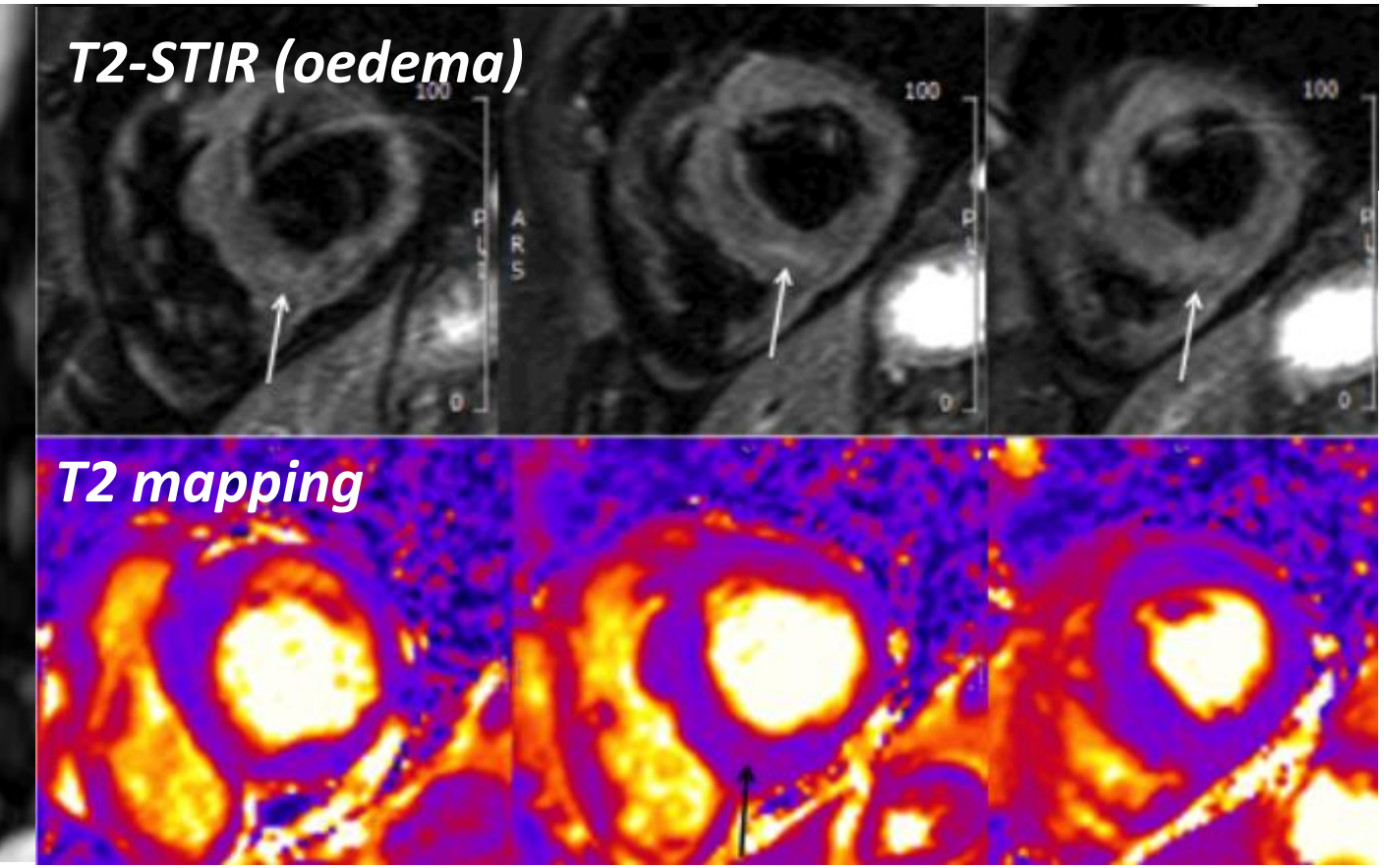
Mitochondrial CMP

Miliou A et al. JACC: Case Reports 2022
Antonopoulos AS et al. Hell J Cardiology 2021

HCM + multiple myocardial recesses / wall thinning

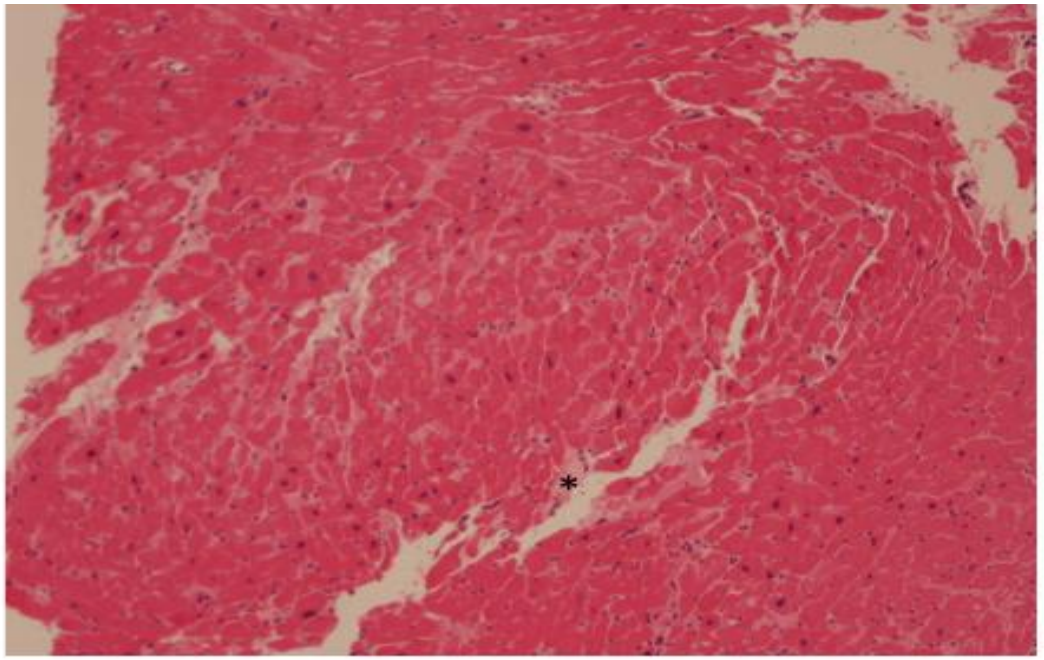
male 34y, episodes of chest pain, hs-TnI (+)
CCTA (-), CTPA (-), mediastinal lymphadenopathy

Barth's syndrome
3-methylglutaconic aciduria type II

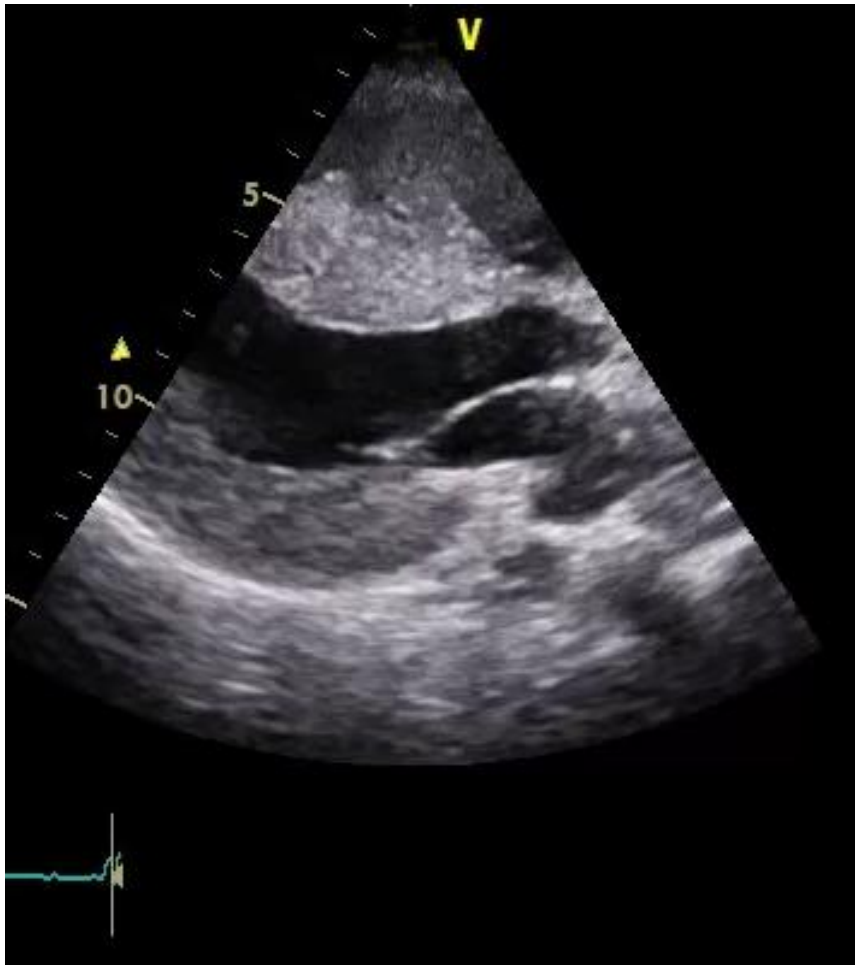


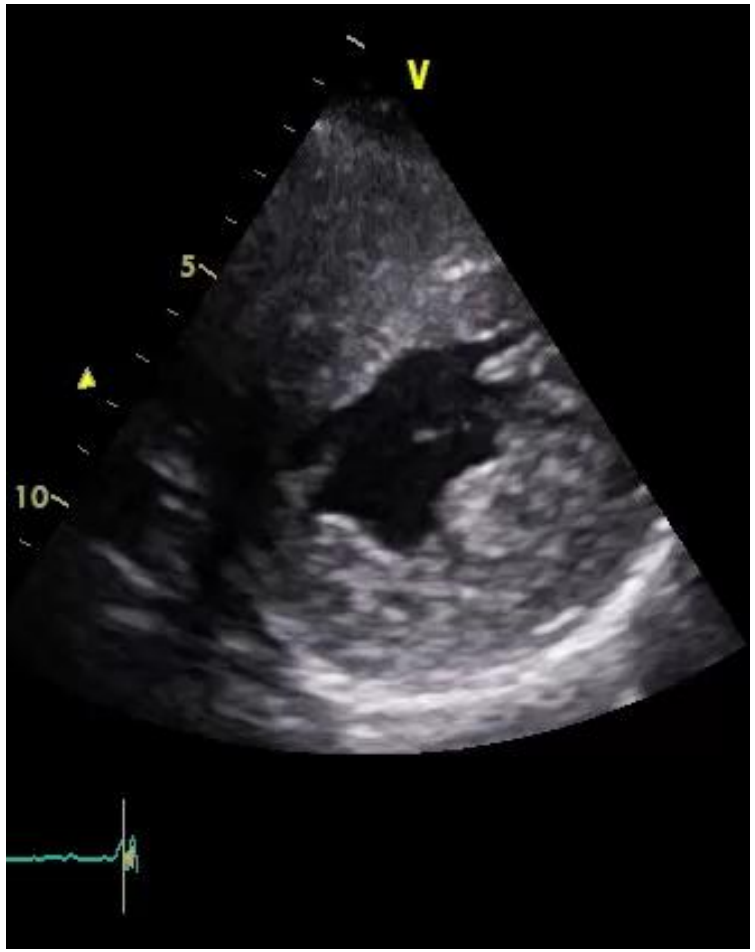
Endomyocardial biopsy

- hypertrophied myocytes
- focal interstitial fibrosis
- increased number of mitochondria

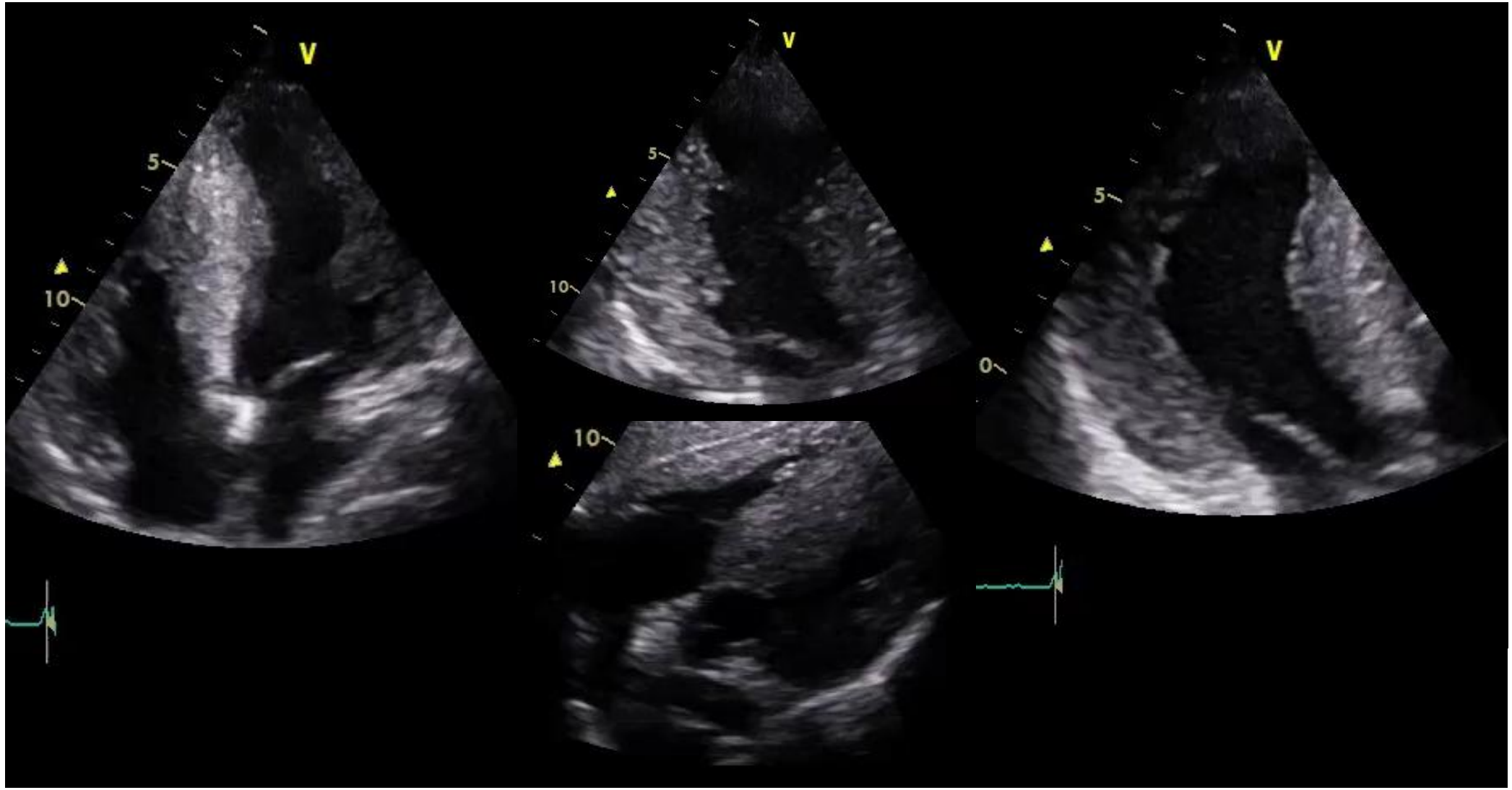


Extreme hypertrophy in metabolic CMP



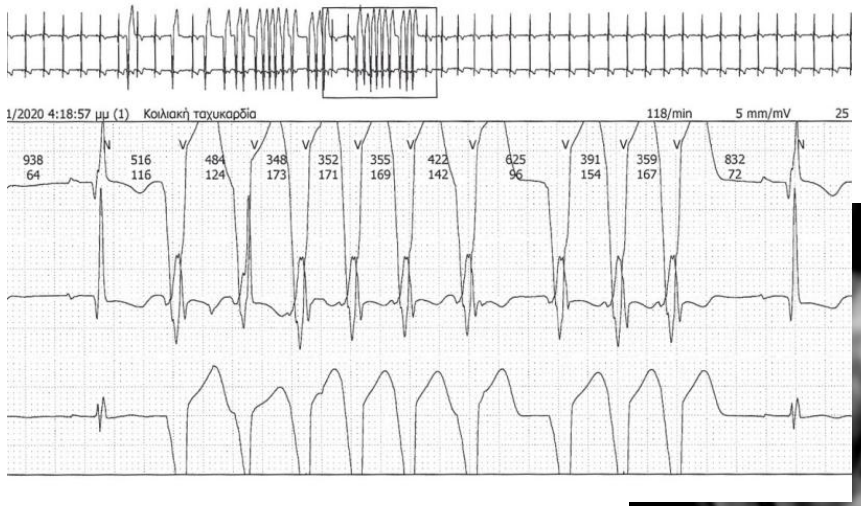


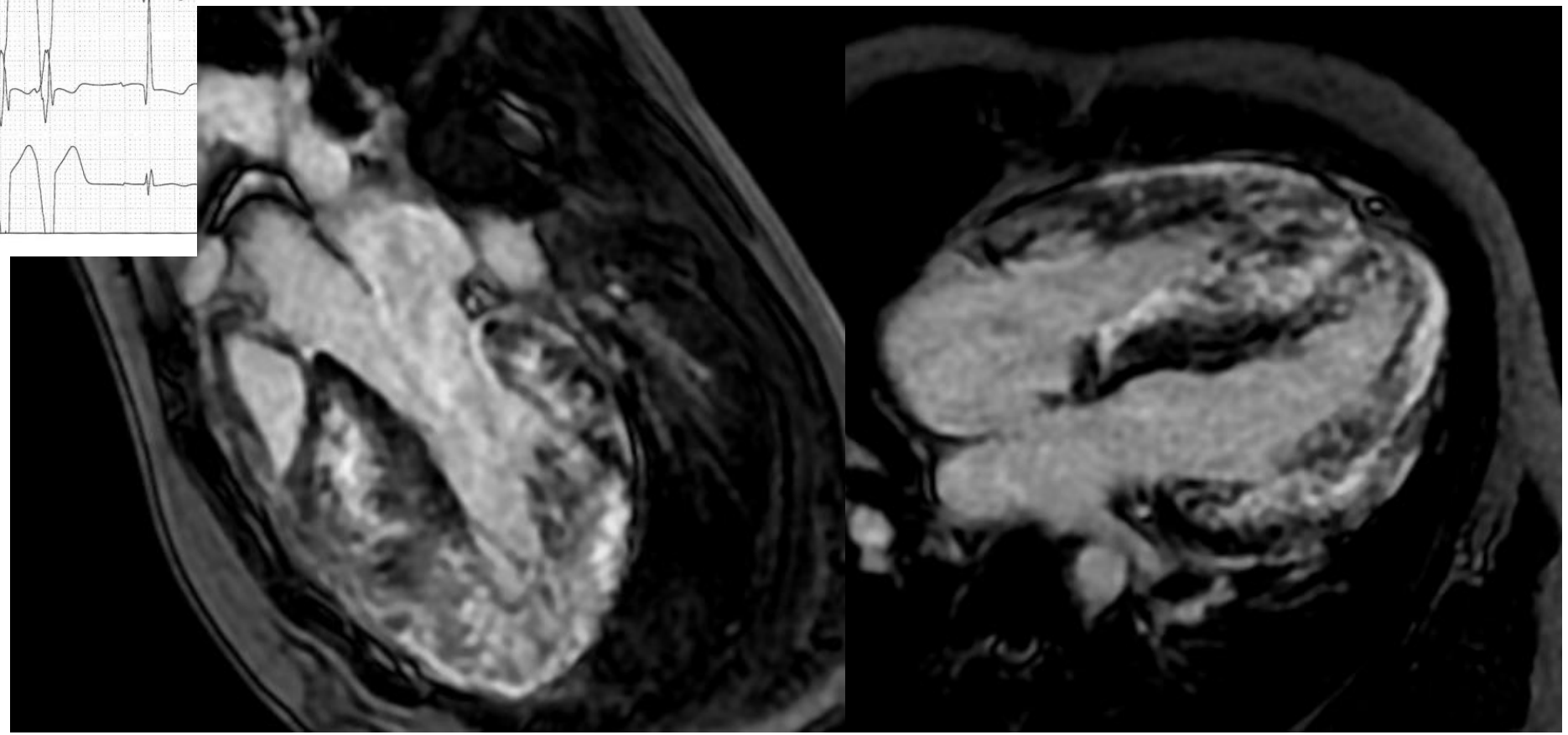
Extreme hypertrophy in metabolic CMP



Cardiogenetics Unit archive

Extensive fibrosis and arrhythmogeneicity





Red flags in Danon Disease

Young male - Fhx of SD

Extreme concentric LVH of 30mm

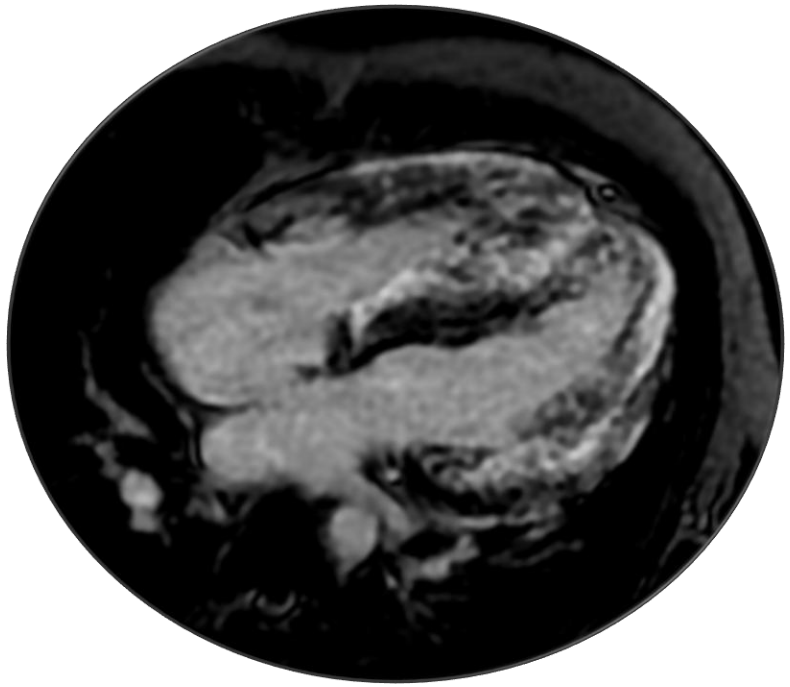
↑ LFT - ↑ CPK

Cognitive status?

Classical triad of DD signs in males:

1. HCM
2. Proximal muscle weakness + ↑LFT
3. Learning problems / Intellectual disability

\+



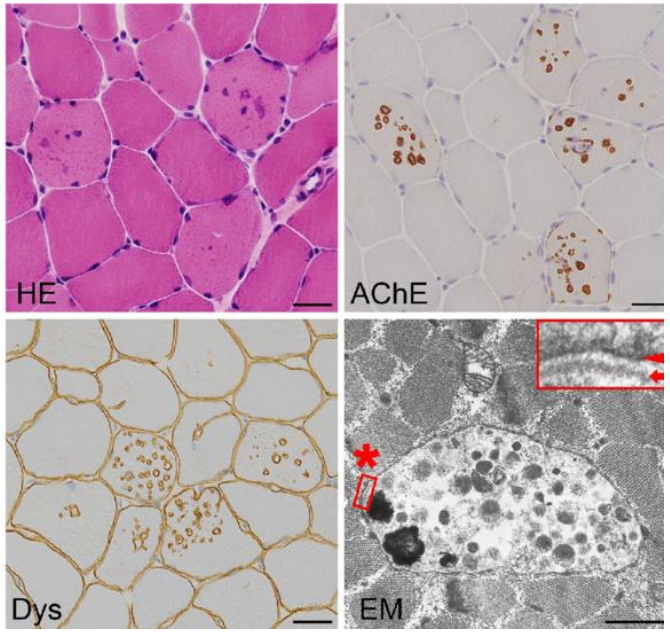
LGE in Danon disease may have different patterns and distributions but typically is:

- Extensive
- Prominent at LV/RV insertion points
- **always sparing the mid IVS**

(100% specificity for DD)

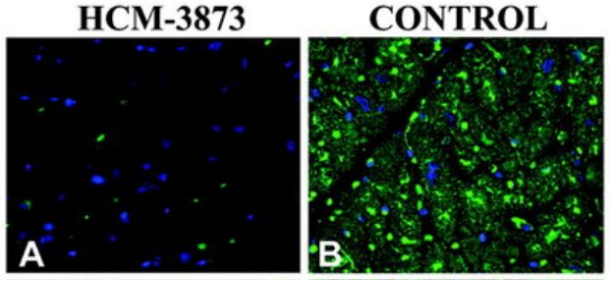
Confirmation of diagnosis of DD cardiomyopathy

Skeletal or cardiac muscle biopsy



Histopathology: accumulation of autophagic material and glycogen in cardiac/skeletal muscle cells.

Immunohistochemistry staining: absence or reduction of LAMP2 protein



Genetic testing

Gene: LAMP2
Finding: NM_002293:c877C>T, p.(Arg293*)
Clinical significance: Pathogenic
Heterozygote

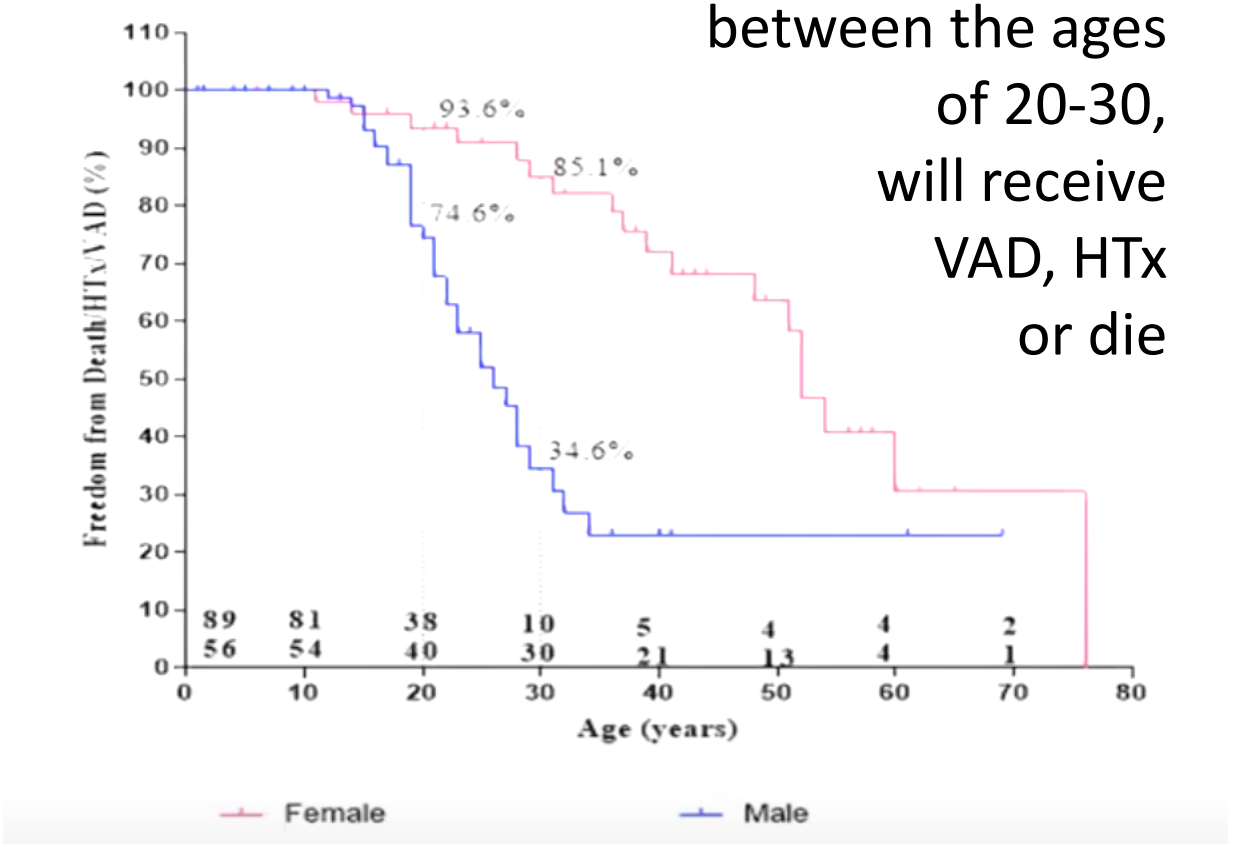
Prognosis of Danon Disease

X-linked - autophagic vacuolar myopathy
Highly penetrant, extremely morbid, multisystemic disorder

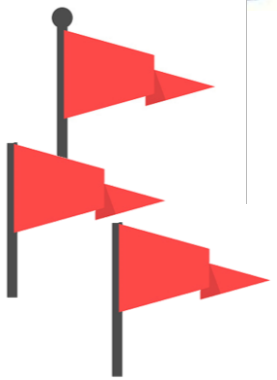
- 4% of paediatric HCM
- 1 / 500 of all HCM cases
- 17% of HCM + pre-excitation on ECG
- Elevated AST/ALT, CPK
- Retinitis pigmentosa (may co-exist)
- Mild cognitive impairment (but fully functional)

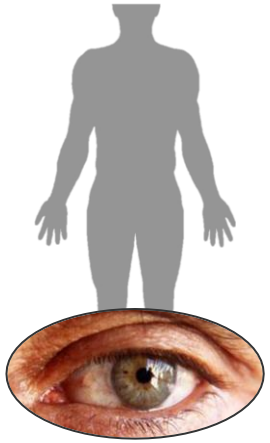
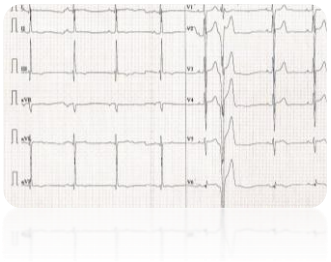
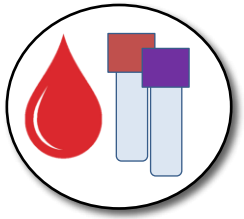
partial levels of a functional LAMP2 protein

Majority of males, between the ages of 20-30, will receive VAD, HTx or die



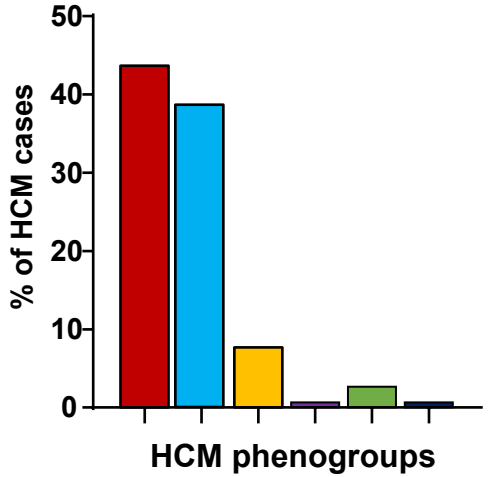
Tips: Phenotype – Genotype associations

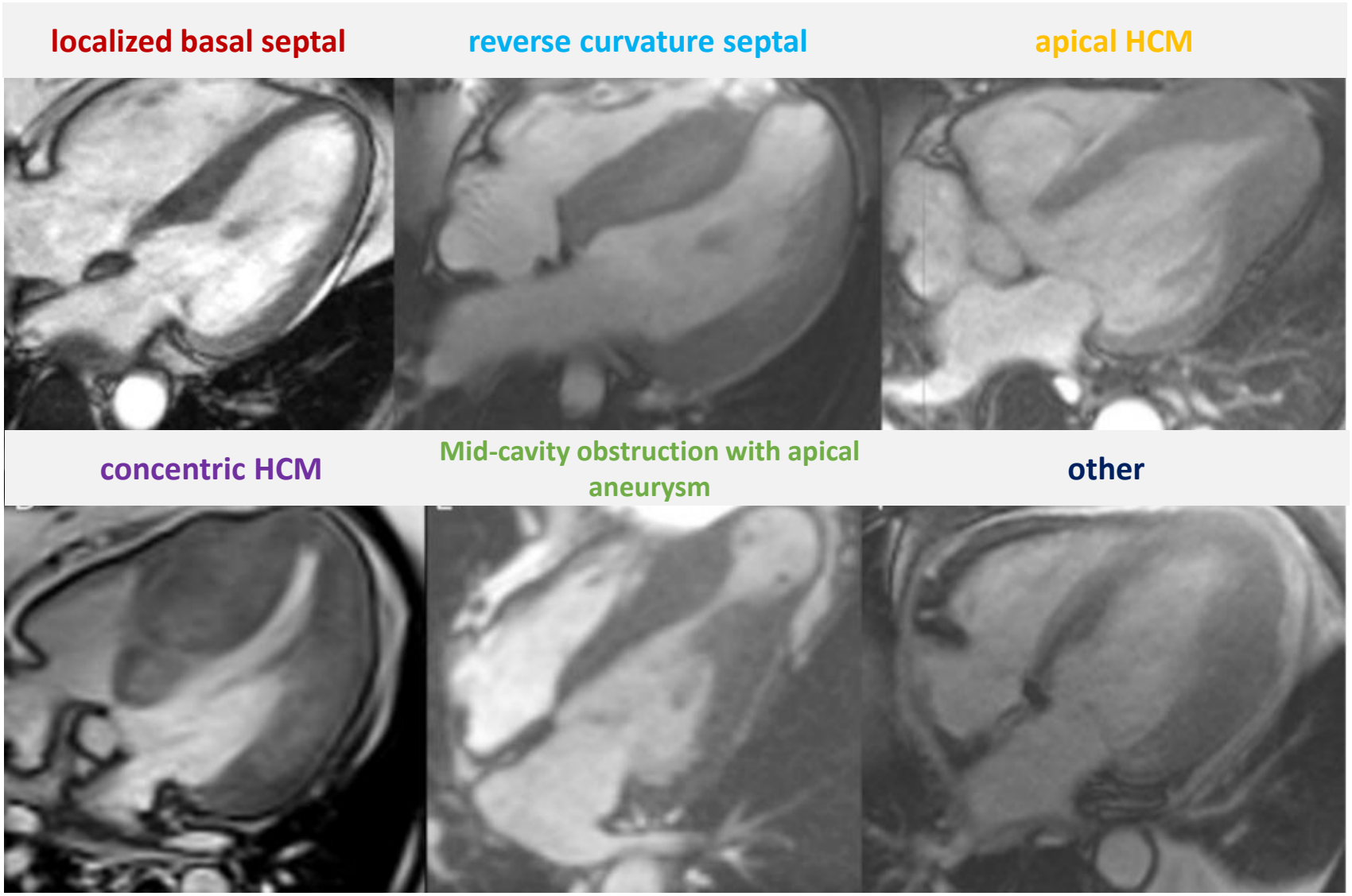


Physical ex. 	Mental retardation / learning difficulties	Mitochondrial Rasopathy
	Neurological symptoms/signs	Amyloidosis
	Carpal tunnel	Amyloidosis
	Musculoskeletal problems / weakness	Neuromuscular diseases Mitochondrial Glycogenosis
	Eye examination	Glycogenosis
ECG 	Short PR / preexcitation	Glycogenosis Fabry Mitochondrial
	Low QRS voltage (or normal despite LVH)	Amyloidosis
Blood biochemistry 	Abnormal liver enzymes	Danon disease Mitochondrial diseases
	Raised CPK	Danon disease Mitochondrial diseases Neuromuscular diseases

Imaging phenotypes of HCM

HCM Registry
2,755 HCM patients

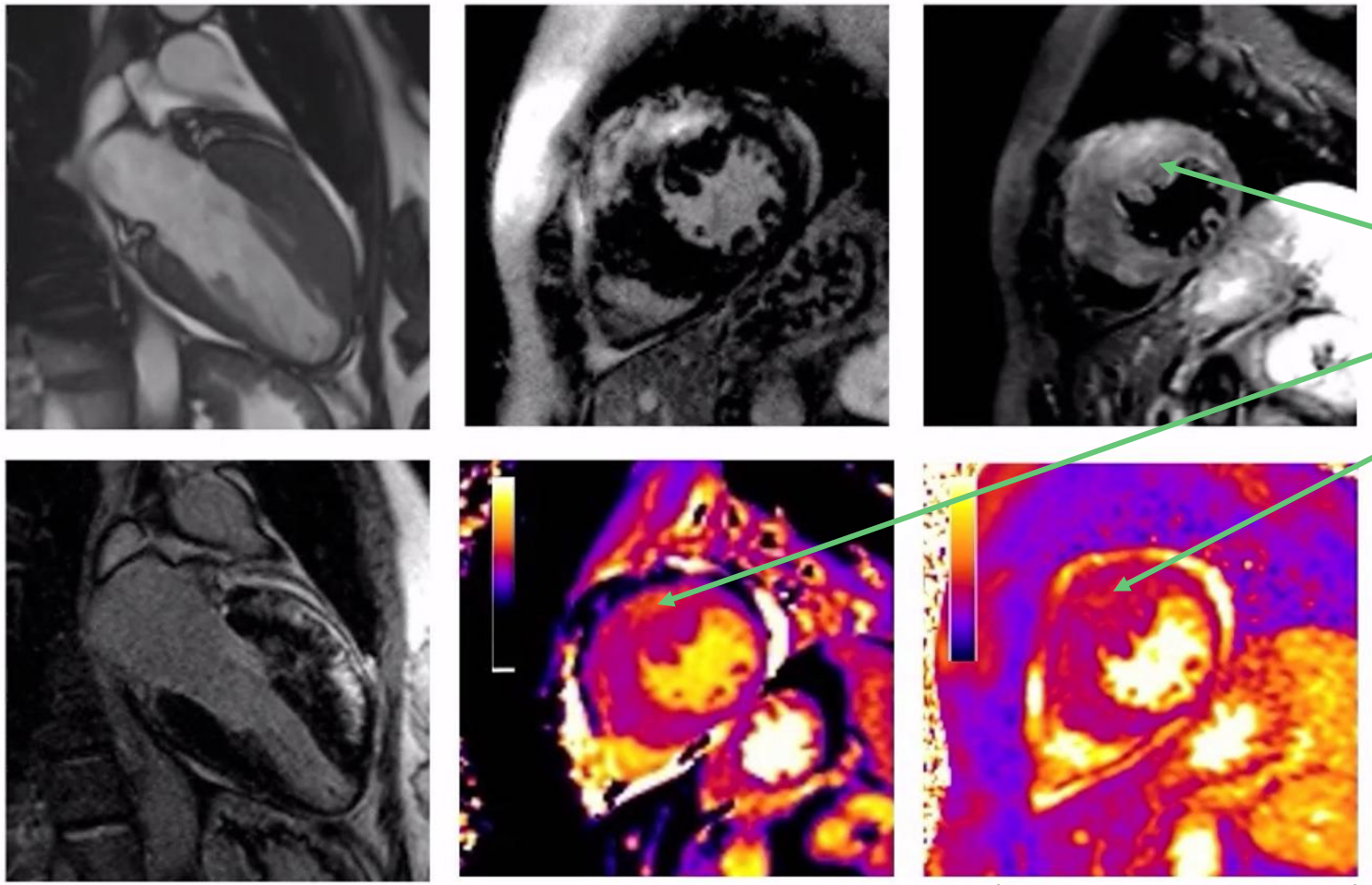




Neubauer et al J Am Coll Cardiol 2019;74:2333–45

Myocardial inflammation in metabolic CMP

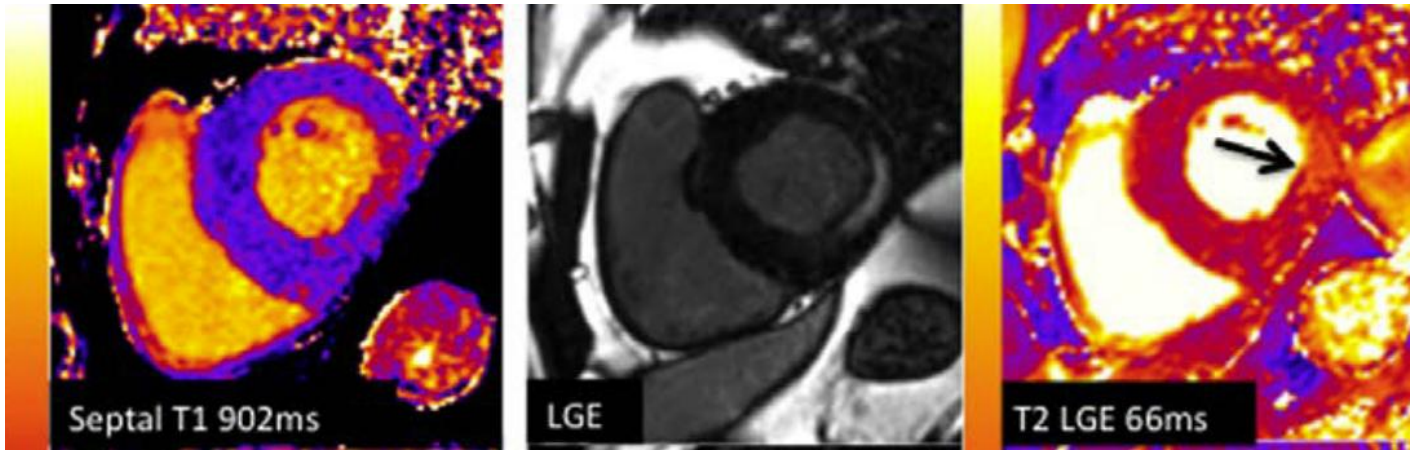
Role in
disease progression?
arrhythmogenicity?



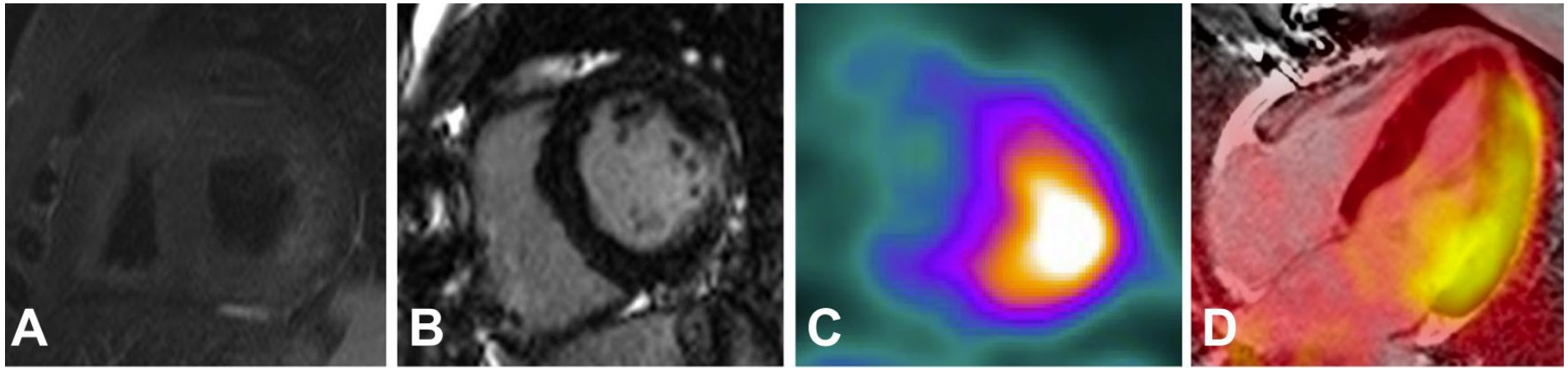
(HCM Summit VII 2021)

Myocardial oedema in metabolic cardiomyopathies

T1 mapping LGE T2 mapping



STIR LGE PET PET/MR



Nappi et al. Insights Imaging (2021) 12:124 - Nordin et al. Circ Cardiovasc Imaging. 2019;12:e009430

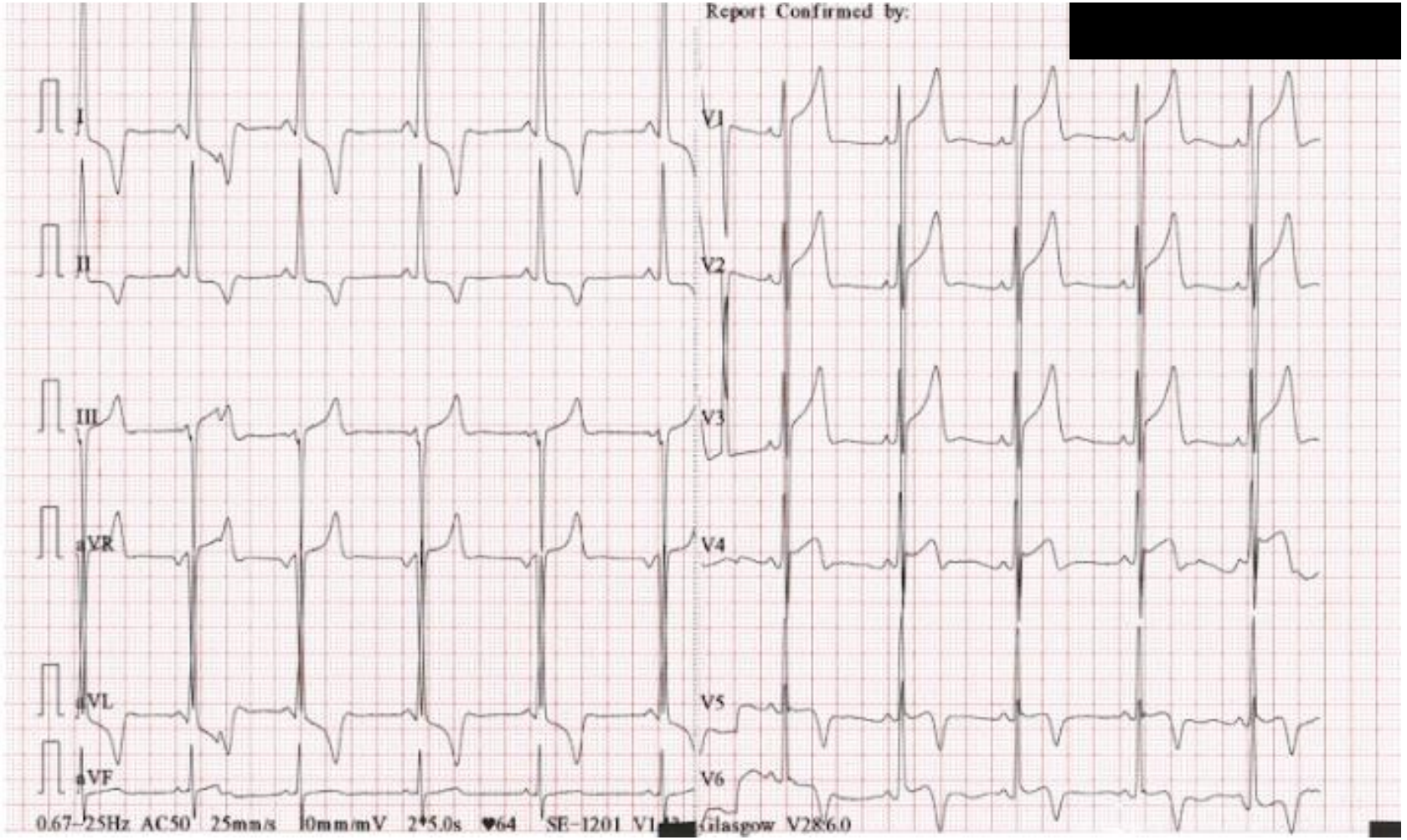
Young male with progressive LVH

Male 26 years old
Farmer
Mild cognitive impairment

No symptoms
Progressive LVH

Diagnosis of HCM (5 years ago)
Referred for further work-up

short PR
LVH voltage criteria
Inferolateral TWI



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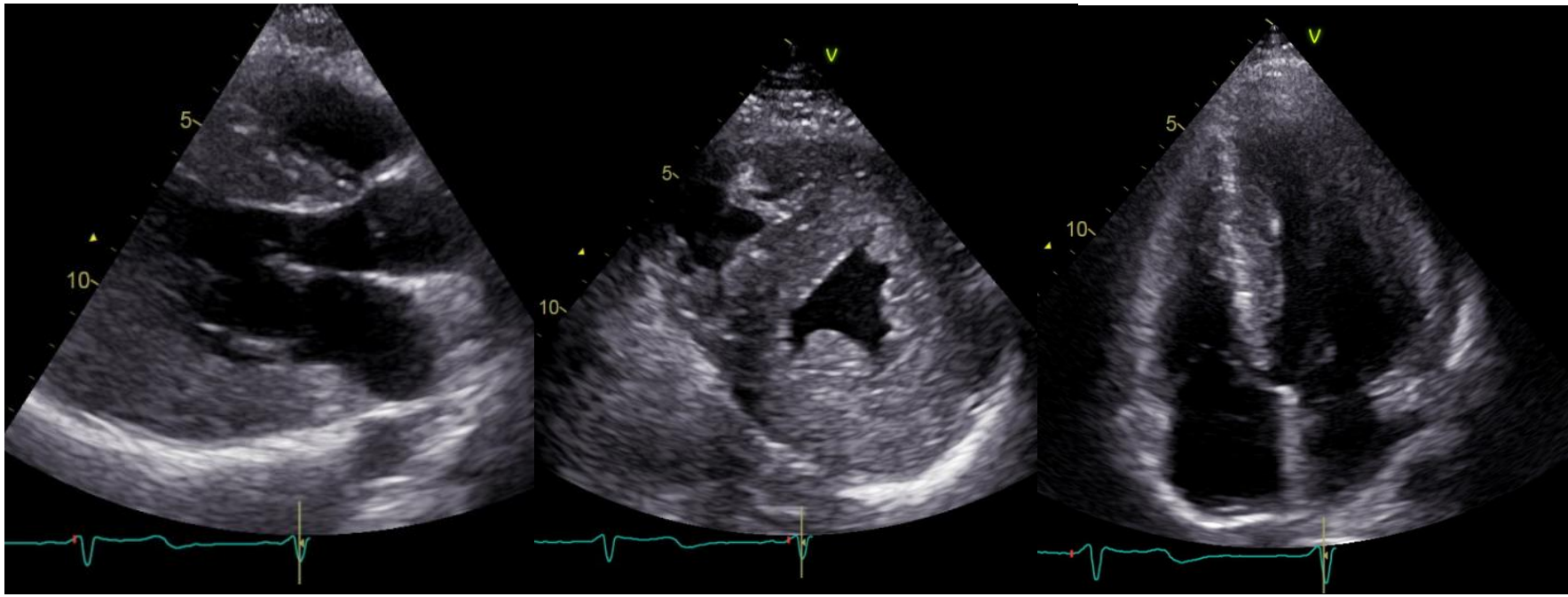

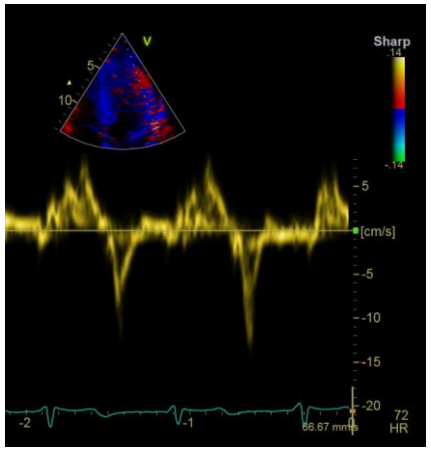

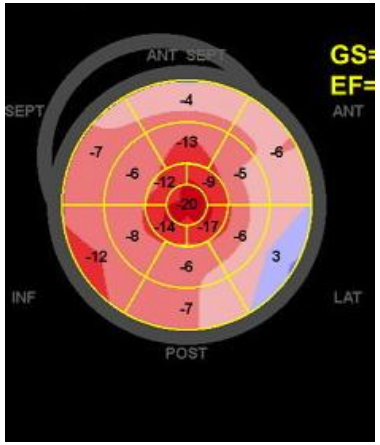

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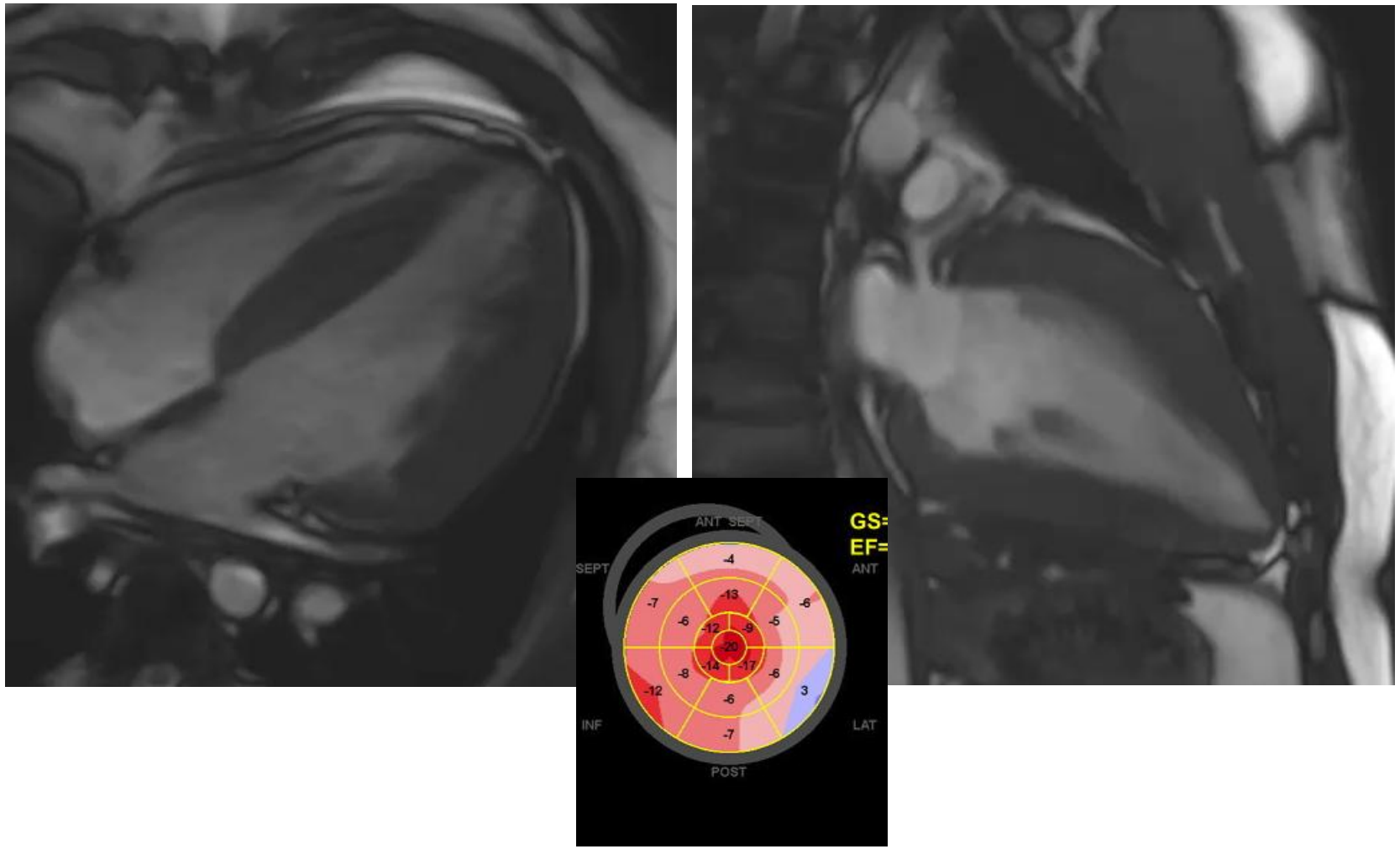
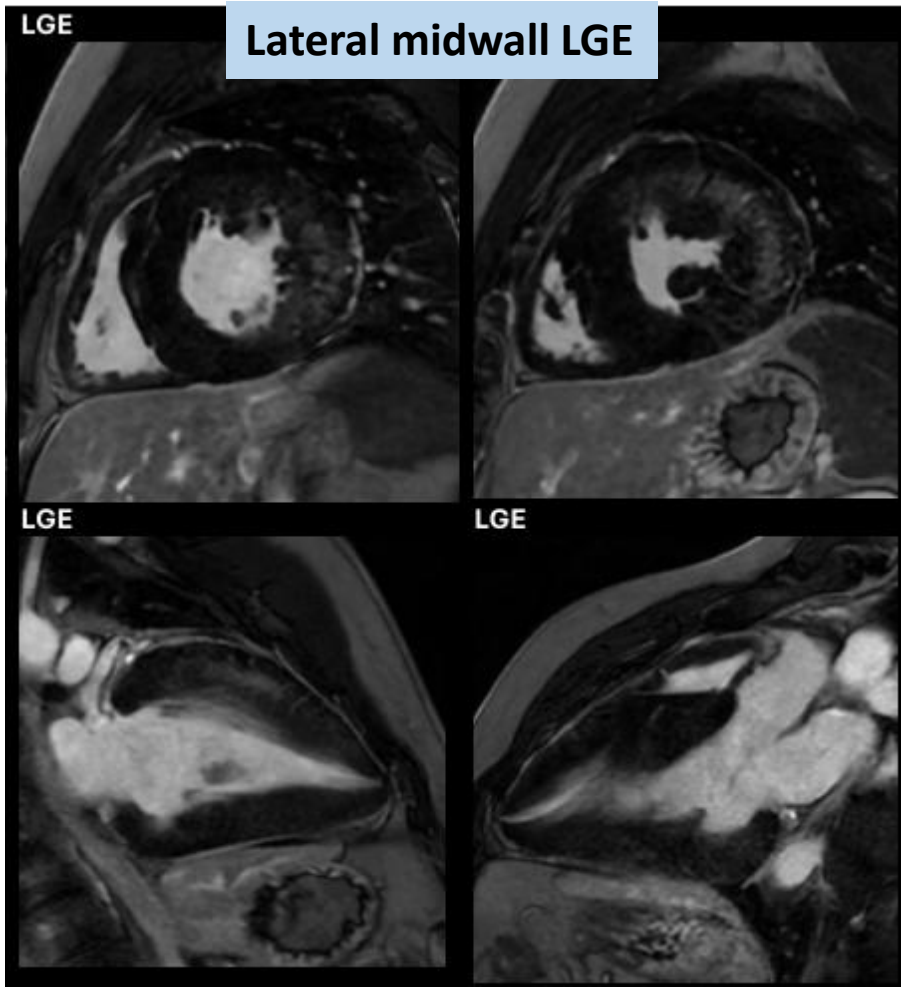
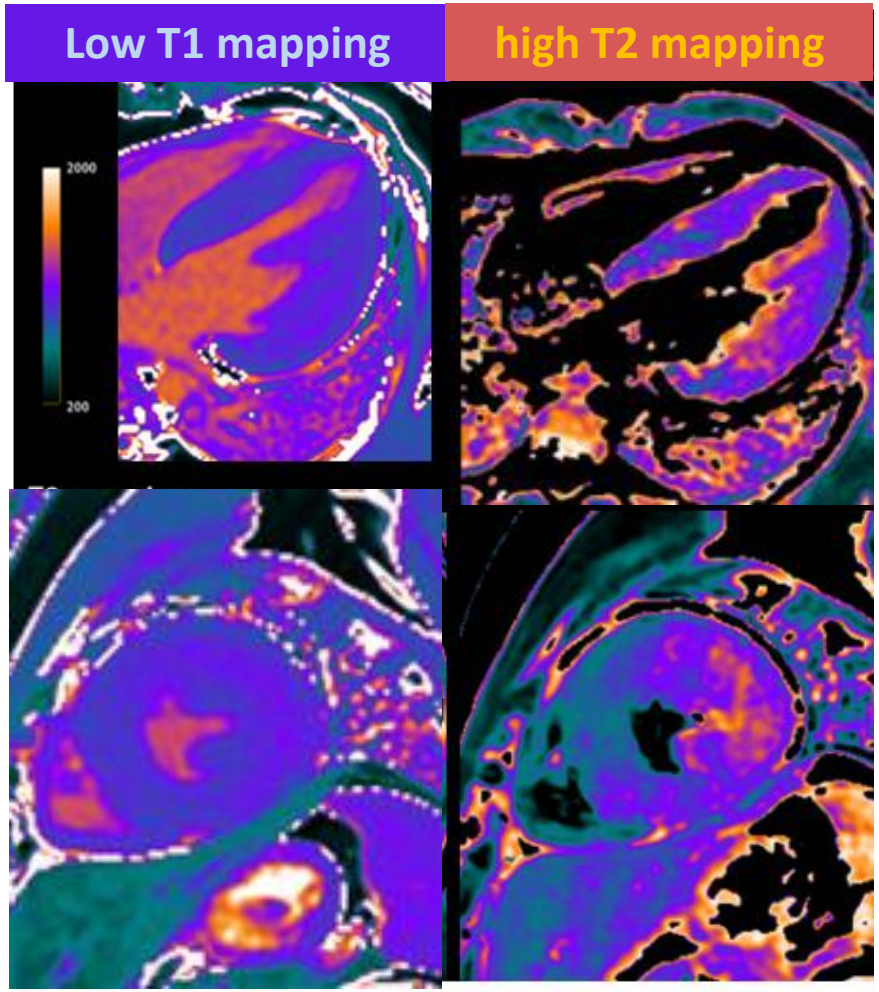
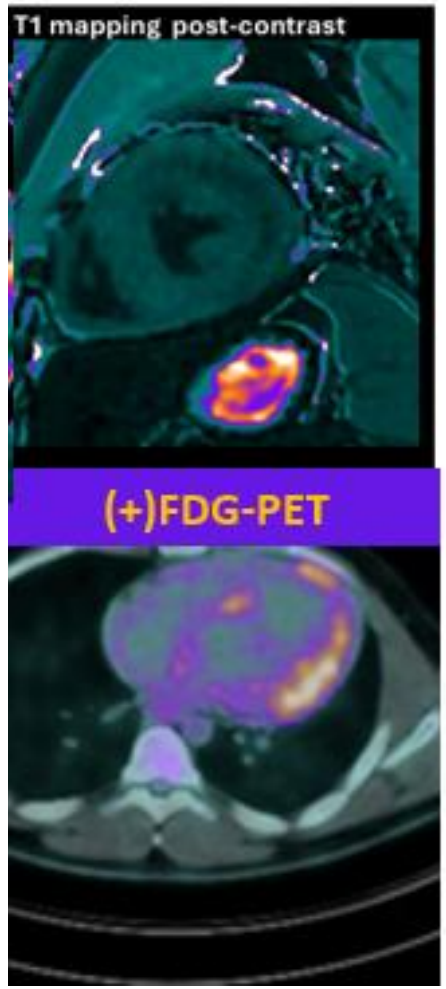


Young male with progressive LVH & episode of myocarditis

Mild chest pain, troponin rise up 4500pg/mL







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Farmer
Mild cognitive impairment

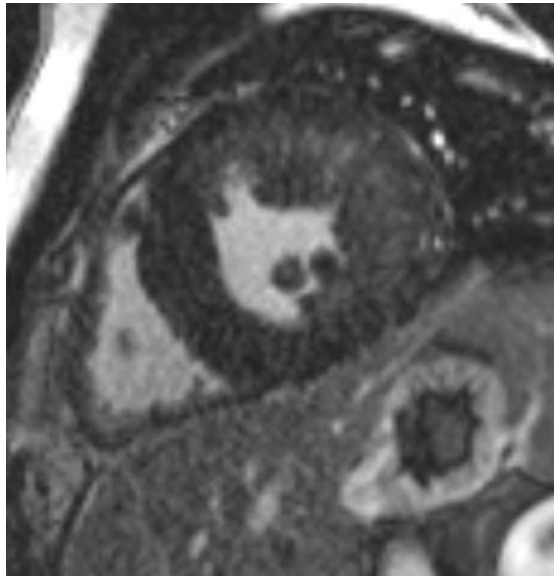
No symptoms
Progressive LVH

Diagnosis of HCM (5 years ago)
Referred for further work-up

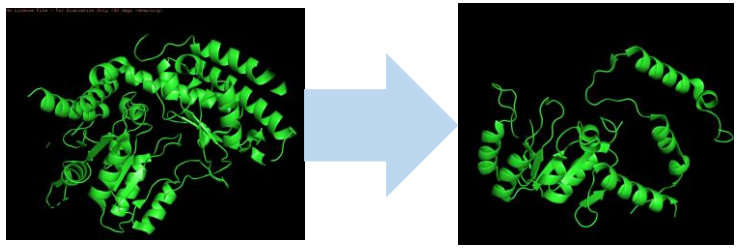
short PR
LVH voltage criteria
Inferolateral TWI

Fabry work-up: negative

Genetic testing:
Compound heterozygote
SHMT2 gene
p.(Arg283*), p.(Ala227Thr)
pathway of folate metabolism???

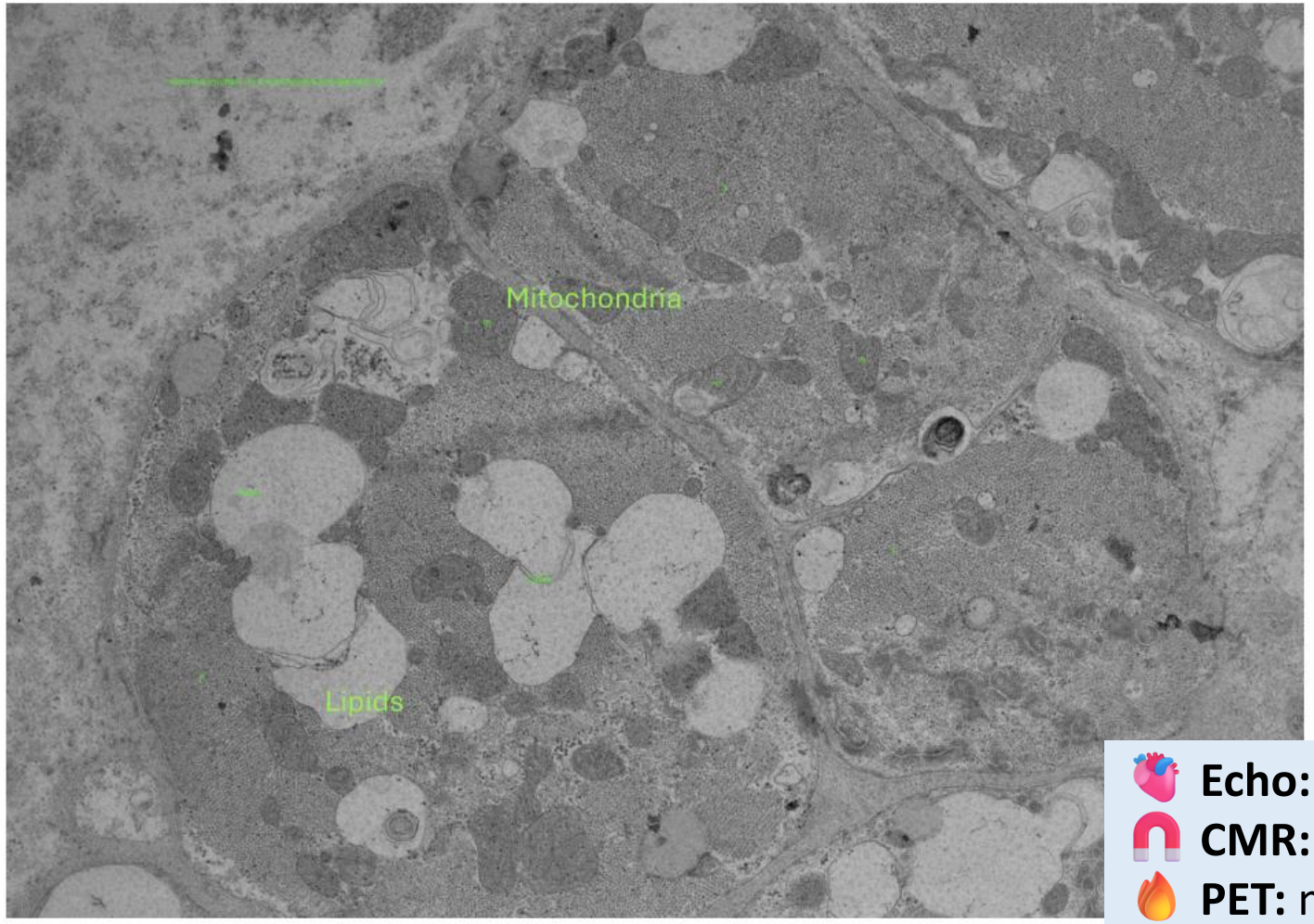


wt SHMT2



mutant SHMT2

SHMT2 cardiomyopathy



- Enlarged and dysmorphic mitochondria with disorganized cristae
- Cytoplasmic vacuoles (autophagy)
- Myofibrillar disarray with loss of sarcomeric alignment
- Interstitial fibrosis and disrupted Z-lines

Causal association of the cardiac phenotype with the genotype

Echo: morphology, systolic function, diastology
CMR: tissue characterization, oedema, fibrosis
PET: metabolic and inflammatory activity
Electron Microscopy: ultrastructural imaging of cells

Metabolic Cardiomyopathies

The Rarest of the Rare

When to suspect in adult life?

- Early onset in life
- Extracardiac findings

  Mental retardation, skeletal myopathy, dysmorphic features, hearing loss, and developmental delay
- Malignant phenotypes
- DCM/HCM: concentric symmetric, extreme LVH
- Inferolateral LGE (AFD)

or other untypical LGE patterns

Prognostic implications

- Poor prognosis (pump failure)
- Amenable to treatment
  - existing /in development,
  - AAV gene therapy