

IL FENOTIPO IPERTROFICO: I FONDAMENTALI

Il fenotipo ipertrofico: una maschera per mille volti

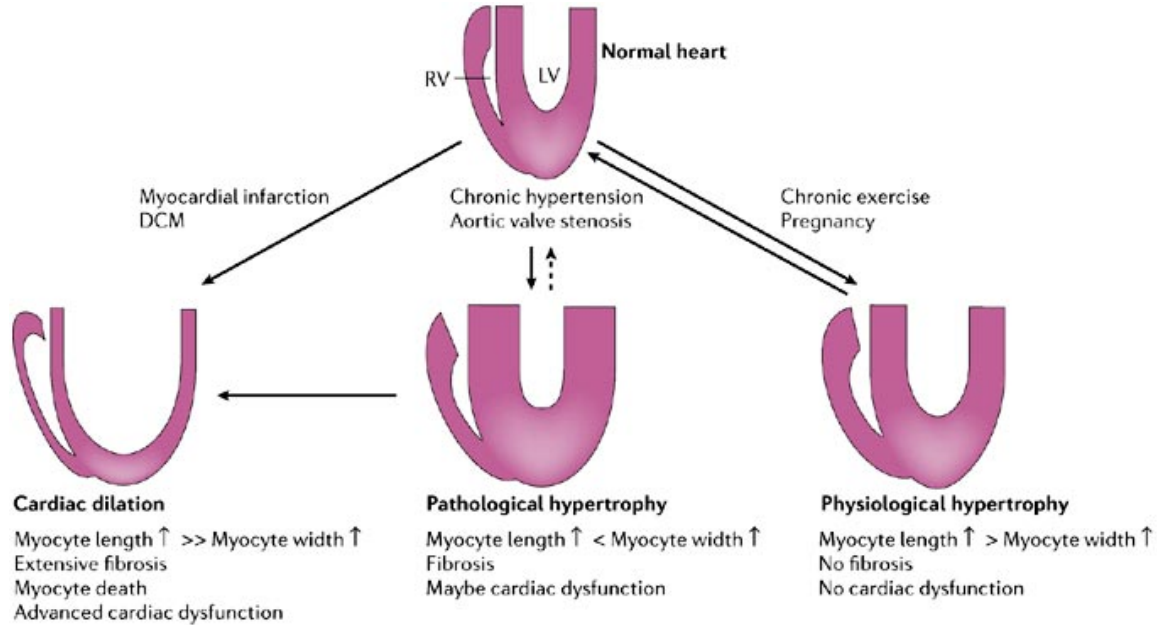
Ines Monte

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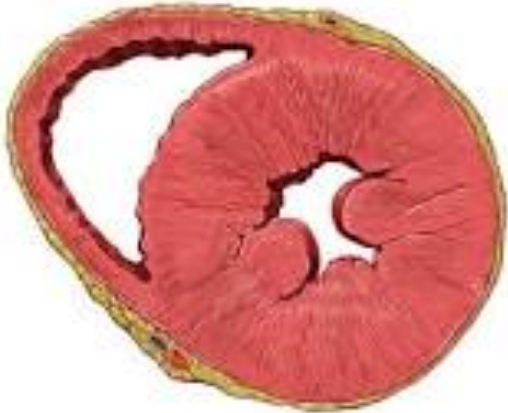
Ipertrofia VS



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- Il fenotipo ipertrofico è definito dalla presenza di un aumento dello spessore parietale ventricolare sinistro non spiegabile dalle condizioni di carico



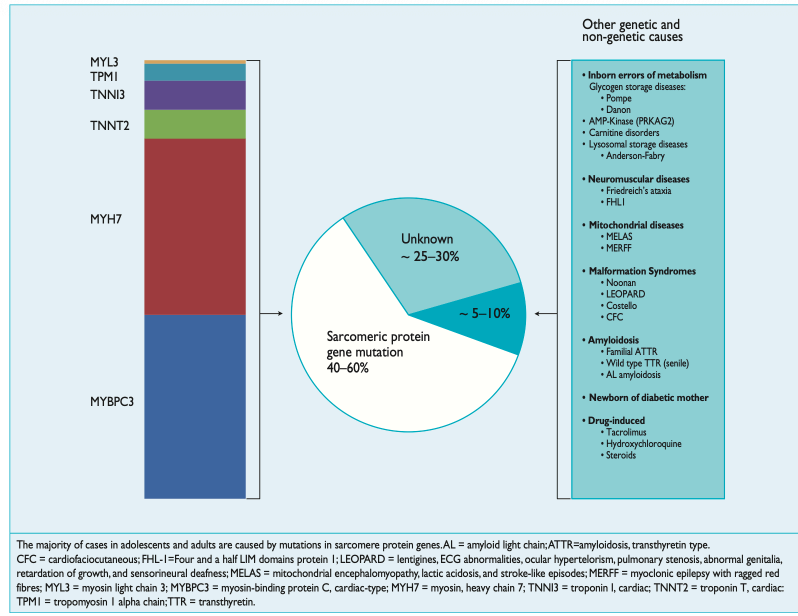
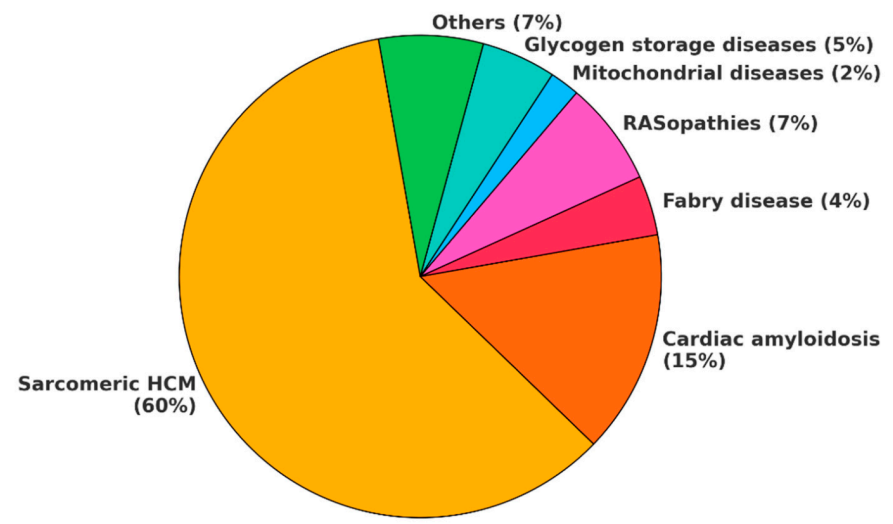


Figure 1 Diverse aetiology of hypertrophic cardiomyopathy.

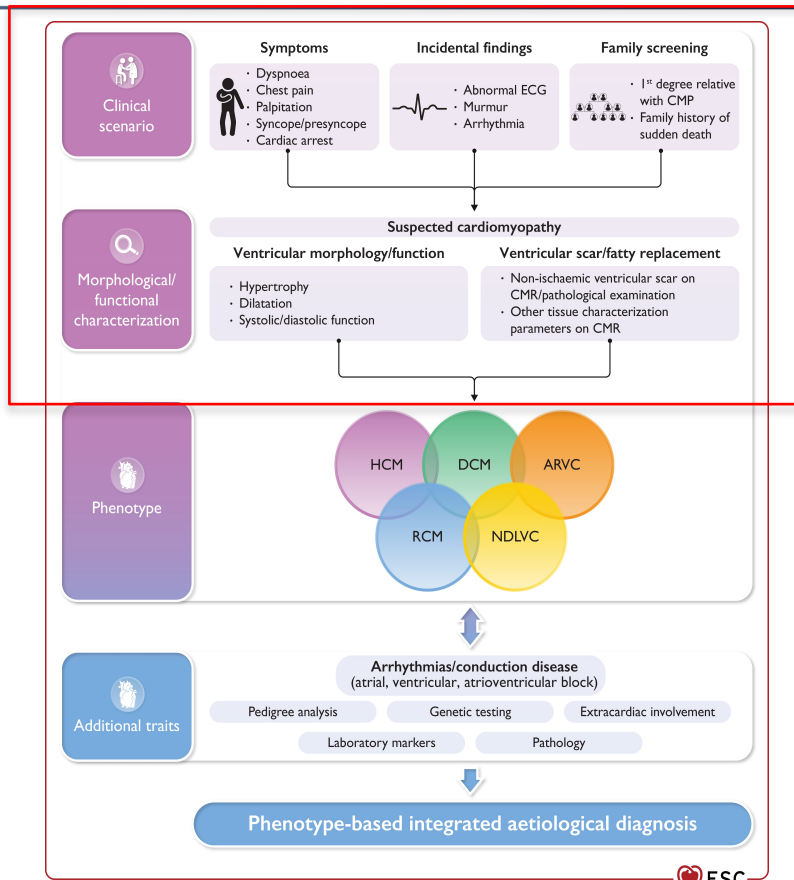
Review
Biomolecules 2025, 13, 3062

Hypertrophic Cardiomyopathy Phenocopies: Classification, Key Features, and Differential Diagnosis

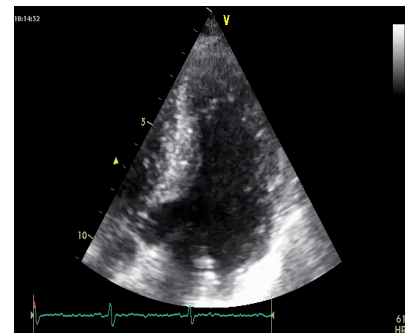
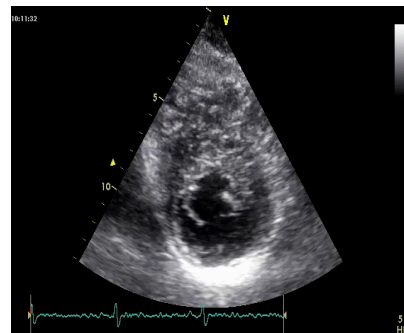
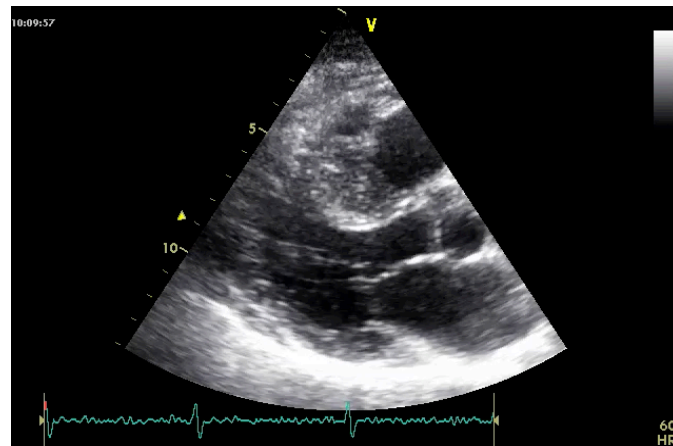
Lucio Tesesi ^{1,2,3,4,5,6}, Giancarlo Trimarchi ^{4,6}, Roberto Licordari ⁷, Davide Restelli ^{1,6}, Giovanni Tavera ^{4,6}, Paolo Liotta ¹, Antonino Micari ¹, Ignazio Simeoni ⁷, Gregory Dendramis ¹, Dario Tortorello ⁷, Alessia Chiara Latini ^{1,4,5,6}, Giulio Falasconi ^{1,6}, Cesare de Gregorio ^{1,6}, Pasquale Cresi ⁷, Giuseppe Dattilo ¹, Antonio Berrone ⁷, Antonio Micari ⁸ and Gianluca Di Bella ¹



Hypertrophic Cardiomyopathies



- HCM is defined by an LV wall thickness ≥ 15 mm in any myocardial segment that is not explained solely by loading conditions.
- Lesser degrees of wall thickening (13–14 mm) require evaluation of other features including family history, genetic findings, and ECG abnormalities.

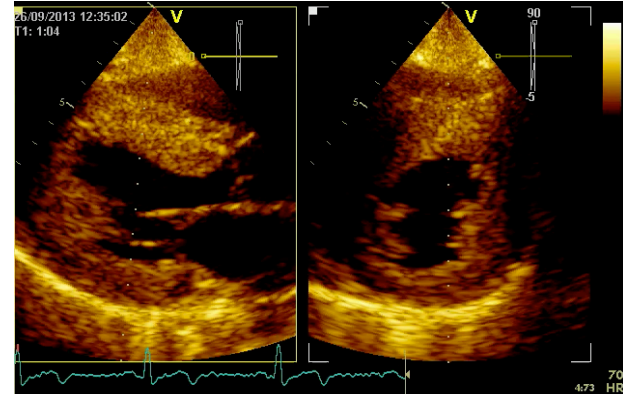


• Children:

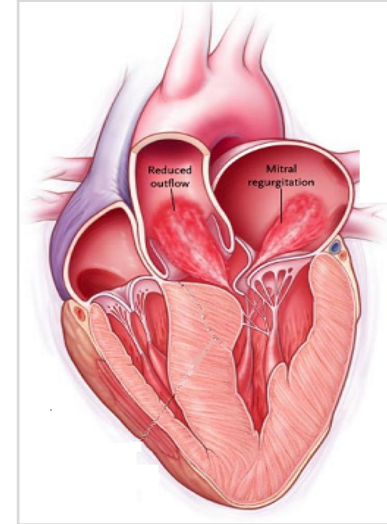
- The diagnosis of HCM requires an LV wall thickness more than 2 standard deviations greater than the predicted mean (z-score >2)

• Relatives:

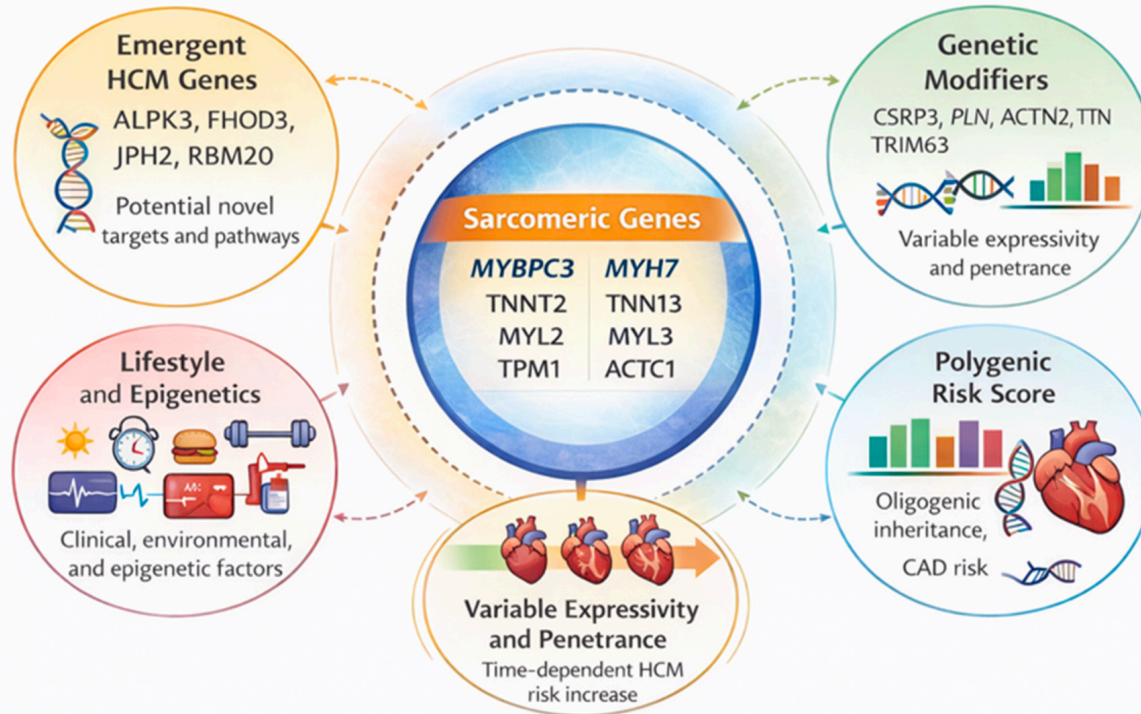
- the clinical diagnosis of HCM in adult first-degree relatives of patients with unequivocal disease is based on the presence of LV wall thickness ≥ 13 mm.
- In child first-degree relatives with LV wall thickness z-scores of <2, the presence of associated morphological or ECG abnormalities should raise the suspicion but are not on their own diagnostic for HCM.



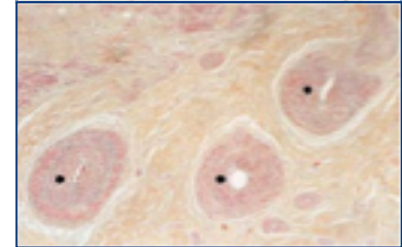
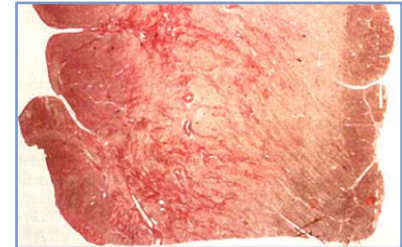
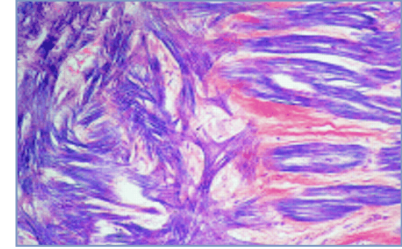
- Prevalenza: 1:200-500 individui nella popolazione generale
- Secondaria ad alterazioni genetiche, con carattere autosomico dominante a penetranza ed espressioni anatomiche variabili
- Sintomi presenti in maniera variabile, in qualsiasi età, meno intensi nelle età più avanzate
- Mortalità 0,8% nella popolazione generale



Genetics of Hypertrophic Cardiomyopathy



- Struttura miofibrillare disorganizzata all'interno delle singole cellule e la disposizione disordinata delle fibre, incrociate a spirale, radiale (*Disarray*)
- *Fibrosi interstiziale* e ispessimento dell'endocardio settale e malattia dei piccoli vasi con arterie intramurali piccole



- **Ipertrofia asimmetrica**

- Coinvolgimento del SIV

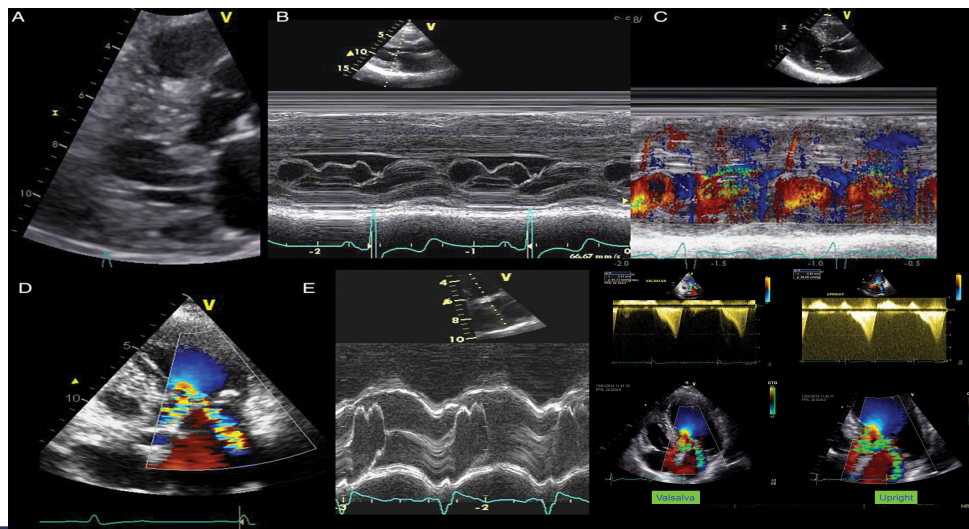
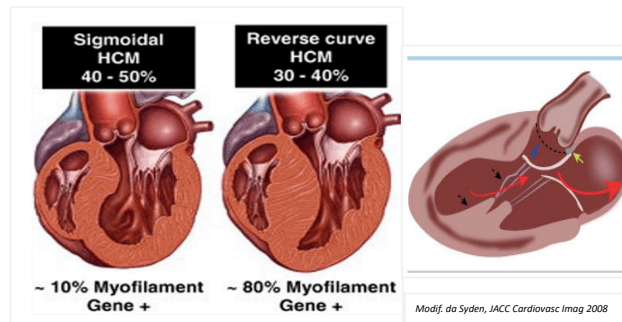
- **Ostruttiva (oHCM)**

- ostruzione dinamica LVOT, *Systolic Anterior Motion*, insufficienza mitralica secondaria

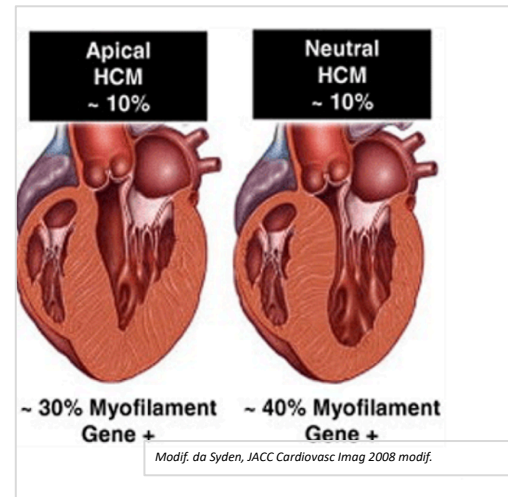
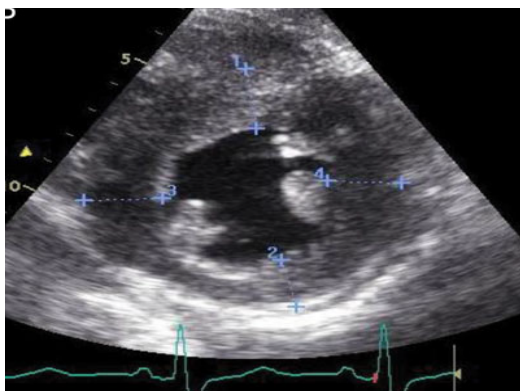
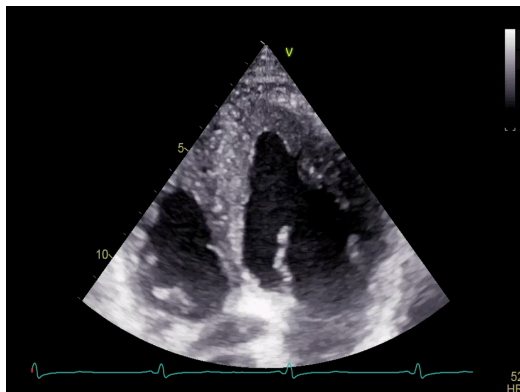
- M-mode: parziale chiusura mesosistolica della valvola aortica

- CW Doppler: evidenza di un PGmax in LVOT o medioventricolare >30 mmHg a riposo e/o >50 mmHg dopo manovre provocative (Valsalva, in piedi, sforzo)

- **Non ostruttiva (nHCM)**

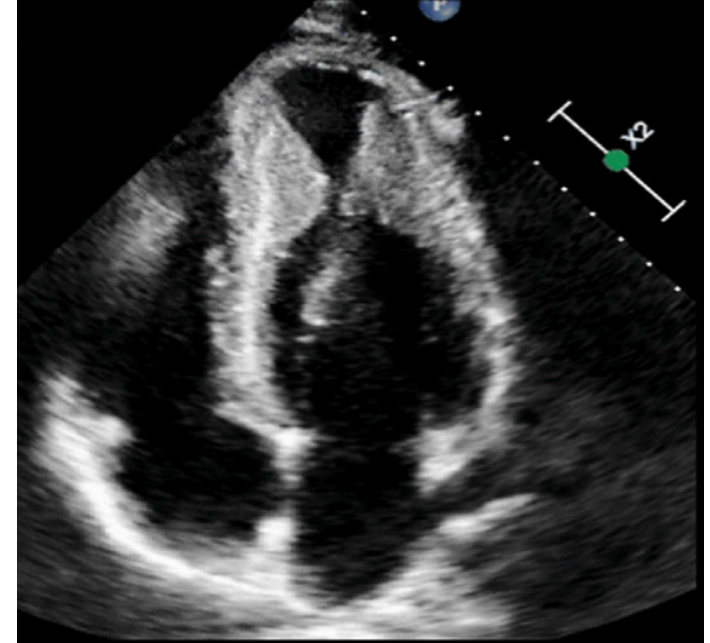


- **Ipertrofia apicale**
 - Aritmie
- **Ipertrofia concentrica**
 - Coinvolgimento diffuso e relativamente uniforme delle pareti del VS



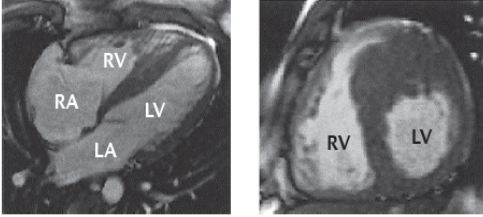
- **Fenotipo con aneurisma apicale**
 - aritmie ventricolari, tromboembolismo, progressione verso scompenso cardiaco
- **Fenotipo ipocinetico**
 - Evoluzione tardiva in una minoranza di pazienti.
 - EF <50%, dilatazione ventricolare e fibrosi estesa

Manifestazioni «non strutturali»: Disfunzione diastolica, fibrosi miocardica, aritmie, coinvolgimento microvascolare e ischemia

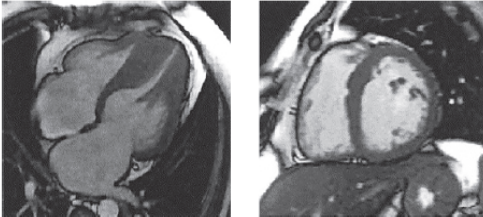


sHCM: Imaging

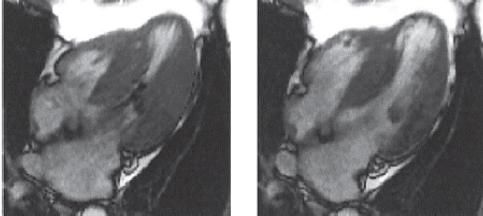
a Asymmetrical septal hypertrophy



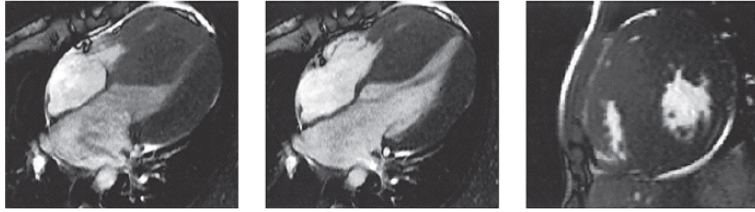
b Apical hypertrophy



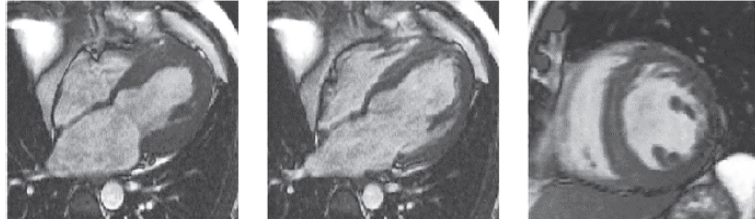
c Midcavity obstruction



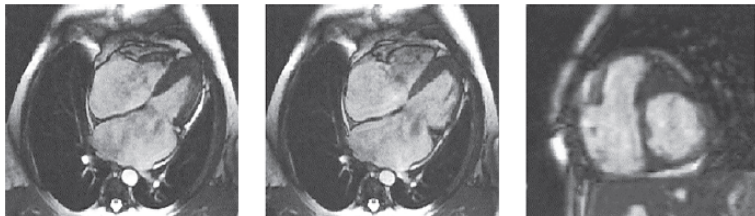
d Biventricular hypertrophic



e 'End-stage' dilatation



f Restrictive cardiomyopathy



Sen-Chowdhry et al. *Nat Rev Cardiol* 2016



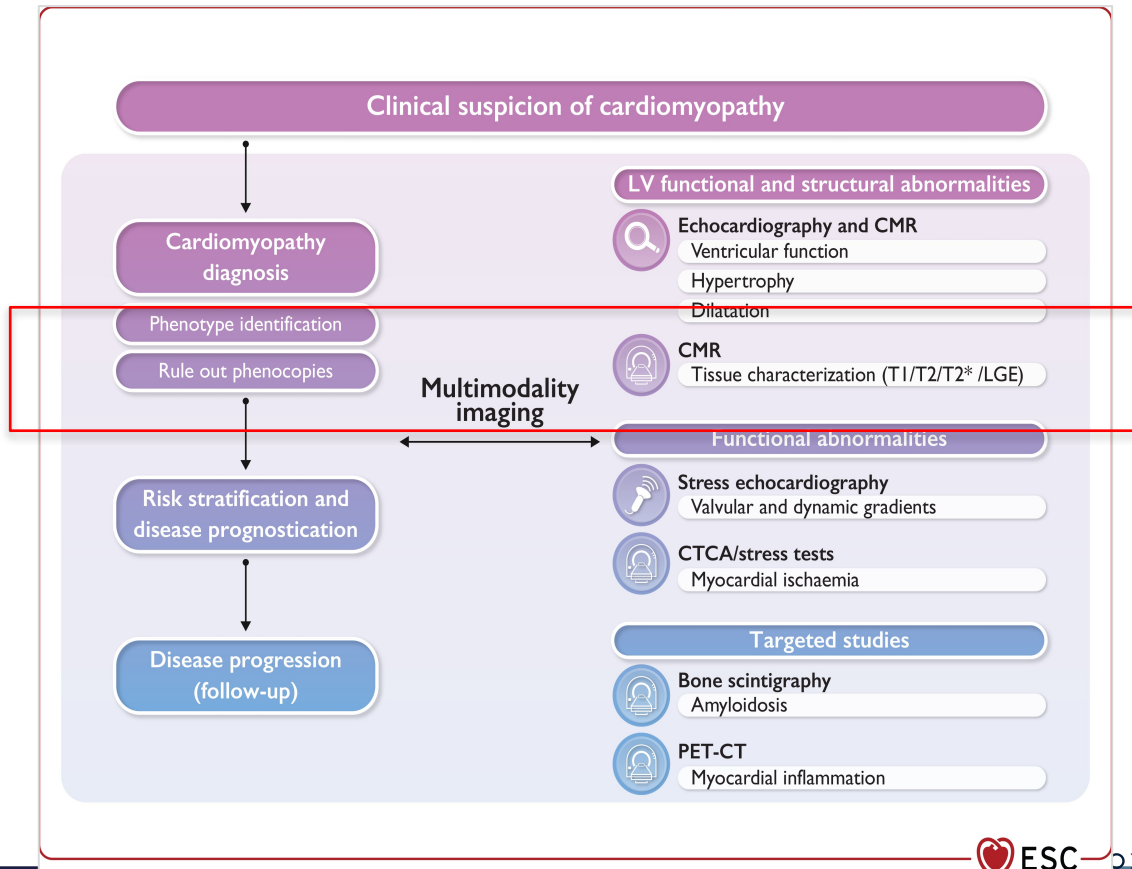
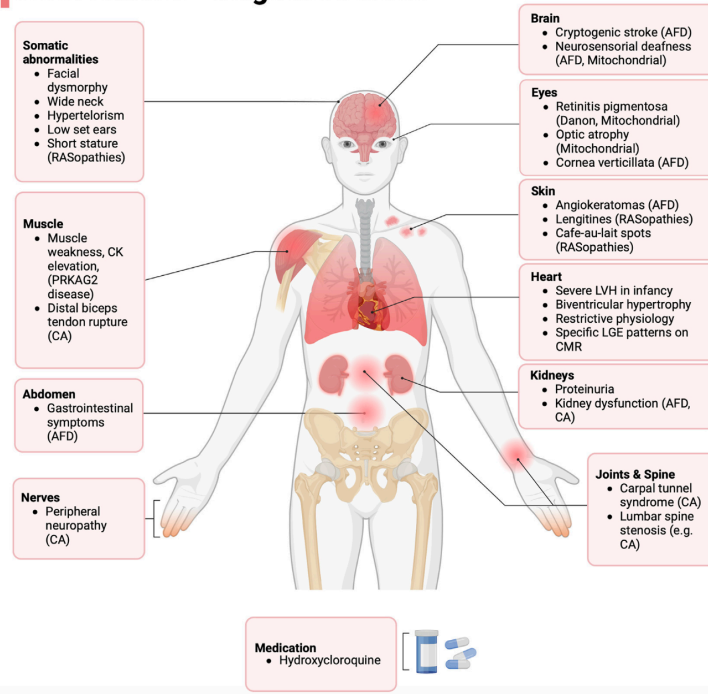


Table 1. Clinical features suggestive specific etiologies of left ventricular (LV) hypertrophy

Etiology	Extracardiac phenotype	Cardiac phenotype
RASopathy	Facial dysmorphisms: broad forehead, down slanting, palpebral fissures, hypertelorism, low-set ears, pterygium colli, epicanthal folds, short and depressed nasal root Dermatological abnormalities: lentigines, café-au-lait spots, pigmented nevi, keratosis pilaris of upper arm and face, sparse curly hair Other systemic features: bleeding disorders, lymphatic dysplasia, sensorineural deafness, cryptorchidism	ECG: extreme right axis deviation, left or right bundle branch block, prolonged QT, or multifocal atrial tachycardia Echocardiography: biventricular hypertrophy, abnormal papillary muscles, associated congenital heart defects (eg, pulmonary valve stenosis, mitral valve dysplasia, atrial or ventricular septal defect, or coronary artery abnormalities)
Pompe disease	Liver: hepatomegaly, increased serum transaminases Muscle involvement: hypotonia, floppy baby, frog leg position, pseudohypertrophy of gastrocnemius muscle, CK elevation, delayed motor milestones	ECG: LV pre-excitation, prominent LV voltages Echocardiography: massive LVH, concentric LVH, LV systolic dysfunction
Cori disease	Hepatic involvement: hepatomegaly, increased serum transaminases, hypoglycemia	ECG: prominent LV voltages
Danon disease	Muscle involvement: muscle weakness, CK elevation Hepatic involvement: hepatomegaly, increased serum transaminases, hypoglycemia Muscle involvement: muscle weakness, CK elevation	Echocardiography: concentric LVH ECG: ventricular pre-excitation, prominent LV voltages Echocardiography: massive LVH, concentric LVH, LV systolic dysfunction, apical sparing strain pattern CMR: extensive LGE with mid-septum sparing
PRKAG2 disease	Muscle involvement: muscle weakness, CK elevation	ECG: ventricular pre-excitation, prominent LV voltages, conduction disorders
Friedreich ataxia	Systemic features: scoliosis, foot deformity, diabetes mellitus, progressive gait ataxia, dysarthria, muscle weakness in lower limbs	Echocardiography: concentric LVH CMR: patchy and irregular LGE distribution, reduced native T1
Mitochondrial disease	Systemic features: hypotonia, lactic acidosis, cataract, bilateral sensorineural deafness, retinitis pigmentosa/optic atrophy, leukoencephalopathy (in Barth syndrome), diabetes, palpebral ptosis, ophthalmoplegia	ECG: ventricular pre-excitation, prominent LV voltages, conduction disorders
Cardiac amyloidosis	Bilateral carpal tunnel syndrome, spontaneous rupture of biceps tendon, lumbar spinal stenosis Neurologic features, including autonomic dysfunction, or peripheral neuropathy	Echocardiography: concentric LVH, LV systolic dysfunction ECG: disproportion between QRS voltages and LV mass (relative low voltages despite hypertrophy), pseudo-infarct Q waves, conduction abnormalities (ie, AV block) Echocardiography: AV valve thickening, interatrial septum thickening, RV wall thickening, granular sparkling appearance, apical sparing strain pattern, increased ejection fraction-to-strain ratio CMR: diffuse subendocardial or transmural LGE in a noncoronary artery distribution, abnormal gadolinium kinetics, elevated T1 native
Anderson-Fabry disease	Systemic features: gastrointestinal symptoms, angiokeratomas, cornea verticillata, hypohidrosis, cryptogenic TIA or stroke, neurosensory deafness, lymphedema, proteinuria, renal failure	ECG: short PR interval, bradycardia, chronotropic incompetence, AV block Echocardiography: concentric LVH, disproportionate hypertrophy of papillary muscles reduced GLS in the posterolateral basal segment, RV wall thickening CMR: mid-myocardial distribution of LGE in the posterolateral basal segment, reduced native T1

AV, atrioventricular; CK, creatine kinase; CMR, cardiac magnetic resonance; ECG, electrocardiography; GLS, global longitudinal strain; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; RV, right ventricular; TIA, transient ischemic attack.

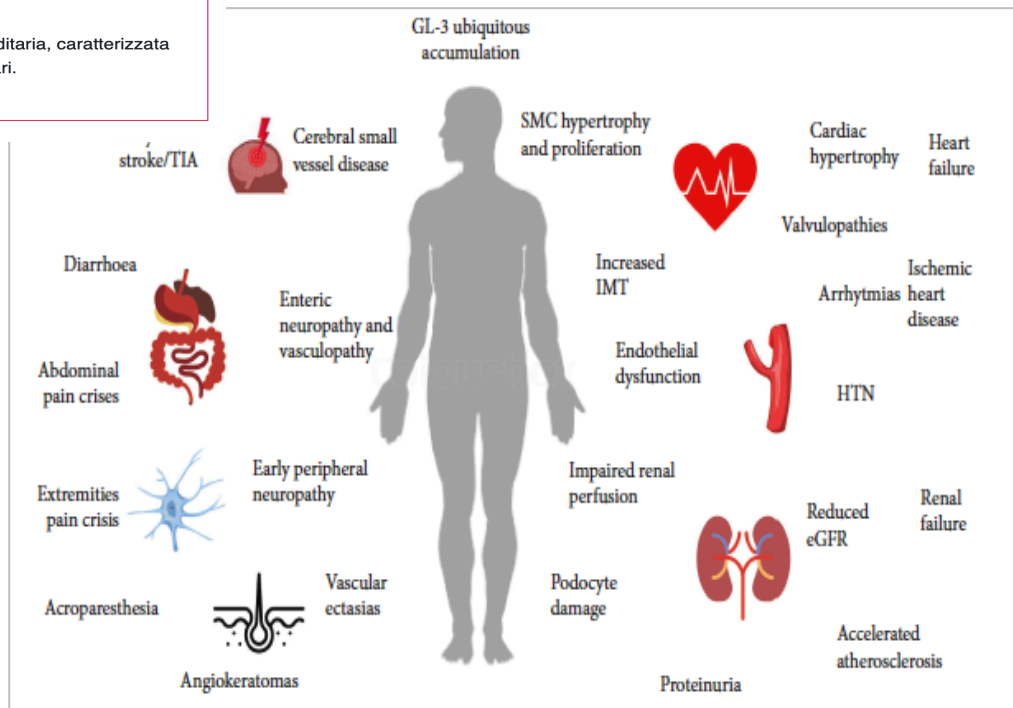
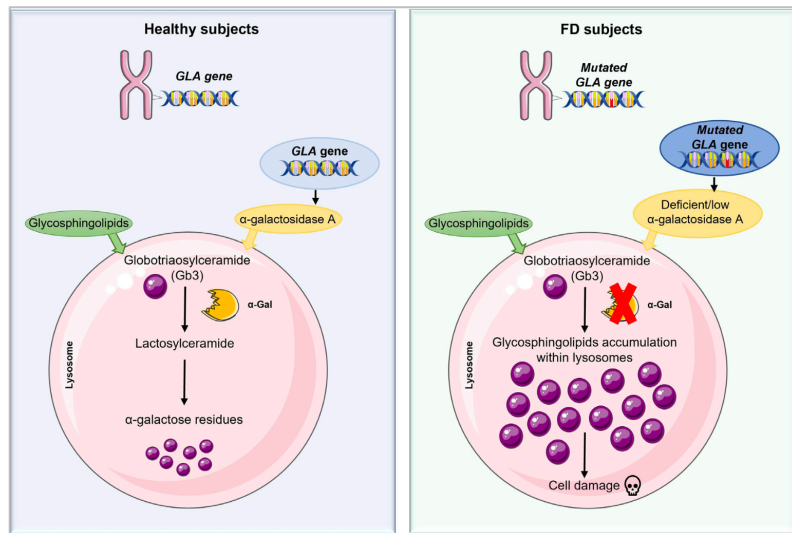
HCM mimics - diagnostic clues



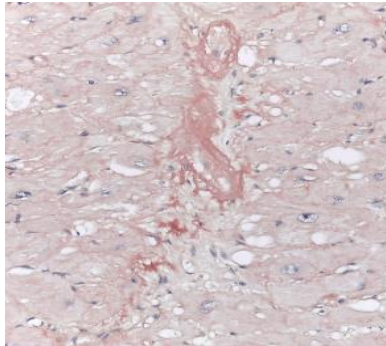
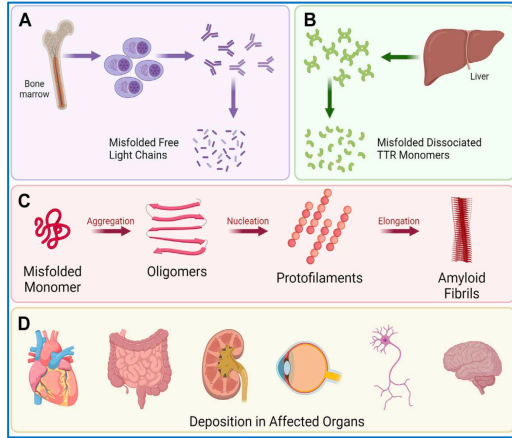
Malattia di Anderson-Fabry (AFD): Deficit di α -galattosidasi

Definizione della malattia

La malattia di Fabry (FD) è una malattia da deposito lisosomiale multisistemica, progressiva, ereditaria, caratterizzata da specifici segni neurologici, cutanei, renali, cardiovascolari, cocleo-vestibolari e cerebrovascolari.

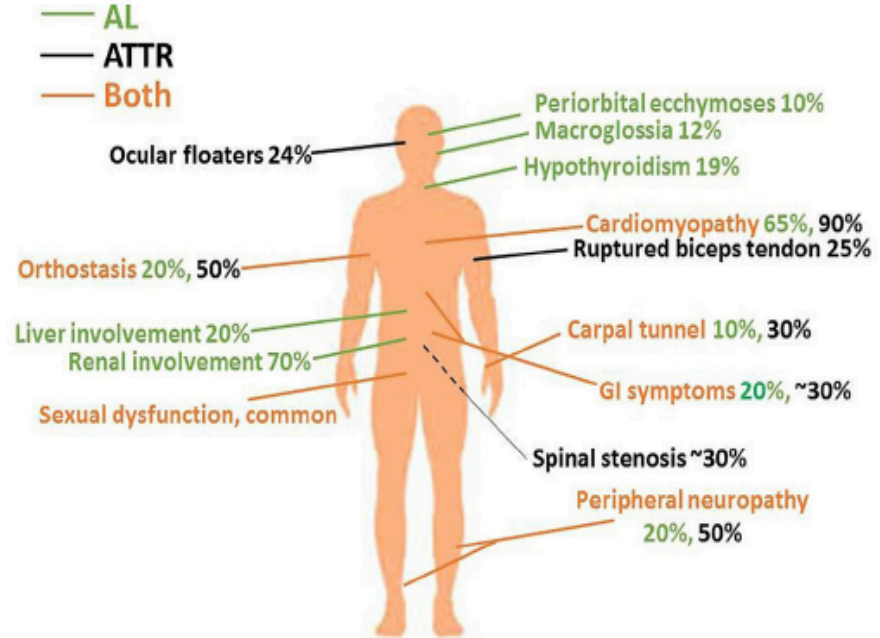


Amiloidosi Cardiaca (CA): AL-ATTR



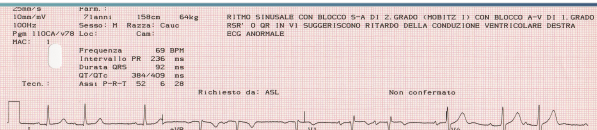
C. Varga et al.

Blood Reviews 45 (2021) 100720



- a. Spesso suggerisce una possibile CMP
- b. Alterazioni ECG possono essere la sola manifestazione della CMP
- c. Alterazioni ECG, associate a specifiche caratteristiche cliniche, possono suggerire la diagnosi di CMP
- d. ECG deve sempre essere interpretato nel contesto di informazioni Eco e RMN





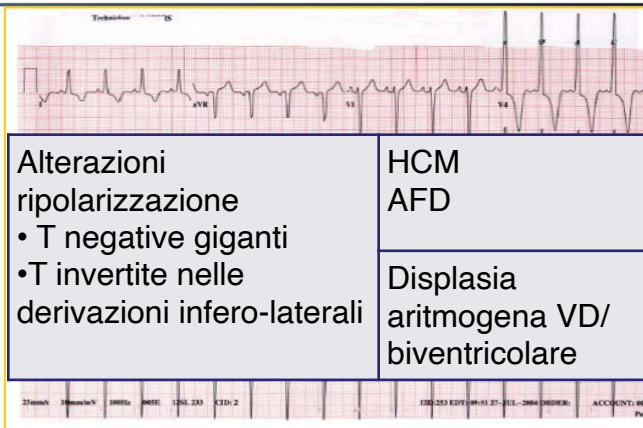
**Blocco AV,
ritardi di
conduzione
intra-
ventricolare**

Laminopatie, malattie
mitocondriali

Glicogenosi, Anderson-
Fabry

Miocardite, sarcoidosi

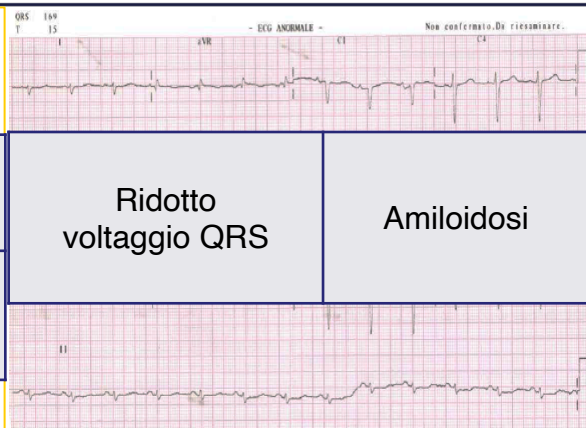
Desminopatie, distrofie



**Alterazioni
ripolarizzazione**
• T negative giganti
• T invertite nelle
derivazioni infero-laterali

**HCM
AFD

Displasia
aritmogena VD/
biventricolare**



**Ridotto
voltage QRS**

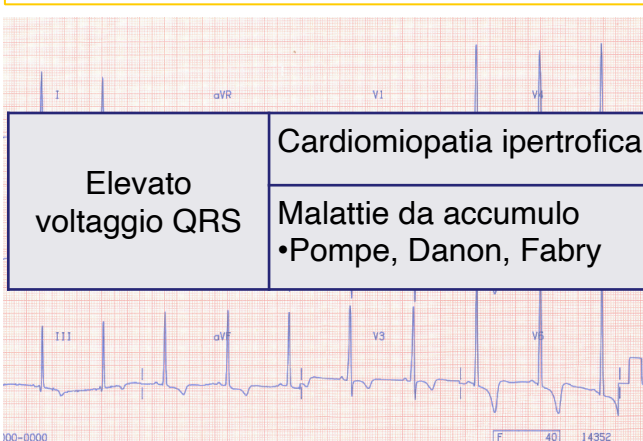
Amiloidosi



**PR corto
Pre-
eccitazione
ventricolare**

Malattie da accumulo.
Pompe, Danon, Fabry

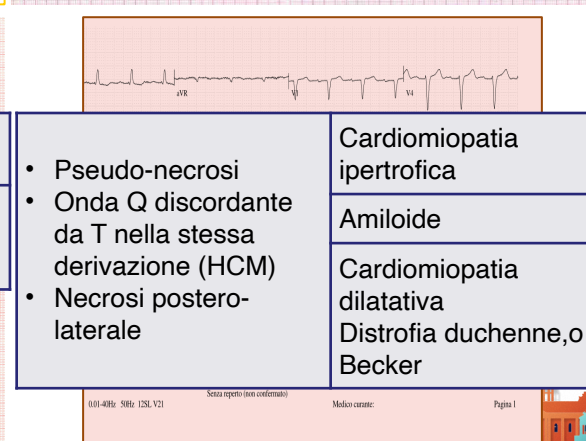
Malattie mitocondriali MELAS,
MERFF



**Elevato
voltage QRS**

Cardiomiopatia ipertrofica

Malattie da accumulo
•Pompe, Danon, Fabry



• Pseudo-necrosi
• Onda Q discordante
da T nella stessa
derivazione (HCM)
• Necrosi postero-
laterale

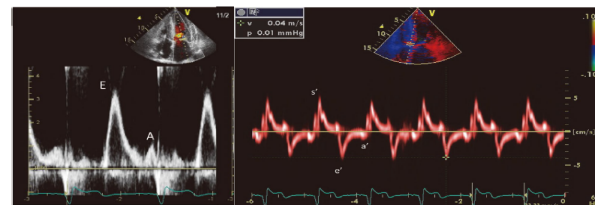
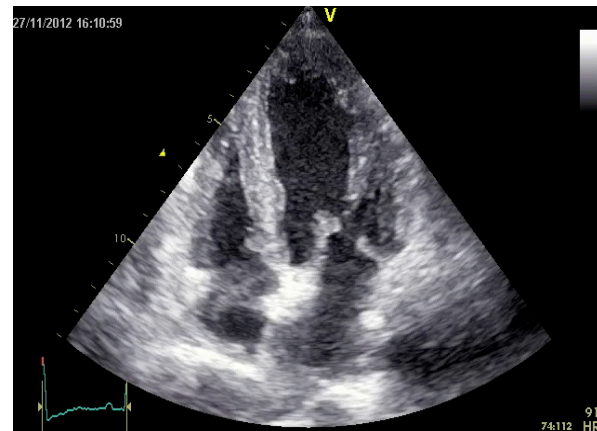
**Cardiomiopatia
ipertrofica**

Amiloide

**Cardiomiopatia
dilatativa
Distrofia duchenne,o
Becker**

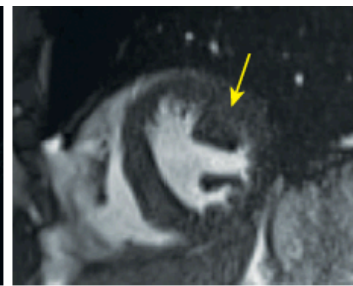
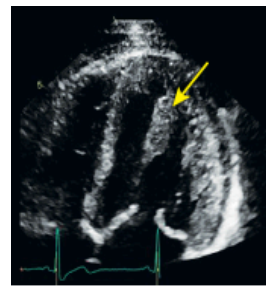
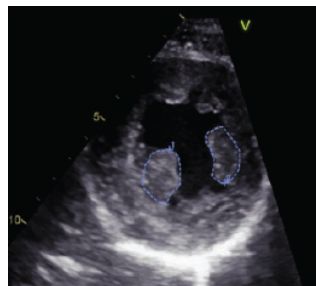
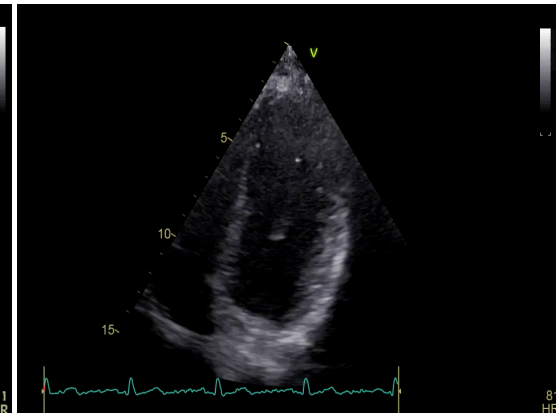
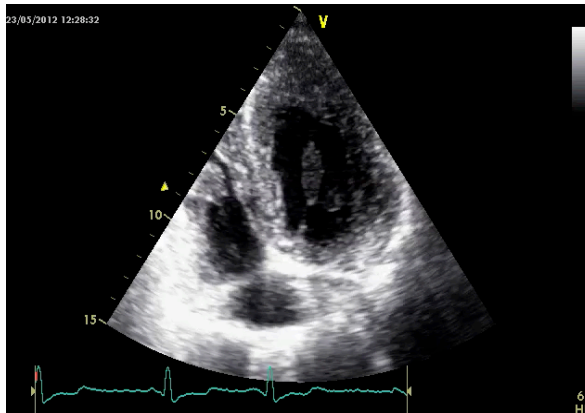
Cardiac Amyloidosis: Echo Findings

- Symmetrically increased LV thickness LV wall >12 mm
- Hypokinesia and decreased systolic thickening of the IVS and LV posterior wall
- Small-to-normal size of the LV cavity and preserved or reduced systolic function
- Left atrial enlargement, increased atrial septum thickness
- Small pericardial effusions
- Presence of very bright or highly refractile echoes in the myocardium.
- Restrictive filling pattern of mitral flow with a markedly shortened deceleration time
- Decreased pulmonary vein peak systolic flow, and increased diastolic flow velocity
- Tissue Doppler mitral annular velocity values are often less than 6 cm/s.



Fabry Disease: Echo Findings

- Increased LV wall thickness and LVM
- Concentric hypertrophy
- Concentric remodelling
- Uniform increase in LV wall thickness
- Absence of restrictive filling
 - *Significant decrease in both systolic and diastolic tissue velocities*
 - *Dynamic LV outflow tract obstruction caused by SAM of the mitral valve is rare*
 - *Asymmetric hypertrophy of the IVS in 5–10*
 - *Hypertrophic papillary muscle: area PM/LV ≥ 0.18*
 - *RV hypertrophy in 31-71%*



Echocardiographic features that suggest specific aetiologies

Finding

Specific diseases to be considered

Increased interatrial septum thickness

Amyloidosis

Increased atrioventricular valve thickness

Amyloidosis; Anderson–Fabry disease

Increased RV free wall thickness

Amyloidosis, myocarditis, Anderson–Fabry disease

Mild–moderate pericardial effusion

Amyloidosis, myocarditis

Ground-glass appearance of ventricular myocardium

Amyloidosis

Concentric LVH

Glycogenosis, Anderson–Fabry disease

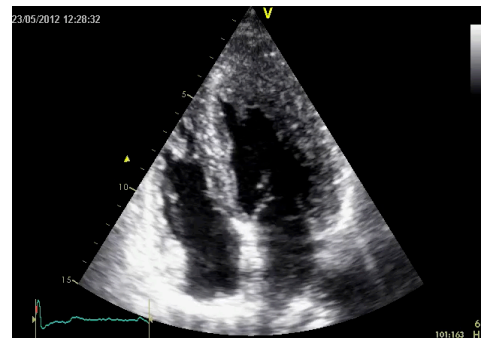
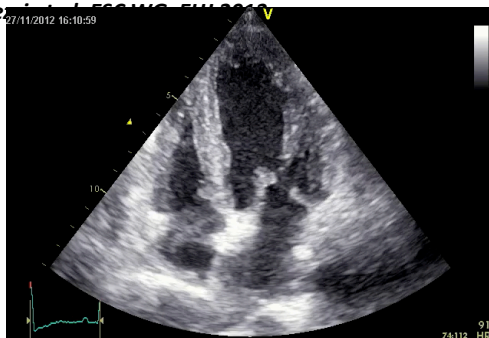
Extreme concentric LVH

Danon disease, Pompe disease

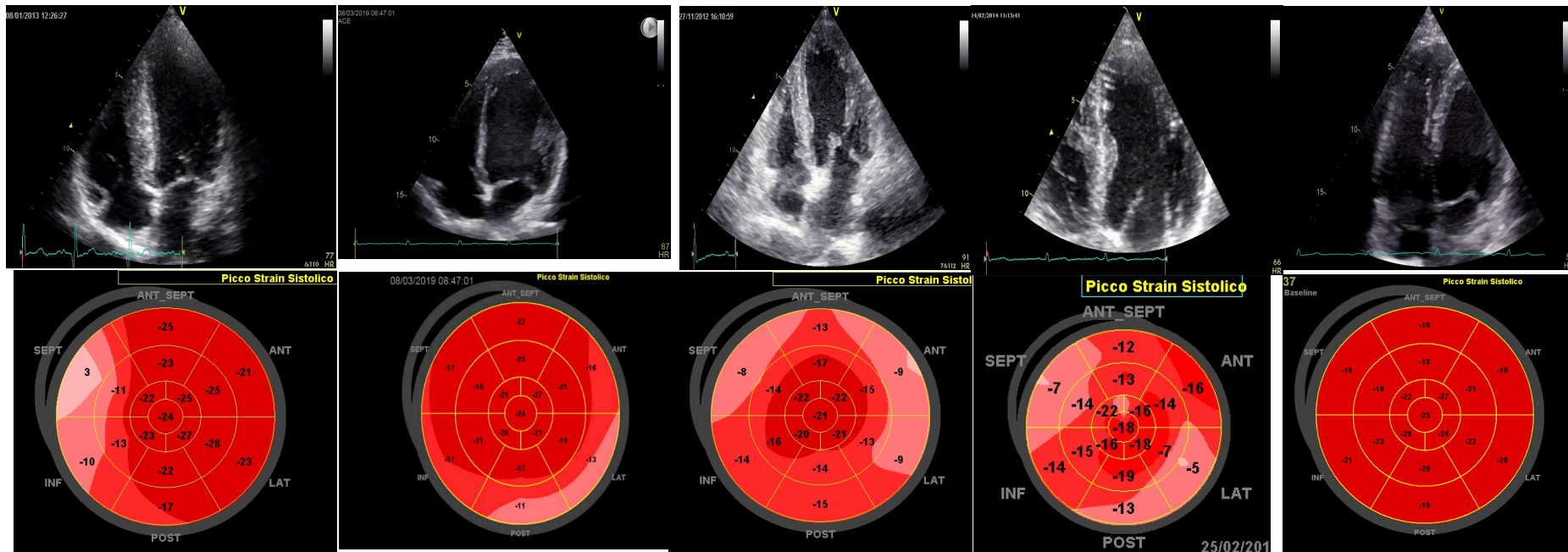
Global hypokinesia (with/without LV dilatation)

Anderson–Fabry; mitochondrial disease; TTR-related amyloidosis; PRKAG2 mutations; Danon disease; myocarditis; end-stage sarcomeric HCM

Rape...



Ecocardio: ipertrofia e GLS



Donna 51 anni, HCM
IVSd: 16 mm LVPWd : 11 mm
LVIDd: 50 mm LVMI: 109 g
EF: 69% GLS -20% MD 91 ms

Uomo, 24 anni, AFD
IVSd: 11 mm LVPWd : 11 mm
LVIDd: 55 mm LVMI: 98 g
EF: 57% GLS -19% MD 44 ms

Donna 75 anni, ATTRwt
IVSd: 13 mm LVPWd : 13 mm
LVIDd: 48 mm LVMI: 101 g
EF: 54% GLS -15% MD 106ms

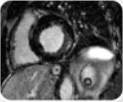
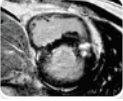
Donna 61 anni, ipertens. art.
IVSd: 13 mm LVPWd : 12 mm
LVIDd: 56 mm LVMI: 105 g
EF: 59% GLS -21% MD 66 ms

Uomo, 41 anni, pallanuoto
IVSd: 13 mm LVPWd : 13 mm
LVIDd: 51 mm LVMI: 110 g
EF: 62% GLS -21% MD 44 ms



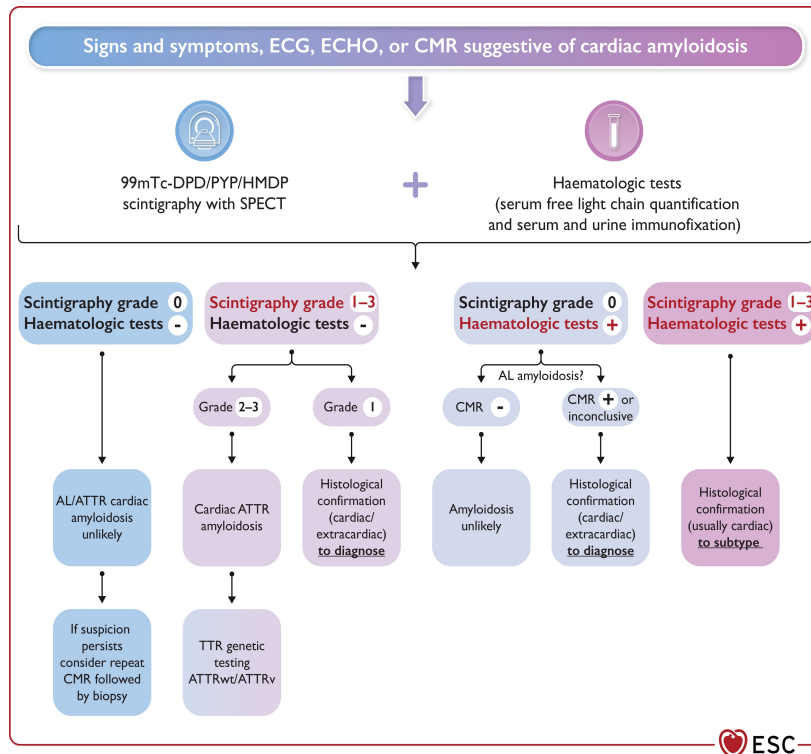
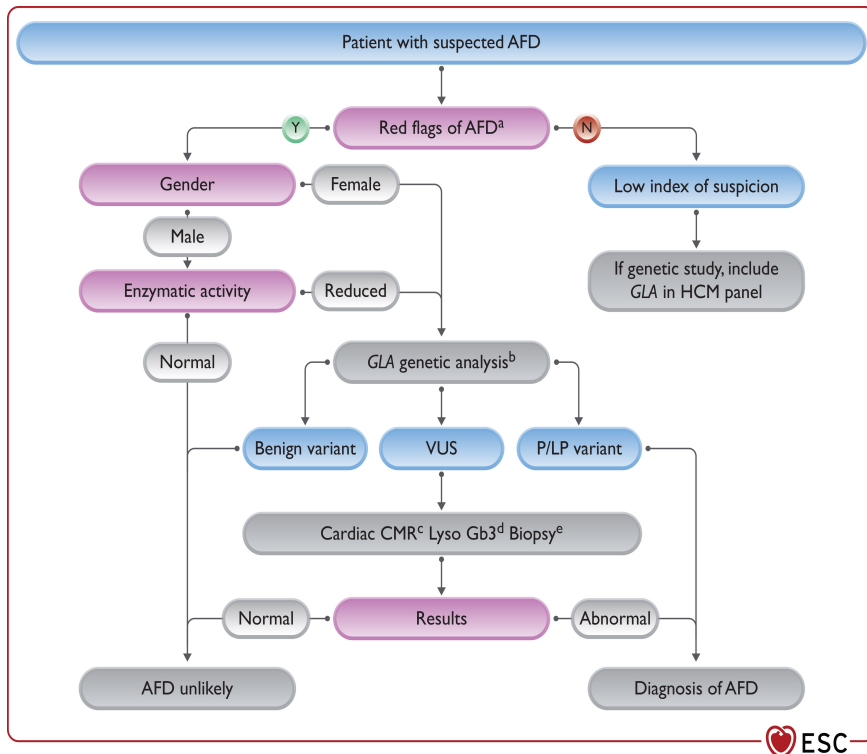
2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

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

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
DCM	Short T2*		Haemochromatosis
	Subepicardial LGE		Post-myocarditis
	Lateral wall epicardial LGE		Dystrophinopathy
	Subepicardial and midwall LGE at basal septum +/- extension into inferolateral wall and RV insertion points		Sarcoidosis
	Apical transmural LGE		Chagas disease
NDLVC	Ring-like and/or subepicardial LGE pattern		DSP variants FLNC variants DES variants
ARVC	Septal mid-wall LGE		Laminopathy
	Fat and LGE (transmural RV plus sub-epicardial-midmural LV free wall)		Desmosomal variants
RCM	Partial LV or RV apical obliteration + LGE at endocardial level		EMF/hypereosinophilia

HCM Fenocopie: AFD, CA



Fenocopie HCM

FENOCOPIA	EZIOLOGIA / GENETICA	CARATTERISTICHE DISTINTIVE	INDIZI CHIAVE
 MALATTIA DI FABRY	Deficit di α -galattosidasi A Eredità X-linked	- Angiokeratomi - Neuropatia (dolore acroparestesie) - Ipoidrosi - Insufficienza renale - Ictus/TIA in età giovane	 Dosaggio α -galattosidasi A $\downarrow$  Depositi di globotriaosilceramide (su biopsia)  Terapia enzimatica disponibile
 AMILOIDOSI CARDIACA	Deposito di proteine amiloidi (AL, ATTR) Non ereditaria o ereditaria (ATTR)	- Spesso ipertrofia concentrica - Bassi voltaggi all'ECG - Dispnea, astenia - Coinvolgimento di altri organi (rene, nervi periferici, GI)	 ECG: bassi voltaggi nonostante ipertrofia  Scintigrafia con PYP/DPD (positiva in ATTR)  Biopsia con rosso Congo +
 MALATTIA DI DANON	Mutazioni del gene LAMP2 Eredità X-linked	- Ipertrofia ventricolare severa - Precoce esordio (adolescenza) - Miopia scheletrica - Deficit cognitivi - Retinopatia	 CK frequentemente $\uparrow$  Inclusioni vacuolari nei miociti (biopsia)  Test genetico LAMP2
 SINDROME DI PRKAG2	Mutazioni del gene PRKAG2 Eredità autosomica dominante	- Ipertrofia ventricolare - Pre-eccitazione (WPW) - Disturbi della conduzione (BAV, bradiaritmie) - Talvolta progressione a scompenso	 ECG: PR corto, onda delta (WPW)  BAV, aritmie  Test genetico PRKAG2
 ATASSIA DI FRIEDREICH	Espansione GAA nel gene FXN Eredità autosomica recessiva	- Atassia progressiva - Disartria, areflessia - Diabete mellito - Ipertrofia cardiaca	 Dosaggio frataxina $\downarrow$  Alterazioni neurologiche caratteristiche  Test genetico (espansione GAA)
 MALATTIA DI POMPE	Deficit di α -glucosidasi acida (GAA) Eredità autosomica recessiva	- Accumulo di glicogeno - Ipotonia, debolezza muscolare - Epatomegalia - Cardiomiopatia ipertrofica (più comune in età pediatrica)	 Attività GAA $\downarrow$  CK $\uparrow$  Terapia enzimatica disponibile
 CARDIOPATIA MITOCONDRIALE	Mutazioni del DNA mitocondriale o geni nucleari Eredità variabile	- Ipertrofia cardiaca - Miopia, neuropatia - Disturbi neurologici, oculari, endocrini - Intolleranza allo sforzo	 Lattato/rapporto lattato-piruvato $\uparrow$  Altre manifestazioni sistemiche  Test genetici specifici

COME DISTINGUERLE DALLA HCM SARCOMERICA



ANAMNESI E FAMILIARITÀ

Modalità di trasmissione, età di esordio e storia familiare.



ECG

Pattern specifici (es. WPW in PRKAG2, bassi voltaggi nell'amiloidosi).



IMAGING

Eco e Risonanza Magnetica Cardiaca con pattern caratteristici (es. LGE subendocardico nell'amiloidosi, preservazione subendocardica in Fabry).



BIOMARCATORI E TEST DI LABORATORIO

Dosaggi enzimatici, biomarcatori specifici (es. α -galattosidasi A, catene leggere, frataxina).



TEST GENETICI

Conferma della mutazione specifica.



MANIFESTAZIONI EXTRACARDIACHE

Ricerca di segni neurologici, renali, muscolari, cutanei, oculari, ecc.

QUANDO SOSPETTARE UNA FENOCOPIA



Ipertrofia ventricolare marcata o atipica (non spiegata).



Coinvolgimento di altri organi o sistemi.



Età di esordio insolita (molto precoce o tardiva).



Disturbi della conduzione o pre-eccitazione.



Storia familiare non compatibile con una HCM sarcomerica.

PERCHÉ È IMPORTANTE RICONOSCERLE?

Perché la prognosi, il trattamento e la consulenza genetica possono essere molto differenti e, in alcuni casi, esistono terapie specifiche.

Il fenotipo ipertrofico

CMP a
fenotipo
ipertrofico

Precisazione
diagnostica:
fenocopie,
multi-imaging,
genetica

Espressione
fenotipica
HCM

Management:
terapia, follow
up, screening
familiari



