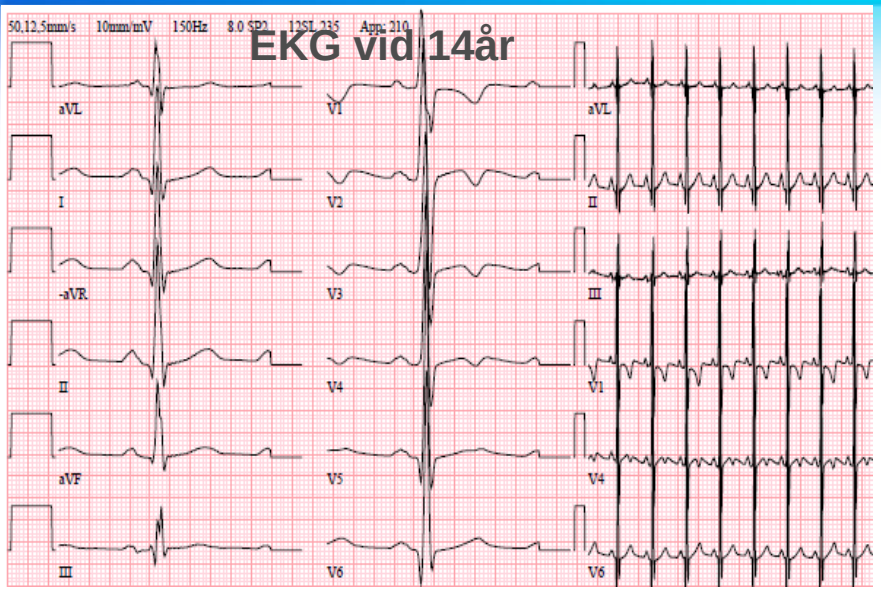
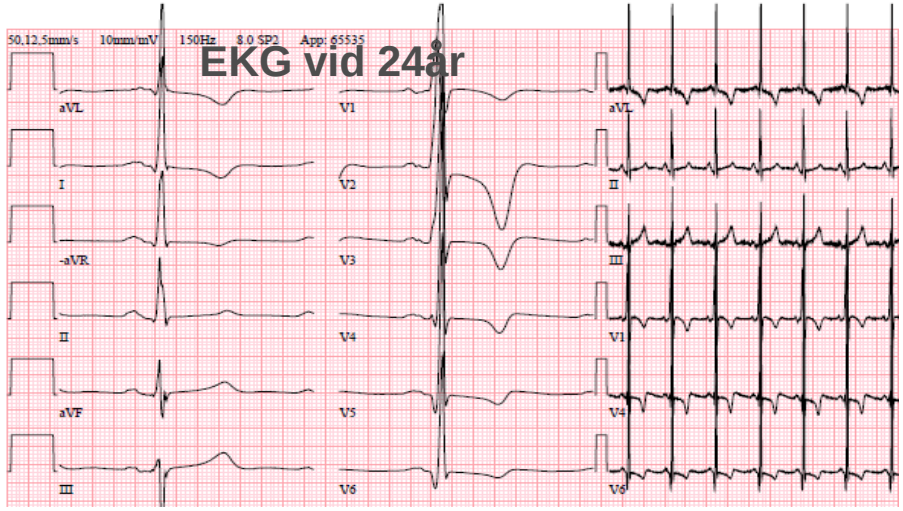
Hypertrofisk kardiomyopati; HCM

Antheia Kissopolou, överläkare, doktorand, Länssjukhuset Ryhov, Jönköping

CASE-FALL





- Index patient haft synkope efter hockeymatch när han var 14 år

Sannolikt vasovagalt ?

- Vid 24års ålder genomgick nefrektomi pga en icke fungerande vänsternjure. Vid EKG i samband med operationen upptäcker man EKG-förändringar

Skulle ni utreda vidare?

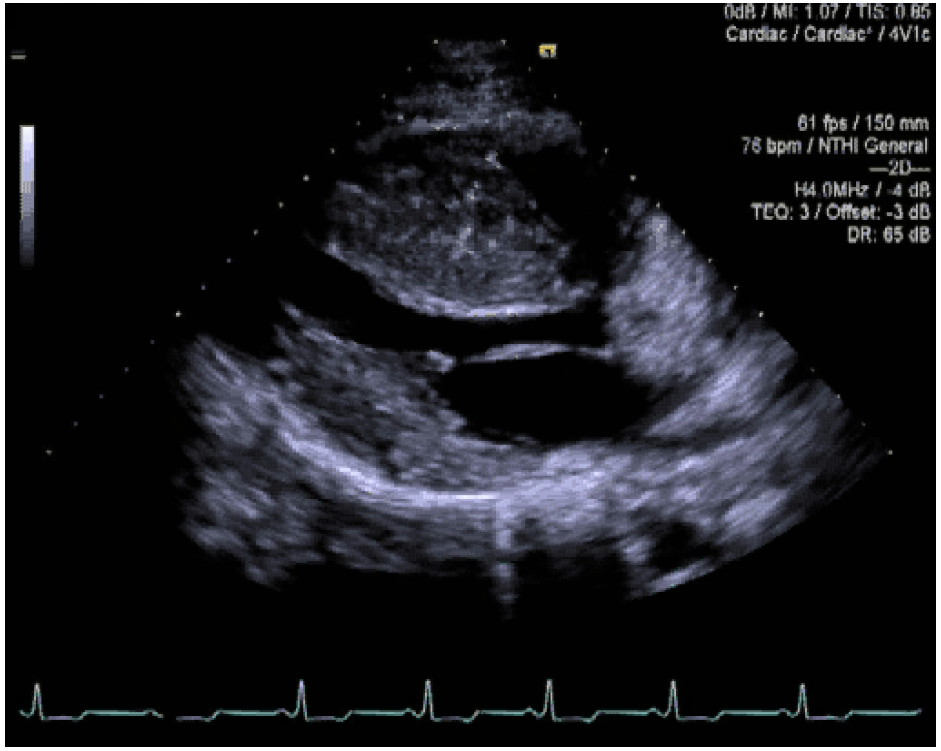
a. JA

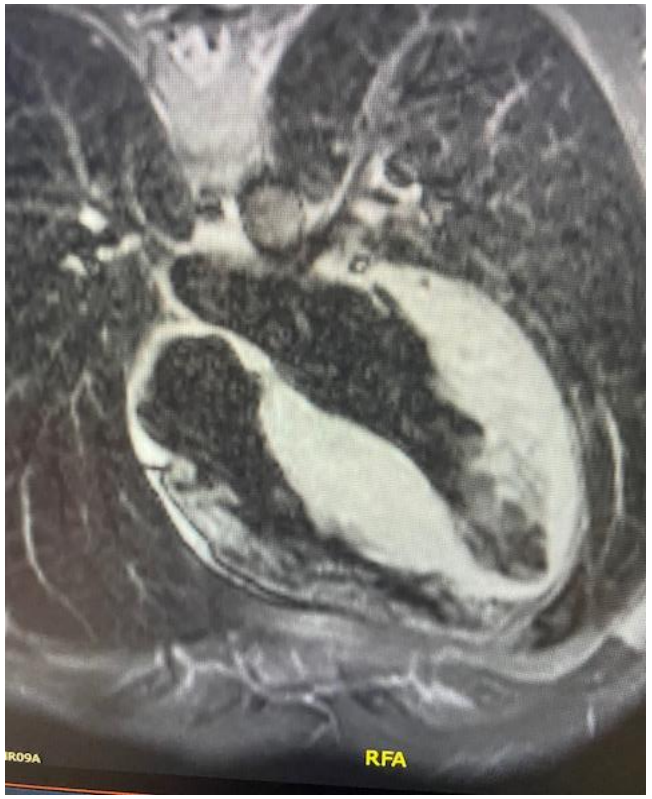
b. NEJ

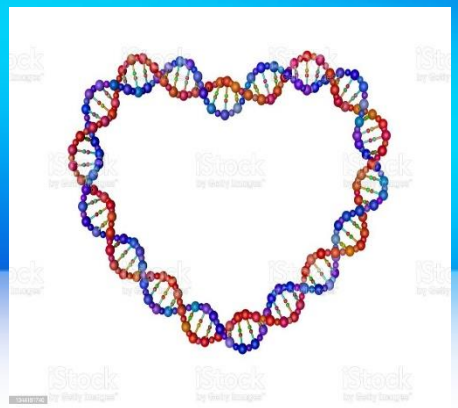
Vidare utredning

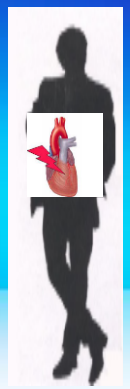
Ekokardiografi: Liten vänsterkammare med **uttalad hypertrofi** septum 24mm och lätt nedsatt systolisk funktion. Inga tecken på utflödesobstruktion

MRT: Assymetriskt ökad väggtjocklek främst omfattande midventrikulära septum, 28 mm med LVEF 49 %, bra slagvolym. Inget ärr, ödem, diffus fibros, inlagring eller fynd talande för Mb Fabry.

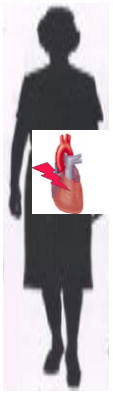




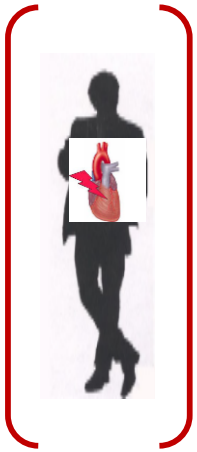




Morfar har en ICD

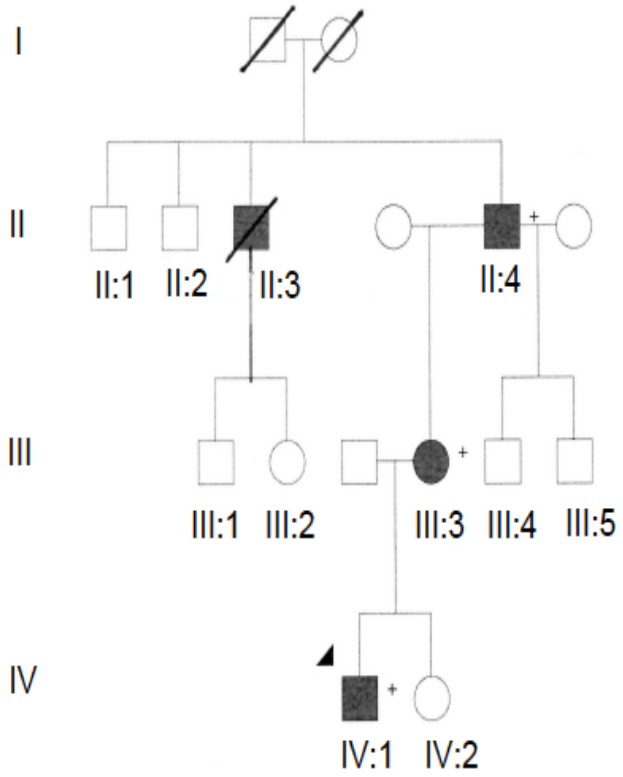


Mamma med hjärtproblem

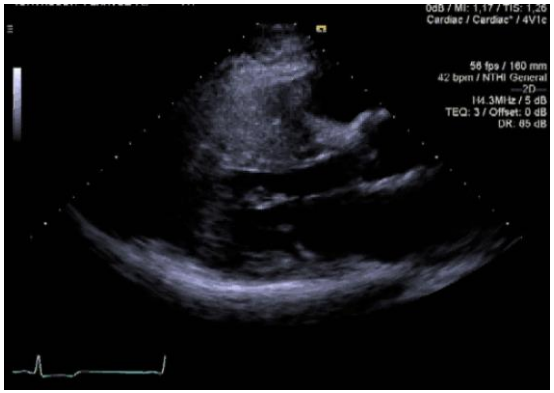


Index

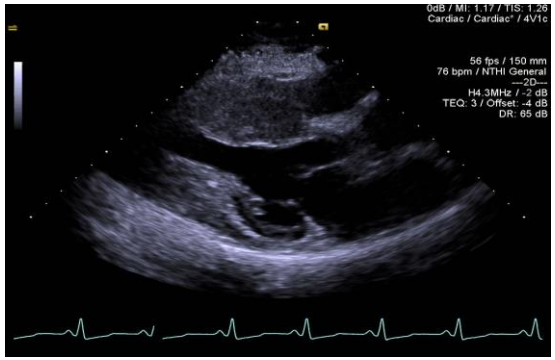
Ärftligt eller INTE?



Bror till morfar dog plötsligt vid 56 års ålder



Morfar fick göra UKG vid 54år
EKO: septum på 30mm
Holter : korta VT, ICD



Mor fick HCM diagnos vid 42 år; dyspné
Septum 22 mm

Gentest hos mor 2015: normal

Gentest hos index 2018: normal

Analysresultat

Ref: **01**

Undersökning:Exome focus panel (Lid:GG183158) **Normal**

Resultat:

Analysen har inte påvisat någon variant i analyserade gener som kan anses vara förknippad med kardiomyopati, se bifogad rapport.

1. Gene Coverage

1.1 Coverage

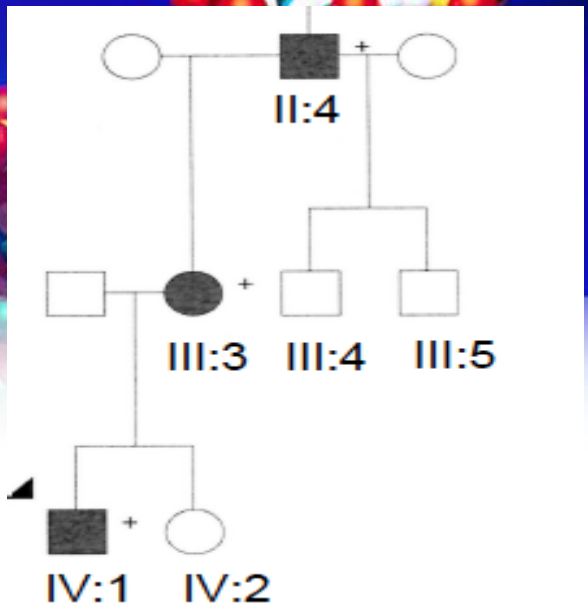
Name	Percentage with coverage above 20	Mean coverage
ABCC9	100	118.34
ACTC1	100	166.16
ACTN2	100	141.88
ANKRD1	100	115.19
BAG3	100	200.17
CRYAB	100	109.07
CSRP3	100	98.52
DES	100	142.90
DMD	100	141.75
DSC2	100	121.62
DSG2	100	147.16
DSP	100	277.05
EPG5	100	180.89
EYA4	100	184.88
FHL1	100	96.54
FKTN	100	181.64
GATAD1	82	86.87
GLA	100	99.89
HAMP	100	126.52
HFE	100	188.32
IDH2	100	139.17
JPH2	100	157.33
JUP	99	117.38
LAMP2	100	102.87
LDB3	100	134.88
LMNA	100	173.66
MYBPC3	98	106.43
MYH6	99	126.99
MYH7	100	129.27
MYL2	100	127.12
MYL3	100	109.96
MYLK2	100	108.06
MYPN	100	154.88

ANKOM
Medicinkliniken
2018 -12- 04
Sign

Name	Percentage with coverage above 20	Mean coverage
NEXN	100	152.49
PKP2	100	97.71
PLN	100	73.18
PRKAG2	100	225.57
PSEN1	100	108.02
PSEN2	100	90.90
RAB3GAP2	100	121.89
RBM20	100	155.82
RYR2	100	129.37
SCN1B	100	186.67
SCN5A	100	139.57
SGCD	100	163.07
SLC40A1	100	152.18
TAZ	100	106.33
TCAP	100	200.82
TFR2	99	98.91
TMEM43	100	103.82
TNNC1	100	119.61
TNNI3	100	113.51
TNNT2	100	174.52
TPM1	100	96.36
TTN	100	176.80
TTR	100	101.14
VCL	100	134.82

Utvidga genetiska anaylsen…

Mor, morfar och sonen har de ngt gemensamt?



TRIO-sekvensering
på patient och hans föräldrar

- Genetisk analys med **Trio-exomsekvensering** : heterozygot variant i **ALPK3 gen,** *ALPK3* (Chr15:85370829NM_020778.4:c.903delC) sannolikt sjukdomsorsakande enligt ACMGs kriterierna

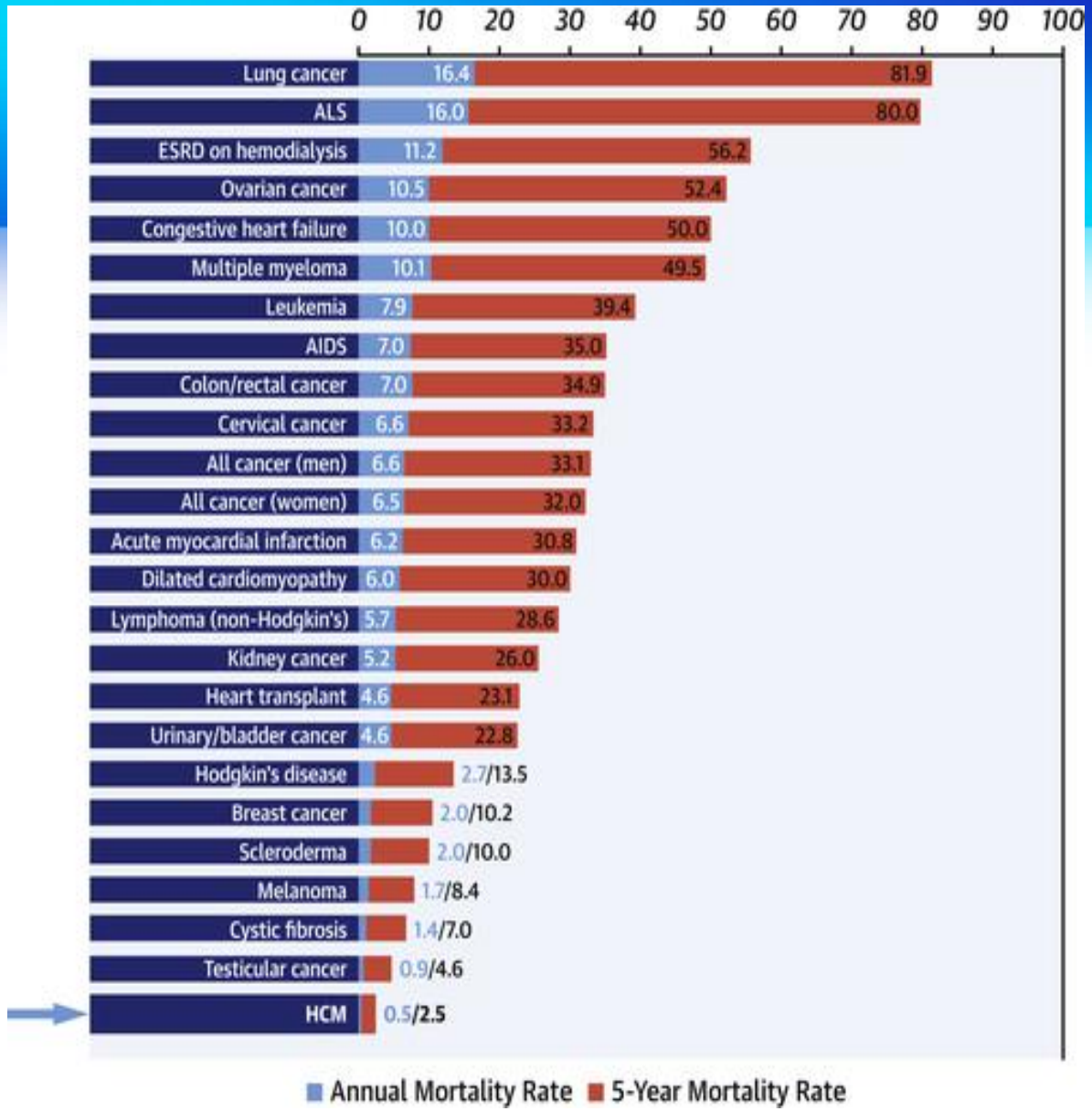
ALPK3, alpha kinase 3, involverad i kardiomyocytdifferentiation

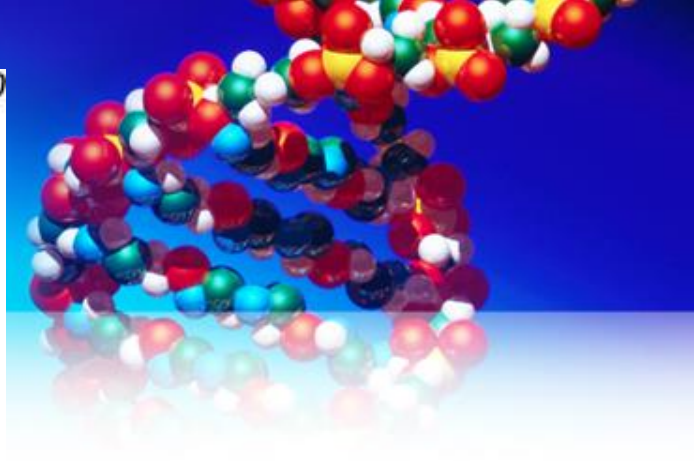
- Varianten har rapporterats kunna orsaka hypertrofisk kardiomyopati i **homozygot form**
- 2 publikation där två heterozygota diagnostiserats med HCM i sena 20-årsåldern

HCM

Vilket är fel?

A. den vanligaste kardiomyopatin med en prevalens på ca 1/500
B. den vanligaste orsaken till plötsliga oväntade dödsfall hos unga idrottare
C. de kliniska manifestationerna är mycket varierande, från symtomfrihet med normal livslängd till svår hjärtsvikt, stroke eller plötslig död
D. med en årlig mortalitet på 10%
E. EKG är patologiskt i 75-90 % av fallen





Barry J. Maron et al. *J Am Coll Cardiol* 2022; 79:390-414.

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Definition

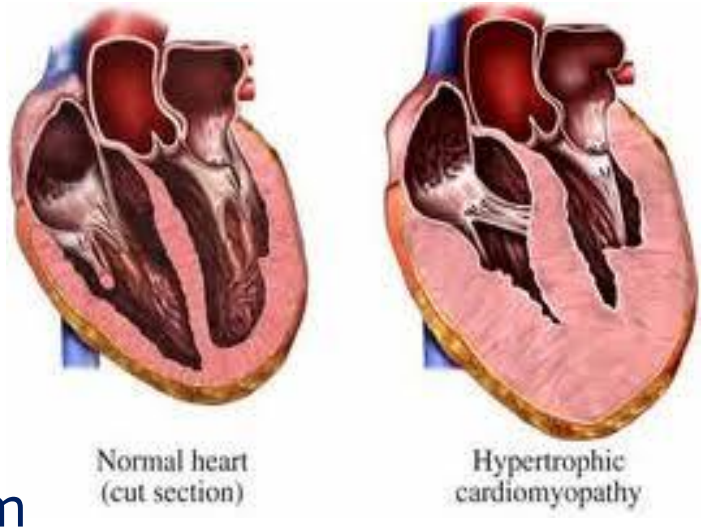
Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions

"2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy"

Kriteria

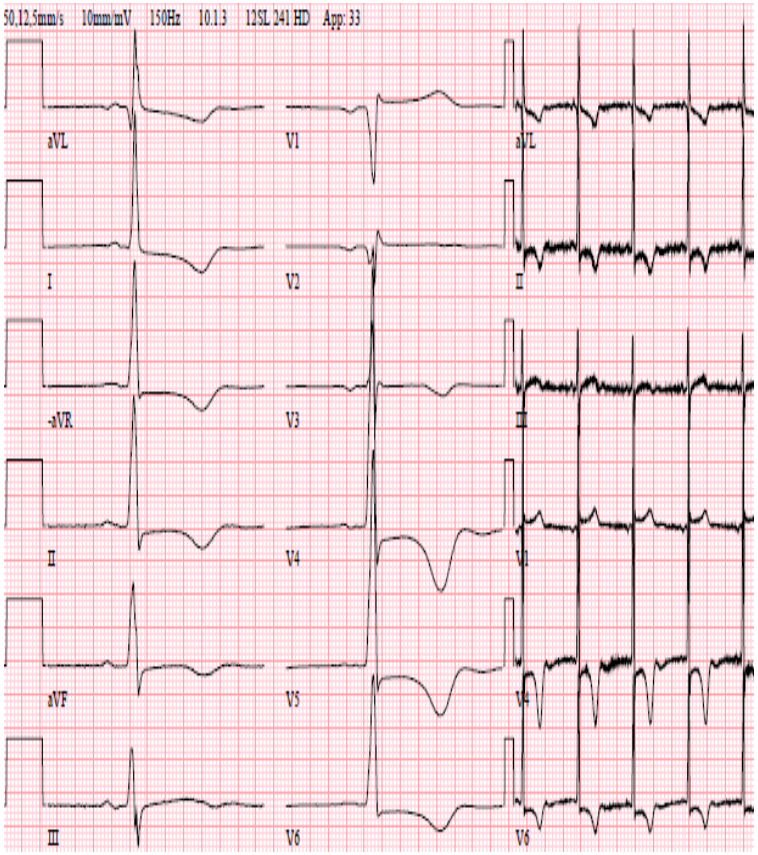
- den maximala vänster kammare (LV) väggtjockleken (MLVWT)
på 2D ekokardiografi **≥ 15 mm** i minst en myocardial segment eller
när MLVWT >2 SD i frånvaro av andra sjukdomar som kan förklara hypertrofi

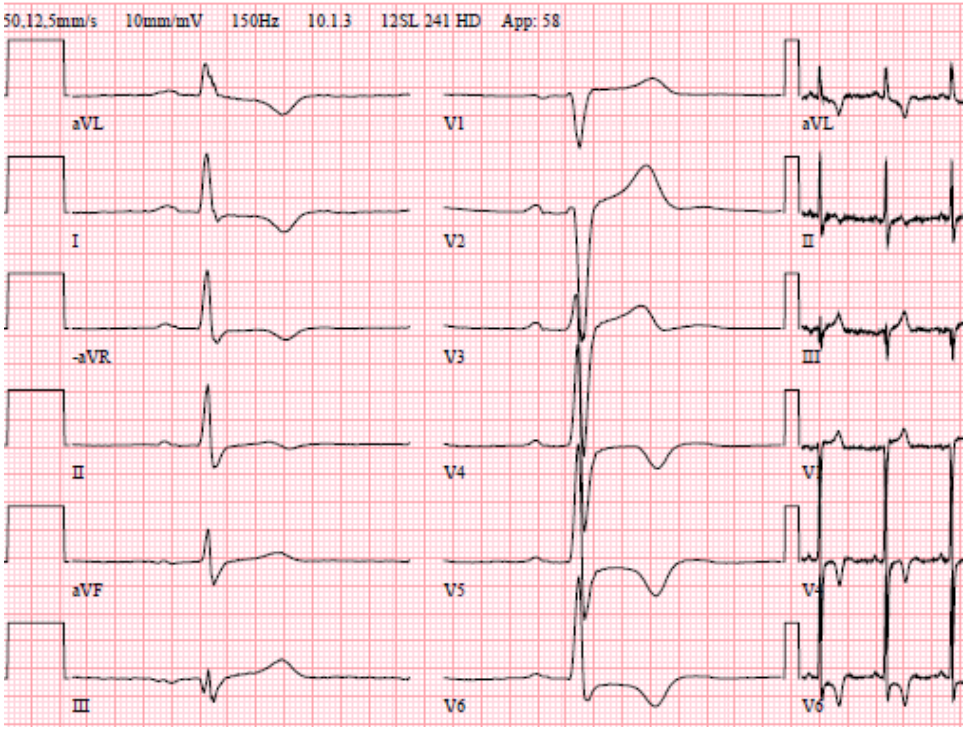
-Hos första gradssläktningar LVH ≥13 mm



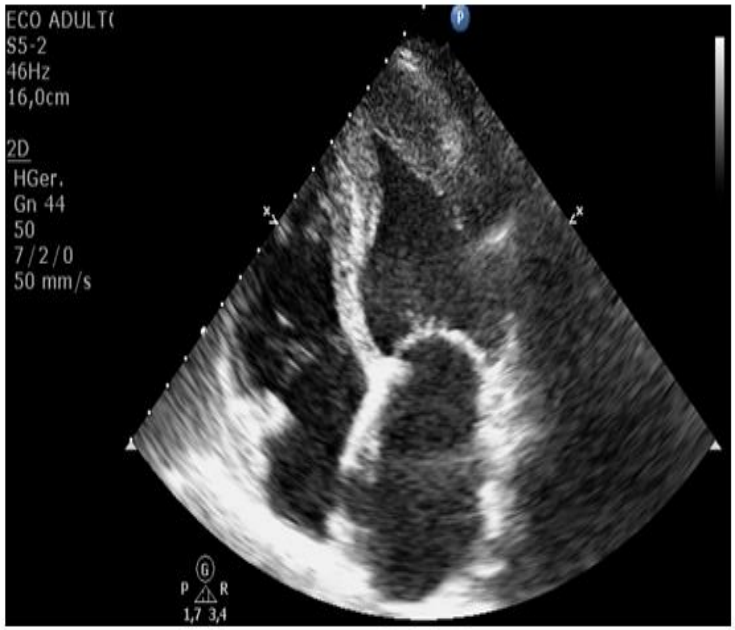
45 årig som varit på VC på kontroll
Inga symtom. Ingen hereditet
Vad gör ni?

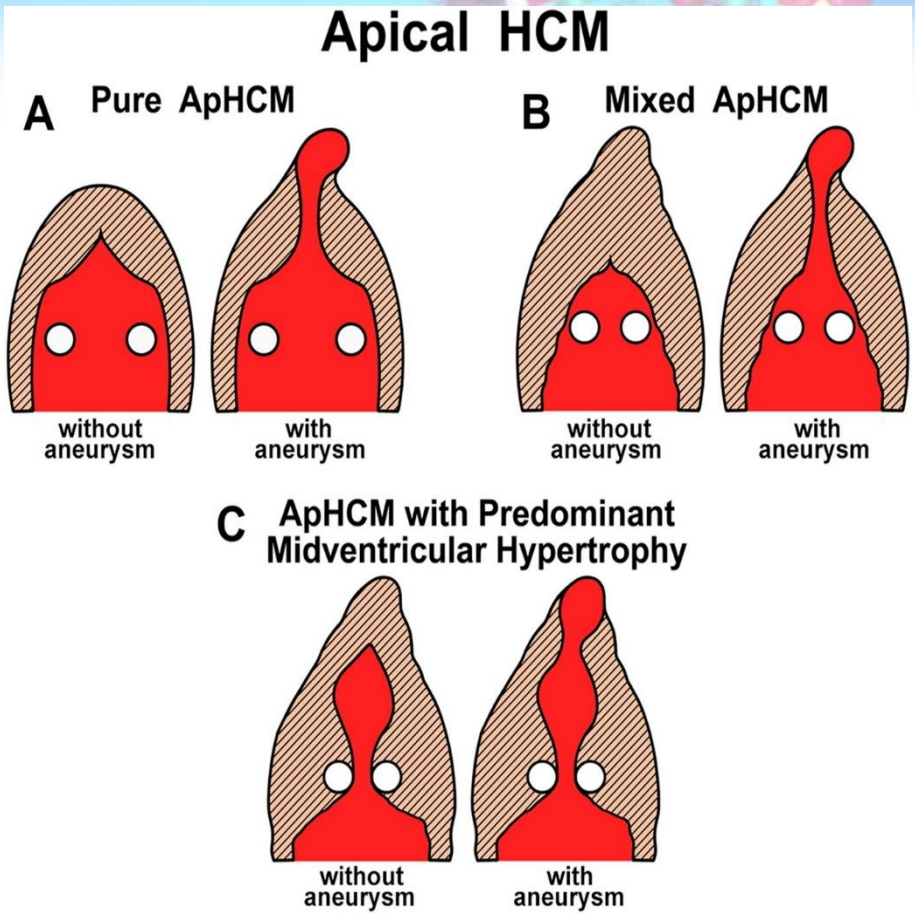
A. Skicka till akuten
B. Normalvariant
C. Vidare utredning med eko



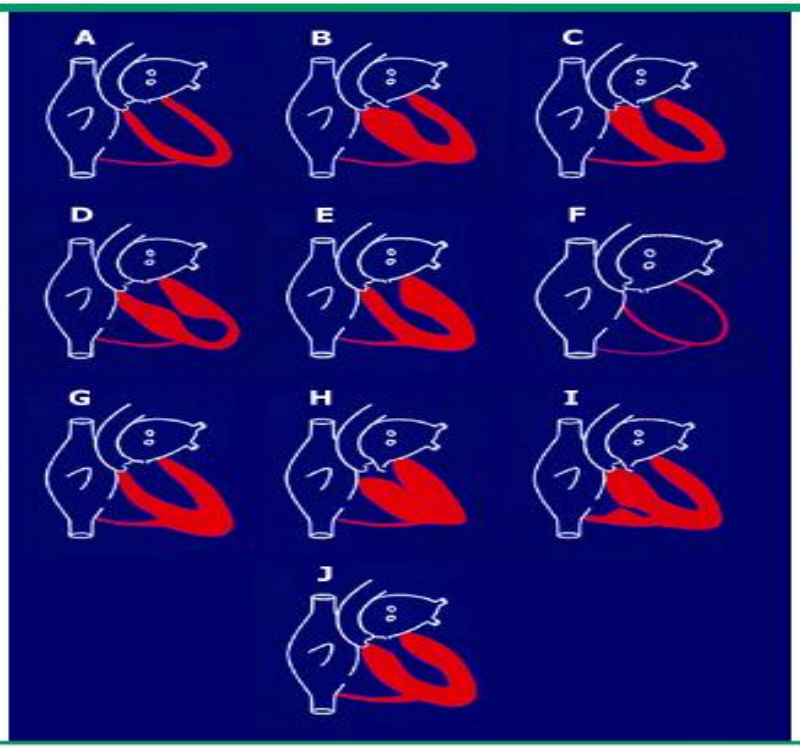


Apical HCM - ApHCM





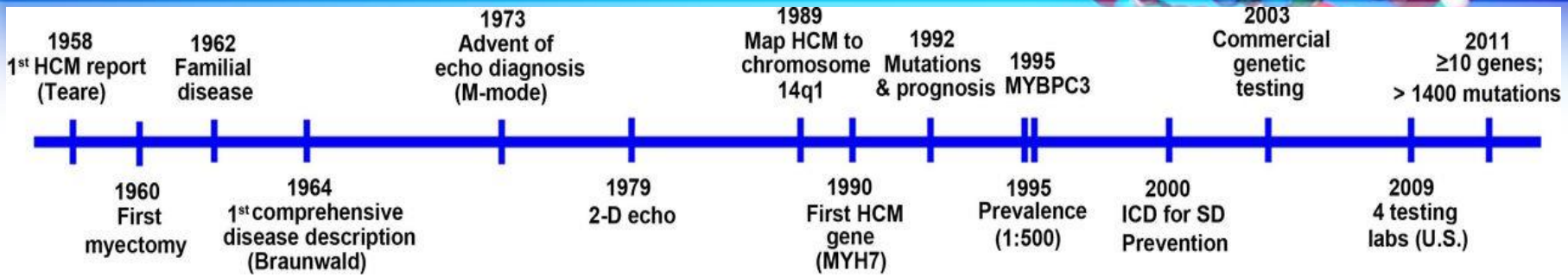
Morphologic variants of hypertrophic cardiomyopathy



HCM typically presents with asymmetric or localized areas of LV hypertrophy, which are diagrammed in B to E.
(A) Normal LV wall thickness.
(B) ASH.
(C) Sigmoid septum, which is more common in older adults.
(D) Midcavity hypertrophy associated with midcavity obstruction.
(E) Predominantly free wall hypertrophy, an unusual pattern in HCM.
(F) LV wall thinning (associated with low LV ejection fraction) and biatrial enlargement.
(G) Predominantly apical LV hypertrophy.
(H) Severe concentric hypertrophy with cavity obliteration.
(I) Biventricular hypertrophy.
(J) Mild to moderate symmetric hypertrophy.

ASH: asymmetrical septal hypertrophy; HCM: hypertrophic cardiomyopathy; LV: left ventricular.

Historiken; genetiska landvinningar

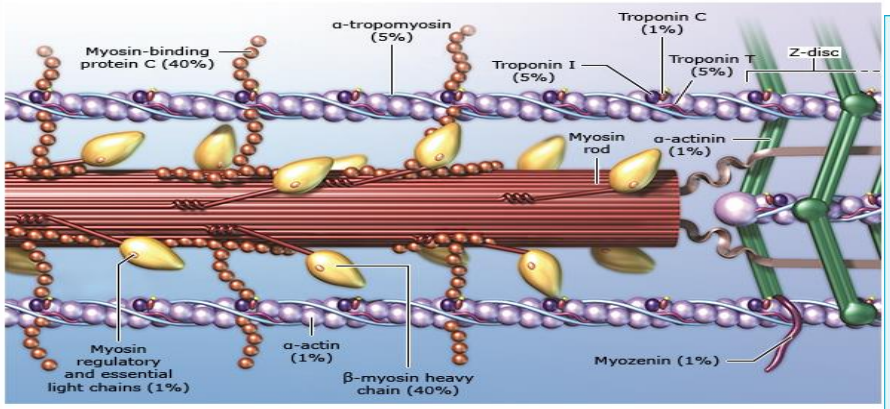


- Nedärvningsmönstret är autosomalt dominant
- **Nedsatt penetrans** och även **variabel expressivitet**
- HCM karakteriseras som en **sarkomersjukdom**
- Sedan 2011 har upp till 11 sjukdomsorsakande gener med över 1500 mutationer i gener som kodar för de tjocka eller tunna myofilamentproteinerna i sarkomeren
- En sjukdomsframkallande mutation i någon av de i dag 11 kända generna kan identifieras hos ca **30–60%** av patienterna
- 5% av patienterna har flera mutationer

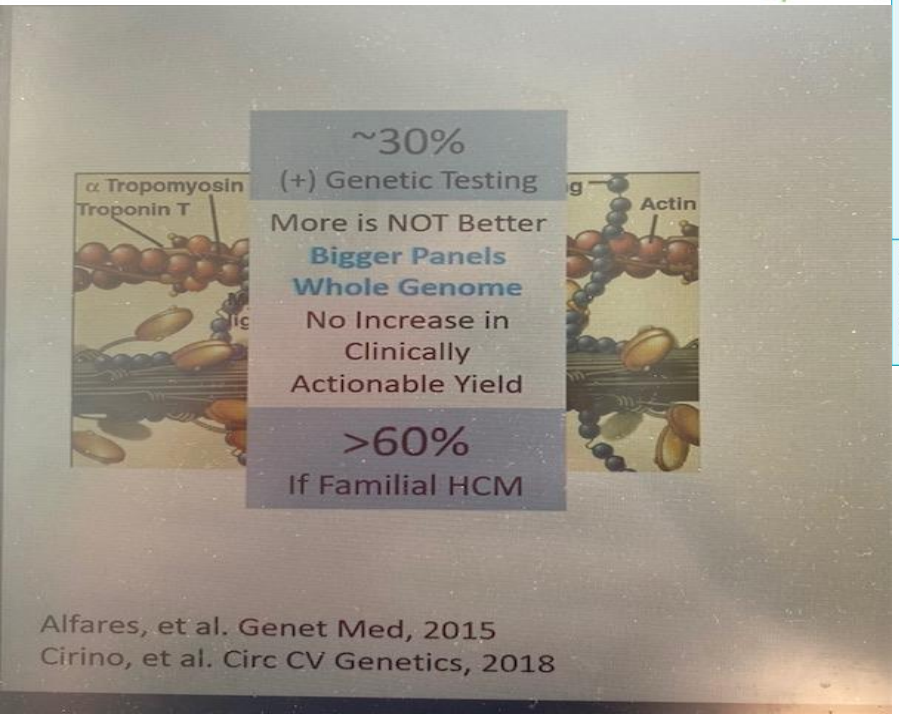
Barry J. Maron et al. JACC 2012;60:705-715

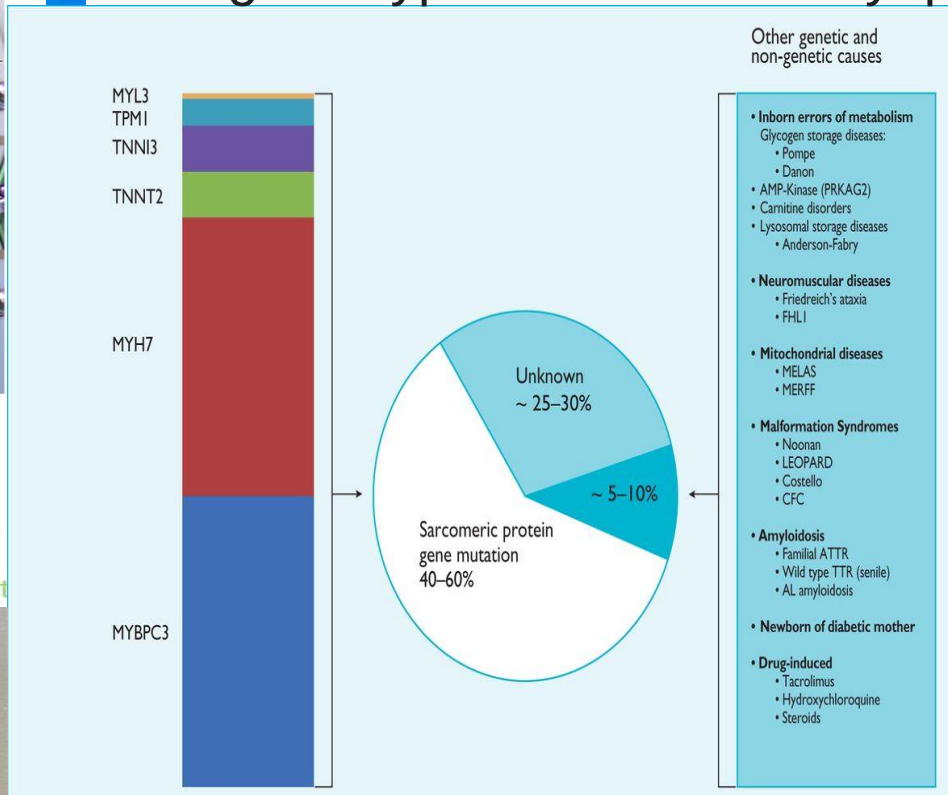
Etiologi av hypertrofisk kardiomyopati

Sarcomeric gene mutation locations in hypertrophic cardiomyopathy (HCM)



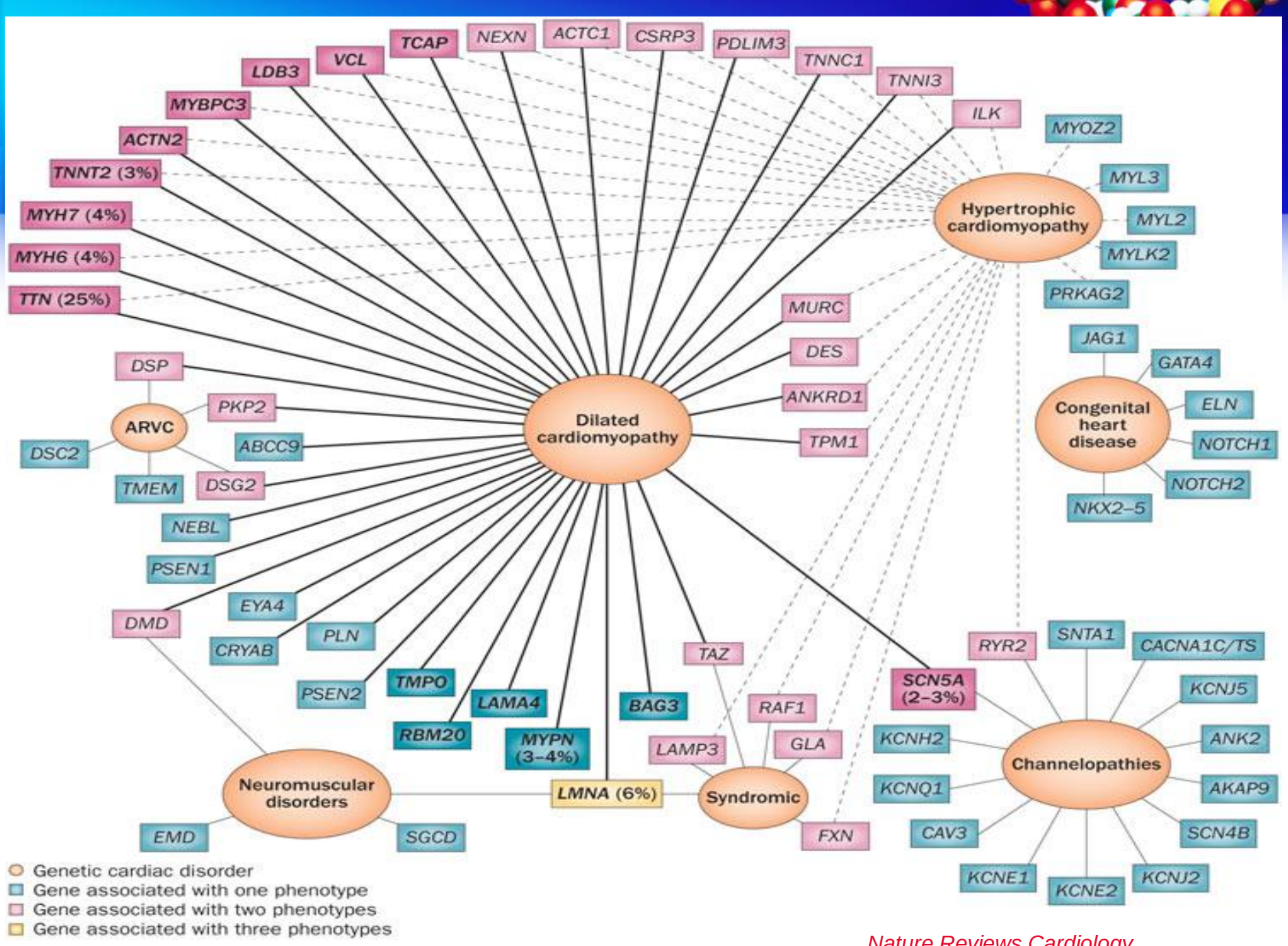
Prevalence for each of the 11 genes derived from studies in unrelated HCM probands with positive genotyping are shown in parentheses. Not shown are genes previously linked to HCM, but with lesser degrees of evidence for pathogenicity: α-myosin heavy chain, titin, muscle LIM protein, telethonin, vincalin/metavinculin, junctophilin 2.





The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

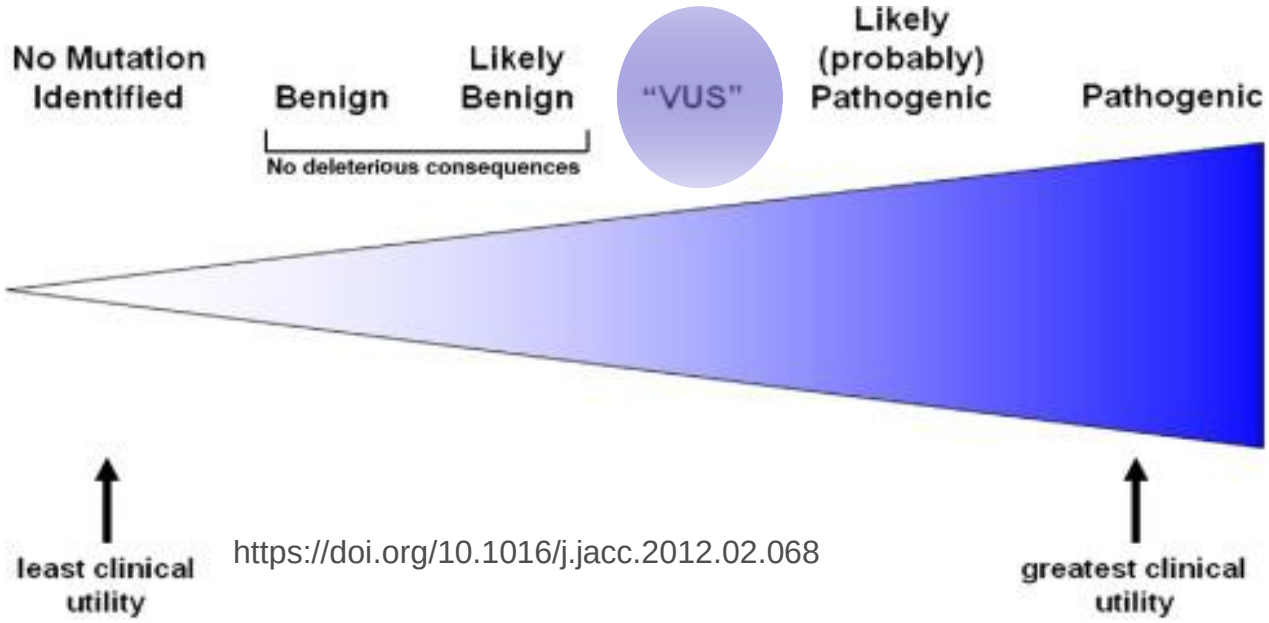
Authors/Task Force members et al. Eur Heart J 2014;eurheartj.ehu284



Nature Reviews Cardiology
Volume10, pages 531–547(2013)

Indikationer för molekylärgenetisk utredning

- för att klarlägga en eventuell genetisk orsak hos patienter som diagnostiserats med HCM
- att identifiera HCM fenokopier/diffdiagnoser
- att identifiera familjemedlemmar med risk för att utveckla sjukdomen, så kallad kaskadscreening



https://doi.org/10.1016/j.jacc.2012.02.068

Genotypning av HCM patienter i Sverige

Mörner et al studerade 46 HCM patienter från **norra Sverige**
35 var sporadiska fall
Totalt 11 olika mutationer upptäcktes:

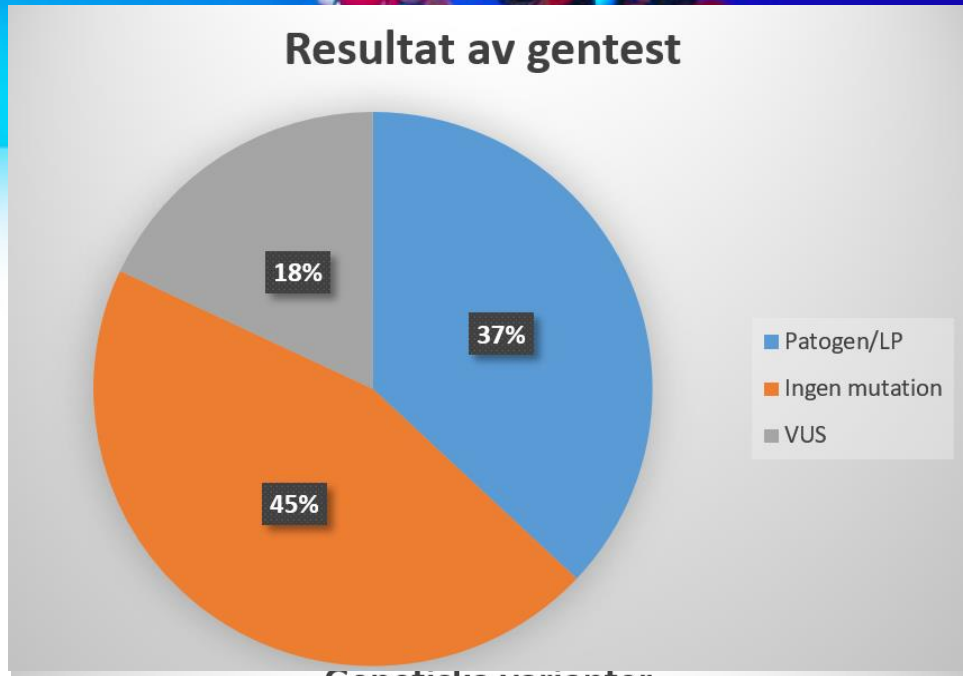
- 7 i MYBPC3 (64 %),
- 2 i MYH7 (18%) och
- 1 i MYL2 och 1 i TNNI3gener (9%)

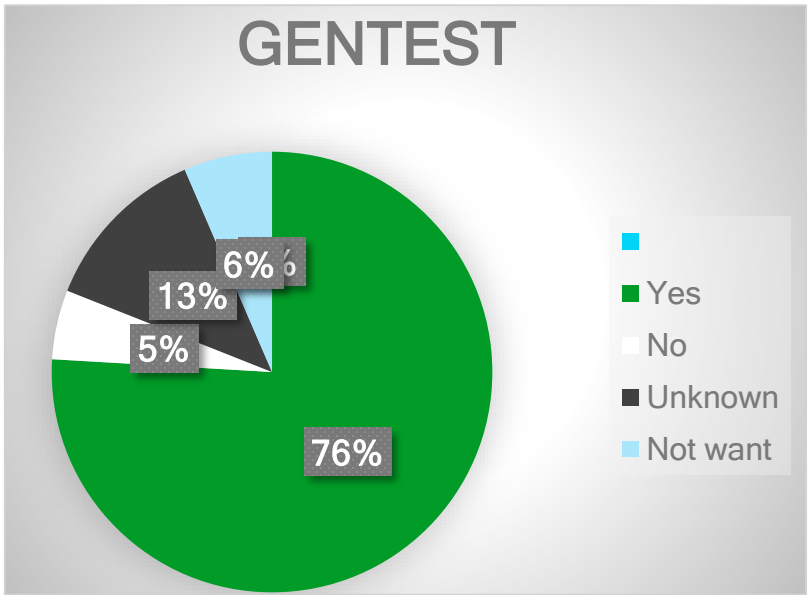
Mutationer identifierades i 91 % av de familjära HCM-fallen
men endast i 9 % av de sporadiska fallen
Mer senare debut av sjukdomen hos de med MYBPC3

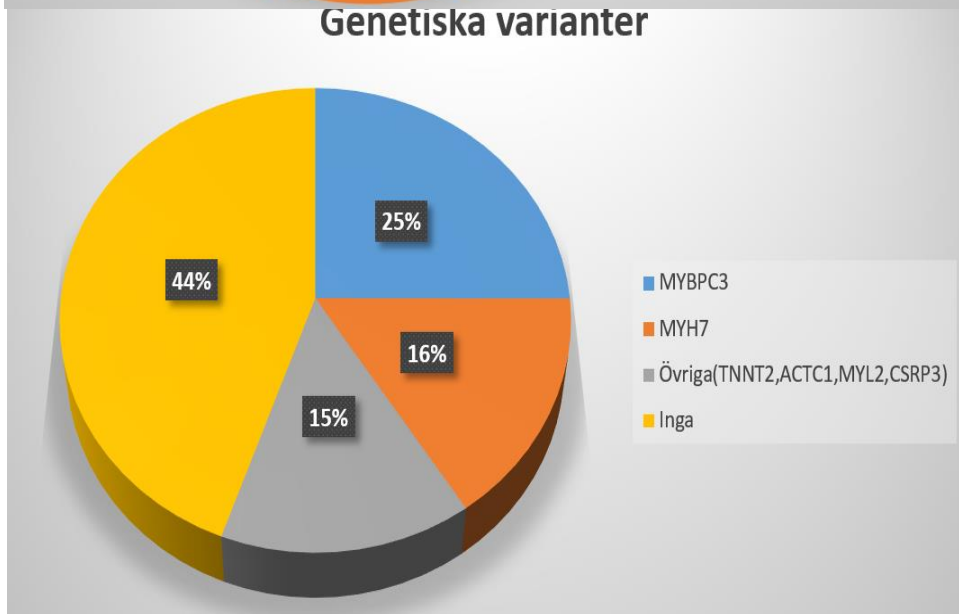
Morner S, Richard P, Kazzam E, Hellman U, Hainque B, Schwartz K, et al. Identification of the genotypes causing hypertrophic cardiomyopathy in northern Sweden. Journal of molecular and cellular cardiology. 2003;35(7):841-9.

Genetisk utredning i Sydöstra Sverige

216 HCM patienter 2010-2021





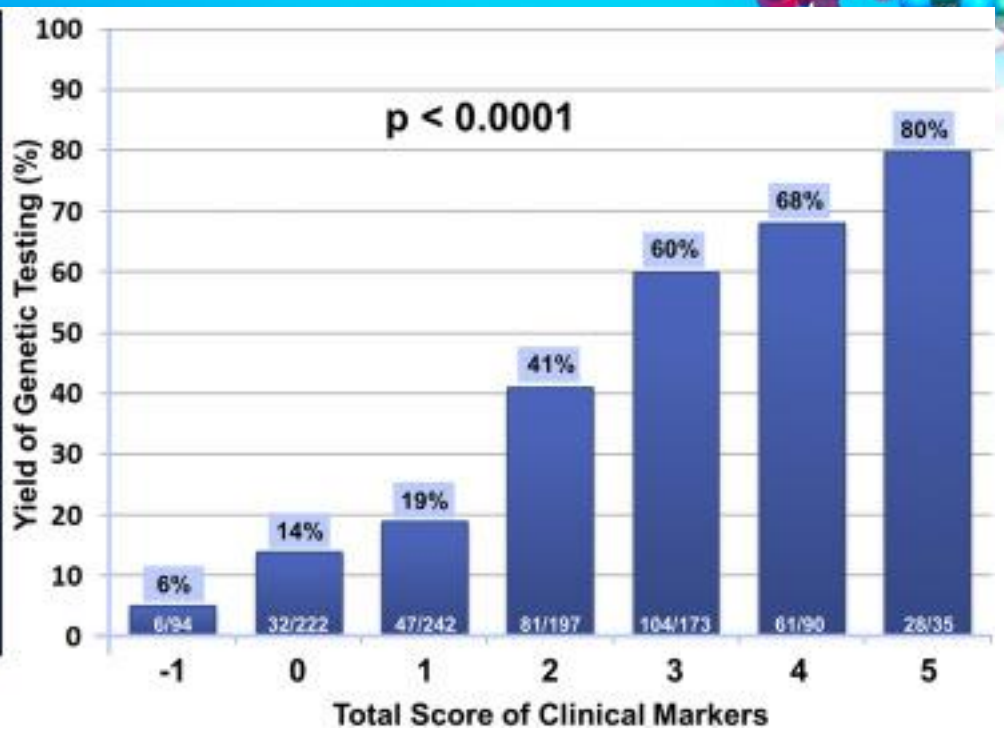


Positiva prediktorer för positiva genetiska resultat

Clinical Markers for Positive Genetic Test

Marker	Pts
❑ Age Dx < 45 yrs	1
❑ MLVWT ≥ 20 mm	1
❑ FH of HCM	1
❑ FH SCD	1
❑ Reverse-curve HCM	1
❑ Hx of Hypertension	-1

Scoring range: -1 to 5 pts



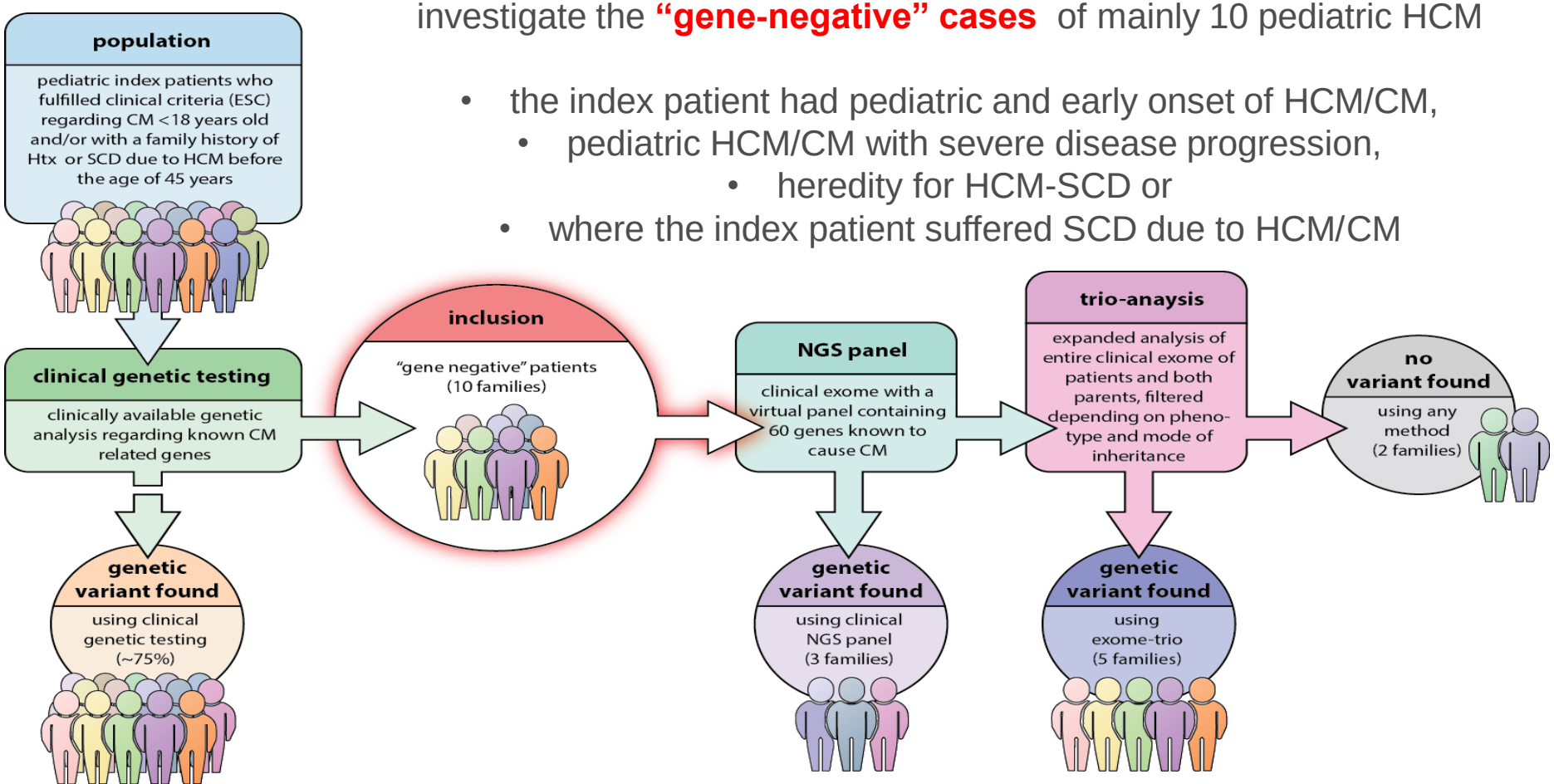
J.M. Bos, M.L. Will, B.J. Gersh, T.M. Kruisselbrink, S.R. Ommen, M.J. Ackerman
Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy
Mayo Clin Proc, 89 (2014), pp. 727-737

Pediatric hereditary hypertrophic cardiomyopathy
- the value of reevaluating and expanding gene panel analyses

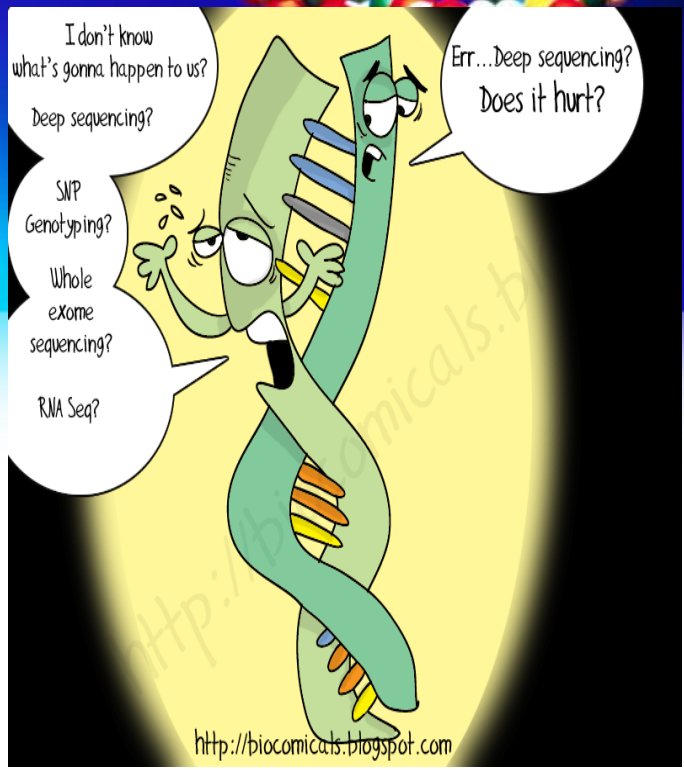
- Antheia Kissopoulou, Eva Fernlund Henrik Green, Jan Erik Karlsson, Rada Ellegård, Hanna Klang Årstrand, Jon Jonasson and Cecilia Gunnarsson
- 2020 Dec 8;11(12):1472. doi: 10.3390/genes11121472

investigate the **"gene-negative" cases** of mainly 10 pediatric HCM

- the index patient had pediatric and early onset of HCM/CM,
- pediatric HCM/CM with severe disease progression,
- heredity for HCM-SCD or
- where the index patient suffered SCD due to HCM/CM



Utöka genpanel?



- Analysen av 51 extra gener utöver de med HCM i 240 sarkomer negativa fall hos vuxna ökade inte diagnostiken (2019 Thomson KL)

- Bagnall et al.2018: patienter med mer allvarligare HCM och <18 år med gen-negativ HCM, WGS ökar diagnostiken: identifierade en variant i 9 av 46 familjer (20%), och utökade genetisk screening till introniska regioner identifierade i 4 av 46 familjer (9 %)
- I pediatrisk ärftlig "gen-negativ" HCM

omvärdera fenotypen och utöka den genetiska med trios, WGS/WES

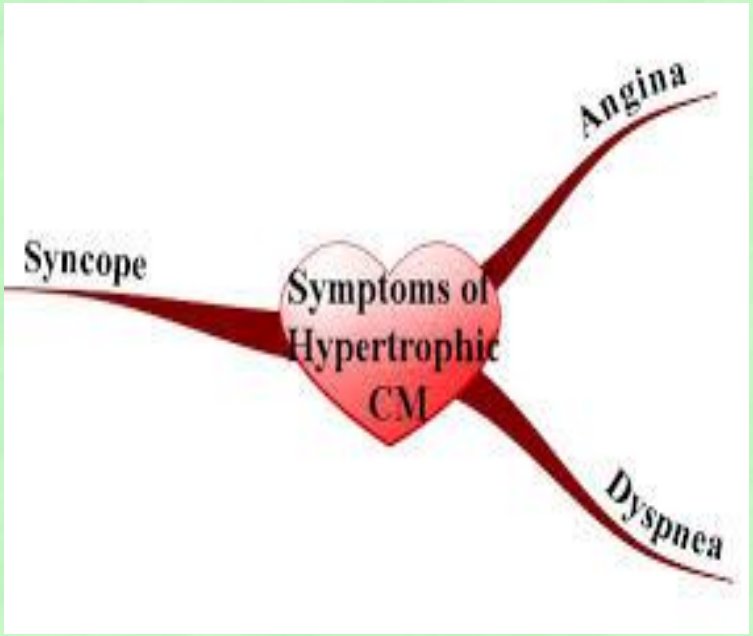
- **Behov av mer omfattande genetiska analyser**

❑ **vid tidig debut av kardiomyopati eller**
❑ **efter oväntad hjärtdöd hos unga,**
❑ **om det finns familjeanamnes**

Symtom

HCM **heterogen** hjärtsjukdom med varierande :
-kliniska manifestationer
-debutåldern
-omfattningen av hypertrofi (LVH)
-graden av obstruktion, fibros
-och risk för plötslig hjärtdöd (SCD)

Inom samma familj, kan personer med samma genotyp ha varierande debut, symtom och kliniska manifestationer av HCM (fenotyp)

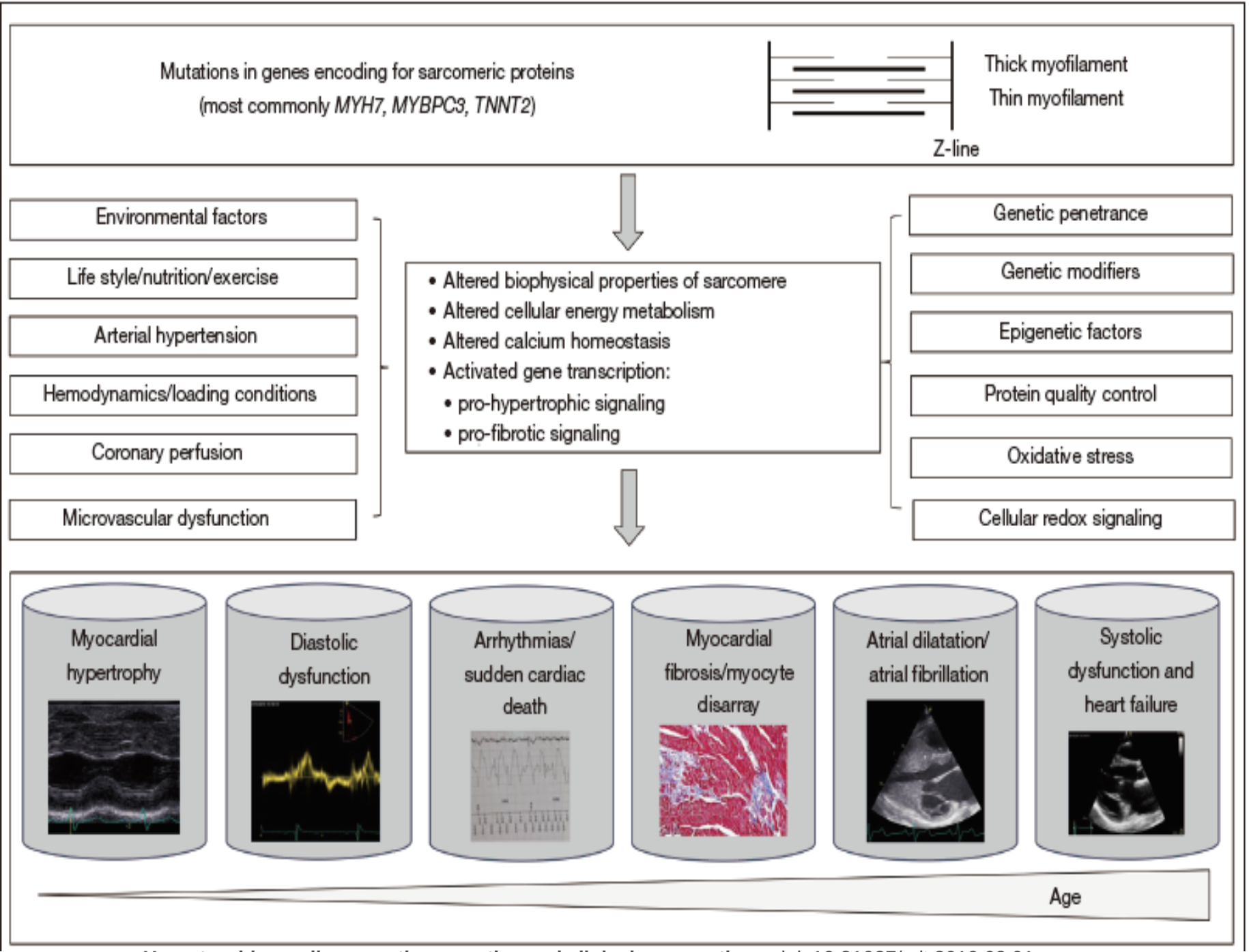


•**variabla expressiviteten inom och mellan familjer**

•**nedsatt penetrans**

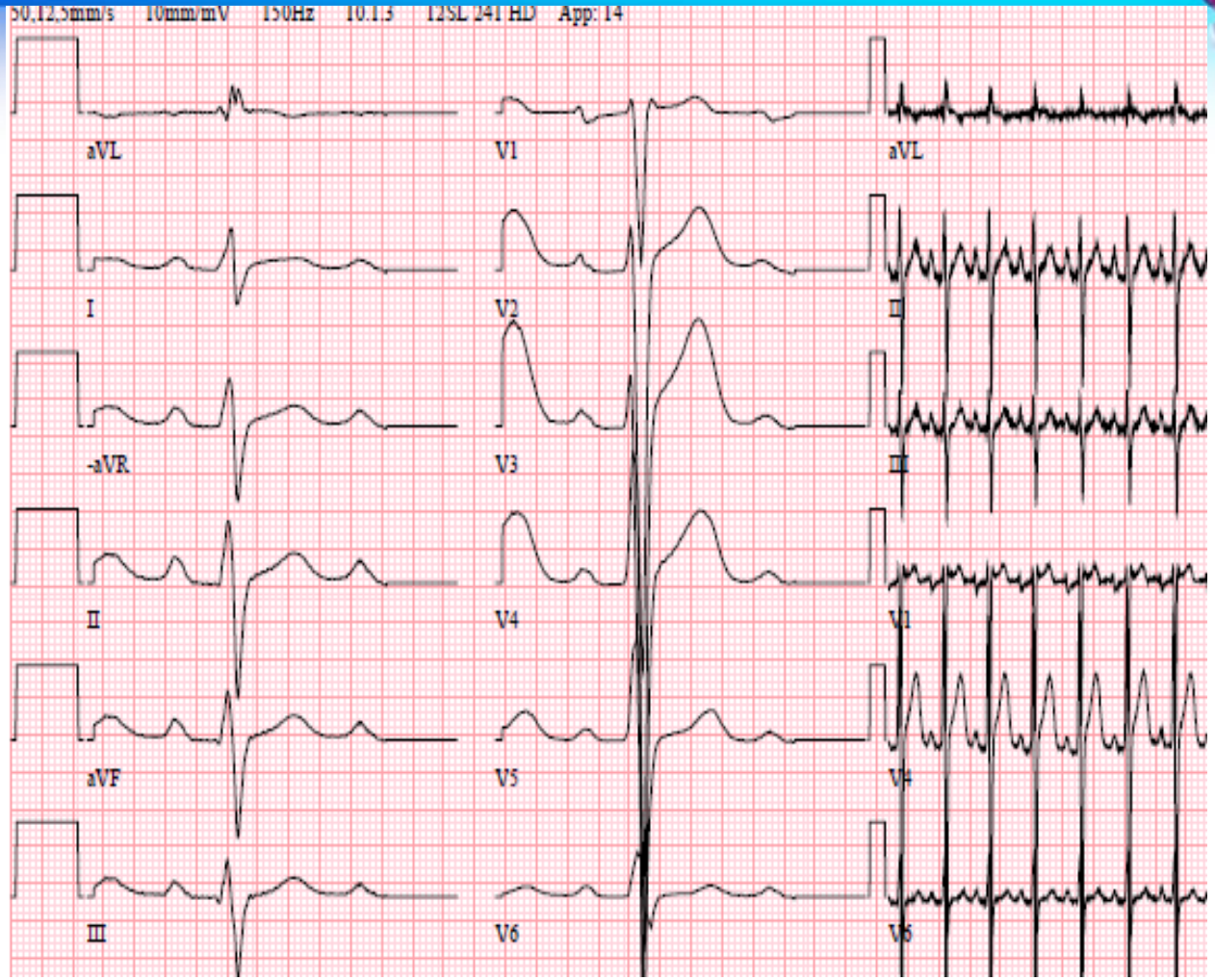
- Trötthet
- Dyspné
- Bröstsmärta
- Palpitationer
- Presyncope eller synkope
- SCD

Symptom beror på
- diastolisk dysfunktion,
- vänster kammaresutflödes (LVOT) obstruktion,
- mitral regurgitation och
- mikrovaskulär dysfunktion



Hypertrophic cardiomyopathy: genetics and clinical perspectives, doi: 10.21037/cdt.2019.02.01

CASE-FALL



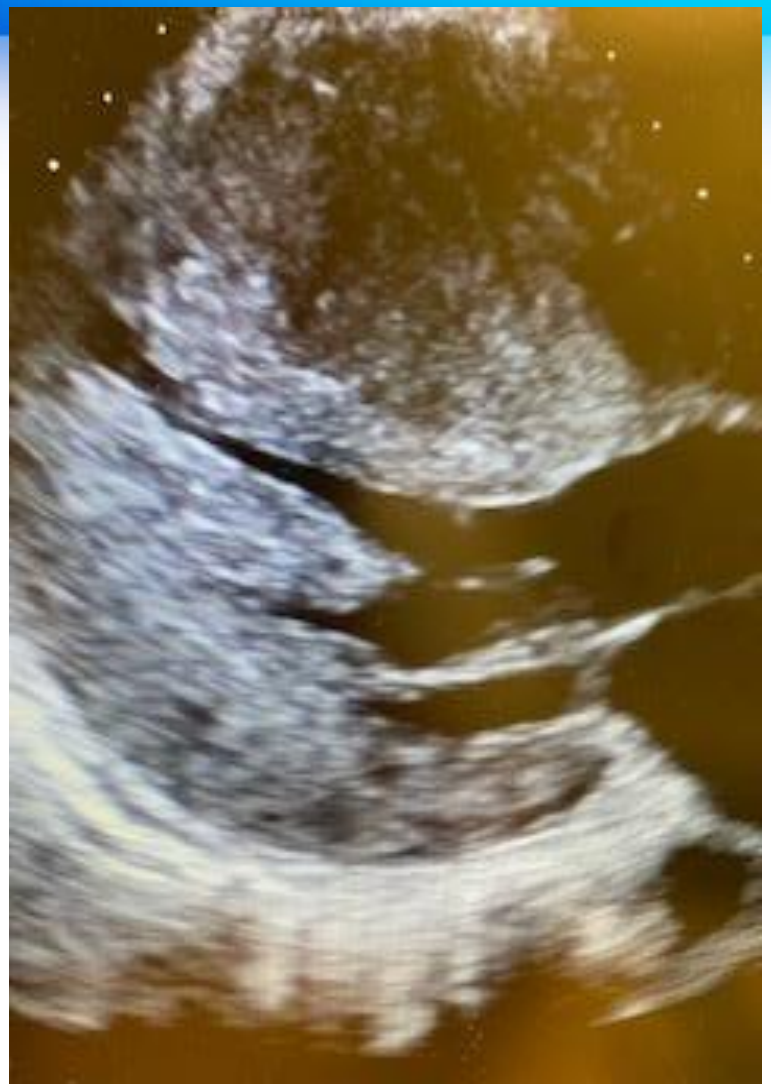
20 årig kille söker VC pga hög puls och tryck i bröstet

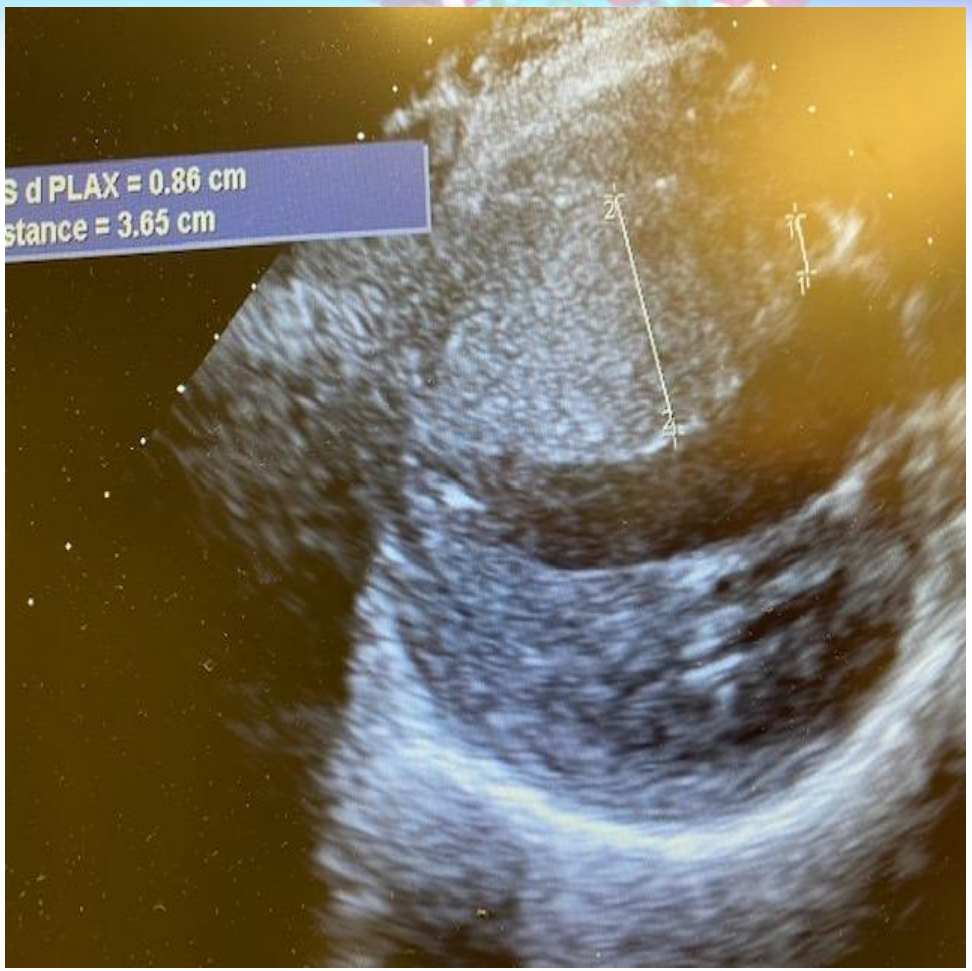
2 års anamnes på dålig ork

Systoliskt strävt blåsljud över hela prekordiet

Normalt blodtryck

Ekokardiografi visar bild som vid **hypertrof obstruktiv kardiomyopati**





Efter myektomi

Hypertrofisk obstruktiv kardiomyopati (HOCM) - LVOTO

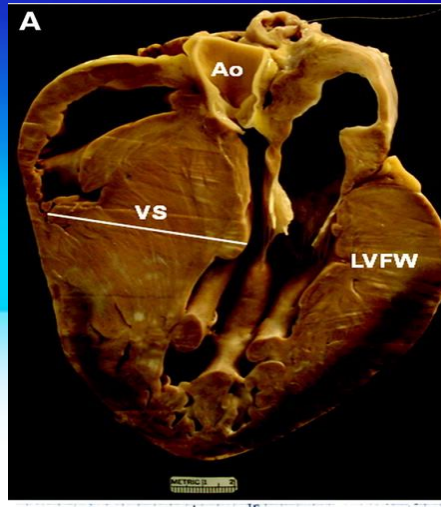
- 30% har utflödesobstruktion i vila och ytterligare 30% efter provokation De med symtom utan LVOT i vila bör göra stresseko

- kombination av septal hypertrofi och anterior förskjutning av mitralisklaffen- SAM

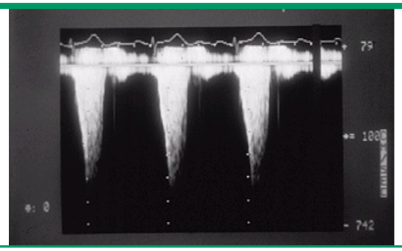
- LVOTO definieras som Dopplers LV utflödestryckgradient ≥30 mmHg vid vila eller under fysiologisk provokation som Valsalva –manöver

- Gradient av ≥50 mm Hg hemodynamiskt betydelse

- LVOT i vila som är ≥30 mmHg är en riskfaktor för progressiv hjärtsvikt symtom



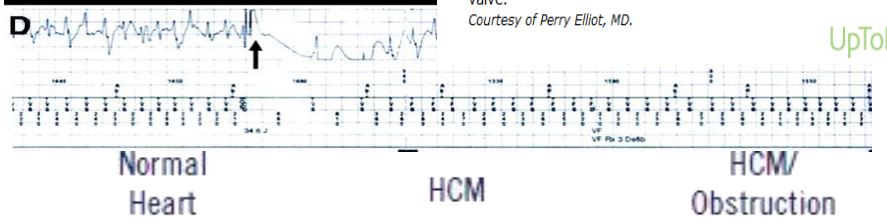
Continuous wave (CW) Doppler echocardiogram showing a 100 mmHg gradient across the left ventricular outflow tract (LVOT) in a patient with hypertrophic cardiomyopathy (HCM)

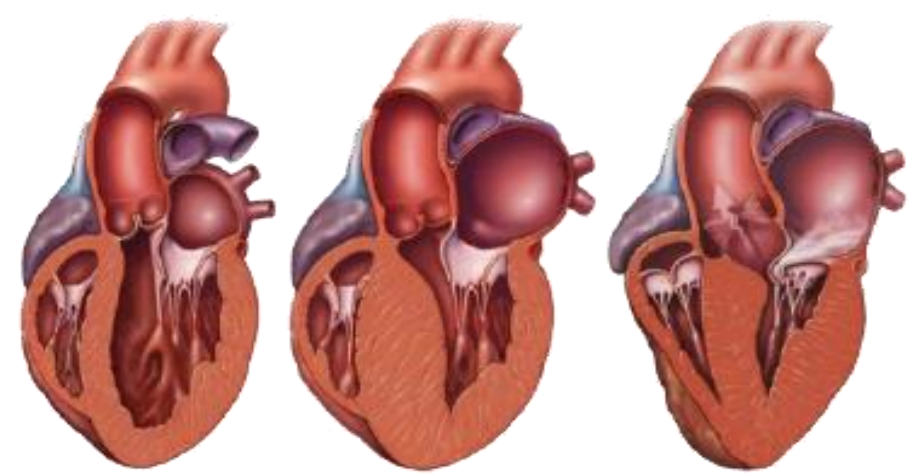


The continuous wave Doppler demonstrates the characteristic profile of dynamic left ventricular outflow tract obstruction; the peak velocity across the obstruction is 5 m/sec or a gradient of 100 mmHg. When severe, outflow tract signal can be difficult to distinguish between the mitral regurgitation that frequently accompanies systolic anterior motion of the mitral valve.

Courtesy of Perry Elliot, MD.

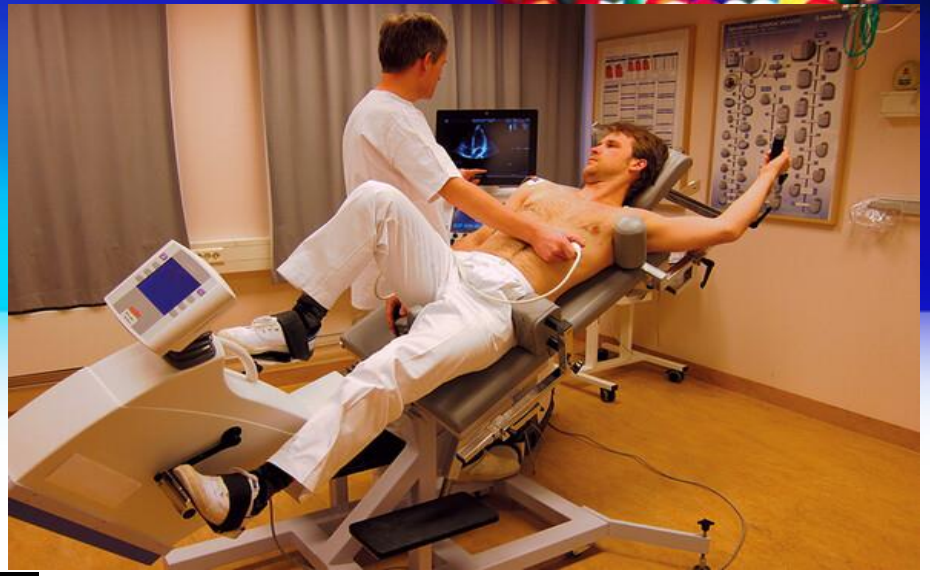
UpToDate

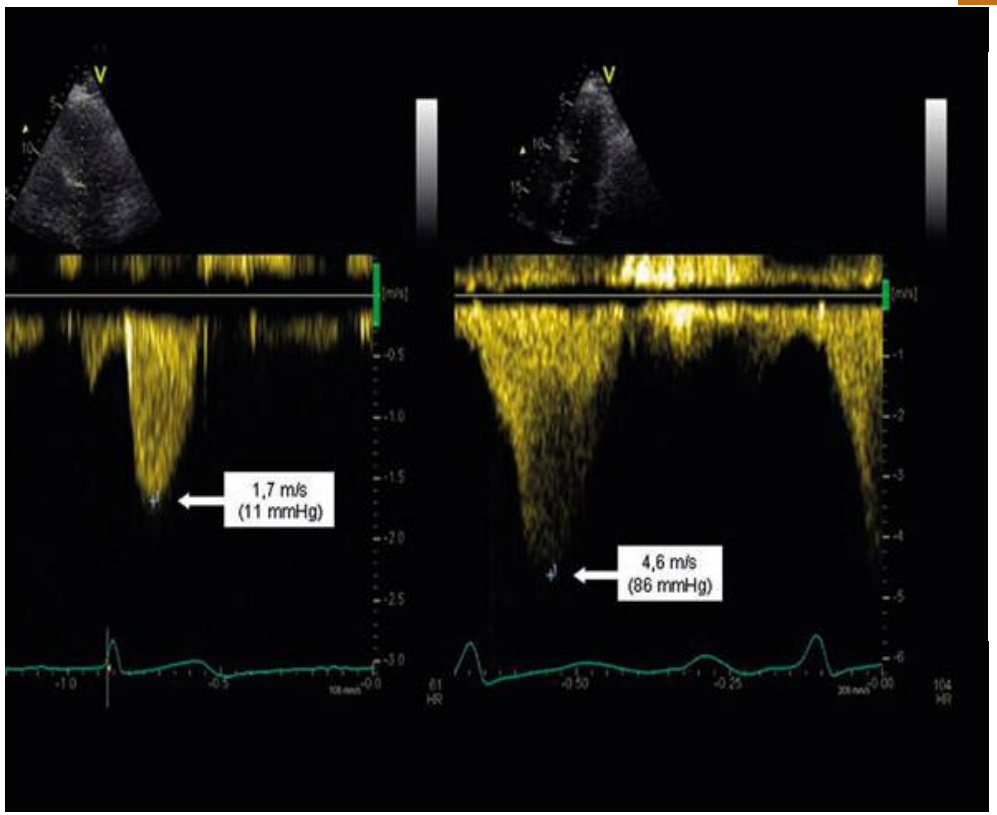


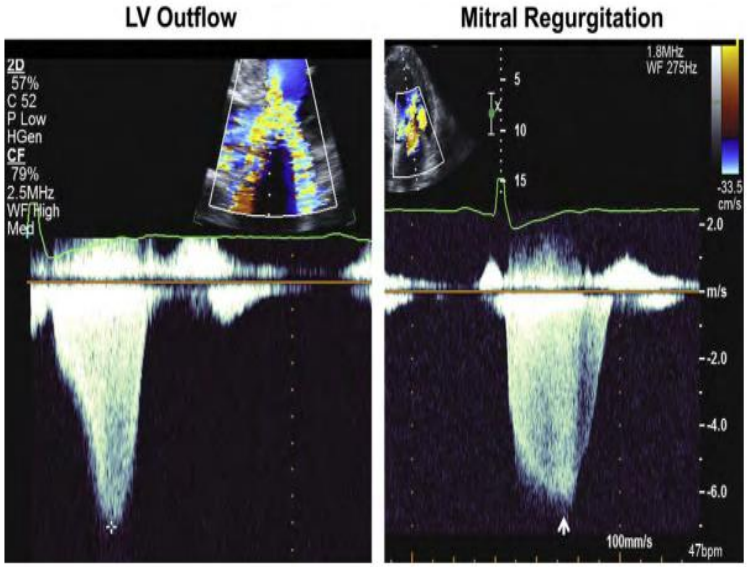


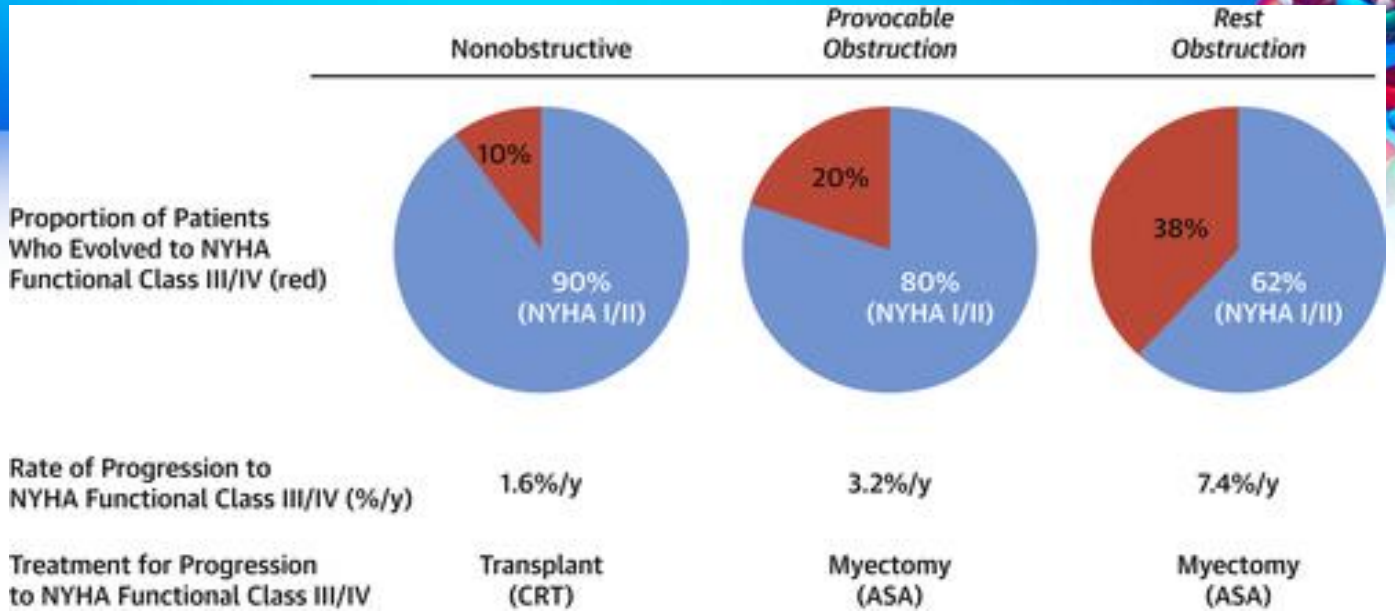
Note the increased left ventricular (LV) muscle wall thickness, decreased LV lumen size, and enlarged left atrium (LA) of the hearts with HCM.

Stressekokardiografi med halvliggande cykel



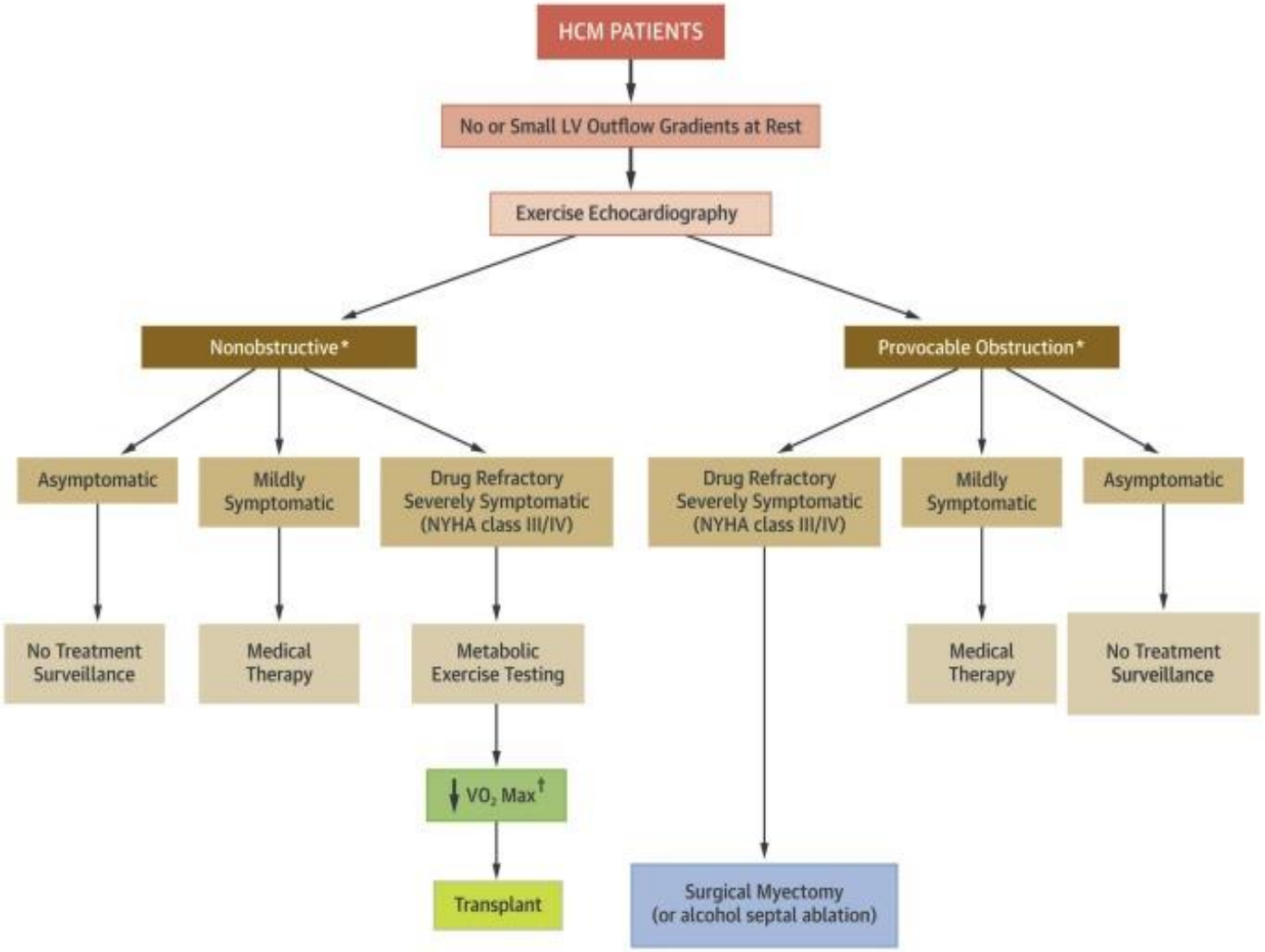






Barry J. Maron et al. *J Am Coll Cardiol* 2022; 79:390-414.

CENTRAL ILLUSTRATION: Flow Diagram Summarizing Applications of Exercise Testing to Diagnosis and Management of HCM

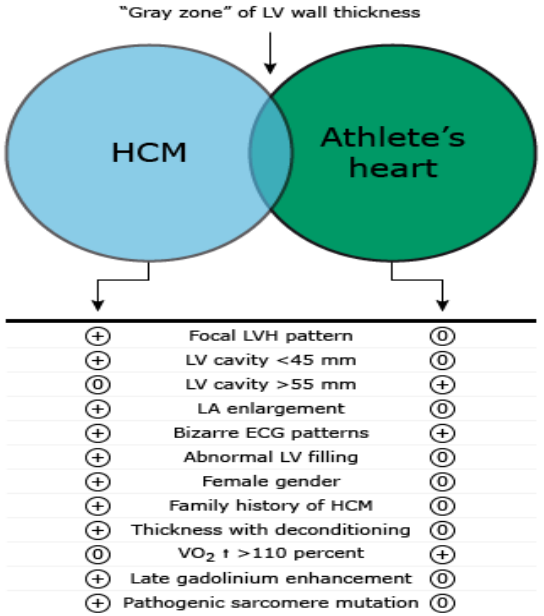


Rowin, E.J. et al. J Am Coll Cardiol Img. 2017;10(11):1374-86.

Diagnostiska utmaningar

- Presentation i den sena fasen av sjukdomen med en vidgad vänsterkammare och förtunning LV-vägg
- Fysiologisk hypertrofi orsakas av intensiv atletisk träning
- Patienter med co-existerande sjukdomar: hypertoni , aortastenos
- Isolerade basal septal hypertrofi hos äldre personer
- Hypovolemi
- Phenocopies-metabola sjukdomar, syndrom, inlagringssjukdomar, gener som är involverade i RAS MAP-kinasvägen orsak Noonans syndrom i samband med LV hypertrofi

Pathologic LVH vs Physiologic LVH



Comparison of features which can be useful in distinguishing Pathologic LVH from Physiologic LVH.

LA: left atrium; LV: left ventricle; LVH: left ventricular hypertrophy; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy.

Additional updated information from:

1. *Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2012.*
2. *Maron BJ, Pelliccia A. The heart of trained athletes: cardiac remodeling and the risks of sports, including sudden death. Circulation 2006; 114:1633.*

Reproduced with permission from: Maron BJ, Pelliccia A, Spirito P. Cardiac disease in young trained athletes. Insights into methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. Circulation 1995; 91:1596.

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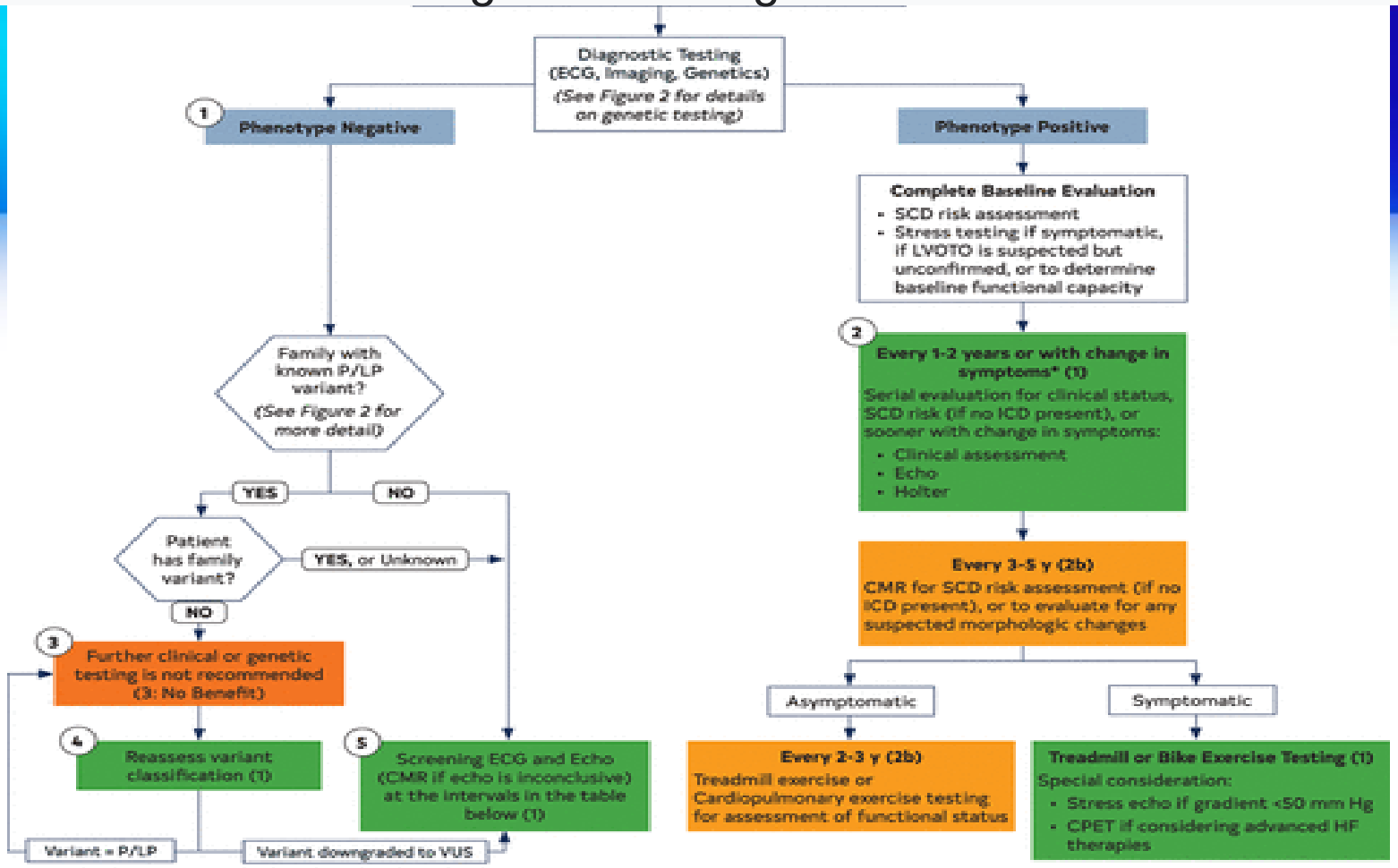
Rekommenderad utvärdering och testning för HCM



Screening Asymptomatic First-Degree Relatives of Patients With HCM		
Age of First-Degree Relative	**Initiation of Screening**	**Surveillance Interval**
Children and adolescents from genotype-positive family and/or family with early onset HCM	At the time of diagnosis in another family member	Every 1-2 y
All other children and adolescents	At any time after the diagnosis in the family, but no later than puberty	Every 2-3 y
Adults	At the time of diagnosis in another family member	Every 3-5 y

Steve R. Ommen. Circulation. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy, Volume: 142, Issue: 25, Pages: e558-e631, DOI: (10.1161/CIR.0000000000000937)

Risk faktorer

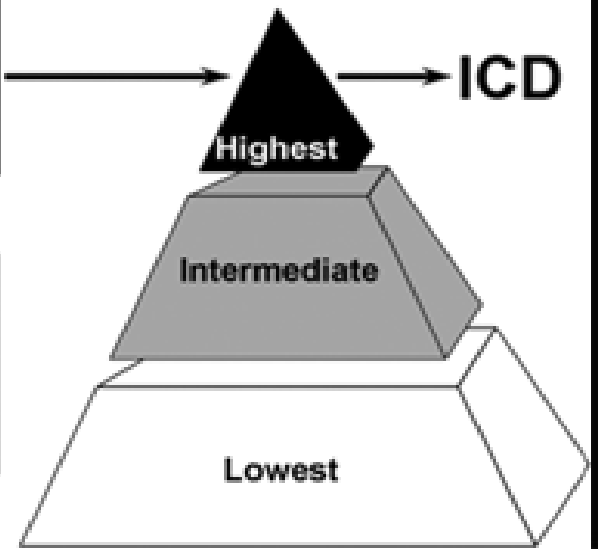
Risk Factor	Comment
Age	• The effect of age on SCD has been examined in a number of studies[7,81,99,208,244,372–374] and two have shown a significant association, with an increased risk of SCD in younger patients.[7,99] • Some risk factors appear to be more important in younger patients, most notably, NSVT,[69] severe LVH[375] and unexplained syncope.[99]
Non-sustained ventricular tachycardia	• NSVT (defined as ≥3 consecutive ventricular beats at ≥120 BPM lasting <30 seconds) occurs in 20–30% of patients during ambulatory ECG monitoring and is an independent predictor of SCD.[69,73,83,246,248,374] • There is no evidence that the frequency, duration or rate of NSVT influences the risk of SCD.[69,376]
Maximum left ventricular wall thickness	• The severity and extent of LVH measured by TTE are associated with the risk of SCD.[69,120,121,373] • Several studies have shown the greatest risk of SCD in patients with a maximum wall thickness of ≥30 mm but there are few data in patients with extreme hypertrophy (≥35 mm).[69,73,120,247,248,373,377,378]
Family history of sudden cardiac death at a young age	• While definitions vary,[7,120,373,377] a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM.
Syncope	• Syncope is common in patients with HCM but is challenging to assess as it has multiple causes.[379] • Non-neurocardiogenic syncope for which there is no explanation after investigation is associated with increased risk of SCD.[7,81,99,244,246–248] • Episodes within 6 months of evaluation may be more predictive of SCD.[99]
Left atrial diameter	• Two studies have reported a positive association between LA size and SCD.[73,99] There are no data on the association between SCD and LA area and volume. Measurement of LA size is also important in assessing the risk of AF (see section 9.4).
Left ventricular outflow tract obstruction	• A number of studies have reported a significant association with LVOTO and SCD.[73,81,83,246,372,380] Several unanswered questions remain, including the prognostic importance of provocable LVOTO and the impact of treatment (medical or invasive) on SCD.
Exercise blood pressure response	• Approximately one third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterised by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve.[241,381] • Various definitions for abnormal blood pressure response in patients with HCM have been reported[69,83,246,377]; for the purposes of this guideline an abnormal blood pressure response is defined as a failure to increase systolic pressure by at least 20 mm Hg from rest to peak exercise or a fall of >20 mm Hg from peak pressure.[237] • Abnormal exercise blood pressure response is associated with a higher risk of SCD in patients aged ≤40 years,[237] but its prognostic significance in patients >40 years of age is unknown.

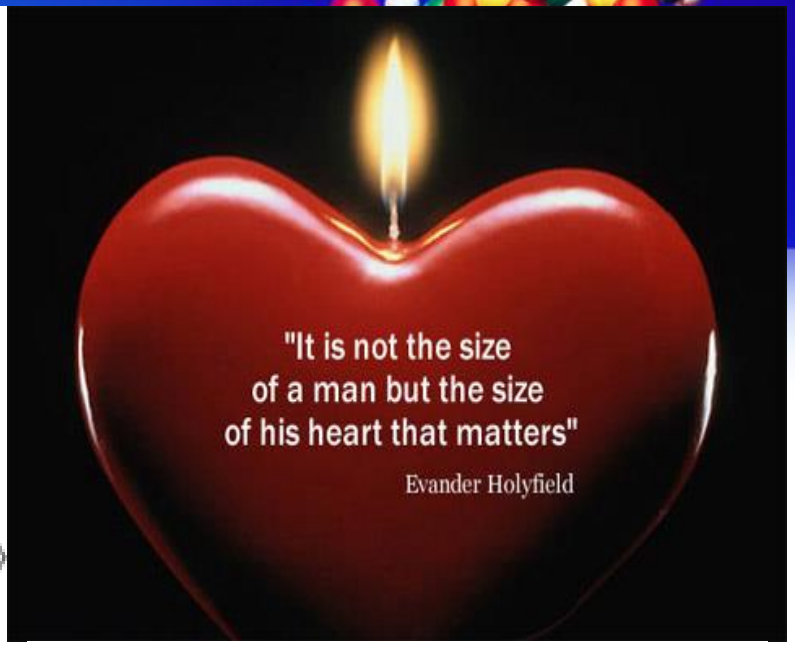
''2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy''

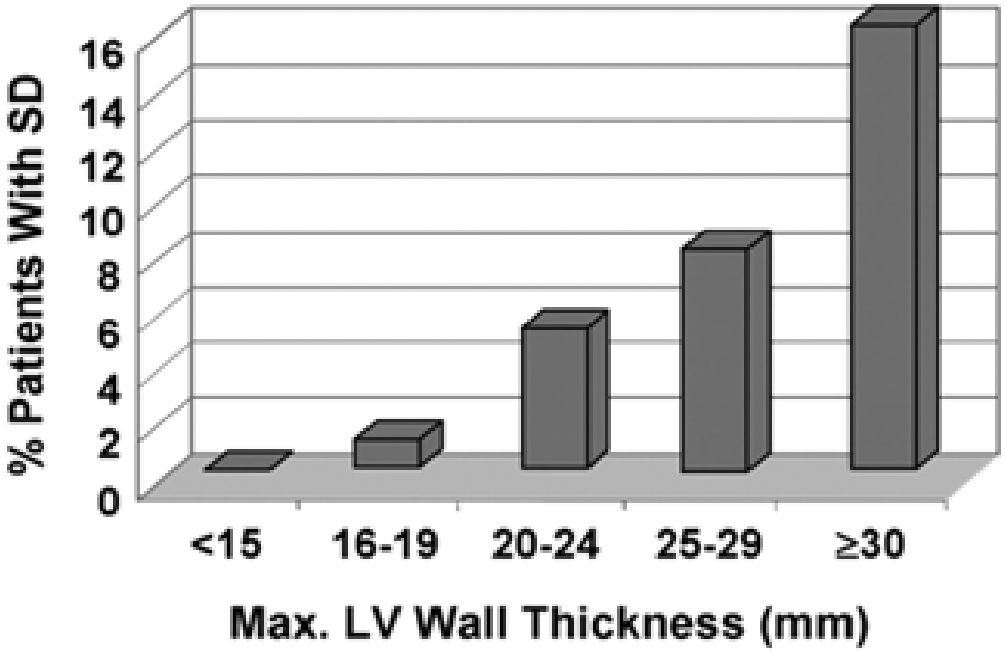
2° prevention
Cardiac arrest/sustained VT

1° prevention
Familial sudden death
Unexplained syncope
Multiple-repetitive NSVT (Holter)
Abnormal exercise BP response
Massive LVH

Potential arbitrators
End-stage phase
LV apical aneurysm
Marked LV outflow obstruction (rest)
Extensive delayed enhancement
Modifiable
- Intense competitive sports
- CAD





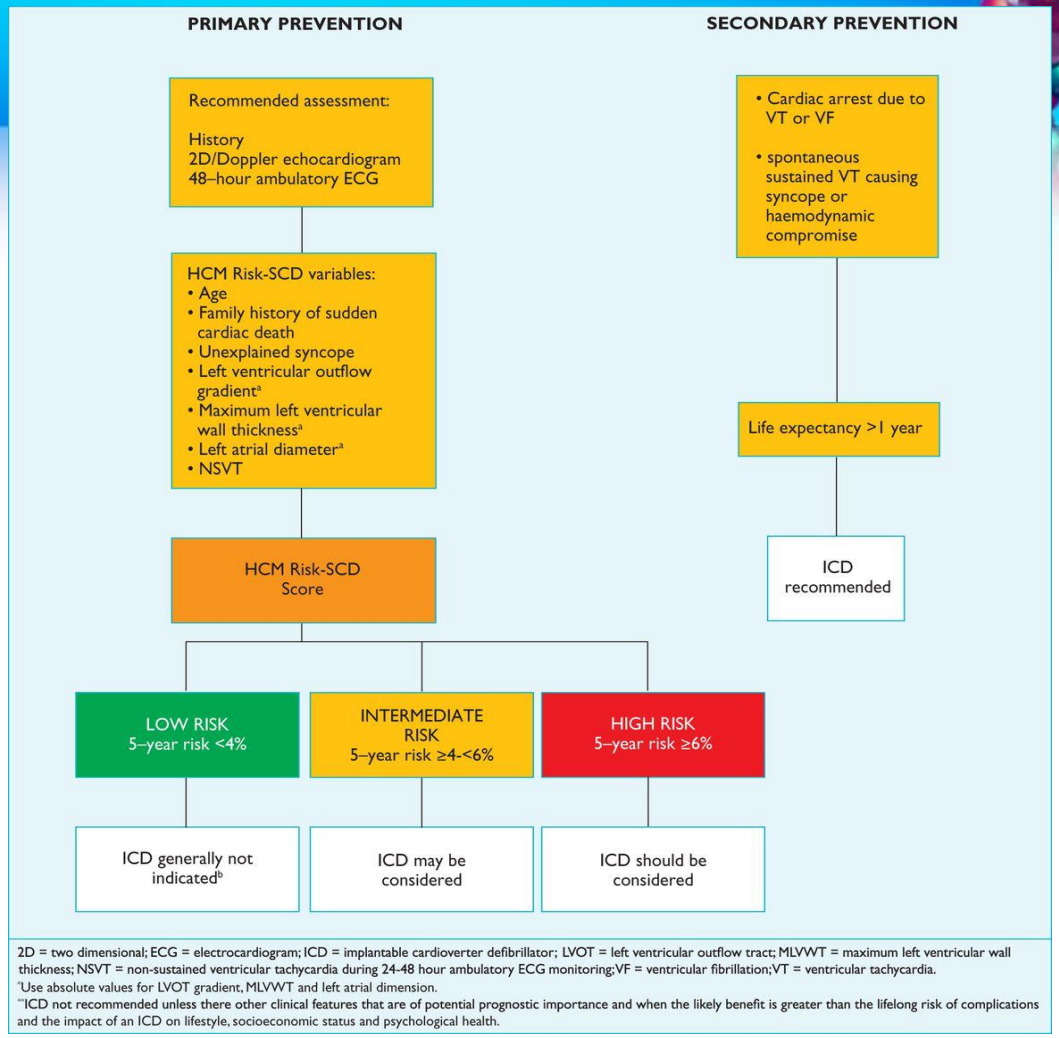


HCM Risk-SCD Calculator

Age	**Years**	*Age at evaluation*
Maximum LV wall thickness	**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	**mmHg**	*The maximum LV outflow gradient determined at rest an with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where is the peak aortic outflow velocity*
Family History of SCD	○ No ○ Yes	*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	○ No ○ Yes	*3 consecutive ventricular beats at a rate of 120 beats pe minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	○ No ○ Yes	*History of unexplained syncope at or prior to evaluation.*

Risk of SCD at 5 years (%):	
ESC recommendation:	

ICD implantation



2D = two dimensional; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; LVOT = left ventricular outflow tract; MLVWT = maximum left ventricular wall thickness; NSVT = non-sustained ventricular tachycardia during 24-48 hour ambulatory ECG monitoring; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Use absolute values for LVOT gradient, MLVWT and left atrial dimension.
[b]ICD not recommended unless there other clinical features that are of potential prognostic importance and when the likely benefit is greater than the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.

Authors/Task Force members et al. Eur Heart J 2014;eurheartj.ehu284

European Heart Journal

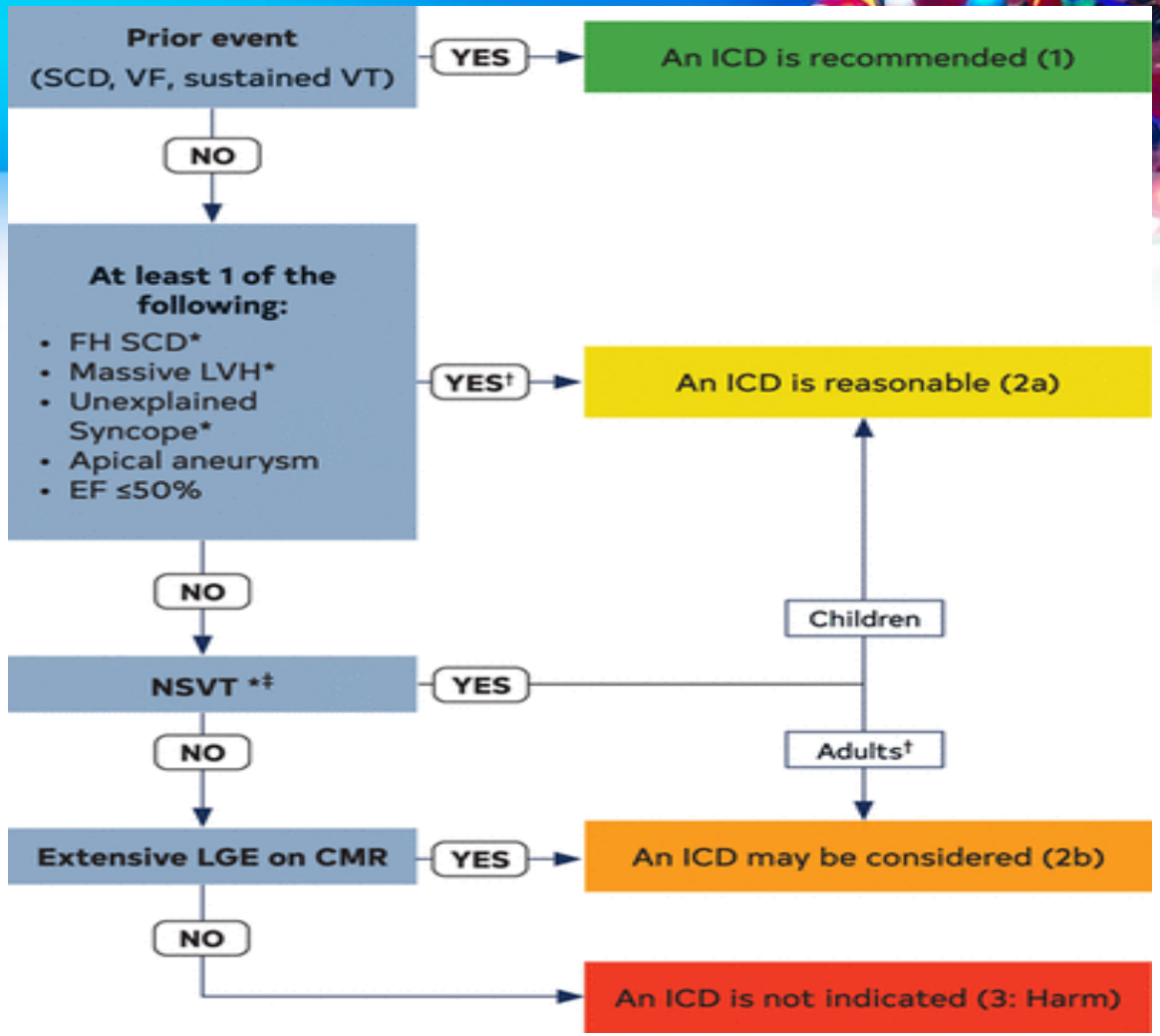
SCD-riskbedömning

Established Clinical Risk Factors for HCM Sudden Death Risk Stratification

Family history of sudden death from HCM	Sudden death judged definitively or likely attributable to HCM in ≥1 first-degree or close relatives who are ≤50 y of age. Close relatives would generally be second-degree relatives; however, multiple SCDs in tertiary relatives should also be considered relevant.
Massive LVH	Wall thickness ≥30 mm in any segment within the chamber by echocardiography or CMR imaging; consideration for this morphologic marker is also given to borderline values of ≥28 mm in individual patients at the discretion of the treating cardiologist. For pediatric patients with HCM, an absolute or z-score threshold for wall thickness has not been established; however, a maximal wall that corresponds to a z-score ≥20 (and >10 in conjunction with other risk factors) appears reasonable.
Unexplained syncope	≥1 Unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology, nor attributable to LVOTO, and especially when occurring within 6 mo of evaluation (events beyond 5 y in the past do not appear to have relevance).
HCM with LV systolic dysfunction	Systolic dysfunction with EF <50% by echocardiography or CMR imaging.
LV apical aneurysm	Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the LV chamber; independent of size.
Extensive LGE on CMR imaging	Diffuse and extensive LGE, representing fibrosis, either quantified or estimated by visual inspection, comprising ≥15% of LV mass (extent of LGE conferring risk has not been established in children).
NSVT on ambulatory monitor	It would seem most appropriate to place greater weight on NSVT as a risk marker when runs are frequent (≥3), longer (≥10 beats), and faster (≥200 bpm) occurring usually over 24 to 48 h of monitoring. For pediatric patients, a VT rate that exceeds the baseline sinus rate by >20% is considered significant.

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy | Circulation (ahajournals.org)

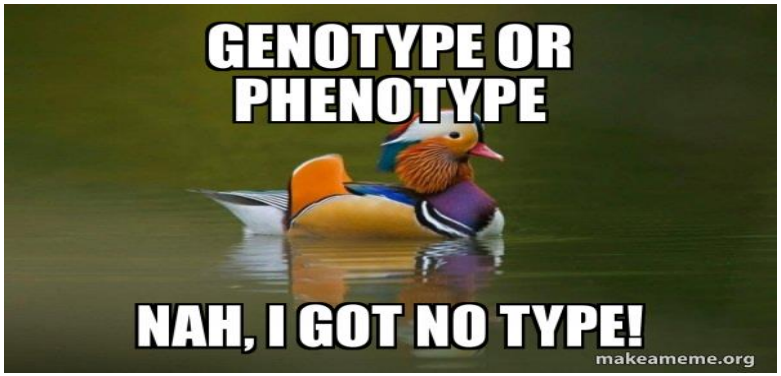
ICD-kandidater



Steve R. Ommen. Circulation. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy, Volume: 142, Issue: 25, Pages: e558-e631, DOI: (10.1161/CIR.0000000000000937)

Kan de genetiska fynden förutsäga sjukdomsförlopp?

1.Ja
2. Nej



Genotyp-fenotyp relation

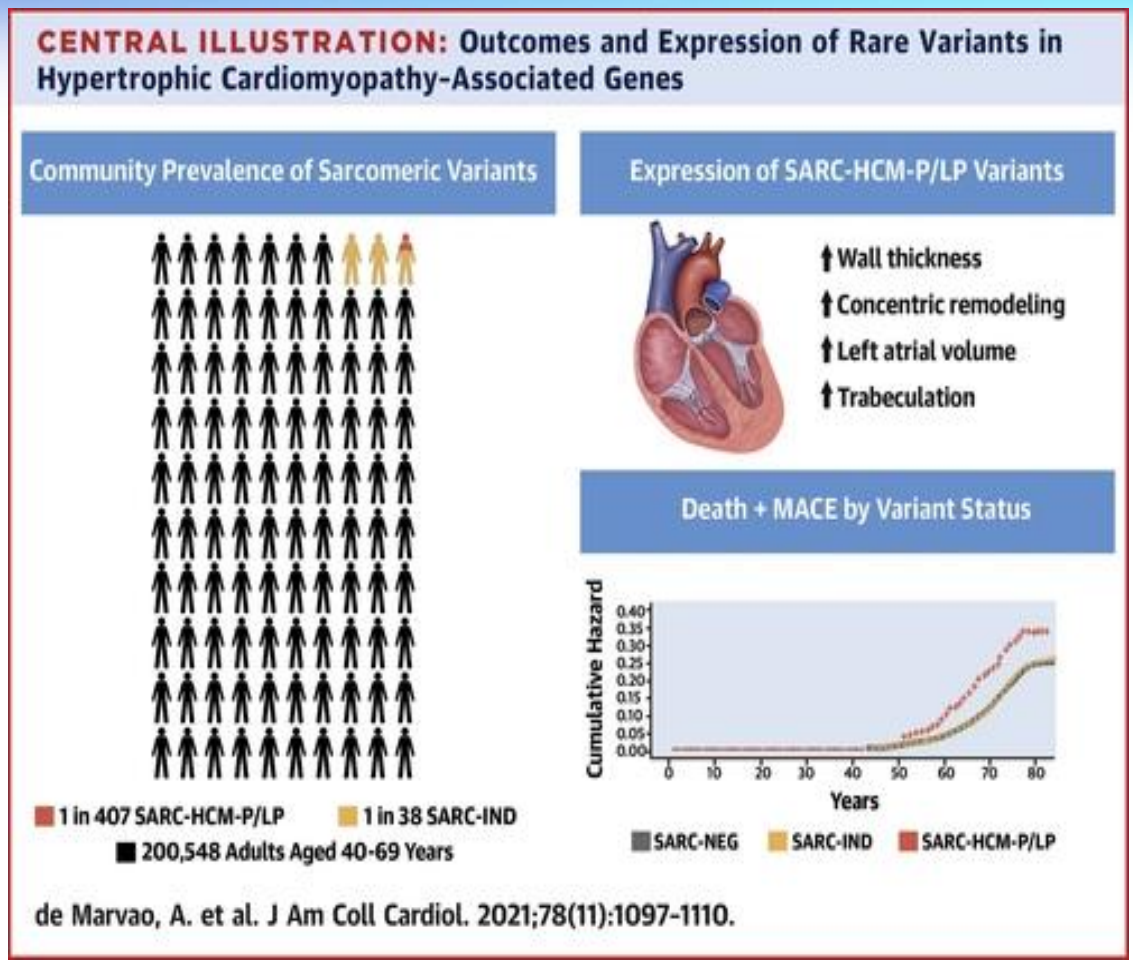
- Patienter som **bär på patogena sarkomera** varianter:

❑ yngre ålder
❑ fler fall med HCM i familjen, ärftlighet för plötslig hjärtdöd och
❑ större maximal väggtjocklek

- Jämförelse av **tjocka** (MYBPC3, MHY7, MYL2) och **tunna** (TNNT2, TNNI3, TPM1, ACTC) filament: mildare och atypiskt fördelad hypertrofi i tunna filament och ökad risk för hjärtsvikt
- TNNT2-mutationer :relativt mild hypertrofi, men dålig prognos
- MYBPC3-varianter: mer gynnsam prognos och sendebut
- >1 sjudomsorsakande varianter ökad risk att drabbas av plötslig hjärtdöd
- DOCK! Stora skillnaderna både inom och mellan familjer med varianter i samma gen

Det genetiska testresultatets roll i riskstratifiering är osäker och används därför inte kliniskt i detta syfte

Phenotypic Expression and Outcomes in Individuals With Rare Genetic Variants of Hypertrophic Cardiomyopathy



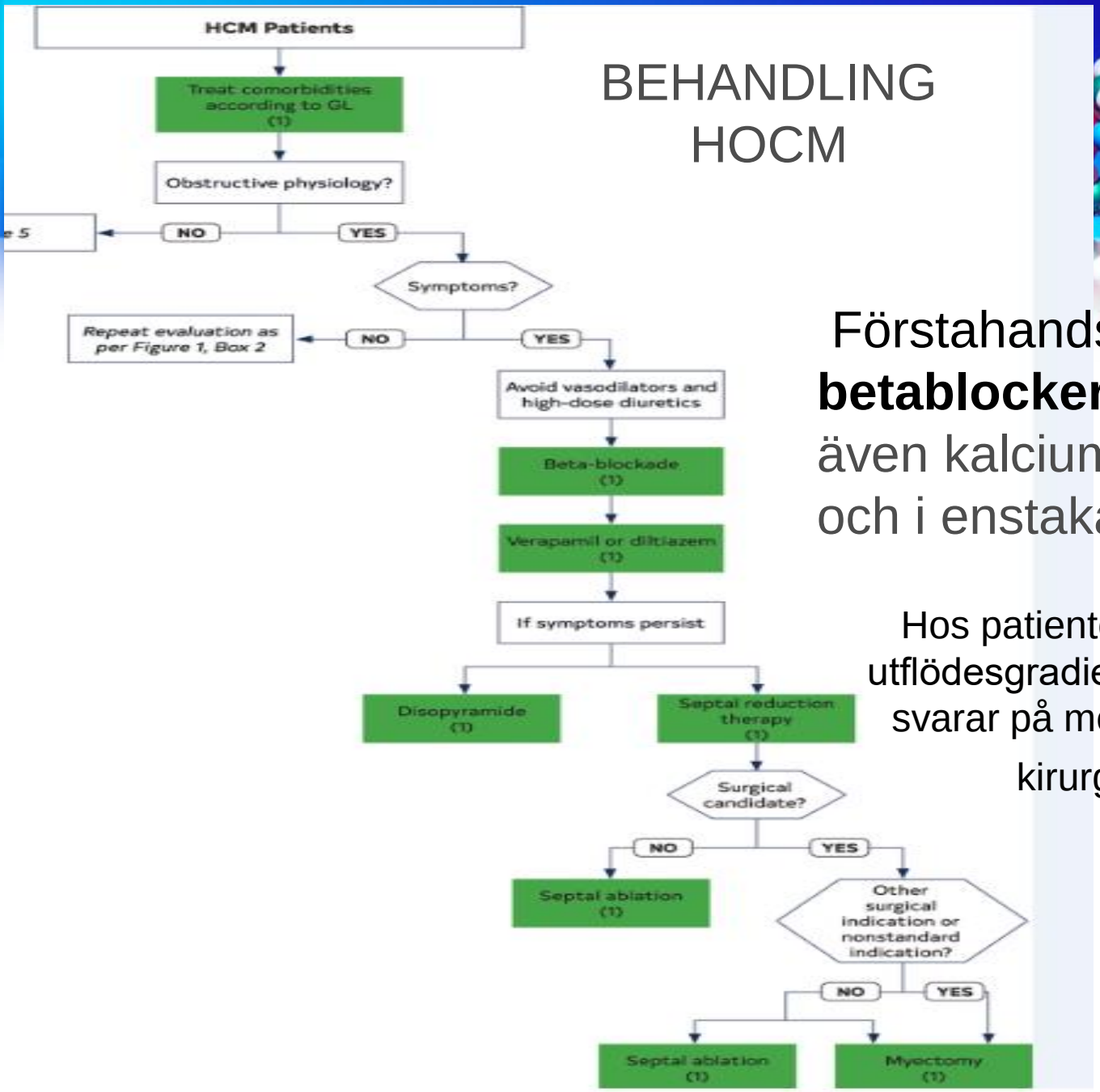
In subjects harboring SARC-HCM-P/LP variants, LVH ≥13 mm was present 18.4%

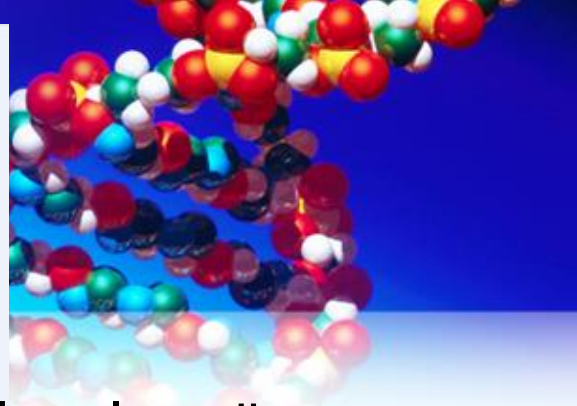
SARC-IND variants 2.9% had WT ≥13 mm.

Most individuals with pathogenic sarcomeric variants do not have overt HCM, but a subclinical phenotype is associated with an increased risk of adverse cardiovascular events.

Antonio de Marvao et al. *J Am Coll Cardiol* 2021; 78:1097-1110.

BEHANDLING HOCM





Förstahandsval utgörs av **betablockerare**

även kalciumflödeshämmare och i enstaka fall disopyramid

Hos patienter med symtomgivande utflödesgradient (≥50 mm Hg) som inte svarar på medicinsk behandling kan kirurgisk intervention

Läkemedel att undvika vid utlödesobstruktion

- Perifert vasodilaterande,
- positivt inotropa och
- diuretiska läkemedel, som alla kan förvärra en utflödesobstruktion:

Nitrater
ACE-hämmare/Angiotensinreceptorblockerare
Vissa kalciumhämmare (nifedipin, amlodipin, felodipin)
Alfablockerare (t ex doxazosin)
PDE-5-inhibitorer (t ex sildenafil, tadalafil och vardenafil)
Positivt inotropa läkemedel (t ex digoxin, dobutamin, dopamin)
Furosemid och andra diuretika (annat än i låg dos)

- De med HOCM och uttalad hypotoni som ej svarar på vätska ge iv **fenylefrin** eller annan vasokonstriktor utan inotrop effekt
- De med HOCM och vilo-dyspné , hypotoni, LVOT **gradient>100mmHg ge ej Verapamil**

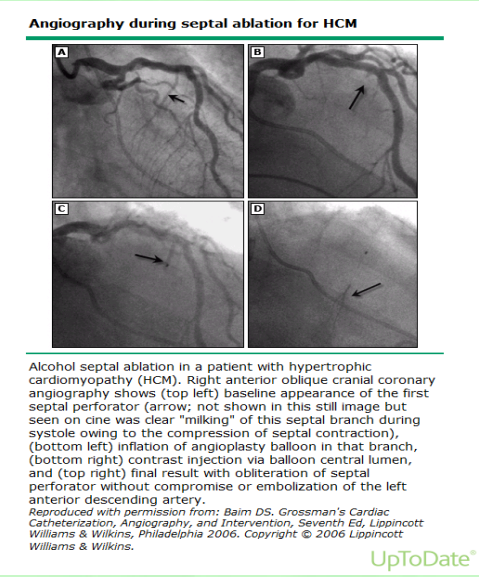
Icke farmakologiskt terapi

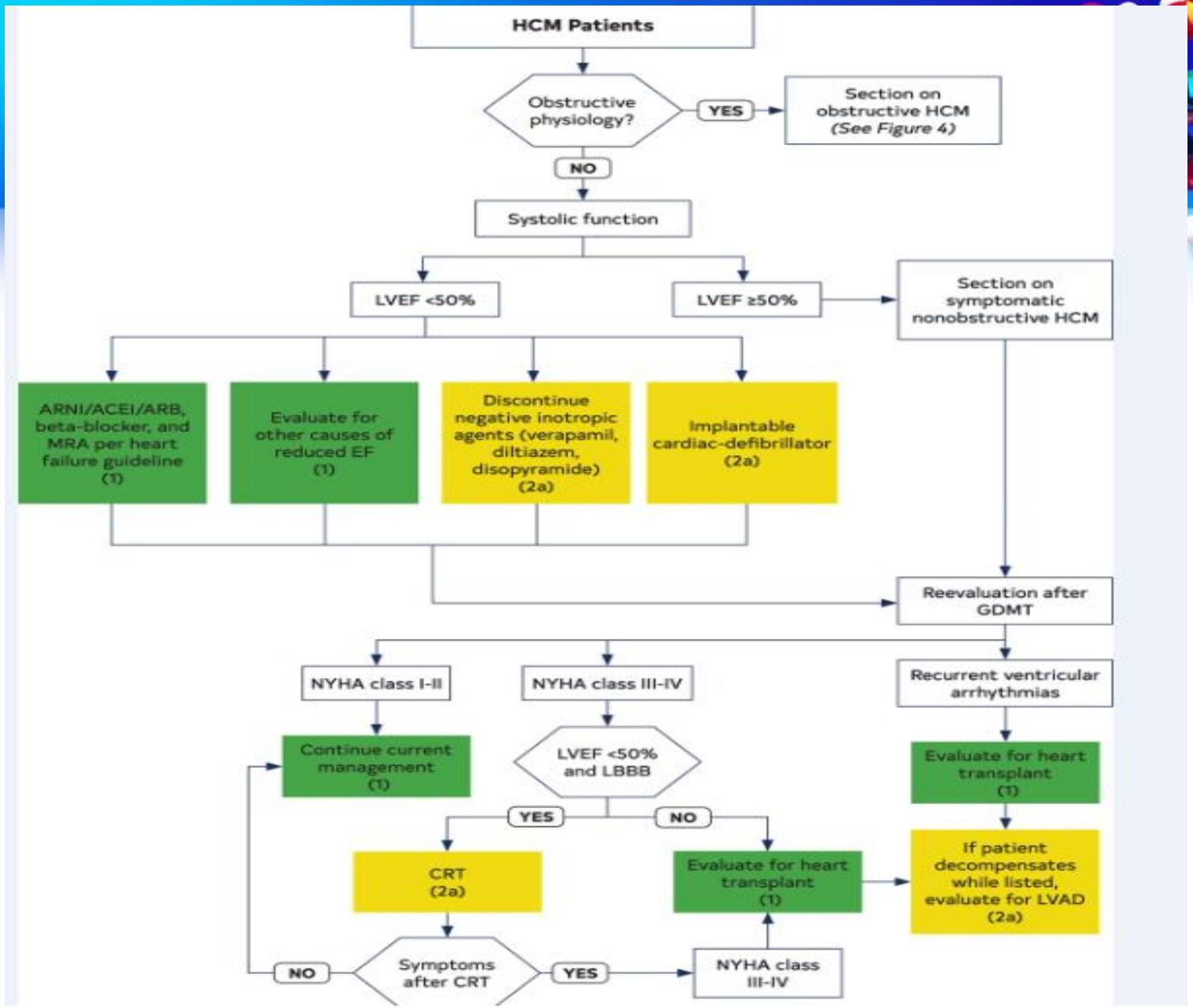
- Vid betydande hjärtsviktssymtom NYHA klass III / IV trots maximal medicinsk behandling eller
- återkommande synkope och
- ett LVOT ≥50 mmHg vid vila eller provokation

Myektomi-Komplikationer
Ventrikelseptumdefekt 2%
Utveckling av vänstergrenblock (LBBB) eller fullständigt hjärtblock 5%

Alkohol- ablation- Komplikationer
- ❑ Kranskärls dissektion,
- ❑ Perikardexsudat
- ❑ Stor hjärtinfarkt
- ❑ Komplett hjärtblock
- ❑ Kammartakyarytmier, arytmidöd

Pacemakerterapi
Dual chamber (RA och RV) stimulering





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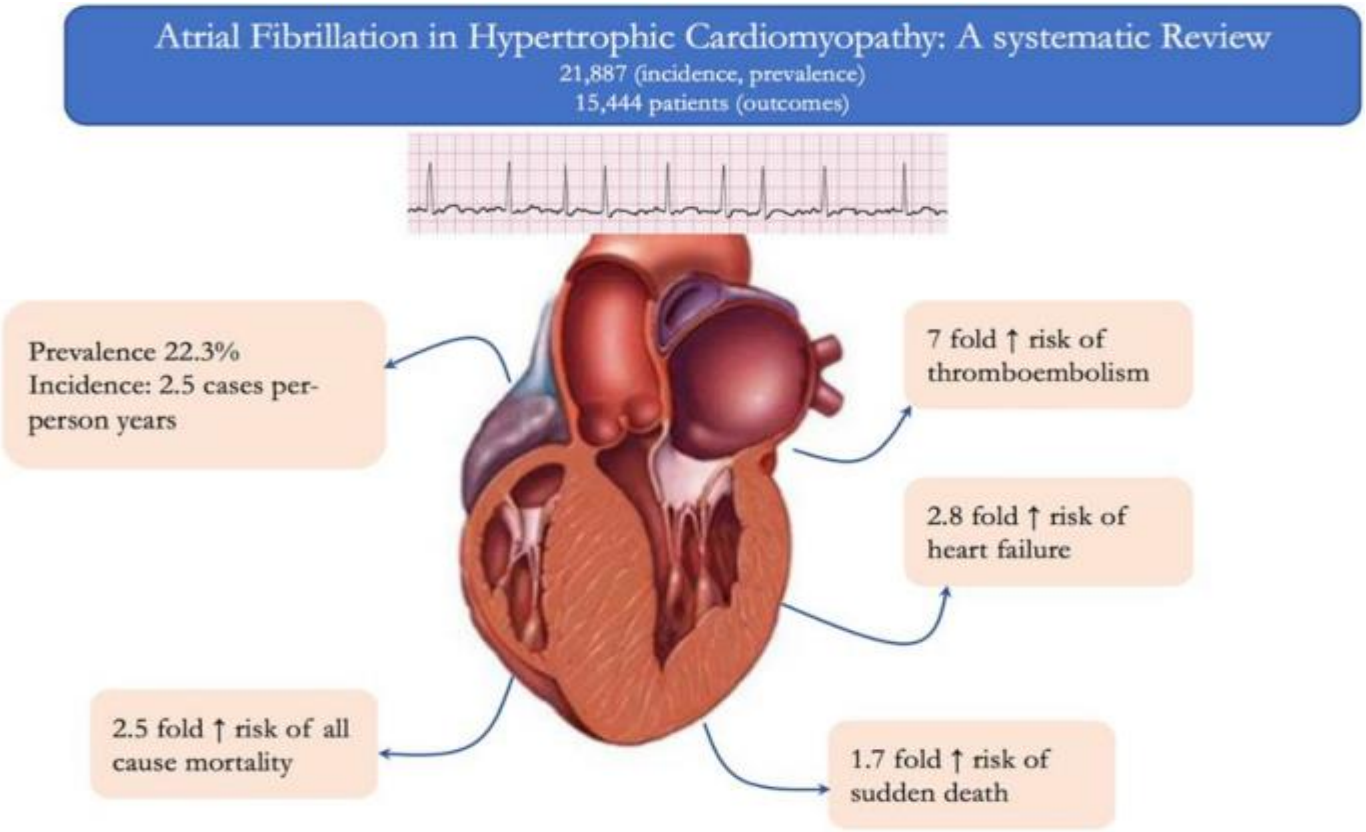
Vid förekomst av Förmaksflimmer hos HCM patienter

Man bör ge NOAK/OAK enligt CHA2DS2-Vasc

1. YA
2. NEJ



Förmaksflimmer och HCM

FF 4-6 gånger högre hos HCM
Riskfaktorer

- Uttalad och diffus hypertrofi
- Fibros
- Förmaksdiameter (> 40 mm)
- Stigande ålder
- Hjärtsviktsymtom

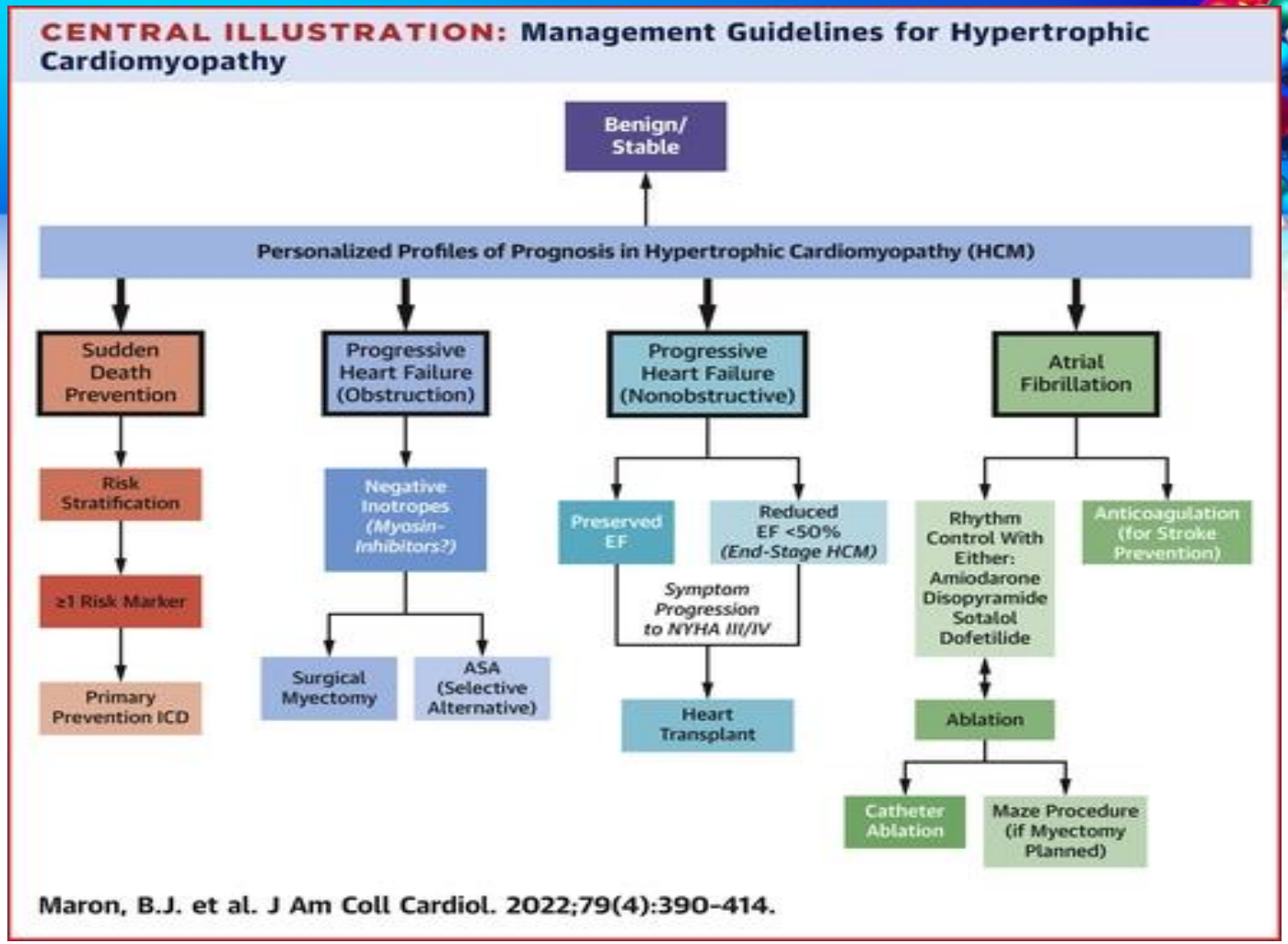
Förekomst eller svårighetsgrad LVOT gradient **inte** är förknippad med en ökad förekomst av FF

Sotalol, Cordarone ge inte digoxin
Eftersom patienter med HCM är inte inkluderade i de flesta kliniska prövningar av trombosprofylax i AF, kan CHA2DS2-Vasc **inte användas** för att avgöra behovet av antikoagulation

även de med isolerade korta episoder av FF bör behandlas med NOAK

1	B-NR	1. In patients with HCM and clinical AF, anticoagulation is recommended with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option, independent of CHA_2DS_2-VASc score.[249-253]
1	C-LD	2. In patients with HCM and subclinical AF detected by internal or external cardiac device or monitor of >24 hours' duration for a given episode, anticoagulation is recommended with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option, independent of CHA_2DS_2-VASc score.[102,103,249,254]
1	C-LD	3. In patients with AF in whom rate control strategy is planned, either beta blockers, verapamil, or diltiazem are recommended, with the choice of agents according to patient preferences and comorbid conditions.[104,255]
2a	C-LD	4. In patients with HCM and subclinical AF detected by internal or external device or monitor, of >5 minutes' but <24 hours' duration for a given episode, anticoagulation with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option can be beneficial, taking into consideration duration of AF episodes, total AF burden, underlying risk factors, and bleeding risk.[102,103,249,254,256]
2a	B-NR	5. In patients with HCM and poorly tolerated AF, a rhythm control strategy with cardioversion or antiarrhythmic drugs can be beneficial with the choice of an agent according to AF symptom severity, patient preferences, and comorbid conditions.[104,210,257-268]

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy | Circulation (ahajournals.org)



Barry J. Maron et al. *J Am Coll Cardiol* 2022; 79:390-414.

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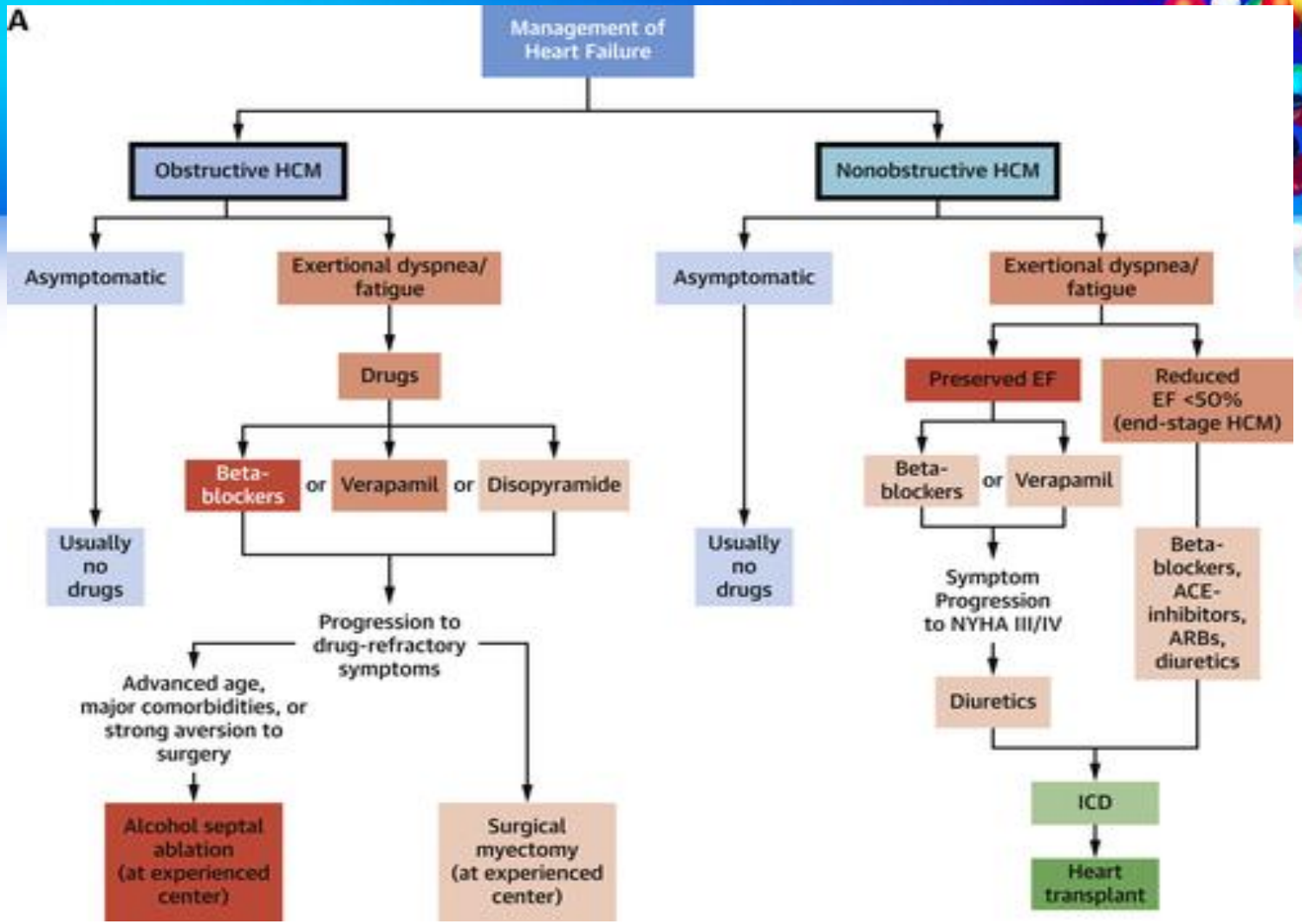

Barry J. Maron et al. *J Am Coll Cardiol* 2022; 79:390-414.

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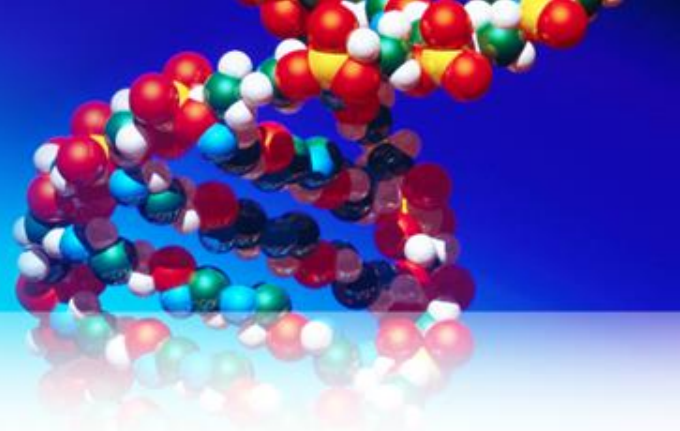
Uppföjlning av HCM patienter



•Återbesök med 1-2 års intervall i stabilt skede, med vilo-EKG, långtids-EKG och ekokardiografi

•Om vänster förmak är förstorat (≥ 45 mm diameter) rekommenderas långtids-EKG varje 6-12 månader

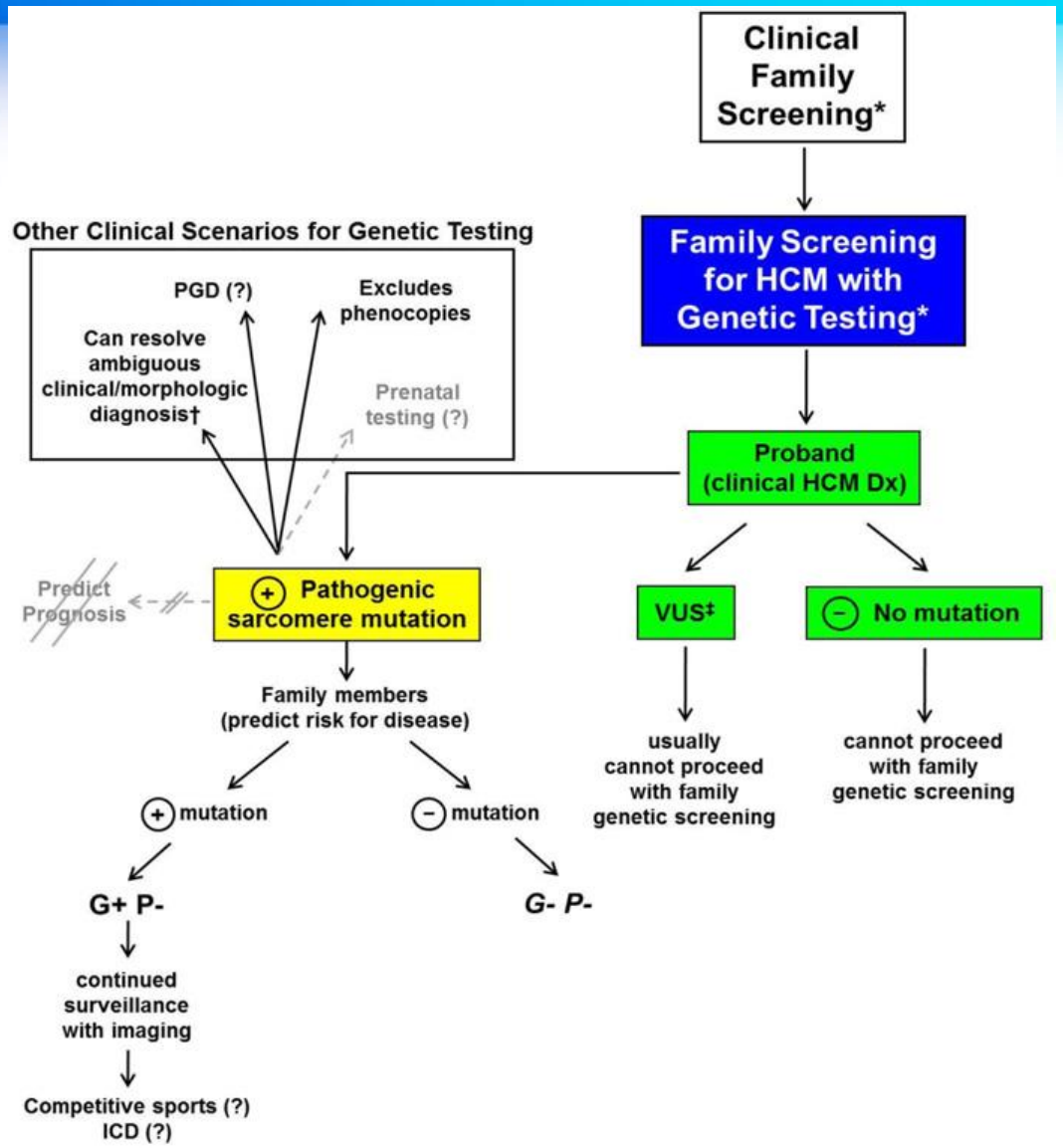
•Arbets-EKG med 2-3 års intervall

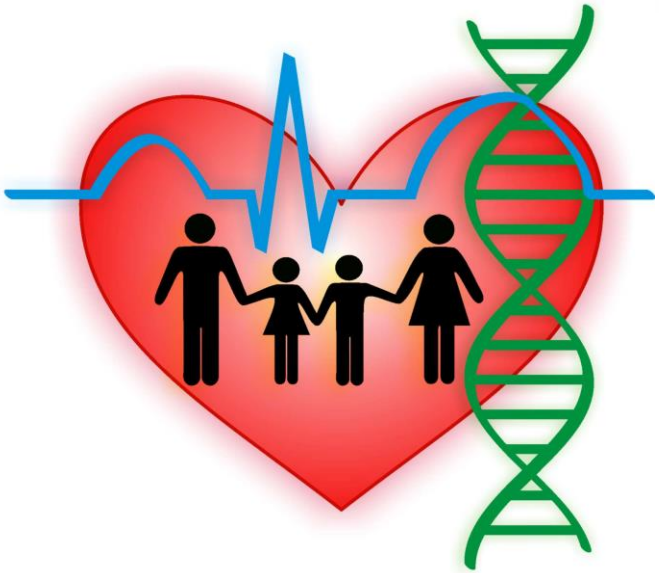
•Återkommande riskvärdering avseende ICD görs med 1-2 års intervall hos patienter som inte har ICD, men kan komma ifråga för sådan om indikation finns

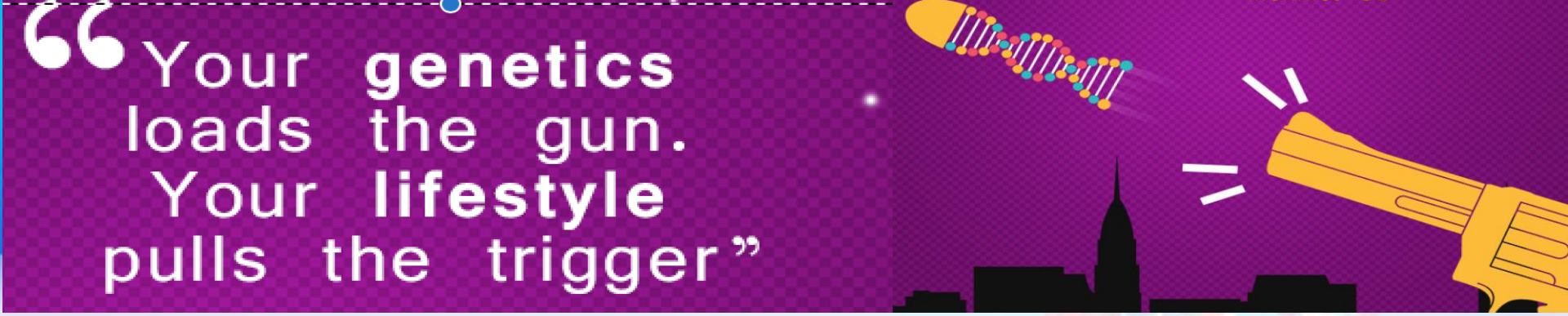
•Tätare undersökningar och ytterligare utredningar kan motiveras vid nytillkomna symtom eller kliniska händelser

1	B-NR	1. For most patients with HCM, mild- to moderate-intensity recreational* exercise is beneficial to improve cardiorespiratory fitness, physical functioning, and quality of life, and for their overall health in keeping with physical activity guidelines for the general population.[292–294]
1	C-EO	2. For athletes with HCM, a comprehensive evaluation and shared discussion of potential risks of sports participation by an expert provider is recommended.[295]
2a	C-EO	3. For most patients with HCM, participation in low-intensity competitive sports is reasonable.[2,297]
2a	C-LD	4. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive athletics of any intensity is reasonable.[2,174,297–301]
2b	C-LD	5. For patients with HCM, participation in high-intensity recreational activities or moderate- to high-intensity competitive sports activities may be considered after a comprehensive evaluation and shared discussion, repeated annually with an expert provider who conveys that the risk of sudden death and ICD shocks may be increased, and with the understanding that eligibility decisions for competitive sports participation often involve third parties (eg, team physicians, consultants, and other institutional leadership) acting on behalf of the schools or teams.[174,295,298–301]
3: Harm	B-NR	6. In patients with HCM, ICD placement for the sole purpose of participation in competitive athletics should not be performed.[2,174,302]

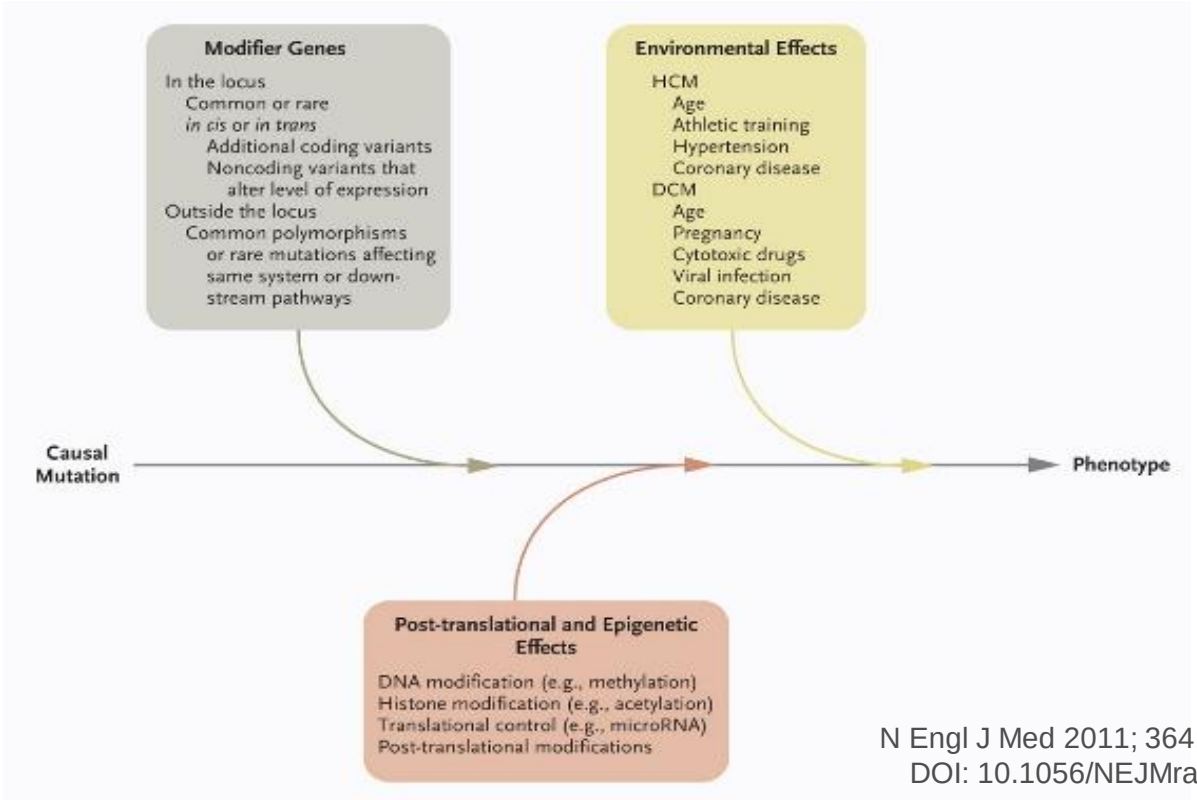
Viktigt att identifiera de som är i riskzonen inom en familj och ge adekvat uppföljning, utbildning, och behandling







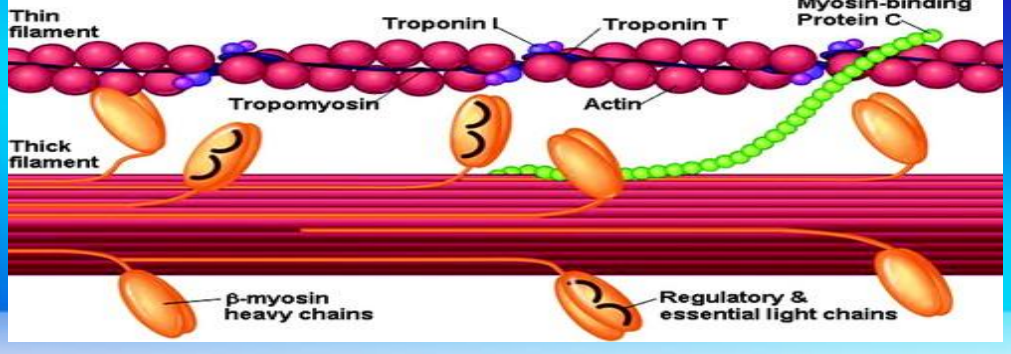
Nedsatt penetrans och även variabel expressivitet

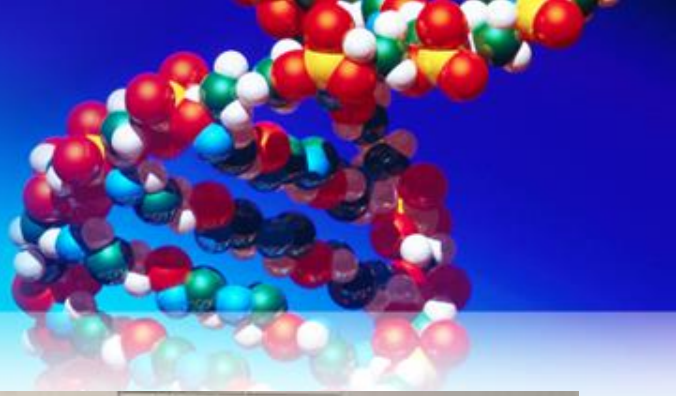


Inte alla individer med en mutation i en av de HCM-generna kommer att uttrycka den kliniska bilden av HCM

Det kliniska uttrycket visar stora variationer, vilket delvis kan hänföras till den genetiska heterogeniteten

N Engl J Med 2011; 364:1643-1656
DOI: 10.1056/NEJMra0902923





Age
Genetic Modifiers
Lifestyle
Comorbidities

LV Outflow Obstruction
β-blockers/CCB/Disopyramide
Invasive Septal Reduction

Sarcomeric Variant

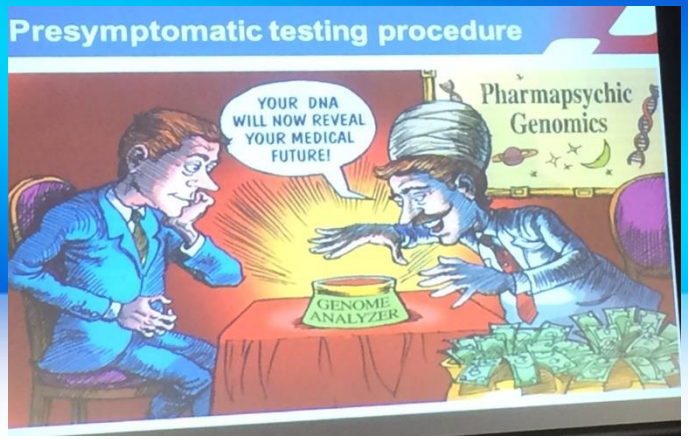
Primary Effects
Small LV Cavity
Hypercontractility
Diastolic Abnormalities
Fibrosis
Impaired Energetics

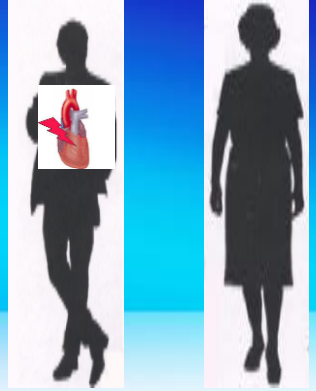
Overt HCM
Adverse Remodeling/ Outcomes
Symptoms

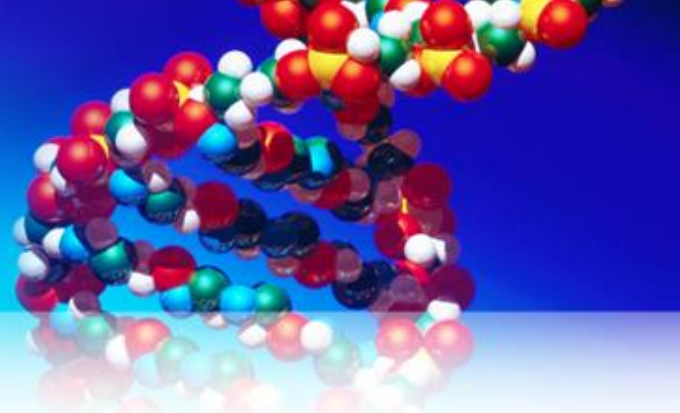
Ventricular Arrhythmias
ICD

Atrial Fibrillation
Anticoagulation
Rate/rhythm control

Advanced Remodeling
Heart Failure Rx
Transplant

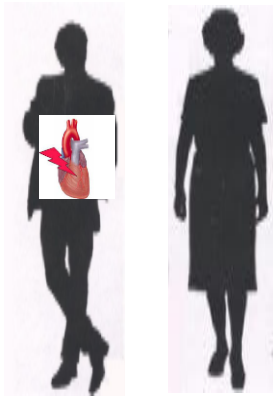


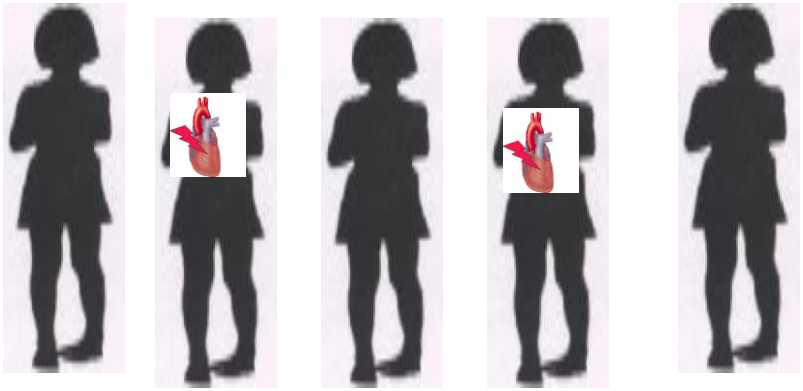




Kaskadscreening

I första hand är det föräldrar, syskon och barn till patienten, dvs förstagradssläktingarna





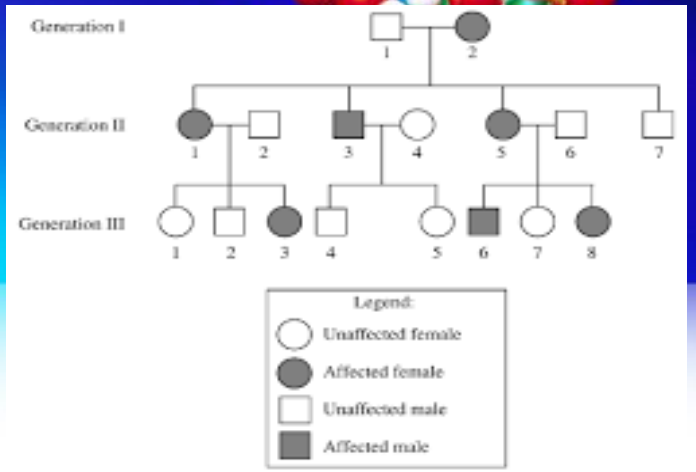
Rekommendationer om genetisk vägledning och testning hos HCM patient

Recommendations	Class[a]	Level[b]	Ref.[c]
Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.	I	B	24,175 178–180
It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.	I	C	168,172,183
In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis.	I	B	36–40, 43–46,67
Genetic testing in patients with a borderline[d] diagnosis of HCM should be performed only after detailed assessment by specialist teams.	IIa	C	168
Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.	IIa	C	181,182

Recommendations	Class[a]	Level[b]	Ref.[c]
Genetic counselling is recommended for all patients with HCM when their disease cannot be explained solely by a non-genetic cause, whether or not clinical or genetic testing will be used to screen family members.	I	B	169–173
Genetic counselling should be performed by professionals trained for this specific task working within a multidisciplinary specialist team.	IIa	C	168–173

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy | European Heart Journal | Oxford Academic (oup.com)

Inför genetisk provtagning- Pre-gentest

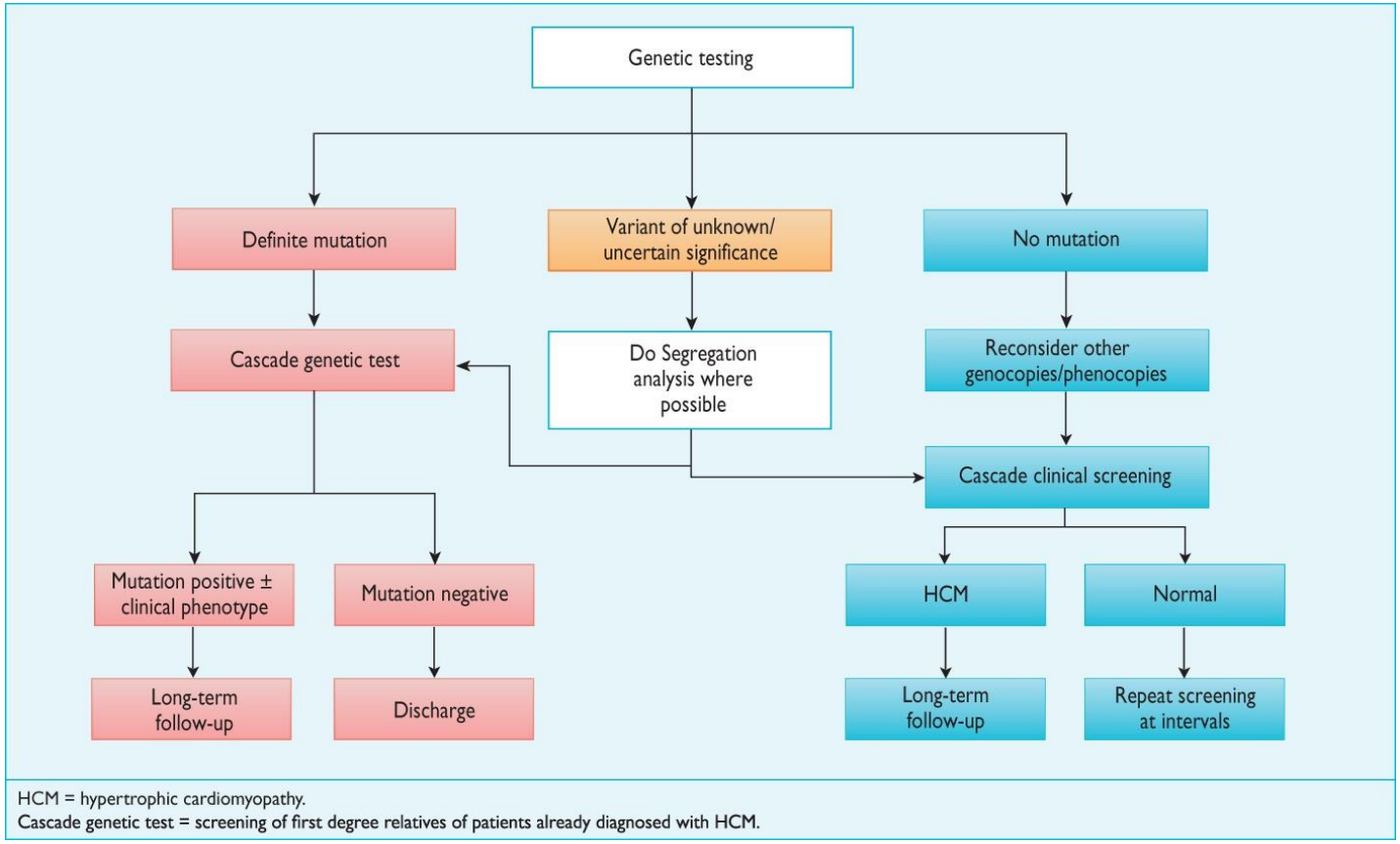


- Viktigt med en 3-generations familjehistoria
- Alla patienter bör erhålla noggrann information innan en eventuell provtagning genomförs
- Detta erbjuds via kardiogenetiska mottagningar som numera även finns på en del regionala sjukhus och inte enbart vid universitetssjukhus
- Det är upp till varje individ att avgöra om en genetisk analys ska göras eller ej. För barn gäller målsman
- I Sverige ansvarar probanden (det vill säga personen hos vilken mutationen först upptäcks) själv för att dennes familjemedlemmar får information om möjligheter till presymtomatisk diagnostik

Genetisk vägledning och testning rekommenderas

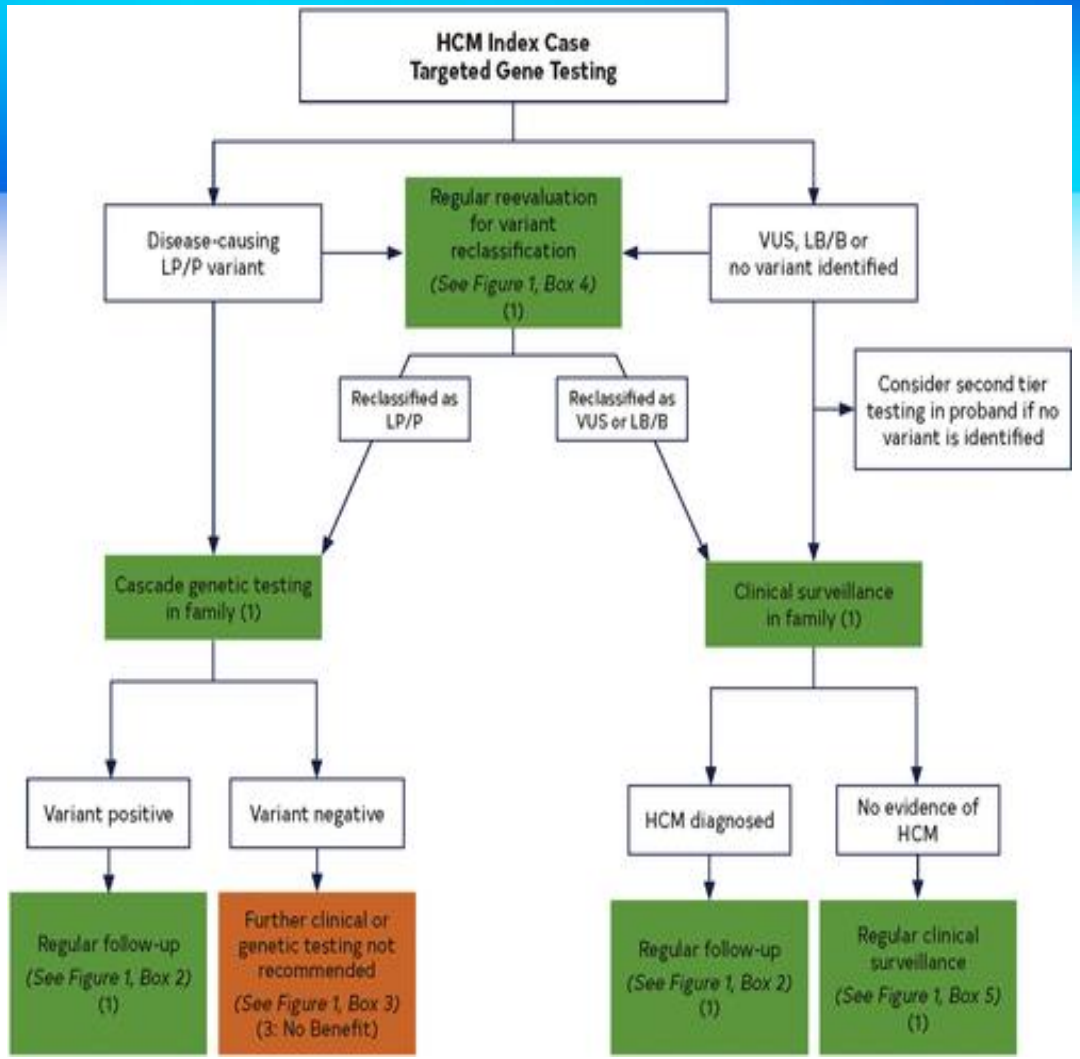
a. Till förstagradssläktingar när index patient har en identifierad mutation
b. Till alla patienter med kammarhypertrofi
c. Till förstagradssläktingar även när en genetisk variant av oklar betydelse finns hos index

Figure 4 Flow chart for the genetic and clinical screening of probands and relatives.



HCM = hypertrophic cardiomyopathy.
Cascade genetic test = screening of first degree relatives of patients already diagnosed with HCM.

Eur Heart J, Volume 35, Issue 39, 14 October 2014, Pages 2733-2779, https://doi.org/10.1093/eurheartj/ehu284



Eftersom screeningen av familjemedlemmar är beroende av patogeniciteten hos de upptäckta varianter, bör den rapporterade patogeniciteten bekräftas vartannat till vart tredje år

Klinisk screening är inte indicerad hos genotypnegativa släktingar i familjer med genotyppositiv HCM, såvida inte den sjukdomsalstrande varianten nedgraderas till VUS/benign variant under uppföljningen

Steve R. Ommen et al. *J Am Coll Cardiol* 2020; 76:3022-3055.

Genotyp positiva-fenotyp negativa bör

a. följas upp årligen till 20års ålder och därefter varje 2-5 år
b. inte kontrolleras alls
c. få betablockad

Rekommendationer om genetisk and klinisk kontroll hos familjemedlemmarna

Recommendations	Class[a]	Level[b]	Ref.[c]
Cascade genetic screening, after pre-test counselling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation.	I	B	24,175,178–180
Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives who have the same definite disease-causing mutation as the proband.[d]	I	C	168
First-degree relatives who do not have the same definite disease-causing mutation as the proband[d] should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.	IIa	B	34,185,186,189
When no definite genetic mutation is identified in the proband[d] or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2–5 years (or 6–12 monthly if non-diagnostic abnormalities are present).	IIa	C	168,185,187,188

Recommendations	Class[a]	Level[b]	Ref.[c]
The children of patients with a definite disease-causing mutation should be considered for predictive genetic testing—following pre-test family counselling—when they are aged 10 or more years and this should be carried out in accordance with international guidelines for genetic testing in children.	IIa	C	168,190,192
In first-degree child relatives aged 10 or more years, in whom the genetic status is unknown, clinical assessment with ECG and echocardiography should be considered every 1–2 years between 10 and 20 years of age, and then every 2–5 years thereafter.	IIa	C	168
If requested by the parent(s) or legal representative(s), clinical assessment with ECG and echocardiography may precede or be substituted for genetic evaluation after counselling by experienced physicians and when it is agreed to be in the best interests of the child.	IIb	C	
When there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity, clinical or genetic testing of first-degree child relatives before the age of 10 years may be considered.	IIb	C	168

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy | European Heart Journal | Oxford Academic (oup.com)

Rekommendationer avseende kliniska kontroller varierar

- Tidigare screenat familjemedlemmar **efter 10 års** ålder pga debut av klinisk HCM i tonåren/ung vuxen ålder
- I de nya amerikanska riktlinjerna **finns inte längre någon nedre** åldersgräns
- Hos barn/ungdomar med patogen mutation

men inte har utvecklat sjukdomen än, samt de från familjer där HCM debuterat tidigt, rekommenderas klinisk uppföljning med EKG och ultraljud av hjärtat varje 1-2 år

- Hos alla andra barn och ungdomar rekommenderas kontroller med 2-3 års intervall. Kontroller vart 3-5 år hos vuxna
- Screeningintervallet kan

modifieras, vid tillkomst av nya symtom eller i familjer med elakartad sjukdomsutveckling

Screening Asymptomatic First-Degree Relatives of Patients With HCM		
Age of First-Degree Relative	**Initiation of Screening**	**Surveillance Interval**
Children and adolescents from genotype-positive family and/or family with early onset HCM	At the time of diagnosis in another family member	Every 1-2 y
All other children and adolescents	At any time after the diagnosis in the family, but no later than puberty	Every 2-3 y
Adults	At the time of diagnosis in another family member	Every 3-5 y

Steve R. Ommen et al. *J Am Coll Cardiol* 2020; 76:3022-3055.

Genotyp positiv-Fenotyp negativ

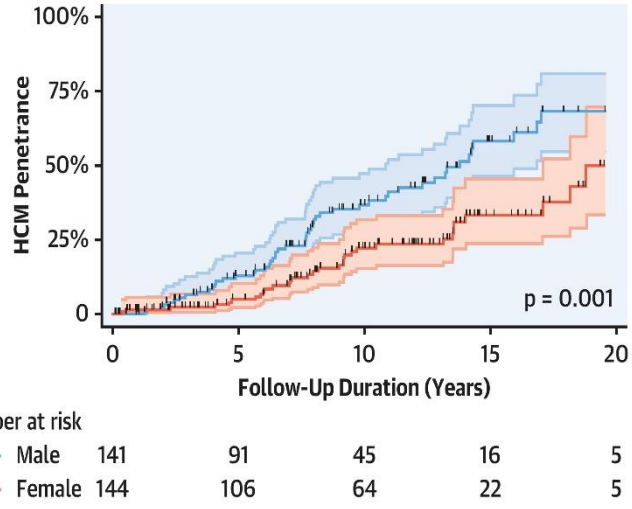
Recommendations for Individuals Who Are Genotype-Positive, Phenotype-Negative
Referenced studies that support the recommendations are summarized in Online Data Supplement 10.

COR	LOE	Recommendations
1	B-NR	1. In individuals who are genotype-positive, phenotype-negative for HCM, serial clinical assessment, electrocardiography, and cardiac imaging are recommended at periodic intervals depending on age (every 1 to 2 years in children and adolescents, and every 3 to 5 years in adults) and change in clinical status.[28,67,69–71] (Figure 1 and Figure 2, Table 6)
2a	C-LD	2. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive athletics of any intensity is reasonable.[132]
3: No benefit	B-NR	3. In individuals who are genotype-positive, phenotype-negative for HCM, ICD is not recommended for primary prevention.[28,69–71,132,145]

CENTRAL ILLUSTRATION: Kaplan-Meier Estimates of Penetrance of Hypertrophic Cardiomyopathy in the Study Cohort by Sex

285 adult and pediatric carriers of pathogenic/likely pathogenic sarcomere protein variants with no hypertrophic cardiomyopathy (HCM)

→ Penetrance of HCM at 15-year follow-up: 46% (95% CI: 38%-54%)



Risk factors for HCM

Male
HR: 2.91
(95% CI: 1.82-4.65)

Abnormal ECG
HR: 4.02
(95% CI: 2.51-6.44)

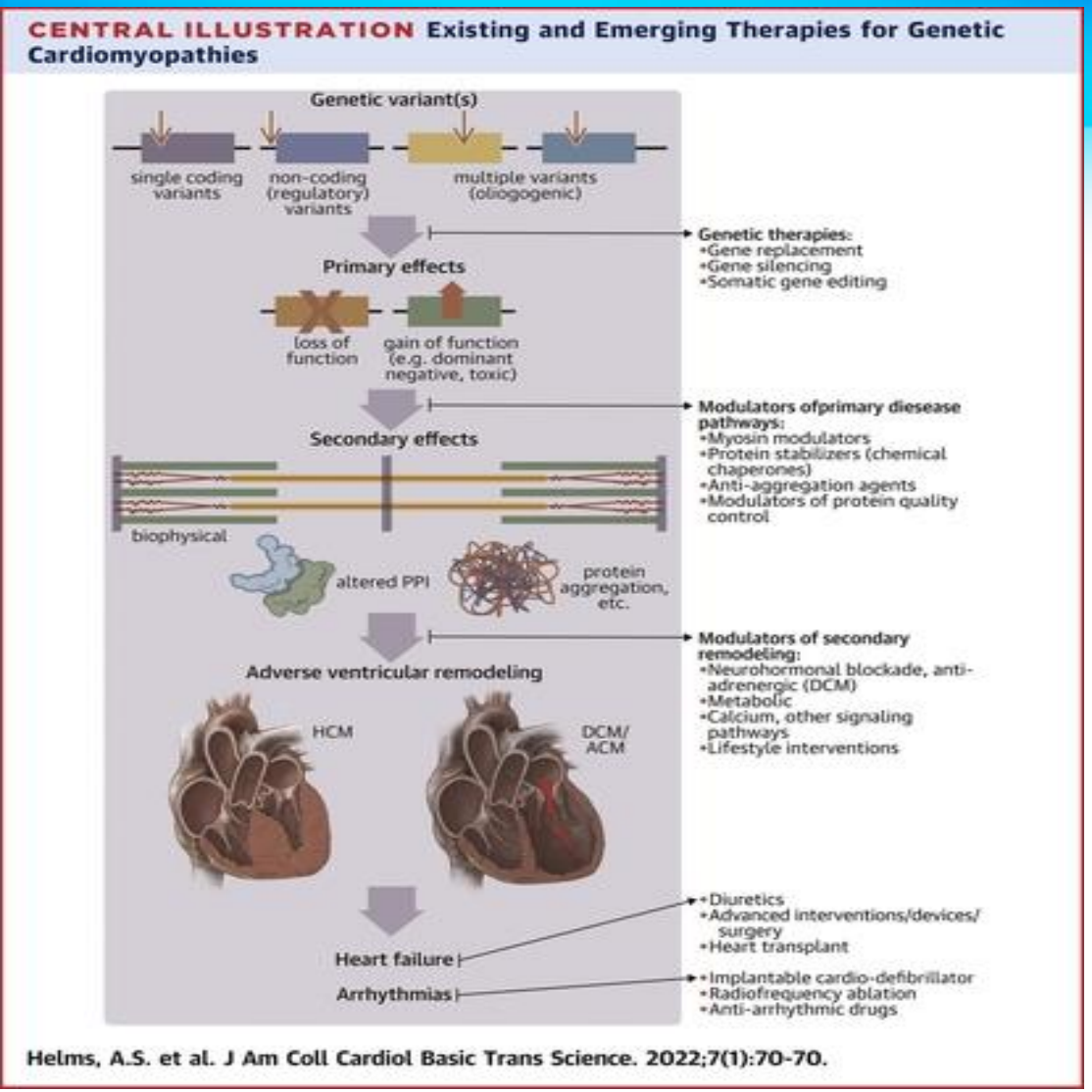
Lowest risk for HCM

TNNI3 variants
HR: 0.19
(95% CI: 0.07-0.55)

Lorenzini, M. et al. J Am Coll Cardiol. 2020;76(5):550-9.

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary | Circulation (ahajournals.org)

Framtida möjligheter

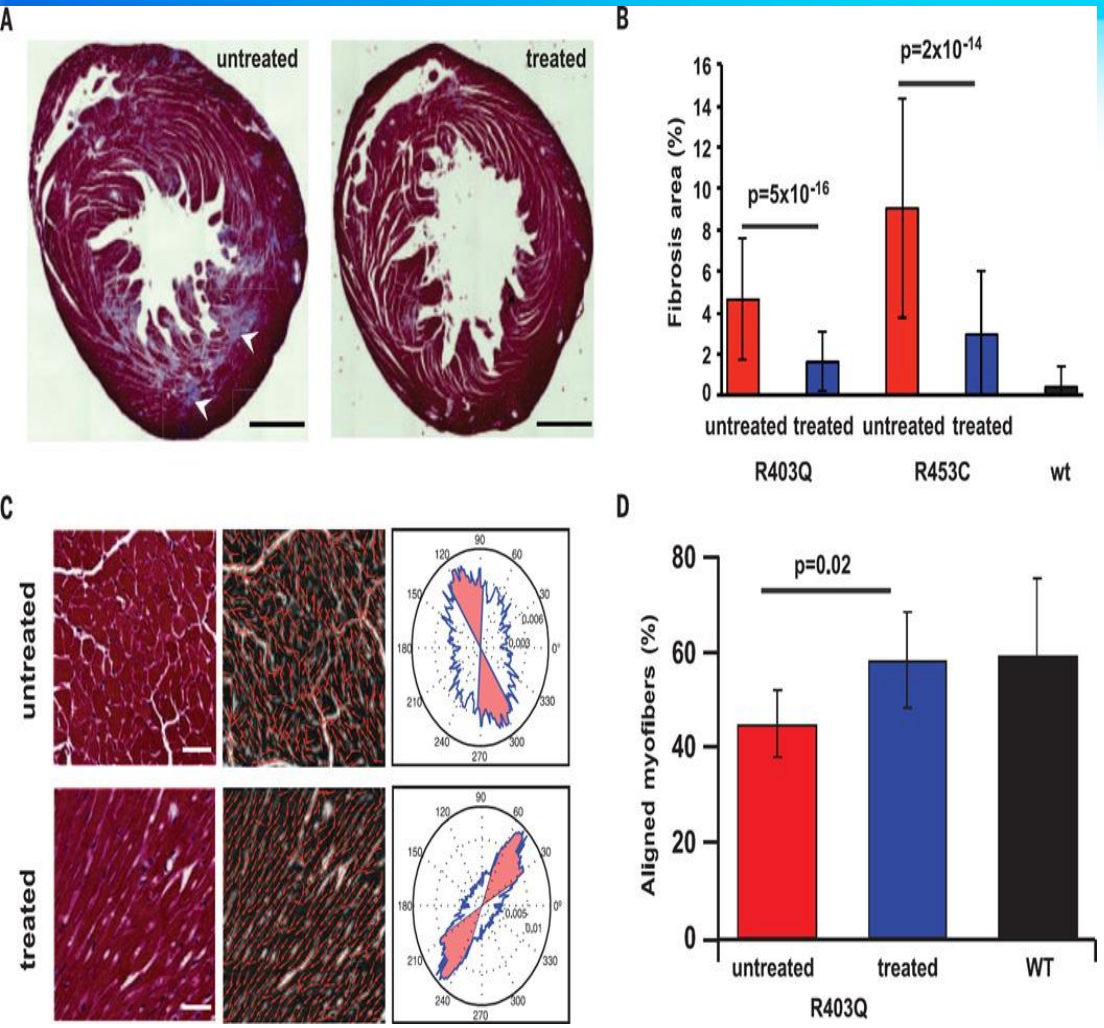


Den genetiska bakgrunden till HCM kan öppna vägar för sjukdomsmodifierande behandling

Adam S. Helms et al. *J Am Coll Cardiol Basic Trans Science* 2021; 7:70-83.

JACC Basic to Translational Science
An Open Access Journal

MYK-461 reduces the development of myocardial disarray and fibrosis in mouse models of HCM



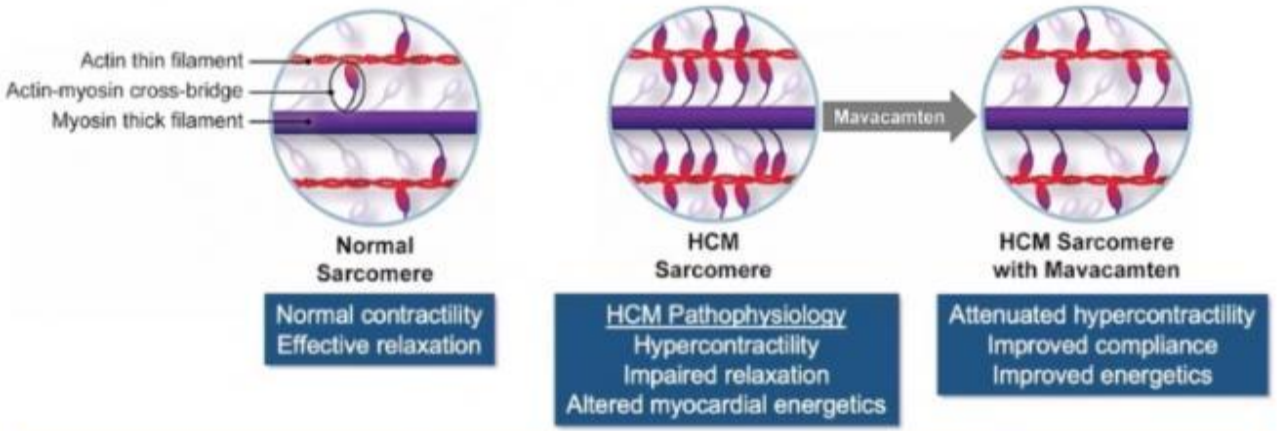
MYK-461 reduces contractility by decreasing the adenosine triphosphatase activity of the cardiac myosin heavy chain.

Early, chronic administration of MYK-461 suppresses the development of ventricular hypertrophy, cardiomyocyte disarray, and myocardial fibrosis and attenuates hypertrophic and profibrotic gene expression **in mice harboring heterozygous human mutations in the myosin heavy chain**

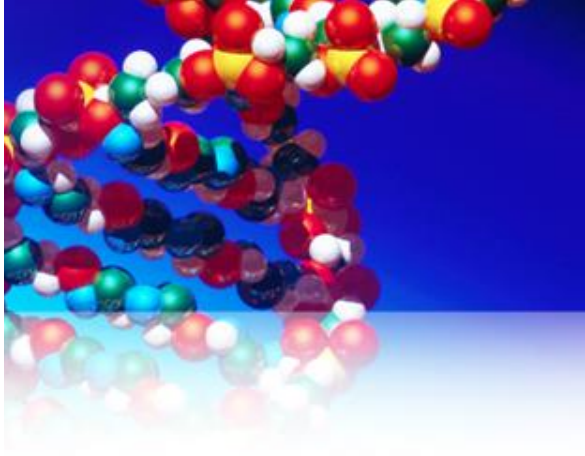
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4784435/

5/2016

Mavacamten: Mechanism of Action



Mavacamten is a targeted inhibitor of cardiac myosin that reduces the number of myosin-actin cross-bridges and decreases contractility



Patienter som erhöll aktiv behandling uppnådde det primära utfallet i 36,6%av fallen, medan i placebogruppen var 17,2 % (P < 0,001)

CAMZYOS
FDA approval April2022

EXPLORER-HCM study design

Multi-national, randomized, double-blind, placebo-controlled

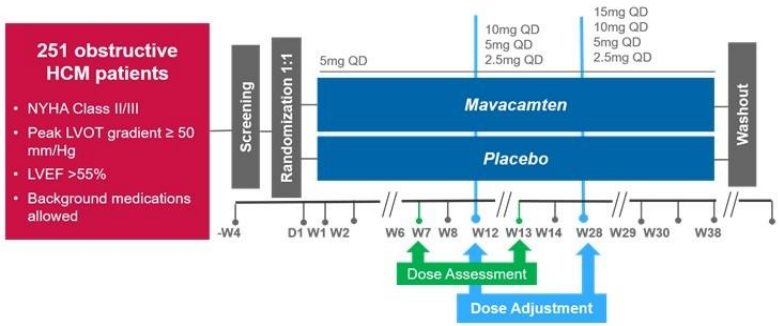
68 clinical sites

13 countries

10 patients enrolled in the U.S.

82 patients enrolled from Europe

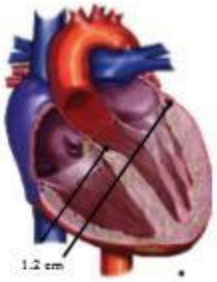
15 patients enrolled from Israel



Hypertrophic Cardiomyopathy

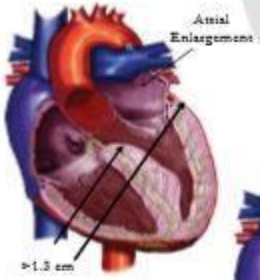
What is HCM? Hypertrophic Cardiomyopathy, (pronounced: Hyper-trō-fic Cardio-my-opathy) HCM, refers to a family of genetic disorders. HCM causes abnormal cell structure and thickening of the heart muscle. Most commonly, the disease involves abnormalities in genes regulating the cardiac contractile function and less commonly, in other genes which alter the normal functioning of the heart muscle.

Normal



How Common is HCM? HCM is a relatively common genetic disorder affecting an estimated 1 in 500 worldwide. Recent data suggests it could be as common as 1 in 200.

Without Obstruction

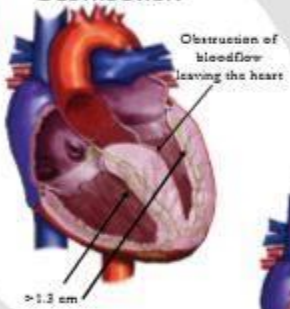


Signs and Symptoms:

- Heart Murmur
- Shortness of breath
- Lightheadedness
- Fainting/Nearly fainting
- Chest, jaw, and neck pain
- Palpitations
- Family history of sudden death <55 yrs

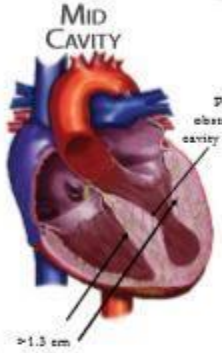
♥ symptoms can range from extremely mild to severe

With Obstruction

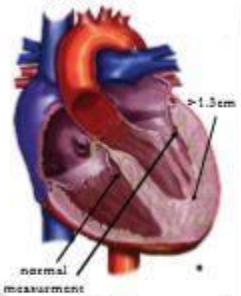


Screening: If you have been diagnosed with HCM all first degree family members should be screened with cardiac imaging, and/or genetic testing, and check up with a cardiologist knowledgeable in HCM.

Mid Cavity



Apical



HCM can come in many patterns. These are a few: *Papillary muscles only shown in some.

Treatment Options

Medications

- Beta-blockers
- Calcium channel blockers
- Norpace/Disopyramide
- Antiarrhythmic drugs
- Diuretics
- Anticoagulants
- Antibiotics
- New medications under investigation

♥ 90% may require medication

Septal Reduction

- Surgery
  - > Septal Myectomy
- Nonsurgical
  - > Alcohol Septal Ablation

♥ 20-25% may require septal reduction therapy

Rhythm Management

- Pacemakers
- Implantable cardiovert defibrillator
- Atrial Fibrillation Ablation

♥ 20% may require ICD
♥ 20% may experience Atrial Fibrillation

Transplant

♥ Approximately 3-5% may require transplant

For more information and support contact:

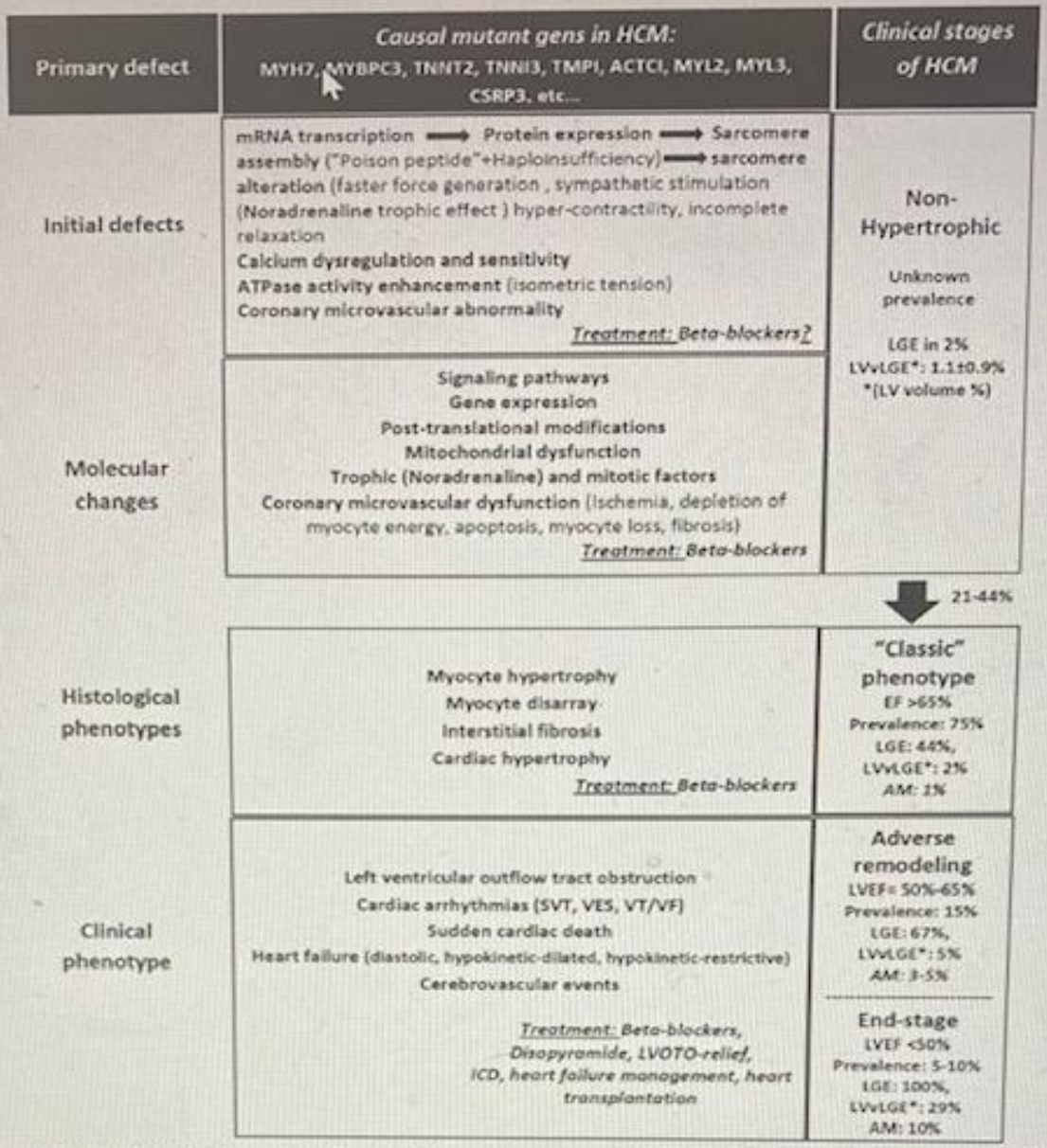
Hypertrophic Cardiomyopathy Association

18 E Main St
Suite 202
Denville, NJ 07834
(973) 983-7429

4HCM.org
support@4hcm.org
@4HCM.org
@4HCMwarriors

Figure K1

Pathogenesis and treatment of hypertrophic cardiomyopathy



AM= Annual mortality, EF=Ejection fraction, LV=Left ventricle, LGE=Late gadolinium enhancement, LVv=Left ventricle volume, SVT=supraventricular tachycardia, VES=ventricular extra systole, VT/VF=ventricular tachycardia/fibrillation, LVOTO=Left ventricle outflow obstruction, ICD= Implantable Cardioverter-Defibrillator

Modified from: Ostman-Smith, Clin Sci (Lond), 1981 sep, 3: 265-72, Olivotto et al, Circ Heart Fail. 2012 Jul 1;5(4):535-46. Marian et al, Circ Res. 2017 Sep 15;121(7):749-770

D Javid 2019

Tack!

"IF WE DIDN'T HAVE GENETIC MUTATIONS, WE WOULDN'T HAVE US. YOU NEED ERROR TO OPEN THE DOOR TO THE ADJACENT POSSIBLE."

STEVEN JOHNSON