# Genetisk utredning vid kardiomyopati – vem bör testas?

Pyotr Platonov

2025

# Varför gör vi genetisk testning?

- För den som redan har klinisk diagnos?
  - Bättre diagnos?
  - Prognos?
  - Behandlingsval?
- För de friska familjemedlemmarna?
  - Vem ska avskrivas från uppföljning?
  - Vem ska följas upp?

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European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Official ESC Guidelines slide set

# 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)


# För patient med Ds

| Disease | Diagnostic | Prognostic | Therapeutic |
|---|---|---|---|
| **Arrhythmia syndromes** | | | |
| Long QT syndrome | +++ | +++ | +++ |
| CPVT | +++ | + | + |
| Brugada syndrome | + | + | + |
| Progressive cardiac conduction disease | + | + | + |
| Short QT syndrome | + | + | + |
| Sinus node disease | – | + | – |
| Atrial fibrillation | – | + | – |
| Early repolarization syndrome | – | – | – |
| **Cardiomyopathies** | | | |
| Hypertrophic cardiomyopathy | +++ | ++ | ++ |
| Dilated cardiomyopathy | ++ | +++ | ++ |
| Arrhythmogenic cardiomyopathy | +++ | ++ | ++ |
| Left ventricular non-compaction | + | + | – |
| Restrictive cardiomyopathy | + | + | + |
| **Congenital heart disease** | | | |
| Syndromic CHD | +++ | + | – |
| Non-syndromic CHD | + | – | – |
| Familial CHD | ++ | – | |

EHRA 2022

Kommer jag att behandla min patient annorlunda om jag vet genetisk bakgrund Ds?

Har det betydelse för utredning av familjemedlemmar?

Finns det risk för plötslig död som första symtom?

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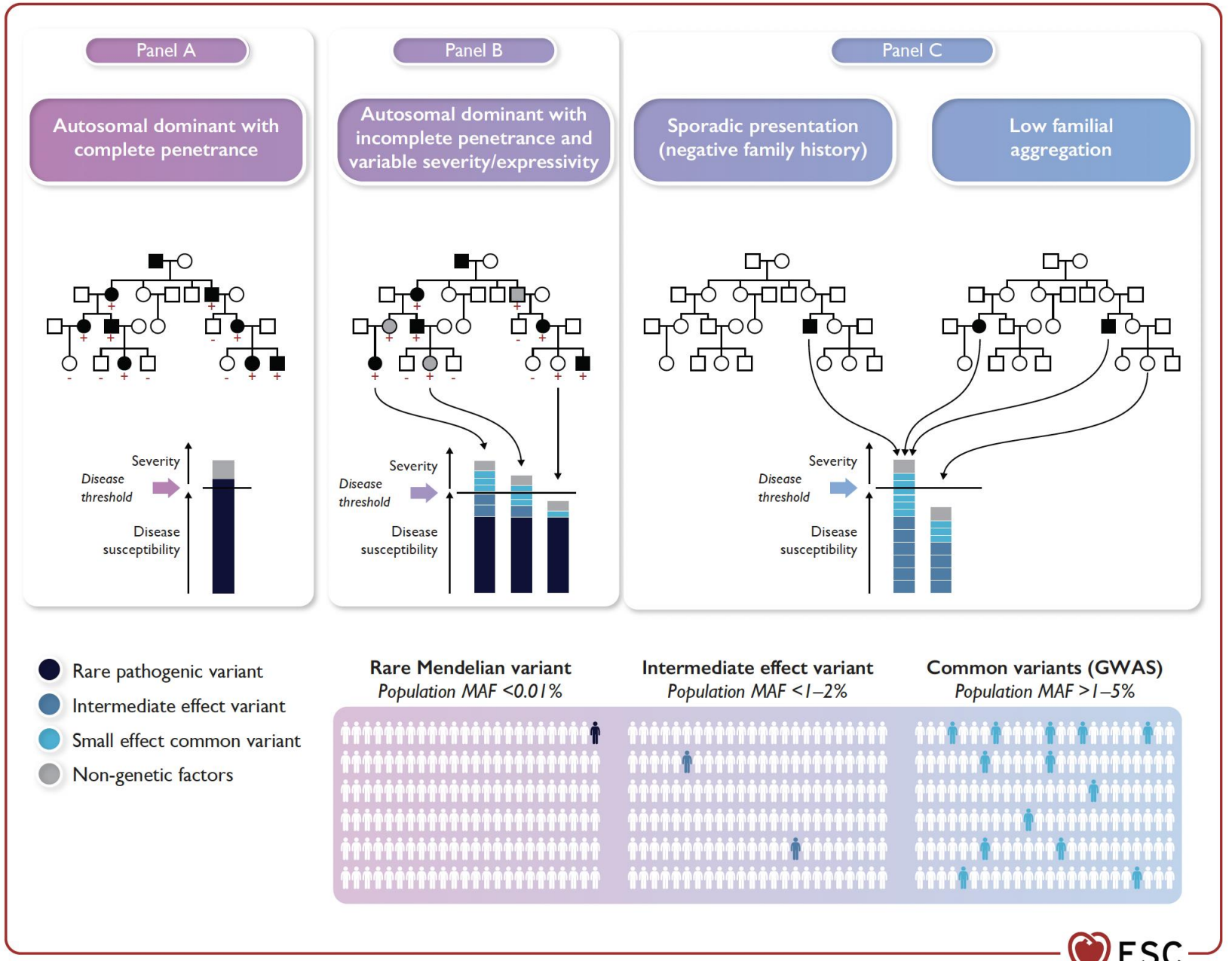
# Inte alltid enkelt!

- Vilka gener ska vi testa för?
- Vilka stavfel är tillräckligt allvarliga för att förklara sjukdomen?
- Vad händer om vi ta fel på genen? På genetiska varianten?

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# 2023 ESC Guidelines for the management of cardiomyopathies

| Gene | Cardiomyopathy phenotype | | | | | Associated phenotype |
|---|---|---|---|---|---|---|
| | HCM | DCM | NDLVC | ARVC | RCM | |
| *ABCC9* | ● [a] | ○ | | | | [a] Cantu syndrome |
| *ACTA1* | ○ | | | | | |
| *ACTC1* | ● | ◐ | ◌ | ○ | ◌ | |
| *ACTN2* [b] | ◐ | ◐ | ◌ | | | |
| *ALPK3* | ● | | | | | |
| *ANKRD1* | ○ | ○ | | | | |
| *BAG3* | ● [a] | ●● | | | ◌ | [a] Myofibrillar myopathy |
| *CACNA1C* | ● [c] | | | | | [c] Timothy syndrome |
| *CACNB2* | ○ | | | | | |
| *CALR3* | ○ | | | | | |
| *CASQ2* | ○ | | | | | |
| *CAV3* | ● [a] | | | | | [a] Caveolinopathy |
| *CDH2* | | | | ○ | | |
| *COX15* | ● [a] | | | | | [a] Leigh syndrome |
| *CRYAB* | ● [a] | | | | | [a] Alpha-B crystallinopathy |
| *CSRP3* | ◐ | ○ | | | | |
| *CTF1* | | ○ | | | | |
| *CTNNA3* | | | | ○ | | |
| *DES* | ● [c] | ● | ◌ | ◐ | ◌ | [c] Desminopathy |
| *DMD* | | ● [c] | ◌ | | | [c] X-linked progressive MD |
| *DMPK* | | | ◌ | | | |
| *DSC2* | | | | ●● | | |
| *DSG2* | | ○ | | ●● | | |
| *DSP* | ○ | ●● | ◌ | ● | | |
| *DTNA* | | ○ | ◌ | | | |
| *EYA4* | | ○ | | | | |
| *FHL1* | ● [c] | | | | | [c] Emery–Dreifuss MD |
| *FLNC* | ● [c] | ●● | ◌ | ◌ | ◌ | [c] Myofibrillar myopathy |
| *FHOD3* | ◌ | | | | | |
| *FXN* | ● [a] | | | | | [a] Friedreich ataxia |
| *GAA* | ● [a] | | | | | [a] Pompe disease |

| Gene | Cardiomyopathy phenotype | | | | | Associated phenotype |
|---|---|---|---|---|---|---|
| | HCM | DCM | NDLVC | ARVC | RCM | |
| *HCN4* | | | ◌ | | | |
| *ILK* | | ○ | ◌ | | | |
| *JPH2* | ◐ | ◐ | | | | |
| *JUP* | | | | ● [a] | | |
| *KCNQ1* | ○ | | | | | |
| *KLF10* | ○ | | | | | |
| *LAMA4* | | ○ | | | | |
| *LAMP2* | ● [c] | | | | | |
| *LDB3* | ● [a] | ○ | ◌ | ○ | | |
| *LMNA* | | ●● | ◌ | ○ | | |
| *LRRC10* | | ○ | | | | |
| *MIB1* | | ○ | ◌ | | | |
| *MYBPC3* | ●●● | ○ | ◌ | ○ | ◌ | |
| *MYH6* | ○ | ○ | | | | |
| *MYH7* | ●●● | ●● | ◌ | ○ | ◌ | |
| *MYL2* | ●● | ○ | ◌ | ○ | ◌ | |
| *MYL3* | ●● | ○ | ◌ | ○ | ◌ | |
| *MYLK2* | ○ | | | | | |
| *MYOM1* | ○ | | | | | |
| *MYOZ2* | ○ | | | | | |
| *MYPN* | ○ | ○ | | | ◌ | |
| *NEBL* | | ○ | | | | |
| *NEXN* | ○ | ◐ | | | | |
| *NKX2–5* | | ○ | ◌ | | | |
| *NNT* | | | ◌ | | | |
| *NONO* | | | ◌ | | | |
| *NPPA* | | ○ | | | | |
| *OBSCN* | ○ | ○ | ◌ | | | |
| *PDLIM3* | ○ | ○ | | | | |
| *PKP2* | | ○ | | ●●● | | |
| *PLEKHM2* | | ○ | | | | |
| *PLN* [b] | ● | ● | ◌ | ◌ | | |

● [a] definitive/strong evidence

◐ moderate evidence

○ limited, no association or dispute evidence

◌ generally rare, sporadic, yet not classified/ evaluated by ClinGen

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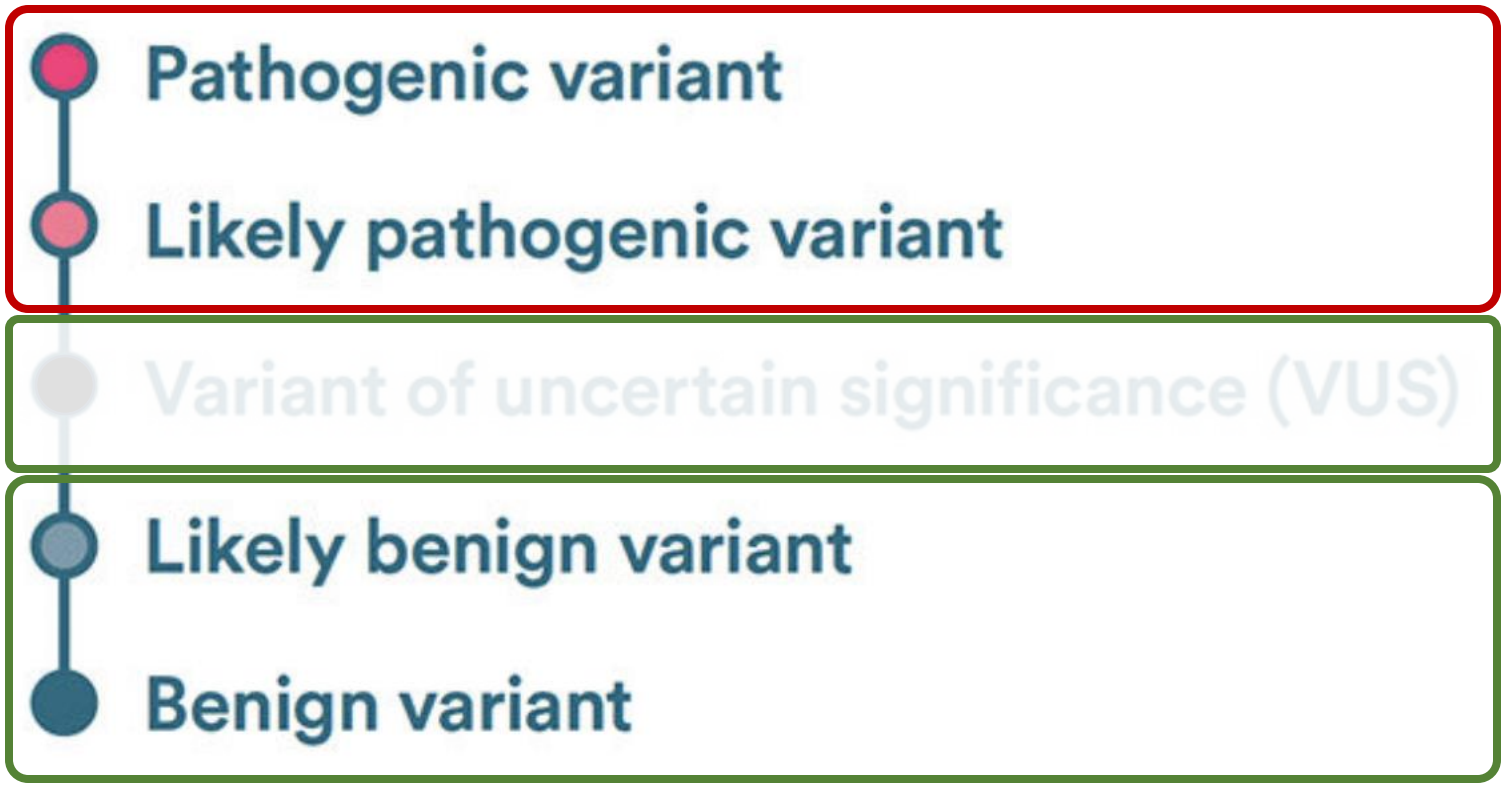
# Vilka genetiska varianter är ”sjuka nog” för att användas för genetisk screening i familjen?

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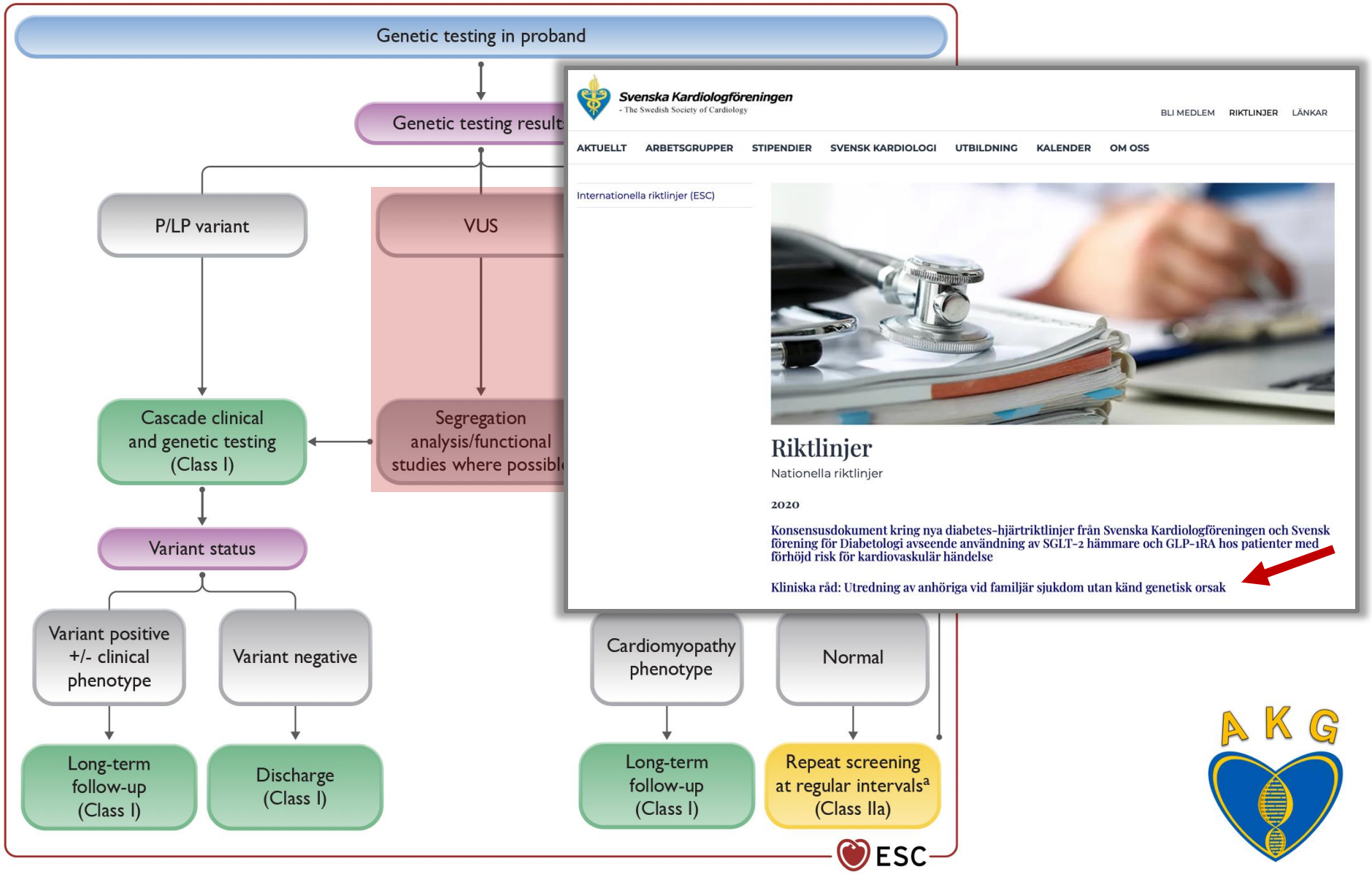
# Från gen sekvensering till familjeskreening

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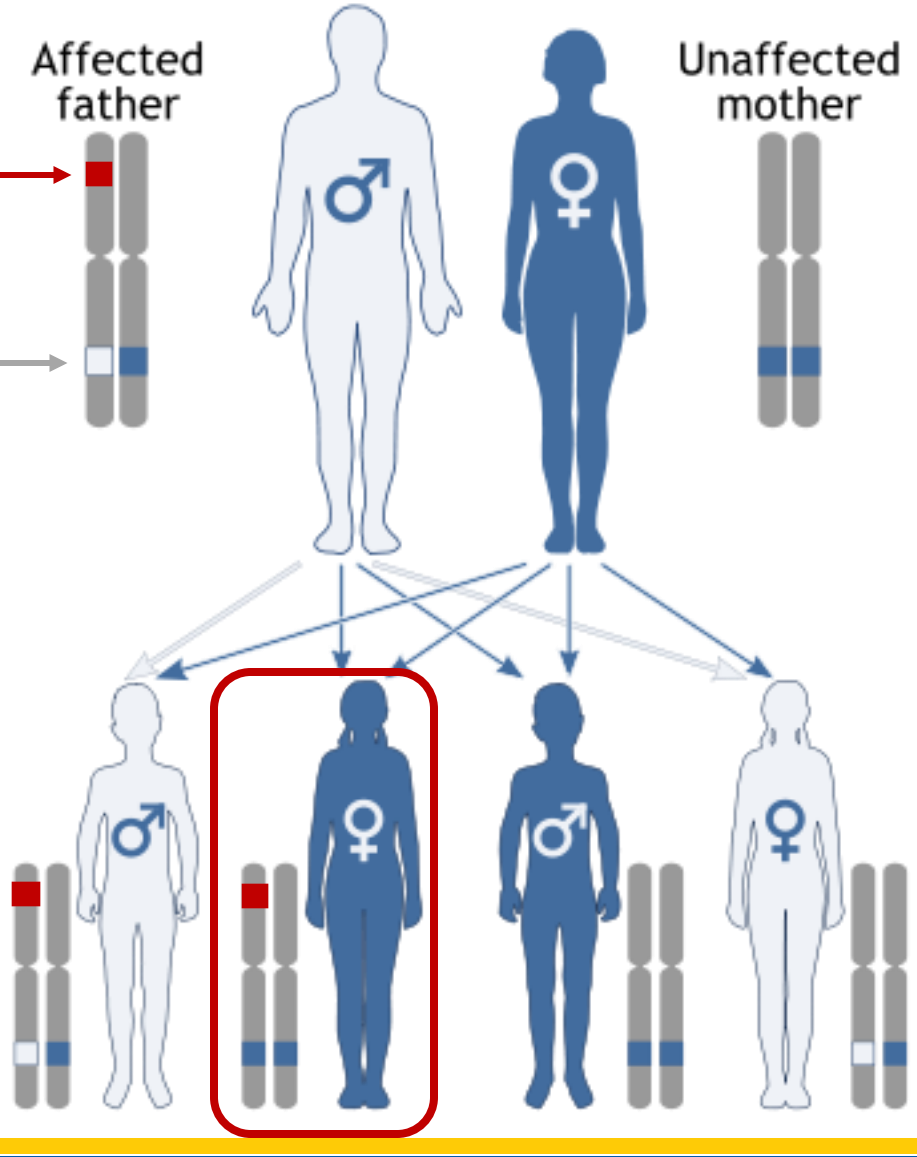
# Vad händer om vi tar fel på genen eller varianten?

Äkta sjukdomsorsakande variant

Genenetisk variant som vi **tror** är sjukdomsorsakande

- Gen ska ha klinisk relevans
- Genetisk variant ska vara patogen/troligen patogen.
- Ej VUS!

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# Dilaterad kardiomyopati – hur gör vi nu?


## *7.2.2.1. Genetic testing*

Causative gene variants occur in up to 40% of DCM patients in contemporary cohorts,[185,186,853,854] and between 10 and 15% in chemotherapy-induced, alcoholic, or peripartum DCM.[42–44] Although the prevalence of genetic variants is higher in familial DCM, causative genetic variants are also identified in over 20% of non-familial DCM

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# ”Where resources are limited….”

## Madrid DCM Genotype Score

This calculator was designed to estimate the probability of identification of pathogenic or likely pathogenic genetic variants in patients with Dilated Cardiomyopathy or Left ventricular systolic disfunction by NGS genetic testing.

**Family history of DCM***

Yes

*__Family history of DCM:__ Non-ischemic DCM (excluding severe valvular heart disease) in any first-, second-, or third-degree relative.

**Skeletal muscle disease***

Yes

*__Skeletal muscle disease:__ Clinically diagnosed myopathy by a neurologist based on physical examination findings, electromyography, or histopathological alterations

**Absence of LBBB***

Yes

*__Absence of Left bundle branch block (LBBB):__ QRS duration >0,12 sec with a LBBB pattern.

**Low QRS voltage limb leads***

Yes

*__Low QRS voltage limb leads:__ QRS amplitude ≤ 5 mm (0.5 mV) in all limbs leads.

**Absence of Hypertension***

Yes

*__Absence of Hypertension__ Hypertension preceding DCM diagnosis or diagnosed at the first evaluation.

Calculate

Press button to calculate results

Result

6.57%

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# ”Where resources are limited….”

**Key priorities for the implementation of the 2023 ESC Guidelines for the management of cardiomyopathies in low-resource settings**

**PRIORITY 7. Establish pathways for referral for genetic testing, particularly for cases more likely to have a positive yield and where the genetic test result can impact management decisions.** **2025**

”Cases associated with familial SCD, extensive LGE, conduction disorders, or specific metabolic red flags should be evaluated as a priority.”

”Where available, phenotype-genotype correlations (e.g. presence of red flags suggestive for Fabry or ATTR cardiomyopathy could prompt to first test for these diseases) and predictive scores (e.g. Toronto and Mayo scores for HCM, Madrid score for DCM) may be used to prioritize genetic testing in patients who may be more likely to have a positive genetic yield.”

”Cases where the implications of the genetic test go beyond aetiological diagnosis should be prioritized”

- Fabry disease or ATTRv cardiomyopathy which could benefit from specific therapies
- High-risk mutations in DCM and NDLVCM

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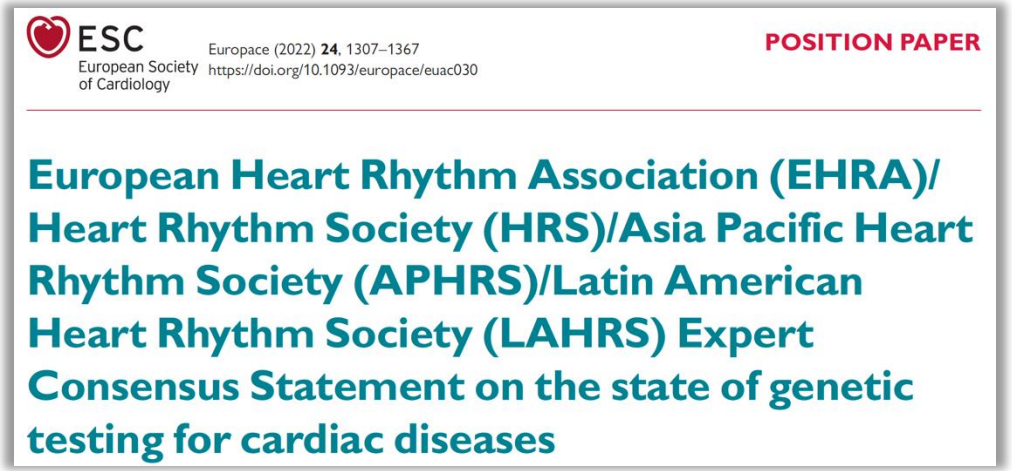
# Dilaterad kardiomyopati – hur gör vi nu?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# Dilaterad kardiomyopati – hur gör vi nu?


Genetic testing is recommended for probands with DCM and family history of DCM, and the initial tier of genes tested should include genes with definitive or strong evidence of pathogenicity (currently *BAG3*, *DES*, *FLNC*, *LMNA*, *MYH7*, *PLN*, *RBM20*, *SCN5A*, *TNNC1*, *TNNT2*, *TTN*, *DSP*).

Genetic testing is recommended for patients with DCM and family history of premature unexpected sudden death or in a DCM patient with clinical features suggestive of a particular/rare genetic disease (such as atrioventricular block or sinus dysfunction or creatine phosphokinase elevation).

Genetic testing can be useful for patients with apparently sporadic DCM, particularly in the presence of either severe systolic dysfunction (left ventricular ejection fraction < 35%), or a malignant arrhythmia phenotype (e.g. sustained ventricular tachycardia/fibrillation), or particularly at a younger age.

Genetic testing may be considered for patients with DCM related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy).

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# Dilaterad kardiomyopati – hur gör vi nu?

ESC European Society of Cardiology
European Heart Journal (2022) **43**, 3997–4126
https://doi.org/10.1093/eurheartj/ehac262
ESC GUIDELINES

**2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death**

| | |
|---|---|
| Genetic testing (including at least *LMNA*, *PLN*, *RBM20*, and *FLNC* genes) is recommended in patients with DCM/HNDCM and AV conduction delay at <50 years, or who have a family history of DCM/HNDCM or SCD in a first-degree relative (at age <50 years).[641–645] | **I** |
| Genetic testing (including at least *LMNA*, *PLN*, *RBM20*, and *FLNC* genes) should be considered for risk stratification in patients with apparently sporadic DCM/HNDCM, who present at young age, or with signs suspicious for an inherited aetiology.[641–645] | **IIa** |

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# När ska jag planera för genetisk testning?

- Sjukdomen är ärftlig (även om inga andra kända fall i familjen)
- Genetisk information är användbar
- Det är den med diagnosen som testas först
- Var tydlig ang diagnosen/fenotypen i remiss till klinisk genetik – det kan påverka tolkning av genetiska fynd
- Enbart klass 4 (sannolikt patogen) och 5 (patogen) räknas

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