Counseling considerations in inherited cardiac disorders

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No conflicts of interest to declare

UNIVERSITAIR ZIEKENHUIS ANTWERPEN

Genetic Counseling
Introduction

Genetic counseling is the process of:

- **Advice** → individuals and families
- Affected by or at risk of **genetic** disorders

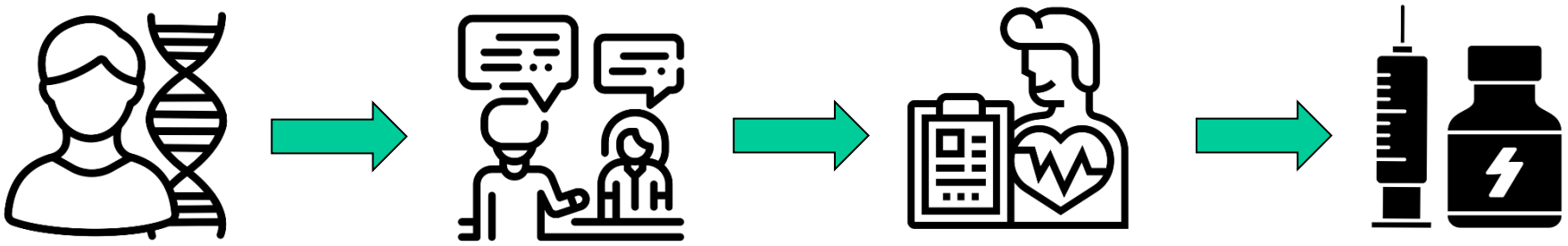
Goal:

- **Understand and adapt** to the medical, psychological and familial implications of genetic contributions to disease

Genetic Counseling
Introduction

PRE-TEST GENETIC COUNSELING

POST-TEST GENETIC COUNSELING



Genetic Counseling, roles in clinical care

PRE-TEST GENETIC COUNSELING

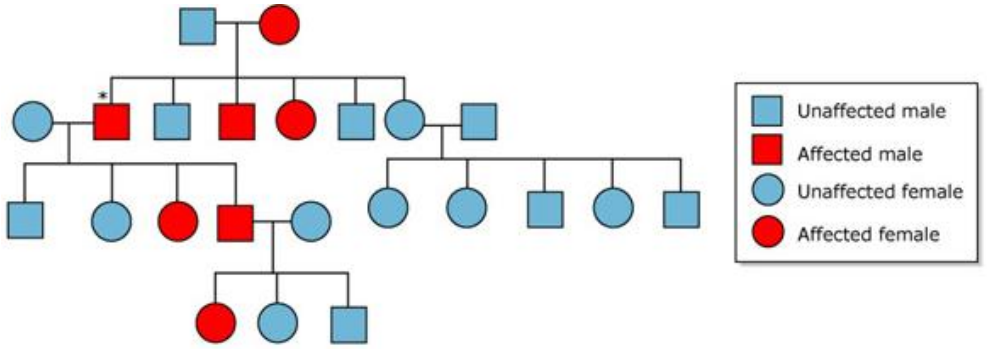
Risk assessment

Pedigree

→ Inheritance: usually AD, but some AR, XL and mitochondrial

→ Penetrance & expressivity

→ Sudden death under 45 years of age (autopsy?), sudden syncopes



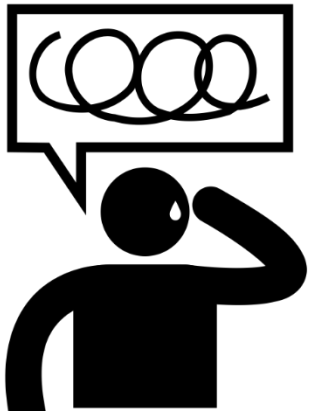
Genetic Counseling, roles in clinical care

PRE-TEST GENETIC COUNSELING

Education

screening, prevention and management

incomplete penetrance



VUS and incidental findings

variable expression

Genetic Counseling, roles in clinical care

PRE-TEST GENETIC COUNSELING

Identify psychological distress

- More difficult to process/retain information
- Less engaged decision making
- Lower adherence to medical plans
- More difficulties in communicating risk to family members

Genetic Counseling, roles in clinical care

POST-TEST GENETIC COUNSELING

Result interpretation

- Literature + laboratory → accurate & up-to-date information
- E.g. variant classification, variant specific penetrance,…

Result disclosure

- Explain genetic test result and implications for patient and family
- Provide witten documentation for families and providers

Genetic Counseling, roles in clinical care

POST-TEST GENETIC COUNSELING

Client-centered counseling

- Concerns
- Family planning
- Family communication → family letters
- Resources for additional support (psychologist, …)

Potential consequences of genetic testing: Psychological impact of mutation testing

Mutation in a symptomatic patient

- Relief → uncertainty about the cause of disease
- Depression since quality of life can be affected by:
    - Uncertainty about severity and prognosis of their condition
    - Risk of death (at young age)
    - Treatment
    - Adverse medication side effects
    - Activity restrictions
    - ….
- Anxiety → sharing test results

Potential consequences of genetic testing: Psychological impact of mutation testing

Mutation in an unaffected individual

- Disappointment → need for increased surveillance
- Anxiety → onset/severity
- Frustration → activity restrictions (!)
- Guilt → passed mutation to to future generations
- Concern → privacy, insurance and employment discrimination, reproductive decision-making

Potential consequences of genetic testing: Psychological impact of mutation testing

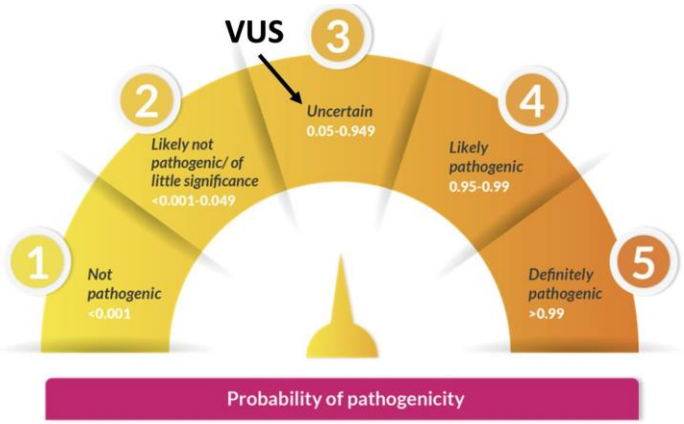
A negative test result with mutation in an affected family member.

- Relief of anxiety and psychological distress
- Survivor guilt
- Concern

Potential consequences of genetic testing: Psychological impact of mutation testing

A VUS in a sympatomatic patient (~35–40%)

- Uncertainty
- Confusion
- Frustration
- Misinterpretation



Counseling considerations in inherited cardiac disorders

- What is specific to cardiogenetic counseling?

Role of genetic testing in inherited cardiovascular disease (CVD)

For patient

- Clinical diagnosis often already made
- Familial sudden death
- Benefit genetic testing often unclear
- Research vs individual & family

For clinician

- Expectation managment & clinical benifit

Condition	Main genes	Detection rate	Diagnostic criterium	Effect on management	Predictive testing
Hypertrophic CMP	Sarcomere	30-60%	+/-	+	YES
Isolated LVH	ACTN2, FLNC, GLA, LAMP2, PLN, PRKAG2, TTR	<5%	+/-	+	YES
Dilated CMP	Sarcomers/cyto skeleton *LMNA*	30-40% 5-10%	+/-	NA ++	YES
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Loeys Dietz	TGFB pathway	70-90%	YES	++	YES
Familial TAAD	*ACTA2, MYH11, MYLK*	20-25%	+/-	++	YES
Vascular EDS	*COL3A1*	~95%	YES	++	YES

Adjusted from JAMA Cardiol. 10.1001/jamacardio.2017.2352 and Heart, Lung and Circulation, doi.org/10.1016/j.hlc.2019.10.014

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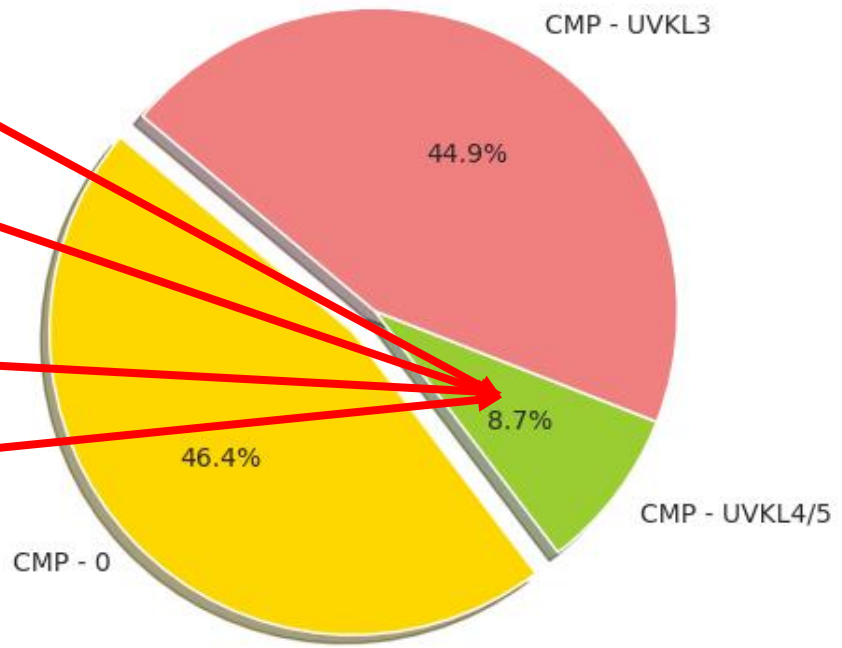

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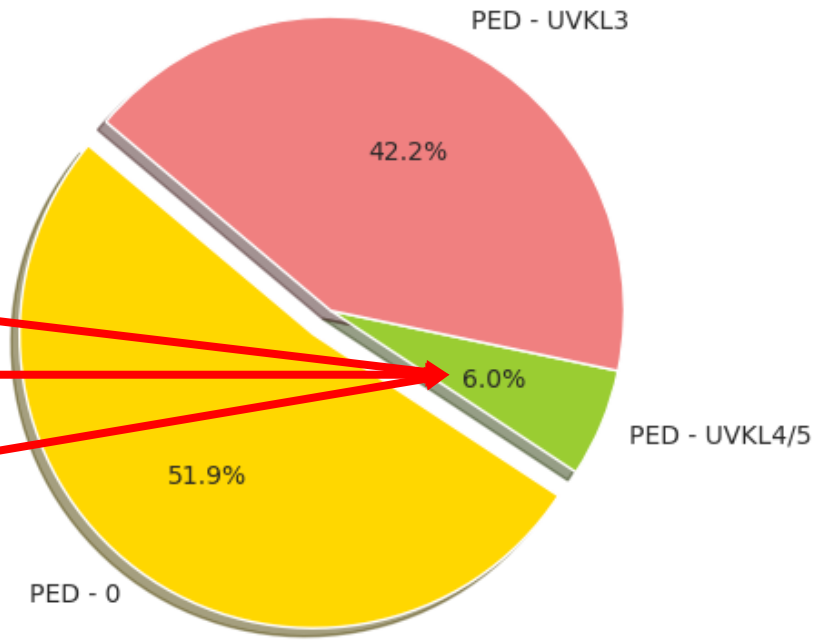

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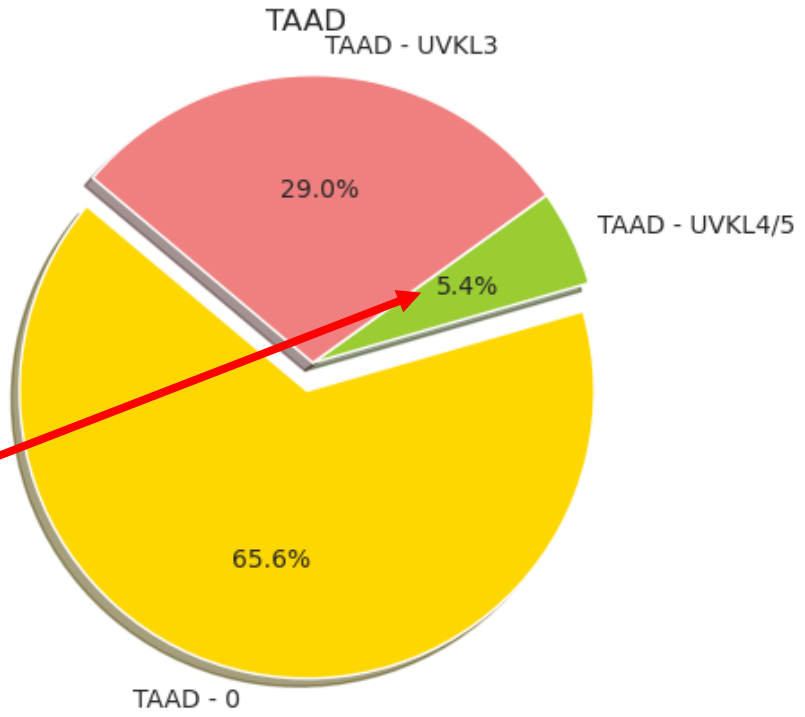

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Diagnosing inherited cardiac disease

Complex diagnostic criteria

- Masked and subtle phenotypes
- Need for specialised testing

Modified Task Force Criteria for ARVC – Diagnostic Categories Major and Minor Criteria

Definite: 2 major OR 1 major and 2 minor, OR 4 minor criteria from different categories
Borderline: 1 major and 1 minor, OR 3 minor criteria from different categories
Possible: 1 major, OR 2 minor criteria from different categories

	Major	Minor
Global or regional dysfunction and structural alterations determined by echo, MRI, or RV angiography:		
Echo	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): a) PLAX RVOT ≥32 mm (PLAX/BSA ≥19 mm/m^2) b) PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m^2) c) Fractional area change ≤33%	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): a) PLAX RVOT ≥29 mm to <32 mm (PLAX/BSA ≥16 to <19 mm/m^2) b) PSAX RVOT ≥32 to <36 mm (PSAX/BSA ≥18 to <21 mm/m^2) c) Fractional area change >33 to ≤40%
MRI	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: a) Ratio RVEDV/BSA ≥110 mL/m^2 (male), ≥100 mL/m^2 (female) b) RVEF ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: a) Ratio RVEDV/BSA ≥100 to <110 mL/m^2 (male), ≥90 to 100 mL/m^2 (female) b) RVEF >40 to ≤45%
RV angiography	Regional RV akinesia, dyskinesia, or aneurysm	
Tissue characterization of wall		
Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement and with:	Residual myocytes <60% by morphometric analysis (or <50% if estimated)	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated)
Repolarization abnormalities		
ECG	Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120ms)	I. Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete RBBB) or in V_4, V_5, or V_6. II. Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB
Depolarization/conduction abnormalities		
ECG	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	I. Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110ms on the standard ECG: a) Filtered QRS duration (fQRS) ≥114 ms b) Duration of terminal QRS <40 µV (low-amplitude signal duration) ≥38 ms c) Root-mean-square voltage of terminal 40 ms ≤20 µV II. Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′ in V_1, V_2, or V_3 in the absence of complete RBBB
Arrhythmias		
	Nonsustained or sustained VT of LBBB with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	I. Nonsustained or sustained VT or RV outflow configuration, LBBB morphology with inferior axis (positive QRS in II, III and aVF and negative in lead aVL) or of unknown axis II. >500 ventricular extrasystoles per 24 hours (Holter)
Family history		
	I. ARVC confirmed in a first-degree relative who meets current Task Force Criteria II. ARVC confirmed pathologically at autopsy or surgery in a first-degree relative III. Identification of a pathogenetic mutation categorized as associated or probably associated with ARVC in the patient under evaluation	I. History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force Criteria II. Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative III. ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative

Diagnosing inherited cardiac disease

Complex diagnostic criteria

Early vs late presentations

- Early ACM ~ CPVT (arrhythmogenic phase before cardiomyopathy phase)
- ‘Burned out’ HCM ~ DCM

Diagnosing inherited cardiac disease

Complex diagnostic criteria

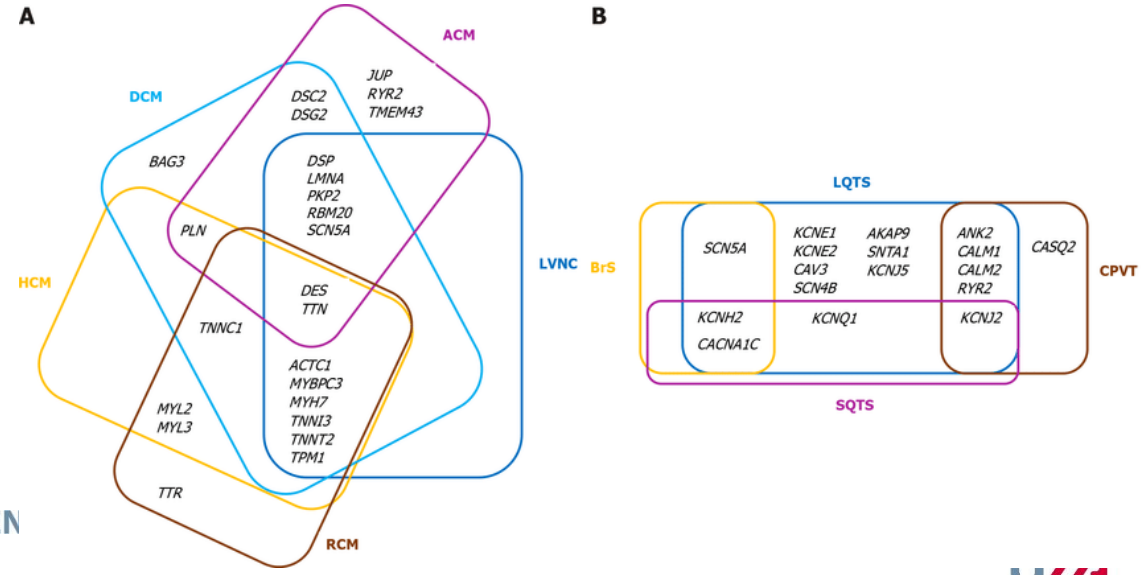
Early vs late presentations

Overlapping syndromes

- Left-dominant ACM ~ DCM
- Brugada ECG pattern in ACM
- Brugada/LQTS overlap syndrome

Diagnosing inherited cardiac disease

Complex diagnostic criteria
Early vs late presentations
Overlapping syndromes
Genetic pleiotropy



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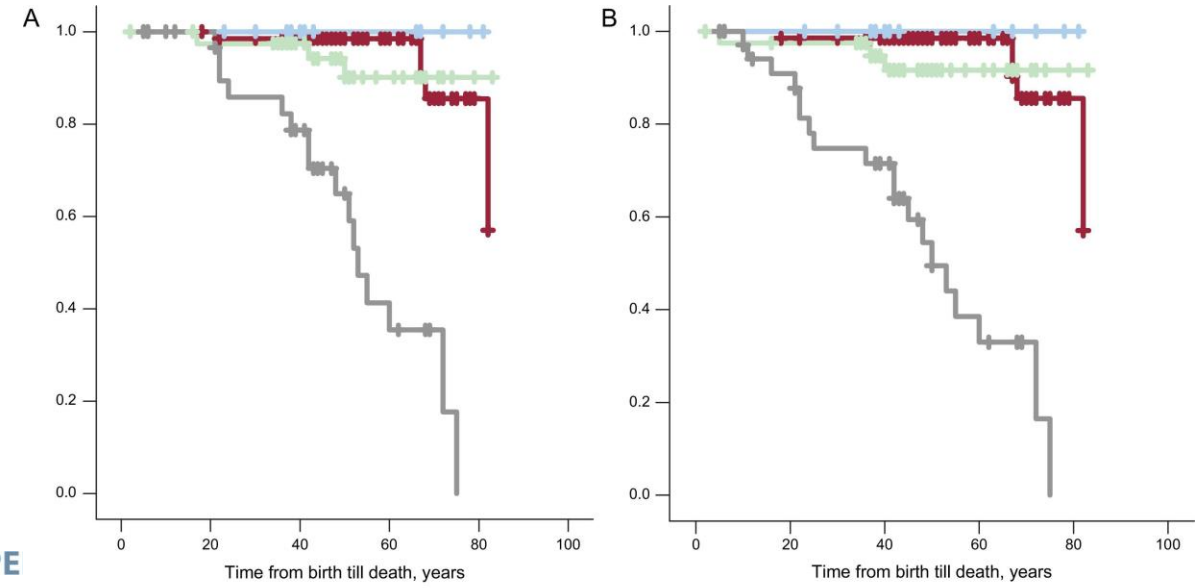
Genetic testing and treatment

Adjusted patient follow up and management

- Adjusted surgical thresholds for TAA in Marfan/LDS
- Preference for no ICD placement in CPVT
- High risk variants



Genetic testing and treatment

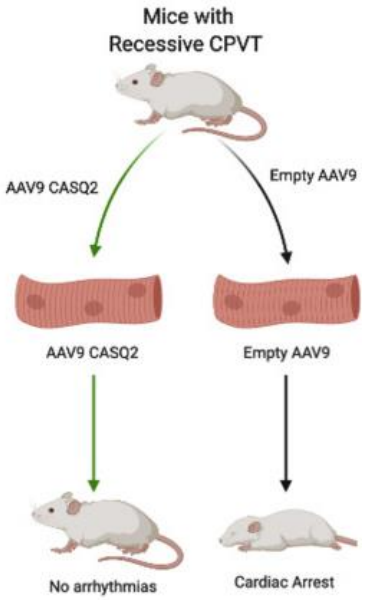
Adjusted patient follow up and management

Specific therapeutic options guided by genetic testing

- Mexiletine for type-3 LQTS (SCN5A)
- Enzyme replacement (GLA)

Genetic testing and treatment

Adjusted patient follow up and management
Specific therapeutic options guided by genetic testing
Future: potential for gene replacement / editing therapy?



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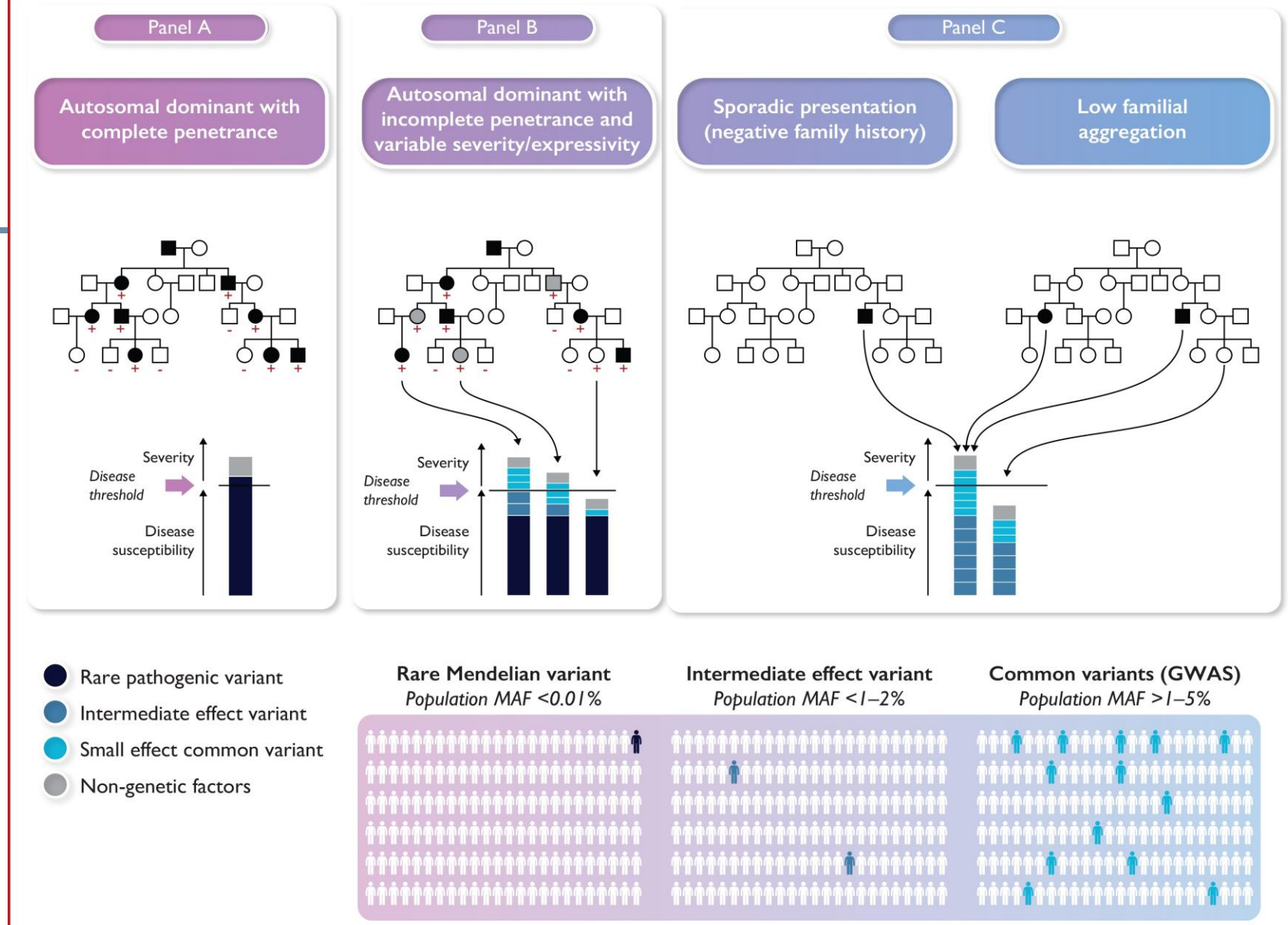
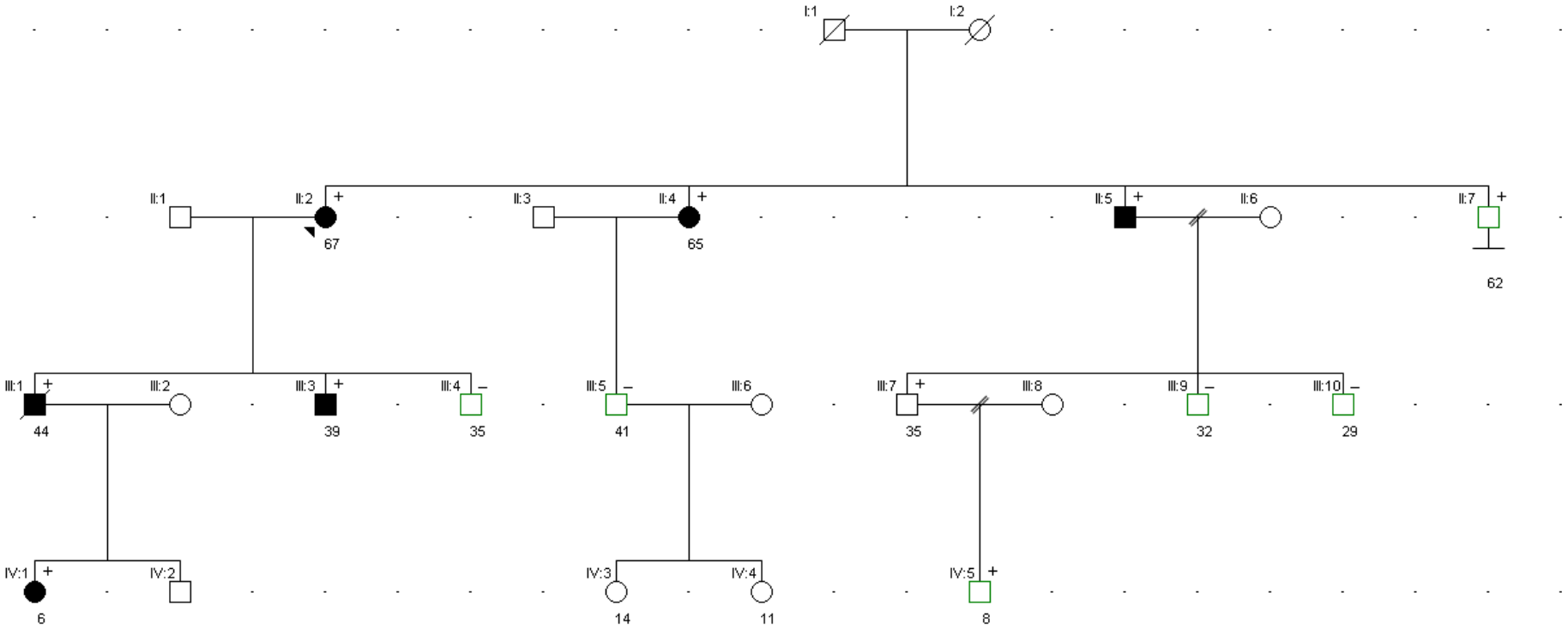
Role of genetic testing in inherited cardiovascular disease (CVD)

- Genetic architecture



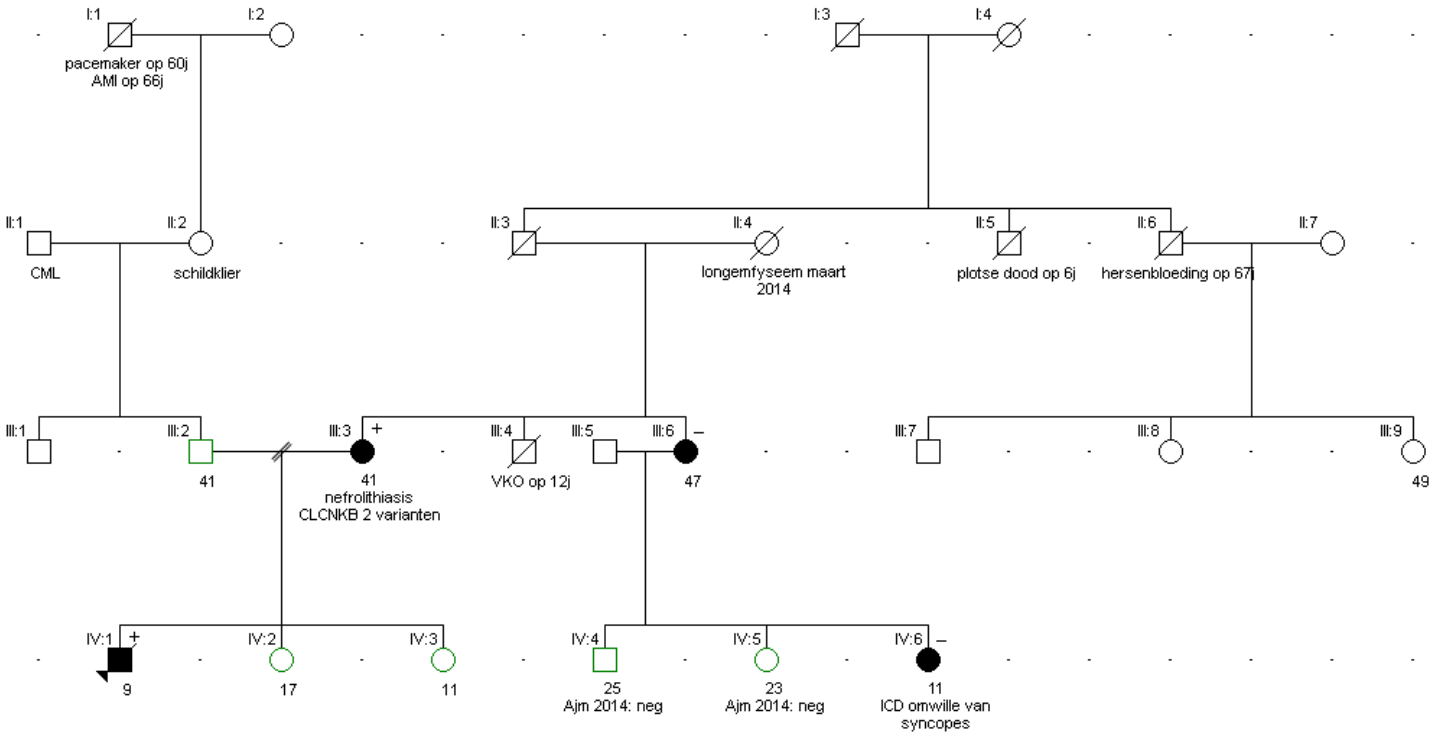
2023 ESC Guidelines for the management of cardiomyopathies

Some examples: Brugada pedigrees



SCN5A splice site mutation

Some examples: Brugada pedigrees



SCN5A LoF mutation

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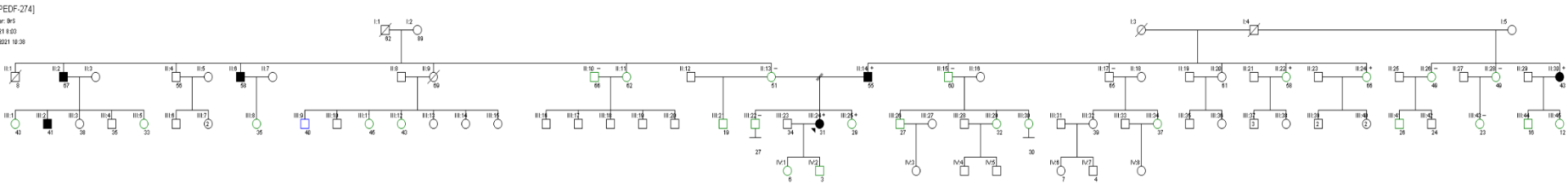
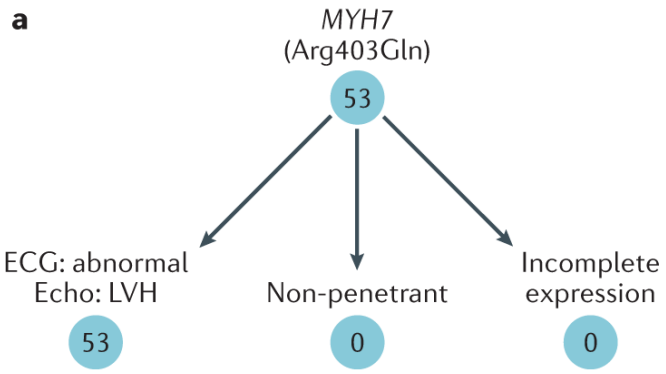
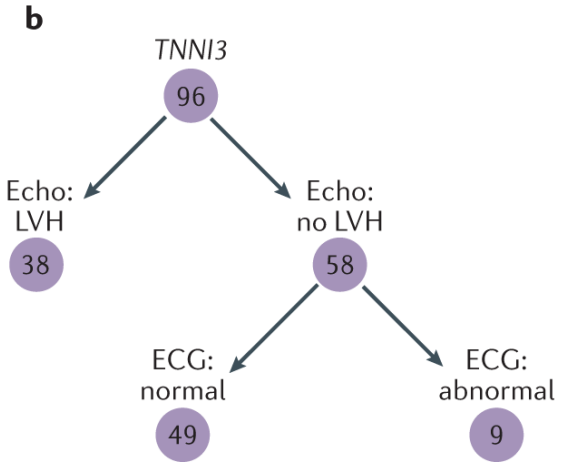


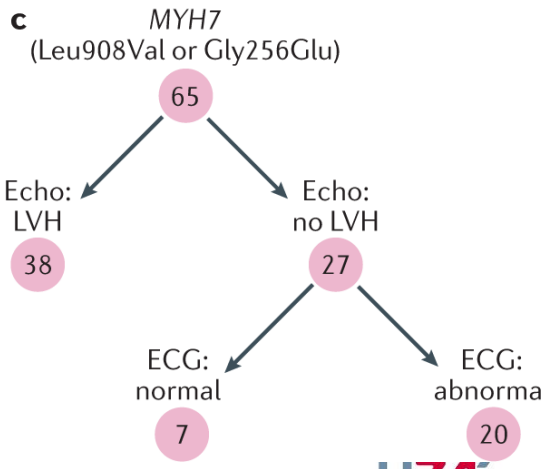
No SCN5A variants

Gene/variant related penetrance

- Overall penetrance in population databases for HCM and DCM (likely) pathogenic variants : ~11%
- Gene-related penetrance (e.g. TTN 5-6% penetrance)
- Variant-related penetrance
- Familial context!







Nat rev cardiol 10.1038/s41569-020-0428-2 and AJHG, doi 10.1016/j.ajhg.2023.08.003

Role of genetic testing in inherited cardiovascular disease (CVD)

Accurate and realistic expectations!

- Yield is never 100%
- Unique features (eg.variable penetrance and expressivity, VUS) → complicate the interpretation and application of results
- Guiding therapy and assessing prognosis
- Negative test result =/= no risk to family members!

Considerations to succesfully integrate genetic testing into clinical management/practice

⇧ Yield of genetic testing by:

- Comprehensive clinical evaluation before genetic testing → (precise) clinical diagnosis → type of test & interpretation of results
- Detailed family history → benefit from genetic testing

Counseling considerations in inherited cardiac disorders

- Which patients should receive genetic test?
  - Clinical diagnosis + affected family members
  - Clinical diagnosis + NO affected family members
  - No clinical diagnosis + untested SCD in family

Incorporating genetic testing into clinical practice

Definitive clinical diagnosis + positive family history

Increases the pretest probability of a positive genetic test result

→ **genetic testing definitively advised**

Incorporating genetic testing into clinical practice

Definitive clinical diagosis + absence family history

Does not preclude the use of genetic testing.
Genetic forms of CVD may be present without affected relatives
(de novo mutations, reduced penetrance, recessive inheritance)

→ **Genetic testing still advised**

Problem: validating test result (segregation not available)

Incorporating genetic testing into clinical practice

No clinical diagnosis + untested SCD in family

→ **Genetic testing is unlikely to be useful**

Unaffected family members of untested SCD proband

→ Unlikely to yield informative results

→ May provide false reassurance

→ Can lead to incorrect diagnosis

Predictive genetic testing with ambiguous genetic test result:

→ Variant may not be a reliable marker for disease risk

Interpretation of test results

- No variant identified in Brugada syndrome patient?
- No variant found in patient referred for Marfan syndome screening?
- Advice for family?
- VUS

Testing in childeren

- Depends on condition and expected age of onset (CPVT = paediatric vs non-syndromic DCM usually adult)
- Clinical screening ~10 years old for CMP and teenage for non-syndromic TAA/Brugada (Ajmaline test)
- Predictive genetic testing can be considered in diseases with childhood onset and availability of treatment
- Children worry about family members (parents) at risk
- Impact of positive predictive test on parents/environment

Genetic Counseling in ICVD

INVOLVEMENT OF A GENETIC COUNSELOR

- Part of the multidisciplinary team
- Evaluation, diagnosis and continuing management of patient and family

→ Integrating genetic medicine into cardiology practice

EFFECTIVE COMMUNICATION and PSYCHOSOCIAL COUNSELING

Conclusion

Considering the complexity of diagnosing inherited diseases,

dedicated services are very important.

Counselling should be performed by trained healthcare professionals, working within multidisciplinary teams to help patients understand and manage the psychological, social, professional, ethical and legal implications of genetic disease.