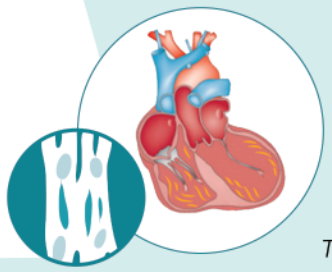
RECOGNIZING MENDELIAN (MONOGENIC) CARDIOVASCULAR DISEASE

Cascade Family Screening

- Clinical screening for all 1st degree (2nd and 3rd degree if needed) to determine SCD risk
- Adolescents = Annual screening; ≥18 years = every 2-3 years
- If putative gene identified:
  - **+ve:** Follow annually at minimum
  - **-ve:** Extend panel; if familial pattern consider exome or genome trio/quartets
  - **VUS:** Consider co-segregation analysis as part of VUS resolution

CARDIOMYOPATHIES

- DCM (1 in 250), HCM (1 in 500), ACM (1 in 5,000), RCM, or neuromuscular and systemic disease
- Presents as HF, AF, VT/VF, or SCD
- Most are autosomal dominant, but some are X-linked or recessive
- Genetic variants often 'private' to family
- Multi-modality imaging for deep phenotyping



Select a "cardiomyopathy" panel or extended panel/exome sequencing

HCM	*MYH7, MYBPC3, TNNT2, TNNI3, MYL2, MYL3, TPM1, ACTC1, ALPK3, GLA, PRKAG2, LAMP2*
DCM	*TTN, BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, DSP*
ACM	*PKP2, DSP, DSG2, DSC2, JUP, TMEM43, CDH2, PLN, DES, FLNC*
RCM	DCM and HCM plus *TTR, HFE*

Select phenotype-focused panel and exclude important phenocopies

KCNQ1, KCNH2, SCN5A, CALM1, CALM2, TRDN, CACNA1C, KCNE1,	**LQTS**	**SQTS** *KCNH2, KCNJ2, KCNQ1, SLC4A3*
SCN5A	**BrS**	**Familial AF** *SCN5A, KCNQ1, MYL4, TTN*
RYR2, CASQ2, TRDN, TECRL, CALM1, CALM2	**CPVT**	**PCCD** *SCN5A, TRPM4, TBX5, HCN4, TTR*

ARRHYTHMIAS

Clinical clues:

- Palpitations, syncope, pre-syncope
- Exercise-induced arrhythmias especially CPVT
- Seizure or epilepsy diagnosis
- Drowning/near-drowning
- Deafness
- Low fetal heart rate

AORTOPATHIES

- Multifactorial aortic aneurysms and dissection
- Work-up (must) for connective tissue disorders as management may be different
- hTAAD make up the majority of cases

Select phenotype-focused panel and exclude important phenocopies

MFS	*FBN1*
LDS	*SMAD3, TGFBR1, TGFBR2, TGFB2*
vEDS	*COL3A1*
hTAAD	*PRKG1, ACTA2, MYH11, MYLK, LOX, FBN2*

DYSLIPIDEMIA *GENES*

- **FH (AD, also biallelic):** *LDLR, APOB, LDLRAP1, PCSK9*
- **Familial chylomicronemia:** biallelic *LPL, APOC2, APOA5, LMF1, GPIHBP1*
- **Sitosterolemia (biallelic):** biallelic *ABCG5/ABCG8*
- **Cerebrotendinous xanthomatosis (biallelic):** biallelic *CYP27A1*
- **Cholesterol ester storage disease:** biallelic *LIPA*
- **Abetalipoproteinemia:** biallelic *MTTP*
- **Familial hypobetalipoproteinemia:** biallelic *APOB*

LIPID DISORDERS

- Prevalence: 1 in 200
- Most frequent monogenic is FH
- 3-fold increase in CAD risk with FH variant
- Other dyslipidemias can have an even more adverse prognosis
- Genetics aid precision therapies for management

Abbreviations: ACM: Arrhythmogenic Cardiomyopathy | AF: Atrial Fibrillation | ARB: Angiotensin II Receptor Blocker | BRS: Brugada Syndrome | CK: Creatine Kinase | CPVT: Catecholaminergic Polymorphic Vt | DCM: Dilated Cardiomyopathy | FH: Familial Hypercholesterolemia | HCM: Hypertrophic Cardiomyopathy | HF: Heart Failure | hTAAD: Hereditary Thoracic Aortic Aneurysm And Dissection | LDS: Loeys Dietz Syndrome | LQTS: Long QT Syndrome | MI: Myocardial Infarction | PCCD: Progressive Cardiac Conduction Disease | RCM: Restricted Cardiomyopathy | SCD: Sudden Cardiac Death | SQTS: Short Qt Syndrome | TTRWT: Transthyretin Wild Type | vEDS: Vascular Ehlers Danlos Syndrome | VT: Ventricular Tachycardia | VF: Ventricular Fibrillation | VUS: Variant Of Unknown Significance

References:

1. Adler A, et al. Circulation. 2020;141(6):418-428.
2. Hosseini SM, et al. Circulation. 2018;138(12):1195-1205.
3. Ingles J, et al. Circ Genom Precis Med. 2019;12(2):e002460.
4. James CA, et al. Circ Genom Precis Med. 2021;14(3):e003273.
5. Jordan E, et al. Circulation. 2021;144(1):7-19.
6. Musunuru K, et al. Circ Genom Precis Med. 2020;13(4):e000067.
7. Renard M, et al. J Am Coll Cardiol. 2018;72(6):605-615.
8. Sturm AC, et al. J Am Coll Cardiol. 2018;72(6):662-680.
9. Walsh R, et al. Eur Heart J. 2022;43(15):1500-1510.
10. Wilde AAM, et al. Heart Rhythm. 2022;19(7):e1-e60.

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