**CASE EXAMPLE:** Hypertrophic Cardiomyopathy (HCM)

**WHO IS THE PATIENT?**

- 24 year-old male with no cardiac symptoms; assessed due to family history
- Normal ECG (no left ventricular hypertrophy or conduction disease),
cardiac echocardiogram, cardiac MRI
- No prior cardiovascular genetic testing

**WHAT IS THE FAMILY HISTORY?**

- Family history of sudden cardiac arrest (SCA) and hypertrophic obstructive
cardiomyopathy
- Father died at age 45 from SCA: HCM found on requested autopsy report
- Paternal grandfather died at age 60 from SCA
- No prior cardiovascular genetic testing done on family members

**WHAT HAPPENED WITH GENETIC TESTING?**

- Cardiologist ordered HCMFirst panel (MYH7 and MYBPC3 genes) with reflex option on patient (clinical rationale below):
  - Up to 50% of HCM due to a mutation in one of the HCMFirst genes, which represent ~80% of known genetic causes of HCM
  - Tiered approach: HCMFirst panel reflexes to larger HCMNext panel, only if needed
- Positive finding: MYH7 variant, likely pathogenic: p.G584S
- This alteration is reported in multiple patients with HCM.\textsuperscript{1,2,3} MYH7 mutations account for ~40% of HCM and 5-8% of dilated
cardiomyopathy (DCM). MYH7 mutations can also cause left ventricular non-compaction (LVNC) and skeletal myopathies, with/without cardiac involvement.\textsuperscript{4,5}

**HOW DID GENETIC TESTING HELP THE PATIENT AND FAMILY?**

- Confirmed patient to be at risk for HCM and sudden cardiac arrest, despite negative clinical presentation
- Tiered testing allowed quicker results (no need for larger panel)
- Cardiologist referred patient to HCM specialist to develop cardiac surveillance plan
- Patient could tell at-risk family members to speak to physicians about individualized cardiac surveillance
- Patient could tell at-risk family members about targeted genetic testing option
  - Brother had targeted testing and was negative for MYH7 variant, confirming no increased risk for HCM in him based on this
WHAT IS HCM?

- Left ventricular hypertrophy, myocyte disarray, and fibrosis
- Severity varies widely, even within the same family
- Can be asymptomatic, sudden death sometimes first and only symptom
- Age of onset childhood to early adulthood
- Occurs in approximately 1 in 500 individuals worldwide
- When inherited, follows autosomal dominant pattern

WHO SHOULD HAVE GENETIC TESTING FOR HCM?

- Patients with a clinical diagnosis of HCM
- Patients with autopsy findings consistent with HCM
- Patients with a family history of HCM, based on clinical findings or autopsy

WHAT ARE AMBRY’S TESTING OPTIONS FOR HCM?

**HCMFirst**
- Next generation sequencing (NGS) and deletion/duplication (del.dup) panel of MYBPC3 and MYH7 genes; TAT is 3-4 weeks

**HCMNext**
- NGS and del.dup panel of 27 genes implicated in HCM: ACTC1, ACTN2, ANKR1D1, CSRIP3, FXN, GLA, JPH2, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEXN, PLN, PRKAG2, PTPN11, RAF1, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTR, VCL; TAT is 6-8 weeks (same for reflex option)

Details about our cardiovascular genetic testing options can be found at ambrygen.com/hereditary-cardiovascular-testing

REFERENCES


GENES IMPLICATED IN HCM

- Mutations in 27 genes have been identified in HCM
- MYBPC3 and MYH7 account for over 80% of known genetic causes
- “Other” includes the remaining genes in HCMNext

GENETIC TESTING GUIDELINES FROM HEART RHYTHM SOCIETY (HRS) AND EUROPEAN HEART RHYTHM ASSOCIATION (EHRA)

HCM genetic testing is a **Class I recommendation** for all patients with HCM.

Once a pathogenic gene mutation is identified in a family, mutation-specific testing of family members is a **Class I recommendation**.

Adapted from Ackerman MJ, et al., Heart Rhythm., 2011.

GENETIC TESTING FOR HCM

- Up to 50% of all patients with HCM have a mutation in one of the HCMFirst genes, which represent about 80% of known genetic causes of HCM
- An additional 10% of patients with HCM may have a mutation in one of the HCMNext genes

Our more comprehensive cardiovascular genetics panels (CMNext and CardioNext) may be better for more complicated families, or if HCMFirst/HCMNext testing is uninformative.