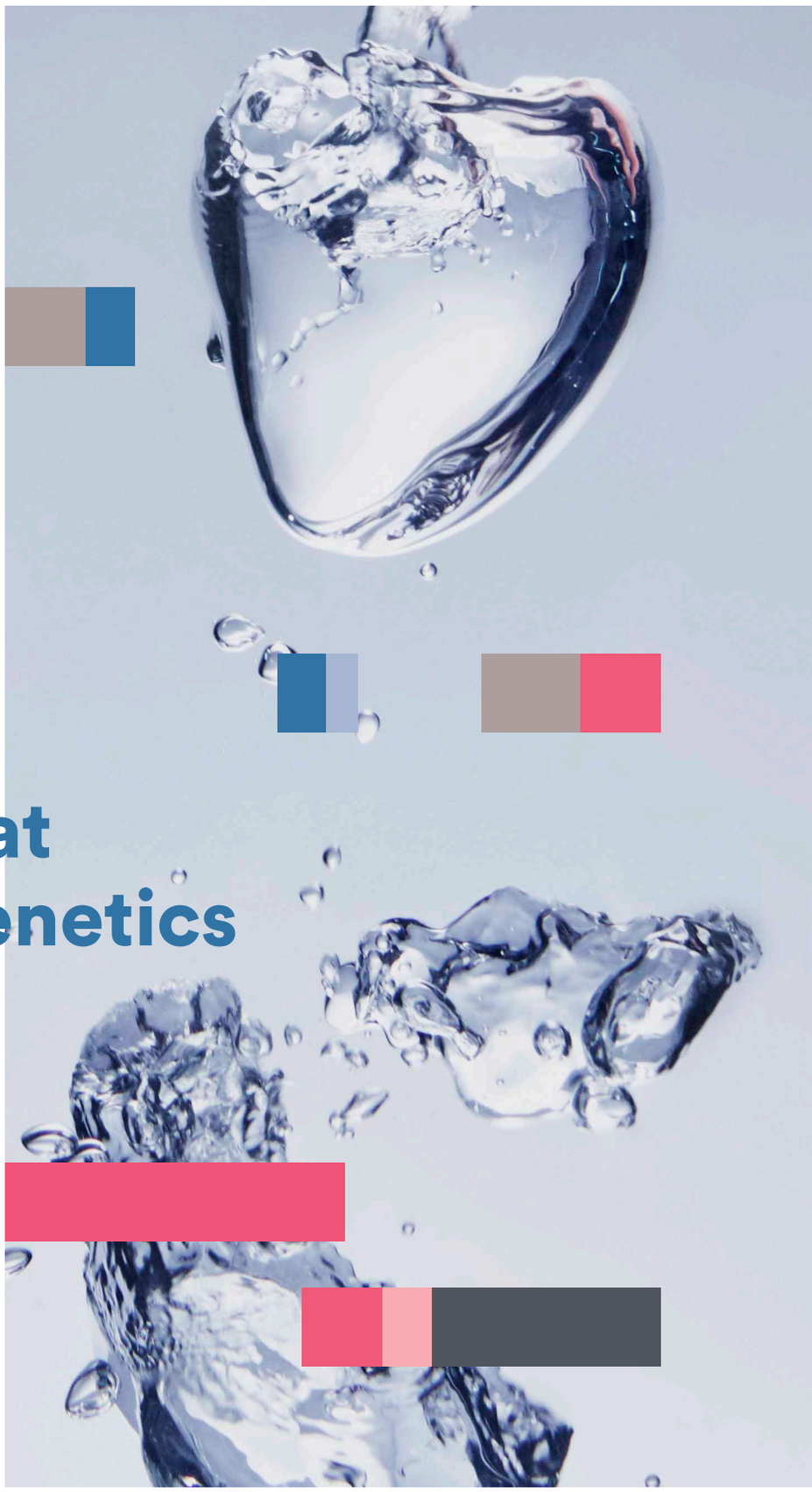


Cardiology at Blueprint Genetics

Join the conversation
#GeneticKnowledge

Blueprint Genetics

What is the impact of inherited cardiovascular conditions?

Inherited cardiovascular conditions affect approximately 1 in 200 people worldwide. They are an important cause of sudden cardiac death in otherwise young, healthy individuals.

What are the most common inherited cardiovascular conditions?

- **Cardiomyopathies**
  - Hypertrophic cardiomyopathy
  - Dilated cardiomyopathy
  - Arrhythmogenic (Right Ventricular) cardimyopathy
- **Familial Hypercholesterolemia**
- **Inherited arrhythmias**
  - Long QT syndrome
  - Brugada syndrome
  - Catecholaminergic Polymorphic Ventricular Tachycardia
- **Aortopathies/Connective Tissue disorders**

Why perform genetic testing for inherited cardiovascular conditions?

- Knowing the the underlying genetic cause of the condition may guide medical management and lifestyle interventions for your patient
- It may be the only way to identify relatives who are at increased risk of sudden death and in whom ongoing surveillance is indicated
- Genetic testing in inherited cardiovascular conditions is a published guideline recommendation [1,3,4,5,6,7,8,9,10]

When should I consider genetic testing?

Patients who are young and otherwise healthy with a personal or family history of one or more of the following may benefit from genetic testing:

- Electrocardiographic or imaging findings consistent with an inherited cardiovascular condition
- Unexplained cardiac arrest/sudden death at a young age
- Unexplained syncope and/or seizures
- Unexplained elevated cholesterol/history of premature cardiovascular disease
- Aortic dissection/aneurysm at a young age

Why choose Blueprint Genetics for Cardiology genetic testing?

- Over 10 000 cardiology cases have been analyzed at Blueprint Genetics
- Our cardiology offering includes 23 high quality panels that are carefully curated and frequently reviewed

  A recent example is the addition of the *TECRL* gene to the Long QT syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia, Arrhythmia and Comprehensive Cardiology Panels given newly published research[11]
- Clinical findings are reported and reviewed by experienced laboratory geneticists and expert cardiologists
- Blueprint Genetics' founding team is composed of several experienced cardiologists with multiple academic collaborating publications

  Our team recently contributed to a study which further supports the role of the *JPH2* gene in hypertrophic cardiomyopathy[12]
- If your patient's panel testing is inconclusive or there is a diagnostic finding that doesn't explain the whole phenotype, you can provide your patient with the most comprehensive genetic test by utilizing whole exome sequencing

CASE 1

A 9-year-old girl who is an experienced swimmer collapses when diving into a pool. Her electrocardiogram has features suggestive of Long QT syndrome (LQTS), including a prolonged QTc interval (480ms) and a broad base 'early onset' T wave.

The Blueprint Genetics LQTS Panel is ordered. Offering genetic testing to patients fulfilling the diagnostic criteria for LQTS is a Class I recommendation[4,8].

A pathogenic (known to be disease-causing) variant is identified in the *KCNQ1* gene, c.1129-2A>G. Variants in this gene are the most common cause of LQTS.

Implications

- Genetic testing confirms a diagnosis of LQTS
- The patient must avoid medications that are known to prolong the QT interval (www.crediblemeds.org)[2,8]
- Medical therapy such as beta-blockers may be recommended[2,8]
- LQTS is inherited in an autosomal dominant manner; each of the patient's sibling(s) and parents have an up to 50% chance of inheriting Long QT syndrome; those at risk will need ongoing cardiac screening, and must avoid QT prolonging medications[2,8]
- Offering genetic tesing to first degree relatives of individuals with a disease causing variant is a Class I recommendation[4,8]

CASE 2

A 25-year-old basketball player experiences worsening chest pain and shortness of breath. An echocardiogram shows asymmetric hypertrophy of the left ventricle; the left ventricular wall thickness measures 17mm. He has no history of syncope or arrhythmias.

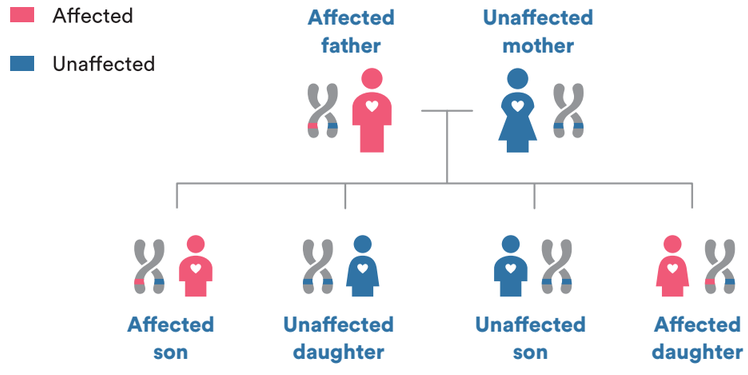
The Blueprint Genetics Hypertrophic Cardiomyopathy (HCM) Panel is ordered. Offering genetic testing to patients fulfilling the diagnostic criteria for HCM to confirm a diagnosis and enable the identification of at risk relatives is a Class I recommendation[3,8].

A pathogenic variant is identified in the *MYBPC3* gene; a 2-bp deletion c.913_914del p.(Phe305Profs*27). Variants in the *MYBPC3* and *MYH7* gene account for 80% of positive genetic test results in HCM patients[13].

Implications

- Genetic testing confirms a diagnosis of HCM
- The patient requires regular evaluations at regular intervals to evaluate the risk of complications such as obstruction, heart failure and cardiac arrest/sudden death[3,8]
- HCM is inherited in an autosomal dominant manner; each of the patient's sibling(s) and parents have an up to 50% chance of inheriting HCM; those at risk will need ongoing cardiac screening and surveillance[3,8]
- Offering genetic testing to first degree relatives of individuals with a disease causing variant is a Class I recommendation[3,8]

Autosomal dominant inheritance – it's all about the family



Affected individuals:

- Ongoing follow-up and surveillance

Unaffected individuals:

- Can be discharged from further care

A Selection of Blueprint Genetics Cardiology Offering

Comprehensive Cardiology Panel (184 Genes)

Arrhythmia Panel (57 Genes)

Atrial Fibrillation Panel (19 Genes)

Long QT Syndrome (LQTS) Panel (16 Genes)

Brugada Syndrome Panel (9 Genes)

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Panel (9 Genes)

Aorta Panel (41 Genes)

Cardiomyopathy Panel (155 Genes)

Dilated Cardiomyopathy (DCM) Panel (69 Genes)

Hypertrophic Cardiomyopathy (HCM) Panel (38 Genes)

Left Ventricular Non-Compaction Cardiomyopathy (LVNC) Panel (32 Genes)

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Panel (17 Genes)

For a full list of our cardiology panels visit blueprintgenetics.com/tests/panels/cardiology

Blueprint Genetics offers four types of high-quality Whole Exome Sequencing tests

Whole Exome

High-quality Whole Exome Sequence analysis of single patient cases.

Whole Exome Plus

High-quality Whole Exome Sequence analysis of single patient cases, coupled with Whole Exome Deletion/Duplication analysis. Whole Exome Plus allows detection of single-nucleotide and indel variants, as well as larger deletions/duplications.

Whole Exome Family

High-quality Whole Exome Sequence analysis of and index patient and parents (trio), or other family members. The trio approach in WES improves diagnostic rate by facilitating sequence variant analysis and by enabling detection of *de novo* variants.

Whole Exome Family Plus

High-quality Whole Exome Sequence analysis of an index patient and parents (trio), or other family members, coupled with Whole Exome Deletion/Duplication analysis. Whole Exome Plus is essential tool for detecting *de novo* variants and copy number variants, which underlie many of the early-onset diseases.

Roadmap for the evaluation of inherited cardiovascular conditions[1]

1. **Comprehensive family history**
2. **Expert phenotypic evaluation of the proband and at-risk family members to confirm a diagnosis to guide genetic test selection and interpretation**
3. **Referral to expert centers as needed**
4. **Genetic testing, with pre- and post-test genetic counseling**
5. **Specific guidance as indicated for drug and device therapies**

1. Hershberger RE et al. J Card Fail 2018;24(5):281–302
2. Priori SG et al. Heart Rhythm 2013;10(12):1932–58.
3. Elliott PM et al. Eur Heart J 2014;35:2733–79.
4. Ackerman MJ et al. Heart Rhythm 2011;8(8):1309–39.
5. Priori SG et al. Europace 2015;17:1601–87.
6. Hershberger RE et al. Genet Med 2018;20(9):899–909.
7. Gersh BJ et al. Circulation 2011;124:e783–e831.
8. Al-Khatib SM et al. Heart Rhythm 2018;15(10):e73–e189.
9. Erbel R et al. Eur Heart J 2014;35:2873-2926.
10. Sturm AC et al. J Am Coll Cardiol 2018;72(6):662–80.
11. Devalla HD et al. EMBO Mol Med 2016;8(12):1390–1408.
12. Vanninen SUM et al. PLoS One 2018;13(9):e0203422.
13. Alfares AA et al. Genet Med. 2015. 17(11):880-888