

GENETIC TESTING: CARDIAC DISORDERS

OVERVIEW

Arrhythmias and cardiomyopathies can be multifactorial, hereditary, or caused by a known environmental factor, such as a drug. Hereditary arrhythmias and cardiomyopathies are primarily diagnosed clinically and symptoms can be variable, even within the same family. Most hereditary cardiac conditions are associated with multiple genes and while genetic test results may not guide medical management for those with a clinical diagnosis, identification of a pathogenic or likely pathogenic variant can allow for cascade testing of asymptomatic family members who might benefit from lifesaving treatment.

Congenital heart defects (CHDs) are structural heart defects that are present at birth. CHDs affect 1-1.2% of live births and can be caused by genetic and environmental factors. Determining an underlying genetic cause for CHD can aid in assessing recurrence risks for at-risk family members, evaluating for associated extracardiac involvement, assessing for neurodevelopmental delays, and providing a more accurate prognosis for the patient.

Familial hypercholesterolemia (FH) is the most common inherited cardiovascular disease and is characterized by severely elevated LDL cholesterol (LDL-C) levels that lead to atherosclerotic plaque deposition in the coronary arteries and proximal aorta at an early age, leading to an increased risk for cardiovascular disease. An estimated 70-95% of FH results from a heterozygous pathogenic variant in one of three genes (*APOB*, *LDLR*, *PCSK9*) and determining the genetic cause of FH can aid in identifying at-risk family members and directing treatment options.

This document addresses genetic testing for cardiac disorders, focusing on cardiomyopathy, arrhythmia, congenital heart defects, and cholesterol disorders.

POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Known Familial Variant Analysis for Cardiac Disorders	Targeted Mutation Analysis for a Known Familial Variant	81403		19
Comprehensive Cardiomyopathy Panels	Cardiomyopathy Panel (GeneDx)	81439	I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, Z13.71, Z82.4, Z82.49, Z84.81, Z84.89	1, 8
	Cardiomyopathy Comprehensive Panels (Invitae)			
	CMNext (Ambry Genetics)			
Comprehensive Arrhythmia Panels	Arrhythmia Panel (GeneDx)	81413, 81414	I45.81, I49.8, Z13.71, Z82.4, Z82.49, Z84.81, Z84.89	8
	Rhythm Next (Ambry Genetics)			
	Arrhythmia Comprehensive Panel (Invitae)			
	Genomic Unity Cardiac Ion Channelopathies Analysis (Variantyx Inc)	0237U		
Comprehensive Arrhythmia & Cardiomyopathy (Sudden Cardiac or Unexplained Death) Panels	Arrhythmia and Cardiomyopathy Comprehensive Panel- Primary Genes (Invitae)	81413, 81414, 81439	I42.0, I42.1, I42.2, I42.5, I45.81, I49.8, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	8
	Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication (ARUP Laboratories)			
Hypertrophic Cardiomyopathy (HCM)				
	Hypertrophic Cardiomyopathy Panel (Invitae)	81439, S3865	I42.1, I42.2, I42.9, Z13.71,	2, 3, 13

Hypertrophic Cardiomyopathy Panels	HCMNext (Ambry Genetics)		Z82.41, Z82.49, Z84.81, Z84.89	
	Hypertrophic Cardiomyopathy (HCM) Panel (GeneDx)			
Dilated Cardiomyopathy (DCM)				
Dilated Cardiomyopathy Panels	Dilated Cardiomyopathy Panel (GeneDx)	81439	I42.0, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	1, 4, 5 6, 20
	DCMNext (Ambry Genetics)			
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)				
Arrhythmogenic Right Ventricular Cardiomyopathy Panels	Arrhythmogenic Right Ventricular Cardiomyopathy Panel (GeneDx)	81439	I42.8, I42.9, Z82.41, Z82.49, Z84.81, Z84.89	7
	Arrhythmogenic Right Ventricular Cardiomyopathy Panel- Primary Genes (Invitae)			
Restrictive Cardiomyopathy (RCM)				
Restrictive Cardiomyopathy Panels	Restrictive Cardiomyopathy (RCM) Panel (Cincinnati Children's Hospital Medical Center - Molecular Genetics and Cytogenetics Laboratories)	81439	I42.5, I42.8, I42.9, Z82.41, Z82.49	4, 5
Left Ventricular Non-Compaction Cardiomyopathy (LVNC)				
Left Ventricular Non-Compaction Cardiomyopathy Panels	Left Ventricular Non-Compaction (LVNC) Panel (PreventionGenetics)	81439	I42.8, I42.9, Z82.41, Z82.49, Z84.81, Z84.89	4, 5
Long QT Syndrome (LQTS)				
Long QT Syndrome Panels	Long QT Syndrome Panel (Invitae)	81403, 81406, 81407, 81413,	I45.81, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4, 12, 18
	LQTS Panel (GeneDx)	81414, 81479		

Short QT Syndrome (SQTS)				
Short QT Syndrome Panels	Short QT Syndrome Panel- Primary Genes (Invitae)	81403, 81406, 81413, 81414, 81479	Z13.71, Z82.4, Z82.49, Z84.81, Z84.89	4, 12
	Short QT Syndrome Panel (PreventionGenetics)			
Brugada Syndrome (BrS)				
Brugada Syndrome Panels or SCN5A Variant Analysis	Brugada Panel (GeneDx)	81404, 81406, 81407, 81413, 81414, 81479	I49.8, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4
	Brugada Syndrome Panel- Primary Genes (Invitae)			
	SCN5A-Brugada Panel (GeneDx)	81407, S3861		
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)				
Catecholaminergic Polymorphic Ventricular Tachycardia Panels	Catecholaminergic Polymorphic Tachycardia Panel (Invitae)	81403, 81405, 81408, 81413, 81414, 81479	Z13.71, Z82.4, Z82.49, Z84.81, Z84.89	4
	Catecholaminergic Polymorphic Ventricular Tachycardia Panel (GeneDx)			
Familial Hypercholesterolemia (FH)				
Familial Hypercholesterolemia (FH) Panels	Familial Hypercholesterolemia (FH) Panel (GeneDx)	81401, 81405, 81406, 81407, 81479	E78, E78.01	9, 10, 17
	Invitae Familial Hypercholesterolemia Panel - Primary Genes (Invitae)			
Congenital Heart Malformations				
Congenital Heart Malformation Panels	Nonsyndromic Congenital Heart Disease Panel (PreventionGenetics)	81405, 81406, 81407, 81408, 81479	Q20, Q21, Q22, Q23, Q24	11
	Congenital Heart Disease Panel (Invitae)			

Post Heart Transplant Gene Expression Panels for Rejection Risk				
Post Heart Transplant Gene Expression Panels for Rejection Risk	AlloMap (CareDX)	81595	Z94.1, Z48.21	14
Donor-Derived Cell-Free DNA for Heart Transplant Rejection				
Donor-Derived Cell-Free DNA for Heart Transplant Rejection	AlloSure (CareDX)	81479	Z94.1, Z48.21	15, 16
	Viracor TRAC Heart ddcfDNA	0118U		
	myTAIHEART	0055U		

OTHER RELATED POLICIES

This policy document provides coverage criteria for genetic testing for cardiovascular disorders. Please refer to:

- **Genetic Testing: Aortopathies and Connective Tissue Disorders** for coverage criteria related to other genetic disorders affecting the heart and connective tissue.
- **Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for coverage criteria related to genetic disorders that affect multiple organ systems.
- **Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- **Genetic Testing: Preimplantation Genetic Testing** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- **Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to cardiac disorders not specifically discussed in this or another non-general policy.

COVERAGE CRITERIA

KNOWN FAMILIAL VARIANT ANALYSIS FOR CARDIAC DISORDERS

- I. Targeted mutation analysis for a known familial variant (81403) for a cardiac and connective tissue disorder is considered **medically necessary** when:
 - A. The member has a [close relative](#) with a known pathogenic or likely pathogenic variant causing the condition.
- II. Targeted mutation analysis for a known familial variant (81403) for a cardiac disorder is considered **investigational** for all other indications.

[back to top](#)

COMPREHENSIVE CARDIOMYOPATHY PANELS

- I. Comprehensive cardiomyopathy panels (81439) are considered **medically necessary** when:
 - A. The member has a diagnosis of cardiomyopathy, **OR**
 - B. The member has a [first-degree relative](#) with sudden unexplained cardiac death (SCD), **AND**
 1. Autopsy revealed unspecified cardiomyopathy (e.g., cardiomegaly or cardiomyopathy), **OR**
 2. Autopsy results do not reveal a cause of death.
- II. Comprehensive cardiomyopathy panels (81439) are considered **investigational** for all other indications.

Note: Multigene panels that are targeted to the cardiomyopathy phenotype observed are recommended by professional guidelines

[back to top](#)

COMPREHENSIVE ARRHYTHMIA PANELS

- I. Comprehensive arrhythmia panels (81413, 81414, 0237U) are considered **medically necessary** when:
 - A. The member meets one of the following:
 1. The member has a [first-degree relative](#) with sudden unexplained cardiac death (SCD) or sudden unexplained death (SUD) at age 40 or younger, **OR**
 2. The member has a [first-degree relative](#) with sudden unexplained cardiac death (SCD) over 40 years of age, with additional family history of sudden unexplained cardiac death, **AND**
 - a) Autopsy results do not reveal a cause of death, **OR**
 - B. The member has aborted sudden cardiac death, **AND**
 1. Clinical tests were non-diagnostic (e.g., EKG, cardiac stress tests, echocardiogram, intravenous pharmacologic provocation testing).
- II. Comprehensive arrhythmia panels (81413, 81414, 0237U) are considered **investigational** for all other indications.

[back to top](#)

COMPREHENSIVE ARRHYTHMIA AND CARDIOMYOPATHY (SUDDEN CARDIAC OR UNEXPLAINED DEATH) PANELS

- I. Comprehensive panels including genes for both cardiomyopathies and arrhythmias (81413, 81414, 81439) are considered **medically necessary** when:
 - A. The member meets clinical criteria for [Comprehensive Cardiomyopathy Panels](#), **AND**
 - B. The member meets clinical criteria for [Comprehensive Arrhythmia Panels](#)
- II. Comprehensive panels including genes for both cardiomyopathies and arrhythmias (81413, 81414, 81439) are considered **investigational** for all other indications.

[back to top](#)

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Hypertrophic Cardiomyopathy Panels

- I. Genetic testing for hypertrophic cardiomyopathy via a multigene panel (81439, S3865) is considered **medically necessary** when:
 - A. The member has unexplained left ventricular hypertrophy (LVH), **a** defined by myocardial wall thickness of 15mm or greater (in adults), or **a-z**core of 2 or greater (in children) based on echocardiogram or cardiac MRI **OR**
 - B. The member has a [first-degree relative](#) with sudden unexplained cardiac death (SUDS) and autopsy revealed an HCM phenotype.
- II. Genetic testing for hypertrophic cardiomyopathy via a multigene panel (81439, S3865) is considered **investigational** for all other indications.

Note: If a panel is performed, the appropriate panel code should be used

[back to top](#)

DILATED CARDIOMYOPATHY (DCM)

Dilated Cardiomyopathy Panels

- I. Genetic testing for dilated cardiomyopathy (DCM) via a multigene panel (81439) is considered **medically necessary** when:
 - A. The member meets both of the following:
 1. The member has a diagnosis of DCM by left ventricular enlargement and systolic dysfunction (e.g., ejection fraction less than 50%) based on echocardiogram, cardiac MRI, or left ventricular angiogram **AND**
 2. Non-genetic causes of DCM have been ruled out, such as prior myocardial infarction from coronary artery disease, valvular **and**

congenital heart disease, toxins (most commonly, anthracyclines or other chemotherapeutic agents; various drugs with idiosyncratic reactions), thyroid disease, inflammatory or infectious conditions, severe long-standing hypertension, and radiation, **OR**

- B. The member has a [first-degree relative](#) with sudden unexplained cardiac death (SUD) and autopsy revealed a DCM phenotype.
- II. Genetic testing for dilated cardiomyopathy (DCM) via a multigene panel (81439) is considered **investigational** for all other indications.

Note: If a panel is performed, the appropriate panel code should be used

[back to top](#)

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

Arrhythmogenic Right Ventricular Cardiomyopathy Panels

- I. Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) via a multigene panel (81439) is considered **medically necessary** when:
 - A. The member has a possible diagnosis of ARVC meeting the task force criteria (defined as having one major criterion, or two minor criteria from different categories); see major and minor criteria below in corresponding [Background and Rationale](#) section.
- II. Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) via a multigene panel (81439) is considered **investigational** for all other indications.

Note: If a panel is performed, the appropriate panel code should be used

[back to top](#)

RESTRICTIVE CARDIOMYOPATHY (RCM)

Restrictive Cardiomyopathy Panels

- I. Genetic testing for restrictive cardiomyopathy (RCM) via a multigene panel (81439) is considered **investigational** .

Note: If a panel is performed, the appropriate panel code should be used

[back to top](#)

LEFT VENTRICULAR NONCOMPACTION CARDIOMYOPATHY (LVNC)

Left Ventricular Non -Compaction Cardiomyopathy Panels

- I. Genetic testing for left ventricular non-compaction cardiomyopathy (LVNC) (81439) via a multigene panel when the LVNC phenotype is identified serendipitously in asymptomatic individuals with otherwise normal cardiovascular structure and function is considered **investigational** .

Note: The left ventricular noncompaction (LVNC) phenotype may be observed in conjunction with all other cardiomyopathy phenotypes and considerations related to genetic testing should always be directed by findings of a cardiomyopathy (or other cardiovascular) phenotype.

[back to top](#)

LONG QT SYNDROME (LQTS)

Long QT Syndrome Panels

- I. Genetic testing for long QT syndrome (LQTS) via multigene panel (81403, 81404, 81406, 81407, 81413, 81414, 81479) is considered **medically necessary** when:
 - A. The member is asymptomatic and has [a close relative](#) with a clinical diagnosis of LQTS, whose genetic status is unknown, **OR**
 - B. The member is symptomatic, **AND**

1. The member meets either of the following:
 - a) The member has a confirmed prolonged QTc (greater than 460ms prepuberty, greater than 450ms for men, greater than 460ms for women) on resting ECG and/or provocative stress testing with exercise or during intravenous pharmacologic provocation testing (eg, with epinephrine), **OR**
 - b) The member has a Schwartz score of 3.0 or more, **AND**
 2. Non-genetic causes of a prolonged QTc interval have been ruled out, such as QT-prolonging drugs, hypokalemia, structural heart disease, or certain neurologic conditions including subarachnoid bleed.
- II. Genetic testing for long QT syndrome (LQTS) via multigene panel (81403, 81404, 81406, 81407, 81413, 81414, 81479) is considered **investigational** for all other indications.

Note: If a panel is performed, the appropriate panel code should be used

[back to top](#)

SHORT QT SYNDROME (SQTS)

Short QT Syndrome Panels

- I. Genetic Testing for Short QT syndrome (SQTS) via multigene panel (81403, 81406, 81413, 81414, 81479) is considered **investigational** for all indications.

[back to top](#)

BRUGADA SYNDROME (BrS)

Brugada Syndrome Panels or *SCN5A* Variant Analysis

- I. Genetic testing for Brugada syndrome (BrS) via *SCN5A* variant analysis (81407, S3861) or multigene panel analysis (81404, 81406, 81407, 81413, 81414, 81479) is considered **medically necessary** when:
 - A. The member has one of the following ECG patterns:
 1. Type 1 ECG (elevation of the J wave 2 mm or larger with a ~~negative~~ T wave and ST segment that is coved type and gradually descending) in more than one right precordial lead with or without administration of a sodium channel blocker (i.e., flecainide, pilsicainide, ajmaline, or procainamide), **OR**
 2. Type 2 ECG (elevation of the J wave 2 mm or larger with a positive or biphasic T wave; ST segment with saddleback configuration and elevated greater than or equal to 1 mm) in more than one right precordial lead under baseline conditions with conversion to type 1 ECG following challenge with a sodium channel blocker, **OR**
 3. Type 3 ECG (elevation of the J wave 2 mm or larger with a positive T wave; ST segment with saddleback configuration and elevated less than 1 mm) in more than one lead under baseline conditions with conversion to type 1 ECG following challenge with a sodium channel blocker, **AND**
 - B. Any of the following:
 1. Documented ventricular fibrillation, **OR**
 2. Self-terminating polymorphic ventricular tachycardia, **OR**
 3. A family history of sudden cardiac death, **OR**
 4. Coved-type ECGs in family members, **OR**
 5. Electrophysiologic inducibility, **OR**
 6. Syncope or nocturnal agonal respiration, **OR**
 7. Cardiac arrest.

- II. Genetic testing for Brugada syndrome (BrS) via *SCN5A* variant analysis (81407, S3861) or multigene panel analysis (81404, 81406, 81407, 81413, 81479) is considered **investigational** for all other indications.

Note: If a panel is performed, the appropriate panel code should be used

[back to top](#)

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

Catecholaminergic Polymorphic Ventricular Tachycardia Panels

- I. Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) (81403, 81405, 81408, 81413, 81414, 81479) via multigene panel is considered **medically necessary** when:
 - A. The member has any of the following:
 1. Syncope occurring during physical activity or acute emotion, **OR**
 2. History of exercise- or emotion-related palpitations and dizziness in some individuals, **OR**
 3. Sudden unexpected cardiac death triggered by acute emotional stress or exercise, **OR**
 4. Family history of juvenile sudden cardiac death triggered by exercise or acute emotion, **OR**
 5. Exercise-induced polymorphic ventricular arrhythmias, **OR**
 6. Ventricular fibrillation occurring in the setting of acute stress, **AND**
 - B. An absence of structural cardiac abnormalities.
- II. Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) (81403, 81405, 81408, 81413, 81414, 81479) via multigene panel is considered **investigational** for all other indications.

Note: If a panel is performed, the appropriate panel code should be used

[back to top](#)

FAMILIAL HYPERCHOLESTEROLEMIA (FH)

Familial Hypercholesterolemia (FH) Panels

- I. Genetic testing for familial hypercholesterolemia (FH) via multigene panel (81401, 81405, 81406, 81407, 81479) to establish or confirm a diagnosis of familial hypercholesterolemia (FH) is considered **medically necessary** when:
 - A. The member is required to have a definitive genetic diagnosis in order to be eligible for specialty medications (eg, PCSK9 inhibitors) **AND**
 - B. The member is categorized as having possible, probable, or definite familial hypercholesterolemia by at least one of the following:
 1. Dutch Lipid Clinic Network Criteria*, **OR**
 2. Simon-Broome Register Criteria**, **OR**
 3. Make Early Diagnosis Prevent Early Death (MEDPED) Diagnostic Criteria***, **AND**
 - C. The panel contains at a minimum the following genes: *APOB*, *LDLR* and *PCSK9*.
- II. Genetic testing for familial hypercholesterolemia (FH) via multigene panel (81401, 81405, 81406, 81407, 81479) to establish or confirm a diagnosis of familial hypercholesterolemia (FH) is considered **investigational** for all other indications.

*Dutch Lipid Clinic Network Criteria. A score of 8 or greater on the Dutch Lipid Clinic Network criteria is considered definitive FH. Scores between 3 and 7 are considered “possible” or “probable” FH.

**Simon-Broome Register Criteria. A definitive diagnosis of FH is made based on a total cholesterol level greater than 290 mg/dL in adults (or low-density lipoprotein greater than 190 mg/dL), together with either positive physical exam findings or a positive genetic test. Probable FH is diagnosed using the same cholesterol levels, plus family history of premature coronary artery disease or total cholesterol of at least 290 mg/dL in a first- or a second-degree relative.

***Make Early Diagnosis Prevent Early Death (MEDPED) Diagnostic Criteria. These criteria provide a yes/no answer for whether an individual has FH, based on family history, age, and cholesterol levels. An individual who meets criteria for FH can be considered to have definitive FH.

[back to top](#)

CONGENITAL HEART MALFORMATIONS

Congenital Heart Malformation Panels

- I. Genetic testing for congenital heart malformations via multigene panel analysis (81405, 81406, 81407, 81408, 81479) may be considered **medically necessary** when:
 - A. The member has a complex congenital heart malformation (e.g., hypoplastic left heart, transposition of the great vessels, tetralogy of fallot, etc) **AND**
 - B. The member's clinical features do not fit a known genetic disorder for which targeted testing could be performed (e.g., 22q11.2 deletion syndrome, Down syndrome/Trisomy 21, Williams syndrome, etc) **AND**
 - C. Prenatal teratogen exposure has been considered, and ruled out when possible.
- II. Genetic testing for congenital heart malformations via multigene panel analysis (81405, 81406, 81407, 81408, 81479) is considered **investigational** for all other indications, including "simple" congenital heart defects (e.g. ventricular septal defects, atrial septal defects, patent ductus arteriosus).

[back to top](#)

POST HEART TRANSPLANT GENE EXPRESSION PANELS FOR REJECTION RISK

- I. The use of post heart transplant gene expression panels for rejection risk to determine management of patients after heart transplantation (81595) is considered **medically necessary** when:
 - A. The member is low-risk and has acute cellular rejection of grade 2R or greater, **AND**
 - B. The member is between 6 months and 5 years after heart transplant.

- II. The use of post heart transplant gene expression panels for rejection risk to determine management of patients after heart transplantation (81595) is considered **investigational** for all other indications.

[back to top](#)

DONOR-DERIVED CELL-FREE DNA FOR HEART TRANSPLANT REJECTION

- I. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after heart transplantation (81479, 0118U) (e.g., Allosure, Viracor TRAC® Heart dcfDNA) is considered **investigational** for all indications, including but not limited to:
 - A. Detection of acute heart transplant rejection
 - B. Detection of heart transplant graft dysfunction

[back to top](#)

NOTES AND DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives:
 - a. **First-degree relatives** are parents, siblings, and children
 - b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
 - c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

CLINICAL CONSIDERATIONS

Due to the complexity of genetic testing for cardiomyopathy and the potential for misinterpretation of results, the decision to test and the interpretation of test results should

be performed by, or in consultation with, an expert in the area of medical genetics and/or hypertrophic cardiomyopathy.

To inform and direct genetic testing for at-risk individuals, genetic testing should initially be performed in at least one close relative with definite cardiomyopathy (index case), if possible.

Consultation with an expert in medical genetics and/or the genetics of cardiomyopathy, in conjunction with a detailed pedigree analysis, is appropriate when testing of second- or third-degree relatives is considered.

[back to top](#)

BACKGROUND AND RATIONALE

Known Familial Variant Analysis for Cardiac Disorders

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

Comprehensive Cardiomyopathy Panels

Heart Failure Society of America and American College of Medical Genetics and Genomics (ACMG)

The Heart Failure Society of America published joint guidelines with the American College of Medical Genetics and Genomics (Hershberger et al, 2018) and made the following recommendations:

- **Guideline 4: Genetic testing is recommended for patients with cardiomyopathy (Level of evidence A)**
 - 4a: Genetic testing is recommended for the most clearly affected family member.
 - 4b: Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
 - 4c: In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered (p. 289)

Per the guideline, multigene panel genetic testing is recommended over a serial single-gene testing approach owing to the genetically and heterogeneous nature of cardiomyopathy. (p.290)

Asia Pacific Heart Rhythm Society (APHRS) and Heart Rhythm Society (HRS)

The Asia Pacific Heart Rhythm Society (APHRS) and Heart Rhythm Society (HRS) published an expert consensus statement (Stiles et al, 2020) on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families that includes the following “take-home messages” related to genetic testing:

- For survivors of sudden cardiac arrest (SCA), victims of sudden unexplained death (SUD), and their relatives, a multidisciplinary team is central to thorough investigation, so as to maximize the opportunity to make a diagnosis. Where there has been an SCD or resuscitated SCA and a genetic cause is suspected, genetic testing and counseling is essential for families, to ensure that risks, benefits, results, and the clinical significance of genetic testing can be discussed. (p. e3)
- A comprehensive autopsy is an essential part of the investigation of SUD and should include collection and storage of tissue suitable for genetic analysis. When the autopsy suggests a possible genetic cause, or no cause and the heart is normal, referral to a multidisciplinary team for further investigation is indicated. (p. e3)
- For victims of SCD or survivors of cardiac arrest where the phenotype is known, genetic testing of the proband focused on likely candidate genes, along with clinical evaluation of family members, aids in identifying family members with, or at risk of developing, the same condition. (p. e3)
- For the investigation of SCA survivors, essential inquiry includes detailed personal and family history, witness accounts, physical examination, multiple electrocardiograms (ECGs), and cardiac imaging. Ambulatory monitoring and/or provocative testing (exercise, pharmacological, and invasive electrophysiological)

may provide additional useful information. A sample suitable for future DNA testing should be taken early in the patient's course and stored. (p. e4)

- Genetic investigation of SCA survivors is best undertaken at a center with multidisciplinary care infrastructure and should focus on likely candidate genes known to be causally related to the suspected phenotype. In some cases, genetic evaluation without a suspected phenotype may be undertaken with appropriate genetic counseling, although genetic evaluation of patients with a known nongenetic cause of cardiac arrest is discouraged. (p. e4)

Comprehensive Arrhythmia Panels

Asia Pacific Heart Rhythm Society (APHRS) and Heart Rhythm Society (HRS)

The Asia Pacific Heart Rhythm Society (APHRS) and Heart Rhythm Society (HRS) published an expert consensus statement (Stiles et al, 2020) on the investigation of decedents with sudden unexplained death and patients/ families with sudden cardiac arrest.

“Three scenarios may trigger arrhythmia syndrome-focused genetic evaluation of SCD [sudden cardiac death] even if the phenotype remains unknown: ...3) young age (less than 40 years). (p. e24)

“Where there has been an SCD or resuscitated SCA and a genetic cause is suspected, genetic testing and counseling is essential for families...” (p. e3)

“For victims of SCD or survivors of cardiac arrest where the phenotype is known, genetic testing of the proband focused on likely candidate genes, along with clinical evaluation of family members, aids in identifying family members with, or at risk of developing, the same condition.” (p. e3)

“For victims of SCD or survivors of cardiac arrest where the phenotype is not known, arrhythmia syndrome-focused genetic testing may help arrive at a secure diagnosis...” (p. e4)

Comprehensive Arrhythmia & Cardiomyopathy (Sudden Cardiac or Unexplained Death) Panels

Asia Pacific Heart Rhythm Society (APHRS) and Heart Rhythm Society (HRS)

The Asia Pacific Heart Rhythm Society (APHRS) and Heart Rhythm Society (HRS) published an expert consensus statement (Stiles et al, 2020) on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families.

For victims of sudden cardiac death (SCD) or survivors of cardiac arrest where the phenotype is not known, arrhythmia syndrome–focused genetic testing may help arrive at a secure diagnosis, whereas wider testing without careful consideration of the implications of indeterminate results by experienced clinicians may only serve to add uncertainty and lead to misinterpretation of results. (p. e4) Additionally, the paper states that hypothesis-free genetic testing is not indicated in cases of SCD where the phenotype remains unknown. Genetic testing using any range from large unfocused gene panels to whole-exome or whole-genome sequencing in the absence of a clinical phenotype or diagnosis may be considered in the context of a scientific effort but is not recommended for routine patient care and counseling. (p.e26)

Hypertrophic Cardiomyopathy Panels

American College of Cardiology and American Heart Association

The American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines published an updated guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy (2020), which stated the following with regard to genetic testing for HCM:

“Counseling patients with HCM regarding the potential for genetic transmission of HCM is one of the cornerstones of care. Screening first-degree family members of patients with HCM, using either genetic testing or an imaging/electrocardiographic surveillance protocol, can begin at any age and can be influenced by specifics of the patient/family history and family preference. As screening recommendations for family members hinge on the pathogenicity of any detected variants, the reported pathogenicity should be reconfirmed every 2 to 3 years.” (p. e161)

American College of Cardiology Foundation and American Heart Association

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) (2011) issued joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy. They state that hypertrophic cardiomyopathy is clinically recognized by a maximal left ventricular wall thickness of 15mm or greater in adults, and the equivalent

relative to body surface area in children. They also recommended that screening (with or without genetic testing) be performed in first-degree relatives of individuals with hypertrophic cardiomyopathy. (p. e792)

European Society of Cardiology

The European Society of Cardiology (2014) issued guidelines on the diagnosis and management of hypertrophic cardiomyopathy, including the diagnostic criteria for adults and children as defined by the left ventricle wall thickness of more than two standard deviations greater than predicted mean, or z-score of greater than 2. (p. 2739)

Dilated Cardiomyopathy Panels

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (ACMG) (2018) published clinical practice recommendations for the genetic evaluation of cardiomyopathy. The following recommendations were made for DCM:

“Evidence indicates that clinical genetic testing can identify the cause of DCM in families with autosomal dominant inheritance in approximately 25-40% of cases, whereas in isolated cases of DCM, the yield of testing is commonly estimated at 10-25%. Core genes to be tested in individuals with DCM include genes encoding sarcomeric and cytoskeletal proteins, although DCM testing panels typically carry several dozen genes, some with uncertain significance. In most cases, all HCM and ARVC genes are included in DCM panels because of gene/phenotype overlap.” (p. 903)

“As in HCM, infants and children with DCM may require additional diagnostic evaluation.” (p. 904)

This guideline also acknowledges that DCM can be caused by non-genetic factors including “...coronary artery disease, primary valvular or congenital heart disease, or previous exposure to cancer chemotherapy or other injurious drugs...” and therefore these causes must be excluded when considering genetic testing. (p. 282)

American Heart Association

The American Heart Association (2016) published a scientific statement regarding diagnostic and treatment strategies for dilated cardiomyopathy and made the following recommendations regarding genetic testing for dilated cardiomyopathy (p. e619):

- Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.
- In patients with familial or idiopathic cardiomyopathy, genetic testing can be useful in conjunction with genetic counseling.
- Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to facilitate cascade screening within the family, and to help with family planning.

Additionally, the following recommendations were made regarding genetic testing for pediatric dilated cardiomyopathy:

- Comprehensive or targeted DCM genetic testing (*LMNA* and *SCN5A*) is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) or a family history of premature unexpected sudden death. (p. e622)
- Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case. (p. e619)
- Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, facilitate cascade screening within the family, and help with family planning. (p. e619)
- In pediatric patients with DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered. (p. e623)

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (2011) published joint recommendations and made the following recommendations for genetic testing for dilated cardiomyopathy (p. 1312):

- Comprehensive or targeted (*LM* and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) and/or with a family history of premature unexpected sudden death. (Class I)

- Mutation-specific [familial variant] testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case. (Class I)
- Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning. (Class IIa)

Hershberger, et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline (2018)

Hershberger, et al published guidelines on cardiomyopathy genetic evaluation. They state:

“That familial dilated cardiomyopathy (DCM) has a genetic basis is also well accepted. (The term DCM is used herein instead of the more technical attribution, “idiopathic dilated cardiomyopathy”, where the other common and easily clinically detected causes of systolic dysfunction such as coronary artery disease, primary valvular or congenital heart disease, or previous exposure to cancer chemotherapy or other injurious drugs, have been excluded).” (p.282)

GeneReviews: Dilated Cardiomyopathy Overview

GeneReviews is an expert authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended diagnostic screening for dilated cardiomyopathy is as follows:

“An ejection fraction of less than 50% is considered systolic dysfunction. The left ventricular ejection fraction is the most commonly used clinical measure of systolic function, and is usually estimated from a two-dimensional echocardiogram or from cardiac MRI. ... Ejection fractions can also be estimated from a left ventricular angiogram.”

Arrhythmogenic Right Ventricular Cardiomyopathy Panels

Marcus et al 2010

Modification of the Task Force Criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) were published in 2010 and outlined clinical criteria for individuals

with possible ARVC, which the Task Force defined as individuals with one major criteria or two minor criteria from different categories. The major and minor criteria are as follows:

Major Criteria:

- 1.) By 2D echo:
 - a.) Regional right ventricular (RV) akinesia, dyskinesia, or aneurysm; AND
 - b.) ONE of the following (end diastole):
 - i.) PLAX (parasternal long axis) RVOT (right ventricular outflow tract) greater than or equal to 32 mm; corrected for body surface area (PLAX/BSA) greater than or equal to 19 mm/m²
 - ii.) PSAX (parasternal short axis) RVOT greater than or equal to 36 mm; corrected for BSA greater than or equal to 21 mm/m²
 - iii.) Fractional area change less than or equal to 33%
- 2.) By MRI:
 - a.) Regional RV akinesia or dyskinesia or dyssynchronous RV contraction; AND
 - b.) ONE of the following:
 - i.) Ratio of RV end-diastolic volume to BSA greater than or equal to 110 mL/m² (male), or greater than or equal to 100 mL/m² (female)
 - ii.) RV ejection fraction less than or equal to 40%
- 3.) By right ventricular angiography: Regional RV akinesia, dyskinesia or aneurysm
- 4.) On endomyocardial biopsy or autopsy: Residual myocytes lower than 60% by morphometric analysis (or less than 50% if estimated), with fibrous replacement of the RV free wall myocardium in at least one sample, with or without fatty replacement of tissue
- 5.) On EKG: Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals age older than 14 years (in the absence of complete right bundle branch block QRS greater than or equal to 120 ms)
- 6.) Depolarization/conduction abnormalities: Epsilon waves (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)
- 7.) Arrhythmia: Nonsustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
- 8.) Family history (any of the following):
 - a.) ARVC confirmed in a first-degree relative who meets current task force criteria
 - b.) ARVC confirmed pathologically at autopsy or surgery in a first-degree relative

Minor Criteria:

- 1.) By 2D echo:
 - a.) Regional right ventricular akinesia or dyskinesia; AND
 - b.) ONE of the following (end diastole):
 - i.) PLAX RVOT greater than or equal to 29 to less than 32 mm; corrected for BSA greater than or equal to 16 to less than 19 mm/m²
 - ii.) PSAX RVOT greater than or equal to 32 to less than 36 mm; corrected for BSA greater than or equal to 18 to less than 21 mm/m²
 - iii.) Fractional area change greater than 33% to less than or equal to 40%
- 2.) By MRI:
 - a.) Regional RV akinesia or dyskinesia or dyssynchronous RV contraction; AND
 - b.) ONE of the following:
 - i.) Ratio of RV end-diastolic volume to BSA greater than or equal to 100 to less than 110 mL/m² (male) or greater than or equal to 90 to less than 100 mL/m² (female)
 - ii.) RV ejection fraction greater than 40% to less than or equal to 45%
- 3.) On endomyocardial biopsy or autopsy: Residual myocytes 60% to 75% by morphometric analysis (or 50%-65% if estimated), with fibrous replacement of the RV free wall myocardium in at least one sample, with or without fatty replacement of tissue
- 4.) On EKG (any of the following):
 - a.) Inverted T waves in leads V1 and V2 in individuals age older than 14 years (in absence of complete right bundle branch block) or in V4, V5, or V6
 - b.) Inverted T waves in leads V1, V2, V3, and V4 in individuals age older than 14 years in the presence of complete right bundle branch block
- 5.) Depolarization/conduction abnormalities (any of the following):
 - a.) Late potential by signal-averaged EKG in at least one of three parameters in the absence of a QRS duration of greater than or equal to 110 ms on the standard EKG
 - b.) Filtered QRS duration (fQRS) greater than or equal to 114 ms
 - c.) Duration of terminal QRS less than 40 uV (low amplitude signal duration) greater than or equal to 38 ms
 - d.) Root-mean-square voltage of terminal 40 ms less than or equal to 20 uV
 - e.) Terminal activation duration of QRS greater than 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 in the absence of complete right bundle branch block
- 6.) Arrhythmia (any of the following):

- a.) Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis
 - b.) More than 500 ventricular extrasystoles per 24 hours (Holter)
- 7.) Family history (any of the following):
- a.) 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
 - b.) Premature sudden death (age less than 35 years) due to suspected ARVC in a first-degree relative
 - c.) ARVC confirmed pathologically or by current task force criteria in second-degree relative (p. 808 and 809)

Restrictive Cardiomyopathy Panels

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (ACMG) (2018) published clinical practice recommendations for the genetic evaluation of cardiomyopathy. The following recommendations were made for RCM:

In regard to selecting genes to test in association with the cardiomyopathy, “Consider HCM or DCM panel.”

“Genetic causes of RCM continue to be identified, but because RCM is a relatively rare form of cardiomyopathy, numbers remain limited. A recent study identified a pathogenic variant in 60% of subjects, primarily occurring in genes known to cause HCM. Family members were frequently identified with HCM or HCM with restrictive physiology... Cardiac amyloidosis resulting from pathogenic variants in TTR needs to be differentiated from other forms of RCM due to the age demographic in which this occurs, the slowly progressive nature of this disease, and therefore different management strategies. The TTR allele p.Val142Ile (commonly referred to as Val122Ile based on nomenclature for the circulating protein after Nterminal peptide cleavage) has been found in 10% of African Americans older than age 65 with severe congestive heart failure. Substantial recent progress with amyloidosis, both in imaging strategies, including cardiac magnetic resonance and pyrophosphate scanning, and therapeutic interventions in ongoing clinical trials, provide new incentives for genetic diagnosis.” (p. 904)

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (2011) published joint recommendations and made the following recommendations for genetic testing for restrictive cardiomyopathy (p. 1312):

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a RCM-causative mutation in the index case. (Class I)
- RCM genetic testing may be considered for patients in whom a cardiologist has established a clinical index of suspicion for RCM based on examination of the patient's clinical history, family history, and electrocardiographic/ echocardiographic phenotype. (Class IIb)

Left Ventricular Non -Compaction Cardiomyopathy Panels

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (ACMG) (2018) published clinical practice recommendations for the genetic evaluation of cardiomyopathy. The following recommendations were made for LVNC (p. 904):

“The left ventricular noncompaction (LVNC) phenotype may be observed in conjunction with all other cardiomyopathy phenotypes, so considerations related to genetic testing should always be directed by findings of a cardiomyopathy (or other cardiovascular) phenotype. Genetic testing is not recommended when the LVNC phenotype is identified serendipitously in asymptomatic individuals with otherwise normal cardiovascular structure and function.”

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (2011) published joint recommendations and made the following recommendations for genetic testing for left ventricular noncompaction (p. 1312):

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a LVNC-causative mutation in the index case. (Class I)

- LVNC genetic testing can be useful for patients in whom a cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype. (Class IIa)

Long QT Syndrome Panels

American Heart Association, American College of Cardiology, and Heart Rhythm Society

In 2017, the American Heart Association, American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (p. 149160):

- In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended. (I - Strong)
- In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information (I - Strong)
- In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable. Genetic testing may confirm a diagnosis; however, therapy for these patients is not guided by genotype status. (IIa - Moderate)
- In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives, allowing for lifestyle modification and potential treatment. (IIb - Weak)
- In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives. (IIb - Weak)

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (2011, p. 1311) published joint recommendations and made the following recommendations for genetic testing for LQTS:

- Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong

clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype. (Class I)

- Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc, ie, otherwise idiopathic) on serial 12-lead ECGs defined as QTc.480 ms (prepuberty) or 500 ms (adults). (Class I)
- Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case. (Class I)
- Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values 460 ms (prepuberty) or 480 ms (adults) on serial 12-lead ECGs. (Class I)

Schwartz, Crotti; 2012

Schwartz and Crotti published a scoring system in which to diagnose LQTS. They suggest using the Schwartz score for “selection of those patients who should undergo molecular screening (everyone with a score greater than or equal to 3.0) and in the use of “cascade screening” for the identification of all affected family members including the silent mutation carriers (p. 5)”.

SCORE: less than or equal to 1 point: low probability of LQTS.

1.5 to 3 points: intermediate probability of LQTS.

3.5 points or more: high probability.

Brugada Syndrome Panels or *SCN5A* Variant Analysis

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (2011) published joint recommendations and made the following recommendations for genetic testing for BrS (p. 13):¹

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case. (Class I)
- Comprehensive or BrS1 (*SCN5A*) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype. (Class IIa)
- Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern. (Class III)

Catecholaminergic Polymorphic Ventricular Tachycardia Panels

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (2011) published joint recommendations and made the following recommendations for genetic testing for CPVT (p. 1311):

- Comprehensive or CPVT1 and CVPT2 (*RYR2 & CASQ2*) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion. Mutation specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case. (Class I)

Familial Hypercholesterolemia (FH) Panels

Migliara et al. (2017)

Migliara et al. (2017) conducted a systematic review of guidelines on genetic testing and management of individuals with familial hypercholesterolemia (FH). The literature search, conducted through April 2017, identified 10 guidelines for inclusion. Three of the guidelines were developed within the U. S.: those by the National Lipid Association, International FH Foundation, and American Association of Clinical Endocrinologists and American College of Endocrinology. Guidance from the National

Institute for Health and Care Excellence was also included in the review. The quality of the guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation II instrument, with guideline quality ranging from average to good. Most guidelines agreed that genetic testing follows cholesterol testing, physical findings distinctive of FH, and highly suggestive family history of FH. Universal screening for FH was not recommended. This review highlighted the importance of genetic testing for FH in children, because aggressive treatment at an earlier age may prevent premature coronary heart disease.

Musunuru et al, (2020)

"An international expert panel convened by the FH Foundation wrote a scientific statement on clinical genetic testing for FH. This statement generally recommends genetic testing of FH genes (*LDLR, APOB, PCSK9*, and potentially other genes if warranted by the patient phenotype; Table 3) for individuals with hypercholesterolemia for which an inherited variant is a likely cause. The statement highlights individuals with some combination of persistent elevated low-density lipoprotein cholesterol levels, personal history of premature coronary artery disease, family history of hypercholesterolemia, and family history of premature coronary artery disease who should be offered or may be considered for genetic testing (Table 4). In addition, cascade genetic testing should be offered to all at-risk family members of an individual found to have a pathogenic variant in a FH gene. Genetic testing for FH is expected to result in a higher rate of diagnosis among patients with FH, more effective cascade testing, the initiation of therapies at earlier ages, and more accurate risk stratification" (p. 381).

National Heart, Lung and Blood Institute

Recommendations from a National Heart, Lung, and Blood Institute expert panel on cardiovascular health and risk reduction in children and adolescents were published in 2011. The report contained the following recommendations (see Table 1 below from p. S230).

Table 1. Recommendations on Cardiovascular Health and Risk Reduction in Children and Adolescents

Recommendation	GOE
"The evidence review supports the concept that early identification and control of dyslipidemia throughout youth and into adulthood	B

will substantially reduce clinical CVD risk beginning in young adult life. Preliminary evidence in children with heterozygous FH with markedly elevated LDL-C indicates that earlier treatment is associated with reduced subclinical evidence of atherosclerosis.”	
“TC and LDL-C levels fall as much as 10-20% or more during puberty.”	B
“Based on this normal pattern of change in lipid and lipoprotein levels with growth and maturation, age 10 years (range age 9-11 years) is a stable time for lipid assessment in children. For most children, this age range will precede onset of puberty.”	D
CVD: cardiovascular disease; FH: familial hypercholesterolemia; GOE: grade of evidence; LDL-C: low-density lipoprotein cholesterol; TC: triglycerides.	

Congenital Heart Malformation Panels

American Heart Association

The American Heart Association published a statement entitled “Genetic Basis for Congenital Heart Disease: Revisited” in September 2018 (correction published in November 2018) which states the following: “Uncovering a genetic pathogenesis for congenital HD is increasingly clinically relevant, in part because of the aforementioned improved survival. For the clinician caring for a child or adult with congenital HD, important reasons for determining the genetic cause can include (1) assessing recurrence risks for the offspring of the congenital HD survivor, additional offspring of the parents, or other close relatives; (2) evaluating for associated extracardiac involvement; (3) assessing risk for neurodevelopmental delays for newborns and infants; and (4) providing more accurate prognosis for the congenital HD and outcomes for congenital HD-related interventions.” (p. 3).

Post Heart Transplant Gene Expression Panels for Rejection Risk

International Society of Heart and Lung Transplantation Guidelines

The International Society of Heart and Lung Transplantation Guidelines (Conzan et al, 2010) has the following recommendations for the non-invasive monitoring of acute cellular rejection after heart transplant, and specifically addresses Allomap:

“Gene Expression Profiling (Allomap) can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years after HT”. (p. 926)

Donor-Derived Cell-Free DNA for Heart Transplant Rejection *Khush et al (2019)*

Khush et al (2019) published a study using an Allomap registry to investigate donor-derived cell free DNA in heart transplant rejection compared to biopsy results. The study included several protocol changes during the course of the study, making conclusions difficult to draw. Future directions highlighted in this study included clinical utility studies, but those studies have not been published to date.

Qian et al (2022)

A recent review (Qian et al, 2022) on noninvasive biomarkers in heart transplant pointed out the high sensitivity for detection of allograft injury, but low specificity for acute rejection, and concluded with the need for well-designed clinical utility studies. (p. 89)

[back to top](#)

REFERENCES

1. Hershberger RE, Givertz MM, Ho CY, et al. Genetic Evaluation of Cardiomyopathy. Heart Failure Society of America Practice Guideline. J Card Fail. 2018;24(5):280-292. doi:10.1016/j.cardfail.2018.03.004
2. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-2779. doi:10.1093/eurheartj/ehu284

3. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124(24):e783-e831. doi:10.1161/CIR.0b013e318223e2bd
4. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011;8(8):1308-1339. doi:10.1016/j.hrthm.2011.05.020
5. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG) [originally accepted 2018, published correction appears in *Genet Med*. 2019 Oct;21(10):2406-2409]. *Genet Med*. 2018;20(9):899-909. doi:10.1038/s41436-018-0039-z
6. Bozkurt B, Colvin M, Cook J, et al. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association [published correction appears in *Circulation*. 2016 Dec 6;134(23):e652]. *Circulation*. 2016;134(23):e579-e646. doi:10.1161/CIR.0000000000000455
7. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J*. 2010;31(7):806-814. doi:10.1093/eurheartj/ehq025
8. Stiles MK, Wilde AAM, Abrams DJ, et al. 2020 APHRS/HRS Expert Consensus Statement on the Investigation of Decedents with Sudden Unexplained Death and Patients with Sudden Cardiac Arrest, and of Their Families [published online ahead of print, 2020 Oct 13]. *Heart Rhythm*. 2020;S1547-5271(20)30953-X. doi:10.1016/j.hrthm.2020.10.010
9. Migliara G, Baccolini V, Rosso A, et al. Familial Hypercholesterolemia: A Systematic Review of Guidelines on Genetic Testing and Patient Management. *Front Public Health*. 2017;5:252. Published 2017 Sep 25. doi:10.3389/fpubh.2017.00252
10. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128 Suppl 5(Suppl 5):S213-S256. doi:10.1542/peds.2009-2107C
11. Pierpont ME, Brueckner M, Chung WK, et al. Genetic Basis for Congenital Heart Disease: Revisited: A Scientific Statement From the American Heart Association [published correction appears in *Circulation*. 2018 Nov 20;138(21):e713]. *Circulation*. 2018;138(21):e653-e711. doi:10.1161/CIR.0000000000000606

12. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published correction appears in *Circulation*. 2018 Sep 25;138(13):e419-e420]. *Circulation*. 2018;138(13):e272-e391. doi:10.1161/CIR.0000000000000549
13. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2020;76(25):e159-e240. doi:10.1016/j.jacc.2020.08.045
14. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2010;29(8):914-956. doi:10.1016/j.healun.2010.05.034
15. Khush KK, Patel J, Pinney S, et al. Noninvasive detection of graft injury after heart transplant using donor-derived cell-free DNA: A prospective multicenter study. *Am J Transplant*. 2019;19(10):2882-2899. doi:10.1111/ajt.15339
16. Qian X, Shah P, Agbor-Enoh S. Noninvasive biomarkers in heart transplant: 2020-2021 year in review. *Curr Opin Organ Transplant*. 2022;27(1):74. doi:10.1097/MOT.0000000000000945.
17. Musunuru K, Hershberger RE, Day SM, Klinedinst NJ, Landstrom AP, Parikh VN, Prakash S, Sensarian C, Sturm AC; American Heart Association Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. *Circ Genom Precis Med*. 2020 Aug;13(4):e000067. doi: 10.1161/HCG.0000000000000067. Epub 2020 Jul 23. PMID: 32698598.
18. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation*. 2011 Nov 15;124(20):2448-1doi: 10.1161/CIRCULATIONAHA.111.062182. PMID: 22083145
19. Genetic Support Foundation. Genetics 101 Inheritance Patterns: Familial Pathogenic Variant. Accessed 10/4/2022. <https://geneticsupportfoundation.org/genetics-101/#>
20. Hershberger, R and Jordan, E. Dilated Cardiomyopathy Overview. 2007 Jul 27 [Updated 2022 Apr 7]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1309/>

[back to top](#)