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 life-saving 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	Targeted Mutation Analysis for a Known Familial Variant	81403		
Comprehensive Cardiomyopathy Panels	Cardiomyopathy Panel (GeneDx)	81439, 81403, 81404, 81405, 81406, 81407, 81408	I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	1, 8
	Cardiomyopathy Comprehensive Panel-Primary Genes (Invitae)			
Comprehensive Arrhythmia Panels	Arrhythmia Panel (GeneDx)	81413, 81414	I45.81, I49.8, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4, 7, 8, 12
	Arrhythmia Comprehensive Panel-Primary Genes (Invitae)	81405, 81406, 81407, 81414, 81479		
Comprehensive Arrhythmia & Cardiomyopathy (Sudden Cardiac or Unexplained Death) Panels	Arrhythmia and Cardiomyopathy Comprehensive Panel - Primary Genes (Invitae)	81161, 81406, 81479	I42.0, I42.1, I42.2, I42.5, I45.81, I49.8, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	7, 8, 12, 18
	Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication (ARUP Laboratories)	81228, 81413, 81414		
Hypertrophic Cardiomyopathy (HCM)				
Hypertrophic Cardiomyopathy Panels	Invitae Hypertrophic Cardiomyopathy Panel - Primary Genes (Invitae)	81439	I42.1, I42.2, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	1, 2, 3, 4, 15
	Hypertrophic Cardiomyopathy (HCM) Panel (GeneDx)	81405, 81406, 81407		

Dilated Cardiomyopathy (DCM)				
Dilated Cardiomyopathy Panels	Dilated Cardiomyopathy Panel (GeneDx)	81405, 81406, 81407	I42.0, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4, 5, 6, 8
	DCMNext (Ambry Genetics)	81439		
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)				
Arrhythmogenic Right Ventricular Cardiomyopathy Panels	Arrhythmogenic Right Ventricular Cardiomyopathy Panel (GeneDx)	81406	I42.8, I42.9, Z82.41, Z82.49, Z84.81, Z84.89	4, 6, 19
	Arrhythmogenic Right Ventricular Cardiomyopathy Panel - Primary Genes (Invitae)	81439		
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, 6
Left Ventricular Non-Compaction Cardiomyopathy (LVNC)				
Left Ventricular Non-Compaction Cardiomyopathy Panels	Left Ventricular Non-Compaction (LVNC) Panel (PreventionGenetics)	81479	I42.8, I42.9, Z82.41, Z82.49, Z84.81, Z84.89	4, 6
Long QT Syndrome (LQTS)				
Long QT Syndrome Panels	Long QT Syndrome Panel - Primary Genes Only (Invitae)	81403, 81406, 81407, 81414, 81479	I45.81, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4, 14
	LQTS Panel (GeneDx)	81403, 81404, 81406, 81414		
Short QT Syndrome (SQTS)				

Short QT Syndrome Panels	Short QT Syndrome Panel - Primary Genes (Invitae)	81403, 81406, 81414	Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4
	Short QT Syndrome Panel (PreventionGenetics)	81479		
Brugada Syndrome (BrS)				
Brugada Syndrome Panels or SCN5A Variant Analysis	Brugada Panel (GeneDx)	81404, 81406, 81407	I49.8, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4
	Brugada Syndrome Panel - Primary Genes (Invitae)	81407, 81479		
	SCN5A-Brugada Panel (GeneDx)			
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)				
Catecholaminergic Polymorphic Ventricular Tachycardia Panels	Catecholaminergic Polymorphic Tachycardia Panel (Invitae)	81403, 81405, 81408, 81479	Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4
	Catecholaminergic Polymorphic Ventricular Tachycardia Panel (GeneDx)	81403, 81405, 81408		
Familial Hypercholesterolemia (FH)				
Familial Hypercholesterolemia (FH) Panels	Familial Hypercholesterolemia (FH) Panel (GeneDx)	81401, 81405, 81406	E78, E78.01	9, 10, 11
	Invitae Familial Hypercholesterolemia Panel - Primary Genes (Invitae)	81405, 81406, 81407, 81479		
Congenital Heart Malformations				
Congenital Heart Malformation Panels	Nonsyndromic Congenital Heart Disease Panel (PreventionGenetics)	81405, 81406, 81407, 81408, 81479	Q20, Q21, Q22, Q23, Q24	13
	Congenital Heart Disease Panel (Invitae)	81404, 81405, 81406, 81479		
Post Heart Transplant Panels for Rejection Risk				

Post Heart Transplant Gene Expression Panels for Rejection Risk	AlloMap (CareDX)	81595	Z94.1, Z48.21	16, 17, 18
	MMDX Heart	0087U		
Donor-Derived Cell-Free DNA for Heart Rejection	AlloSure (CareDX) Prospera Heart (Natera)	81479		
	Viracor TRAC® Heart dd-cfDNA (Eurofins/Viracor)	0118U		

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.

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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) or sudden unexplained death (SUD), **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

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COMPREHENSIVE ARRHYTHMIA PANELS

I. Comprehensive arrhythmia panels (81405, 81406, 81407, 81413, 81414, 81479) are considered **medically necessary** when:

   A. 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 less, **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 (81405, 81406, 81407, 81413, 81414, 81479) are considered **investigational** for all other indications.

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

I. Comprehensive panels including genes for both arrhythmias and cardiomyopathies (81161, 81228, 81406, 81413, 81414, 81479) are considered **investigational**.

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HYPERTROPHIC CARDIOMYOPATHY (HCM)

Hypertrophic Cardiomyopathy Panels

I. Genetic testing for hypertrophic cardiomyopathy via a multigene panel (81405, 81406, 81407, 81439) is considered **medically necessary** when:

   A. The member has unexplained left ventricular hypertrophy (LVH), **AND**

      1. Myocardial wall thickness of 15mm or greater (in adults), or a z-score greater than or equal to 2 (in children) based on echocardiogram or cardiac MRI, **AND**

      2. Non-genetic causes of HCM have been ruled out, such as chronic hypertension, aortic stenosis, extreme physiologic hypertrophy (aka "athletes heart"), **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 (81405, 81406, 81407, 81439) is considered **investigational** for all other indications.

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

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DILATED CARDIOMYOPATHY (DCM)

Dilated Cardiomyopathy Panels

I. Genetic testing for dilated cardiomyopathy (DCM) via a multigene panel (81405, 81406, 81407, 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, and/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 DCM (81405, 81406, 81407, 81439) is considered **investigational** for all other indications.

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

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ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

Arrhythmogenic Right Ventricular Cardiomyopathy Panels

I. Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) via a multigene panel (81406, 81439) is considered **medically necessary** when:

A. The member has a confirmed diagnosis of ARVC by electrocardiogram, MRI, or angiogram meeting the task force criteria for at least possible ARVC (defined as having one major or two minor criteria), **OR**

B. The member has a first-degree relative with sudden unexplained cardiac death (SCD) and autopsy revealed an ARVC phenotype.

II. Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) via a multigene panel (81406, 81439) is considered **investigational** for all other indications.

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

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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

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LEFT VENTRICULAR NON-COMPACTION CARDIOMYOPATHY (LVNC)

Left Ventricular Non-Compaction Cardiomyopathy Panels

I. Genetic testing for left ventricular non-compaction cardiomyopathy (LVNC) (81479) 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.

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LONG QT SYNDROME (LQTS)

Long QT Syndrome Panels

I. Genetic testing for long QT syndrome (LQTS) via multigene panel (81403, 81404, 81406, 81407, 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 460 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 greater than or equal to 2, **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

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SHORT QT SYNDROME (SQTS)

Short QT Syndrome Panels

I. Genetic testing for short QT syndrome (SQTS) (81403, 81406, 81414, 81479) via a multigene panel is considered **investigational**.

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BRUGADA SYNDROME (BrS)

Brugada Syndrome Panels or SCN5A Variant Analysis

I. Genetic testing for Brugada syndrome (BrS) via *SCN5A* variant analysis (81407, 81479) or multigene panel analysis (81404, 81406, 81407, 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 greater than or equal to 2 mm 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)

2. Type 2 ECG (elevation of the J wave greater than or equal to 2 mm with a positive or biphasic T wave; ST segment with saddle-back configuration and elevated ≥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

3. Type 3 ECG (elevation of the J wave greater than or equal to 2 mm with a positive T wave; ST segment with saddle-back 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
2. Self-terminating polymorphic ventricular tachycardia
3. A family history of sudden cardiac death
4. Coved-type ECGs in family members
5. Electrophysiologic inducibility
6. Syncope or nocturnal agonal respiration
7. Cardiac arrest

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

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

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CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

Catecholaminergic Polymorphic Ventricular Tachycardia Panels

I. Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) (81403, 81405, 81408, 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
      2. History of exercise- or emotion-related palpitations and dizziness in some individuals
      3. Sudden unexpected cardiac death triggered by acute emotional stress or exercise
      4. Family history of juvenile sudden cardiac death triggered by exercise or acute emotion
      5. Exercise-induced polymorphic ventricular arrhythmias
      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, 81479) via multigene panel is considered **investigational** for all other indications.

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

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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*

      2. Simon-Broome Register Criteria**

      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.

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CONGENITAL HEART MALFORMATIONS

Congenital Heart Malformation Panels

I. Genetic testing for congenital heart malformations via multigene panel analysis (81404, 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 (81404, 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).

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POST HEART TRANSPLANT GENE EXPRESSION PANELS FOR REJECTION RISK

I. The use of gene expression panels for rejection risk to determine management of patients after heart transplantation (81595) (Allomap) is considered **medically necessary** for members 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 post-heart transplant.

II. The use of other gene expression panels for rejection risk to determine management of patients after heart transplantation (0087U) (MMDX Heart) is considered **investigational** for all indications.

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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, Prospera Heart, Viracor TRAC® Heart dd-cfDNA) 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

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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

2. **ARVC major and minor criteria:** See Marcus, et. al. 2010 for details regarding major and minor criteria.

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.

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BACKGROUND AND RATIONALE

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

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.
- 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.
- 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.
- 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.
- 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.

Comprehensive Arrhythmia Panels

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

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European Society of Human Genetics, European Council of Legal Medicine, and European Society of Cardiology

The European Society of Human Genetics, European Council of Legal Medicine, European Society of Cardiology working group on myocardial and pericardial diseases, European Reference Network for rare, low prevalence and complex diseases of the heart (ERN GUARD-Heart), Association for European Cardiovascular Pathology (2019) made the following recommendations related to genetic testing in the context of sudden cardiac death:

- Increasing the proportion of both medicolegal and medical autopsy in case of sudden, unexpected natural death should be a major objective. This should be mandatory for deaths under the age of 40, it should be considered for deaths between ages 40 and 65, and evaluated on a case by case basis after age 65.
- In cases of sudden (cardiac) death, a full autopsy should be performed, including heart dissection, sampling for possible genetic and toxicological analysis, and examination should adhere to minimal standards as per European guidelines. Guidelines should be made mandatory in European countries by seeking support from Ministries of Health and Justice.
- Information on genetic testing and communication of genetic test results should be given in compliance with standard procedures in clinical genetics and with the appropriate national legislation. Familial communication and appropriate cascade testing should be approached in a systematic fashion using genetic services where possible. We consider that there can be no duty to warn all relatives, but that a responsible system will make attempts to alert relatives when appropriate.
- A multidisciplinary cardiogenetic team should conduct the family investigation. The appropriate genetic test should be considered according to a combination of pathology findings, family history, and the results of cardiac family screening. The genetic test should be performed on the DNA of the deceased in the first instance, and testing of relatives should then be offered if a variant affecting function (pathogenic or likely pathogenic variant) is identified.

Heart Rhythm Society, European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society

The Heart Rhythm Society, European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society (2013) issued an expert consensus statement on the diagnosis and

management of patients with inherited primary arrhythmia syndromes, which included the following guidelines on genetic testing in SUDS and SUDI:

- Collection of blood and/or suitable tissue for molecular autopsy/postmortem genetic testing is recommended in all SUDS victims. (Class I)
- Collection of blood and/or suitable tissue for molecular autopsy is recommended in all SUDI victims. (Class I)
- Genetic screening of the first-degree relatives of a SUDS victim is recommended whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDS victim. (Class I)
- An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing can be useful for all SUDI victims. (Class IIa)
- Genetic screening of the first-degree relatives of a SUDI victim is recommended whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDI victim. Obligate mutations carriers should be prioritized. (Class I)

Heart Rhythm Society

The HRS published guidelines that included genetic testing for arrhythmogenic cardiomyopathy (Towbin et al, 2019). They recommend testing for arrhythmogenic cardiomyopathy for the following genes: *BAG3, DES, DSC2, DSG2, DSP, FLNC, JUP, LDB3, LMNA, NKX2-5, PKP2, PLN*, *RBM20, SCN5A, TMEM43*.

Hypertrophic 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 HCM:

> "The diagnostic yield of HCM testing is approximately 30–60%. The yield of testing is higher in individuals who have a known family history of HCM. Pathogenic variants in MYH7 and MYBPC3 account for approximately 80% of all cases for which a molecular diagnosis is achieved. Beyond sarcomeric genes, core genes to screen in patients with HCM include *GLA*, *PRKAG2*, and *LAMP2*."

> "Infants and children with HCM may require more specialized evaluation and diagnostic testing because of the rate of syndromic conditions and inborn errors of metabolism associated with HCM at these ages. Consultation with a geneticist is indicated."

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 corner-stones 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."

American College of Cardiology Foundation and American Heart Association

The American College of Cardiology Foundation and the American Heart Association (2011) issued joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy and made the following recommendations in regards to genetic testing:

- Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM.
- Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause.
- The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain.
- Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.
- Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM.
- Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient.

- Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM.

European Society of Cardiology

The European Society of Cardiology (2014) issued guidelines on the diagnosis and management of hypertrophic cardiomyopathy, which included the following recommendations related to genetic testing:

- Genetic testing is recommended in patients fulfilling diagnostic criteria for hypertrophic cardiomyopathy when it enables cascade genetic screening of their relatives.
- It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.
- In the presence of symptoms and signs of disease suggestive of specific causes of hypertrophic cardiomyopathy, genetic testing is recommended to confirm the diagnosis.
- Cascade genetic screening, after pre-test counseling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation.
- Genetic testing in patients with a borderline diagnosis of hypertrophic cardiomyopathy should be performed only after detailed assessment by specialist teams.

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 hypertrophic cardiomyopathy:

- Comprehensive or targeted … HCM genetic testing is recommended for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype. (Class I)
- Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case. (Class I)

Dilated Cardiomyopathy Panels

GeneReviews

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 testing for dilated cardiomyopathy panels (Hershberger and Jordan, 2022) is as follows (in 1. Dilated Cardiomyopathy (DCM): Definition section):

- The diagnosis of DCM is established when both of the following are present:
    - Left ventricular enlargement. Enlargement is most commonly assessed in adults by either echocardiography or cardiac MRI. Because of rapid growth in children, expert cardiovascular assessment is recommended to assess left ventricular enlargement in the pediatric population.
- Systolic dysfunction, a reduction in the myocardial force of contraction. 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. Another noninvasive approach is a cardiac nuclear study. Ejection fractions can also be estimated from a left ventricular angiogram.

Hershberger and Jordan (updated 2022) categorizes DCM into multiple categories, including acquired (secondary) DCM which is defined as (in 2. Dilated Cardiomyopathy (DCM): Categories section):

> The most common cause of acquired DCM is ischemic injury, such as that caused by prior myocardial infarction from coronary artery disease. Other less common causes include 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. While emerging evidence suggests that DCM arising after chemotherapy exposure may also have a genetic background, the clinical relevance of this information is currently undefined.

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (ACMG) (Hershberger et al, 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.
>
> Infants and children with DCM may require additional diagnostic evaluation. (p. 903)

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (Ackerman et al, 2011) published joint recommendations and made the following recommendations for genetic testing for dilated cardiomyopathy:

- 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) (Table 1 p. 1312)

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

The APHRS and HRS (Stiles, 2020), published joint recommendations on genetic testing in the case of sudden unexplained death (SUD) as follows:

- Family screening should be advised in first-degree relatives of SUD subjects with a negative autopsy (or with no autopsy) when the decedent's age is <45 years (and in all patients with a clear phenotype regardless of age). (p. 43)

Arrhythmogenic Right Ventricular 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 ARVC:

> "Genetic testing of *PKP2, DSP, DSG2, DSC2, JUP, TMEM43*, and *PLN* resulted in a molecular diagnosis in 63% of patients who fulfilled Task Force criteria for ARVC. Digenic inheritance and compound heterozygosity are frequent and, combined with decreased penetrance that is a feature of ARVC, may significantly complicate genetic counseling. ARVC overlaps with arrhythmogenic left ventricular cardiomyopathy, sometimes more broadly referred to as arrhythmogenic cardiomyopathy. This reflects genetic and phenotypic overlap among these forms of cardiomyopathy. Accordingly, genetic testing for ARVC using a larger cardiomyopathy panel may identify nondesmosomal genes with pathogenic variants. Similarly, desmosome gene pathogenic variations have also been identified in patients diagnosed with DCM."

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 arrhythmogenic right ventricular cardiomyopathy:

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the ACM/ARVC-causative mutation in an index case. (Class I)
- Comprehensive or targeted (*DSC2, DSG2, DSP, JUP, PKP2*, and *TMEM43*) ACM/ARVC genetic testing can be useful for patients satisfying task force diagnostic criteria for ACM/ARVC. (Class IIa)

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 N-terminal 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."

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:

- 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:

> "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:

- 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:

- 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) 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)

Short QT Syndrome 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 SQTS:

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case. (Class I)
- Comprehensive or SQT1-3 (*KCNH2, KCNQ1, KCNJ2*) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient's clinical history, family history, and electrocardiographic phenotype. (Class IIb)

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:

- 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:

- 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 patient 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."

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).

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 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."	B
"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." (page 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 (Constanzo 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.

Donor-Derived Cell-Free DNA for Heart Transplant

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. Additionally, 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.

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