Coverage of any medical intervention discussed in a Medica medical policy is subject to the limitations and exclusions outlined in the member's benefit certificate or summary plan description (SPD) and applicable state and/or federal laws.

GENETIC TESTING: CARDIAC DISORDERS MP9589

Covered Service: Yes

Prior Authorization Required: No

Additional Information: Use the current applicable CPT/HCPCS code(s). An appropriate diagnosis code must appear on the claim. Claims will deny in the absence of applicable diagnosis and procedure code(s) and/or if the criteria for coverage outlined below are not met. The following codes are included below for informational purposes only, and may be subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Medica Medical Policy:

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.

Gene expression profiles and cell-free DNA testing can also be utilized following a heart transplant to assess for risk and/or presence of organ rejection.

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This document addresses genetic testing for cardiac disorders, focusing on cardiomyopathy, arrhythmia, congenital heart defects, cholesterol disorders, and assessment of organ rejection following a heart transplant.

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

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		13
Comprehensive Cardiomyopathy Panels	Cardiomyopathy Panel (GeneDx)	81439	I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	1, 6
	Cardiomyopathy Comprehensive Panels (Invitae)			
	CMNext (Ambry Genetics)			
Comprehensive Arrhythmia Panels	Arrhythmia Panel (GeneDx)	81413, 81414	I45.81, I49.8, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	15
	RhythmNext (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	6
	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, 9

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Hypertrophic Cardiomyopathy Panels	HCMNext (Ambry Genetics) Hypertrophic Cardiomyopathy (HCM) Panel (GeneDx)		Z82.41, Z82.49, Z84.81, Z84.89	
Dilated Cardiomyopathy (DCM)				
Dilated Cardiomyopathy Panels	Dilated Cardiomyopathy Panel (GeneDx) DCMNext (Ambry Genetics)	81439	I42.0, I42.9, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	1, 14, 15
Arrhythmogenic Cardiomyopathy				
Arrhythmogenic Cardiomyopathy Panels	Arrhythmogenic Right Ventricular Cardiomyopathy Panel (GeneDx) Arrhythmogenic Cardiomyopathy Panel - Primary Genes (Invitae)	81439	I42.8, I42.9, Z82.41, Z82.49, Z84.81, Z84.89	20
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	5
Left Ventricular Non-Compaction Cardiomyopathy (LVNC)				
Left Ventricular Non-Compaction Cardiomyopathy Panels	Left Ventricular Non-Compaction (LVNC) Panel (Blueprint Genetics)	81439	I42.8, I42.9, Z82.41, Z82.49, Z84.81, Z84.89	5
Long QT Syndrome (LQTS)				
Long QT Syndrome Panels	Long QT Syndrome Panel (Invitae) LQTS Panel (GeneDx)	81403, 81406, 81407, 81413, 81414, 81479	I45.81, Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	4, 8, 12, 16
Short QT Syndrome (SQTS)				
	Short QT Syndrome Panel (Invitae)			

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Short QT Syndrome Panels	Short QT Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81403, 81406, 81413, 81414, 81479	Z13.71, Z82.41, Z82.49, Z84.81, Z84.89	15, 16
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	15, 17
	Brugada Syndrome Panel (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, Z82.41, Z82.49, Z84.81, Z84.89	18
	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	11, 19
	Invitae Familial Hypercholesterolemia Panel - Primary Genes (Invitae)			
Congenital Heart Malformations				
Congenital Heart Malformation Panels	Nonsyndromic Congenital Heart Disease Panel (PreventionGenetics, part of Exact Sciences)	81405, 81406, 81407, 81408, 81479	Q20, Q21, Q22, Q23, Q24	7
	Congenital Heart Disease Panel (Invitae)			
Post Heart Transplant Gene Expression Panels for Rejection Risk via Peripheral Blood				
Post Heart Transplant Gene Expression Panels	AlloMap (CareDx)	81595	Z94.1, Z48.21	10

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
for Rejection Risk via Peripheral Blood				
Post Heart Transplant Gene Expression Panels for Rejection Risk via Tissue				
Post Heart Transplant Gene Expression Panels for Rejection Risk via Tissue	MMDX (Kashi Clinical Laboratories)	0087U	Z94.1, Z48.21	10
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	21
	Prospera Heart (Natera)			
	Viracor TRAC Heart dd-cfDNA (Eurofins)	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 MP9588*** for coverage criteria related to other genetic disorders affecting the heart and connective tissue.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay MP9587*** for coverage criteria related to genetic disorders that affect multiple organ systems.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss MP9576*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Preimplantation Genetic Testing MP9574*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing MP9610*** 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 cardiac death (SCD) or sudden unexplained death (SUD), **AND**

      1. This relative's autopsy revealed unspecified cardiomyopathy (e.g., cardiomegaly or cardiomyopathy), **OR**

      2. This relative's autopsy did not reveal a cause of death and the heart is normal.

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 (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 cardiac death (SCD) or sudden unexplained death (SUD) before age 50 years, **OR**
2. The member has a first-degree relative with sudden cardiac death (SCD) at age 50 years or older, **AND**
    a) The deceased individual had family history of premature SCD, **OR**
    b) The deceased individual's death is suspicious for genetic heart disease, **OR**,

B. The member has aborted sudden cardiac death, **AND**

1. Clinical tests were non-diagnostic for reversible, ischemic, or structural causes (e.g., ECG, cardiac stress tests, echocardiogram, intravenous pharmacologic provocation testing).

II. Comprehensive arrhythmia panels (81413, 81414, 0237U) 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 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.

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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), as defined by myocardial wall thickness of 15mm or greater (in adults), or a z-score of 2 or greater (in children) based on echocardiogram or cardiac MRI, **OR**

B. The member has a first-degree relative with sudden cardiac death (SCD), **AND**

1. 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

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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 cardiac death (SCD), **AND**

1. 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

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ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic Cardiomyopathy Panels

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

A. The member has any one of the following:

1. On echo:

a) Regional RV akinesia, dyskinesia, **OR**

b) Aneurysm, **AND**

c) At least one of the following (end diastole):

(1) PLAX RVOT ≥32 mm (PLAX/BSA ≥19 mm/m2), **OR**

(2) PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m2), **OR**

(3) Fractional area change ≤33%, **OR**

2. On MRI

a) Regional RV akinesia or dyskinesia, **OR**

b) Dyssynchronous RV contraction, **AND**

c) At least one of the following:

(1) Rao RVEDV/BSA ≥110 mL/m2 (male), ≥100 mL/m2 (female), **OR**

(2) RVEF ≤40%, **OR**

3. On RV Angiography

a) Regional RV akinesia, dyskinesia, or aneurysm, **OR**

4. Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in more than 1 sample, with or without fatty replacement, **AND**:

a) Residual myocytes <60% by morphometric analysis (or <50% if estimated), **OR**

5. On ECG

a) Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120ms), **OR**

b) Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3), **OR**

c) Nonsustained or sustained VT of LBBB with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL), **OR**

6. On Family History

a) ARVC confirmed in a first-degree relative who meets current Task Force Criteria, **OR**

b) ARVC confirmed pathologically at autopsy or surgery in a first-degree relative, **OR**

c) Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation, **OR**

B. The member has any two of the following:

1. On echo

a) Regional RV akinesia, dyskinesia, **OR**

b) Aneurysm, **AND**

c) At least one of the following (end diastole):

(1) PLAX RVOT ≥29 mm to <32 mm (PLAX/BSA ≥16 to <19 mm/m2), **OR**

(2) PSAX RVOT ≥32 to <36 mm (PSAX/BSA ≥18 to <21 mm/m2), **OR**

(3) Fractional area change >33 to ≤40%, **OR**

2. On MRI

a) Regional RV akinesia or dyskinesia, **OR**

b) Dyssynchronous RV contraction, **AND**

c) At least one of the following:

(1) Rao RVEDV/BSA ≥100 to <110 mL/m2 (male), ≥90 to 100 mL/m2 (female), **OR**

(2) RVEF >40 to ≤45%, **OR**

3. Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in more than 1 sample, with or without fatty replacement, **AND**

    a) Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), **OR**

4. On ECG

    a) Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete RBBB), or in V4, V5, or V6, **OR**

    b) Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete RBBB, **OR**

    c) Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110ms on the standard ECG:

        (1) Filtered QRS duration (fQRS) ≥114 ms, **OR**

        (2) Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms, **OR**

        (3) Root-mean-square voltage of terminal 40 ms ≤20 μV, **OR**

    d) Terminal activation duration of QRS ≥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 RBBB, **OR**

    e) Nonsustained or sustained VT or RV outflow configuration, LBBB morphology with inferior axis (positive QRS in II, III and aVF and negative in lead aVL) or of unknown axis, **OR**

    f) >500 ventricular extrasystoles per 24 hours (Holter), **OR**

5. On family History

    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, **OR**

    b) Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative, **OR**

    c) ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative

II. Genetic testing for arrhythmogenic cardiomyopathy 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

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) (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.

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LONG QT SYNDROME (LQTS)

Long QT Syndrome Panels

I. Genetic testing for long QT syndrome (LQTS) via multigene panel (81403, 81406, 81407, 81413, 81414, 81479) is considered **medically necessary** when:

   A. The member is asymptomatic, **AND**

      1. The member has a confirmed prolonged QTc (greater than 460ms prepuberty, greater than 480 ms for adults) on resting ECG and/or provocative stress testing with exercise or during intravenous pharmacologic provocation testing (eg, with epinephrine), **OR**

      2. The member has a blood relative with a clinical diagnosis of LQTS, whose genetic status is unknown, **OR**

B. The member is symptomatic (for example: a history of syncope, cardiac arrest, and/or aborted sudden death), **AND**

1. The member meets either of the following:

a) A cardiologist has established a strong clinical suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrographic phenotype, **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, 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) via multigene panel (81403, 81406, 81413, 81414, 81479) is considered **medically necessary** when:

A. The member has a QTc of 330ms or less, **OR**

B. The member has a SQTS diagnostic score of 4 or greater utilizing the following criteria, **OR**

Criteria	**Points**
Electrocardiogram[a]	
QTc less than 370 ms	1
QTc less than 350 ms	2
QTc less than 330 ms	3

Criteria	Points
J point-T peak interval[b] less than 120 ms	1
Clinical history[c]*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history[d]*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative SCD	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

SQTS score: High-probability SQTS: greater than or equal to 4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: less than or equal to 2 points.

a Electrocardiogram: must be recorded in the absence of modifiers known to shorten the QT.

b Jpoint-Tpeak interval must be measured in the precordial lead with the greatest amplitude T-wave.

c Clinical history: events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope.

d Family history: points can only be received once in this section.

*A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.

C. The member is asymptomatic and has a first-degree relative with a clinical diagnosis of SQTS, whose genetic status is unknown.

II. Genetic testing for short QT syndrome (SQTS) via multigene panel (81403, 81406, 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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BRUGADA SYNDROME (BrS)

Brugada Syndrome Panels or *SCN5A* Variant Analysis

I. Genetic testing for Brugada syndrome (BrS) via *SCN5A* variant analysis (81407, S3861) is considered **medically necessary** when:

A. The member meets one of the following:

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 (e.g., flecainide, pilsicainide, ajmaline, or procainamide), **OR**

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 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 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. Conditions causing a Brugada syndrome phenocopy (e.g., as myocardial ischaemia, electrolyte disturbances, and drug intoxications) have been ruled out, **AND**

C. Any of the following:

1. Recurrent syncope, **OR**
2. Ventricular fibrillation, **OR**
3. Self-terminating polymorphic ventricular tachycardia, **OR**
4. Cardiac arrest, **OR**
5. A family history of sudden cardiac death

II. Genetic testing for Brugada syndrome (BrS) via *SCN5A* variant analysis (81407, S3861) is considered **investigational** for all other indications.

III. Genetic testing for Brugada syndrome (BrS) via genes other than *SCN5A*, including multigene panel analysis (81404, 81406, 81407, 81413, 81414, 81479), is considered **investigational**.

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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, 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, **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 bidirectional or 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

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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 (see Background and Rationale section):

      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.

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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).

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POST HEART TRANSPLANT GENE EXPRESSION PANELS FOR REJECTION RISK VIA PERIPHERAL BLOOD

I. The use of post heart transplant gene expression panels for rejection risk via peripheral blood to determine management of patients after heart transplantation (81595) is considered **medically necessary** when:

   A. The member has undergone heart transplant and is at low-risk for organ rejection, **AND**

   B. The member’s heart transplant was performed at least 2 months ago and less than 5 years ago.

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

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POST HEART TRANSPLANT GENE EXPRESSION PANELS FOR REJECTION RISK VIA TISSUE

I. The use of post heart transplant gene expression panels for rejection risk via tissue (0087U) 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) is considered **medically necessary** when:

   A. The member has undergone a heart transplant, **AND**

B. Peripheral blood measurement of donor-derived cell-free DNA testing has not been performed in the past twelve months.

II. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after heart transplantation (81479, 0118U) is considered **investigational** for all other indications.

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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. A **phenocopy** is a trait or disease that resembles the trait expressed by a certain genotype, but in an individual that is not a carrier of that genotype

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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

Known Familial Variant Analysis for Cardiac Disorders

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on genetic testing 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

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, Latin American Hearth Rhythm Society

The EHRA/HRS/APHRS/LAHRS 2022 expert consensus statement on the state of genetic testing for cardiac diseases provided guidance on the investigation of decedents with sudden unexplained death and patients/ families with sudden cardiac arrest. "In relatives of UCA [unexplained cardiac arrest] survivors or SCD [sudden cardiac death] decedents, clinical evaluation of first degree family members should be performed, and targeted to the index case's phenotype if present." (p. 532)

These guidelines also provide a flowchart for workup for a sudden cardiac death or non-fatal cardiac arrest, recommending that for individuals who died from a SUD or UCA in which no autopsy was performed, and were less than age 50 years, and/or had a family history of premature SCD and/or genetic heart disease, and/or circumstances of death were suspicious for genetic heart disease, clinical evaluation of first degree family members is indicated. (p. 533)

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, which 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)

While large unfocused gene panels are generally discouraged for this indication, because there is a path to coverage for both Comprehensive Arrhythmia Panels and Comprehensive Cardiomyopathy Panels (both phenotypically-focused tests), it is the philosophy of Concert Genetics that, if a member meets criteria for both individual panels, that member should also meet criteria for the combined test.

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 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." (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

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, Latin American Hearth Rhythm Society

In their 2022 expert consensus statement, the European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Hearth Rhythm Society state: “Genetic testing is…useful in all DCM [dilated cardiomyopathy] patients, is recommended in DCM patients with the highest yield of pathogenic variant screening and should be considered even in the absence of familial contest or associated clinical features.” (p. 525)

Heart Failure Society of America

Hershberger, et al published guidelines in 2018 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:

DCM is established when a patient has both left ventricular enlargement and systolic dysfunction. “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 Cardiomyopathy Panels

Towbin et al 2019

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

I. Echo:
    A. Regional RV akinesia, dyskinesia, OR

B. Aneurysm and 1 of the following (end diastole):
    1. PLAX RVOT ≥32 mm (PLAX/BSA ≥19 mm/m2)
    2. PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m2)
    3. Fractional area change ≤33%

II. MRI
- A. Regional RV akinesia or dyskinesia, OR
- B. Dyssynchronous RV contraction and 1 of the following:
    1. Rao RVEDV/BSA ≥110 mL/m2 (male), ≥100 mL/m2 (female)
    2. RVEF ≤40%

III. RV Angiography
- A. Regional RV akinesia, dyskinesia, or aneurysm

IV. Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in more than 1 sample, with or without fatty replacement and with:
- A. Residual myocytes <60% by morphometric analysis (or <50% if estimated)

V. ECG
- A. Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120ms)
- B. Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)
- C. Nonsustained or sustained VT of LBBB with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)

VI. Family History
- 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
- C. Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation

Minor Criteria

I. Echo
- A. Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole):
    1. PLAX RVOT ≥29 mm to <32 mm (PLAX/BSA ≥16 to <19 mm/m2)
    2. PSAX RVOT ≥32 to <36 mm (PSAX/BSA ≥18 to <21 mm/m2)
    3. Fractional area change >33 to ≤40%

II. MRI
- A. Regional RV akinesia or dyskinesia, OR
- B. Dyssynchronous RV contraction and 1 of the following:
    1. Rao RVEDV/BSA ≥100 to <110 mL/m2 (male), ≥90 to 100 mL/m2 (female)

2. RVEF >40 to ≤45%

III. Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in more than 1 sample, with or without fatty replacement and with:
   A. Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated)

IV. ECG
   A. Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete RBBB), or in V4, V5, or V6.
   B. Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete RBBB
   C. Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110ms on the standard ECG:
      1. Filtered QRS duration (fQRS) ≥114 ms
      2. Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
      3. Root-mean-square voltage of terminal 40 ms ≤20 μV
   D. Terminal activation duration of QRS ≥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 RBBB
   E. Nonsustained or sustained VT or RV outflow configuration, LBBB morphology with inferior axis (positive QRS in II, III and aVF and negative in lead aVL) or of unknown axis
   F. >500 ventricular extrasystoles per 24 hours (Holter)

V. Family History
   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 (<35 years of age) due to suspected ARVC in a first-degree relative
   C. ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative (p. 311)

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." (p. 904)

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." (p. 904)

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 patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information (I - Strong) (p. 149)

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,* and *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 greater than 480 ms (prepuberty) or greater than 500 ms (adults). (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 greater than 460 ms (prepuberty) or greater than 480 ms (adults) on serial 12-lead ECGs. (Class IIB) (p. 1311)

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.

Heart Rhythm Society, European Heart Rhythm Society, Asia Pacific Heart Rhythm Society

The Priori et al HRS/EHRA/APHRS published an expert consensus statement in 2013 and defined "arrhythmic events" as "...the occurrence of symptomatic or asymptomatic sustained or nonsustained spontaneous ventricular tachycardia, or unexplained syncope/resuscitated cardiac arrest." (p. 1933) and "...produces syncope, cardiac arrest and…sudden death." (p. 1935)

Short QT Syndrome

Heart Rhythm Society, European Heart Rhythm Society, Asia Pacific Heart Rhythm Society

The Priori et al HRS/EHRA/APHRS published an expert consensus statement in 2013 with the following Class 1 clinical diagnostic criteria (which are later referenced in Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on the state of genetic testing for cardiac diseases. *Journal of Arrhythmia*. 2022;38(4):491-553) for short QT syndrome (SQTS): "This group has reached a consensus that a cutoff value less than or equal to 330ms should be used for the diagnosis." (p. 1943)

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, Latin American Hearth Rhythm Society

In 2022, Wilde et al published the following guidelines regarding SQTS: "In any patient satisfying the diagnostic criteria for SQTS (such as Class 1 clinical diagnosis [see Priori et al HRS/EHRA/APHRS 2013 expert consensus statement] or SQTS diagnostic score greater [than or equal to] 4), molecular genetic testing is recommended for the definitive disease associated genes (currently *KCNH2*, *KCNQ1*). Testing of *KCNJ2* and *SLC4A3* may be performed in all index patients in whom a cardiologist has established with a high probability a diagnosis of SQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline or during ECG Holter recording and exercise stress test (SQTS diagnostic score greater than or equal to 4)." (p. 515) Cascade testing for at-risk family members is recommended when a disease-causing mutation is identified. (p. 516)

Supplementary Table 9. Diagnostic score cards for short QT syndrome (4)

Criteria	Points
Electrocardiogram[a]	
QTc less than 370 ms	1
QTc less than 350 ms	2
QTc less than 330 ms	3
J point-T peak interval[b] less than 120 ms	1
Clinical history[c]*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2

Unexplained syncope	1
Atrial fibrillation	1
Family history[d]*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative SCD	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

SQTS score: High-probability SQTS: greater than or equal to 4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: less than or equal to 2 points.

[a] Electrocardiogram: must be recorded in the absence of modifiers known to shorten the QT.

[b] Jpoint-Tpeak interval must be measured in the precordial lead with the greatest amplitude T-wave.

[c] Clinical history: events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope.

[d] Family history: points can only be received once in this section.

*A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.

Brugada Syndrome Panels or *SCN5A* Variant Analysis

GeneReviews: Brugada Syndrome

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 Brugada syndrome is as follows:

“Brugada syndrome [BrS] should be suspected in individuals with any of the following findings:

- Recurrent syncope
- Ventricular fibrillation

- Self-terminating polymorphic ventricular tachycardia
- Cardiac arrest
- Family history of sudden cardiac death

AND one of the following EKG patterns:

Type 1 EKG (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 (V1-V3)*... with or without administration of a sodium channel blocker (e.g., flecainide, pilsicainide, ajmaline, or procainamide)

Type 2 EKG (elevation of the J wave greater than or equal to 2 mm 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 EKG following challenge with a sodium channel blocker

Type 3 EKG (elevation of the J wave greater than or equal to 2 mm 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 EKG following challenge with a sodium channel blocker."

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, Latin American Hearth Rhythm Society

"Brugada syndrome phenocopies such as myocardial ischaemia, electrolyte disturbances and drug intoxications should be excluded before a diagnosis of BrS can be made." (p. 510-511)

"Other genes [besides *SCN5A*] have been implicated in BrS. However, the gene-disease validity of most of those genes (other than *SCN5A*) has been disputed following rigorous assessment of available data using the ClinGen framework. Although a disputed ClinGen status does not challenge a role of the gene product in BrS pathophysiology, it strongly argues against reporting those genes in the diagnostic setting." (p. 511)

* No other factor(s) should account for the EKG abnormality.

Catecholaminergic Polymorphic Ventricular Tachycardia Panels

GeneReviews: Catecholaminergic Polymorphic Ventricular Tachycardia

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 catecholaminergic polymorphic ventricular tachycardia is as follows:

"Catecholaminergic polymorphic ventricular tachycardia (CPVT) should be suspected in individuals who have one or more of the following:

- Syncope occurring during physical activity or acute emotion; mean onset is age seven to 12 years. Less frequently, first manifestations may occur later in life; individuals with a first event up to age 40 years have been reported.
- History of exercise- or emotion-related palpitations and dizziness in some individuals
- Sudden unexpected cardiac death triggered by acute emotional stress or exercise
- Family history of juvenile sudden cardiac death triggered by exercise or acute emotion
- Exercise-induced bidirectional or polymorphic ventricular arrhythmias…
- Ventricular fibrillation occurring in the setting of acute stress

The diagnosis of CPVT is established in the presence of a structurally normal heart, normal resting EKG, and exercise- or emotion-induced bidirectional or polymorphic ventricular tachycardia…"

Familial Hypercholesterolemia (FH) Panels

Austin et al (2004)

"Three groups have developed diagnostic tools for FH [familial hypercholesterolemia]: The US MedPed Program, the Simon Broome Register Group in the United Kingdom, and the Dutch Lipid Clinic Network." (p. 408)

The US (MEDPED) Diagnostic Criteria for FH.
FH is diagnosed if total cholesterol (TC) levels exceed the threshold stated

Age (years)	First Degree relative with FH (TC, mmol/L)	Second Degree relative with FH (TC, mmol/L)	Third Degree relative withF H (TC, mmol/L)	General Population (TC, mmol/L)
less than 20	5.7	5.9	6.2	7
20-29	6.2	6.5	6.7	7.5
30-39	7	7.2	7.5	8.8
40 or older	7.5	7.8	8	9.3

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.

Simon Broome Register Diagnostic Criteria	
A diagnosis of explicit FH requires either (1), (2) or (3)	
1	i. Cholesterol higher than 7.5 mmol/L or LDL-cholesterol above 4.9 mmol/L in adult
	ii. Tendon xanthomas in patient or a 1st degree relative (parent, sibling, child), or in a 2nd degree relative (grand parent, uncle, aunt)
2	i. Cholesterol higher than 6.7 mmol/L or LDL-cholesterol above 4.0 mmol/L in a child under 16

	years of age
	ii. Tendon xanthomas in patient or a 1st degree relative (parent, sibling, child), or in a 2nd degree relative (grand parent, uncle, aunt)
3	i. DNA based evidence of a functional LDLR, PCSK9 and APOB mutation
A diagnosis of probable FH requires either (1), (2) or (3)	
1	i. Cholesterol higher than 7.5 mmol/L or LDL-cholesterol above 4.9 mmol/L in adult
	ii. Family History of myocardial infarction (MI) before 50 years of age in a 2nd degree relative or below age 60 in a 1st degree relative
2	i. Cholesterol higher than 6.7 mmol/L or LDL-cholesterol above 4.0 mmol/L in a child under 16 years of age
	ii. Family History of myocardial infarction (MI) before 50 years of age in a 2nd degree relative or below age 60 in a 1st degree relative
3	i. A family history of raised total cholesterol - higher than 7.5 mmol/L in adult 1st or 2nd degree relative or higher than 6.7 mmol/L in a child or sibling aged under 16 years

Simon Broome 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.

Dutch Lipid Clinic Network Diagnostic Criteria for FH	
Group 1: Family History	**Points**
i. First-degree relative with premature CHD (before age 55 for me, 60 for women)	1
ii. First-degree relative with LDL-C greater than 95th percentile by age, gender for country	1
iii. First-degree relative with tendinous xanthomata and/or arcus cornealis	2
iv. Children under 18 years with LDL-C greater than 95th percentile by age, gender for country	2
Group 2: Clinical History	**Points**
i. Premature CHD	2
ii. Premature cerebrovascular or peripheral vascular disease	1
Group 3: Physical Examination Points	**Points**
i. Tendinous xanthomata	6
ii. Arcus cornealis prior to 45 years	4

Group 4: LDL-C Levels	**Points**
i. LDL-C greater than 8.5 mmol/l (~330 mg/dl)	8
ii. LDL-C 6.5-8.4 mmol/l (~250-329 mg/dl)	5
iii. LDL-C 5.0-6.4 mmol/l (~190-249 mg/dl)	3
iv. LDL-C 4.0-4.9 mmol/l (~155-189 mg/dl)	1
Group 5: DNA Analysis Points	**Points**
i. Causative mutation in the LDLR, ApoB or PCSK9 gene	8
Total Score:	
Definite FH: more than 8 points	
Probable FH: 6–8 points	
Possible FH: 3–5 points	
Unlikely FH: 0–2 points	
Genetic Testing For:	
i. Patients with a score more than 5 points	
ii. Patients with an obvious diagnosis of xanthomata with high cholesterol and a CHD family history	
Causative Mutation Found:	
Genetic testing for all first degree relatives	

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.

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…) 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… 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)

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 via Peripheral Blood

International Society of Heart and Lung Transplantation

The 2022 International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Patients have the following recommendations for the non-invasive monitoring of acute cellular rejection after heart transplant [HT], and specifically addresses Allomap:

> “Gene Expression Profiling (GEP) (i.e., Allomap) of peripheral blood can be used in low-risk patients between 2 months and 5 years after HT to identify adult recipients who have low risk of current ACR [acute cellular rejection] to reduce the frequency of EMB [endomyocardial biopsy]…Class IIa, Level of Evidence: B. (Journal pre-proof p. 69)

Post Heart Transplant Gene Expression Panels for Rejection Risk via Tissue

International Society of Heart and Lung Transplantation

The 2022 International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Patients state the following regarding post heart transplant gene

expression panels for rejection risk via tissue testing: "...the assessment of gene expression within allograft tissue and the identification of rejection-associated gene transcripts (e.g., Molecular Microscope, MMDx) has permitted improved discrimination between T-cell mediated or antibody mediated rejection and tissue injury, but this technology may not be clinically available outside of North America and is currently not in widespread use as a routine diagnostic test." (Journal pre-proof page 62)

Donor-Derived Cell-Free DNA for Heart Transplant Rejection

American Society of Transplant Surgeons

In their position statement approved in March 2023, the American Society of Transplant Surgeons stated the following: "We recommend that dd-cfDNA [donor-derived cell-free DNA] may be utilized to rule out subclinical rejection for heart transplant recipients." (p. 3)

A definitive recommendation for the frequency of this testing is not present in these guidelines from the American Society of Transplant Surgeons, or any other similar professional guideline.

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	Committee/Source	Date(s)
Document Created:	Medical Policy Committee/Health Services Division	November 16, 2022
Revised:	Medical Policy Committee/Health Services Division	February 15, 2023
	Medical Policy Committee/Health Services Division	March 15, 2023
	Medical Policy Committee/Health Services Division	August 16, 2023
Reviewed:	Medical Policy Committee/Health Services Division	February 15, 2023
	Medical Policy Committee/Health Services Division	March 15, 2023
	Medical Policy Committee/Health Services Division	August 16, 2023

Published: 01/01/2024
Effective: 01/01/2024