Cardiomyopathy and Arrhythmia Genetic Testing

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Genetic testing for non-syndromic cardiomyopathy and arrhythmia is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
4q25-AF Risk Genotype	81479
Arrhythmia Single Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Arrhythmia Known Familial Mutation Analysis	81403
Brugada Syndrome Genetic Testing (SCN5A and Variants)	S3861

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Procedures addressed by this guideline	Procedure codes
Cardiomyopathy Single Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Cardiomyopathy Known Familial Mutation Analysis	81403
Cardiac Ion Channelopathies Sequencing Panel (at least 10 channelopathy-related genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A)	81413
Cardiac Ion Channelopathies Deletion/Duplication Panel (at least 2 channelopathy-related genes, including KCNH2 and KCNQ1)	81414
Genomic Unity Cardiac Ion Channelopathies Analysis	0237U
Hereditary Cardiomyopathy Sequencing Panel (at least 5 cardiomyopathy-related genes)	81439
Hypertrophic Cardiomyopathy Comprehensive Gene Sequence Analysis	S3865
Hypertrophic Cardiomyopathy Known Familial Mutation Analysis	S3866

Criteria

Requests for cardiomyopathy and arrhythmia genetic testing are reviewed using these criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic or Predisposition Testing:*
  - Known familial mutation in a 1st or 2nd degree biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Note:

Since symptoms may occur in childhood, testing of children who are at-risk for a pathogenic mutation may be appropriate, but requires genetic counseling and careful consideration of ethical issues related to genetic testing in minors.

Single Gene Tests (Sequencing and Deletion/Duplication Analysis)

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous analysis of the requested gene, and
  - No known mutation in the family that would explain the member's clinical features, AND
- Diagnostic Testing in Symptomatic Individuals:
  - Clinical history points to the specific gene requested, and
  - Single gene analysis is appropriate due to one or more of the following:
    - The requested gene is the only gene that has a confirmed association with the member's cardiac subtype (e.g., SCN5A for individuals with an established or suspected diagnosis of Brugada syndrome), or
    - Analysis of other genes associated with the member's cardiac subtype was previously completed and was not diagnostic, and
  - Non-genetic causes have been ruled out (e.g., hypokalemia for arrhythmia; sarcoidosis, endomyocardial fibrosis, infection, or toxin exposure for

cardiomyopathy), or clinical suspicion for a gene mutation remains high even in the presence of a potential non-genetic cause, and
    - The results of the test will directly impact the diagnostic and treatment options that are recommended for the individual, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Multi-Gene Sequencing Panels

Subtype-specific panels or comprehensive panels with multiple cardiomyopathy and/or arrhythmia subtypes are considered medically necessary when the criteria below are met.

- Genetic Counseling:
    - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
    - No previous gene sequencing for the suspected condition, and
    - No known pathogenic or likely pathogenic mutation in the family that would explain the member's clinical features, AND
- Diagnostic Testing for Symptomatic Individuals:
    - The member meets subtype-specific criteria (see below) for one or more of the following cardiac subtypes:
        - Arrhythmogenic cardiomyopathy (ACM), or
        - Catecholaminergic polymorphic ventricular tachycardia (CPVT), or
        - Dilated cardiomyopathy (DCM), or
        - Hypertrophic cardiomyopathy (HCM), or
        - Long QT syndrome (LQTS) with or without signs of Jervell and Lange-Nielson Syndrome (JLNS), or
        - Progressive cardiac conduction disease or cardiac conduction disease (PCCD/CCD), or
        - Restrictive cardiomyopathy (RCM), or
        - Short QT syndrome (SQTS), and
    - No personal or family history of extra-cardiac features that are highly suggestive of an underlying multi-systemic syndrome for which syndrome-specific genetic testing is available and appropriate (see table titled *Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines*), and
    - Non-genetic causes have been ruled out (e.g., hypokalemia for arrhythmia; sarcoidosis, endomyocardial fibrosis, infection, or toxin exposure for cardiomyopathy), or clinical suspicion for a gene mutation remains high even in the presence of a potential non-genetic cause, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Arrhythmogenic Cardiomyopathy (ACM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: DSC2, DSG2, DSP, JUP, PKP2 (plus FLNC if the left ventricle is affected), AND
- The member meets at least one of the following:
  - Arrhythmogenic right ventricular cardiomyopathy (ARVC) Task Force criteria are met for at least possible ARVC (defined as having at least one major or two minor criteria) based on electrocardiogram, echocardiogram, MRI, and/or angiogram findings, or
  - Clinical documentation is provided supporting a diagnosis or clinical suspicion of ARVC, arrhythmogenic left ventricular cardiomyopathy (ALVC), or bi-ventricular arrhythmogenic cardiomyopathy (BiVACM) and the presence of one or more of the following:
    - One or more first- or second-degree relatives with a diagnosis of cardiomyopathy, or
    - A suspicious family history including a first- or second-degree relative with sudden death or cardiac event at <50 years of age.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: RYR2 and CASQ2, AND
- The member has an established or suspected diagnosis of CPVT based on at least one of the following:
  - A CPVT diagnostic score ≥3.5, or
  - All of the following features are present:
    - A structurally normal heart, and
    - Normal resting ECG, and
    - Exercise- or emotion-induced bidirectional or polymorphic ventricular tachycardia (VT).

Dilated Cardiomyopathy (DCM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: BAG3, FLNC, LMNA, MYH7, RBM20, SCN5A, TNNT2, and TTN, AND
- The member meets at least one of the following:

- Diagnosis of idiopathic DCM (IDCM) based on the following findings from appropriate imaging and/or electrophysiology modality (e.g. echocardiogram, electrocardiogram, MRI, angiogram):
  - Left ventricular (LV) enlargement with end-diastolic dimensions or volumes >2 z-scores above population mean values corrected for body size, sex, and/or age (i.e. in adults, LV end-diastolic diameter >58mm in males and >52 mm in females and an LVEDV index of ≥75 mL/m2 in males and ≥62 mL/m2 in females), and
  - Left ventricular systolic dysfunction, (defined as an ejection fraction of less than 50%), and
  - Absence of abnormal loading conditions (severe hypertension and valve disease) or coronary artery disease sufficient to cause the above features, or
- Clinical documentation is provided supporting a diagnosis of DCM (with or without abnormal loading conditions or coronary artery disease) and at least one of the following:
  - One or more first- or second-degree relatives with a diagnosis of DCM, peripartum cardiomyopathy, or alcoholic cardiomyopathy, or
  - A suspicious family history including a first- or second-degree relative with sudden death or cardiac/thromboembolic event at <50 years of age, or
- Mildly affected individual (defined as having dilated left ventricle but normal ejection fraction, or left ventricular systolic dysfunction without dilatation) with a known diagnosis of IDCM in a first- or second-degree relative who is deceased or otherwise unavailable for testing.

Hypertrophic Cardiomyopathy (HCM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: ACTC1, MYBPC3, MYH7, MYL2, MYL3, PLN, TNNI3, TNNT2, and TPM1, AND
- The member meets at least one of the following:
  - Diagnosis of HCM based on the following findings from appropriate imaging (e.g., echocardiogram or MRI):
    - Left ventricular hypertrophy without obvious cause (valvular disease, hypertension, infiltrative or neuromuscular disorder), and
    - Maximum myocardial wall thickness meeting one of the following parameters:
      - ≥15mm (1.5cm) in adults without a family history of HCM, or
      - ≥13mm (1.3 cm) in adults with a first- or second-degree relative with a known diagnosis of HCM who is deceased or otherwise unavailable for testing, or
      - >2 standard deviations for age in children, or

- Pathognomonic histopathologic features of HCM on endomyocardial biopsy (e.g. myocyte disarray, hypertrophy, increased myocardial fibrosis).

Long QT Syndrome (LQTS) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: KCNQ1, KCNH2, and SCN5A (or KCNQ1 and KCNE1 if Jervell and Lange-Nielson syndrome is suspected), AND
- The member has an established or suspected diagnosis of LQTS based on at least one of the following:
  - Schwartz criteria score ≥1.5, or
  - Confirmation of prolonged QTc or T-wave abnormalities [>460ms (prepuberty) or >480ms (adults) on serial 12-lead ECGs] on exercise or ambulatory ECG, or during pharmacologic provocation testing, or
  - A prolonged or borderline prolonged QT interval on ECG or Holter monitor, or
  - Profound congenital bilateral sensorineural hearing loss and prolonged QTc.

Progressive Cardiac Conduction Disease (PCCD/CCD) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: SCN5A and TRPM4, AND
- Clinical documentation is provided supporting a diagnosis of PCCD/CCD (e.g., complete right bundle branch block, complete left bundle branch block, left anterior fascicular block/hemiblock or left posterior hemiblock, prolonged PR interval or complete atrioventricular block with broad QRS complexes), AND
- The member has one or more of the following:
  - PCCD/CCD diagnosed at <50 years of age, or
  - A first- or second-degree relative with PCCD/CCD.

Restrictive Cardiomyopathy (RCM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNI3, TNNT2, TPM1, and TTR, AND
- Clinical documentation is provided supporting a diagnosis of RCM, AND
- The member has one or more of the following:
  - Left ventricular hypertrophy and/or hypertrophic cardiomyopathy (HCM), or

- A first- or second-degree relative with cardiomyopathy (e.g., RCM, HCM) and/or left ventricular hypertrophy.

Short QT Syndrome (SQTS) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: KCNH2 and KCNQ1, AND
- The member has an established or suspected diagnosis of SQTS based on at least one of the following:
  - An SQTS diagnostic score ≥4, or
  - A QTc ≤330ms, or
  - A QTc <360ms with survival of a ventricular tachycardia/fibrillation episode in the absence of heart disease, or
  - A QTc <360ms with family history of SQTS or sudden death at age ≤40.

Diagnostic criteria, scoring systems, and their associated references are summarized in the background section of this guideline, under "Diagnosis".

Multi-Gene Deletion/Duplication Panels

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous gene deletion/duplication testing for the suspected condition, and
  - A multi-gene sequencing panel was previously performed for the suspected condition, with one of the following results:
    - No pathogenic or likely pathogenic mutation identified, or
    - One pathogenic or likely pathogenic mutation identified in a gene associated with an autosomal recessive condition (e.g., Jervell and Lange-Nielson Syndrome), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for multi-gene sequencing panels, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions and Other Considerations

- Genetic testing (including single-gene or multi-gene panels) for the following conditions, in isolation, is considered experimental, investigational, or unproven:
  - Left ventricular non-compaction (LVNC)

  - The following types of arrhythmia: atrial fibrillation, early repolarization syndrome, sinus node dysfunction ('sick sinus syndrome') and Wolff-Parkinson-White syndrome
- Testing the 4q25 atrial fibrillation risk genotype is considered experimental, investigational, or unproven.
- Due to low diagnostic yield and lack of clinical utility for genes other than SCN5A, multi-gene panel testing for Brugada syndrome (BrS) is considered experimental, investigational, or unproven.
- This guideline may not apply to genetic testing for indications that are addressed in other test-specific guidelines (e.g., testing for multi-system syndromes that may include cardiomyopathy or arrhythmia as a feature). For these indications, please refer to applicable test-specific guidelines in the table titled *Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines*, or the general guideline, *Genetic Testing to Diagnose Non-Cancer Conditions*.
- Genetic testing for cardiomyopathies and/or arrhythmias is only medically necessary once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest (e.g., additional genes are being tested that account for >1% of cases of the member's cardiac subtype and have a definitive association with the subtype according to the **ClinGen Gene-Disease Validity Curation**).

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Multi-gene panel testing for Brugada syndrome (e.g., S3861) is not reimbursable.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
  - A single gene included in a multi-gene panel may not be reimbursed if testing has been performed previously.
  - If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- When otherwise reimbursable, the following limitations apply:

- When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81439, 81413/81414 or 81479)*.
- When use of a panel code is not possible, each billed component procedure will be assessed independently.
- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
- When the test is billed with multiple stacked procedure codes, only the following genes may be considered for reimbursement, based on the cardiac subtype:
  - Arrhythmogenic right ventricular cardiomyopathy: DSC2, DSG2, DSP, JUP, PKP2, TMEM43
  - Catecholaminergic polymorphic ventricular tachycardia: RYR2, CASQ2
  - Dilated cardiomyopathy: TTN, TNNT2, MYH7, SCN5A, MYBPC3, LMNA
  - Hypertrophic cardiomyopathy: MYH7, MYBPC3, TNNT2, TNNI3
  - Long QT syndrome: KCNQ1, KCNH2, SCN5A (if Jervell and Lange-Nielson syndrome is suspected: KCNQ1 and KCNE1)
  - Progressive cardiac conduction disease: SCN5A, LMNA, TRPM4
  - Restrictive cardiomyopathy: ACTC1, MYH7, TNNI3, TTN, TTR
  - Short QT syndrome: KCNH2, KCNQ1

Note: *The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are Cardiomyopathy and Arrhythmia?

Cardiomyopathy is a disease of the heart muscle that compromises heart function. The most relevant subtypes for genetic testing include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM), and restrictive cardiomyopathy (RCM). ACM is further divided into the following, based on which ventricles are involved: arrhythmogenic right ventricular cardiomyopathy (ARVC), arrhythmogenic left ventricular cardiomyopathy (ALVC), and bi-ventricular arrhythmogenic cardiomyopathy (BiVAC). Left ventricular non-compaction (LVNC) is now more often considered a phenotypic trait rather than a primary cardiomyopathy; it may occur alongside other cardiac subtypes or as an isolated finding seen in athletes, pregnant individuals, and healthy adult populations.[1-4]

In addition to non-syndromic forms of cardiomyopathy, more than 100 syndromes have cardiomyopathy as a feature, including various muscular dystrophies and storage disorders.[1,3,4] It is beyond the scope of this guideline to provide detailed descriptions of these syndromes (see table titled *Select Cardiac Syndromes, Associated Genes,*

and Applicable Guidelines for eviCore guidelines that address some of them more specifically).

Arrhythmias (sometimes called channelopathies) are heart rhythm disturbances that may be detected on electrocardiogram (ECG). Genetic arrhythmias are primarily ventricular arrhythmias that occur due to abnormalities in the ion currents that drive the electrical activity of the heart.[5] Subtypes of arrhythmia that are most likely to prompt a genetic evaluation include long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS) and progressive cardiac conduction disease (PCCD). Extra-cardiac features may be present, particularly with certain types of LQTS. Syndromic forms of arrhythmia are included in the table titled *Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines*. Other more common arrhythmias include atrial fibrillation, early repolarization syndrome (ERS), sinus node dysfunction (SND; also called 'sick sinus syndrome') and Wolff-Parkinson-White (WPW) syndrome. These arrhythmias may occur in conjunction with some of the cardiac subtypes listed above; however, isolated cases are generally acquired.[1]

Table: Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines

Syndromes that may include cardiomyopathy and/or arrhythmia, along with their associated clinical features, genes, and eviCore guidelines. Note: Some genes may be associated with both syndromic and non-syndromic forms of disease. .

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Anderson-Tawil Syndrome (ATS or LQTS type 7)[6]	Prominent U waves, prolonged QTc or QUc interval, or bidirectional and/or polymorphic PVCs/ VT; characteristic dysmorphic features; periodic paralysis	KCNJ2	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Barth syndrome[1,7]	DCM; LVNC; neutropenia; muscle weakness; growth delay; infantile/early-childhood onset	TAFAZZIN (TAZ)	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
Danon disease[1,7,8]	In males: HCM; DCM; LVNC; CCD; skeletal myopathy; retinal dystrophy; learning disability. Females may present with isolated cardiac features.	LAMP2	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
Duchenne & Becker muscular dystrophy[1,7]	In males: DCM; CCD; muscle weakness, increased serum creatine kinase (CK); loss of ambulation. Females may present with isolated cardiac features.	DMD	Duchenne and Becker Muscular Dystrophy Testing	MOL.TS.161
Emery-Dreifuss muscular dystrophy[1,7,8]	DCM; HCM; conduction system disease, and/or arrhythmias; joint contractures; increased serum CK; muscle weakness	EMD FHL1 LMNA	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Fabry disease[1,8]	HCM; RCM; CCD; periodic pain crises; angiokeratomas; hypohidrosis; ocular abnormalities (cornea verticillatata); hearing loss; proteinuria and renal dysfunction	GLA	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
Friedreich ataxia[1,8]	HCM; slowly progressive ataxia at <25 years; dysarthria; muscle weakness	FXN	Friedreich Ataxia Genetic Testing	MOL.TS.309
Glycogen storage disease of the heart, lethal congenital[1,8]	HCM; conduction system disease (e.g., sinus node disease, atrial fibrillation, etc.); neonatal hypoglycemia; vacuolar myopathy; facial dysmorphism and/or macroglossia	PRKAG2	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Hereditary transthyretin amyloidosis[1,8]	HCM; RCM; heart failure and/or aortic stenosis at ≥65 years; peripheral sensorimotor neuropathy and autonomic neuropathy; vitreous opacities, central nervous system amyloidosis	TTR	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
HFE hemochromatosis[1,7]	DCM; non-dilated and/or infiltrative cardiomyopathy; cirrhosis; diabetes; hypermelanotic pigmentation; increased serum iron & ferritin	HFE	HFE Hemochromatosis Genetic Testing	MOL.TS.183
Laing distal myopathy[7,8]	DCM; HCM; facial weakness; childhood-onset weakness of ankles, great toes, finger extensors, & neck flexors	MYH7	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Mitochondrial disorders[1,7]	Complex phenotypes including DCM and/or CCD; focal segmental glomerulosclerosis; Kearns-Sayre syndrome (KSS); ptosis; progressive external ophthalmoplegia; ataxia	mtDNA	Mitochondrial Disorders Genetic Testing	MOL.TS.266
Myotonic dystrophy type 1[1,7]	DCM; CCD; adults may present with muscle weakness (especially distal leg, hand, neck & face); myotonia; posterior subcapsular cataracts. Neonates: hypotonia; facial muscle weakness; generalized weakness; clubfoot; respiratory insufficiency.	DMPK	Myotonic Dystrophy Type 1 Genetic Testing	MOL.TS.312
Pompe disease[8]	HCM with onset in first few months of life; poor feeding; macroglossia; motor delay; hypotonia; muscle weakness; respiratory difficulty	GAA	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
RASopathies (Noonan syndrome, cardiofacio-cutaneous syndrome, Costello syndrome, Noonan syndrome with multiple lentigines)[8]	HCM with infant or childhood onset; congenital heart defects; characteristic facies; short stature; developmental delay; broad, webbed neck; unusual chest shape	BRAF HRAS KRAS LZTR1 MAP2K1 MAP2K2 NRAS PTPN11 RAF1 RASA2 RRAS2 RIT1 SOS1 SOS2	Noonan Spectrum Disorder Genetic Testing	MOL.TS.371
Timothy Syndrome (LQTS type 8)[9]	Prolonged QT interval (QTc >480 ms); cardiovascular malformations; cutaneous syndactyly of the fingers/toes; neurological findings (autism, seizures, intellectual disability, and/or hypotonia); facial anomalies	CACNA1C	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Prevalence

Prevalence of cardiomyopathy varies by subtype, and is estimated to be 0.2% for HCM, 0.036-0.400% for DCM, and 0.078% for ARVC in adult populations.[4] Childhood prevalence for these cardiomyopathies is 0.029% for HCM, 0.026% for DCM, and unknown for ARVC.[4] The true prevalence of RCM is unknown; it is considered the rarest cardiomyopathy subtype.[4,10]

Genetic arrhythmias have a prevalence of 1:2,500 for LQTS, 1:1000 to 1:10,000 for BrS (more common in Southeast Asia than in other regions) and 1:10,000 for CPVT.[1,11-15]

Symptoms

The severity of cardiomyopathy ranges from a lifelong asymptomatic course to thromboembolism, arrhythmia, progressive heart failure, and sudden cardiac death (SCD).[5,16] Affected individuals may present with signs and symptoms of heart failure, including peripheral edema, fatigue, orthopnea, dyspnea, syncope, and cardiac ischemia.[16] Sometimes the symptoms may suggest a particular subtype of cardiomyopathy.[4,16]

Cardiac channelopathies can be largely asymptomatic. Symptoms of ventricular arrhythmias may include palpitations, either skipped or extra beats or sustained palpitations, shortness of breath, chest pain, dizziness, near syncope, and syncope.[12] Consideration of a channelopathy is warranted when there is recurrent syncope, aborted cardiac arrest, ventricular fibrillation, or sudden death in a child or young adult.[11]

Variable expressivity and reduced penetrance have been reported for cardiomyopathy and arrhythmia syndromes, and disease onset can span all ages, from the prenatal period to late adulthood.[3,4,11,17] SCD can be the presenting symptom in some cases.[8,13,15,18]

Cause

Cardiomyopathies and arrhythmias may be inherited or acquired disorders.

Non-syndromic cardiomyopathies are "mainly caused by pathogenic variants in genes encoding the structural components of cardiomyocytes."[5] Acquired causes of cardiomyopathy can include myocarditis, stress, and/or tachycardia. Cardiomyopathy may also be associated with pregnancy and delivery.[16,19] Secondary systemic etiologies are extensive in variety, and include but are not limited to, sarcoidosis, endomyocardial fibrosis, autoimmune disease, toxin exposure, and underlying cardiac diseases such as hypertension.[3,16,19] While the percentage varies by subtype, cardiomyopathy is thought to have a genetic etiology in up to 60% of cases.[1,4,5,7,8,20] The presence of an acquired cause does not always preclude the possibility of a genetic etiology; for example, 10-15% of individuals with chemotherapy-induced, alcoholic, or peripartum DCM will have a causative gene variant.[4.]

Genetic arrhythmias are "generally caused by defects in genes encoding cardiac ion channel macromolecular complexes and associated regulatory proteins."[5] Inherited cardiac channelopathies may present with similar clinical and ECG features to other causes for these cardiac symptoms, including heart-rhythm altering drugs, hypokalemia, syndromic genetic disorders, stroke, and structural heart disease. When a genetic etiology is suspected based on initial investigations, but a clear diagnosis cannot be established, molecular testing may help to clarify a cause.[11,14] The yield of genetic testing is highest for LQTS (70-85%) and somewhat lower for other subtypes.[1,11,14]

Inheritance

Non-syndromic cardiomyopathies and arrhythmias most commonly follow an autosomal dominant inheritance pattern.[3-5] Autosomal recessive inheritance is often associated with childhood onset, more severe cardiac disease and/or extra-cardiac manifestations.[3,7,11,20] X-linked and mitochondrial inheritance are rare and typically seen only in syndromic cases.[3,7]

Diagnosis

Diagnosis of a cardiomyopathy or arrhythmia can often be confirmed with cardiac imaging (e.g., echocardiography, cardiac magnetic resonance imaging [CMR]) and/or electrocardiogram (ECG). Cases of arrhythmia may be further evaluated with the use of exercise testing, toxicology, and blood testing.[13,21] Endomyocardial biopsy (EMB) may aid in the diagnosis of a cardiomyopathy in some cases.[4,10] A detailed clinical history and evaluation should aim to exclude acquired and secondary causes when an isolated genetic etiology is under consideration.

Consensus clinical diagnostic criteria have been developed for most recognized subtypes of cardiomyopathy and arrhythmia.

- **Arrhythmogenic cardiomyopathy (ACM):** Task force diagnostic criteria for ARVC were most recently proposed by Corrado et al in 2024 to refine the "Padua criteria" proposed in 2020, which in turn were an update to the criteria by Marcus et al in 2010.[18,22,23] As summarized in an expert-authored review, these criteria use findings from cardiac imaging, EMB, ECG, family history, and/or genetic testing to classify individuals as having a definite, borderline, or possible diagnosis of ARVC.[20] The updated criteria seek to improve the diagnostic sensitivity for ALVC and BiVAC, but have not yet been validated in larger studies.[20,22]
- **Brugada syndrome (BrS):** A clinical diagnosis of BrS is suspected in an individual with a type 1, type 2, or type 3 ECG pattern and at least one of the following: recurrent syncope, ventricular fibrillation, self-termination polymorphic ventricular tachycardia, cardiac arrest, or family history of SCD. The diagnosis is established clinically in the majority of cases, although genetic testing may help confirm it.[14]

- **Catecholaminergic polymorphic ventricular tachycardia (CPVT):** CPVT can be diagnosed clinically based on cardiac findings and/or the presence of a pathogenic or likely pathogenic mutation.[15,24] A scoring system has also been developed to categorize the pretest probability of CPVT, with a score of 3.5 or greater indicating a high probability of having the condition.[1]
- **Dilated cardiomyopathy (DCM):** The diagnosis of DCM is established in individuals having the following findings on echocardiogram or cardiac MRI: left ventricular enlargement and systolic dysfunction.[7]
- **Hypertrophic cardiomyopathy (HCM):** The diagnosis of HCM is typically established with cardiac imaging (echocardiogram and/or cardiac MRI), and is defined by the presence of unexplained left ventricular hypertrophy (LVH) with a maximum wall thickness ≥15 mm in adults or a z-score >3 in children. In individuals with a family history of HCM, a maximum left ventricular wall thickness of ≥13 mm supports the diagnosis.[8]
- **Long QT syndrome (LQTS):** Schwartz et al developed a clinical diagnostic scoring system for this condition, which was last updated in 2011.[25] As described in an expert-authored review, this score is used to calculate the risk of having LQTS, with a score of 1.5-3 indicating an intermediate risk, and a score of ≥3.5 indicating a high risk.[11] A diagnosis of LQTS can be made with a Schwartz diagnostic score ≥3.5, a pathogenic mutation in an LQTS gene, or specific ECG findings.[24]
- **Progressive cardiac conduction disease (PCCD):** A diagnosis of PCCD can be made in individuals with unexplained progressive conduction abnormalities at a young age (<50 years), structurally normal hearts, and absence of skeletal myopathies, especially when there is a family history of PCCD.[24]
- **Restrictive cardiomyopathy (RCM):** Consensus diagnostic criteria for RCM are currently lacking.[10,26] A 2022 expert-authored review proposed an updated strategy for the diagnosis of this condition, which includes identification of a restrictive pathophysiology confirmed in repeated evaluations, absence of ventricular dilatation, and investigation of red flags for specific conditions among clinical, ECG, and imaging findings.[26]
- **Short QT syndrome (SQTS):** A diagnosis of SQTS can be made in the presence of a QTc <330 ms or with a QTc <360 ms when at least one of the following is present: a pathogenic mutation, family history of SQTS, family history of sudden death at age ≤40, or survival of a ventricular tachycardia/fibrillation episode in the absence of heart disease.[24]

The yield of genetic testing varies by subtype, and the presence of a family history usually increases the likelihood of identifying a causative mutation.[1,3-5,27] Genetic testing can be useful to confirm a diagnosis of inherited cardiomyopathy or arrhythmia in persons with cardiac symptoms and has been incorporated into the diagnostic criteria for ARVC, CPVT, LQTS, and SQTS.[1,4,11,15,20,24] Post-mortem genetic testing may be

performed after a sudden death when an inherited cardiomyopathy or arrhythmia is suspected in order to aid in the risk assessment of family members.[1,5,13,21]

Once a disease-causing mutation is identified, at-risk relatives can have reliable genetic testing to define their risk and screening needs. Identifying a gene mutation significantly changes medical management in symptomatic individuals without a clinical diagnosis and may improve life expectancy.[3,4,7,13,17] For relatives who are not found to have the familial pathogenic mutation, it may be possible to eliminate the need for ongoing clinical surveillance and other medical expenditures.[1,3,4,17] Clinical screening is recommended for family members when genetic testing was not performed in the affected individual or failed to identify a causative mutation.[1,12]

Management

Treatment of cardiomyopathies and arrhythmias is focused on controlling and preventing symptoms. Management may include therapy and/or screening for heart failure, activity restriction, pharmacologic therapy (including beta blockers), catheter ablation, consideration of a pacemaker or implantable cardioverter defibrillator (ICD), and heart transplantation.[4,13,19] The identification of a genetic variant may provide prognostic information, guide treatment strategies, and allow for earlier intervention.[1,3,5,13] Genotype-phenotype correlation exists for a subset of genes, and management recommendations have been developed for certain genes/mutations.[1,13,17,20,28] Identification of a syndromic form may also facilitate surveillance and treatment for associated extra-cardiac manifestations.[3,4,13]

Survival

Cardiomyopathy and arrhythmia are both associated with a higher mortality rate than is seen in the general population.[13,19] Some factors that may affect the survival rate include age at diagnosis, presence of symptoms, etiology, and cardiac subtype.[13,19] Diagnosis and appropriate treatment has led to a decrease in the mortality rate for some of these disorders.[3,11]

A significant proportion of SCD is attributed to genetic arrhythmias and, to a lesser extent, cardiomyopathies, especially in individuals under the age of 50 years.[1,13] SCD can occur in all subtypes of cardiomyopathy and arrhythmia.[13] The overall risk, age distribution, and triggering factors vary by subtype.[13]

Test information

Testing for cardiomyopathies may include known familial mutation analysis, single gene sequencing or deletion/duplication analysis, or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Panels may be subtype-specific (e.g., long QT syndrome panel, hypertrophic cardiomyopathy panel, etc.) or broad panels that address multiple cardiomyopathy and/or arrhythmia subtypes. Due to overlapping clinical features and associated genes, panels that include genes for multiple cardiac subtypes are increasingly employed, and often include syndromes with important medical management implications.[3]

Guidelines and evidence

The following section includes relevant guidelines and evidence pertaining to cardiomyopathy and arrhythmia genetic testing.

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

A guideline from the American College of Cardiology, the American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society (ACC/AHA/HRS, 2017) on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (SCD) made the following recommendations regarding genetic testing for these indications:[12]

- "In young patients (<40 years of age) with unexplained SCA [sudden cardiac arrest], unexplained near drowning, or recurrent exertional syncope, who do not have ischemic or other structural heart disease, further evaluation for genetic arrhythmia syndromes is recommended." (Class I, Level B)
- "In first-degree relatives of SCD victims who were 40 years of age or younger, cardiac evaluation is recommended, with genetic counseling and genetic testing performed as indicated by clinical findings." (Class I, Level B)
- "In patients and family members in whom genetic testing for risk stratification for SCA or SCD is recommended, genetic counseling is beneficial." (Class I, Level C)

The ACC/AHA/HRS 2017 guideline also made the following recommendations regarding genetic testing for specific cardiomyopathies and arrhythmias:[12]

- Nonischemic Cardiomyopathy (NICM):
  - "In patients with NICM [nonischemic cardiomyopathy] who develop conduction disease or LV dysfunction at less than 40 years of age, or who have a family history of NICM or SCD in a first-degree relative (<50 years of age), genetic counseling and genetic testing are reasonable to detect a heritable disease that may clarify prognosis and facilitate cascade screening of relatives." (Class IIa, Level C)
- Arrhythmogenic Right Ventricular Cardiomyopathy:
  - "In selected first-degree relatives of patients with arrhythmogenic right ventricular cardiomyopathy, clinical screening for the disease is recommended along with genetic counseling and genetic testing, if the proband has a disease causing mutation." (Class I, Level B)
  - "In patients with clinically diagnosed or suspected arrhythmogenic right ventricular cardiomyopathy, genetic counseling and genetic testing can be useful for diagnosis and for gene-specific targeted family screening." (Class IIa, Level B)
- Hypertrophic Cardiomyopathy (HCM):

  - "In first-degree relatives of patients with HCM due to a known causative mutation, genetic counseling and mutation-specific genetic testing are recommended." (Class I, Level B).
  - "In patients with clinically suspected or diagnosed HCM, genetic counseling and genetic testing are reasonable." (Class IIa, Level B)
- Long QT Syndrome (LQTS):
  - The authors highlighted the ability to stratify risk based on genotype in LQTS and stated, "In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended." (Class I, Level B)
- Catecholaminergic Polymorphic Ventricular Tachycardia:
  - "In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable." (Class IIa, Level B)
- Brugada Syndrome:
  - "In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives." (Class IIb, Level C)
- Short QT Syndrome:
  - "In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives." (Class IIb, Level C)
- Early Repolarization Syndrome:
  - "In patients with early repolarization pattern on ECG, genetic testing is not recommended." (Class III: No Benefit, Level B)

In a guideline for the evaluation and management of patients with bradycardia (including sinus node disease) and cardiac conduction delay authored by the American College of Cardiology, the American Heart Association Task Force, and the Heart Rhythm Society (ACC/AHA/HRS, 2018), genetic testing was not included in the diagnostic algorithms for these conditions, and the authors acknowledged that these disorders are usually acquired. However, they made the following recommendations:[29]

- "In patients in whom a conduction disorder-causative mutation has been identified, genetic counseling and mutation-specific genetic testing of first-degree relatives is recommended to identify similarly affected individuals." (Class I, Level C)
- "In patients with inherited conduction disease, genetic counseling and targeted testing may be considered to facilitate cascade screening of relatives as part of the diagnostic evaluation." (Class IIb, Level C)

American College of Cardiology, American Heart Association Task Force, American College of Clinical Pharmacy, and Heart Rhythm Society

In a guideline for the management of patients with atrial fibrillation (AF), the American College of Cardiology, American Heart Association Task Force, American College of

Clinical Pharmacy and Heart Rhythm Society (ACC/AHA/ACCP/HRS, 2023) stated the following regarding genetic testing for this condition:[30]

- "In patents with an onset of AF before 45 years of age without obvious risk factors for AF, referral for genetic counseling, genetic testing for rare pathogenic variants, and surveillance for cardiomyopathy or arrhythmia syndromes may be reasonable." (Class IIb, Level B)

American College of Cardiology and American Heart Association

A joint committee guideline from the American College of Cardiology and American Heart Association (ACC/AHA, 2020) made the following class 1 recommendations for HCM:[31]

- "When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM."
- "In first-degree relatives of patients with HCM, both clinical screening (ECG and 2D echocardiogram) and cascade genetic testing (when a pathogenic/likely pathogenic variant has been identified in the proband) should be offered."
- "In patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause, a work-up including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy ('HCM phenocopies') is recommended."

Asia Pacific Heart Rhythm Society and Heart Rhythm Society

The Asia Pacific Heart Rhythm Society and the Heart Rhythm Society (APHRS/HRS, 2020) made the following recommendations in regards to sudden cardiac arrest (SCA) and sudden unexplained death (SUD):[21]

- "Genetic evaluation of SCA survivors is recommended for those with a diagnosed or suspected genetic cardiac disease phenotype when the results are likely to influence diagnosis, management, or family screening." (Class 1, Level B)
- "When genetic evaluation is performed in an SCA survivor with a suspected or diagnosed genetic cardiac disease phenotype, it is recommended that evaluations include only genes where there is robust gene–disease association." (Class 1, Level B)
- "Genetic testing in SCA survivors with a well-established nongenetic cause of SCA is not recommended." (Class 3: No benefit, Level C)
- "Family screening should include genetic testing and clinical evaluation when genetic testing of a proband with SUD detects a pathogenic or likely pathogenic variant." (Class 1, Level B)
- "If a pathogenic or likely pathogenic variant that fits the phenotype has been identified in an SUD proband, first-degree relatives should be offered DNA testing, with ongoing clinical evaluation for those testing positive." (Class 1, Level C)

- "It is recommended that genetic testing in families where an SUD or resuscitated SCA due to a heritable cause is suspected is performed only with appropriate genetic counseling." (Class 1, Level C)

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

An expert consensus statement from the European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Heart Rhythm Society (EHRA/HRS/APHRS/LAHRS, 2022) addressed the utility and appropriateness of genetic testing for inherited cardiovascular conditions.[1] The consensus statements were categorized as follows:

- Supported by strong observational evidence and author's consensus
- Some evidence and general agreement favor the usefulness/ efficacy of a test
- There is evidence or general agreement not to recommend a test

Regarding the choice of genetic testing, EHRA/HRS/APHRS/LAHRS (2022) stated the following:[1]

- Genetic testing should occur with genetic counseling. [Supported by strong observational evidence and authors' consensus]
- If an individual has a clear phenotype, it is appropriate to analyze genes with definite/ strong evidence support disease causation [Supported by strong observational evidence and author's consensus] and may be appropriate to analyze genes with moderate evidence for disease causation. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- In some cases with a clear phenotype and negative genetic testing of genes with definite/strong evidence for disease causation, broader genetic testing may be considered. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- "Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting." [There is evidence or general agreement not to recommend a test]
- When a likely pathogenic or pathogenic variant has been identified, genetic counseling should be offered. The inheritance pattern, penetrance, and associated risks can be discussed. Additionally, cascade testing for relatives should be facilitated. [Supported by strong observational evidence and author's consensus]
- Some affected individuals may have had previous genetic testing that was not a comprehensive, such as prior to the use of next generation sequencing or with an incomplete testing panel. Repeat testing should be considered in these cases. [Supported by strong observational evidence and author's consensus]

Regarding genetic testing for specific cardiomyopathies and arrhythmias, EHRA/HRS/APHRS/LAHRS (2022) stated the following:[1]

- Long QT Syndrome (LQTS):
  - Genetic testing for genes with a definitive disease association was recommended for all patients with a high probability of LQTS (Schwartz Score ≥ 3.5) [Supported by strong observational evidence and author's consensus]. Testing of less definitive genes could also be considered in these individuals [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - Genetic testing of definitive disease-associated genes should also be offered to "all patients with acquired LQTS who experienced drug-induced TdP [torsades de pointes], are aged below 40 years and have a QTc >440 ms (males) and >450 ms (females) in the absence of culprit drug" [Supported by strong observational evidence and author's consensus].
  - Targeted gene analysis was recommended in patients with Jervell and Lange-Nielsen syndrome, Timothy syndrome, Andersen–Tawil syndrome, and suspected triadin knockout syndrome [Supported by strong observational evidence and author's consensus].
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):
  - Genetic testing for genes with definite/strong evidence of disease association is recommended for individuals meeting diagnostic criteria for CPVT ("Class 1 clinical diagnosis or CPVT diagnostic score >3.5") [Supported by strong observational evidence and author's consensus].
  - Genetic testing can also be considered for individuals with a modest CPVT phenotype ("i.e. CPVT diagnostic score ≥ 2 but < 3.5") [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - For individuals meeting CPVT diagnostic criteria, genetic testing could also be considered for CPVT phenocopies (e.g., pathogenic variants in the KCNJ2, SCN5A, and PKP2 genes) [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Short QT Syndrome (SQTS):
  - Genetic testing for genes with definite/strong evidence of disease association was recommended for individuals meeting diagnostic criteria for SQTS ("Class 1 clinical diagnosis or SQTS diagnostic score >4") [Supported by strong observational evidence and author's consensus].
  - Testing of the KCNJ2 and SLC4A3 genes could be considered in individuals with an SQTS diagnostic score ≥4. [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Brugada Syndrome (BrS):
  - "Genetic testing with sequencing of SCN5A is recommended for an index case diagnosed with BrS with a type I ECG in standard or high precordial leads occurring either (i) spontaneously, or (ii) induced by sodium-channel blockade in presence of supporting clinical features or family history" [Supported by strong observational evidence and author's consensus].

  - "Rare variants in genes with a disputed or refuted gene-disease clinical validity should not be reported routinely for BrS genetic testing in a diagnostic setting" [There is evidence or general agreement not to recommend a test].
- Progressive Cardiac Conduction Disease (PCCD/CCD):
  - "Targeted genetic testing is recommended as part of the diagnostic evaluation for index patients with isolated cardiac conduction disease (CCD/PCCD) or with concomitant structural heart disease or extracardiac disease, when there is early age of diagnosis or a suspicion of laminopathy, especially when there is documentation of a positive family history of CCD/PCCD" [Supported by strong observational evidence and author's consensus]. Such testing could also be considered for individuals "with isolated cardiac conduction disease (CCD/PCCD) or with concomitant structural heart disease or extracardiac disease, especially in the setting of a positive family history" [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Other Arrhythmias:
  - The authors stated that targeted genetic testing could be considered for individuals with familial atrial fibrillation (AF at age <60), unexplained cardiac arrest survivors with a clinical diagnosis of early repolarization syndrome (ERS), and for individuals "with familial or isolated, but otherwise unexplained sinus node dysfunction (SND)" [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - No recommendations were made regarding genetic testing for Wolff-Parkinson-White (WPW) syndrome, as the authors concluded "only in the presence of the combination of pre-excitation and HCM and/or progressive CCD is genetic testing pertinent."
- Hypertrophic cardiomyopathy (HCM):
  - Comprehensive genetic testing was recommended for all individuals with HCM, using a first tier of genes with a definitive/strong disease association [Supported by strong observational evidence and author's consensus]. According to the authors, the inclusion of genes with moderate evidence of pathogenicity should also be considered [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - The authors also recommended genetic testing in "patients with atypical clinical presentation of HCM, or when another genetic condition associated with unexplained hypertrophy is suspected (e.g. HCM phenocopy)." [Supported by strong observational evidence and author's consensus]
- Dilated cardiomyopathy (DCM):
  - Comprehensive genetic testing was recommended for all individuals with DCM with a family history of DCM, using a first tier of genes with a definitive/strong disease association [Supported by strong observational evidence and author's consensus]. The authors stated that the inclusion of genes with moderate evidence

of pathogenicity could also be considered in these individuals [Some evidence and general agreement favor the usefulness/ efficacy of a test].
    - Genetic testing could be considered in individuals with apparently sporadic DCM, or "patients with DCM related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy)." [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Arrhythmogenic cardiomyopathy (ACM):
    - Comprehensive testing of definitive disease-associated genes was recommended for all individuals with features of ACM [Supported by strong observational evidence and author's consensus].
    - Genetic testing could also be considered in individuals with a borderline ACM phenotype [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Left Ventricular Non-compaction (LVNC):
    - Genetic testing could be considered for individuals with LVNC in whom a cardiologist has established a diagnosis based on clinical history, family history, and electrocardiographic/echocardiographic/MRI phenotype. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
    - "Genetic testing should not be performed in isolated (incidental) LVNC with normal LV function, no associated syndromic features and no family history." [There is evidence or general agreement not to recommend a test]
- Restrictive Cardiomyopathy (RCM):
    - Genetic testing could be considered for individuals with RCM in whom a cardiologist has established a diagnosis based on clinical history, family history, and electrocardiographic/echocardiographic/MRI phenotype. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
    - Genetic testing of the TTR gene was specifically recommended for patients with RCM and a clinical diagnosis of cardiac TTR amyloidosis. [Supported by strong observational evidence and author's consensus]

Lastly, EHRA/HRS/APHRS/LAHRS (2022) made recommendations regarding genetic testing in survivors of unexplained cardiac arrest (UCA) or relatives of individuals with sudden cardiac death (SCD):[1]

- "In selected UCA survivors with idiopathic VF [ventricular fibrillation], genetic testing for founder variants, where relevant, should be considered." [Supported by strong observational evidence and authors' consensus]
- "In relatives of UCA survivors or SCD decedents, clinical evaluation of 1st degree family members should be performed, and targeted to the index case's phenotype if present."
- "In decedents with SCD or survivors with cardiac arrest in whom a non-genetic cause has been identified, genetic testing of the index case and clinical evaluation of

relatives should not be performed." [There is evidence or general agreement not to recommend a test]

European Society of Cardiology

In their 2023 guidelines for the management of cardiomyopathies, the European Society for Cardiology (ESC, 2023) made the following genetic testing recommendations:[4]

- "Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered." (Class I, Level B)
- "It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise." Also, "pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy." (Class I, Level B)
- "Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance." (Class I, Level B)
- "Genetic testing may be considered in patients fulfilling diagnostic criteria for cardiomyopathy when it will have a net benefit to the patient, considering the psychological impact and preference, even if it does not enable diagnosis, prognostication, or therapeutic stratification, or cascade genetic screening of their relatives." (Class IIb, Level C)
- "Genetic testing in patients with a borderline phenotype not fulfilling diagnostic criteria for a cardiomyopathy may be considered only after detailed assessment by specialist teams." (Class IIb, Level C)
- "It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially)." (Class I, Level B)
- "Cascade genetic testing with pre- and post-test counselling should be considered in paediatric at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives, if available, and cascading out sequentially), considering the underlying cardiomyopathy, expected age of onset, presentation in the family, and clinical/legal consequences." (Class IIa, Level B)

- "Testing for the presence of a familial variant of unknown significance, typically in parents and/or affected relatives, to determine if the variant segregates with the cardiomyopathy phenotype should be considered if this might allow the variant to be interpreted with confidence." (Class IIa, Level C)
- "Diagnostic genetic testing is not recommended in a phenotype-negative relative of a patient with cardiomyopathy in the absence of a confident genetic diagnosis (i.e. a P/LP variant) in the family." (Class III, Level C)

2022 European Society of Cardiology guidelines (ESC, 2022), which were endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC, 2022), addressed the management of individuals with ventricular arrhythmias [VA] and the prevention of sudden cardiac death [SCD]. They stated the following regarding genetic testing for these indications:[13]

- "Genetic testing is recommended when a condition is diagnosed in a living or deceased individual with a likely genetic basis and a risk of VA and SCD." (Class I, Level B)
- "When a putative causative variant is first identified, evaluation for pathogenicity is recommended using an internationally accepted framework." (Class I, Level C)
- "When a Class IV or Class V variant has been identified in a living or deceased individual with a condition that carries a risk of VA and SCD, genetic testing of first-degree and symptomatic relatives and obligate carriers is recommended." (Class I, Level C)
- "It is recommended that genetic testing and counselling on its potential consequences should be undertaken by an expert multidisciplinary team." (Class I, Level C)
- "It is recommended that Class III (variants of uncertain significance) and Class IV variants should be evaluated for segregation in families where possible, and the variant re-evaluated periodically." (Class I, Level C)
- "It is not recommended to undertake genetic testing in index patients with insufficient evidence of a genetic disease." (Class III, Level C)

The 2022 ESC guidelines also included the following recommendations regarding testing for specific arrhythmias and cardiomyopathies:[13]

- Long QT Syndrome (LQTS):
  - "In patients with clinically diagnosed LQTS, genetic testing, and genetic counselling are recommended." (Class I, Level C)
  - "It is recommended that LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration." (Class I, Level C) The guideline also noted that genetic testing is useful in providing genotype-specific risks and, in some cases, genotype-specific treatment.
  - "Genetic testing is recommended in patients with suspected Anderson-Tawil syndrome." (Class I, Level C)
- Brugada Syndrome (BrS):

  - "Genetic testing for SCN5A gene is recommended for probands with BrS." (Class I, Level C)
  - The authors also noted: "The yield of genetic testing in BrS patients is approximately 20%, with the SCN5A gene the only gene with evidence of association for clinical testing purposes."
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):
  - "Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT." (Class I, Level C)
  - "It is recommended that CPVT is diagnosed in patients who are carriers of a mutation in disease-causing genes." (Class I, Level C)
- Short QT Syndrome (SQTS):
  - "Genetic testing is indicated in patients diagnosed with SQTS." (Class I, Level C)
  - "It is recommended that SQTS is diagnosed in the presence of a QTc ≤360ms and one or more of the following: (a) a pathogenic mutation, (b) a family history of SQTS, (c) survival from a VT/VF episode in the absence of heart disease." (Class I, Level C)
- Early repolarization syndrome (ERS):
  - "Genetic testing in ERS patients may be considered." (Class IIb, Level C)
- Dilated Cardiomyopathy (DCM):
  - "Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) is recommended in patients with DCM/HNDCM [hypokinetic non-dilated cardiomyopathy] and AV [atrioventricular] conduction delay at <50 years, or who have a family history of DCM/HNDCM or SCD in a first-degree relative (at age <50 years)." (Class I, Level B)
  - "Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) should be considered for risk stratification in patients with apparently sporadic DCM/HNDCM, who present at young age, or with signs suspicious for an inherited aetiology." (Class IIa, Level C)
- Arrhythmogenic right ventricular cardiomyopathy (ARVC):
  - "In patients with a suspected or definite diagnosis of ARVC, genetic counselling and testing are recommended." (Class I, Level B)
- Hypertrophic cardiomyopathy (HCM):
  - "Genetic counselling and testing are recommended in HCM patients." (Class I, Level B)

Heart Failure Society of America and American College of Medical Genetics and Genomics

The Heart Failure Society of America in collaboration with the American College of Medical Genetics and Genomics (HFSA/ACMG, 2018) stated the following regarding cardiomyopathy genetic testing:[3]

- "Guideline 4: Genetic testing is recommended for patients with cardiomyopathy" (Level of evidence A for HCM, DCM, ARVC, and cardiomyopathies associated with extracardiac manifestations; evidence level B for RCM)
  - "4a: Genetic testing is recommended for the most clearly affected family member."
  - "4b: Cascade genetic testing of at-risk family members if 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."
- "Genetic testing is recommended to determine if a pathogenic variant can be identified to facilitate patient management and family screening."
- "Testing should ideally be initiated on the person in a family with the most definitive diagnosis and most severe manifestations. This approach would maximize the likelihood of obtaining diagnostic results and detecting whether multiple pathogenic variants may be present and contributing to variable disease expression or severity."
- "Molecular genetic testing for multiple genes with the use of a multigene panel is now the standard of practice for cardio-vascular genetic medicine. Furthermore, multigene panel genetic testing is recommended over a serial single-gene testing approach owing to the genetically heterogeneous nature of cardiomyopathy. Genetic testing and cascade screening have been shown to be cost-effective."
- "[T]he 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."

The American College of Medical Genetics and Genomics (ACMG, 2018) published a practice resource on genetic testing for cardiomyopathies.[31] This practice resource was an abbreviated version of the Heart Failure Society of America (HFSA) guideline above, on which the ACMG collaborated.

Heart Rhythm Society

In a consensus statement focused on arrhythmogenic cardiomyopathy (ACM), the Heart Rhythm Society (HRS, 2019) stated the following:[33]

- "For individuals and decedent with either a clinical or necropsy diagnosis of ACM, genetic testing of the established ACM-susceptibility genes is recommended." (Class I, Level C)
- "For genetic testing of the established ACM-susceptibility genes, comprehensive analysis of all established genes with full coverage is recommended." (Class I, Level C)

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

An expert consensus statement from the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS, 2013) for the diagnosis and management of inherited primary arrhythmia established diagnostic criteria for multiple arrhythmia syndromes and recommended that genetic test results be incorporated into the criteria for LQTS, CPVT, and SQTS.[24] These recommendations were endorsed by the American College of Cardiology Foundation (ACCF, 2013), American Heart Association (AHA, 2013), Pediatric and Congenital Electrophysiology Society (PACES, 2013), and Association for European Paediatric and Congenital Cardiology (AEPC, 2013). No specific recommendations were made for when to perform genetic testing, since this topic was addressed elsewhere.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for cardiomyopathy and arrhythmia genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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