



Medical Coverage Policy

Effective Date.....12/15/2019
Next Review Date.....11/15/2020
Coverage Policy Number 0517

Genetic Testing for Hereditary Cardiomyopathies and Arrhythmias

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Related Coverage Resources

- [Genetics](#)
- [Implantable Cardioverter Defibrillator \(ICD\)](#)
- [Wearable Cardioverter Defibrillator and Automatic External Defibrillator](#)

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Coverage Policy

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

Pre- and post-test genetic counseling is required for any individual undergoing genetic testing for the hereditary cardiomyopathies and arrhythmias discussed in this Coverage Policy. Please refer to disease specific criteria* for additional information regarding genetic testing.

General Genetic Testing Criteria-Requirement for Genetic Counseling

Medically Necessary

Genetic testing is considered medically necessary when disease specific criteria* for the hereditary cardiomyopathies and/or arrhythmias listed below are met and when a recommendation for testing is confirmed by ONE of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics or American Board of genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

who:

- has evaluated the individual
- completed a three-generation pedigree
- intends to engage in post-test follow-up counseling

Confirmatory (Diagnostic) Genetic Testing

Medically Necessary

Confirmatory (diagnostic) genetic testing for a hereditary cardiomyopathy and/or arrhythmia is considered medically necessary when ALL of the following criteria are met:

- The individual has a suspected or confirmed ~~but not confirmed~~ clinical diagnosis of a specific hereditary cardiomyopathy and /or arrhythmia
- Results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
- The requested testing is targeted to a specific subset of genes related to the suspected condition
- There are no criteria listed below for the disorder for which testing is being requested

Confirmatory (i.e., diagnostic) single gene or multi-gene panel testing is considered medically necessary when an individual meets general criteria for hereditary cardiac genetic testing (as above) and ALL of the following criteria are met:

- individual has a clinical diagnosis of hypertrophic cardiomyopathy (HCM), catecholaminergic polymorphic ventricular tachycardia (CPVT), dilated cardiomyopathy (DCM), Brugada syndrome,

arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC/D), or restrictive cardiomyopathy (RCM),

- EITHER of the following criteria are met:
 - individual has an at-risk first- or second-degree blood relative
 - the individual, the individual's reproductive partner or parent has the capacity and intention to reproduce and genetic test results will be used for reproductive decision-making
-

Dilated Cardiomyopathy (DCM)

***Disease Specific Criteria:**

Medically Necessary

Genetic testing using a panel targeted to genes associated with dilated cardiomyopathy (DCM) is considered medically necessary when the individual meets the general criteria for hereditary cardiac testing and one of the following are met:

- individual has a clinical diagnosis of dilated cardiomyopathy (DCM)
 - individual has significant cardiac conduction disorder (first-, second- or third- degree block) AND/OR a family history of premature cardiac death (<50 years of age) in one or more first- or second-degree relative
 - individual is a candidate for an implantable or wearable cardioverter defibrillator
-

Long QT Syndrome

***Disease Specific Criteria**

Medically Necessary

Genetic testing for long QT syndrome (LQTS) is considered medically necessary for ANY of the following indications:

- confirmatory (i.e., diagnostic) testing with full sequence analysis (Current Procedural Terminology [CPT][®] code 81280) when there is confirmed prolonged QT interval on electrocardiogram (ECG) or Holter monitor, and an acquired cause has been ruled out
- predictive testing with full sequence analysis (CPT code 81280), when there is evidence in a first-degree relative** of EITHER of the following:
 - a history of prolonged QT interval on ECG or Holter monitor (i.e., corrected QT [QTc] interval of >470 msec [males] or >480 msec [females]) and the affected individual is not available for testing OR
 - sudden death of suspected cardiac diagnosis or near sudden death at age 40 or younger with no evidence of ischemia
- predictive testing for the known familial sequence variant when there is a positive genetic test for LQTS

Genetic testing for LQTS with deletion and duplication analysis (CPT code 81282) is considered medically necessary when the criteria listed above for LQTS testing have been met, sequence analysis is negative and the clinical suspicion of LQTS remains high.

Not Medically Necessary

Genetic screening for LQTS in the general population is considered not medically necessary.

Known Familial Variant Mutation Analysis

***Disease Specific Criteria**

Medically Necessary

Single site genetic testing for a known familial pathogenic or likely pathogenic variant is considered medically necessary when there is a positive genetic testing in a first- or second- degree relative** for the following indications:

- hypertrophic cardiomyopathy (HCM)
- catecholaminergic polymorphic ventricular tachycardia (CPVT)
- dilated cardiomyopathy (DCM)
- Brugada syndrome
- arrhythmic right ventricular cardiomyopathy/dysplasia (ARVC/D)
- restrictive cardiomyopathy (RCM)

**A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

Other Genetic Testing Services

Experimental/Investigational/Unproven

Genetic testing for atrial fibrillation is considered experimental, investigational or unproven.

Not Medically Necessary

Genetic testing for hereditary cardiac conditions in the general population is considered not medically necessary.

Overview

This Coverage Policy addresses germline pathogenic or likely pathogenic variant genetic testing for hereditary cardiomyopathies and arrhythmias. Germline gene variants are DNA changes that occur in the egg and sperm cells; also known as the germ cells. These variants are inherited; that is, passed down in families by blood relatives.

Cardiomyopathies are a group of disorders that affect the ability of the heart muscle to function properly. Types of inherited cardiomyopathies are hypertrophic (thickened), dilated (enlarged), arrhythmogenic (replaced by scar tissue), non-compaction (heart muscle fails to fully form during early embryo development) and restrictive (heart fails to fill with blood or contract properly).

Inherited cardiac arrhythmia syndromes are caused by gene variants which affect the function of the heart's electrical system, although the heart muscle itself may be normal. These variants can cause abnormal heart rhythms which may cause life-threatening conditions such as sudden cardiac death and ventricular tachycardia.

General Background

Genetic Counseling

Genetic counseling is required both pre-and post- genetic testing for the hereditary cardiomyopathies and arrhythmias discussed in this Coverage Policy to interpret family and medical histories and assess the chance of disease occurrence and recurrence. Genetic counseling also allows an opportunity to educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition.

Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis (National Society of Genetic Counselors [NSGC]; Edwards, 2010).

A variety of genetics professionals provide these services: Board-Certified or Board-Eligible Medical Geneticists, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, and genetic nurses credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC). Individuals should not be employed by a commercial genetic testing laboratory, although counseling services by these individuals are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself.

Genetic Testing

Genetic testing has been proposed as method to differentiate inherited or familial cardiomyopathies and arrhythmias from those caused by other factors. Cardiomyopathies are a heterogeneous group of acquired or inherited disorders affecting the heart muscle's ability to contract and to relax. They are described by their effect on the heart muscle and include hypertrophic (HCM) (e.g., thickened), dilated (DCM) (e.g., stretched out) and restrictive (RCM) (e.g., stiffened).

Like the cardiomyopathies discussed above, Long QT (LQTS), Brugada (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and short QT syndromes (SQTS) are characterized by symptoms which can develop rapidly and can be life-threatening, including an increased risk of sudden cardiac death, also known as sudden cardiac arrest.

Incomplete penetrance within families and variable expressivity of symptoms are characteristic of inherited cardiomyopathies and arrhythmias and make the clinical usefulness of genetic testing challenging. Individuals may have few symptoms and require no treatment. Depending on the gene involved inheritance patterns differ within defined syndromes and arrhythmias. These include an autosomal dominant pattern (e.g., DCM, HCM, RCM, ARVD/C, LQTS, BrS, SQTS) and an autosomal recessive pattern (e.g., DCM, LQTS). Other cardiomyopathies result from a new gene variant (i.e., de novo) with no history of cardiomyopathy in the family (e.g., RCM, DCM) while for others an X-linked pattern of inheritance is present (e.g., DCM).

Some inherited cardiac disorders present as a phenotype, such as the cardiomyopathies

Confirmatory (Diagnostic) Genetic Testing

Many hereditary cardiomyopathies and arrhythmias are diagnosed clinically using results of EKGs, MRIs and cardiac echocardiogram. When an individual has a suspected, but not confirmed clinical diagnosis of a specific hereditary cardiomyopathy or arrhythmia, confirmatory (i.e., diagnostic) genetic testing may be appropriate. Testing should be targeted to a specific subset of genes related to the individual's suspected condition and results of testing should directly impact clinical decision-making and/or the clinical outcome of the individual being tested.

Diagnostic testing may also be appropriate to determine if there is a pathogenic variant in an individual who has been diagnosed with HCM, CPVT, DCM, Brugada syndrome, ARVC/D or RCM. Clarification of the genetic status of at-risk family members allows longitudinal evaluation to be focused on those who have inherited the pathogenic variant of the condition in question (Gene Reviews, 2017, 2016, 2015, 2014). In contrast to HCM, DCM, RCM and ARVC, the left ventricular non-compaction (LVNC) phenotype remains without consensus as to whether it is a primary cardiomyopathy, a variant morphologic trait or something else. Guidelines from the Heart Failure Society refer to it as a phenotype. According to imaging evidence non-compaction of the myocardium is present in 2-10% of the population. Further, it may progress and regress. Testing for gene variants related to this phenotype would be included in testing for the primary cardiomyopathy (Hershberger et al., 2018). Therefore, genetic testing for LVNC is not separately recommended.

Requests for prenatal testing for hereditary cardiomyopathies or arrhythmias are not common. However, diagnostic molecular testing may be appropriate for reproductive decision-making when an individual has a clinical diagnosis of hypertrophic cardiomyopathy (HCM), CPVT, DCM, Brugada syndrome, ARVC/D or RCM. Testing should be targeted to the disorder(s) corresponding to the individual's clinical diagnosis and the individual, the individual's reproductive partner or parent should have the capacity and intention to reproduce.

Dilated Cardiomyopathy (DCM)

DCM occurs when the heart muscle becomes stretched out in at least one chamber of the heart, primarily the left ventricle. Familial DCM may be syndromic, involving the heart and other organs or nonsyndromic, involving the heart only (Genetics Home Reference [GHR], 2017).

Over 30 gene variants have been identified related to DCM. Single gene analysis or a panel focused on gene(s) associated with DCM may be clinically useful and appropriate for an individual who has been diagnosed with dilated cardiomyopathy (DCM) to aid in treatment planning. DCM predisposes a small subset of individuals to an increased risk of sudden cardiac death (SCD) which may be the first symptom of DCM. Implantation of a cardioverter-defibrillator may be appropriate for these individuals. If single gene testing does not yield a positive result, multi-gene panel testing for DCM variants appropriate. The multi-gene panel should test only for those gene variants implicated in DCM.

Predictive testing is appropriate for an asymptomatic at-risk individual with a first- or second-degree blood relative in whom a variant has been identified. Single site genetic testing for the known familial variant is appropriate to aid in surveillance planning such as annual lab testing, electrocardiograms, echocardiograms and other diagnostic evaluation.

Professional Society/Organizations

Professional society/organization support for genetic testing is available in the form of published consensus guidelines. For a summary of professional society recommendations/guidelines regarding genetic testing for familial dilated cardiomyopathy please click [here](#).

Long QT Syndrome (LQTS)

LQTS is a disorder of the heart's electrical system characterized by prolongation of the QT interval. This condition predisposes the individual to cardiac events and arrhythmias including: torsades de pointes, ventricular tachycardia, syncopal episodes, ventricular fibrillation and cardiac arrest.

More than 900 different variants have thus far been identified in 13 known genes causative for LQTS. Not all patients meeting clinical criteria for LQTS have detectable variants in one of the known genes suggesting that additional LQTS genes may exist. Sporadic cases of LQTS may also occur as a result of spontaneous variants. A lack of family history does not entirely preclude the diagnosis of congenital LQTS (Alders, et al., 2012; Kahn, 2002).

The inability to identify a genetic variant in some LQTS patients limits the utility of genetic testing because a negative result does not exclude the disease (Vincent, 2000). A technology assessment performed by Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center in 2008 to review evidence to determine if genetic testing for LQTS improves health outcomes for patients with known or suspected LQTS. The report notes that genetic testing is most appropriate when undertaken in clinical environments where expertise in genetic testing is available, and genetic counseling provided to patients in order to assist in complex clinical decision-making. As such, genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Please refer to the disease specific criteria for LQT syndrome noted in the Coverage Policy section above for additional information regarding the requirements for genetic testing prior to genetic testing for LQTS.

Several studies have been published in the peer-reviewed scientific literature that indicate genetic testing for LQTS may offer early identification of those patients at high risk to develop LQTS and may provide the opportunity for early intervention (Priori, et al., 2003; Behr, et al., 2003; Imboden, et al., 2006). Genetic testing for LQTS has clinical usefulness in long-term management including lifestyle modification and the potential for use of beta-adrenergic blockers, permanent pacemaker implantation, and implantable cardioverter defibrillators placement.

When an individual has a confirmed prolonged QT interval and an acquired cause of LQTS has been ruled out confirmatory (diagnostic) testing by full sequence analysis is appropriate. Predictive testing of an at-risk blood relative by full sequence analysis is appropriate when there is a history of prolonged QT interval on ECG or Holter monitor in an affected first-degree blood relative but the relative is not available for testing. Deletion/duplication analysis may be appropriate if sequence analysis fails to detect variants. Other circumstances where predictive testing has clinical usefulness include the sudden death with a suspected cardiac diagnosis in a first degree blood relative or near sudden death at age 40 or younger with no evidence of ischemia. When the familial variant is known, predictive genetic testing for the known familial sequence variant evidence is appropriate.

Genetic screening of the general population, including testing of all children, young athletes, or all young persons with unexplained syncope is not feasible. Population screening for LQTS by deoxyribonucleic acid (DNA) testing is neither recommended nor available (Vincent, 2001).

Professional Society/Organizations

Professional society/organizational support for genetic testing is available in the form of published consensus guidelines. For a summary of professional society recommendations/guidelines regarding genetic testing for long QT syndrome please click [here](#).

Known Familial Variant Analysis

Single site testing may be appropriate in an at-risk individual if a familial variant has been identified in a first- or second-degree relative for a number of inherited cardiomyopathies (i.e., HCM, RCM, ARVD/C) and inherited arrhythmias (BrS, CVPT). The clinical utility of such genetic testing, especially in children or adolescents, is the ability to determine whether or not close monitoring or continued surveillance in the form of lab testing, electrocardiograms, echocardiograms, stress testing, cardiac MRI and other diagnostic interventions or activity restriction is required. If there is a known familial variant, a negative test in an at-risk family member can rule out

predisposition to the disorder in question and there is no need for continued surveillance. Although a positive result does not ensure that an individual will develop the disorder, this information may assist in establishing a plan for monitoring.

Professional Society/Organizations

Professional society/organizational support is available for genetic testing in the form of published consensus guidelines. For a summary of professional society recommendations/guidelines regarding genetic testing for HCM click [here](#), for RCM click [here](#), for ARVD/C click [here](#) and for BrS, please click [here](#).

Other Genetic Testing Services

Short QT syndrome (QTS): SQTS is a rare genetically heterogeneous condition associated with a predisposition to ventricular and atrial fibrillation and sudden cardiac death. Approximately 100 cases have been identified since the condition was recognized in 2001. The heart is structurally normal, but the time to recharge between beats is shortened which is exhibited on the electrocardiograph as an abbreviated or shortened QT interval (Genetic Home Reference, 2015). The phenotype varies and may be characterized by no clinical symptoms to dizziness and fainting, or may include cardiac arrest and sudden cardiac death. Six types of SQT (1-6) have been identified; however, data are limited in the published peer-reviewed scientific literature regarding genotype-phenotype correlation. Data are also lacking regarding treatment options targeted to genotype.

Genetic testing has been proposed to determine if a genetic variant is present in an individual with SQTS. Six genes (three gain of function and three loss of function) have been identified. SQTS is transmitted in an autosomal dominant fashion, although rarely sporadic inheritance has been identified. Several genes identified in SQTS are the same as those responsible for LQTS; however, the variations in SQTS increase repolarizing forces which is an effect opposite to that which occurs in LQTS.

There is insufficient evidence in the published peer-reviewed scientific literature regarding the clinical utility of genetic testing for SQTS to establish a genotype-phenotype correlation, stratify risk for developing SQTS or assign treatment if a variant is present. Treatment for sudden cardiac death includes the implantation of a cardioverter defibrillator regardless of the etiology; results of genetic testing do not change treatment. At this time the clinical utility of genetic testing for SQTS has not been established.

Professional Society/Organizations

There is a lack of support for genetic testing for SQTS in the form of published professional society consensus guidelines. For a summary of professional society recommendations/guidelines regarding genetic testing for short QT syndrome and atrial fibrillation please click [here](#).

Inherited Atrial Fibrillation: Inherited or familial atrial fibrillation is characterized by uncoordinated electrical activity in the atria. Symptoms of familial atrial fibrillation are indistinguishable from atrial fibrillation from non-genetic causes and include dizziness, chest pain, a sensation of fluttering or pounding in the chest (palpitations), shortness of breath, syncope and an increased risk of stroke and sudden death. Some individuals with inherited atrial fibrillation do not experience these symptoms.

The incidence of the familial form of atrial fibrillation is unknown. The majority of cases of atrial fibrillation are not caused by a gene variant; however variations in three genes have been identified (i.e., KCNE2, KCNJ2, KCNQ1) and genetic testing for these variants is clinically available (GHR, 2017). There is insufficient evidence to demonstrate improvement in outcomes based on results of genetic testing. At this time the role of genetic testing has not been established.

Professional Society/Organizations

Support for genetic testing by professional society/organizations in the form of published consensus guidelines is lacking for this indication.

Genetic Testing (Screening) in the General Population: The clinical utility of genetic testing in the general population for these familial cardiac conditions is unknown and the role of such testing has not been established.

Rather, confirmatory testing for affected individuals and predictive testing for at-risk individuals may assist in establishing a plan for monitoring or other targeted treatment if a specific variant has been identified.

Professional Society/Organizations

Support for genetic screening for inherited cardiomyopathies and arrhythmias in the general population and for the use of multi-condition is lacking in the form of published professional society/organizational consensus guidelines.

Centers for Medicare and Medicaid Services (CMS)

NCD: No NCDs found

LCD: No LCD found

Use Outside of the US

Please see Appendix A for relevant professional society/organization recommendations/guidelines.

Appendix A

PROFESSIONAL SOCIETY/ORGANIZATION RECOMMENDATIONS/GUIDELINES

Ventricular Arrhythmias and Sudden Cardiac Death

European Society of Cardiology (ESC, 2015): The ESC published Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. The Task Force made the following recommendations:

- Population screening: Cannot provide recommendations for population screening at this time because the consequences of screening strategies that detect a still-undefined number of ‘false positives’ and miss an unknown percentage of affected cases (‘false negatives’) have not been established.
- Screening of family members of sudden unexplained death syndrome or sudden arrhythmic death syndrome
 - Targeted genetic testing and genetic counseling if there is the clinical suspicion of a disease
 - Referral to a tertiary centre specialized in evaluation of the genetics of arrhythmias
- Short QT syndrome: the yield of genetic screening remains low (<20% overall)
- Brugada syndrome: Results of genetic screening do not currently influence prognosis or treatment.

European Society of Cardiology and European Association for Cardio-Thoracic Surgery (2016): Kirchoff et al. published guidelines for the management of atrial fibrillation (AF). Regarding genetic testing, the guideline notes while genomic analysis may provide an opportunity to improve the diagnosis and management of AF in the future, routine genetic testing for common gene variants associated with AF cannot be recommended at present. The guideline also notes that monogenic defects only account for 3–5% of all patients with AF, even in younger populations. Furthermore, there is no clear link between detected variants and specific outcomes or therapeutic needs. Genetic testing is not recommended in the general population.

Dilated Cardiomyopathy

Heart Failure Society of America ([HFSA], 2010): On behalf of the HFSA Lindenfield et al. published guidelines for the genetic evaluation of cardiomyopathy. The guidelines note:

- Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended (Strength of evidence A: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in reasonably large studies from multiple centers).

- Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management (Strength of evidence B: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in small or single center studies).

Long QT Syndrome

Heart Failure Society (HFS)/European Heart Rhythm Association (EHRA) (2008): The HFS/EHRA published guidelines regarding genetic testing for LQTS which note:

- 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 electrocardiograms [ECGs] and/or provocative stress testing with exercise or catecholamine infusion) phenotype. (Class I)
- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and 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., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults). (Class I)
- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs. (Class IIb)
- Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case. (Class I)

Arrhythmogenic Cardiomyopathy (ACM)/Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Heart Failure Society (HFS)/European Heart Rhythm Association (EHRA) (2008): Regarding ARVC

- Comprehensive or targeted (DSC2, DSG2, DSP, JUP, PKP2, and TMEM43) ACM/ARVC genetic testing can be useful for patients satisfying task force diagnostic criteria for ACM/ARVC. (Class IIa)
- Genetic testing may be considered for patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 task force criteria. (Class IIb)
- Genetic testing is not recommended for patients with only a single minor criterion according to the 2010 task force criteria. (Class III)
- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the ACM/ARVC-causative mutation in an index case. (Class I)

Hypertrophic Cardiomyopathy (HCM):

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): On behalf of the ACCF/AHA, Gersh et al. (2011) published Guidelines regarding the diagnosis and treatment of hypertrophic cardiomyopathy. The Guidelines included the following recommendations for genetic testing:

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

- Ongoing clinical screening is not indicated in genotype negative relatives in families with HCM.

Heart Failure Society (HFS)/European Heart Rhythm Association (EHRA) (2008): On behalf of the HFS/EHRA, Ackerman et al. (2011) published joint consensus guidelines regarding genetic testing for hypertrophic cardiomyopathy. Comprehensive or targeted (i.e., MYBPC3, MYH7, TNN13, TNNT2, TPM1) genetic testing is recommended for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history, and electrocardiographic phenotype. Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case.

Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group (2008):

Genetic testing is not recommended for diagnosis of hypertrophic cardiomyopathy outside the setting of expert clinical and detailed family assessment. Genetic testing should be considered for patients with a firm clinical diagnosis of hypertrophic cardiomyopathy as a means of cascade screening of relatives in the setting of expert clinical, and detailed family assessment.

Brugada Syndrome

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) (2011): On behalf of the HRS/EHRA, Ackerman et al. (2011) published joint consensus Guidelines regarding genetic testing for channelopathies and the cardiomyopathies. Regarding Brugada syndrome the Guideline notes the following: Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the Brugada syndrome-causative mutation in an index case; comprehensive or Brugada syndrome 1 (i.e., SCN5A) targeted genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype; genetic testing is not recommended in the setting of an isolated type 2 Brugada electrocardiogram pattern.

Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group (2008): Genetic testing is not recommended as routine in known or suspected cases of Brugada syndrome, but may be considered in the setting of expert clinical and detailed family assessment.

Restrictive Cardiomyopathy and Left Ventricular Non-Compaction

Heart Failure Society of America ([HFSA], 2018): On behalf of the HRSA, Hershberger et al. (2018) published a practice guideline regarding the Genetic Evaluation of Cardiomyopathy. The Guideline notes In contrast to HCM, DCM, RCM and ARVC, LVNC remains without a consensus whether or not it should be considered a primary cardiomyopathy or a phenotype; however, the designation of a phenotype is favored by the HRS. LVNC may be present in 2-10% of the population and may also progress and regress. LVNC may be observed in conjunction with other cardiomyopathy phenotypes, and if so, recommendations for that cardiomyopathy derive clinical screening recommendations. Because of the high prevalence of the LVNC phenotype in otherwise normal individuals in population-based studies and limited evidence of disease causation from the LVNC phenotype itself HRS provides no recommendations regarding family-based phenotype screening of LVNC that is not accompanied by other cardiovascular phenotypes with known disease risks.

Heart Rhythm Society ([HRS], 2019): In collaboration with, and endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the American Society of Echocardiography (ASE), the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Failure Society of America (HFSA), the International Society for Heart & Lung Transplantation (ISHLT), the Japanese Heart Rhythm Society (JHRS), the Latin American Heart Rhythm Society (LAHRS), the National Society of Genetic Counselors (NSGC), the Pediatric & Congenital Electrophysiology Society (PACES), and the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC), Towbin et al. published an expert consensus statement on the evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy, which includes LVNC.

Regarding genetic testing for LVNC the consensus statement notes in individuals with the clinical diagnosis of pathologic LVNC, genetic counseling and genetic testing are reasonable for diagnosis and for gene-specific targeted cascade family screening (Class of evidence [COR IIa; moderate strength of evidence], Level of evidence [LOE B-NR; : Moderate strength of evidence [moderate, non-randomized]).

Short QT Syndrome

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) (2011): On behalf of the HRS/EHRA Ackerman et al. (2011) published an expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Regarding SQTs, the statement notes:

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

Atrial Fibrillation

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) (2011): On behalf of the HRS/EHRA Ackerman et al. (2011) published an expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. The statement notes:

- Genetic testing is not indicated for atrial fibrillation at this time. (Class III, "Should not" or "is not recommended.")
- Single nucleotide polymorphism (SNP) genotyping in general and SNP rs2200733 genotyping at the 4q25 locus for AF is not indicated at this time based on the limited outcome data currently available. (Class III, Class III, "Should not" or "is not recommended.")

American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society (2014): On behalf of these societies January et al. published guidelines related to the management of atrial fibrillation. According to the guideline the routine genetic testing related to AF is not indicated.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)

81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, and TTN)
81479†	Unlisted molecular pathology procedure
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

†**Note:** Considered Medically Necessary when used to report any genetic testing for hereditary cardiomyopathy and/or arrhythmia that does not have an assigned CPT or HCPCS code

HCPCS Codes	Description
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

*Current Procedural Terminology (CPT®) ©2019 American Medical Association: Chicago, IL.

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