## Clinical Appropriateness Guidelines

# Genetic Testing for Hereditary Cardiac Disease

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AIM SpecialtyHealth.
8600 West Bryn Mawr Avenue
South Tower - Suite 800 Chicago, IL 60631
www.aimspecialtyhealth.com

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# Scope

This document addresses genetic testing for inherited arrhythmias and cardiomyopathies. Aortopathies and other connective tissue disorders with cardiac manifestations as well as congenital heart defects are NOT included in this document; see Clinical Appropriateness Guidelines: Genetic Testing for Single-Gene and Multifactorial Conditions. All tests listed in this guideline may not require prior authorization; please refer to the health plan.

# Genetic Counseling Requirement

**Genetic testing included in these guidelines is covered when:**

1. The patient meets coverage criteria outlined in the guidelines
2. A recommendation for genetic testing has been made by one of the following:
   - An independent board-certified or board-eligible medical geneticist not employed by a commercial genetic testing laboratory*
   - An American Board of Medical Genetics or American Board of Genetic Counseling-certified genetic counselor not employed by a commercial genetic testing laboratory*
   - A genetic nurse 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) who is not employed by a commercial genetic testing laboratory*

   Who:

   - Has evaluated the individual and performed pre-test genetic counseling
   - Has completed a three-generation pedigree
   - Intends to engage in post-test follow-up counseling

**A physician, genetic counselor or genetic nurse employed by a laboratory that operates within an integrated, comprehensive healthcare delivery system is not considered to be an employee of a commercial genetic testing laboratory for the purpose of these guidelines.*

# Appropriate Use Criteria

## Confirmation/Diagnostic Testing of Affected Individuals

Confirmatory or diagnostic genetic testing for hereditary arrhythmias and cardiomyopathies is medically

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necessary when all of the following criteria are met:

- The individual has a clinical diagnosis of a hereditary cardiac condition
- The requested testing is as targeted as possible to a specific subset of genes related to the suspected condition (e.g. hypertrophic cardiomyopathy OR arrhythmogenic right ventricular cardiomyopathy/dysplasia)
- There are no additional relevant disease-specific criteria listed below

## Testing of Asymptomatic Individuals

Single-site genetic testing for a known familial deleterious or suspected deleterious pathogenic or likely pathogenic (P/LP) variant is medically necessary for the following indications:

- Long QT syndrome (LQTS)
- Dilated cardiomyopathy (DCM)
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Hypertrophic cardiomyopathy (HCM)
- Brugada syndrome (BrS)
- Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)
- Left ventricular non-compaction cardiomyopathy (LVNC)
- Restrictive cardiomyopathy (RCM)

## Post-Mortem Testing

Post-mortem cardiac genetic testing of an individual with sudden unexplained death, whose first degree family member is a covered member, is reasonable in the following circumstances:

- When the autopsy reveals evidence for a specific underlying heritable cardiac condition (e.g. ARVC, HCM, DCM, RCM) AND all of the following criteria are met:
    a. The corresponding targeted testing is ordered (e.g. HCM panel testing in cases where autopsy revealed evidence for HCM)
    b. No other living relative has clinical evidence for the suspected condition (e.g. should a living relative have evidence for HCM, then testing for the living relative is recommended)
- In ‘autopsy negative’ cases when all of the following criteria are met:
    a. The deceased individual meets one of the following:
        i. Age 40 years or younger at death

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ii. Over 40 years at death and there is a documented family history of sudden death or cardiomyopathy

b. Cause of death remains unknown after completion of autopsy and toxicology testing (if completed)
c. The test requested is a single gene or targeted panel test for common genetic causes of sudden cardiac arrest/death and/or is as targeted as possible for the clinical indication

## Long QT

Genetic testing for long QT syndrome (LQTS) is medically necessary when the individual meets general criteria for hereditary cardiac genetic testing (above) and one of the following indications:

- Confirmatory (i.e., diagnostic) testing when there is confirmed prolonged QT interval on electrocardiogram (ECG) or Holter monitor (i.e., corrected QT [QTc] interval of >470 msec [males] or >480 msec [females]), and an acquired cause has been ruled out
- Predictive testing, 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
  - Sudden death of suspected cardiac diagnosis or near sudden death at age 40 or younger with no evidence of ischemia and no genetic testing was performed

## Dilated Cardiomyopathy

Genetic testing is medically necessary when the general criteria for hereditary cardiac genetic testing (above) are met in addition to one of the following:

- Individual has a clinical diagnosis of dilated cardiomyopathy (DCM)
- Individual has significant cardiac conduction disease (first-, second- or third- degree block) and/or family history of premature cardiac death (<50 years) in a first- or second-degree relative
- Individual is a candidate for an ICD

## Tests Not Clinically Appropriate

- Broad “multi-condition” panel testing (e.g. pan-cardio panel, arrhythmia panel) is not medically necessary
- Genetic testing for short QT syndrome and atrial fibrillation is not medically necessary
- Genetic testing for isolated left ventricular noncompaction cardiomyopathy (LVNC) is not medically necessary

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# CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive. Medical plans may have additional coverage policies that supersede these guidelines.

Covered when medical necessity criteria are met:

| | |
|---|---|
| 81403 | Molecular Pathology Procedure Level 4 |
| 81404 | Molecular Pathology Procedure Level 5 |
| 81405 | Molecular Pathology Procedure Level 6 |
| 81406 | Molecular Pathology Procedure Level 7 |
| 81407 | Molecular Pathology Procedure Level 8 |
| 81408 | Molecular Pathology Procedure Level 9 |
| 81413 | Cardiac ion channelopathies (eg, Brugada syndrome, long 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, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1 |
| 81439 | Inherited cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYPBC3, MYH7, PKP2, and TTN |

# Background

Most forms of arrhythmias and cardiomyopathies are multifactorial. There are, however, several forms of Mendelian hereditary cardiac disease that cause severe and early-onset symptoms. The hereditary arrhythmias and cardiomyopathies are primarily diagnosed clinically and symptoms can be variable within the same family. Although genetic test results may not guide medical management for those with a clinical diagnosis, identification of a P/LP variant can allow for detection of asymptomatic family members who might benefit from life-saving treatment. Most hereditary cardiac conditions are associated with multiple genes. Targeted panel testing is reasonable in most cases.

## Rationale for Genetic Counseling for Hereditary Cardiac Conditions

Pre-test genetic counseling provides individuals seeking genetic testing the opportunity to make informed decisions about their genetic testing and subsequent medical management options. Genetic counseling combines expertise in obtaining and interpreting family history information, the ability to identify the most beneficial individual in a family to initiate testing, identification of the most appropriate testing options, experience in obtaining informed consent for testing and proficiency in genetic variant

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interpretation, in order to maximize the genetic testing experience for patients and their healthcare providers. The genetic counseling informed consent process also educates and empowers patients to consider the psychological, financial, employment, disability, and insurance implications of genetic testing and results (Al-Khatib et al. 2018). Patients who receive genetic counseling report increased knowledge, understanding, and satisfaction regarding their genetic testing experience (Armstrong et al. 2015; Harvey et al. 2007).

The advent of multi-gene panels and genome-scale sequencing have increased the complexity of the genetic testing landscape. Misuse of genetic testing increases the risk for adverse events and patient harm, including missed opportunities for diagnosis and disease prevention (Bellcross et al. 2011; Plon et al. 2011). Genetic information requires expert interpretation and ongoing re-evaluation to ensure the most accurate interpretation is utilized to inform medical management decision making. The multitude of genetic testing options as well as the complex information revealed by genetic testing can make choosing the most appropriate test and interpretation of results difficult for non-genetics healthcare providers (Ray 2011). Involvement of a clinical genetics provider has been shown to ensure the correct test is ordered, limit result misinterpretation and allow patients to make informed, evidence-based medical decisions with their healthcare providers (Cragun et al. 2015).

Genetic counseling not only improves patient outcomes but also reduces unnecessary healthcare spending. Pre-test genetic counseling has been shown to reduce inappropriate test ordering and prevent unnecessary medical procedures and interventions that follow from inaccurate result interpretation (DHHS 2011). While genetic testing is now available for almost all clinical specialties, correct use and interpretation is necessary to prevent adverse outcomes. While genetic counseling may benefit any patient considering or undergoing genetic testing, tests that offer predictive information or have a higher chance of identifying variants of uncertain significance often carry stronger recommendations in the form of consensus guidelines and professional statements recommending genetic counseling by trained genetics professionals.

Both the joint consortium of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (AHA/ACC/HRS) as well as the ACMG have issued strong recommendations for genetic counseling for individuals undergoing evaluation for inherited cardiac disease.

In their Task Force publication from 2017 (Al Khatib et al. 2018), the AHA/ACC/HRS provided this recommendation:

> *The decision to proceed with genetic testing requires discussion, regarding the clinical use of genetic information to be obtained for both the proband and family members, as well as consideration of the important psychological, financial, employment, disability, and life insurance implications of positive genotyping. Balancing privacy of health care information for the proband with the "right to know" for family members, and the ability to provide appropriate communication of information to all potentially affected family members can be challenging on many levels, including family dynamics, geographic proximity, and access to healthcare. For these reasons, genetic counseling generally occurs before proceeding with genetic testing, and, from a patient's perspective, is optimally provided by genetic counselors, if available, in collaboration with physicians. A combined approach of genetic counseling with medical guidance may appropriately balance the decision as to whether genetic testing would be beneficial on an individual basis.*

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In the joint statement put forth by the ACMG and Heart Failure Society (Hershberger et al. 2018), genetic counseling performed by a board-certified or board-eligible genetic specialist or specialized physician in the absence of a genetics professional is recommended as a key component of the evaluation of individuals with suspected familial cardiomyopathies with a level of evidence of A, their strongest recommendation. In addition, this recommendation includes specific guidance regarding genetic counseling which notes that genetics professionals are specially trained to provide: review of medical records essential for phenotyping, obtaining a pedigree, patient and family education, evaluating genetic testing options, obtaining consent for genetic testing, facilitating family communication, and ordering and interpreting genetic test results while addressing psychosocial issues.

## Long QT

Long QT syndrome (LQTS) is characterized by prolongation of the QT interval on electrocardiogram (ECG). LQTS disorders are considered channelopathies, or diseases that affect cardiac ion channels. This condition predisposes the individual to cardiac events and arrhythmias including: torsades de pointes, ventricular tachycardia, syncopal episodes, ventricular fibrillation and cardiac arrest.

LQTS is diagnosed by considering the clinical features, the family history, and the ECG findings of the patient. LQTS may be diagnosed when the prolongation of the QTc interval is >470 msec (males) or >480 msec (females) (Crotti 2008). The clinical features may range from minor symptoms such as dizziness, to more severe symptoms such as seizure, syncope and sudden death. Congenital LQTS will usually manifest before the age of 40 years, generally in childhood and adolescence with the age of onset associated with the genotype. Long-term management of LQTS may include lifestyle modification, beta-adrenergic blockers, permanent pacemaker implantation, and implantable cardioverter defibrillators.

At least 15 genes have been found to be associated with LQTS; however, P/LP variants in 3 genes represent the most common causes: KCNQ1 (30-35%), KCNH2 (25-30%), and SCN5A (5-10%). Not all patients meeting clinical criteria for LQTS have detectable P/LP variants in one of the known associated genes. The recommended testing approach includes either single gene sequencing or a multi-gene sequencing panel, which may be more cost effective given the multiple associated genes. Genetic screening may provide unique assistance to a family member with normal QT interval (Schwartz 2006), as at-risk individuals can be identified prior to the onset of symptoms.

## Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by enlargement of the left ventricle of the heart and systolic impairment, in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic dysfunction (Haas 2015). The symptoms of DCM are similar to heart failure including shortness of breath, chest pain/tightness, fainting episodes and cardiac arrhythmias. The most serious complication of DCM is sudden, irregular heart rhythms that can be life threatening. Some individuals with DCM will have no symptoms throughout their lifetime.

DCM is a heterogeneous condition caused by ischemia, systemic disease (e.g. mitochondrial or muscular dystrophy), toxins, or infection. Twenty to 50 percent of cases of idiopathic DCM are inherited. DCM can be inherited as an X-linked, autosomal recessive or autosomal dominant condition. Autosomal dominant is the most common form of inherited DCM. There are at least 38 different genes known to cause DCM and many more genes implicated as associated with the condition. Genetic testing is available for

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multiple DCM genes, typically in large multi-gene panels. Genetic testing identifies a P/LP variant in 22-50% of cases.

The 2011 HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies recommends comprehensive (testing all clinically available DCM genes) or targeted (LMNA and SCN5A) DCM genetic testing for patients with DCM and significant cardiac conduction disease (i.e. first, second or third degree heart block) and/or family history of premature unexplained death. In addition, they state that genetic testing can be useful for patients with familial DCM to confirm diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family and to help with family planning. Known familial P/LP variant testing is recommended when a P/LP variant has been identified in the family.

Although genetic testing is useful in differentiating between familial versus isolated DCM, and therefore facilitates identification of at-risk family members, management for the individual affected with DCM typically does not change once a diagnosis of familial DCM is established. The one exception to this is when a LMNA P/LP variant is identified. In individuals identified with a LMNA P/LP variant requiring pacemaker placement (i.e. history of arrhythmia or known risk of arrhythmia), the use of a pacing ICD rather than a pacemaker has been recommended due to the risk of ventricular arrhythmias and sudden death (Meune 2006).

In families where a P/LP variant is not yet identified, clinical screening (physical exam, echocardiogram, and ECG) for DCM is recommended for asymptomatic at-risk relatives yearly in childhood and every 1-3 years in adults (Journal of Cardiac Failure Vol. 15 No. 2 2009). If there is a family history of early onset disease or family history of sudden death, increased frequency of screening may be more appropriate.

Once a familial P/LP variant is identified, genetic testing for the known familial P/LP variant in asymptomatic family members can differentiate between relatives who are at high risk of DCM and sudden death, versus relatives who did not inherit the familial variant and for whom clinical screening is not warranted.

## Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare form of cardiac arrhythmia in which emotional or physical stress triggers catecholamine release, which leads to abnormal heartbeat and symptoms such as dizziness, fainting, cardiac arrest, and even sudden death. The estimated prevalence of CPVT is 1 in 10,000, and symptoms tend to be earlier onset and more common among males than females (Fernández-Falgueras et al. 2017). The mean age of onset is between 7 and 12 years old, but onset can occur as late as 40. Mortality rate from sudden cardiac death may be as high as 30% (Hickey and Elzomor 2018).

Typically, baseline echocardiogram among individuals with CPVT is normal but diagnostic findings can be identified upon exercise ECG or in the setting of emotional stress. These findings include premature ventricular complexes, nonsustained ventricular tachycardia, and ventricular fibrillation. Genetic testing is required to confirm a diagnosis of CPVT (Hickey and Elzomor 2018).

RYR2 is the most common genetic cause of CPVT, with P/LP variants found in about 60% of individuals with this condition. Additional genes that have been associated with CPVT include KCNJ2, CALM1, CALM2, CALM3, TRDN, CASQ2 and ANK2 (Fernández-Falgueras et al. 2017; Baltogiannis et al. 2019). The majority of cases of CPVT are inherited in an autosomal dominant manner; however, CASQ2 and

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TRDN P/LP variants cause autosomal recessive forms of CPVT. Genetic testing can confirm a diagnosis of CPVT, clarify risks to family members, and allow for family-specific testing. Guidelines from the Heart Rhythm Society recommend that at-risk relatives undergo genetic testing when a familial P/LP variant has been detected. Beta blockers are suggested for treatment in those with P/LP variants, even if they have had negative ECG findings (Ackerman et al. 2011).

## Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by increased size of the left ventricle of the heart, typically caused by thickening of the walls of the heart. The symptoms of HCM can be variable, ranging from no symptoms to shortness of breath or irregular heart rhythms, or sudden death. The irregular heart rhythms can occur without warning and may be life threatening. HCM has a prevalence of 1/500 individuals, making it one of the most common cardiac genetic diseases. It is inherited as an autosomal dominant trait with reduced penetrance. Family history focused on history of sudden death and age of onset in family members can be helpful in risk stratification.

HCM is the most common cause of sudden death in athletes, accounting for 30% of cases of young sudden death during competition. Approximately 5%-10% of individuals with HCM progress to end-stage disease with impaired systolic function and, in some cases, left ventricular dilatation and regression of LVH. The annual mortality rate in individuals with end-stage disease is estimated at 11% and cardiac transplantation may be required. Current testing is estimated (depending on number of genes tested - from 10 to 31 genes) to detect a P/LP variant in 60-80% of individuals with HCM. Most of the P/LP variants are found in sarcomeric proteins that are involved with contraction of the heart muscle, but undiagnosed glycogen storage disease can also present as HCM, as can transthyretin amyloidosis; some panels include these genes. Approximately 5% of patients will have two or more P/LP variants identified (compound heterozygote); these patients often have an earlier age of onset and worse prognosis.

HCM is typically diagnosed clinically with cardiac imaging, physical exam, electrocardiogram, or based on histopathologic features at autopsy. Among persons with clinically diagnosed HCM, genetic testing is of unclear benefit for risk stratification, specifically sudden cardiac death (SCD) (Gersh et al. 2011). The major benefit of genetic testing in non-syndromic HCM lies in at-risk family member identification, prenatal testing, preimplantation genetic diagnosis, and, occasionally, distinguishing hereditary HCM from a secondary cause (e.g. uncontrolled hypertension, athlete's heart).

In the absence of an identifiable pathogenic variant in the family, medical management for individuals with a family history of HCM includes increased cardiac screening with physical examination, 12-lead EKG, annual two-dimensional echocardiography during adolescence, and in some cases cardiac MRI, with screening continuing every 5 years in adulthood. Given the possibility for late-onset disease, screening well into adulthood is recommended. Once a P/LP variant has been identified, testing negative for a known familial variant allows at-risk family members to discontinue all screening (which can be both costly and time-consuming) (Gersh et al. 2011).

## Brugada Syndrome

The diagnosis of Brugada Syndrome (BrS) is based on symptoms, electrocardiogram (EKG) and family history. A diagnosis can be made based on EKG results and clinical history in approximately 75% of persons. Genetic testing can also be helpful to make a diagnosis of BrS.

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BrS is characterized by a specific pattern of EKG (ST segment elevation in leads V1-V3). This can be associated with right bundle branch block, a defect in the heart's conduction system that can also be seen on EKG. This pattern may be seen on resting EKG or may require an EKG while receiving a drug known as a sodium channel blocker. Symptoms of BrS can include arrhythmia or irregular heartbeats and fainting spells. These symptoms often occur at rest. Other triggers include high fever, large meals and excessive alcohol consumption. These BrS symptoms may be fatal if untreated.

Brugada syndrome typically presents in males in their 30s or 40s and is the second cause of death in men from Southeast Asia under the age of 40 years. Implantable cardioverter defibrillators (ICDs) are the only therapy currently known to be effective in persons with BrS with syncope or cardiac arrest. Avoidance of certain medications is recommended for persons with Brugada syndrome, as well as particular attention during a febrile state as this can be a risk factor for syncope.

At least sixteen genes are associated with Brugada syndrome. However, a recent study did not find a significant association between P/LP variants in genes other than SCN5A and arrhythmia in a European population and warns about interpretation of variants in such other genes (Le Scouarnec 2015). P/LP variants in the SCN5A gene are the most common genetic cause for Brugada syndrome (20-30%) and account for >75% of BrS genotype positive persons. Targeted testing of SCN5A can be useful among persons with clinical suspicion for BrS, according to HRS guidelines (2011). Genetic testing is not indicated among persons with an isolated type 2 or 3 Brugada pattern on EKG. In most cases, the primary value of genetic testing for Brugada syndrome is to benefit at-risk family members.

## Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is a form of heart disease that is characterized by fibro-fatty replacement of heart cells predominantly in the right ventricle of the heart. The average age of presentation is 31 years, but presentation is highly variable. In its early stages, ARVD/C is typically asymptomatic. When symptoms do occur, they can include irregular heart rhythms, shortness of breath, and fainting episodes. Individuals with ARVD/C are at risk for sudden cardiac death, especially during strenuous exercise. The estimated prevalence of ARVD/C in the US is 1 in 1,000 to 1 in 2,000, with greater than 50% of cases being familial (Teo et al. 2015). The disease accounts for 5% of sudden cardiac deaths of young individuals in the US.

Clinical diagnosis of ARVD/C can be confirmed based on demonstration of characteristic ECG, arrhythmic, structural, and/or histological abnormalities. Diagnostic criteria, initially proposed by an international task force were revised by Marcus et al. (2010) to incorporate new knowledge and technology to improve diagnostic sensitivity while maintaining diagnostic specificity. With this revised task force criteria (rTFC), individuals are classified as having a definite, borderline, or possible diagnosis of ARVD/C. Family history and genetic test results may also help to confirm a diagnosis (Ackerman et al. 2011). The rTFC should be used with caution in children under the age of 18, given the progressive nature of this disease, thus genetic testing may have a higher diagnostic value in this population (Steinmetz et al. 2018).

There are at least 13 genes in which P/LP variants have been identified to cause ARVD/C, most of which are inherited as an autosomal dominant disease with reduced penetrance and variable expressivity. PKP2, DES, RYR2, TMEM43, DSP, DSG2, DSC2, TGFB3, and JUP are some of the more common causative genes. The estimated diagnostic yield of genetic testing panels targeted to these genes has ranges between 10-50% (Hershberger et al. 2018; Elliot et al. 2019). Less commonly, ARVC can be inherited as an autosomal recessive condition when it is associated with palmoplantar keratoderma and

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woolly hair, namely Naxos disease and Carvajal syndrome (Teo et al. 2015). P/LP variants in CDH2 have also been identified in a few individuals with ARVD/C (Mayosi et al. 2017).

Specific medical management and lifestyle modifications are recommended for individuals with ARVD/C, and may depend on the specific gene involved. It is well established that desmosome gene P/LP variants (PKP2, DSC2, DSG2) are specifically associated with disease pathogenesis related to exercise, therefore, individuals with identified P/LP variants in these genes should avoid endurance and frequent exercise (James et al. 2013; Hershberger et al. 2018). Further studies evaluating ideal genotype-specific exercise recommendations are underway (James and Calkins 2019). PKP2 P/LP variants seem to be associated with earlier onset and ventricular arrhythmia (Teo et al. 2015). In addition, individuals with multiple pathogenic variants identified by panel testing have earlier-onset disease and a higher risk for sudden death (James and Calkins 2018).

Multiple professional organizations have commented on the appropriateness of genetic testing for individuals and families with ARVD/C, including the Heart Rhythm Society, the European Heart Rhythm Association (HRS/EHRA), and the Heart Failure Society of America (HFSA). It is generally agreed that genetic testing panels are appropriate for patients who have been clinically diagnosed with ARVD/C or who are strongly suspected to have this diagnosis. Genetic testing panels used in the initial workup may also include genes associated with dilated cardiomyopathy, given the overlap of causative genes among these conditions. However, providers should be cautious of the risk for variants of uncertain significance when deciding to order large multi-gene panels. Care in the utilization of genetic testing for ARVD/C is needed as up to 6% of healthy controls have been noted to have identified variants in ARVD/C associated genes (Kapplinger et al. 2011). If a syndromic cause of ARVD/C is suspected based on clinical examination and family history, relevant genetic testing panels are also appropriate. When a genetic cause of ARVD/C is identified, P/LP variant-specific testing in at-risk family members is also important given the benefits of screening and treatment for presymptomatic individuals (Ackerman et al. 2011; Hershberger et al. 2018; Towbin et al. 2019). It is recommended that first degree relatives of patients with ARVD/C receive regular cardiac screening, with frequency varying by age, unless they test negative for a known P/LP family variant (Hershberger et al. 2018).

## Left Ventricular Non-Compaction Cardiomyopathy

Left ventricular noncompaction cardiomyopathy (LVNC) is a cardiac disorder involving the abnormal development of the left ventricle of the heart. This condition is typically diagnosed clinically with cardiac imaging when the left ventricle appears to be spongy and “non-compacted,” having unusual and excessive trabeculations. Some individuals with LVNC are asymptomatic, but complications such as arrhythmia, palpitations, fatigue, shortness of breath, fainting, lymphedema, and blood clotting can occur. There is also a risk of sudden cardiac death for individuals with LVNC (van Waning et al. 2018).

P/LP variants in at least 15 genes have been reported in association with LVNC including TNNT2, MYBPC3, ZASP (LBD3), MYH7, and TAZ (van Waning et al. 2018). The majority of these genes are typically associated with additional syndromic phenotypes, such as Barth syndrome and Noonan syndrome (Arbustini et al. 2014). In a study of 128 individuals diagnosed with LVNC prior to age 21, 9% were found to have a syndromic or metabolic diagnosis, and 32% had a family history of cardiac disease. Among those with isolated LVNC, none had a genetic P/LP variant identified (Miller et al. 2017). Individuals with genetic P/LP variants and LVNC have higher rates of heart transplantation and higher risks of death, thus genetic testing may be useful in risk prediction (Li et al. 2018). However, limited data regarding detection rates, possible non-penetrant P/LP variants, genetic and epigenetic modifiers,

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environmental causes, and variants of uncertain significance all lend to the complexity of interpreting LVNC-related gene testing for both affected individuals and their at-risk relatives (Arbustini et al. 2015).

There is some debate as to whether LVNC on its own should be considered a primary cardiomyopathy, given that it may be present in 2-10% of the population when highly sensitive screening methodologies are used, and that LVNC has been observed to progress and regress when followed in athletes and pregnant women. Guidelines from the Heart Failure Society of America suggest considering LVNC to be a phenotype rather than a unique type of cardiomyopathy. When additional features of hypertrophic, dilated, or restrictive cardiomyopathy are present in an individual or family, guidelines for that type of cardiomyopathy should be followed. When isolated LVNC is detected incidentally in an asymptomatic individual with no apparent family history of cardiomyopathy, there is limited evidence to support genetic or family screening (Hershberger et al. 2018). Therefore, gene testing has limited clinical utility in diagnosing LVNC or establishing molecular confirmation for the purpose of testing at risk family members of individuals with a confirmed clinical diagnosis of LVNC, unless there are other phenotypic features suggestive of a known syndrome or other type of cardiomyopathy.

## Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is a rare cardiac disorder in which the heart muscle is stiff and cannot fully relax after each contraction. RCM is characterized by the presence of impaired ventricular filling and diminished diastolic volume with normal or nearly normal LV wall thickness and ejection fraction.

The genetic spectrum of RCM remains largely unknown, and the diagnostic yield of currently available genetic testing panels may range from 10-60% (Hershberger et al. 2018). In patients with non-syndromic (idiopathic) RCM, RCM-specific P/LP variants have been described in over 18 of sarcomeric and cytoskeletal genes, including TNNI3, MYH7, MYBPC3, BAG3, and ACTN2. Many of these have also been implicated in dilated and hypertrophic cardiomyopathies and arrhythmias (Kostareva 2016). Familial RCM often occurs along with skeletal muscle involvement or abnormalities of other organ systems due to syndromic causes such as Noonan syndrome, hemochromatosis, or glycogen storage disorders. Familial TTR amyloidosis related to TTR gene variants is another common cause of RCM, and is important to identify given recent advances in treatment (Hershberger et al. 2018; Muchtar et al. 2017). Therefore, a diagnosis of RCM should prompt a thorough evaluation for associated conditions (Stollberger 2007). When a syndromic cause of RCM is identified, medical management changes may be indicated based on other specific health risks. For example, hemochromatosis is treated with therapeutic phlebotomy, while RCM due to sarcoidosis may be treated with antiarrhythmics or immunosuppressive agents (Brown and Diaz 2019).

Multiple professional organizations have commented on the appropriateness of genetic testing for individuals and families with RCM, including the Heart Rhythm Society, the European Heart Rhythm Association (HRS/EHRA), and the Heart Failure Society of America (HFSA). It is generally agreed that genetic testing panels are appropriate for patients who have been clinically diagnosed with RCM based on clinical evaluation. Genetic testing panels used in the initial workup may include those targeted to hypertrophic or dilated cardiomyopathies, given the overlap of causative genes among these conditions. If a syndromic form of RCM is suspected based on clinical examination and family history, relevant genetic testing panels are also appropriate. When a genetic cause of RCM is identified, P/LP variant-specific testing in at-risk family members is also important (Ackerman et al. 2011; Hershberger et al. 2018). It is recommended that first degree relatives of patients with RCM receive regular cardiac

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screening, with frequency varying by age, unless they test negative for the known P/LP family variant (Hershberger et al. 2018).

### Short QT Syndrome

Short QT syndrome (SQTS) is a congenital, inherited, primary electric disorder of the heart characterized by abnormally short QT intervals on the surface ECG (<360 ms) and an increased proclivity to develop atrial and/or ventricular tachyarrhythmias (Gussak 2005). SQTS is a genetically heterogeneous disease caused by P/LP variants in five different genes (KCNH2, KCNQ1, KCNJ2, CACNA1C, and CACNB2B). All follow autosomal dominant inheritance; KCNH2 P/LP variants are by far the most common cause in affected individuals (Patel 2010). However, P/LP variant frequency and penetrance of these genes are uncertain.

HRS/EHRA guidelines regarding channelopathies and cardiomyopathies state that comprehensive or 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) (HRS/EHRA 2011).

### Atrial Fibrillation

Atrial fibrillation is characterized by uncoordinated electrical activity in the atria. Symptoms include dizziness, chest pain, palpitations, shortness of breath, syncope and an increased risk of stroke and sudden death. Some individuals with atrial fibrillation do not experience any symptoms. While the majority of cases of AF are not hereditary, familial clustering does occur. Familial cases of AF are indistinguishable from acquired cases. Although a number of genes have been associated with an increased risk of AF, the role of these common genetic variants in risk stratification, assessment of disease progression, and determination of clinical outcomes is limited. Routine genetic testing related to AF is not indicated (January; ACC/AHA/HRS Practice Guidelines 2014).

### Post-Mortem Testing

When plans cover genetic testing for the benefit of family members, postmortem genetic testing to confirm a diagnosis and allow for early detection of other family members should be considered. Best practice guidelines describe appropriate testing scenarios that include young (<40) unexplained sudden death and cases of suspected cardiomyopathies. Recent evidence suggests that genetic testing can help identify inherited cardiac disease in 25-35% of cases of sudden cardiac deaths.

Examples of suspicious circumstances at the time of death include: drowning in an experienced swimmer, single motor vehicle accident when no other factors are present (negative toxicology screen), unexplained seizure in young person and sudden death during exercise or sleep.

# Professional Society Guidelines

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# Revision History

**Medical Advisory Board Review:**

v2.2020 05/08/2020: Reviewed

v1.2020 11/04/2019: Reviewed

v2.2019 05/23/2019: No Criteria Changes

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

**Clinical Steering Committee Review:**

v2.2020 04/06/2020: Approved

v1.2020 10/11/2019: Approved

v2.2019 04/03/2019: Approved

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v3.2017 09/20/2017: Approved

v2.2017 03/29/2017: Approved

v1.2017 01/25/2017: Approved

**Revisions:**

| Version | Date | Editor | Description |
|---|---|---|---|
| v2.2020 | 03/13/2020 | Samantha Freeze, MS, CGC | Semi-annual review. Criteria was clarified for Non-Covered Tests to include genetic testing for isolated LVNC. Background and references updated. |
| v1.2020 | 09/11/2019 | Samantha Freeze, MS, CGC | Semi-annual update. No criteria changes. Background and references updated. |

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|---|---|---|---|
| v2.2019 | 4/03/2019 | Samantha Freeze, MS, CGC | Semi-annual review. No criteria changes. Updated references. |
| v1.2019 | 10/03/2018 | Samantha Freeze, MS, GCG | Semi-annual review. PMID added. Updated professional society guidelines. Reformatted CPT code list. Administrative change to genetic counseling requirement - moved from client policy to guidelines. Renumbered to 2019. |
| v1.2018 | 03/31/2018 | Heather Dorsey, MS, CGC | Semi-annual review. Disclaimer sentence added to Scope. Reformatted placement of Long QT familial variant coverage, no change to criteria. Clarified Dilated Cardiomyopathy criteria. Updated professional society guidelines. No additional criteria changes. Renumbered to 2018. |
| v3.2017 | 10/27/2017 | Kate Charyk, MS, CGC | Quarterly review. No criteria changes. |
| v3.2017 | 09/15/2017 | Megan Czarniecki, MS, CGC | Revised general criteria language. Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Renumbered to v3.2017 and submitted to CSC for approval. |
| v2.2017 | 06/19/2017 | Kate Charyk, MS, CGC | Quarterly review. No criteria changes. Updated references. |
| v2.2017 | 04/21/2017 | Kate Charyk, MS, CGC | Quarterly review. No criteria changes. Updated references. |
| v2.2017 | 03/29/2017 | Kate Charyk, MS, CGC | Added criteria for post-mortem genetic testing. Updated references. |
| v1.2017 | 01/23/2017 | Kate Charyk, MS, CGC | Quarterly review. No criteria changes. Updated references. Renumbered to 2017 version. |

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|---|---|---|---|
| v1.2016 | 09/27/2016 | Gwen Fraley, MS, CGC | Added general criteria. Updated references. |
| v1.2015 | 06/18/2015 | Tricia See, MS, CGC | Original version |

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**Primary Author:** Tricia See, MS, CGC

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