Genetic Testing for Cardiac Disease

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Instructions for Use

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Related Medical Management Guidelines

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Coverage Rationale

Multi-gene panel testing for the diagnosis of a hereditary cardiomyopathy or arrhythmia syndrome is proven and medically necessary in members with a confirmed or suspected diagnosis of the following conditions:

- Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C); or
- Brugada syndrome (BrS); or
- Catecholaminergic polymorphic ventricular tachycardia (CPVT); or
- Dilated cardiomyopathy (DCM), without an identifiable cause, when one of the following criteria are met:
  - Member has cardiac conduction disease (first-, second- or third- degree block); or
  - Sudden cardiac death in a first- or second-degree relative at age 45 or younger
- Familial long QT syndrome (LQTS) when acquired causes have been ruled out and one of the following criteria are met:
  - Prolonged QTc [>460ms] on exercise or ambulatory electrocardiogram (ECG), Holter monitoring or during pharmacologic provocation testing; or
  - T wave abnormalities on ECG suggestive of LQTS (i.e., Torsade de pointes, T wave alternans or notched T wave in 3 leads); or
  - Profound congenital bilateral sensorineural hearing loss and prolonged QTc; or
  - Schwartz score ≥1.5 points.
- Hypertrophic cardiomyopathy (HCM) without an identifiable cause (e.g., valvular disease, hypertension, infiltrative or neuromuscular disorder); or
- Short QT syndrome (SQTS).

Multi-gene panel testing in members with inherited thoracic aortic disease is proven and medically necessary.

Multi-gene panel testing for the diagnosis of inherited arrhythmic disorders or cardiomyopathy is proven and medically necessary in asymptomatic members with a close blood relative with one of the following conditions:

- Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C); or
- Brugada syndrome (BrS); or
- Catecholaminergic polymorphic ventricular tachycardia (CPVT); or
- Congenital long QT syndrome (LQTS); or

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- Familial dilated cardiomyopathy (DCM); or
- Hypertrophic cardiomyopathy (HCM); or
- Short QT syndrome (SQTS); or
- A first-degree relative experienced sudden cardiac death or near sudden death at age 45 or younger.

Genetic testing for cardiomyopathies, arrhythmias or aortic vascular disease is unproven and not medically necessary for all other indications due to insufficient evidence of efficacy.

Genetic testing for coronary artery disease (CAD) is unproven and not medically necessary due to insufficient evidence of efficacy. This includes, but is not limited to, the following tests:
- Gene expression tests
- Microarray or other genetic profiles for cardiac disease risk (e.g., Cardiac DNA Insight®, Cardiac Healthy Weight DNA Insight®, Cardio IQ® gene tests and panels).

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

Required Clinical Information
Genetic Testing for Cardiac Disease
Medical notes documenting all of the following: • Personal history of the condition, if applicable, including age at diagnosis • Complete family history (usually three-generation pedigree) relevant to condition being tested • Genetic testing results of family member, if applicable, and reason for testing • Ethnicity/ancestry (e.g., Ashkenazi Jewish), if reason for testing • Any prior genetic testing results • How clinical management will be impacted based on results of genetic testing • Genetic counseling (if available)

Definitions

Close Blood Relatives:
- First-degree relatives include parents, siblings and offspring.
- Second-degree relatives include half-brothers/sisters, aunts/uncles, grandparents, grandchildren and nieces/nephews affected on the same side of the family.
- Third-degree relatives include first cousins, great-aunts/uncles, great-grandchildren and great-grandparents affected on same side of family

(National Comprehensive Cancer Network, 2020)

Multi-gene Panel: Genetic tests that use next-generation sequencing to test multiple genes simultaneously. Also called multiple gene panel (National Cancer Institute Dictionary of Genetic Terms).

Schwartz Score: A set of diagnostic criteria for long QT syndrome (LQTS). The criteria are divided into three main categories with a maximum score of nine; however, scores of greater than three indicate a high probability of LQTS (Schwartz and Crotti, 2011).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws

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that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81410	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
81413	Cardiac ion channelopathies (e.g., 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 (e.g., 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 (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)
81479	Unlisted molecular pathology procedure
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score

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Description of Services

Technologies used for genetic testing of cardiac syndromes and coronary artery disease can vary. Tests can include, but are not limited to, those that evaluate variations in the genes, such as chromosome microarray and next generation sequencing (NGS), as well as others that assess the gene products, such as gene expression arrays and microRNA analysis. The number of genes evaluated can range from a single gene to the whole exome or genome of a member. Results of genetic testing may assist members and healthcare providers with determining a diagnosis, prognosis and identification of appropriate clinical interventions (Jabbari et al., 2013; Millat et al., 2014; Ladapo et al., 2017). This policy addresses genetic test panels or microarray profiles with five or more genes for cardiac related syndromes and other coronary artery disease risk or monitoring. Cardiomyopathies that present primarily as neuromuscular disorders and related genetic testing are covered in the Medical Management Guideline titled Genetic Testing for Neuromuscular Disorders.

Clinical Evidence

Arrhythmias

Congenital Long QT Syndrome (LQTS)

LQTS is a disorder of the heart's electrical system classified as a channelopathy. This disorder affects the cardiac ion channels and predisposes the individual to irregular heartbeats, syncope and possible sudden cardiac death (SCD). Symptoms may occur in young, otherwise healthy individuals and events such as stress or exercise may cause symptoms (Priori et al., 2004). It is characterized by a QT interval prolongation on an electrocardiogram (ECG) and screening is generally performed by

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electrocardiography. Clinical features and family history may also be helpful in the diagnosis. An ECG finding of a prolonged QTc interval of >470 msec (males) or >480 msec (females) is diagnostic (Ackerman et al., 2011). The Schwartz score has been used as a means of establishing diagnostic criteria which focuses on ECG finding and clinical/family history (Alders et al., 2018). Approximately 10-40% of individuals with LQTS will not demonstrate ECG changes (Ackerman et al., 2011). LQTS can be congenital or may be acquired through other heart conditions or exposure to certain medications or dietary deficiencies (Alders et al., 2015).

There are several congenital LQTS. These include Anderson-Tawil syndrome, Jervell and Lange-Nielsen syndrome, Romano-Ward syndrome and Timothy syndrome. All forms of LQTS are estimated to affect at least 1 in 2500 people (Ackerman et al., 2011). The autosomal dominant Romano-Ward syndrome is the most common; with a prevalence of 1 in 3000 to 1 in 5000. Jervell and Lange-Nielsen syndrome is a rare recessive form that is associated with congenital deafness, early clinical manifestations and a poorer prognosis. Congenital LQTS has been associated with mutations in at least 13 genes, many of which are related to the ion channels in the heart. The majority of cases are associated with mutations in three genes: KCNQ1 (30-35%), KCNH2 (25-30%) and SCN5A (5-10%) (Goldenberg and Moss, 2008). As part of the National Heart, Lung and Blood Institute (NHLBI) GO exome sequencing project (ESP) sequence variations of LQTS was reported. In a sample of 5,400 individuals who did not have a diagnosis of heart disease and/or channelopathies (Refsgaard et al., 2012), 33 mutations across the studied genes were identified (all of them being missense variations). There are multiple subtypes that correlate to different genes and some of these genetic subtypes are also associated with non-cardiac abnormalities. For familial testing after a mutation has been identified in an affected family member, other at-risk family members may be identified by testing for the specific mutation and does not require screening a panel of genes. This method of testing for known familial mutation analysis has been shown to be greater than 99% accurate (Alders et al., 2015).

Tester et al. (2011) described the technologies used for testing of channelopathies. The majority of testing is performed by gene sequencing analysis where point mutations are identified. Occasionally, chromosomal microarray analysis may be employed to identify deletions/duplications. Analytical sensitivity was described as 95-100% for these methodologies in the detection of mutations (nucleotide substitutions and small insertion/deletions); however, there is limited published data on the analytical validity of testing for LQTD. Individual laboratories have reported the analytical sensitivity and specificity for the assays they perform.

Compared with ECG criteria and family history, the positive predictive value of genetic testing for LQTS is 70% to 80% (Modell et al., 2012) and a genetic variant can be identified in approximately 72% to 80% of individuals with a clinical diagnosis of LQTS. However, the clinical criteria for LQTS are neither sensitive nor specific for the syndrome and potential clinical outcomes. Genetic testing may identify more individuals with possible LQTS compared with clinical diagnosis. Hofman et al. (2007) evaluated 513 relatives of 77 LQTS probands who had a known LQTS mutation. Only 41 of 208 carriers were identified with the Schwartz criteria as having a “high probability” of LQTS, which yielded 19% sensitivity for these clinical criteria. The researchers concluded that the use of clinical criteria, while specific, had low sensitivity as compared to genetic testing; and, for families with a known LQTS mutation, genetic testing is the preferred diagnostic approach. Another large study performed by Tester et al. (2006) evaluated the percent of individuals with a clinical diagnosis of LQTS that were found to have a genetic variant. Clinical phenotyping was completed on 541 patients that were referred for evaluation of LQTS and 123 (22.7%) of those had “definite” LQTS defined by clinical criteria. Of the 541 patients, 274 (50.6%) were found to have a LQTS-associated genetic variant and of the 123 clinically diagnosed LQTS patients, 72% (89/123) were found to have a genetic variant. Lieve et al. (2013) examined the diagnostic yield of genetic testing for LQTD in 855 patients. Using NGS, the authors determined that 259 patients had one mutation and 18 patients had two mutations. In comparison with clinical signs, genetic testing had a sensitivity of 72% and a specificity of 49%.

Published studies support the clinical utility of genetic testing by identifying patients for early intervention opportunities including lifestyle modification, prescription drugs or surgical procedures (Priori et al., 2004).

The use of beta-blockers has been shown to decrease the risk of cardiac events in individuals with LQTS. In pre-post studies using registry data, Moss et al. (2000) evaluated 869 LQTS patients who were treated with beta-blockers and Priori et al. (2004) studied 335 LQTS patients treated with beta-blockers. In both of these studies, cardiac events still occurred particularly in those patients who were symptomatic prior to therapy; however, there was an overall reduction in events. Another drug-based approach for treatment includes sodium-channel blockers such as mexiletine. Mazzanti et al. (2016) evaluated 34 LQT3 genotype patients and determined that this intervention had a clinically significant reduction in arrhythmic events.

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Other treatment options such as an implantable cardioverter-defibrillator (ICD) are available for patients who are unable to take beta-blocker therapy. Zareba et al. (2003) studied 125 LQTS patients who were treated with an ICD and compared to 161 LQTS patient who did not receive ICDs. With the 8-year follow-up, there was one death in the ICD group as compared to 26 deaths in the non-ICD group. The researchers reported that ICD treated patients had a greater than 60% reduction in cardiovascular events. One study evaluated the treatment of mutation carrying relatives of a proband. Hofman et al. (2010) performed cascade testing on 66 LQTS proband patients and identified 308 pathogenic variant carriers in relatives. All carriers received lifestyle education and for 199 of the carriers, treatment was initiated. Beta-blockers were started in 163 patients, a pacemaker was inserted in 26 patients and an ICD was inserted in 10 patients.

Genetic testing for LQTS to determine prognosis is also performed as different subtypes of LQTS may have varying risks of cardiac events. Several studies have indicated that there are varying rates of cardiovascular events among different subtypes (Priori et al., 2003; Schwartz et al., 2001; Albert et al., 2010; Migdalovich et al., 2011; Costa et al., 2012; Kolder et al., 2015; Amin et al., 2012; Park et al., 2012; Earle et al., 2014; Mullally et al., 2013).

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT is an inherited channelopathy which can present with either autosomal dominant or autosomal recessive inheritance. CPVT is rare with an estimated prevalence between 1 in 7000 and 1 in 10,000 persons (Ackerman et al., 2013). This condition typically presents during childhood or adolescence.

The clinical presentation of CPVT is similar to LQTS; however, CPVT is thought to be a more malignant condition. Many patients are asymptomatic before a cardiac event. Individuals with CPVT often present with symptoms such as syncope or cardiac arrest, which are triggered by exercise or stress. Untreated individuals have a mortality rate of 30 to 50 % by age 40 years. ECG studies are usually normal, but exercise stress testing can create arrhythmia in the majority of cases (75-100%) (Napolitano et al., 2016; Perrin and Gollob, 2012). Therefore, evaluation for CPVT includes exercise stress testing, Holter monitoring and genetic screening. The management of individuals with CPVT is usually with beta-blockers or antiarrhythmics if beta-blockers fail to provide complete protection from cardiac events. An ICD may be necessary if there is a recurrence of symptoms. CPVT individuals will also need to commit to lifestyle modification by the avoidance of strenuous exercise.

Four genes with pathogenic variants have been demonstrated to cause CPVT; however, there may be other genes that are unidentified. Only 55-65% of individual with CPVT have an identified variant. The autosomal dominant pattern of CPVT is associated with variants in *RYR2* or *KCNJ2.* Variants in *CASQ2* and *TRDN* are associated with autosomal recessive inheritance (Napolitano et al., 2016). The majority of cases (50-55%) are represented by *RYR2* variants and most of these (90%) are missense mutations (Ackerman et al., 2013). *CASQ2* accounts for 1-2% and *TRDN* accounts for an unknown percentage of cases. *RYR2* variants have a penetrance of approximately 83%.

Clinical sensitivity has been studied using a three gene CPVT gene card and was estimated to be 50-75% by the manufacturer (Napolitano et al., 2014). The variability in phenotype in ventricular tachycardia syndromes affects the estimated clinical validity and yield of this multi-gene panel. Thus, the specificity of CPVT known pathogenic variants is not certain. A study by the National Heart, Lung and Blood Institute ESP described sequence variations in 6503 patients without a diagnosis of CPVT (Jabbari et al., 2013). Exome data were reviewed to identify missense variations that are previously associated with CPVT. The researchers identified 11% of the previously described variants in this population resulting in 41 presumed CPVT cases. This study demonstrated that false positive results are likely low (<0.6%), but the presence of one of these variants may not always translate into the development of CPVT.

The clinical utility for CPVT genetic testing is similar to LQTS. Genotype-based risk stratification for management or prognosis of CPVT has not been studied. However, diagnosis confirmation of CPVT by genetic testing may lead to improved health outcomes by allowing patients to perform lifestyle modification or receive medications. Patients who have a clinical diagnosis of CPVT may not need genetic testing for confirmation if they are receiving lifestyle modification and treatment; however, confirmation may allow other family members at risk to be identified.

Brugada Syndrome (BrS)

BrS is an inherited channelopathy that is described by a characteristic ECG abnormality and an increased risk of syncope, ventricular fibrillation and SCD and is estimated to be responsible for 12% of unexpected SCD cases (Abriel et al., 2013).. In an individual with BrS, the heart remains structurally normal. This disorder often presents in adulthood; however, it has been

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reported at all ages (Huang et al., 2004) and is more common in males than females (8:1 ratio). There is a high clinical suspicion of BrS when the characteristic ECG pattern is present with at least one of the following clinical features: documented ventricular arrhythmia, SCD in a family member <45 years old, characteristic ECG pattern in a family member, inducible ventricular arrhythmias on EP studies, syncope or nocturnal agonal respirations. In general, management of BrS focuses on ICDs and medication in individuals with syncope or cardiac events. Those who have BrS and are asymptomatic are followed closely.

BrS is usually inherited in an autosomal dominant pattern and has incomplete penetrance. Genetic abnormalities causing BrS have been linked to mutations in 16 different genes; however, 15-30% of cases are associated with the ion channel gene SCN5A (Ackerman et al., 2013). Other genes including SCN10A are minor significance and only account for 5% of cases (Bennett et al., 2013). In individuals with a high clinical suspicion of BrS, testing yields variants in only 25-35% of cases (Brugada et al., 2016). Even though there are eight suspected genes, SCN5A is most commonly identified and identified in 20% of genotype positive cases.

A Japanese registry trial studied the SCN5A variant genotype/phenotype with symptoms of BrS (Yamagata et al., 2017). The researchers studied 415 patients who were previously diagnosed with BrS and evaluated them for SCN5A mutations. Those with pathogenic mutations were compared to those without over a period of 72 months. They determined that those individuals with BrS and a SCN5A pathogenic variant had significantly more ECG abnormalities and an increased risk for cardiac events.

Behr et al. (2015) evaluated seven candidate genes (SCN10A, HAND1, PLN, CASQ2, TKT, TBX3 and TBX5) among patients negative for SCN5A variants (n=156) with symptoms indicative of BrS (64%) and/or a family history of sudden death (47%) or BrS (18%). Eighteen patients (11.5%) were found to have variants, most often in SCN10A (12/18; 67%). A study by Hu et al. (2014) analyzed the prevalence of SCN10A variants in 150 probands for BrS. Seventeen SCN10A variants were identified in 25 probands, with a variant detection rate of 16.7% in BrS probands. This study identified SCN10A variant as a major susceptibility gene for BrS. Another genome-wide association study by Bezzina et al. (2013) evaluated 312 individuals with BrS and found two significant variants were identified, one at the SCN10A locus (rs10428132) and another near the HEY2 gene (rs9388451). These findings suggest that there may be more variants associated with BrS.

Short QT Syndrome (SQTS)

SQTS is a rare genetic condition that is characterized by a shortened QT interval on ECG, reflecting a shortened action potential of the heart. This results in an increased risk of ventricular and atrial fibrillation as well as SCD. As approximately only 100 cases of SQTS have been identified, the prevalence and risk of SCD remains unknown (Bennett et al., 2013). The symptomology can range from no clinical symptoms, to dizziness and fainting, or may include cardiac arrest and SCD.

Several genes, *KCNH2*, *KCNJ2*, and *KCNQ1,* C*ACNA1C* and *CACNB2* are associated with SQTS. However, some patients with SQTS do not have variants in any these genes suggesting that other genetic mutations may also cause this disorder. As SQTS is proposed to be an autosomal dominant inheritance pattern, patients should have a family history of the syndrome or SCD.

Treatment for SCD includes ICD regardless of diagnosis. While it is unclear if testing results will change management or improve health outcomes, the rarity of SQTS limits the ability to conduct prospective trials to comprehensively evaluate the clinical validity and utility of genetic testing.

Inherited Atrial Fibrillation

Inherited atrial fibrillation (AF) is an abnormality of the heart's rhythm where there are episodes of uncoordinated electrical activity (fibrillation) in the upper chambers causing an irregular, fast heartbeat. Symptoms from genetic-based disease is generally indistinguishable from atrial fibrillation caused by non-genetic reasons. This familial type of atrial fibrillation has an unknown incidence (Genetics Home Reference, October 2017). There are some genes that have been of focus; however, there has not been sufficient evidence to show that genetic testing improves outcomes.

Roselli et al. (2018) worked with global researchers to study the genetic basis of AF. The researchers compiled data from over 65,000 individual with AF and identified several new genetic risk factors. Of the nearly 100 genetic regions associated with risk of developing AF, 67 were never before linked to the disease. The study demonstrated that there are methods for genetic testing for AF; however, there will need to be further study to determine the specific genes involved and the role for genetic testing in clinical management.

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Professional Societies

American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Rhythm Society (HRS)

ACC, AHA and HRS guidelines guideline for the management of patients with atrial fibrillation state that routine genetic testing related to AF is not indicated (January et al., 2014). A 2019 focused update did not address genetic testing (January et al., 2019).

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/Asia Pacific Heart Rhythm Society (APHRS)

The HRS, EHRA and APHRS incorporated genetic testing for LQTS in a 2013 consensus statement (Priori et al., 2013). In this consensus statement, LQTS may be diagnosed by an unequivocally pathogenic mutation in one of the LQTS genes or in the absence of a pathogenic mutation with additional clinical criteria.

In 2011, the HRS and EHRA also created an expert consensus statement with recommendations regarding genetic testing for LQTS (Ackerman et al., 2011). The HFS/EHRA published guidelines regarding genetic testing for LQTS noted:

- Comprehensive or LQT1-3 (KCNQ1, KCNH2 and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype. (Class I)
- Comprehensive or LQT1-3 (KCNQ1, KCNH2 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)

All consensus recommendations are Level of Evidence C – based on experts' opinions.

Class I – is recommended
Class IIa – can be useful
Class IIb – may be considered
Class III – is not recommended (failure to provide any additional benefit and may be harmful)

There are not yet recommendations for general population genetic screening for LQTS (Tester et al., 2011).

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)

Ackerman et al. (2011) reported on guidelines for genetic testing in inherited cardiac syndromes.

CPVT

- Comprehensive or CPVT1 and CVPT2 (RYR2 and CASQ2) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill or catecholamine infusion. (Class I)
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative variant in an index case. (Class I)

BrS

- Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case. (Class I)
- Comprehensive or BrS 1 (i.e., SCN5A) targeted genetic testing can be useful for any patient in whom a cardiologist has

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established a clinical index of suspicion based on examination of the patient's clinical history, family history and expressed electrocardiographic phenotype. (Class IIa)
- Genetic testing is not recommended in the setting of an isolated type 2 or type 3 Brugada ECG pattern. (Class III)

SQTS

- 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)
- 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)

Inherited AF

Genetic testing is not indicated for AF at this time. (Class III)

All consensus recommendations are Level of Evidence C – based on experts' opinions.

Class I – is recommended
Class IIa – can be useful
Class IIb – may be considered
Class III – is not recommended (failure to provide any additional benefit and may be harmful)

Cardiomyopathies

Hypertrophic Cardiomyopathy (HCM)

HCM is the most common genetic cardiovascular condition and is associated with thickening of the heart wall surrounding the left ventricle (also called left ventricular hypertrophy or LVH) (Bos et al., 2009; Cirino and Ho, 2019). Clinical diagnosis can be demonstrated by a non-dilated left ventricle with a wall thickness of 13-15mm or more in adults (McKenna et al., 1997; Maron et al., 2003; Cirino and Ho, 2019). LVH can be determined by echocardiogram or magnetic resonance imaging (MRI). There are also other conditions that can lead to LVH and must be ruled out to diagnose HCM (Cirino and Ho, 2019). HCM has a phenotypic prevalence of approximately 1 in 500 adults (0.2%) and is the most common cause of SCD in young adults, including athletes (Ramaraj, 2008; Alcalai et al., 2008). Overall, the death rate for HCM patients is estimated to be 1% per year in the adult population (Marian, 2008; Roberts and Sigwart, 2005).

Symptoms range from asymptomatic to heart failure to SCD (Bos et al., 2009; Cirino and Ho, 2019). Even in family members that present with the same variant, and symptoms may be different due to variations in the environment or the influence of other genes. It is thought that the majority of HCM patients are asymptomatic or have few symptoms. However, some patients have significant symptoms that may lead to heart failure or SCD (Maron et al., 2003). Patient management includes treating any cardiac comorbidities, avoiding therapies that may worsen obstructive symptoms and treating symptoms with medications and surgery.

The genetic component of HCM includes a defect in the cardiac sarcomere, which is the basic contractile unit of cardiac myocytes (Keren et al., 2008). While other non-sarcomeric genes have been assessed. Walsh et al. (2010) determined that the majority of these genes were not associated with the condition. Eighteen different genes and approximately 1400 individual mutations have been identified as genetic components of HCM (Maron et al., 2012; Cirino and Ho, 2019; Ghosh and Haddad, 2011). Pathogenic variants in MYH7 and MYBPC3 account for approximately 80% of all cases for which a molecular diagnosis is determined (Teekakirikul et al., 2013). Generally, these defects are inherited in an autosomal dominant pattern. In approximately 60% of patients with clinical HCM, a genetic abnormality can be identified (Cirino and Ho, 2019; Elliott and McKenna, 2004). A study in 2013 reported that 19 of 200 patients (9.5%) with HCM had more than one pathogenic mutation (Zou et al., 2013). The researchers also determined that the number of mutations correlated with severity of disease. The screening of at-risk family members is an important consideration in the management of HCM. Many guidelines recommend this screening with physical examination, ECG and echocardiography (Maron et al., 2012).

The analytic sensitivity for HCM mutation detection has been demonstrated to be high regardless of technology used, either Sanger sequencing or NGS. The available information on specificity of genetic testing for HCM, mainly from series of patients

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without a personal or family history of HCM, suggests that false-positive results for known pathologic mutations using Sanger sequencing are uncommon. An older study by Niimura et al. (1998), analyzed 16 probands and 574 at risk family members for HCM gene variations in cardiac myosin-binding protein C using Sanger sequencing. The researchers determined that the clinical expression of mutations is often delayed until later ages. Similarly, Watkins et al. (1995) studied a rare mutation causing HCM and also determined that family members were at high risk for SCD and should be screened. A study by Oliveira et al. (2015) compared HCM variant detection by NGS with Sanger sequencing. The researchers found a maximum 96.7% sensitivity for single-nucleotide variants and a positive predictive value above 95% for the NGS panels. NGS may have a higher yield of variants of unknown significance, which may impact the positive and negative predictive value of the test.

The clinical validity of genetic testing for HCM is considerably lower than the analytic validity, ranging from 33-67% (Pan et al., 2012). In a study by Ingles et al. (2013), 265 individuals with HCM were evaluated and found that 138 (52%) had at least one mutation identified. In probands with a family history of HCM, the detection rate of a mutation was higher (72 versus 29%, $P < 0.0001$), and the rate increased even higher when there was a positive family history of SCD (89 versus 59%, $P < 0.0001$). The researchers concluded that family history was a predictor of mutation detection in genetic testing for HCM. Pan et al. (2012) analyzed data from the National Heart, Lung and Blood Institute's ESP to determine the clinical significance of variants in genes in inherited cardiomyopathies. The researchers found that many of the variants were rare and determined that these genes carry very low rates of population variations. Another study reported on 2,912 patients being tested for HCM (Alfares et al., 2015). The genetic testing was performed by Sanger sequencing, CardioChip and NGS. These testing methods all varied in number of genes studied and had a detection rate of approximately 32% with an additional 15% inconclusive results. The expanded panel of over 50 genes only identified a few additional variants beyond the smaller 11-gene panel.

The mutation detection rate or clinical sensitivity has been reported through case series. In general, it is thought that the low detection rate may be due to testing methods, unknown variants or other factors. Erdmann et al. (2003) screened HCM patients for pathogenic mutation in six sarcomeric genes: myosin-binding protein C3 (MYBPC3), MYH7, cardiac troponin T (TNNT2), alpha-tropomyosin (TPM1), cardiac troponin I (TNNI3) and cardiac troponin C (TNNC1). One hundred and eight patients who were clinically diagnosed with HCM were tested and a total of 34 different mutations were identified (18 in MYBPC3; 13 in MYH7; 1 in TPM1; 1 in TNNT2; 1 in TNNI3). The researchers noted that MYBPC3 was determined to be the gene that most frequently caused HCM in this population. A different cohort study of 203 unrelated patients with HCM was performed by Olivotto et al. (2008). The patient samples were analyzed for eight HCM genes and in this cohort, 87 mutations were identified in 126 patients. These patients were considered to be myofilament-positive and had an increased risk of cardiac events as compared to the myofilament-negative patients.

Richard et al. (2003) aimed to study the most common genes associated with HCM and determine the distribution of these genes. The researchers analyzed the entire sequence of nine genes (MYH7, MYBPC3, TNNI3, TNNT2, MYL2, MYL3, TPM1, ACTC and TNNC1) in 197 cases with familial HCM. Pathogenic mutations were identified in 124 patients (63%) with 97 different mutations, including 60 novel ones. In 82% of families, the cardiac myosin-binding protein C (MYBPC3) and beta-myosin heavy chain (MYH7) genes were identified. These results suggested that screening for HCM should start with these two genes and then move to additional genes if necessary. Van Driest et al. (2003) analyzed exons of cardiac troponin T, cardiac troponin I, alpha-tropomyosin and cardiac actin 389 patients with HCM and determined that 18 (4.6%) of patients had the thin filament mutations (eight had troponin T, six had troponin I, three had alpha-tropomyosin and one had an actin). They concluded that this type of mutation is less prevalent than had previously been estimated making risk stratification with these mutations a challenge. Manrai et al. (2016) evaluated publicly available data and identified variants that had previously been considered causal for HCM that were also overrepresented in the general population. The researchers found that a number of patients, all of African or unspecified ethnicity, had variants that were misclassified as pathogenic based on the understanding at the time. However, all of these variants were now categorized as benign. Furthermore, these reclassified variants were more common among black Americans than white Americans. This study that was funded by the National Institutes of Health concluded that there is a need to sequence genomes of varying populations to determine the pathogenicity of a variant.

NGS is recognized as the most efficient way to identify HCM mutations due to the large number of genes associated with HCM. In 2014, D'Argenio et al. (2014) used NGS to sequence 202 genes associated with cardiomyopathies and then analyzed the information to only review the HCM related genes. They determined that this method was more efficient and cost saving versus traditional PCR based methods. They also found several unique or missense variants that may add to the causes of HCM. Likewise, Mook, et al. (2013) evaluated NGS as a replacement for Sanger sequencing for HCM. The study evaluated exons of 23 HCM-related genes and determined that the rate of detection was increased due to being able to study a larger amount of

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genes. The researchers concluded that NGS was as accurate as Sanger sequencing, therefore with the increased efficiency, NGS is a preferred method.

A study in 2016 used whole exome sequencing (WES) for HCM genes (Nomura et al., 2016). This study evaluated seven relatives from a family with inherited HCM. Five relatives were clinically affected. The WES detected 60,020 rare variants in this group and of those, 3439 were missense, nonsense, splice-site or frameshift variants. After analysis was completed linking the genotype-phenotype, 13 pathogenic variants remained. In addition, one variant in MYL3 was shared with the five affected relatives. A larger cohort study by Gomez et al. (2014), analyzed NGS in 136 patients with HCM. First, the researchers amplified the exons of MYH7, MYBPC3, TNNT2, TNNI3, ACTC1, TNNC1, MYL2, MYL3 and TPM1 and then performed NGS. In the validation cohort of 60 patients, Sanger sequencing was performed for nine genes as well as NGS. The NGS method was found to have a specificity of 97% for single nucleotide variants, sensitivity of 100% and specificity of 80% for insertion/deletion variants compared with Sanger sequencing. Next, 76 cases in a discovery cohort were analyzed. A total of 19 mutations were discovered in this cohort, which led the researchers to conclude that NGS is valuable in screening large cohorts of HCM patients.

Another cohort of 75 patients with HCM and DCM were studied by Millat et al. (2014). NGS was performed on these patients and found a sensitivity of 98.9% for detection of mutations in the covered regions. Rubattu et al. (2016) performed NGS studies on 17 associated HCM genes in a cohort of 70 patients. These researchers hypothesized that age at diagnosis and family history may increase the mutation yield. In the cohort of 70 patients, 35 had an early age of diagnosis (<25 years) and 35 had a late age of diagnosis (>65 years). Forty-one mutations were detected in nine genes. The detection rate of mutations was 30/35 (85.7%) in early-onset and 8/35 (22.9%) in late-onset. Additionally, the detection rate for patients with a family history of HCM was 84%, and 90.5% in those with early-onset.

The penetrance of HCM is still under research and debated. Charron et al. (1997) reported on a genotyped population with inherited HCM. They studied 178 individuals, of which 90 had HCM mutations (9 different mutations in 3 genes), and noted that the penetrance was incomplete (69%). Additionally, the researchers found that not everyone with a mutation will develop HCM and that age and gender had different penetrance. A 2011 study by Pinto et al., however, determined that disease penetrance was 100% with advanced ages (Pinto et al., 2011). Two older studies describe cohorts with a mutation and identified varying penetrance (Fananapazir and Epstein, 1994; Page et al., 2012). The researchers suggest that it is difficult to determine penetrance for any given mutation and the identification of a mutation does not always confer disease.

There is a significant amount of attention on trying to match up clinical symptoms with the likelihood of positive test results. Some researchers have developed “scores” for predicting the possibility of a mutation. Gruner et al. (2013) developed the Toronto Hypertrophic Cardiomyopathy Genotype Score. The researchers evaluated 471 patients through genetic testing. A mutation was identified in 163 of the 471 (35%). Other “independent predictors”, including age at diagnosis, gender, arterial hypertension, family history and cardiac morphology, were combined with the mutation status to create a score. After analysis, the researchers stated that this tool was accurate to predict mutation status. Murphy et al. (2016) published a similar study on the Mayo Clinic Phenotype-Based Predictor Score. This Mayo score used six clinical parameters to derive a genotype score that was then compared to the genetic testing results. There were 564 patients that were in the original cohort seeking genetic counseling for HCM and of those 198 received genetic testing. Of the 198 patients, 101 were genotype positive and the predictor score was significantly associated with a positive test. Similarly, Bos et al. (2014) designed a study to evaluate genotype-phenotype relationships to create a pregenetic testing score. A retrospective review of 1,053 patients was performed and phenotyping was completed through electronic medical records (EMR) information. Of these patients, 359 (34%) were determined to have at least one HCM mutation. As positive predictors of positive genetic test results, the study used the following: echocardiographic reverse curve morphological subtype, an age at diagnosis younger than 45 years, a maximum left ventricular wall thickness of 20 mm or greater, a family history of HCM and a family history of SCD. The researchers concluded that when all five positive markers were present, the chance of a positive genetic test was 80%.

Another study that connected factor-associated phenotypes to genotypes evaluated 268 patients clinically diagnosed with HCM (Marsiglia et al., 2014). Mutations were found in 131 (48.8%) of the 268 patients (79 in the MYH7 gene; 50 in the MYBPC3 gene; 3 in the TNNT2 gene). Through this discovery, the researchers noted that they have developed a screening method that analyzes clinical data to determine who will have positive genetic results. These factors include family history of confirmed HCM, high mean heart frequency, history of nonsustained ventricular tachycardia (NSVT) and lower age.

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Loar et al. (2015) studied a cohort of 137 patients with HCM who were diagnosed before 21 years of age. The researchers wanted to determine the genotype-phenotype correlations in this group of patients and found that 71 patients (52%) were genotype positive. These patients had increased maximum left ventricular wall thickness and higher incidence of reverse-curve ventricular septal morphology than the genotype negative patients.

A pediatric study sought to add to the literature more information on the genotype-phenotype association in pediatric patients with HCM (Ellepola et al., 2018). The researchers performed a retrospective review of 70 individuals with HCM who had a mean age at presentation of 5.48 years. Genetic testing was positive in 54/70 patients (77%). Of the 23 patients with a positive family history, 13 had mutations (57%).

Michels et al., (2009) investigated the ability to risk stratify asymptomatic HCM mutation carriers. The researchers performed cardiac evaluation on 76 HCM mutation carriers from 32 families. Using published clinical diagnostic criteria, HCM was diagnosed in 31 asymptomatic members (41%). However, the disease penetrance was age related and risk factors for SCD were present in carriers with and without HCM.

HCM genetic screening is generally not useful to predict prognosis and is instead useful to provide genetic screening and counseling to at risk individuals. A study by Alejandra Restrepo-Cordoba et al. (2017) evaluated the role of HCM genetic testing in clinical practice. The study analyzed genetic results from 100 HCM patients for over ten genes. The patients were then split into two groups depending on clinical course: poor (group A) or favorable (group B). Mutations were identified in group A (28; 56%) and in group B (23; 46%). The researchers also found that pathogenic mutations associated with poor prognosis were found in only five group A patients. They concluded that genetic findings are not useful in predicting prognosis. Similarly, McTaggart et al. (2017) followed 14 asymptomatic individuals with pathogenic HCM mutations over several years. Only one patient had developed phenotypic HCM by MRI and echocardiogram, and two others had features suggestive of HCM by MRI only. The researchers underscore that the best strategy for genetic testing is to start with an affected family member. Once this testing is done, then at risk relatives may be tested to determine if there is a hereditary basis to the mutation.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

ARVD/C is a cardiac condition that is characterized by progressive fibro-fatty replacement of the myocardium (McNally et al., 2017). This creates the risk of ventricular tachycardia and SDS. This condition primarily affects the right ventricle; however, it may also affect the left.

Diagnostic criteria for ARVD/C were established by an international task force (ITF) in 1994 and modified in 2010 (McKenna et al., 1994; Marcus et al., 2010). Often a patient will present with an arrhythmia. The ITF criteria combine results of ECG and signal averaged ECGs, imaging studies that include 2D echocardiography, cardiac MRI or RV angiography, and arrhythmia presence documented by telemetric monitoring, genetic testing and family history to determine if criteria are met for a diagnosis. The management of individuals with ARVD/C is complicated. Most affected individuals can live a normal lifestyle; however, some must avoid activity that will strain the right side of the heart. Some individuals with a higher risk of cardiac events or SDS are treated with anti-arrhythmic medications or may be considered for an ICD.

ARVD/C prevalence is thought to be 1 case per 10,000 and an autosomal dominant inheritance pattern has been demonstrated. However, there is variable penetrance and around half of the cases are new mutations and do not have a family history of disease. There are several genes that are more commonly associated with ARVD/C and include: *DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2* and *TMEM43*. Other genes that have been implicated include: *CTNNA3*, *DES*, *LMNA*, *PLN, RYR2*, *TGFB3* and *TTN* (McNally et al., 2017). Even with this genetic knowledge, a high number of cases have been reported with no known genetic loci (50%) (Corrado et al., 2000).

For at-risk family members where the pathogenic variant of the proband is known, it is reasonable to perform genetic testing. However, if the affected family member was not screened or a pathogenic variant was not determined, clinical screening for at-risk family members may be appropriate. The use of the ITF criteria for diagnosis of ARVD/C has been shown to be acceptable. The ITF criteria is based on adult presentation, thus pediatric cases may not meet criteria and need to be evaluated differently. Deshpande et al. (2016) reviewed 16 pediatric cases of ARVD/C that were diagnosed through modified diagnostic criteria, genetic testing and pathology. Only two patients had a previously described gene mutation and another patient had a novel mutation. For pediatric cases, the authors note that pathology and clinical findings alone may be sufficient for diagnosis.

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Even though there are associated genes with ARVD/C, only 30-50% of patients will have mutations in these genes. In a study by Campuzano et al. (2012), the researchers sought to identify additional mutations in candidate genes associated with intercalate disks that could be potentially involved in ARVD/C. They analyzed a cohort of 14 Spanish unrelated patients clinically diagnosed with ARVC/D. These patients were without any genetic alteration in all previously known responsible genes. Further analysis of seven potential genes did not identify any mutations as well.

Barahona-Dussault et al. (2010) studied a cohort of patients and found that genetic testing is useful in confirming the diagnosis in suspected cases, especially in those patients who do not meet the ITF criteria. This allows for the appropriate testing of family members that may be at risk.

A study by Riele et al. (2016) aimed to determine the predictors of ARVD/C and optimize risk stratification for at-risk family members. Data from 274 first-degree relatives of 138 ARVD/C probands was analyzed. Of the 274 relatives, 96 (35%) were diagnosed with ARVD/C by using the ITF criteria. Siblings had a three-fold increased risk compared to parents and children. Similarly, Sen-Chowdhry et al. (2007) noted that while genetic studies have provided information in regarding the role of genetics in ARVD/C, there is not enough insight into genotyping yet. These researchers state that the key clinical application of genetic testing in ARVD/C is for confirmatory testing of index cases to facilitate interpretation of borderline investigations and cascade screening of families.

Familial Dilated Cardiomyopathy (DCM)

DCM occurs when the cardiac muscle becomes thin and weakened resulting in an enlarged heart (Genetics Home Reference, April 2017). Symptoms of DCM may include arrhythmia, shortness of breath, fatigue, swelling of the legs and feet, syncope and an increased risk of SCD. DCM is a leading cause of heart transplantation (Mestroni and Taylor, 2013). For many years, the cause of DCM was unknown, possibly viral or autoimmune. However, some cases are hereditary (30-50%) (Mestroni and Taylor, 2013). Familial DCM may be inherited as an X-linked, autosomal recessive, or autosomal dominant condition. Genetic testing identifies a mutation in 22–50% of cases (Roncarati et al., 2013). Over 30 gene mutations have been identified, including mutations in DES, LMNA and SCN5A. Mutations in one gene, TTN, account for approximately 20% of familial DCM cases (Begay et al., 2015).

Predictive genetic testing is described as appropriate for an asymptomatic at-risk individual with a first- or second-degree blood relative in whom a mutation has been identified. This testing can aid in planning for appropriate surveillance including diagnostics like lab testing and ECGs. Early treatment is not indicated for individual with a pathogenic mutation; however, close monitoring would be appropriate. In patients with lamin A/C gene mutations (LMNA), ICD placement may be indicated (Meune et al., 2006). McNally and Mestroni (2017) provided two options for genetic testing including cascade screening and clinical genetic testing. Cascade testing is recommended for first-degree relatives of probands. The authors suggest that this first line of screening in cascade should be ECG and echocardiography. Genetic testing is recommended in patients with familial DCM when there is a specific mutation to be tested.

Familial screening can identify DCM patients at an earlier stage of disease. Moretti et al. (2010) aimed to compare long-term prognosis of familial DCM and sporadic forms. The study enrolled 637 DCM patients and of these 130 had familial DCM. This group of patients included 82 proband and 48 non-proband familial patients. The researchers then compared the 48 non-proband patients with a cohort of sporadic DCM patients. They determined that the non-proband patients were younger, less symptomatic, had a higher left ventricular ejection fraction and were less intensively treated with drugs than the sporadic DCM group. The study concluded that family screening should be recommended for all DCM patients.

Professional Societies

American College of Cardiology (ACC)/American Heart Association (AHA)

In 2011, the ACC and the AHA published guidelines on the diagnosis and treatment of HCM (Gersh et al., 2011). The following recommendations were issued concerning 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.
- Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM.
- Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause.

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- 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 SCD in HCM is uncertain.
- Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.
- Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM.

Heart Failure Society of America (HFSA)

The workup recommended for all cardiomyopathies, which includes a comprehensive family history, phenotypic evaluation of the proband and at risk family members and genetic testing with genetic counseling and drug/device therapies (Hershberger et al., 2018) is as follows:

- Obtaining a family history of at least 3 generations, including the creation of a pedigree, is recommended for all patients with a primary cardiomyopathy.
- Clinical (phenotypic) screening for cardiomyopathy in at-risk first-degree relatives is recommended.
- Referral of patients with genetic, familial or other unexplained forms of cardiomyopathy to expert centers is recommended.
- Genetic testing is recommended for patients with cardiomyopathy.
    - Genetic testing is recommended for the most clearly affected family member.
    - Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
    - In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.
- Genetic counseling is recommended for all patients with cardiomyopathy and their family members. (Level of Evidence A)
- Focused cardiovascular phenotyping is recommended when pathogenic or likely pathogenic variants in cardiomyopathy genes, designated for reporting of secondary findings by the ACMG, are identified in an individual.
    - If a cardiovascular phenotype is identified as would be predicted by currently available knowledge of the gene/variant pair, all usual approaches described in this document for a genetic evaluation, including family based approaches, are recommended.
    - If no cardiovascular disease phenotype is identified in the individual, recommendations for surveillance screening at intervals should be considered.
    - If no cardiovascular phenotype is identified in the individual, cascade evaluation of at-risk relatives may be considered, tempered by the strength of evidence supporting the pathogenicity of the variant, the usual age of onset of the gene/variant pair, and pedigree information (e.g., the ages of at-risk family members, other previously known cardiovascular clinical data in the pedigree, and related information).
- Medical therapy based on cardiac phenotype is recommended, as outlined in consensus guidelines. (Level of Evidence A)
- Device therapies for arrhythmia and conduction system disease based on cardiac phenotype are recommended, as outlined in consensus guidelines. (Level of Evidence B)
- In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia, an ICD may be considered before the left ventricular ejection fraction falls below 35%. (Level of Evidence C)

Levels of Evidence
A – genetic evaluation or testing has a high correlation with the cardiomyopathic disease of interest in studies with a moderate or large sample size
B – genetic evaluation or testing has a high correlation with the cardiomyopathic disease of
interest in smaller or single-center studies
C – genetic evaluation or testing correlates with the cardiomyopathic disease of interest in case reports

Heart Failure Society (HFS)/European Heart Rhythm Association (EHRA)

In the HFS/EHRA, consensus guidelines regarding genetic testing for HCM, it states that (Ackerman et al., 2011):

- 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. (Class I)
- Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case. (Class I)

The HFS/EHRA guidelines have recommendations regarding genetic testing for ARVC including:

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- 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)

The HFS/EHRA guidelines have recommendations regarding genetic testing for DCM including:

- Comprehensive or targeted (*LMNA* and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (i.e., first-, second- or third-degree heart block) and/or a family history of premature unexpected sudden death. (Class I)
- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case. (Class I)
- Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family and to help with family planning. (Class IIa)

All consensus recommendations are Level of Evidence C – based on experts' opinions.

Class I – is recommended
Class IIa – can be useful
Class IIb – may be considered
Class III – is not recommended (failure to provide any additional benefit and may be harmful)

Heart Rhythm Society

The Heart Rhythm Society (HRS) in collaboration with several other organizations published an expert consensus statement on the evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy including left ventricular non-compaction cardiomyopathy (LVNC) (Towbin et al, 2019). The consensus statement noted that genetic testing is reasonable for the diagnosis of LVNC. In addition, gene-specific familial testing has a moderate strength of evidence and is recommended.

Inherited Thoracic Aortic Disease

Aortic diseases are the 18th most common cause of death worldwide, and about 20% are genetic, but this could be an underestimate as genetic testing is not frequently used in the clinical setting. Heritable thoracic aortic aneurysm and dissection (TAAD) refers to a permanent dilation of the thoracic aorta, and may involve different segments of the aorta. Overtime, an aneurysm can weaken as it gets bigger, resulting in blood leaking through a tear in the wall, called a dissection. Some dissections are acute and have a high rate of mortality, while others can be chronic and less likely to be fatal. Most heritable TAAD are inherited in an autosomal dominant fashion with high penetrance, so getting a clear family history as part of any workup is important. Some cases may occur as *de novo* mutations. The four most common inherited TAADs are Marfan syndrome, caused by mutations in the *FBN1* gene, Loeys-Dietz syndrome, caused by mutations in *TGFBR1, TGFBR2, SMAD3, TGFB2* and *TGFB3,* Ehlers-Danlos Syndrome, caused by mutations in *COL3A1* and Familial TAAD. Familial TAAD represents a group of non-syndromic disorders that presents with isolated aortopathy and no other characteristic features. Genes that have been implicated in the latter group include *ACTA2, MYH11, TGFBR2, MYLK, PRKG1*, *LOX, MAT2A* and more. About 70% of non-syndromic inherited TAAD do not yet have an identifiable genetic cause. In recent reviews, it is recommended to target testing based on clinical features. If an individual has characteristics of Marfan syndrome, test for *FBN1,* otherwise due to the clinical overlap between other syndromes, consider a panel of 15-16 genes associated with inherited TAAD (Milewicz and Regaldo, 2017).

Overwater et al. (2018) described the clinical validity of a panel of genes associated with inherited TAAD in 810 TAAD patients at the VU University Medical Center in the Netherlands. The genes included ACTA2*, COL3A1, EFEMP2, ELN, FBN1, FBN2, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SCARF2, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1* and *TGFBR2*. A pathogenic or likely pathogenic variant was found in 66 patients (8%). Of these, six were copy number variants not detectable by NGS, but through additional studies. The authors noted that the prevalence of mutations in this study was

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lower than found in other studies that had detection rates up to 35%, and felt that this was because other studies required a family history or other indicator of a familial form of TAAD prior to testing. In the Netherlands, it is common to test all individuals with TAAD, which may explain the lower yield.

The diagnostic yield of a seven-gene NGS panel for TAAD was examined by Campens et al. (2015) in 264 patients. Patients represented consecutive cases referred to a genetic testing lab for analysis. Patients that were reported to have Marfan syndrome features were tested first for common *FBN1* variants and were included in this study only if the result was negative. Thoracic aneurysm was present in 233 patients, and of these, 27% had a positive family history, and 33% had syndromic features. The 31 non-TAD patients included 23 with a dissection with either a positive family history or syndromic features. Eight patients had only a positive family history or other syndromic features, but no evidence of TAAD. A causal mutation was found in 13% of patients including 12 FBN1 (35.3%), one TGFBR1 (2.9%), two TGFBR2 (5.9%), three TGFB2 (8.8%), nine SMAD3 (26.5%), three COL3A1 (8.8%) and four ACTA2 (11.8%) mutations. The authors noted that the turnaround time for traditional Sanger sequencing is about 12 weeks, but the NGS test was completed in 8 weeks. For this reason, the authors suggest that even those who have a high likelihood of having a *FBN1* mutation based on their clinical phenotype be tested with panel approach.

Yang et al. (2016) developed a panel of 15 genes associated with aortopathies in the Chinese population, which included genes for Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome, vascular type (vEDS) and various genes associated with other thoracic aortic aneurysms. Between February 2014 and April 2016, patients referred to the vascular surgery center of Fuwai hospital were informed of the study, and 248 consented to enroll. Of the 248 individuals, all had various stages of aortopathy and were suspected to have Marfan syndrome (117), Loeys-Dietz syndrome (10) or were not categorized and were likely non-syndromic (121). The results identified a pathogenic or likely pathogenic variant in 92 (37%) of individuals. The vast majority were *FBN1* mutations (82), consistent with the suspected diagnosis of Marfan syndrome. Mutations were additionally identified in *ACTA2* (2), *COLA3A1* (1), *MYH11* (1), *SLC2A10* (1) and *TGFBR1* (2) and *TGFBR2* (1). The authors noted that variant analysis and classification was challenging due to a deficient variant database for the Chinese population, so novel variants were difficult to classify.

Professional Societies

American College of Cardiology (ACC/ American Heart Association (AHA)/American Association for Thoracic Surgery (AATS)/American College of Radiology (ACR)/American Stroke Association (ASA)/Society of Cardiovascular Anesthesiologists (SCA)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Interventional Radiology (SIR)/Society of Thoracic Surgeons (STS)/Society for Vascular Medicine (SVM)/North American Society for Cardiovascular Imaging (NASCI)

Hiratzka et al. (2010) published the consensus guidelines of multiple professional societies involved in the care of individuals who have, or are at risk for, a TAAD. The guidelines note that identification of a genetic mutation as the underlying cause of a TAAD is important in providing care for the individual and at risk family members. For example, if a patient harbors a mutation in a *FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2* or *MYH11* gene, first-degree relatives should have genetic counseling and testing. Only family members with an inherited genetic mutation should have aortic imaging (Level of Evidence C). Genetic testing to verify the underlying disorder can help identify the best treatment plan. For example, patients with Loeys-Dietz syndrome or a confirmed *TGFRB1* or *TGFBR2* mutation should have yearly MRI from the cerebrovascular circulation to the pelvis (Level of Evidence B) and if there is an aortic diameter 4.2 cm or greater by ultrasound, surgical repair should be considered (Level of Evidence C). Sequencing of the *ACTA2* gene in individuals with a family history of TAAD is reasonable, and sequencing of *TGFBR1, TGFBR2, and MYH11* in individuals with a family and clinical history consistent with disease can be considered (Level of Evidence B). The authors note that inherited TAAD is often asymptomatic until a life-threatening event occurs, so evaluating at risk family members can save lives.

Levels of Evidence

A – multiple populations evaluated; data derived from multiple randomized clinical trials or meta-analyses
B – limited populations evaluated; data derived from a single randomized trial or nonrandomized studies
C – very limited populations evaluated; consensus opinion, case studies or standard of care

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Coronary Artery Disease

The evidence is insufficient to support the use of genomic risk scores or gene expression testing for cardiac disease. Further studies with a larger number of patients and longer follow-up are needed to determine if these tests provide clinical utility in cardiac patients.

Genetic Profiles for Cardiac Disease Risk

Most genomic cardiac risk profile studies have focused on Caucasian Europeans. To explore the value of genomic profiles in different populations, Iribarren et al. (2018) examined the clinical utility of using multi-locus genomic profiling and risk scores in individuals of Latino (n=4349), East Asian (n=4804) and African (n=2089) ancestry. They utilized available data from the Genetic Epidemiology Resource in Adult Health and Aging (GERA) cohort of 110,266 adult male and female Kaiser Permanente of Northern California (KPNC) members. Two genomic profiles, one with 12 single-nucleotide polymorphisms (SNPs) and another with 51 SNPs, and the Framingham Risk score were utilized to estimate the 10 year coronary heart disease (CHD) risk. The median years of follow-up available were 8.7, and in the cohort overall there were 450 CHD events. In this subset, the CHD events included 95 in African, 316 in Latino and 39 in East Asian ancestry. After modeling and adjusting for principal components and risk factors, the 12 SNP genomic risk score was strongly associated with CHD independent of other risk factors and self-reported family history, and when the risk score included the Framingham risk score, the risk in the top tertile of patients was more strongly associated with outcome, particularly in African-Americans. In the 51-SNP genomic risk score analysis, there was an independent statistical association only in Latinos. Including the Framingham risk score improved the risk categorization only a small percentage across groups. The authors concluded that universal use of DNA tests for determining cardiovascular risk is not recommended at this time, consistent with guidelines. They argue, however, that their data shows that the value of genomic risk scores demonstrated in European populations applies to other ethnic groups, particularly African-American, Latino and to some degree East Asians. Intermediate risk groups who could benefit from more aggressive interventions may benefit from further risk assessments using genomic risk scores.

Iribarren et al. (2016) examined the clinical utility of genomic risk scores for cardiac disease in a study of 51,954 individuals of European ancestry. They utilized available data from the GERA cohort of 110,266 adult male and female KPNC members. Four different genomic profiles using between 8-51 SNPs were developed using known genetic variants. The mean follow-up was 5.9 years. There were 1864 CHD events in this group, and all four models were linearly associated with CHD events. The hazard ratios, respectively for the 8, 12, 36 and 51 SNP panels were 1.21, 1.20, 1.23 and 1.23. Adding the genomic risk score improved the overall classification of risk in this group by 5% for SNP profiles on 8, 12 and 36 SNPs, and 4% for 51 SNPs. When using the SNP profiling only in those who were intermediate risk by the Framingham score, the net reclassification improvement was 9% for SNP profiles 8 and 12, and 7% for SNP profiles 36 and 51. Using the latter approach, to prevent 1 CHD you would treat 36 individuals with statins in the high risk 8 SNP and 12 SNP groups, 41 in the 36 SNP group and 43 in the 51 SNP group.

Cardiac disease is caused by a combination of genomic and lifestyle factors. To study the extent that a healthy lifestyle can influence genetic risk, Khera et al. (2016) combined the results of four studies of 55,685 white participants that looked at lifestyle factors in the context of genetic risk. The four studies included Atherosclerosis Risk in Communities (ARIC) study, the Women's Genome Health Study (WGHS), the Malmö Diet and Cancer Study (MDCS) and the BioImage Study. All are described in detail elsewhere. The sub-cohort of each group that was selected for this study resulted in a final study group that had an average age of 58, 75% female, 42% with hypertension at baseline, 6.5% with diabetes mellitus, 25% with a family history positive for CHD, and an average BMI of 26. Additional risk factors related to lipid levels and use of lipid lowering medications were reported in detail for each group. Healthy lifestyle factors such as exercise, non-smoking and a healthy diet were combined into a healthy lifestyle score per group. A genomic panel of up to 50 SNPs was utilized to derive a genomic risk score for participants. Individual participant scores were created by adding up the number of risk alleles at each SNP and then multiplying the sum by the literature-based effect size. The genomic risk score was highly predictive of CHD events, and the relative risk was 91% higher in those at high genetic risk than among those at low genetic risk. A family history of CHD was also strongly associated with CHD events, but not as tightly as the genomic risk score. Levels of LDL cholesterol were also modestly associated with CHD events. Genetic risk categories were not associated with other cardiometabolic risk factors or risk modelling provided by the ACC. As expected, unfavorable lifestyle risk factors were strongly correlated with CHD events. When lifestyle risk factors were analyzed in the context of genomic risk scores, those with a favorable lifestyle had a 45% lower risk of a CHD in the low genomic risk group, a 47% lower risk in the intermediate genomic risk group and a 46% lower risk in the high genomic risk group. The inverse was true as well; an unfavorable lifestyle was strongly correlated with an adverse CHD event even in the low genomic risk group. When an adjustment was made for traditional risk factors, the decreased risk for those with

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a favorable lifestyle remained statistically significant across all groups. In conclusion, regardless of genetic risk, adherence to a healthy lifestyle substantially reduces the risk of coronary artery disease.

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice reviewed the available evidence on the use of genomic risk scores in identifying individuals at risk for coronary artery disease, and preventing subsequent disease (Piepoli et al., 2016). The joint task force concluded that while there is strong pressure to use genomic testing, there is no consensus on what genetic markers should be included, how genomic risk scores should be calculated and how to use the information to prevent cardiac disease. Therefore, use of genetic markers in the prediction of CHD is not recommended.

Gene Expression Testing

Gene expression is the process by which the coded information of a gene is translated into the structures present and operating in the cell (either proteins or ribonucleic acids (RNA)). Gene expression profiling (GEP) studies the patterns of many genes in a tissue sample at the same time to assess which ones are turned on (producing RNA and proteins) or off (not producing RNA or proteins). By simultaneously measuring the levels of RNA of thousands of genes, GEP creates a snapshot of the rate at which those genes are expressed in a tissue sample.

Assimes and Roberts (2016) summarized the evolution and discovery of genetic risk variants for CAD and their current and future clinical applications. In order to maximize the clinical utility of the current knowledge gained, the authors propose future tasks which include the identification of the remaining susceptibility loci for CAD, proving the clinical utility of genetic data in the prevention of CAD, and acquiring a solid appreciation of the cellular and/or extracellular mechanisms responsible for genetic associations observed at the population level. They conclude that extremely large sample sizes are needed for additional discoveries, given the distribution of effect sizes observed to date for both common and rare variants, as well as the estimated proportion of the heritability of CAD explained by these variants to date. In the coming years, the authors suggest that this need could be fulfilled by mega-biobanks to assist in the determination of the clinical utility of genetic risk scores, and to conduct additional, well-powered MR studies to complement studies published to date.

Using a series of microarray and real-time polymerase chain reaction (RT-PCR) data sets, comprising more than 1000 patients, Elashoff et al. (2011) developed a blood-based gene expression algorithm for assessing obstructive CAD in non-diabetic patients. The algorithm consists of the expression levels of 23 genes, sex and age.

Wingrove et al. (2008) performed a microarray analysis on 41 patients with angiographically significant CAD and 14 controls without coronary stenosis to identify genes expressed in peripheral blood that may be sensitive to the presence of CAD. A multistep approach was used, starting with gene discovery from microarrays, followed by real-time polymerase chain reaction (RT-PCR) replication. The authors observed that gene expression scores based on 14 genes, independently associated with the presence or absence of CAD, were proportional to the extent of disease burden. This study is limited by its size and retrospective nature. Larger, prospective studies are needed to confirm these initial results.

The U.S. Preventive Services Task Force (USPSTF) recommendations on the use of nontraditional risk factors in coronary heart disease risk assessment do not address genetic/genomic markers (USPSTF, 2009).

Professional Societies

American College of Cardiology (ACC)

ACC guidelines do not address gene expression profiling for predicting the likelihood of obstructive coronary artery disease.

American Heart Association (AHA)

In a scientific statement, the AHA summarizes the emergence and state of the science of several transformational technologies for the refinement of cardiovascular disease mechanisms. Technologies such as epigenomics, transcriptomics, proteomics and metabolomics, are now making it possible to address the contributions of the expressed genome to cardiovascular disorders. The statement also identifies issues that need to be addressed to enable the use of the expressed genome for diagnosis and prediction in the clinical setting. Each of the approaches remains a work in progress, and many of the initial findings are still awaiting systematic replication in independent studies (Musunuru et al., 2017).

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In a separate AHA scientific statement, Mital et al. (2016) affirm that advances in genomics are enhancing the understanding of the genetic basis of cardiovascular diseases, both congenital and acquired, and stroke. These advances include finding genes that cause or increase the risk for childhood and adult-onset diseases, finding genes that influence how patients respond to medications, and the development of genetics-guided therapies for diseases. The AHA recommends that cardiovascular and stroke clinicians develop a set of core competencies in genetics so that they can systematically and effectively integrate genetics into clinical practice.

In an AHA policy statement on genetics and cardiovascular disease, Ashley et al. (2012) strongly advocate the involvement of physicians and centers with expertise in cardiovascular genetics to guide the appropriate initiation, interpretation, and implementation of genetic testing and to gain clinical consensus as to what constitutes clinical utility. The potential of whole-genome sequencing to impact medicine is highly significant and as such, they recommend that genetics and genomics be included as a fundamental part of the training curriculum for all health professionals.

In a published scientific statement on the relevance of genetics and genomics for the prevention and treatment of cardiovascular disease (CVD), the AHA states that RNA gene expression profiling shows great promise. However, further results from large, patient cohorts are needed to determine the clinical utility of this methodology. The statement also proposes several recommendations to guide future research (Arnett et al. 2007).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform genetic tests for cardiac disease are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed April 24, 2020)

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Guideline History/Revision Information

Date	Summary of Changes
01/01/2021	**Template Update** • Reformatted policy; transferred content to new template **Applicable Codes** • Updated list of applicable CPT codes to reflect annual edits; added 0237U **Supporting Information** • Archived previous policy version MMG049.K

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