

# Genetic Testing for Cardiac Disease

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[Instructions for Use](#)

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Related Policies
<ul style="list-style-type: none"> <li>• <a href="#">Cardiovascular Disease Risk Tests</a></li> <li>• <a href="#">Genetic Testing for Neuromuscular Disorders</a></li> <li>• <a href="#">Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions</a></li> <li>• <a href="#">Pharmacogenetic Testing</a></li> </ul>

## Coverage Rationale

Multi-Gene Panel testing for the diagnosis of a hereditary cardiomyopathy or arrhythmia syndrome is proven and medically necessary in individuals 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:
  - Individual 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 [ $> 460\text{ms}$ ] 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](#)  $\geq 1.5$  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 individuals with a confirmed or suspected diagnosis of heritable 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 individuals 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
- 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<sup>®</sup>, Cardiac Healthy Weight DNA Insight<sup>®</sup>, Cardio IQ<sup>®</sup> 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.

CPT Codes*	Required Clinical Information
<b>Genetic Testing for Cardiac Disease</b>	
0237U	Medical notes documenting the following, when applicable: <ul style="list-style-type: none"> <li>• Personal history of the condition, if applicable, including age at diagnosis</li> <li>• Complete family history (usually three-generation pedigree) relevant to condition being tested</li> <li>• Genetic testing results of family member, if applicable, and reason for testing</li> <li>• Ethnicity/ancestry (e.g., Ashkenazi Jewish), if reason for testing</li> <li>• Any prior genetic testing results</li> <li>• How clinical management will be impacted based on results of genetic testing</li> <li>• Genetic counseling (if available)</li> </ul>
81410	
81411	
81413	
81414	
81439	
81479	

\*For code descriptions, refer to the [Applicable Codes](#) section.

## 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 Genetics 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 policy 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 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 may apply.

CPT Code	Description
0237U	Cardiac ion channelopathies (e.g., 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

*CPT® is a registered trademark of the American Medical Association*

## 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 an individual. Results of genetic testing may assist individuals 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 Clinical Policy titled [Genetic Testing for Neuromuscular Disorders](#).

## 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 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)

Adler et al. (2020) coordinated three, blinded, gene-curation teams to score the level of evidence for 17 genes with strong associations for LQTS. A Clinical Domain Channelopathy Working Group then determined a final classification of the causative LQTS genes after independent assessment by the blinded teams was completed. 3/17 (KCNQ1, KCNH2, SCN5A) were determined to be definitive LQTS genes; 9/17 causative genes (AKAP9, ANK2, CAV3, KCNE1, KCNE2, KCNJ2, KCNJ5, SCN4B, SNTA1) were re-classified as having limited/disputed evidence for being LQTS genes; 4/17 (CALM1, CALM2, CALM3, TRDN) were shown to have strong evidence for atypical LQTS; 1/17 (CACNA1C) demonstrated moderate evidence for LQTS. The evidence in the study revealed that more than 50% of previously reported LQTS causative genes have limited/disputed evidence to support causation. The authors suggested that variants in these genes should not be used for clinical decision-making unless new future genetic evidence is revealed. Furthermore, evidence-based evaluations for disease-causing genes are recommended to ensure appropriate use in precision medicine.

Van Lint et al. (2019) reported on the detection rates for variants of unknown, likely, and certain pathogenicity in cardiac gene panels. 936 arrhythmia panels and 1,970 cardiomyopathy panels were performed. Unknown, likely, and certain variants were detected in 34.8%, 4.2%, and 4.6% of arrhythmia panels, respectively. The cardiomyopathy panel revealed unknown, likely and certain variants in 40.8%, 7.9%, and 12% of patients, respectively. The arrhythmia panel revealed variants in 44% of patients overall, while the cardiomyopathy panels revealed variants in 61% of patients. The authors concluded that "larger gene panels can increase the detection rate of likely pathogenic and pathogenic variants but may increase the frequency of variants of unknown significance."

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 LQTS. 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 LQTS 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%.

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 long QT type 3 (LQT3) genotype patients and determined that this intervention had a clinically significant reduction in arrhythmic events.

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.

Walsh et al. (2021) conducted an evidence-based reappraisal of genes that have been reported to cause CPVT and short QT syndrome (SQTS). Results related to SQTS are discussed in SQTS section of this policy below. For this evaluation, published evidence for 11 CPVT implicated genes was collected via the ClinGen gene curation framework. An expert panel of 10 individuals with extensive experience in clinical care and/or research related to clinical genetics, CPVT and SQTS performed a comprehensive evaluation and final classification for each gene. Definitive to moderate evidence for disease causation in CPVT was found for seven genes, either with autosomal dominant (RYR2, CALM1, CALM2, CALM3) or autosomal recessive (CASQ2, TRDN, TECRL) inheritance. Four genes for CPVT were disputed; of those, 3 (KCNJ2, PKP2, SCN5A) were determined to be reported for phenotypes that did not represent CPVT and the fourth gene variant (ANK2) was found to be too common in the general population to be causative for disease. This evaluation and reappraisal of the relationships between genes and diseases for CPVT provides evidence-based support regarding which genes may be considered valid, disease-causing genes and therefore included in genetic testing panels. The authors caution that a systematic and evidence-based approach should be performed for assessment of validity for any new gene-disease relationship prior to use in patient care and assert that both genetic and phenotypic data should be subject to careful assessment when exploring any new genetic causes related to CPVT.

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 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.

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.

Walsh et al. (2021) conducted an evidence-based reappraisal of genes that have been reported to cause CPVT and SQTS. Results related to CPVT are discussed in CPVT section of this policy above. Published evidence for 9 SQTS implicated genes was collected and evaluated by a panel of experts in clinical genetics, CPVT and SQTS. The expert team performed final evaluation and classification of each gene. For SQTS, only one gene (KCNH2) could be classified as definitive. Three other genes (KCNQ1, KCNJ2, SLC4A3) had strong to moderate evidence. Although CACNA1C, CACNB2, and CACNA2D1 are included in most commercial SQTS panels, rare variants in these genes are likely to be interpreted as variants of unknown significance (VUS) and would not increase yield of panel but would contribute to increased turnaround time and/or lead to anxiety or uncertainty because of VUS outcome. Notably, most of the evidence for SQTS genes came from very few variants (a total of 5 in KCNJ2, 2 in KCNH2 and 1 in KCNQ1/SLC4A3). This reevaluation of gene-disease relationships for SQTS provides an evidence-based analysis of genes to be considered as valid disease genes and included in multi-gene panels. The researchers recommend that a systematic, evidence-based approach be used to evaluate and assess validity of any reported or new gene-disease relationship before use in clinical care and that both phenotype and genetic data must be carefully reviewed and evaluated when assessing potential genetic cause of SQTS.

### ***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 AF caused by non-genetic reasons. This familial type of AF has an unknown incidence (MedLinePlus, 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.

To investigate the results of genetic testing for early onset AF, Yoneda et al. (2021) conducted a prospective, observational cohort study including 1293 participants. The study participants were enrolled from an academic medical center from November 1999 through June 2015. Each participant had been diagnosed with AF prior to 66 years of age and underwent whole genome sequencing with evaluation of 145 genes commonly included on commercially available cardiomyopathy and arrhythmia panels. Sequencing data were evaluated using automation followed by manual review performed by a panel of independent, blinded reviewers. Primary outcome was the classification of rare variants via the American College of Medical Genetics and Genomics criteria including benign, likely benign, VUS, likely pathogenic or pathogenic. The study defined disease-associated variants as pathogenic or likely pathogenic variants in genes associated with autosomal dominant or X-linked dominant disorders. Of the 1293 participants, 10.1% (131) were found to have a disease-associated variant identified by

genetic testing performed and 62.8% (812) were found to have a VUS. Heterozygous carriers for autosomal recessive disorders made up 7.1% (92) of the study population and 20% (258) had no suspicious variants reported. Participants diagnosed with AF prior to the age of 30 were most likely to have a disease-associated variant and those diagnosed after the age of 60 were least likely to have a disease-associated variant. Of note, disease-associated variants were more likely to be associated with inherited cardiomyopathy syndromes than inherited arrhythmias. The authors assert that these results support use of genetic testing in the case of early-onset AF. Study limitations included disagreement on ACMG classification for given variants and limited evidence on many of the genes that are typically included on commercial panels for specific cardiac phenotypes. In addition, this study population came from a single center and was primarily made up of people of European ancestry so is not representative of all ethnicities.

Roselli et al. (2018) worked with global researchers to study the genetic basis of AF. The researchers compiled data from over 65,000 individuals 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.

### ***Clinical Practice Guidelines***

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

ACC, AHA and HRS guidelines for the management of patients with AF 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)

ACC, AHA and HRS published guidelines for management of patients with ventricular arrhythmias and the prevention of SCD (Al-Khatib Sana et al., 2018) which recommended the following general guidelines related to genetic testing:

- The availability of genetic testing for inherited arrhythmia syndromes can provide opportunity to confirm a suspected diagnosis for the proband and offer cascade screening of potentially affected family members when a disease-causing mutation is identified in the proband.
- Genotyping is frequently most useful when a pathogenic mutation is identified in the proband, such that screening can be applied to relatives who are in a preclinical phase, allowing institution of lifestyle changes, therapy, or ongoing monitoring for those who are gene mutation positive.
- In young patients (< 40) without structural heart disease who have unexplained cardiac arrest, unexplained near drowning, or recurrent exertional syncope, genetic testing may be important to identify an inherited arrhythmia syndrome as a likely cause.

#### **European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS)**

In an Expert Consensus Statement on genetic testing for cardiac disease, the EHRA, HRS, APHRS and LAHRS (Wilde et al., 2022). provide the following recommendations for genetic testing in arrhythmias:

### ***LQTS***

- Molecular genetic testing for definitive disease associated genes (currently KCNQ1, KCNH2, SCN5A, CALM1, CALM2, and CALM3) should be offered to all index patients with a high probability diagnosis of LQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score > or = 3.5).
- Analysis of specific genes should be offered to patients with a specific diagnosis as follows: KCNQ1 and KCNE1 in patients with Jervell and Lange-Nielsen syndrome, CACNA1C in Timothy syndrome, KCNJ2 in Andersen-Tawil syndrome, and TRDN in patients suspected to have triadin knockout syndrome.
- An analysis of CACNA1C and KCNE1 may be performed in all index patients in whom a cardiologist has established a diagnosis of LQTS with a high probability, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score > or = 3.5).
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causing variant.
- Predictive genetic testing in related children is recommended from birth onward (any age).



## *CPVT*

- In any patient satisfying the diagnostic criteria for CPVT (such as Class 1 clinical diagnosis or CPVT diagnostic score > 3.5<sub>b</sub>), molecular genetic testing is recommended for the currently established definite/strong evidence CPVT-susceptibility genes: RYR2, CASQ2, CALM1-3, TRDN, and TECRL.
- In phenotype-positive CPVT patients who are negative for those established CPVT-susceptibility genes, genetic testing may be considered for CPVT phenocopies resulting from pathogenic variants in the KCNJ2, SCN5A, and PKP2 genes.
- In patients with a modest phenotype for CPVT (i.e., CPVT diagnostic score > or = 2 but < 3.5<sub>b</sub>), genetic testing may be considered for the established definite/strong evidence CPVT-susceptibility genes: RYR2, CASQ2, CALM1-3, TRDN, and TECRL.
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.
- Predictive genetic testing in related children at risk of inheriting a pathogenic (L)/likely pathogenic (LP) variant is recommended from birth onward (any age).

## *BrS*

- Genetic testing with sequencing of SCN5A is recommended for an index case diagnosed with BrS with a type I ECG in standard or high precordial leads occurring either (i) spontaneously, or (ii) induced by sodium-channel blockade in presence of supporting clinical features or family history.
- Rare variants in genes with a disputed or refuted gene-disease clinical validity should not be reported routinely for BrS genetic testing in a diagnostic setting.
- Targeted sequencing of variant(s) of unknown significance in SCN5A with a population allele frequency < 1 X 10<sup>-5</sup> identified in an index case can be considered concurrently with phenotyping for family members, following genetic counselling, to assess variant pathogenicity through co-segregation analysis.
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.
- Predictive genetic testing (of pathogenic SCN5A variants) in related children is recommended from birth onward (any age).

## *SQTS*

- In any patient satisfying the diagnostic criteria for SQTS (such as Class 1 clinical diagnosis or SQTS diagnostic score > 4), molecular genetic testing is recommended for the definitive disease associated genes (currently KCNH2, KCNQ1).
- Testing of KCNJ2 and SLC4A3 may be performed in all index patients in whom a cardiologist has established with a high probability a diagnosis of SQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline or during ECG Holter recording and exercise stress test (SQTS diagnostic score > or = 4).
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.
- Predictive genetic testing in related children may be considered in specific settings.

## *Inherited AF*

- An analysis of SCN5A, KCNQ1, MYL4 and truncating TTN variants may be performed in all index patients in whom the diagnosis of familial (young = age < 60) AF, is established, based on examination of the patient's clinical history, family history, and ECG characteristics.
- Variant-specific genetic testing may be recommended for family members and appropriate relatives following the identification of the disease-causative variant.
- Predictive genetic testing in related children may be considered in specific settings.

Nielsen et. al (2020) published an expert consensus on behalf of the EHRA, HRS, APHRS and LAHRS addressing risk assessment in cardiac arrhythmias. This consensus recommends consideration of genetic testing for inherited arrhythmic disease associated with increased risk of ventricular arrhythmia and SCD and notes that clinically applicable genetic testing is intended to be driven by phenotype. Pre-test probability of specific diagnosis is the determinant for utility of the genetic evaluation. Because of incomplete penetrance of genetic arrhythmia syndromes, identification of a genetic variant with known pathogenicity is rarely, if ever, enough to meet diagnostic criteria for a given syndrome. Genetic testing can prove useful for family members of a genotype identified proband but is not recommended without the presence of a diagnostic ECG. In

addition, the document notes that searching for common genetic variants associated with AF risk has not been found to be useful in the clinical setting and further studies are required to assess whether genetic information improves ability to predict AF in conjunction with clinical variables.

## 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.

Christian et al. (2022) published the results of a systematic review and meta-analysis summarizing the diagnostic validity and clinical utility of genetic testing for individuals diagnosed with HCM and their relatives who may be at risk. In all, 132 articles from inception through March 2020 (span of 25 years in total) met inclusion criteria for the study. Of these, 80 reported on detection rate, 44 described genotype-phenotype associations and 51 addressed penetrance estimates. Sensitivity analyses and subgroup were prespecified for individual sarcomere genes, pediatric and adult cohorts, family history, inclusion of probands, presence/absence of pathogenic variants and variant classification method. The review found significantly higher detection rate of pathogenic variants in pediatric cohorts than in adult cohorts (56% vs 42%;  $p = 0.01$ ) and in adults with a family history compared with sporadic cases (59% vs 33%;  $p = 0.005$ ). In studies using current, improved variation interpretation standards, detection rate decreased significantly from 42% to 33% ( $p = 0.0001$ ) since fewer variants met the criteria to be considered pathogenic. Age of onset in adults differed significantly for genotype-positive vs genotype-negative cohorts (mean difference 8.3 years;  $p < 0.0001$ ). MYH7 vs MYBPC2 cohorts and individuals with multiple variants also had a significant difference in age of onset (8.2 years;  $p < 0.0001$  and 7.0 years;  $p < 0.0002$ , respectively). Disease penetrance in adult cohorts was 62% overall, but significant differences were seen based on whether probands were included or excluded (73% vs 55%;  $p = 0.003$ ). This analysis collectively quantified historical understandings of rate of detection, disease penetrance and genotype-phenotype associations for HCM and confirmed some previously established trends and associations, serving as to bridge to further understanding of the clinical utility of genetic testing for HCM. The authors point out the variabilities in study design and outcome reporting that limited the analysis but stress the importance of the large volume of data analyzed that will help provide answers regarding detection rates and genotype-phenotype correlations. Important areas for further study include expansion of genotype-phenotype associations and disease penetration estimates across varying populations. Authors Mazzarotto (2019), Restrepo-Cordova (2017), Murphy (2016), Rubattu, (2016), Alfares (2015), Loar (2015), Gruner (2013), Ingles (2013), Zou (2013), Michels (2009), Olivotto (2008), Richard (2003), Van Driest (2003), Niimura (1998), Charron (1997), and Watkins (1995), which were previously cited in this policy, are included in the Christian (2022) systematic review.

Hathaway et al. (2021) studied the diagnostic yield of genetic testing in persons with a suspected diagnosis of HCM who were referred for testing to multiple, world-wide centers. The authors performed a retrospective review of these patients who had testing performed by Blueprint Genetics. Variants categorized as P/LP were determined to be diagnostic. 369/1,376 samples (26.8%) were diagnostic; 373 P or LP variants were reported. Sarcomeric genes (85%) comprised the majority of diagnostic variants; 4.3% of diagnostic variants were reported in RASopathy genes; cardiomyopathy genes other than HCM/arrhythmia were identified in 2%. An increased likelihood of identifying a diagnostic variant was associated with earlier age of diagnosis ( $p < 0.0001$ ), a higher maximum wall thickness ( $p < 0.0001$ ), a positive family history ( $p < 0.0001$ ), absence of hypertension ( $p = 0.0002$ ), and the presence of an ICD ( $p = 0.0004$ ). While the reported diagnostic yield was lower in this cohort compared to

other patient cohorts, the authors concluded that the spectrum of genes implicated illustrates the necessity of pre-and post-test counseling when performing genetic testing to a broad-based HCM population.

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). 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)

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%).

Manrai et al. (2016) evaluated publicly available data and identified variants that had previously been considered causal for HCM that were 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.

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 Gómez et al. (2014), used next generation sequencing (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.

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 without a personal or family history of HCM, suggests that false-positive results for known pathologic mutations using Sanger sequencing are uncommon. 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 VUS, which may impact the positive and negative predictive value of the test.

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.

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%.

NGS is recognized as the most efficient way to identify HCM mutations due to the large number of genes associated with HCM. 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 number of genes. The researchers concluded that NGS was as accurate as Sanger sequencing, therefore with the increased efficiency, NGS is a preferred method.

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 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 (Fanapanazir 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.

### ***Arrhythmogenic Cardiomyopathy (ACM)***

ACM is a cardiac condition that is characterized by progressive fibro-fatty replacement of the myocardium. This creates the risk of ventricular dysfunction and arrhythmias. The structural alterations present with ACM can impact left, right or both ventricles leading to three recognized phenotypes: the most common, dominant-right (arrhythmogenic right ventricular cardiomyopathy (ARVC), the biventricular variant (BivACM), and the dominant-left (arrhythmogenic left ventricular cardiomyopathy (ALVC). Identification of a LP/P variant is a major diagnostic criterion for each of these types and can actually be a requirement for diagnosis of the ALVC variant. (Wilde et. al, 2022)

Diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) 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 ARVC/D 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.

ARVC/D 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 ARVC/D 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 ARVC/D 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 ARVC/D 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.

A study by Riele et al. (2016) aimed to determine the predictors of ARVC/D 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 ARVC/D 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 ARVC/, there is not enough insight into genotyping yet. These researchers state that the key clinical application of genetic testing in ARVC/D 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 (MedLinePlus, 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)

In a 2022 systematic review, Peters et al. focused on a review of phenotypes, functional effects, natural history and treatment outcomes of DCM-associated rare variants specific to the SCN5A gene. The researchers identified 18 SCN5A rare variants in 173 affected individuals from 29 families. Eleven of the variants had undergone evaluation and 7 of these had a consistent phenotype that was characterized by frequent multifocal narrow and broad complex ventricular premature beats (VPB; 72% of affected relatives), atrial arrhythmias (32%), ventricular arrhythmias (33%), DCM (56%) and SCD (13%). The VPD variant was not seen either with variants that increased late sodium current or with variants that reduced peak current density/had mixed effects. In the absence of arrhythmias, DCM did not occur for any variant. Of note, 12 studies with a total of 23 patients reported success with the use of sodium channel-blockers for the VPB-predominant cardiomyopathy. The authors concluded that SCN5A can present with varied primary arrhythmic features, with the majority of DCM-associated variants causing a multifocal VPD-predominant cardiomyopathy (reversible with sodium channel-blocking therapy). They assert that early recognition of the distinctive phenotype associated with this variant and associated genetic testing is very important for management of SCN5A variants in DCM patients.

Rangaraju et al. (2021) laid out the following genetic testing recommendations for cardiomyopathies and channelopathies and broadly summarized genetic testing recommendations from the ACGM, ACC and EHRA as follows:

- Genetic testing is recommended as a Class I indication in probands with a confirmed diagnosis of cardiomyopathies and channelopathies.
- Genetic testing is recommended in at-risk family members of the proband.
- Testing is recommended in presymptomatic individuals with a strong family history of cardiac disorders.
- Genetic testing is recommended even in diagnosed patients with no family history of inherited cardiac disease or sudden death, as this may reflect incomplete information of family history and screening, incomplete penetrance, or a de novo mutation in the proband.

Mazzarotto et al. (2020) studied the largest genetically characterized cohort of DCM patients to-date to determine the frequency of rare variation in 2,538 DCM patients for 56 commonly tested genes. In order to increase accuracy and reduce uncertainty for DCM clinical genetic testing, the authors also sought to provide evidence for curation efforts for the ClinGen initiative to validate DCM disease genes and to validate gene/variant classes. The results compared 912 confirmed healthy controls and a reference population of 60,706 to identify clinically interpretable genes that are definitively associated with dominant monogenic DCM. Using the TruSight Cardio sequencing panel, 12 strong-association genes were identified. Truncating variants in TTN and DSP were associated with DCM in all comparisons; MYH7, LMNA, BAG3, TNNT2, TNNC1, PLN, ACTC1, NEXN, TPM1, and VCL were significantly enriched in certain patient subsets; TPM1 and VCL contributed primarily to early-onset forms of DCM. The authors stated that burden of rare variation comparison showed that most genes associated with DCM do not have a significant enrichment or rare variants in cases making them unlikely to be causative. They should, therefore, be

evaluated further to determine their clinical validity for DCM. The authors also stated that they were able to evaluate the basis of DCM genetics and revealed variants that were particularly associated with early onset disease.

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.

### ***Clinical Practice Guidelines***

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

The 2020 AHA/ACC Guideline for HCM published the following key perspectives regarding genetic testing: (Ommen et al., 2020)

- Genetic testing should be offered to HCM patients. For HCM patients with variants of unknown significance, serial re-evaluation of test results is recommended to assess variant reclassification.
- If a proband has a pathogenic or likely pathogenic variant on genetic testing, cascade genetic testing should be offered.

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.
- 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.

#### **American College of Medical Genetics (ACMG)/Heart Failure Society of America (HFSA)**

Hershberger et al. (2018), in conjunction with a group of cardiologists and genetics professionals, updated the ACMG/HFSA recommendations that were first published in 2009 for the genetic evaluation of cardiomyopathies. Genetic testing is recommended for the most clearly affected family member; testing should initially be performed in the person most likely to possess a variant and is frequently the person in the family with the earliest disease onset and/or most severe disease. If the ideal person is unavailable/unwilling to be tested, genetic testing should be considered for another unequivocally affected family member. Cascade testing of at-risk family members is recommended for pathogenic and likely pathogenic variants. Specialized evaluation of infants with cardiomyopathy is recommended in addition to newborn screening; genetic testing should also be considered. Genetic testing should optimally be performed at the time of cardiomyopathy diagnosis but can be performed at any time. Repeat testing is reasonable if test sensitivity has increased by 5-10% and retesting should also be performed if the patient's phenotype is consistent with a newly identified gene. Genetics providers should also revisit results as variants are reclassified over time. Multigene panel molecular testing is the standard of care and preferred over single-gene

testing due to the heterogeneous nature of the disorders. Both genetic testing and cascade screening have been shown to be cost-effective according to the authors.

### American Heart Association (AHA)

The American Heart Association Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology (Musunuru et al., 2020) published a scientific statement recommending that:

- Genetic testing should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease, or for persons at high a priori risk resulting from a previously identified familial pathogenic variant.
- Disease-appropriate phenotyping with a three-generation family history should be performed.
- If genetic testing is performed, the clinician should choose the appropriate testing which ranges from targeted sequencing of a single or few genes, to large panels that include limited evidence genes, to unbiased exome or genome sequencing.

### European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS)

In an Expert Consensus Statement on genetic testing for cardiac disease, the EHRA, HRS, APHRS and LAHRS (Wilde et al., 2022). provide the following recommendations for genetic testing in cardiomyopathies:

#### *HCM*

- For genetic testing in a proband with HCM (including those cases diagnosed post-mortem), the initial tier of genes tested should include genes with definitive or strong evidence of pathogenicity (currently MYH7, MYBPC3, TNNI3, TPM1, MYL2, MYL3, ACTC1, and TNNT2).
- For genetic testing in a proband with HCM, the initial tier of genes tested may include genes with moderate evidence of pathogenicity (CSRP3, TNNC1, JPH2).
- In patients with HCM, genetic testing is recommended for identification of family members at risk of developing HCM.
- In patients with atypical clinical presentation of HCM, or when another genetic condition associated with unexplained hypertrophy is suspected (e.g., HCM phenocopy) genetic testing is recommended.
- Predictive genetic testing in related children is recommended in those aged > 10–12 years.
- In patients with HCM who harbor a variant of uncertain significance, the usefulness of genetic testing of phenotype-negative relatives for the purpose of variant reclassification is uncertain.
- Predictive genetic testing in related children aged below 10–12 years may be considered, especially where there is a family history of early-onset disease.
- In patients with HCM who harbor a variant of uncertain significance, testing of affected family members for the purpose of variant classification may be considered.
- For patients with HCM in whom genetic testing found no LP/P variants, cascade genetic testing of family relatives is not recommended.
- Ongoing clinical screening is not recommended in genotype-negative relatives in most families with genotype-positive HCM.

#### *ACM*

- Comprehensive genetic testing is recommended for all patients with consistent phenotypic features of ACM, including those cases diagnosed post-mortem, whatever familial context.
- Genetic testing of first tier definitive disease-associated genes (currently PKP2, DSP, DSG2, DSC2, JUP, TMEM43, PLN, FLNC, DES, LMNA) is recommended.
- Owing to the possibility of complex genotypes, in families with multiple affected members, the case with the more severe and/or earlier phenotype may be considered the ‘genetic proband’ and be tested first.
- In patients with a borderline ACM phenotype, comprehensive genetic testing may be considered. The identification of a LP/P genetic variant would be useful to confirm the diagnosis.
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.
- Predictive genetic testing in related children is recommended in those aged > 10–12 years.
- Predictive genetic testing in related children aged below 10–12 years may be considered, especially where there is a family history of early-onset disease.

## DCM

- Genetic testing is recommended for probands with DCM and family history of DCM, and the initial tier of genes tested should include genes with definitive or strong evidence of pathogenicity (currently BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN, DSP).
- For genetic testing in a proband with DCM, the initial tier of genes tested may include genes with moderate evidence of pathogenicity (ACTC1, ACTN2, JPH2, NEXN, TNNT3, TPM1, VCL).
- Genetic testing is recommended for patients with DCM and family history of premature unexpected sudden death or in a DCM patient with clinical features suggestive of a particular/rare genetic disease (such as atrioventricular block or sinus dysfunction or creatine phosphokinase elevation).
- Genetic testing can be useful for patients with apparently sporadic DCM, particularly in the presence of either severe systolic dysfunction (left ventricular ejection fraction < 35%), or a malignant arrhythmia phenotype (e.g., sustained ventricular tachycardia/fibrillation), or particularly at a younger age.
- Genetic testing may be considered for patients with DCM related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy).
- Genetic testing is useful for patients with DCM to improve risk stratification and guide therapy.
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.
- Predictive genetic testing in related children is recommended in those aged > 10–12 years.
- Predictive genetic testing in related children aged below 10–12 years may be considered, especially where there is a family history of early-onset disease.

## 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.

## Inherited Thoracic Aortic Disease

Aortic diseases are the 18<sup>th</sup> 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. Thoracic aortic aneurysm 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 thoracic aortic diseases (HTADs) 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 HTADs 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 thoracic aortic disease (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 HTADs 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 HTAD. (Milewicz and Regalado, 2017)

Genetic factors have been proposed as a very important mechanism for ascending aortic dilatation (AAD) involving both the aortic root and the tubular segment. Ma et al. (2021) sought to investigate the rare genetic variants that contribute to the pathogenesis of aortic roots in individuals affected with bicuspid aortic valve (BAV). In this study, aortic root or ascending aorta with diameter greater than or equal to 40mm was considered AAD. In a cohort of 96 unrelated individuals with BAV including 34 with AAD, a custom-designed testing panel of 13 BAV-associated genes was performed using targeted next-generation sequencing. Rare variants with allele frequency < 0.05% were selected and evaluated, compared with the Exome aggregation consortium (ExAC) (Karczewski et al., 2020) and evaluated for pathogenicity of variants according to ACMG guidelines. Ultimately, 27 rare nonsynonymous coding variants involving 9 different genes were identified in 25 participants. Variants in GATA5, GATA6, and NOTCH1 had significant associations with BAV. Detection rate of rare variants was higher in the group of individuals with root dilatation (71.4%) than in the group with normal aorta (29.0%) and the group with tubular dilatation (29.6%). The authors concluded that although a broad genetic spectrum was identified in individuals with BAV, rare variants of BAV genes contribute most significantly to root-type phenotypes. They recommend further study on rare variants associated with BAV including long-term follow up to assess potential pathogenicity of rare genetic variants.

Using the ClinGen Aortopathy Working Group, Renard et al. (2018) attempted to identify hereditary thoracic aortic aneurysm and dissection (HTAAD) predisposition genes. This curation research was intended to aid and inform clinical laboratories in the development, interpretation, and establish subsequent clinical implications of clinical testing for aortic disease. Presumed gene-disease relationships between 53 candidate genes and HTAAD were explored. Genes were chosen based on published data and those tested in clinical aortopathy gene panels; six genes were added based on newly published literature and seven were added because they were offered on diagnostic panels for aortic disease. 37/53 genes were autosomal dominant; 4/53 were x-linked recessive; 1/53 were x-linked dominant; 11/53 were autosomal recessive. Gene-disease causations were evaluated by a pre-defined curator-expert pair and reviewed by an expert panel. Causative genes were determined for HTAAD if they were associated with isolated thoracic aortic disease and were clinically actionable, triggering routine aortic surveillance, intervention and family cascade testing. 9/53 genes (ACTA2, COL3A1, FBN1, MYH11, MYLK, SMAD3, TGFB2, TGFBR1, TGFBR2) were categorized as having definitive causation; 2/53 (PRKG1, LOX) strong; 4/53 moderate; 15/53 limited; 23/53 no evidence. The authors concluded that the ClinGen framework is useful when semi-quantitatively determining the strength of gene-disease relationships for HTAAD.

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 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 TAAO prior to testing. In the Netherlands, it is common to test all individuals with TAAO, which may explain the lower yield.

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 MFS (117), LDS (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 MFS. Mutations were additionally identified in ACTA2 (2), COL3A1 (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.

The diagnostic yield of a seven-gene NGS panel for TAAO 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 TAAO. 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.

### ***Clinical Practice Guidelines***

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 TAAO. The guidelines note that identification of a genetic mutation as the underlying cause of a TAAO 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 LDS or a confirmed TGFBR1 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 TAAO 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 TAAO 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

## American Heart Association (AHA)

In a 2020 scientific statement from the AHA, Musunuru et al. highlight 11 genes with strong or definitive evidence supporting association with penetrant heritable thoracic aortic aneurysms or dissections (HTADs) with or without syndromic features (ACTA2, COL3A1, FBN1, MYH11, SMAD3, TGFB2, TGFBR1, TGFBR2, MYLK, LOX, PRKG1) and 8 additional genes with significant evidence for risk associated with HTADs (EFEMP2, ELN, FBN2, FLNA, NOTCH1, SLC2A10, SMAD4, SKI) as per the ClinGen Aortopathy Working Group (Renard et. al., 2018). Identification of the causal gene can provide information allowing providers to take clinical action related to aortic disease presentation, associated clinical disorders, risk for dissection with or without aortic dilation and risk for other vascular diseases. Of note, genetic testing is negative for 70% of families with HTADS who do not present with systemic features, so it is clear that additional genes associated with HTADs have not yet been identified. In these cases, referral to research studies should be considered.

## 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*

Sun et al. (2021) sought to explore the clinical utility of polygenic risk scores (PRSs) in cardiovascular disease (CVD) focusing on coronary heart disease (CHD) and stroke outcomes as opposed to CHD only. Clinical implications of guideline-recommended intervention were also studied. The incremental predictive gain of PRSs over conventional risk factors was determined using data from the UK Biobank which included 306,654 persons without a history of CVD and not on lipid-lowering treatments. Population health implications of statin therapy were then modeled as recommended by current guidelines from 2.1 million persons from the Clinical Practice Research Datalink. Conventional risk prediction with PRSs data increased the C-index and enhanced risk stratification of cases and non-cases. The C-index, a measure of risk discrimination, was 0.710 (95% CI 0.703-0.717) for a CVD prediction model containing conventional risk predictors alone. The C-index was increased by 0.012 (95% CI 0.009-0.015) with the addition of information on PRSs and resulted in continuous reclassification improvements of 10% and 12% in cases and non-cases, respectively. The authors reported that “if a PRS were assessed in the entire UK primary care population aged 40-75 years, assuming that statin therapy would be initiated in accordance with the UK National Institute for Health and Care Excellence guidelines (i.e., for persons with a predicted risk of  $\geq 10\%$  and for those with certain other risk factors, such as diabetes, irrespective of their 10-year predicted risk), then it could help prevent 1 additional CVD event for approximately every 5,750 individuals screened. However, targeted assessment in persons at intermediate (i.e., 5% to  $< 10\%$ ) 10-year CVD risk could help prevent 1 additional CVD event for approximately every 340 individuals screened.” The authors added, further, that a targeted strategy could help prevent 7% more CVD events than conventional risk prediction alone. Potential gains from the assessment of PRSs in addition to conventional risk factors would result in a 1.5-fold increase over those provided by assessment of C-reactive protein, a plasma biomarker included in some risk prediction guidelines. The participants included in this study were all middle-aged individuals from the UK with European ancestry, however, so ability to generalize results is limited. The researchers recommend further studies to evaluate a range of different CVD screening strategies and include participants from differing ethnic groups and countries, as well as including health economic evaluation and investigation of potential psychological harms of using genetic information to predict CVD risk.

A retrospective cohort study was performed by Mosley et al. (2020) to determine whether PRS improved CHD event prediction compared to guideline-recommended clinical risk equations. The accuracy of previously validated PRS among 4,847 white European adults participating in the Atherosclerosis Risk in Communities (ARIC- mean age 62.9 [5.6 SD]) study and 2,390 individuals from the Multi-Ethnic Study of Atherosclerosis (MESA-mean age 61.8 [9.6 SD]) was reported. PRS performance data from 1996 to 2015 was compared to data taken from the 2013 American College of Cardiology/American Heart Association pooled cohort equations. Each individual’s genetic risk was calculated by adding the product of weights (international genome-wide association study) and allele dosage for 6,630,149 SNPs. A 10-year initial CHD event prediction was assessed using model discrimination, calibration, and net reclassification improvement. CHD events occurred in 14.4% (n = 696 ARIC participants) and 9.5% (n = 227 MESA participants) over a median follow-up period of 15.5 years. PRS was significantly associated with a 10-year CHD occurrence in ARIC with hazard ratios per standard deviation increments of 1.24 (95% CI, 1.15-1.34) and in MESA, 1.38 (95% CI, 1.21-1.58). From the two-cohort study, the PRS was associated with incident CHD events but did not significantly improve discrimination, calibration, or risk reclassification compared with conventional predictors. The authors concluded that based on their findings, a PRS may not enhance risk prediction in the general, white middle-aged population.

Dikilitas et al. (2020) researched the associations of restricted and genome-wide PRSs with CHD in three major US ethnic and racial groups. The eMERGE cohort (US based cohort with 99,185 participant DNA samples linked to EHR data to enable large-scale high-throughput genomic studies) included 45,645 European ancestry (EA), 7,597 African ancestry (AA), and 2,493 Hispanic ethnicity (HE) participants. Two restricted PRSs (PRS<sub>Tikkanen</sub> and PRS<sub>Tada</sub>; 28 and 50 variants, respectively) and two genome-wide PRSs (PRS<sub>metaGRS</sub> and PRS<sub>LDPred</sub>; 1.7M and 6.6M variants, respectively), were assessed from EA cohorts. The strength of associations of available PRSs with CHD in EA, AA, and HE adults was quantified by using a high-density genotype dataset linked to electronic health record data from the electronic health records and genomics (eMERGE) network. Within a median 11.1-year follow-up, 2,652 CHD incidents occurred. Hazard and odds ratios for the association of PRSs with CHD were similar in EA and HE groups, but lower in AA. Genome-wide PRSs exhibited a stronger association with CHD than restricted PRSs. PRS<sub>metaGRS</sub> performed the strongest in all three groups. Hazard ratios (95% CI) per 1 SD increase were 1.53(1.46-1.60), 1.53 (1.23-1.90), and 1.27 (1.13-1.43) for CHD incidents in EA, HE and AA persons, respectively. Hazard ratios were comparable in EA and HE cohorts ( $p_{\text{interaction}} = 0.77$ ), but lower in AA individuals ( $p_{\text{interaction}} = 2.9 \times 10^{-3}$ ). The authors replicated previous reports of PRS association with CHD in EA individuals which were similar to HE individuals, but the associations were significantly lower in AA individuals. The authors concluded that genome-wide PRSs were more strongly associated with CHD than restricted PRSs and PRS<sub>metaGRS</sub> had the strongest association with CHD in all three groups; however, the frequency of variants and the genetic architecture of the traits of interest in such groups limited the generalizability of PRS across ancestral and ethnic groups. The potential clinical utility of PRSs for CHD in the clinical setting was emphasized by the authors, however they explained that until ancestry and ethnic-specific PRSs become available, a genome-wide PRS could be adopted for use in AA individuals.

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.

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)

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.

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 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 coronary artery disease (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, 2018)

### ***Clinical Practice Guidelines***

#### **American College of Cardiology (ACC)**

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

#### **European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS)**

In an Expert Consensus Statement on genetic testing for cardiac disease, the EHRA, HRS, APHRS and LAHRS (Wilde et al., 2022) address the state of genetic testing for CAD. The major genes associated with prediction of CAD are APOB, LDLR and PCSK9. In recent decades, widespread contribution of polygenic risk has been shown to contribute to CAD susceptibility and novel genetic mechanisms such as clonal hematopoiesis of indeterminate potential (somatic rather than germline) have also been shown to play a role. Research has indicated that genetic predisposition may prove useful for risk prediction related to CAD, but the predictive utility of PRS for CAD are widely debated and as such, are not commonly used in clinical practice today.

## **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 March 22, 2022)

## **References**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2022T0552Q]

Abriel H, Zaklyazminskaya EV. Cardiac channelopathies: genetic and molecular mechanisms. *Gene*. 2013 Mar 15;517(1):1-11.

Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011 Aug;8(8):1308-39. Reaffirmed April 11, 2018.

Ackerman MJ, Marcou CA, Tester DJ. Personalized medicine: genetic diagnosis for inherited cardiomyopathies/channelopathies. *Rev Esp Cardiol*. 2013 Apr;66(4):298-307.

Adler A, Novelli V, Amin A, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital Long QT Syndrome. *Circulation*. 2020 Feb 11;141(6):418-428.

Albert CM, MacRae CA, Chasman DI, et al. Common variants in cardiac ion channel genes are associated with sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2010 Jun;3(3):222-9.

Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. *J Cardiovasc Electrophysiol*. 2008;19:104-10.

Alders M, Bikker H, Christiaans I. Long QT Syndrome. 2003 Feb 20 [Updated 2018 Feb 8]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1129/>. Accessed March 22, 2022.

Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, et al. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. *Genet Med* 2015;17:880–8.

Al-Khatib S, Stevenson W, Ackerman M, et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation* 2018 Oct 2;72(14):e91-e220.

American Heart Association. AHA Sets Genetic testing guidelines for cardiovascular disease. 2020 Jul. Available at: <https://www.modernhealthcare.com/patients/american-heart-association-sets-genetic-testing-guidelines-cardiovascular-disease>. Accessed March 22, 2022.

American Heart Association. Dilated cardiomyopathy (2016). Available at: <https://www.heart.org/en/health-topics/cardiomyopathy>. Accessed March 22, 2022.

Amin AS, Giudicessi JR, Tijssen AJ, et al. Variants in the 3' untranslated region of the KCNQ1-encoded Kv7.1 potassium channel modify disease severity in patients with type 1 long QT syndrome in an allele-specific manner. *Eur Heart J*. 2012 Mar;33(6):714-23.

Assimes TL, Roberts R. Genetics: implications for prevention and management of coronary artery disease. *J Am Coll Cardiol* 2016;68:2797–2818.

Begay RL, Graw S, Sinagra G, et al.; Familial Cardiomyopathy Registry. Role of titin missense variants in dilated cardiomyopathy. *J Am Heart Assoc*. 2015 Nov 13;4(11).

Behr ER, Savio-Galimberti E, Barc J, et al. Role of common and rare variants in SCN10A: results from the Brugada syndrome QRS locus gene discovery collaborative study. *Cardiovasc Res*. 2015 Jun 1;106(3):520-9. Erratum in: *Cardiovasc Res*. 2016 May 1;110(1):3.

Bennett, MT, Sanatani, S, Chakrabarti, et al. Assessment of genetic causes of cardiac arrest. *Can J Cardiol*. 2013 Jan;29(1):100-10.

Bezzina, CR, Barc, J, Mizusawa, Y, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat Genet*. 2013 Sep;45(9):1044-9.

Bos JM, Towbin JA, Ackerman MJ. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2009 Jul 14;54(3):201-11.

Bos JM, Will ML, Gersh BJ, et al. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2014 Jun;89(6):727-37.

Brugada R, Campuzano O, Sarquella-Brugada G, et al. Brugada Syndrome. 2005 Mar 31 [Updated 2016 Nov 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1517/>. Accessed March 22, 2022.

Campens L, Callewaert B, Muiño Mosquera L, et al. Gene panel sequencing in heritable thoracic aortic disorders and related entities - results of comprehensive testing in a cohort of 264 patients. *Orphanet J Rare Dis*. 2015 Feb 3;10:9.

Charron P, Carrier L, Dubourg O, et al. Penetrance of familial hypertrophic cardiomyopathy. *Genet Couns*. 1997;8(2):107-14.

Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. 2008 Aug 5 [Updated Jun 2019, revised Feb 2021]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1768/>. Accessed March 22, 2022.

Corrado D, Fontaine G, Marcus FI, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: need for an international registry. Study Group on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy of the Working Groups on Myocardial and Pericardial Disease and Arrhythmias of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the World Heart Federation. *Circulation*. 2000 Mar 21;101(11):E101-6.

Costa J, Lopes CM, Barsheshet A, et al. Combined assessment of sex- and mutation specific information for risk stratification in type 1 long QT syndrome. *Heart Rhythm*. 2012 Jun;9(6):892-8.

D'Argenio V, Frisso G, Precone V, et al. DNA sequence capture and next-generation sequencing for the molecular diagnosis of genetic cardiomyopathies. *J Mol Diagn*. 2014 Jan;16(1):32-44.

Deshpande SR, Herman HK, Quigley PC, et al. Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D): Review of 16 Pediatric Cases and a Proposal of Modified Pediatric Criteria. *Pediatr Cardiol*. 2016 Apr;37(4):646-55.

Dikilitas O, Schaid D, Kosel M, et al. Predictive utility of polygenic risk scores for coronary heart disease in three major racial and ethnic groups. *Am J Hum Gen*. 2020 May 7; 106(5):707-716.

Earle N, Yeo Han D, Pilbrow A, et al. Single nucleotide polymorphisms in arrhythmia genes modify the risk of cardiac events and sudden death in long QT syndrome. *Heart Rhythm*. 2014 Jan;11(1):76-82.

Elashoff MR, Wingrove JA, Beineke P, et al. Development of a blood-based gene expression algorithm for assessment of obstructive coronary artery disease in non-diabetic patients. *BMC Med Genomics*. 2011 Mar 28;4:26.

Ellepola CD, Knight LM, Fischbach P, Deshpande SR. Genetic testing in pediatric cardiomyopathy. *Pediatr Cardiol*. 2018 Mar;39(3):491-500.

Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet*. 2004 Jun 5;363(9424):1881-91.

Erdmann J, Daehmlow S, Wischke S, et al. Mutation spectrum in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy. *Clin Genet*. 2003 Oct;64(4):339-49.

Fananapazir L, Epstein ND. Genotype-phenotype correlations in hypertrophic cardiomyopathy. Insights provided by comparisons of kindreds with distinct and identical beta-myosin heavy chain gene mutations. *Circulation*. 1994 Jan;89(1):22-32.

Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011 Dec 13;124(24):2761-96.

Ghosh N, Haddad H. Recent progress in the genetics of cardiomyopathy and its role in the clinical evaluation of patients with cardiomyopathy. *Curr Opin Cardiol*. 2011 Mar;26(2):155-64.

Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol*. 2008 Jun 17;51(24):2291-300.

Gómez J, Reguero JR, Morís C, et al. Mutation analysis of the main hypertrophic cardiomyopathy genes using multiplex amplification and semiconductor next-generation sequencing. *Circ J*. 2014;78(12):2963-71.

Gray B, Semsarian C. Genetic testing for inherited cardiovascular disease: implications of the AHA scientific statement for cardiologists. *Heart, Lung and Circulation*. 2020 Nov;29(11):1581-1584.

Gruner C, Ivanov J, Care M, et al. Toronto hypertrophic cardiomyopathy genotype score for prediction of a positive genotype in hypertrophic cardiomyopathy. *Circ Cardiovasc Genet*. 2013 Feb;6(1):19-26.

Hathaway J, Helio K, Saarinen I, et al. Diagnostic yield of genetic testing in a heterogeneous cohort of 1376 HCM patients. *BMC Cardiovasc Disord*. 2021 Mar 5;21(1):126.

Hershberger RE, Givertz M, Ho CY, et al. Genetic Evaluation of Cardiomyopathy – a Heart Failure Society of America Practice Guideline. *J Card Fail*. 2018 May;24(5):281-302.

Hershberger RE, Givertz M, Ho C, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Gen Med*. 2018 Sep;20(9):899-909.

Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010 Apr 6;55(14):e27-e129. Erratum in: *J Am Coll Cardiol*. 2013 Sep 10;62(11):1039-40.

Hofman N, Tan HL, Alders M, et al. Active cascade screening in primary inherited arrhythmia syndromes: does it lead to prophylactic treatment? *J Am Coll Cardiol*. 2010 Jun 8;55(23):2570-6.

Hofman N, Wilde AA, Kaab S, et al. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? *Eur Heart J*. 2007 Mar;28(5):575-80.

Hu D, Barajas-Martinez H, Pfeiffer R, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. *J Am Coll Cardiol*. 2014 Jul 8;64(1):66-79.

Huang MH, Marcus FI. Idiopathic Brugada-type electrocardiographic pattern in an octogenarian. *J Electrocardiol*. 2004 Apr;37(2):109-11.

Ingles J, Sarina T, Yeates L, et al. Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy. *Genet Med*. 2013 Dec;15(12):972-7.



Iribarren C, Lu M, Jorgenson E, et al. Weighted multi-marker genetic risk scores for incident coronary heart disease among individuals of African, Latino and East-Asian Ancestry. *Sci Rep*. 2018 May 1;8(1):6853.

Iribarren C, Lu M, Jorgenson E, et al. Clinical utility of multimarker genetic risk scores for prediction of incident coronary heart disease: a cohort study among over 51 thousand individuals of European ancestry. *Circ Cardiovasc Genet*. 2016 Dec;9(6):531-540.

Jabbari J, Jabbari R, Nielsen MW, et al. New exome data question the pathogenicity of genetic variants previously associated with catecholaminergic polymorphic ventricular tachycardia. *Circ Cardiovasc Genet*. 2013 Oct;6(5):481-9.

January CT, Wann LS, Alpert JS, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014 Dec 2;64(21):e1-76. Erratum in: *J Am Coll Cardiol*. 2014 Dec 2;64(21):2305-7.

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019 Jul 9;74(1):104-132. Erratum in: *J Am Coll Cardiol*. 2019 Jul 30;74(4):599.

Karczewski KJ, Francioli LC, Tiao G, et al.; Genome Aggregation Database Consortium. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*. 2020 May;581(7809):434-443.

Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. *Nat Clin Pract Cardiovasc Med*. 2008 Mar;5(3):158-68. Erratum in: *Nat Clin Pract Cardiovasc Med*. 2008 Nov;5(11):747.

Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016 Dec 15;375(24):2349-2358.

Kolder IC, Tanck MW, Postema PG, et al. Analysis for genetic modifiers of disease severity in patients with long-QT syndrome type 2. *Circ Cardiovasc Genet*. 2015 Jun;8(3):447-456.

Lieve KV, Williams L, Daly A, et al. Results of genetic testing in 855 consecutive unrelated patients referred for long QT syndrome in a clinical laboratory. *Genet Test Mol Biomarkers*. 2013 Jul;17(7):553-61.

Loar RW, Bos JM, Will ML, et al. Genotype-phenotype correlations of hypertrophic cardiomyopathy when diagnosed in children, adolescents, and young adults. *Congenit Heart Dis*. 2015 Nov-Dec;10(6):529-36.

Ma M, Li Z, Mohamed MA, Liu L, Wei X. Aortic root aortopathy in bicuspid aortic valve associated with high genetic risk. *BMC Cardiovasc Disord*. 2021 Aug 30;21(1):413.

Manrai AK, Funke BH, Rehm HL, et al. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med*. 2016 Aug 18;375(7):655-65.

Marcus FI, McKenna WJ, Sherrill D et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Eur Heart J*. 2010 Apr;31(7):806-14.

Marian AJ. Genetic determinants of cardiac hypertrophy. *Curr Opin Cardiol*. 2008 May;23(3):199-205.

Maron BJ, McKenna WJ, Danielson GK, et al.; American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents; European Society of Cardiology Committee for Practice Guidelines. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *Eur Heart J*. 2003 Nov;24(21):1965-91.

Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *J Am Coll Cardiol*. 2012 Aug 21;60(8):705-15.

Marsiglia JD, Credidio FL, de Oliveira TG, et al. Clinical predictors of a positive genetic test in hypertrophic cardiomyopathy in the Brazilian population. *BMC Cardiovasc Disord*. 2014 Mar 13;14:36.

Mazzanti, A, Maragna, R, Faragli, A, et al. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. *J Am Coll Cardiol*. 2016 Mar 08;67(9):1053-8.

Mazzarotto F, Girolami F, Boschi B, et al. Defining the diagnostic effectiveness of genes for inclusion in panels: the experience of two decades of genetic testing for hypertrophic cardiomyopathy at a single center. *Gen Med*. 2019 Feb;21(2):284-292.

Mazzarotto F, Tayal U, et al. Reevaluating the genetic contribution of monogenic dilated cardiomyopathy. *Circulation*. 2020 Feb 4;141(5):387-398.

McKenna WJ, Spirito P, Desnos M, et al. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. *Heart*. 1997 Feb;77(2):130-2.

McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J*. 1994 Mar;71(3):215-8.

McNally E, MacLeod H, Dellefave-Castillo L. Arrhythmogenic Right Ventricular Cardiomyopathy. 2005 Apr 18 [Updated 2017 May 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1131/>. Accessed March 22, 2022.

McNally EM, Mestroni L. Dilated cardiomyopathy: genetic determinants and mechanisms. *Circ Res*. 2017 Sep 15;121(7):731-748.

MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2022 March 22]. Familial atrial fibrillation; [updated 2020 Aug 18; reviewed 2017 Oct 1]. Available at: <https://ghr.nlm.nih.gov/condition/familial-atrial-fibrillation>. Accessed March 22, 2022.

MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2022 March 22]. Familial dilated cardiomyopathy; [updated 2020 Aug 18; reviewed 2017 April 1]. Available at: <https://ghr.nlm.nih.gov/condition/familial-dilated-cardiomyopathy>. 2022. Accessed March 22, 2022.

Mestroni L, Taylor MR. Genetics and genetic testing of dilated cardiomyopathy: a new perspective. *Discov Med*. 2013 Jan;15(80):43-9.

Meune C, Van Berlo JH, Anselme F, et al. Primary prevention of sudden death in patients with lamin A/C gene mutations. *N Engl J Med*. 2006 Jan 12;354(2):209-10.

Michels M, Soliman OI, Phefferkorn J, et al. Disease penetrance and risk stratification for sudden cardiac death in asymptomatic hypertrophic cardiomyopathy mutation carriers. *Eur Heart J*. 2009 Nov;30(21):2593-8.

Migdalovich D, Moss AJ, Lopes CM, et al. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. *Heart Rhythm*. 2011 Oct;8(10):1537-43.

Milewicz DM, Regalado E. Heritable Thoracic Aortic Disease Overview. 2003 Feb 13 [Updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1120/>. Accessed March 22, 2022.

Millat G, Chanavat V, Rousson R. Evaluation of a new NGS method based on a custom AmpliSeq library and Ion Torrent PGM sequencing for the fast detection of genetic variations in cardiomyopathies. *Clin Chim Acta*. 2014 Jun 10;433:266-71.

Mital S, Musunuru K, Garg V, et al. American Heart Association Council on Functional Genomics and Translational Biology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Stroke Council; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. Enhancing literacy in cardiovascular genetics: a scientific statement from the American Heart Association. *Circulation: Cardiovascular Genetics*. 2016; 9: 448-467.

Modell SM, Bradley DJ, Lehmann MH. Genetic testing for long QT syndrome and the category of cardiac ion channelopathies. *PLoS Curr*. 2012 May 3:e4f9995f69e6c7.

Mook OR, Haagmans MA, Soucy JF, et al. Targeted sequence capture and GS-FLX Titanium sequencing of 23 hypertrophic and dilated cardiomyopathy genes: implementation into diagnostics. *J Med Genet*. 2013 Sep;50(9):614-26.

Moretti M, Merlo M, Barbati G, et al. Prognostic impact of familial screening in dilated cardiomyopathy. *Eur J Heart Fail*. 2010 Sep;12(9):922-7.

Mosley J, Gupta D, Tan J, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease *JAMA*. 2020 Feb 18;323(7):627-635.

Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation*. 2000 Feb 15;101(6):616-23.

Mullally J, Goldenberg I, Moss AJ, et al. Risk of life-threatening cardiac events among patients with long QT syndrome and multiple mutations. *Heart Rhythm*. 2013 Mar;10(3):378-82.

Murphy SL, Anderson JH, Kapplinger JD, et al. Evaluation of the Mayo Clinic phenotype-based genotype predictor score in patients with clinically diagnosed hypertrophic cardiomyopathy. *J Cardiovasc Transl Res*. 2016 Apr;9(2):153-61.

Musunuru K, Ingelsson E, Fornage M, et al.; American Heart Association Committee on Molecular Determinants of Cardiovascular Health of the Council on Functional Genomics and Translational Biology and Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology; and Stroke Council. The expressed genome in cardiovascular diseases and stroke: refinement, diagnosis, and prediction: a scientific statement from the American Heart Association. *Circ Cardiovasc Genet*. 2017 Aug;10(4). pii: e000037.

Musunuru K, Hershberger R, Day S, et al. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. *Circulation: Genomic and Precision Medicine*. 2020 Aug;13(4). Available at: <https://www.ahajournals.org/doi/10.1161/HCG.0000000000000067>. Accessed March 22, 2022.

Napolitano C, Priori SG, Bloise R. Catecholaminergic Polymorphic Ventricular Tachycardia. 2004 Oct 14 [Updated 2016 Oct 13]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*<sup>®</sup> [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1289/>. Accessed March 22, 2022.

Napolitano C, Bloise R, Memmi M, Priori SG. Clinical utility gene card for: Catecholaminergic polymorphic ventricular tachycardia (CPVT). *Eur J Hum Genet*. 2014 Jan;22(1).

National Cancer Institute. NCI Dictionary of Genetics Terms. Multigene Test. Available at: <https://www.cancer.gov/publications/dictionaries/genetics-dictionary>. Accessed March 22, 2022.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian and pancreatic. v1.2020.

Nielsen JC, Lin YJ, de Oliveira Figueiredo MJ, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. *Heart Rhythm*. 2020 Sep;17(9):e269-e316.

Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. *N Engl J Med*. 1998 Apr 30;338(18):1248-57.

Nomura A, Tada H, Teramoto R, et al. Whole exome sequencing combined with integrated variant annotation prediction identifies a causative myosin essential light chain variant in hypertrophic cardiomyopathy. *J Cardiol*. 2016 Feb;67(2):133-9.

Oliveira TG, Mitne-Neto M, Cerdeira LT, et al. A variant detection pipeline for inherited cardiomyopathy-associated genes using next-generation sequencing. *J Mol Diagn*. 2015 Jul;17(4):420-30.

Olivotto I, Girolami F, Ackerman MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2008 Jun;83(6):630-8.

Ommen S, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Am Coll Cardiol* 2020 Nov. Available at: <https://www.jacc.org/doi/10.1016>. Accessed March 22, 2022.

Overwater E, Marsili L, Baars MJH, et al. Results of next-generation sequencing gene panel diagnostics including copy-number variation analysis in 810 patients suspected of heritable thoracic aortic disorders. *Hum Mutat*. 2018 Sep;39(9):1173-1192.

Page SP, Kounas S, Syrris P, et al. Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. *Circ Cardiovasc Genet*. 2012 Apr 1;5(2):156-66.

Park JK, Martin LJ, Zhang X, et al. Genetic variants in SCN5A promoter are associated with arrhythmia phenotype severity in patients with heterozygous loss-of-function mutation. *Heart Rhythm*. 2012 Jul;9(7):1090-6.

Perrin MJ, Gollob MH. The genetics of cardiac disease associated with sudden cardiac death: a paper from the 2011 William Beaumont Hospital Symposium on molecular pathology. *J Mol Diagn*. 2012 Sep;14(5):424-36.

Peters S, Thompson BA, Perrin M, et al. Arrhythmic phenotypes are a defining feature of dilated cardiomyopathy-associated SCN5A variants: a systematic review. *Circ Genom Precis Med*. 2022 Feb;15(1):e003432.

Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315–2381.

Pinto YM, Wilde AA, van Rijsingen IA, et al. Clinical utility gene card for: hypertrophic cardiomyopathy (type 1-14). *Eur J Hum Genet*. 2011 Aug;19(8).

Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA*. 2004 Sep 15;292(11):1341-4.

Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003 May 8;348(19):1866-74.

Ramaraj R. Hypertrophic cardiomyopathy: etiology, diagnosis, and treatment. *Cardiol Rev*. 2008 Jul-Aug;16(4):172-80.

Refsgaard L, Holst AG, Sadjadieh G, et al. High prevalence of genetic variants previously associated with LQT syndrome in new exome data. *Eur J Hum Genet*. 2012 Aug;20(8):905-8.

Restrepo-Cordoba MA, Campuzano O, Ripoll-Vera T, et al. Usefulness of genetic testing in hypertrophic cardiomyopathy: an analysis using real-world data. *J Cardiovasc Transl Res*. 2019 Aug;12(4):389-390.

Rangaraju A and Dalal A. Scope of genetic testing for inherited cardiovascular diseases in the clinical practice. *J Indian College Cardiol*. 2021. Available at: <https://www.joicc.org>. Accessed March 22, 2022.

Renard M, Francis C, Ghosh R, et al. Clinical validity of genes for heritable thoracic aortic aneurysm and dissection. *J Am Coll Cardiol*. 2018 Aug 7;72(6):605-615.

Richard P, Charron P, Carrier L, et al.; EUROGENE Heart Failure Project. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation*. 2003 May 6;107(17):2227-32.

Roberts R, Sigwart U. Current concepts of the pathogenesis and treatment of hypertrophic cardiomyopathy. *Circulation*. 2005 Jul 12;112(2):293-6.

Roncarati R, Viviani Anselmi C, Krawitz P, et al. Doubly heterozygous LMNA and TTN mutations revealed by exome sequencing in a severe form of dilated cardiomyopathy. *Eur J Hum Genet*. 2013 Oct;21(10):1105-11.

Roselli C, Chaffin MD, Weng LC, et al. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet*. 2018 Sep;50(9):1225-1233.

Rubattu S, Bozzao C, Pennacchini E, et al. A next-generation sequencing approach to identify gene mutations in early- and late-onset hypertrophic cardiomyopathy patients of an Italian cohort. *Int J Mol Sci*. 2016 Jul 30;17(8).

Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation*. 2011 Nov 15;124(20):2181-4.

Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*. 2001 Jan 2;103(1):89-95.

Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the management of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2007 Nov 6;50(19):1813-21.

Sun L, Pennells L, Kaptoge S, et al. Polygenic risk scores in cardiovascular risk prediction: a cohort study and modelling analysis. *PLoS Med*. 2021 Jan; 18(1):e1003498.

Te Riele AS, James CA, Groeneweg JA, et al. Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Eur Heart J*. 2016 Mar 1;37(9):755-63.

Teekakirikul P, Kelly MA, Rehm HL, et al. Inherited cardiomyopathies: molecular genetics and clinical genetic testing in the postgenomic era. *J Mol Diagn*. 2013 Mar;15(2):158-70.

Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. *Circulation*. 2011 Mar 8;123(9):1021-37.

Tester DJ, Will ML, Haglund CM, Ackerman MJ. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol*. 2006 Feb 21;47(4):764-8.

U.S. Preventive Services Task Force (USPSTF). Cardiovascular disease: risk assessment with nontraditional risk factors. July 2018.

Van Driest SL, Ellsworth EG, Ommen SR, et al. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. *Circulation*. 2003 Jul 29;108(4):445-51.

Van Lint F, Mook M, Alders R, et al. Large next-generation sequencing gene panels in genetic heart disease: yield of pathogenic variants and variants of unknown significance. *Neth Heart J*. 2019 Jun;27(6):304-309.

Walsh R, Adler A, Amin AS, et al. Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. *Eur Heart J*. 2021 Sep 24;ehab687. Epub ahead of print.

Walsh R, Rutland C, Thomas R, Loughna S. Cardiomyopathy: a systematic review of disease-causing mutations in myosin heavy chain 7 and their phenotypic manifestations. *Cardiology*. 2010;115(1):49-60.

Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med*. 1995 Apr 20;332(16):1058-64.

Wilde AAM, Semsarian C, Márquez MF, et al.; Document Reviewers. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *Heart Rhythm*. 2022 Apr 1:S1547-5271(22)01697-6. Epub ahead of print.

Wingrove JA, Daniels SE, Sehnert AJ, et al. Correlation of peripheral-blood gene expression with the extent of coronary artery stenosis. *Circ Cardiovasc Genet*. 2008 Oct;1(1):31-8.

Yamagata K, Horie M, Aiba T, et al. Genotype-phenotype correlation of SCN5A mutation for the clinical and electrocardiographic characteristics of probands with Brugada syndrome: a Japanese multicenter registry. *Circulation*. 2017 Jun 6;135(23):2255-2270.

Yang H, Luo M, Fu Y, et al. Genetic testing of 248 Chinese aortopathy patients using a panel assay. *Sci Rep*. 2016 Sep 9;6:33002.

Yoneda ZT, Anderson KC, Quintana JA, et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol*. 2021 Dec 1;6(12):1371-1379.

Zareba W, Moss AJ, Daubert JP, et al. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol*. 2003 Apr;14(4):337-41.

Zou Y, Wang J, Liu X, et al. Multiple gene mutations, not the type of mutation, are the modifier of left ventricle hypertrophy in patients with hypertrophic cardiomyopathy. *Mol Biol Rep*. 2013 Jun;40(6):3969-76.

## Policy History/Revision Information

Date	Summary of Changes
01/01/2023	<b>Documentation Requirements</b> <ul style="list-style-type: none"><li>Added list of applicable CPT codes</li></ul> <b>Supporting Information</b> <ul style="list-style-type: none"><li>Removed <i>Prior Authorization Requirements</i> section</li><li>Archived previous policy version LABORATORY 015.19 T2</li></ul>

## Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual<sup>®</sup> criteria, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.