

Genetic Testing for Cardiac Disease

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Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Pre-test genetic counseling is strongly recommended in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

Inherited Arrhythmias

Multi-Gene Panel testing for the diagnosis of a hereditary arrhythmia syndrome is proven and medically necessary in individuals with a confirmed or suspected diagnosis of any of the following conditions:

- Brugada syndrome (BrS); or
- Catecholaminergic polymorphic ventricular tachycardia (CPVT); or
- Familial long QT syndrome (LQTS) when acquired causes have been ruled out and one of the following criteria are met:
 - Prolonged QTc (> 460ms) on exercise or ambulatory electrocardiogram (ECG), Holter monitoring, or during pharmacologic provocation testing; or

- T wave abnormalities on ECG suggestive of LQTS (i.e., Torsade de pointes, T wave alternans, or notched T wave in 3 leads); or
- Profound congenital bilateral sensorineural hearing loss and prolonged QTc; or
- [Schwartz Score](#) ≥ 1.5 points
- or
- Short QT syndrome (SQTS)

Inherited Cardiomyopathies

Multi-Gene Panel testing for the diagnosis of a hereditary cardiomyopathy is proven and medically necessary in individuals with a confirmed or suspected diagnosis of any of the following conditions:

- Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C); 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
 or
- Hypertrophic cardiomyopathy (HCM) without an identifiable cause (e.g., valvular disease, hypertension, infiltrative or neuromuscular disorder); or
- Left ventricular noncompaction cardiomyopathy (LVNC)

Inherited Thoracic Aortic Disease

Multi-Gene Panel testing is proven and medically necessary for either of the following:

- Individual has confirmed thoracic aortic disease; or
- Thoracic aortic disease is suspected based on family history of thoracic aortic disease in a First- or Second-Degree Relative

Testing Based Only On Family History

Multi-Gene Panel testing for the diagnosis of inherited arrhythmic disorders or cardiomyopathy is proven and medically necessary in asymptomatic individuals who have a First-Degree or Second-Degree 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
- Left ventricular noncompaction cardiomyopathy (LVNC); or
- Short QT syndrome (SQTS); or
- A First-Degree Relative experienced sudden cardiac death or near sudden death at age 45 or younger

All other genetic testing for cardiomyopathies, arrhythmias, or aortic vascular disease is unproven and not medically necessary due to insufficient evidence of efficacy. (This does not apply to chromosome microarray analysis for isolated severe congenital heart disease.)

Genetic testing for coronary artery disease (CAD) is unproven and not medically necessary due to insufficient evidence of efficacy. This includes but is not limited to the following tests:

- Gene expression tests
- Microarray or other genetic profiles for cardiac disease risk (e.g., Cardiac DNA Insight®, Cardiac Healthy Weight DNA Insight®, Cardio IQ® gene tests and panels)

Medical Records Documentation Used for Reviews

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. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled [Medical Records Documentation Used for Reviews](#).

Definitions

First-Degree Relative: First-Degree Relatives include parents, siblings, and offspring [National Comprehensive Cancer Network, (NCCN), 2025].

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, 2025).

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. (Schwartz and Crotti, 2011).

Schwartz Score Calculation		
EKG ¹		Points
QTc ²	≥ 480 ms	3
	460 to 479 ms	2
	450 to 459 ms (in males)	1
QTc fourth minute of recovery from exercise stress test ≥ 480 ms		1
Torsades de pointes ³		2
T wave alternans		1
Notched T wave in 3 leads		1
Low heart rate for age ⁴		0.5
Clinical History		Points
Syncope ³	With stress	2
	Without stress	1
Congenital deafness		0.5
Family History		Points
Family members with definite LQTS ⁵		1.0
Unexplained sudden cardiac death < 30 years in immediate family ⁵		0.5
Total Score		

Scoring: ≤ 1.0 point = low probability of LQTS; 1.5-3.0 points = intermediate probability of LQTS; ≥ 3.5 points = high probability of LQTS:

1. In the absence of medications or disorders known to affect these electrocardiographic features.
2. QTc calculated by Bazett's formula where $QTc = QT/\sqrt{RR}$.
3. Mutually exclusive.
4. Resting heart rate < 2nd percentile for age.
5. The same family member cannot be counted for both criteria.

Second-Degree Relative: Second-Degree Relatives include half-brothers/sisters, aunts/uncles, grandparents, grandchildren, and nieces/nephews affected on the same side of the family (NCCN, 2025).

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 and Guidelines 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
0401U	Cardiology (coronary heart disease [CHD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event
0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD
0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1], cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD
0466U	Cardiology (coronary artery disease [CAD]), DNA, genome-wide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease
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, TGFB1, TGFB2, 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 TGFB1, TGFB2, MYH11, and COL3A1
81413	Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
81439	Hereditary cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)
81479	Unlisted molecular pathology procedure
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score

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Description of Services

Technologies used for genetic testing of cardiac syndromes and coronary artery disease can vary. Tests can include, but are not limited to, those that evaluate variations in genes, such as chromosome microarray analysis (CMA) and next generation sequencing (NGS), as well as others that assess 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 determination of a diagnosis, prognosis, and identification of appropriate clinical interventions (Jabbari et al., 2013; Millat et al., 2014; Ladapo et al., 2017; Seidelmann 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

Clinical Evidence

Arrhythmias

d'Apolito et al. (2025) investigated the genetic variants and clinical phenotypes of an Italian cohort diagnosed with heritable arrhythmia syndromes and arrhythmogenic cardiomyopathy (ACM) using whole-exome sequencing (WES). The study comprised 62 individuals with confirmed diagnoses of various inherited arrhythmia syndromes including Brugada syndrome (BrS) (n = 48, 77%), long QT syndrome (LQTS) (n = 7, 11%), arrhythmogenic dilated cardiomyopathy (AR-DCM) (n = 4, 6.5%), arrhythmogenic right ventricular dysplasia (ARVD) (n = 2, 3%), and short QT syndrome (SQTS) (n = 1, 1.6%). The researchers identified a total of 22 variants in 15 genes associated with BrS in 21 participants (34%); the *SCN5A* gene had the highest number of variants, (6, 27%), followed by *KCNJ5* and *CASQ2*, each with 2 variants. The remaining genes each had a single variant. There were no gene variants detected in 27/48 individuals clinically diagnosed with BrS. In individuals confirmed to have LQTS and SQTS, a total of 10 variants in nine genes were identified. Of the participants with ARVD and AR-DCM, six variants in five genes were detected. The variants identified in this cohort were classified as pathogenic (P) (n = 6), likely pathogenic (LP) (n = 3), of uncertain significance (n = 26 variants), and benign (n = 1). An additional two gene variants were classified as risk factors. The authors indicate that this study identified 13 novel genetic variations associated with inherited arrhythmogenic cardiomyopathies and confirmed that individuals with arrhythmias may harbor multiple rare gene variations. The authors further highlight the discovery of new gene-phenotype associations. They propose that using WES may positively impact the molecular diagnosis of cardiomyopathies and allow for earlier detection of individuals at risk for arrhythmia. The study was limited by its small sample size and the high volume of participants with BrS. Further study focused on the clinical utility of WES for use in this population is needed.

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 QT interval prolongation on an electrocardiogram (ECG) and screening is generally performed by electrocardiography. Clinical features and family history may also be helpful in 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 (Groffen et al., 2024). 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 (Groffen et al., 2024).

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 2,500 people (Ackerman et al., 2011). The autosomal dominant Romano-Ward syndrome is the most common; with a prevalence of 1 in 3,000 to 1 in 5,000. Jervell and Lange-Nielsen syndrome is a rare recessive form that is associated with congenital deafness, early clinical manifestations, and 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 were reported. In a sample of 5400 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 (Groffen et al., 2024).

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 1970 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 subjects, respectively. The arrhythmia panel revealed variants in 44% of subjects overall, while the cardiomyopathy panels revealed variants in 61%. The authors concluded that “larger gene panels can increase the detection rate of LP and p variants but may increase the frequency of variants of unknown significance.”

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 percentage of individuals with a clinical diagnosis of LQTS that were found to have a genetic variant. Clinical phenotyping was completed on 541 individuals referred for evaluation of LQTS and 123 (22.7%) of those had “definite” LQTS defined by clinical criteria. Of the 541 participants, 274 (50.6%) were found to have an LQTS-associated genetic variant and of the 123 clinically diagnosed with LQTS, 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 participants. Using NGS, the authors determined that 259 individuals had one mutation and 18 individuals had two mutations. In comparison with clinical signs, genetic testing had a sensitivity of 72% and a specificity of 49%.

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 7,000 and 1 in 10,000 people (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 individuals 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., 2022; 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 implantable cardioverter-defibrillator (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.

The autosomal dominant pattern of CPVT is associated with variants in *RYR2*, *CALM1*, *CALM2*, *CALM3* or *KCNJ2*. Variants in *CASQ2*, *TECRL* and *TRDN* are associated with autosomal recessive inheritance. (Napolitano et al., 2022). The majority of cases are represented by *RYR2* variants and most of these (90%) are missense mutations (Ackerman et al., 2013). *CASQ2* accounts for approximately 5% and *TRDN* accounts for less than 1% percent of cases. *RYR2* variants have a penetrance of approximately 83%. Approximately 25% of individuals with CPVT have no p variant identified in any of the known genes mentioned above (Napolitano et al., 2022).

Walsh et al. (2022) 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 clinical care and assert that both genetic and phenotypic data should be subject to careful assessment when exploring any new genetic causes related to CPVT.

In a Clinical Utility Evaluation, Hayes indicated that evidence demonstrating improved health outcomes for individuals who had undergone genetic testing after clinical diagnosis of CPVT was insufficient and recommended additional investigation (Hayes 2018a, updated 2022). For family members of individuals with CPVT, Hayes found probable clinical utility, stating that genetic testing for CPVT can lead to preventative treatment and activity restrictions when family members test positive. The Hayes report also states that genetic testing is most helpful when the familial variant is identified in a clinically diagnosed individual (Hayes 2018b, updated 2022).

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 phenotypes in ventricular tachycardia syndromes affects the estimated clinical validity and yield of this multi-gene panel. Thus, the specificity of CPVT known p variants is not certain. A study by the National Heart, Lung and Blood Institute ESP described sequence variations in 6503 individuals without a diagnosis of CPVT (Jabbari et al., 2013). Exome data were reviewed to identify missense variations that were 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.

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).

A Hayes Clinical Utility Evaluation suggests insufficient evidence exists to support the use of genetic testing for individuals who have been clinically diagnosed with BrS, as no existing studies were found that would indicate improved health outcomes for the affected individual related to such testing (Hayes 2018c, updated 2022). Limited evidence supported the use of genetic testing in family members of individuals with BrS (Hayes 2018d, updated 2022).

A Japanese registry trial studied the *SCN5A* variant genotype/phenotype with symptoms of BrS (Yamagata et al., 2017). The researchers studied 415 participants 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* p 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 individuals 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 subjects (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 *the*

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. 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. (2022) conducted an evidence-based reappraisal of genes that have been reported to cause CPVT and SQTS. Results related to CPVT are discussed in the 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 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 the 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, 2017a). 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, LP or P. The study defined disease-associated variants as p or LP 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) collaborated 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)/American College of Clinical Pharmacy (ACCP)/Heart Rhythm Society (HRS)

ACC/AHA/ACCP/HRS guidelines for the diagnosis and management of AF (Joglar et al. 2023) indicate that for patients who develop AF before the age of 45 without clear risk factors, it may be reasonable to consider genetic counseling, genetic testing for rare p variants (most commonly *TTN*, *MYH7*, *MYH6*, *LMNA*, and *KCNQ1*), and monitoring for cardiomyopathy or arrhythmia syndromes. The effectiveness and relevance of consumer-based or targeted genetic testing for AF are still unclear. Polygenic risk scores (PRS) have also been suggested for use; while PRS can suggest a higher likelihood of AF, the role of genetic testing in influencing clinical surveillance, management, and outcomes remains uncertain.

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

- The availability of genetic testing for inherited arrhythmia syndromes can provide an 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
 - *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 > 3.5b), 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 p variants in the *KCNJ2*, *SCN5A*, and *PKP2* genes.
- In patients with a modest phenotype for CPVT (i.e., CPVT diagnostic score > or = 2 but < 3.5b), 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 P/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 $< 1 \times 10^{-5}$ 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 $> \text{or} = 4$).
- 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, 2021). Clinical diagnosis can be made when an individual demonstrates 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, 2021). 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, 2021). 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 individuals with HCM is estimated to be 1% per year in the adult population (Marian, 2008; Roberts and Sigwart, 2005).

Symptoms range from asymptomatic cardiomyopathy to heart failure to SCD (Bos et al., 2009; Cirino and Ho, 2021). 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 individuals with HCM are asymptomatic or have few symptoms. However, some individuals have significant symptoms that may lead to heart failure or SCD (Maron et al., 2003). Management includes treating any cardiac comorbidities, avoiding therapies that may worsen obstructive symptoms and treating symptoms with medications and surgery.

Topriceanu et al. (2024) performed meta-analyses on studies addressing the prevalence and penetrance of sarcomeric P/LP genetic variations and compared findings from family- and clinically-based studies with findings reported in general population studies that had genetic and cardiac imaging data available. In addition, meta-analyses were also conducted for longitudinal studies that followed up on carriers of genetic variants, with a goal of summarizing the current knowledge base regarding the transition from subclinical to clinically diagnosed HCM. The researchers first conducted a systematic search of the literature to identify applicable studies; a total of 455 full-text publications were identified and assessed. In the family/clinical studies, the prevalence of sarcomere variants in individuals diagnosed with HCM was 34%. Across all genes in non-proband relatives carrying P/LP variations (identified via cascade screening), the penetrance was 57% [95%, confidence interval (CI), 52%–63%]. The mean age of HCM diagnosis in this group was 38 years, and there was variation in penetrance from approximately 32% for myosin light chain 3 (*MYL3*) to approximately 55% for myosin binding protein C3 (*MYBPC3*), approximately 60% for troponin T2 (*TNNT2*) and troponin I3 (*TNNI3*), and approximately 65% for myosin heavy chain 7 (*MYH7*). Results from population-based genetic studies revealed that variants in P/LP sarcomeres do exist in the background population but the prevalence in this population is very low (< 1%). With respect to the presence of HCM in P/LP variation carriers that were incidentally identified, prevalence is again lower ranging from approximately 0% to 18% dependent on the study population. Pooled phenotypic conversion across all genes was found to be 15% over approximately eight years of follow up, but notably, short term phenotypic conversion specific to *MYBPC3* and *MYH7* varied between approximately 12% and 23%, respectively. After the analyses, the authors concluded that the included studies revealed that the likelihood of developing clinically diagnosed HCM is significantly higher in HCM cohorts and their families than in the general population. They found that the penetrance of L/LP variants was highly varied and impacted by both genetic and environmental factors that are yet to be determined. Additional high-quality longitudinal studies are needed to better define factors which influence the shift from subclinical disease to clear HCM and enhance understanding of the pathogenesis of this disease.

A study by Neilsen et al. (2023) evaluated disease expression and penetrance of relatives of individuals carrying P/LP variants in known HCM genes. This multicenter longitudinal cohort study included 453 unrelated index individuals with HCM who received both clinical and genetic analysis. In addition, 757 relatives of index individuals found to have gene-positive results were incorporated into the study; these participants also underwent clinical and genetic evaluation. Factors including penetrance, expression of disease and the incidence rate of major adverse cardiac events (MACEs) were examined for all individuals found to be carriers of P/LP variants. Of the 453 index individuals with HCM, 183 (40%) were found to carry a P/LP variant. Fifty-four percent (407/757) of relatives of index individuals with P/LP variants also carried a P/LP variant. Among these relatives, the penetrance of HCM was 39% (160/407). Age at diagnosis was similar between the index individuals and the relatives with HCM (43 +/- 18 years vs 46 +/- 15 years; $p = 0.11$). No significant differences in clinical presentation or incidence rates of MACE were identified during eight years of follow up. The study was limited by its inclusion of only tertiary referral hospitals (including one transplant center) which could bias the results toward more severely impacted individuals/families with HCM. In addition, carriers that were healthy were typically younger than their affected relatives, potentially leading to underestimation of age-dependent penetrance. Lastly, 16% of invited relatives declined participation, which could have led to selection bias toward relatives that were more symptomatic. Despite these limitations, the authors infer from their results that the expression of HCM among index individuals and their affected relatives carrying known HCM P/LP variants is comparable and has similar risk of MACEs. As such, they endorse family screening and associated follow up for genotype-positive family members to ultimately reduce potential complications and improve overall disease management.

In a 2022 systematic review and meta-analysis, Cirino et al. summarized data regarding the use of genetic counseling and testing for individuals with HCM and their at-risk family members and the impact of counseling and testing on patient reported outcomes (PROs). A total of 48 studies (47 observational, 1 randomized) were included. The uptake of genetic testing in probands was 57% (95% CI, 40, 73) and the uptake of cascade testing for family members with risk was 61% (95% CI: 45, 75) for genetic testing, 58% for cardiac screening (e.g., echocardiography) (95% CI: 40, 73), and 69% for /both approaches (95% CI: 43, 87). Family members of probands with positive results were substantially more likely to proceed with cascade screening in comparison to family members of probands whose results were negative (odds ratio = 3.17, 95% CI: 2.12, 4.76). The range of uptake of genetic counseling for both probands and their family members ranged

from 37% to 84%. Several studies found the difference in PROs between those individuals receiving positive versus negative results was minimal, but some studies showed worse psychological outcomes in participants that had positive test results. Genetic counseling was related to high levels of satisfaction, an increase in perceived personal control and sense of empowerment and a decrease in anxiety. The authors concluded that PROs after genetic testing varied, but genetic counseling showed an association with high satisfaction and increased PROs. They encourage study around the decision-making process for probands, new methods for promotion of cascade screening, factors impacting psychological outcomes after genetic testing and counseling and collaboration among cardiovascular genetic teams to ensure systematic assembly of outcomes with consistent variable definition and standardized reporting.

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 p variants and variant classification method. The review found significantly higher detection rate of p 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. Key areas for further study include expansion of genotype-phenotype associations and disease penetration estimates across varying populations. Publications by 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 those individuals who had testing performed by Blueprint Genetics. Variants categorized as P/LP were determined to be diagnostic. 369/1376 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 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. Multiple genes and individual mutations have been identified as genetic components of HCM (Maron et al., 2012; Cirino and Ho, 2021; Ghosh and Haddad, 2011). p 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 individuals with clinical HCM, a genetic abnormality can be identified (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 more information to the literature 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 subjects (77%). Of the 23 individuals 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, 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 WES for HCM genes (Nomura et al.). 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 p 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 NGS in 136 individuals 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 participants, 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 individuals with HCM.

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

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, an individual will present with 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. These 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).

Bariani et al. (2022) published findings from a systematic review evaluating the understanding of the genetic background and clinical features of ALVC. Overall, 31 studies were included in the review. The DSP gene had the highest representation in the literature and was the gene in focus for about half of the published studies. FLNC had the second-highest representation in the literature. Abnormalities in ECG results was reported in 58% of individuals. In 26% of included cases, major ventricular arrhythmias were found and an ICD was implanted in 29%. Heart failure symptoms were seen in 6% of individuals and 15% of the individuals had myocarditis-like episodes. In addition, assessment of the reported clinical features of individuals with ALVC indicated electrical instability that often led to implantation of an ICD.

Deshpande et al. (2016) reviewed 16 pediatric cases of ARVC/D that were diagnosed through modified diagnostic criteria, genetic testing, and pathology. Only two of the children had a previously described gene mutation, and another had a novel mutation. For pediatric cases, the authors note that pathology and clinical findings alone may be sufficient for diagnosis.

A study by te 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 ARVC/D 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 regarding the role of genetics in ARVC/D, 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, 2017b). 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 an effort to ascertain the prevalence of genetic-associated DCM in the overall DCM population, Myers et al. (2024) performed a systematic review and meta-analysis of the currently published literature addressing the prevalence of genetic DCM in various populations. Focus was placed on the *TTN* gene and the *MYH7* gene, as variants in these genes account for the largest proportion of contributing genetic factors in DCM. A total of 57 studies met inclusion criteria and were included in the evaluation. In the global adult or mixed (predominantly adult) DCM population, the median disease prevalence for overall genetic DCM was 20.2%. For *TTN*-associated DCM, prevalence was 11.4% and for *MYH7*-associated DCM, prevalence was 3.2%. The overall prevalence of pediatric genetic DCM within the greater DCM population was comparable (weighted mean of 21.3%). The authors note that data on prevalence of genetic DCM in the general population has been rarely reported. They concluded that based on their findings, current evidence may be underestimating the impact of genetics on DCM related to limited screening and discovery of individuals who may have DCM. Further epidemiological studies and large-population studies using whole genome sequencing to detect structural/non-coding variations are recommended.

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 subjects 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 individuals with DCM.

Rangaraju and Dalal (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, included in the 2023 Myers publication discussed above) studied the largest genetically characterized cohort of individuals with DCM to-date to determine the frequency of rare variation in 2538 individuals with DCM 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 subsets; *TPM1* and *VCL* contributed primarily to early-onset forms of DCM. The authors stated that the 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 individuals with a pathogenic mutation; however, close monitoring would be appropriate. In individuals 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 individuals with familial DCM when there is a specific mutation to be tested.

Left Ventricular Noncompaction (LVNC)

Left ventricular noncompaction (LVNC) is a heart (cardiac) muscle disorder that occurs when the lower left chamber of the heart (left ventricle), which helps the heart pump blood, does not develop correctly. Instead of the muscle being smooth and firm, the cardiac muscle in the left ventricle is thick and appears spongy. Some individuals with LVNC experience no symptoms at all; others have heart problems that can include sudden cardiac death. Some affected individuals have features of other heart defects. LVNC can be diagnosed at any age, from birth to late adulthood. Approximately two-thirds of individuals with LVNC develop heart failure. Variants in the *MYH7* and *MYBPC3* genes have been estimated to cause up to 30 percent of cases; variants in other genes are each responsible for a small percentage of cases. (MedlinePlus, 2020). *MYH7* and *ACTC1* variants have been shown to have a lower risk of major adverse cardiac events than *MYBPC3* and *TTN* in adults. Genetic diagnosis may help predict the outcome of LVNC (van Waning 2018, 2019).

In a systematic review, van Waning et al. (2019) evaluated genotype-phenotype correlations in noncompaction cardiomyopathy (NCCM) from 172 published studies. NCCM is a rare genetic cardiomyopathy with clinical features ranging from asymptomatic cardiomyopathy to heart failure with major adverse cardiac events (MACE). The researchers compared age at diagnosis, cardiac characteristics, and risk for MACE in relation to mode of inheritance and molecular effects for defects in common sarcomere genes and NCCM subtypes. A total of 561 participants including 244 children and 297 adults were incorporated into the analysis. The main findings in adults were single missense mutations in sarcomere genes, whereas children more frequently had x-linked or mitochondrial inherited defects ($p = 0.001$) or chromosomal abnormalities ($p < 0.001$). Children had an increased risk of congenital heart defects ($p < 0.001$) and MACE ($p < 0.001$). Forty-eight percent of the sarcomere gene variations involved *MYH7*. *MYH7* and *ACTC1* mutations had lower risk for MACE than *MYBPC3* and *TTN* ($p = 0.001$). The NCCM/dilated cardiomyopathy cardiac phenotype was the most common subtype (56%; $p = 0.022$), and was associated with an elevated risk for MACE as well as high risk for left ventricular systolic dysfunction (< 0.001). In multivariate binary logistic regression analysis *MYBPC3*, *TTN*, arrhythmia, non-sarcomere non-arrhythmia cardiomyopathy, and X-linked genes were genetic predictors for MACE. The study was limited by the inclusion of mostly case reports or small case series and the study design did not allow identification of the differences in prognosis between identified genetic and other causes of NCCM. The authors concluded that based on their results, the most common cause of genetic NCCM are sarcomere gene mutations, which occurred primarily in adults and were associated with a lower risk of adverse effects. More severe effects were seen with rare x-linked and chromosome defects in children. Thus, the authors propose that clinical and diagnostic management should be modified according to age at presentation and assert that identifying the genetic cause of NCCM could aid in the management of individuals with NCCM and their families.

Van Waning et al. (2018) conducted a retrospective multicenter study to evaluate the role of genetics in NCCM. The focus of this study was to investigate the relationship between clinical and cardiologic features at diagnosis, the risk of LV systolic dysfunction, and the occurrence of MACE in both children and adults. The study included a total of 327 participants with a diagnosis of NCCM. *MYH7*, *MYBPC3*, and *TTN* mutations were the most common mutations (71%) found in genetic NCCM. The risk of having reduced left ventricular systolic dysfunction was higher for individuals with

NCCM categorized as genetic compared with individuals categorized as having a probable genetic cause or sporadic cases ($p = 0.024$), with the highest risk in participants found to have multiple mutations and *TTN* mutations. Mutations were more frequent in children ($p = 0.04$) and were associated with MACE ($p = 0.025$), while adults were more likely to have sporadic NCCM. High risk for cardiac events in children and adults was related to left ventricular systolic dysfunction in individuals with genetic mutations, but not in sporadic cases. Individuals with *MYH7* mutations had low risk for MACE ($p = 0.03$). While there were study limitations, the authors note that genetics can play a role in management and prediction of outcomes in individuals with NCCM.

Clinical Practice Guidelines

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

In 2024, updated guidelines addressing the management of HCM were published by the AHA/ACC in collaboration with the American Medical Society for Sports Medicine (AMSSM), the Heart Rhythm Society (HRS), the Pediatric and Congenital Electrophysiology Society (PACES), and the Society for Cardiovascular Magnetic Resonance (SCMR) (Ommen et al.) The guidelines were developed through a comprehensive evaluation of applicable literature published through May 23, 2023, by the writing committee. With regard to genetic testing of affected individuals and screening of family members, the following recommendations were made:

- Evaluation of familial inheritance including a three-generation family history is recommended for individuals with HCM as part of the initial assessment. [Class of Recommendation (COR) 1/Strong, Level of Evidence (LOE) B-NR (moderate quality evidence from one or more well-executed studies including nonrandomized, observational or registry as well as meta-analyses of such studies)].
- Genetic testing of individuals with HCM is helpful to determine whether there is a genetic basis for disease and thereby aid in the identification of family members who may be at risk, for developing HCM (cascade testing). (COR 1/Strong, LOE B-NR).
- When HCM presents atypically or when another genetic condition is suspected, work-up including genetic testing for HCM along with other causes of unexplained cardiac hypertrophy is recommended. (COR 1/Strong, LOE B-NR).
- Genetic counseling by qualified experts is recommended for all individuals with HCM to discuss risks, benefits, tests results and the clinical significance of those results in a shared decision-making process. (COR 1/Strong, LOE B-NR).
- When genetic testing is performed in a proband with HCM, the initial genes testing should include those with strong evidence associated with HCM disease (at the time of publication, these include *MYH7*, *MYBPC3*, *TNNI3*, *TNNT2*, *TPM1*, *MYL2*, *MYL3*, and *ACTC1*). (COR 1/Strong, LOE B-NR).
- Both clinical screening as well as cascade testing should be offered to relatives of individuals with HCM when a P/LP variant has been identified in the proband. (COR 1/Strong, LOE B-NR).
- When sudden unexplained death has occurred with a postmortem diagnosis of HCM, postmortem genetic testing is helpful to assist with cascade testing as well as clinical screening in first degree relatives. (COR 1/Strong, LOE B-NR).
- In individuals with HCM who have undergone genetic testing, serial testing of the clinical significance of the variants is recommended to evaluate for variant reclassification that could impact diagnosis and familial cascade testing. (COR 1/Strong, LOE B-NR).
- Preconception and prenatal reproductive and genetic counseling should be offered in families affected by HCM. (COR 1/Strong, LOE B-NR).
- The utility of genetic testing for the purpose of assessing risk of SCD in individuals with HCM is uncertain (COR 2b/Weak, LOE B-NR).
- The utility of genetic testing for the purposes of variant reclassification performed on phenotype-negative family members of individuals with HCM who were found to have only VUS is uncertain (COR 2b/Weak, LOE B-NR).
- In individuals with HCM where genetic testing revealed no p variants, cascade testing of relatives is not useful. (COR 3/No benefit, LOE B-NR).
- Ongoing clinical screening in genotype-negative relatives where genotype-positive HCM has been identified in the family is not indicated unless the variant has been downgraded to a VUS, likely benign variant, or benign variant.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA)

The 2022, the AHA/ACC/HFSA (Heidenreich et al.) published updated heart failure guidelines which advise that genetic screening and counseling is recommended to detect cardiac disease and prompt consideration of treatments to decrease HF progression and sudden death in first degree relatives of select individuals with genetic or inherited cardiomyopathies.

American Heart Association (AHA)

In a 2025 Scientific Statement (Hull et al.), the AHA addressed direct-to-consumer genetic testing for cardiovascular disease, as such tests are becoming increasingly available for purchase directly from laboratories. The publication reports that there is insufficient evidence to support the use of these tests in routine clinical care. The lack of oversight and

regulation, variability in scope/testing methodologies, and lack of standardized reporting and counseling can cause much confusion for both individuals seeking care and their clinicians. The authors advise ongoing efforts to develop standards in the direct-to-consumer genetic testing industry overall.

A 2022 AHA Scientific Statement (O'Sullivan et al.) focused on the use of polygenic risk scores (PRS) for cardiovascular disease, noting that large genome-wide association studies have confirmed the polygenic basis of cardiometabolic diseases and have demonstrated that many single nucleotide variants throughout the genome are associated with cardiometabolic diseases. Institutions such as universities, academic medical facilities and direct-to-consumer laboratories are currently providing PRS to consumers and research participants or patients. The authors acknowledge that although there are promising applications for PRS, there are also significant limitations. These include the lack of less common variants in the current state-of-the-art polygenic risk models; rare variants have not yet been fully investigated, though recent evidence shows that rare and low-frequency variants explain a sizable fraction of heritable disease. In addition, PRSs are not consistently transferrable across different populations and ethnic groups. The AHA recommends future research in randomized clinical trials including younger adults and children for assessment of clinical utility, focusing on the incremental value of PRS use over clinical scoring, and treatment changes/clinical outcomes related to the use of PRS. Potential negative consequences of PRS must also be considered (e.g., unequal benefit of PRS across differing race/ethnicity populations, unequal access to care, misinterpretation, or misapplication of PRS information and possible risks to the well-being of affected individuals due to genetic data security and insurance coverage/health care costs).

The AHA (Landstrom et al.) published a scientific statement in 2021 addressing genetic testing for heritable cardiovascular diseases in pediatric patients, indicating that genetic testing can be considered in children who are suspected of having or are at risk for cardiovascular disease with focus placed on the importance of appropriate multidisciplinary counseling and the timing of testing. Such details must be individualized to each patient, family, and potential disease. In addition, the authors stress the importance of ongoing follow up for reevaluation of variant pathogenicity and to address the evolving needs of the individual and their family.

The AHA 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 p 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 an 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*, *TNNI3*, *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.

LVNC

- LVNC cardiomyopathy genetic testing may be useful for patients in whom a cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic/MRI phenotype.
- Genetic testing may be useful for patients with a clinical diagnosis of LVNC cardiomyopathy associated with other cardiac or non-cardiac syndromic features.
- Genetic testing should not be performed in isolated (incidental) LVNC with normal LV function, no associated syndromic features, and no family history.
- Variant specific genetic testing may be considered for family members and appropriate relatives following the identification of the disease-causative variant.

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

In 2018, the HFSA updated their guideline addressing the genetic evaluation of cardiomyopathy in collaboration with the ACMG (Hershberger et al., 2018). This document, written by cardiologists and genetics professionals with expertise in both adult and pediatric cardiomyopathy, provides the following directives:

- 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 P/LP 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 P/LP variants in cardiomyopathy genes, designated for reporting of secondary findings by the ACMG, are identified in an individual.
 - If a cardiovascular phenotype is identified as would be predicted by currently available knowledge of the gene/variant pair, all usual approaches described in this document for a genetic evaluation, including family-based approaches, are recommended.
 - If no cardiovascular disease phenotype is identified in the individual, recommendations for surveillance screening at intervals should be considered.
 - If no cardiovascular phenotype is identified in the individual, cascade evaluation of at-risk relatives may be considered, tempered by the strength of evidence supporting the pathogenicity of the variant, the usual age of onset of the gene/variant pair, and pedigree information (e.g., the ages of at-risk family members, other previously known cardiovascular clinical data in the pedigree, and related information).
- Medical therapy based on cardiac phenotype is recommended, as outlined in consensus guidelines. (Level of Evidence A)
- Device therapies for arrhythmia and conduction system disease based on cardiac phenotype are recommended, as outlined in consensus guidelines. (Level of Evidence B)
- In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia, an ICD may be considered before the left ventricular ejection fraction falls below 35%. (Level of Evidence C)

Levels of Evidence:

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

Heart Rhythm Society (HRS)

In 2019, Towbin et al. published an HRS expert consensus statement on the evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy, which includes LVNC. HRS provided the following recommendations for genetic testing and counseling for LVNC:

- If the proband has a disease-causing gene variant, it is recommended that first-degree relatives of individuals with LVNC undergo clinical screening for the disease along with genetic counseling and genetic testing.
- In individuals with the clinical diagnosis of pathologic LVNC, genetic counseling and genetic testing are reasonable for diagnosis and for gene-specific targeted cascade family screening.

Inherited Thoracic Aortic Disease

Aortic diseases are the 18th most common cause of death worldwide, and about 20% are genetic, but this could be an underestimate as genetic testing is not frequently used in the clinical setting. 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 Regaldo, 2017).

Rare genomic copy variations (CNVs) have been associated with the development of bicuspid aortic valve (BAV) and thoracic aortic aneurysms. In a recent study, Carlisle et al. (2024) sought to describe the burden and penetrance of rare CNVs in a cohort of young adults with early onset complications of bicuspid aortic valve disease (EBAV). The frequency and gene content of rare CNVs in EBAV was investigated in a group of 272 probands through the use of SNP microarray analysis and three CNV detection algorithms. A group of unselected controls from the Database of Genotypes and Phenotypes was also analyzed with identical methodology. The data was then filtered to identify large genic CNVs that were detectable via multiple algorithms. These findings were replicated in a cohort of 5040 individuals with BAV and late onset sporadic disease. Three large, rare (< 1:1000 in control group) CNVs were found in EBAV probands. In case-controlled examination, the burden of CNVs that intersected with genes known to cause BAV when mutated was increased. CNVs that intersected specifically with *GATA4* and *DSCAM* were enriched in EBAV cases, showed recurrence in other datasets, and were segregated with disease in multiple families. Overall, the researchers identified large rare CNVs in a significant percentage of BAV disease cases, including a subset of CNVs that may forecast early onset complications of BAV disease. The authors indicate that their results support the evidence showing that the identification of rare CNVs may eventually be useful for clinicians for stratification of risk and individualized clinical care for individuals with BAV.

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 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. The 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*, *TGFB1*, *TGFB2*) 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 individuals with TAAD 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*, *TGFB1* and *TGFB2*. A P/LP variant was found in 66 subjects (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 TAAD prior to testing. In the Netherlands, it is common to test all individuals with TAAD, 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 P/LP 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.

Clinical Practice Guidelines

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

The 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease (Isselbacher et al.) states that up to 20% of individuals with a thoracic aortic aneurysm or aortic dissection have a family history of thoracic aortic disease (TAD), with at least 1 affected first-degree relative. The guideline provides the following recommendations related to genetic testing and screening of family members for TAD:

- For individuals with aortic root/ascending aortic aneurysms or aortic dissection, obtain a multigenerational family history of thoracic aortic disease (TAD), unexplained sudden deaths, and peripheral and intracranial aneurysms.
- For individuals with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify P/LP variants should be performed.
- For individuals with an established P/LP variant in a gene predisposing to HTAD, genetic counseling should be provided and the individual's clinical management should be guided by the specific gene and variant in the gene.
- For individuals with TAD who have a P/LP variant, genetic testing of at-risk biological relatives (i.e., cascade testing) should be performed.

At the time of publication of the 2022 ACC/AHA guideline, existing HTAD genetic testing panels included eleven genes that have confirmed association with highly penetrant risk for TAD. These include: *FBN1*, *LOX*, *COL3A1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *ACTA2*, *MYH11*, *MYLK*, and *PRKG1*. The panels typically also include genes that increase risk for TAD or that may lead to systemic features overlapping with Loeys-Dietz syndrome, Marfan syndrome or vascular Ehler-Danlos syndrome.

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

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

Levels of Evidence:

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

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 (CAD)

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

Liu et al. (2025) systematically reviewed studies focused on coronary atherosclerosis (CAD) genomic testing and its use in early diagnosis, risk stratification, and personalized treatment. Studies were selected based on their focus on the genomic aspects of coronary atherosclerosis, such as genetic markers for diagnosis and risk assessment, molecular mechanisms, and the use of genomic technologies. Each study included was required to have a detailed methodology, robust results, and data-supported conclusions. Studies were excluded if their focus was primarily on non-genomic factors. The researchers found that genome-wide association studies (GWASs) and sequencing studies have identified key genetic variations associated with CAD, including *JCAD/KIAA1462*, *GUCY1A3*, *PCSK9*, and *SORT1*. These markers play a critical role in regulating inflammation, lipid metabolism, and vascular function. Twin and familial studies have indicated that genetic factors contribute about 40–60% to the risk of developing CAD. Additionally, transcriptomic and epigenomic studies have identified unique gene expression profiles correlating risk, DNA methylation signatures, and regulatory non-coding RNAs specific to the disease, offering new methods for early detection. Despite significant progress in identifying promising genetic markers, implementation of genomic analysis of CAD faces substantial obstacles such as marker dynamics, difficulty with standardization, and integration of genomic testing with traditional diagnostics. To continue to advance genomic diagnostics in the setting of CAD, the authors recommend further study with large-scale prospective trials, prioritizing the development of standardized guidelines, and improving data integration.

Boccanelli and Scardovi (2023) reported on findings from the PRE-DETERMINE cohort study, the objective of which is to determine whether biomarkers and electrocardiogram can be used to determine whether individuals are more likely to experience SD. In the study, the utility of the genome-wide polygenic scores for coronary artery disease (GPSCAD) for the stratification of risk in a population of individuals with intermediate-risk and stable CAD without severe systolic dysfunction and/or an indication for an implantable cardioverter defibrillator for prevention. Individuals were followed for a mean of 8 years. Individuals in the top decile of GPSCAD were found to have a higher absolute (8.0% vs. 4.8%; $p < 0.005$) and relative (29% vs. 16%; $p < 0.0003$) risk of SD related to the remainder of the cohort. There was no association found between the highest decile of GPSCAD and other causes of death, both cardiac and non-cardiac. The authors conclude that these data can be used only for a theoretical estimate on potential effectiveness of implantable defibrillator in the group of individuals with chronic CAD and moderately depressed left ventricular function as the number needed to treat and potential reduction of mortality for individuals at high risk (defined as the top decile of GPSCAD). They advise that further research is needed in the coming years.

Sun et al. (2021) sought to explore the clinical utility of 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 people 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_{Tikkanen} and PRS_{Tada}; 28 and 50 variants, respectively) and two genome-wide PRSs (PRS_{metaGRS} and PRS_{LDPred}; 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_{metaGRS} 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_{metaGRS} 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 subjects 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 among Latinos. Including the Framingham risk score improved the risk categorization by 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 BiImage 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.

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.

American Heart Association (AHA)

The AHA's 2020 Scientific Statement on genetic testing for inherited cardiovascular disease (Musunuru et al.) mentions that in recent years, reports of polygenic risk scoring for complex cardiovascular diseases such as CAD have suggested that individuals with extremely high scores have a substantially increased risk of disease that is considerably higher than that of the average population. Whether this information is clinically actionable and can result in meaningful changes to medical management, however, has yet to be determined.

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.

United States Preventive Services Task Force (USPSTF)

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).

U.S. Food and Drug Administration (FDA)

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

Laboratories that perform genetic tests for cardiac disease are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at:

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm>.

(Accessed April 25, 2024)

Refer to the following website for a list of nucleic acid-based tests/platforms that have been cleared or approved by the FDA's Center for Devices and Radiological Health: <https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests>. (Accessed April 25, 2025)

References

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

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

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.

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.

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.

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.

Bariani R, Rigato I, Cason M, et al. Genetic background and clinical features in arrhythmogenic left ventricular cardiomyopathy: a systematic review. *J Clin Med*. 2022 Jul 25;11(15):4313.

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.

Boccanelli A, Scardovi AB. Sudden death in ischemic heart disease: looking for new predictors: polygenic risk. *Eur Heart J Suppl*. 2023 Apr 21;25(Suppl B):B31-B33.

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.

Brugada R, Campuzano O, Sarquella-Brugada G, et al. Brugada Syndrome. 2005 Mar 31 [Updated 2022 Aug 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1517/>. Accessed April 30, 2025.

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.

Carlisle SG, Albasha H, Michelena HI, et al.; EBAV Investigators; BAVCon Investigators. Rare genomic copy number variants implicate new candidate genes for bicuspid aortic valve. *PLoS One*. 2024 Sep 6;19(9):e0304514.

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

Christian S, Cirino A, Hansen B, et al. Diagnostic validity and clinical utility of genetic testing for hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Open Heart*. 2022 Apr;9(1):e001815.

Cirino AL, Harris SL, Murad AM, et al. The uptake and utility of genetic testing and genetic counseling for hypertrophic cardiomyopathy-A systematic review and meta-analysis. *J Genet Couns*. 2022 Dec;31(6):1290-1305.

Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. 2008 Aug 5 [Updated Jun 2025, March 6]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1768/>. Accessed April 30, 2025.

[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'Apolito M, Santoro F, Ranaldi A, et al. Genetic background and clinical phenotype in an Italian cohort with inherited arrhythmia syndromes and arrhythmogenic cardiomyopathy (ACM): a whole-exome sequencing study. *Int J Mol Sci*. 2025 Jan 30;26(3):1200.

[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.

[Ellepolá 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.

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.

Groffen A.J., Bikker H, Christiaans I. Long QT Syndrome. 2003 Feb 20 [Updated 2024 Mar 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1129/>. Accessed April 30, 2025.

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.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for family members of individuals with Brugada syndrome. Hayes, Inc.; September 28, 2018d, updated August 1, 2022.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for family members of individuals with catecholaminergic polymorphic ventricular tachycardia. Hayes, Inc.; December 11, 2018b, updated October 24, 2022.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for individuals clinically diagnosed with Brugada syndrome. Hayes, Inc.; September 2018c, updated August 1, 2022.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for individuals clinically diagnosed with catecholaminergic polymorphic ventricular tachycardia. Hayes, Inc.; December 11, 2018a, updated October 24, 2022.

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022 May 3;79(17):e263-e421.

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.

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, 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.

Hull LE, Aday AW, Bui QM, et al.; American Heart Association Data Science and Precision Medicine Committee of the Council on Genomic and Precision Medicine and Council of Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Direct-to-consumer genetic testing for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2025 Apr 8;151(14):e905-e917.

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. 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.

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.

Isselbacher EM, Preventza O, Hamilton Black J 3rd, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022 Dec 13;146(24):e334-e482.

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, 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.

Joglar JA, Chung MK, Armbruster AL, et al. Peer Review Committee Members. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024 Jan 2;149(1):e1-e156.

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.

Landstrom AP, Kim JJ, Gelb BD, et al.; American Heart Association Council on Genomic and Precision Medicine; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Arteriosclerosis, Thrombosis and Vascular Biology; and Council on Lifestyle and Cardiometabolic Health. Genetic testing for heritable cardiovascular diseases in pediatric patients: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2021 Oct;14(5):e000086.

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.

Liu H, Zhang Y, Zhao Y, et al. Research progress and clinical translation potential of coronary atherosclerosis diagnostic markers from a genomic perspective. *Genes (Basel)*. 2025 Jan 18;16(1):98.

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

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.

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 2023 May 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1131/>. Accessed April 30, 2025.

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 2020 Jun 24]. Familial atrial fibrillation; [updated 2017a Oct 1]. Available at: <https://ghr.nlm.nih.gov/condition/familial-atrial-fibrillation>. Accessed April 30, 2025.

MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. Familial dilated cardiomyopathy; [updated 2017b April 1]. Available at: <https://ghr.nlm.nih.gov/condition/familial-dilated-cardiomyopathy>. Accessed April 30, 2025.

MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. Left ventricular noncompaction; [updated 2022 June 22]. Available at: <https://medlineplus.gov/genetics/condition/left-ventricular-noncompaction/>. Accessed April 30, 2025.

MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. What are the different types of genetic tests?; [updated 2021 July 28]. Available at: <https://medlineplus.gov/genetics/understanding/testing/types>.

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, Pfefferkorn 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 2023 May 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1120/>. Accessed April 30, 2025.

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.

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.

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, Hershberger RE, Day SM, et al.; American Heart Association Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. Circ Genom Precis Med. 2020 Aug;13(4):e000067.

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):e000037.

Myers MC, Wang S, Zhong Y, et al. Prevalence of genetically associated dilated cardiomyopathy: a systematic literature review and meta-analysis. Cardiol Res. 2024 Aug;15(4):233-245.

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).

Napolitano C, Priori SG, Bloise R. Catecholaminergic Polymorphic Ventricular Tachycardia. 2004 Oct 14 [Updated 2022 Jun 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1289/>. Accessed April 30, 2025.

National Cancer Institute. NCI Dictionary of Genetics Terms. Multigene Test. Available at: <https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/multigene-test>. Accessed April 30, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian, pancreatic, and prostate. v3.2025.

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.

Nielsen SK, Hansen FG, Rasmussen TB, et al. Major cardiac events in patients and relatives with hereditary hypertrophic cardiomyopathy. JACC Adv. 2023 Sep 12;2(8):100604.

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.

Olivetto 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 SR, Ho CY, Asif IM, et al.; Peer Review Committee Members. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Jun 4;149(23):e1239-e13112024.

O'Sullivan JW, Raghavan S, Marquez-Luna C, et al.; American Heart Association Council on Genomic and Precision Medicine; Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2022 Aug 23;146(8):e93-e118.

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.

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.

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.

Rangaraju A and Dalal A. Scope of genetic testing for inherited cardiovascular diseases in the clinical practice. *J Indian College Cardiol*. 2021 Jan-Mar;11(1):p 5-12.

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.

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.

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*. 2017 Aug;12(4):389-390.

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.

Seidemann SB, Smith E, Subrahmanyam L, et al. Application of whole exome sequencing in the clinical diagnosis and management of inherited cardiovascular diseases in adults. *Circ Cardiovasc Genet*. 2017 Feb;10(1):e001573.

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 analyses. *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, 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.

Topriceanu CC, Pereira AC, Moon JC, et al. Meta-analysis of penetrance and systematic review on transition to disease in genetic hypertrophic cardiomyopathy. *Circulation.* 2024 Jan 9;149(2):107-123.

Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy: Executive summary. *Heart Rhythm.* 2019 Nov;16(11):e373-e407.

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.

van Waning JI, Caliskan K, Hoedemaekers YM, et al. Genetics, clinical features, and long-term outcome of noncompaction cardiomyopathy. *J Am Coll Cardiol.* 2018 Feb 20;71(7):711-722.

van Waning JI, Moesker J, Heijnsman D, et al. Systematic review of genotype-phenotype correlations in noncompaction cardiomyopathy. *J Am Heart Assoc.* 2019 Dec 3;8(23):e012993.

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.* 2022 Apr 14;43(15):1500-1510.

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 Jul;19(7):e1-e60.

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.

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
10/01/2025	<p>Related Policies</p> <ul style="list-style-type: none"> Added referenced link to the Medical Policy <i>Chromosome Microarray Testing (Non-Oncology Conditions)</i> <p>Coverage Rationale Testing Based Only on Family History</p> <ul style="list-style-type: none"> Replaced language indicating “genetic testing for cardiomyopathies, arrhythmias, or aortic vascular disease is unproven and not medically necessary <i>for all other indications [not listed in the policy as medically necessary]</i> due to insufficient evidence of efficacy” with “<i>all other</i> genetic testing for cardiomyopathies, arrhythmias, or aortic vascular disease [not listed in the policy as medically necessary] is unproven and not medically necessary due to insufficient evidence of efficacy; <i>this does not apply to chromosome microarray analysis for isolated severe congenital heart disease</i>”

Date	Summary of Changes
	Supporting Information <ul style="list-style-type: none"> Updated <i>Description of Services</i>, <i>Clinical Evidence</i>, <i>FDA</i>, and <i>References</i> sections to reflect the most current information Archived previous policy version 2025T0552Z

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare 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 reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical 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.