Genetic Testing for Hereditary Cardiomyopathies and Arrhythmias

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DESCRIPTION

Genetic testing has been proposed as a method to differentiate inherited or familial cardiomyopathies and arrhythmias from those caused by other factors.

Cardiomyopathies are a heterogeneous group of acquired or inherited disorders affecting the heart muscle's ability to contract and to relax. They are described by their effect on the heart muscle and include hypertrophic (HCM) (e.g., thickened), dilated (DCM) (e.g., stretched out) and restrictive (RCM) (e.g., stiffened)

Inherited cardiac arrhythmia syndromes are caused by gene variants which affect the function of the heart's electrical system, although the heart muscle itself may be normal.

These variants can cause abnormal heart rhythms which may cause life-threatening conditions such as sudden cardiac death and ventricular tachycardia.

- Brugada (RrS) Syndrome
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Long QT (LQTS)
- Short QT syndrome (SQTS)

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

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

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

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

Genetic Testing for Cardiac Ion Channelopathies

Genetic testing is available for patients suspected of having cardiac ion channelopathies, including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and short QT syndrome (SQTS). These disorders are clinically heterogeneous and may range from asymptomatic to presenting

with sudden cardiac death. Testing for variants associated with these channelopathies may assist in diagnosis, risk-stratify prognosis, and/or identify susceptibility for the disorders in asymptomatic family members.

Cardiac ion channelopathies result from variants in genes that code for protein subunits of the cardiac ion channels. These channels are essential to cell membrane components that open or close to allow ions to flow into or out of the cell. Regulation of these ions is essential for the maintenance of a normal cardiac action potential. This group of disorders is associated with ventricular arrhythmias and an increased risk of sudden cardiac death (SCD). These congenital cardiac channelopathies can be difficult to diagnose, and the implications of an incorrect diagnosis could be catastrophic.

The prevalence of any cardiac channelopathy is still ill-defined but is thought to be between 1 in 2000 and 1 in 3000 persons in the general population.

Cardiac Ion Channelopathies	**Description**	**Genetic Variants**
Brugada Syndrome (BrS)	Is characterized by cardiac conduction abnormalities that increase the risk of syncope, ventricular arrhythmia, and sudden cardiac death (SCD). The disorder primarily manifests during adulthood, although ages between 2 days and 85 years have been reported. Brugada syndrome is an autosomal dominant disorder with an unexplained male predominance. XY individuals are more likely to be affected than XX individuals (approximate ratio, 8:1). Brugada syndrome is estimated to be responsible for 12% of SCD cases. For both sexes, there is an equally high risk of ventricular arrhythmias or sudden	Variants in 16 genes have been identified as causative of BrS, all of which led to a decrease in the inward sodium or calcium current or an increase in one of the outward potassium currents. Of these, *SCN5A* is the most important, accounting for more than an estimated 20% of cases *SCN10A* has also been implicated. The other genes are of minor significance and account together for approximately 5% of cases. The absence of a positive test does not indicate the absence of BrS, with more than 65% of cases not having an identified genetic cause. Penetrance of BrS among persons with an *SCN5A* variant is 80% when undergoing ECG with sodium-channel blocker challenge and 25% when not using the ECG challenge. A 2021 analysis of 49 patients with channelopathies identified 1 rare variant that was pathogenic for BrS and 3 rare variants that were likely pathogenic for BrS, all involving the *SCN5A* gene.

	death. Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.	
Catecholaminergic Polymorphic Ventricular Tachycardia (CPTV)	Catecholaminergic polymorphic ventricular tachycardia is a rare, inherited channelopathy that may present with autosomal dominant or autosomal recessive inheritance. The disorder manifests as a bidirectional or polymorphic ventricular tachycardia precipitated by exercise or emotional stress. The prevalence of CPVT is estimated between 1 in 7000 and 1 in 10,000 persons. Catecholaminergic polymorphic ventricular tachycardia has a mortality rate of 30% to 50% by age 35 and is responsible for 13% of cardiac arrests in structurally normal hearts. Catecholaminergic polymorphic ventricular tachycardia was previously believed to manifest only during childhood, but studies have now identified presentation between infancy and 40 years of age.	Variants in 4 genes are known to cause CPVT, and investigators believe other unidentified loci are involved as well. Currently, only 55% to 65% of patients with CPVT have an identified causative variant. Variants of the gene encoding the cardiac ryanodine receptor (*RYR2*) or to *KCNJ2* result in an autosomal dominant form of CPVT. *CASQ2* (cardiac calsequestrin) and *TRDN*-related CPVT exhibit autosomal recessive inheritance. A channelopathy expert panel review has also found moderate to definitive evidence for an autosomal dominant inheritance of *CALM1*, *CALM2*, and *CALM3* and an autosomal recessive inheritance of *TECRL*.[16,] Some have reported heterozygotes for *CASQ2* and *TRDN* variants for rare, benign arrhythmias. *RYR2* variants represent most CPVT cases (50% to 55%), with *CASQ2* accounting for 1% to 2% and *TRDN* accounting for an unknown proportion of cases. The penetrance of *RYR2* variants is approximated at 83%. An estimated 50% to 70% of patients will have the dominant form of CPVT with a disease-causing variant. Most variants (90%) to *RYR2* are missense variants, but in a small proportion of unrelated CPVT patients, large gene

		rearrangements or exon deletions have been reported. Additionally, nearly a third of patients diagnosed as LQTS with normal QT intervals have CPVT due to identified *RYR2* variants. Another misclassification, CPVT diagnosed as Anderson-Tawil syndrome may result in more aggressive prophylaxis for CPVT whereas a correct diagnosis can spare this treatment because Anderson-Tawil syndrome is rarely fatal.
Long QT Syndrome (LQTS)	Congenital LQTS is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential, increasing the risk for arrhythmic events, such as torsades de pointes, which may, in turn, result in syncope and sudden cardiac death (SCD). Congenital LQTS usually manifests before the age of 40 years. It is estimated that more than half of the 8000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1% to 2% per year, although this figure will vary with the genotype.	There are more than 1200 unique variants on at least 13 genes encoding potassium-channel proteins, sodium-channel proteins, calcium channel-related factors, and membrane adaptor proteins that have been associated with LQTS. In addition to single variants, some cases of LQTS are associated with deletions or duplications of genes. The absence of a variant does not imply the absence of LQTS; it is estimated that variants are only identified in 70% to 75% of patients with a clinical diagnosis of LQTS. A negative test is only definitive when there is a known variant identified in a family member and targeted testing for this variant is negative. Variants involving *KCNQ1*, *KCNH2*, and *SCN5A* are the most commonly detected in patients with genetically confirmed LQTS. Some variants are associated with extra-cardiac

		abnormalities in addition to the cardiac ion channel abnormalities.
Short QT Syndrome (SQTS)	Short QT syndrome is characterized by a shortened QT interval on the electrocardiogram (ECG) and, at the cellular level, a shortening of the action potential. The clinical manifestations are an increased risk of atrial and/or ventricular arrhythmias. Because of the disease's rarity, the prevalence and risk of sudden death are currently unknown.	Short QT syndrome has been linked predominantly to variants in 3 genes (*KCNH2*, *KCNJ2*, *KCNQ1*). Variants in genes encoding alpha- and beta-subunits of the L-type cardiac calcium channel (*CACNA1C*, *CACNB2*) have also been associated with SQTS. Some individuals with SQTS do not have a variant in these genes, suggesting changes in other genes may also cause this disorder. A channelopathy expert panel concluded that only *KCNH2* had a definitive relationship with SQTS and *KCNQ1*, *KCNJ2*, and *SLC4A3* had strong to moderate causative evidence. Short QT syndrome is believed to be inherited in an autosomal dominant pattern. Although sporadic cases have been reported, patients frequently have a family history of the syndrome or SCD.

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The true clinical sensitivity and specificity of genetic testing for specific cardiac ion channelopathies cannot be determined with certainty because there is no independent criterion standard for the diagnosis. The clinical diagnosis can be compared with the genetic diagnosis, and vice versa, but neither the clinical diagnosis nor the results of genetic testing can be considered an adequate criterion standard.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Clinical Context and Test Purpose
The purpose of genetic testing in patients with unexplained cardiac arrhythmias and/or other conduction abnormalities is to confirm the presence or absence of a cardiac ion channelopathy and inform clinical management.

Populations
The population of interest are individuals with suspected cardiac ion channelopathies or asymptomatic individuals with a close relative(s) with a known cardiac ion channelopathy variants.

The channelopathies discussed herein are genetically heterogeneous with hundreds of identified variants, but the group of disorders shares basic clinical expression. The most common presentation is spontaneous or exercise-triggered syncope due to ventricular dysrhythmia. These can be self-limiting or potentially lethal cardiac events. The electrocardiographic features of each channelopathy are characteristic, but the electrocardiogram (ECG) is not diagnostic in all cases, and some secondary events (e.g., electrolyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an ECG similar to those observed in a cardiac channelopathy.

Interventions
The intervention being considered is genetic testing for variants associated with cardiac ion channelopathies. Genetic tests are conducted in clinical laboratories. Genetic testing should be accompanied by genetic counseling including discussions with the patient or guardians about the importance and interpretation of genetic information and sharing of information with potentially affected family members as appropriate.

Genetic testing can be comprehensive (testing for all possible variants in multiple genes) or targeted (testing for a single variant identified in a family member). For comprehensive testing, the probability that a specific variant is pathophysiologically significant is greatly increased if the same variant has been reported in other cases. A variant may also be found that has not been associated with a disorder and therefore may or may not be pathogenic. Variants are classified by their pathogenic potential; an example of such a classification system used in the Familion assay is as follows in below table:

Familion Assay Classification System

Class	Description
I	Deleterious and probable deleterious mutations. They are mutations that have either previously been identified as pathogenic (deleterious mutations), represent a major change in the protein, or cause an amino acid substitution in a

	critical region of the protein(s) (probable deleterious mutations).
II	Possible deleterious mutations. These variants encode changes to protein(s) but occur in regions that are not considered critical. Approximately 5% of unselected patients without LQTS will exhibit mutations in this category.
III	Variants not generally expected to be deleterious. These variants encode modified protein(s); however, they are considered more likely to represent benign polymorphisms. Approximately 90% of unselected patients without LQTS will have one or more of these variants; therefore, patients with only class III variants are considered "negative."
IV	Non-protein-altering variants. These variants are not considered to have clinical significance and are not reported in the results of the Familion test.

Genetic testing for specific disorders, which may include 1 or more specific genes, is available from multiple academic and commercial laboratories, generally by next-generation sequencing or Sanger sequencing. Also, panel testing for 1 or more cardiac ion channelopathies is available from several genetic diagnostics laboratories, but there is some variation among manufacturers on the included genes.

There are also commercially available panels that include genetic testing for cardiac ion channelopathies along with other hereditary cardiac disorders, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy.

Comparators
The following practice is currently being used: standard management without genetic testing. Diagnosis and management are described below:

Brugada Diagnosis and Management
The diagnosis of Brugada Syndrome (BrS) is made by the presence of a type 1 Brugada pattern on the ECG in addition to other clinical features. This ECG pattern includes a coved ST-segment and a J-point elevation of 0.2 mV or higher followed by a negative T wave. This pattern should be observed in 2 or more of the right precordial ECG leads (V_1-V_3). This pattern may be concealed and can be revealed by administering a sodium-

channel-blocking agent (e.g., flecainide). Two additional ECG patterns have been described (type 2, type 3) but are less specific for the disorder. The diagnosis of BrS is considered definitive when the characteristic ECG pattern is present with at least 1 of the following clinical features: documented ventricular arrhythmia, sudden cardiac death (SCD) in a family member younger than 45 years old, characteristic ECG pattern in a family member, inducible ventricular arrhythmias on electrophysiology studies, syncope, or nocturnal agonal respirations.

Management has focused on the use of ICDs in patients with syncope or cardiac arrest and isoproterenol for electrical storms. Patients who are asymptomatic can be closely followed to determine if ICD implantation is necessary.

Catecholaminergic Polymorphic Ventricular Tachycardia Diagnosis and Management

Patients generally present with syncope or cardiac arrest during the first or second decade of life. The symptoms are nearly always triggered by exercise or emotional stress. The resting ECG of patients with catecholaminergic polymorphic ventricular tachycardia **(**CPVT) is typically normal, but exercise stress testing can induce a ventricular arrhythmia in most cases (75% to 100%). Premature ventricular contractions, couplets, bigeminy, or polymorphic ventricular tachycardia (VT) are possible outcomes to the ECG stress test. For patients who are unable to exercise, an infusion of epinephrine may induce ventricular arrhythmia, but this is less effective than exercise testing.

Management of CPVT is primarily with the β-blockers nadolol (1 to 2.5 mg/kg/d) or propranolol (2 to 4 mg/kg/d). If protection is incomplete (i.e., recurrence of syncope or arrhythmia), then flecainide (100 to 300 mg/d) may be added. If recurrence continues, an ICD may be necessary with optimized pharmacologic management continued post-implantation. Lifestyle modification with the avoidance of strenuous exercise is recommended for all CPVT patients.

Long QT Syndrome (LQTS) Diagnosis and Management

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS:

Schwartz Score Diagnostic Criteria for LQTS

	Points
Electrocardiographic findings* (* In the absence of medications or disorders known to affect these electrocardiographic features)	
A. QTc ▪ ≥480 ms ▪ 460 to 479 ms	 3 2

▪ 450 to 459 ms (in males)	1
B. QTc fourth minute of recovery from exercise stress test ≥ 480 ms	1
C. Torsades de points	2
D. T-wave alternans	1
E. Notched T wave in 3 leads	1
F. Low heart rate for age (resting heart rate below the second percentile for age)	0.5
Clinical history	
A. Syncope ▪ With stress	2
▪ Without stress	1
B. Congenital deafness	0.5
Family History	
A. Family members with definite LQTS (the same family member cannot be counted in A or B)	1
B. Unexplained sudden cardiac death below age 30 among immediate family members (the same family member cannot be counted in A or B)	0.5

SCORE:

- ≤1 point = low probability of long QT syndrome (LQTS)
- 1.5 to 3 points = intermediate probability of LQTS
- ≥3.5 points = high probability of LQTS

Primary management of asymptomatic or symptomatic long QT is β-blocker treatment with an intensification of therapy, if necessary due to recurrent arrhythmic events or intolerable side effects, including additional medication, left cardiac sympathetic denervation or placement of an implantable cardioverter-defibrillator (ICD). Avoidance of medications known to prolong the QT interval and the aggressive treatment of electrolyte imbalances are also advised.

Short QT Syndrome Diagnosis and Management

Patients generally present with syncope, pre-syncope, or cardiac arrest. An ECG with a corrected QT interval less than 330 ms, sharp T wave at the end of the QRS complex, and a brief or absent ST-segment are characteristic of the syndrome. However, higher QT intervals on ECG might also indicate short QT syndrome (SQTS), and the clinician has to determine if this is within the normative range of QT values. An index patient with suspected SQTS would be expected to have a shortened (<2 standard deviations below from the mean) rate-corrected shortened QT interval (QTc). Cutoffs below 350 ms for men and 360 ms for women have been derived from population normal values. The length of the QT interval was not associated with severity of symptoms in a 2006 series of 29 patients with SQTS. Electrophysiologic studies may be used to diagnose SQTS if the diagnosis is uncertain to evaluate for short refractory periods and inducible VT. However, in the series of 29 patients with SQTS described above, VT was inducible in only 3 of 6 subjects who underwent an electrophysiologic study. A diagnostic scoring system (see below table) was proposed by Gollob et. al., to help decision making after a review of 61 SQTS cases:

Diagnostic Scoring System for SQTS

Gallob Criteria	**Points**
Electrocardiographic Findings	
• QT corrected <370 ms	1
• QT corrected <350 ms	2
• QT corrected <330 ms	3
• J point-T peak interval <120 ms	1
Clinical History	
• History of SCD	2
• Documented polymorphic ventricular fibrillation or VT	2
• Unexplained syncope	1
• AF	1
Family History	
• First – or second-degree relative with high probability SQTS	2
• First-or second-degree relative with autopsy – negative SCD	1
• Sudden infant death syndrome	1

AF: atrial fibrillation; SCD: sudden cardiac death; SQTS: short QT syndrome; VT: ventricular tachycardia.

The primary management of SQTS is with ICD therapy. Decisions about ICD therapyare based on the degree to which SQTS is considered likely, which depends on ECG features,

family history, personal history of cardiac arrest or ventricular arrhythmias, and the ability to induce VT on electrophysiologic studies.

Anti-arrhythmic drug management of the disease is complicated because the binding target for QT-prolonging drugs (e.g., sotalol) is Kv11.1, which is coded for by *KCNH2*, the most common site for variants in SQTS (subtype 1). Treatment with quinidine (which can bind to both open and inactivated states of Kv11.1) is an appropriate QT-prolonging treatment. This treatment has been reported to reduce the rate of arrhythmias from 4.9% to 0% per year. For those with recurrence while on quinidine, an ICD is recommended

Outcomes
The general outcomes of interest are overall survival (OS), test validity, changes in reproductive decision making, and morbid events (e.g., cardiac events).

- A positive diagnosis of LQTS or CPVT in symptomatic patients may lead to treatment with β-blockers or with ICDs, which can reduce the risk for ventricular arrhythmias and SCD.
- A positive test for BrS in symptomatic patients may influence the decision for treatment with an ICD.
- It is unknown how a positive SQTS test in symptomatic patients would influence treatment decisions.
- Positive tests in asymptomatic family members can inform lifestyle changes and prevention treatment decisions.
- The genetic assays may be recommended as part of a diagnostic strategy for patients who exhibit clinical symptoms that are not considered definitive.
- The tests may also be recommended for asymptomatic family members of patients with known cardiac ion channel variants.

The evidence related to the clinical validity and utility of genetic testing for the cardiac channelopathies consists primarily of studies that evaluate the yield of genetic testing and the impact of genetic testing on the diagnosis and subsequent management of a specific cardiac channelopathy. Many cardiac channelopathies lead to a common clinical outcome - increased risk of ventricular arrhythmias leading to an increased risk of SCD.

Survivors of Sudden Cardiac Arrest
In 2021, Chiu et. al. performed genetic tests on 36 survivors of pediatric cardiac arrest (median age, 13.3 years).[7] The yield rate of genetic testing in the study cohort was 84.6%, including 14 pathogenic and 8 likely pathogenic variants. Long QT syndrome, CPVT, and BrS were diagnosed in 25%, 16.7%, and 6% of patients, respectively; genetic testing led to a change in diagnosis from CPVT to LQTS in 1 patient. Assessment of long-term outcomes showed that 10-year transplant-free survival was higher among patients who received genetic testing soon after the cardiac arrest event. Subsequent testing of family members of 15 probands identified 8 family members with positive genetic tests, but information on subsequent management of these patients was lacking.

In 2019, Asatryan et. al., evaluated the diagnostic validity and clinical utility of genetic testing in sudden cardiac arrest (SCA) survivors (n=60) with or without previous clinical evidence of heart disease.[28,] Patients without coronary artery disease were included; 24 (40%) with clear detectable cardiac phenotype [Ph (+) SCA] and 36 (60%) with no clear cardiac phenotype [Ph (-) SCA]. Targeted exome sequencing was performed using the TruSight-One Sequencing Panel (Illumina). A total of 32 pathogenic or likely pathogenic gene variants were found in 27 (45%) patients: 17 (71%) in the Ph (+) SCA group and 10 (28%) in the Ph (-) SCA group. Mutations in 16 (67%) Ph (+) SCA patients were congruent with the suspected phenotype, consisting of 12 (50%) cardiomyopathies and 4 (17%) channelopathies. Mutations in 6 (17%) Ph (-) SCA patients revealed a cardiac ion channelopathy explaining their SCA event. An additional 4 (11%) mutations in this group could not explain the phenotype and require additional studies. Overall, cardiac genetic testing was positive in 2/3 of the Ph (+) SCA group and 1/6 of the Ph (-) SCA group. The study was limited in its description of clinical criteria for establishing a diagnostic clinical phenotype. While the authors suggest the testing was useful to identify or confirm an inherited heart disease, with important impact on patient care and first-degree relatives at risk, health outcomes pertaining to clinical management of patients or asymptomatic familial probands were not reported.

Brugada Syndrome

In 2021, Millman et. al., published an observational study of 678 patients from 14 countries with a first arrhythmic event due to BrS. Of the 392 probands, 23.5% were *SCN5A* (+) with 44 pathogenic/likely pathogenic variants and 48 variants of unknown significance. The remaining probands were *SCN5A* (-). Patients with pathogenic/likely pathogenic variants were more likely to be aged <16 years (p=.023), female (p=.013), and have a family history of SCD (p<.001) compared to patients who were *SCN5A* (-). Logistic regression found that White ethnicity (odds ratio, 5.41; 95% CI, 2.8 to 11.19; p<.001) and family history of SCD (odds ratio, 2.73; 95% CI, 1.28 to 5.82; p=.009) were associated with having a pathogenic/likely pathogenic genotype. Sacillotto et. al., (2020) reported data from the Genetics of Brazillian Arrhythmias (GenBra) registry. From 1999 to 2020, 138 (22 symptomatic) consecutive patients with type-1 BrS were assessed for invasive and noninvasive parameters and *SCN5A* mutation status. No difference in the rate of *SCN5A*-positive patients was found between asymptomatic and symptomatic groups (20/76 [26.3%] vs. 5/17 [29.4%]; p=.770). *SCN5A* carriers had a significantly higher frequency of aVR sign, S wave, and QRS-f.

In 2019, Monasky et. al., evaluated 15 BrS-associated genes (*CACNA1C, CACNA2D1, CACNB2, GPD1L, HCN4, KCND2, KCND3, PKP2, RANGRF, SCN10A, SCN1B, SCN2B, SCN3B, SCN5A,* and *TRPM4*) with the TruSight One sequencing kit and NextSeq platform in 297 BrS patients screened for study enrollment. The 2 most common mutations were *SCN5A* (84 [28.3%]) followed by *SCN10A* (8 [2.7%]). Clinical characteristics of BrS patients harboring *SCN5A* or *SCN10A* mutations were not found to be significantly different between probands, although patients with a variety of type I-III ECG patterns were represented in both cohorts.

Chen et. al., (2019) conducted a meta-analysis of 17 studies involving 1780 unrelated and consecutive patients with BrS to assess the relationship between *SCN5A* mutation status and phenotypic features. A history of syncope and spontaneous type 1 ECG pattern were observed in 31% and 59% of BrS patients, respectively. A total of 52% of patients had ICD implantation. The average frequency of *SCN5A* mutations was 20%, which ranged from 11% to 43% across studies. The onset of symptoms was found to occur at a younger age in the *SCN5A* (+) group (34 ± 17 vs. 42 ± 16 years; p=.0003). The presence of a spontaneous type 1 ECG pattern was associated with an increased risk of cardiac events in BrS patients based on a pooled analysis of 12 studies (71% vs. 57%; p=.0002). *SCN5A* (+) patients had a higher proportion of sick sinus syndrome (43% vs. 5%; p<.001) and atrial ventricular block (71% vs. 30%; p=.01). However, there was a lower rate of VT/ventricular fibrillation inducibility during electrophysiology study (41% vs. 51%; p=.01), which may partially be explained by heterogeneity in electrophysiology study protocols. The *SCN5A* mutation was associated with an increased risk of major adverse events in the overall BrS (odds ratio, 1.78; 95% confidence interval [CI], 1.19 to 2.26; p=.005), Asian (odds ratio, 1.82; 95% CI, 1.07 to 3.11; p=.03), and Caucasian (odds ratio, 2.24; 95% CI, 1.02 to 4.90; p=.04) patient population.

In 2016, Andorin et. al. (2016) described the yield of *SCN5A* genetic testing in 75 patients younger than 19 years of age from 62 families who had a Brugada type I ECG pattern; only 20% were symptomatic. The ECG pattern was spontaneous in 34% and drug-induced in 66%. The yield was very high compared to previous studies at 77%. The authors hypothesized that the high yield might have been due to the inclusion of only a pediatric population.

The diagnostic testing yield for Brugada Syndrome (BrS) limits its clinical usefulness. A finding of a genetic variant is not diagnostic of the disorder but is an indicator of high risk for development of BrS. The diagnostic criteria for BrS do not presently include the presence of a genetic variant. Furthermore, treatment decisions are based on the presence of symptoms such as syncope or documented ventricular arrhythmias. Treatment is primarily with an implantable ICD, which is reserved for high-risk patients. However, for family members of patients with a known BrS variant, a negative test can rule out the disorder.

Rattanawong et. al., (2019) conducted a systematic review and meta-analysis of 7 cohort and case-control studies investigating the association of *SCN5A* mutations with major arrhythmic events (e.g., VT, ventricular fibrillation, appropriate implantable ICD shocks, aborted cardiac arrest, and SCD) in patients with BrS (n=1049).[59,] *SCN5A* mutations were associated with major arrhythmic events in Asian patients (risk ratio, 2.03; 95% CI, 1.37 to 3.00; p=.0004; I^2=0.0%), symptomatic patients (risk ratio, 2.66; 95% CI, 1.62 to 4.36; p=.0001; I^2=23.0%), and patients with spontaneous Brugada type 1 ECG pattern (risk ratio, 1.84; 95% CI, 1.05 to 3.23; p=.03; I^2=0.0%). The inclusion criteria did not specify criteria for establishing a clinical diagnosis of BrS, and therefore, the analysis was limited by heterogeneity in clinical, genetic, and outcome reporting among included studies.

Reporting on specific major arrhythmic events relevant to health outcomes such as delivery of appropriate ICD shocks and aborted cardiac arrests was not individually reported. Therefore, the clinical utility of *SCN5A* genetic variant risk stratification in this population remains unclear.

Catecholaminergic Polymorphic Ventricular Tachycardia
Studies reporting the yield of *RyR2* testing in catecholaminergic polymorphic ventricular tachycardia (CPVT) have been conducted in patients with clinically diagnosed (CPVT). The specificity of known pathogenic variants for CPVT is uncertain but is likely high. The clinical utility for genetic testing in CPVT follows a similar chain of logic as that for long QT syndrome (LQTS). In individuals for whom the clinical diagnosis can be made with certainty, there is a limited utility for genetic testing. However, there are some individuals in whom signs and symptoms of CPVT are present, but for whom the diagnosis cannot be made with certainty. In this case, documentation of a pathogenic variant that is known to be associated with CPVT confirms the diagnosis. When the diagnosis is confirmed, treatment with β-blockers is indicated, and lifestyle changes are recommended. Although high-quality outcome studies are lacking to demonstrate a benefit of medication treatment, it is very likely that treatment reduces the risk of sudden cardiac death (SCD). Therefore, there is a clinical utility.

There is currently no direct method of genotype-based risk stratification for management or prognosis of CPVT. However, testing can have important implications for all family members for presymptomatic diagnosis, counseling, or therapy. Asymptomatic patients with confirmed CPVT should also be treated with β-blockers and lifestyle changes. Also, CPVT has been associated with sudden infant death syndrome, and some investigators have considered testing at birth for prompt therapy in infants who are at-risk due to CPVT in close family members.

Long QT Syndrome
Long QT syndrome (LQTS) may lead to catastrophic outcomes (i.e., sudden cardiac death [SCD]) in otherwise healthy individuals. Diagnosis using clinical methods alone may lead to underdiagnosis of LQTS, thus exposing undiagnosed patients to the risk of SCA. For individuals in whom the clinical diagnosis of LQTS is uncertain, genetic testing may be necessary to clarify whether LQTS is present. Individuals who are identified as genetic carriers of LQTS variants have a non-negligible risk of adverse cardiac events even in the absence of clinical signs and symptoms of the disorder. Therefore, treatment is likely indicated for individuals found to have an LQTS variant, with or without other signs or symptoms.

Treatment with β-blockers has been demonstrated to decrease the likelihood of cardiac events, including SCA.

Sodium-channel blockers (e.g., mexiletine) are sometimes used, particularly in those with *SCN5A* variants. Preliminary modeling studies by Zhu et al (2018) designed to

predict LQT3 mutations with enhanced mexiletine sensitivity have been successfully validated in a small initial cohort of patients.

Treatment with an ICD is available for patients who fail or cannot take β-blockers. Cuneo et. al., (2020) conducted a multicenter retrospective analysis of 148 pregnancies from 103 families with the 3 most common heterozygous pathogenic LQTS genotypes (*KCNQ1*, *KCNH2*, or *SCN5A*).[58,] Fetal death at >20 weeks gestation was 8 times more frequent compared to the general population. The likelihood of fetal death was found to be significantly greater with maternal versus paternal LQTS (24.4% vs. 3.5%; p=.36).

In 2019, Biton et. al., studied long QT syndrome (LQTS) patients (n=212) enrolled in the Rochester LQTS ICD registry who underwent ICD implantation for primary prevention of SCD. During median follow-up duration of 9.2 ± 4.9 years, 42 patients experienced at least 1 appropriate shock. The cumulative probability of appropriate shock at 8 years was 22%. $QT_c \geq 550$ ms (HR, 3.94; 95% CI, 2.08 to 7.46; p<.001) and prior syncope on β-blockers (HR, 1.92, 95% CI, 1.01 to 3.65; p=.047) were associated with an increased risk of appropriate shock. Importantly, LQT2 genotype (HR, 2.10; 95% CI, 1.22 to 3.61; p=.008) and the presence of multiple mutations (HR, 2.87; 95% CI, 1.49 to 5.53; p=.002) were associated with an increased risk of recurrent shocks compared to LQT1 genotype, suggesting that both clinical and genetic variables may have utility in the risk stratification of high-risk patients undergoing evaluation for an ICD.

Shimizu et. al. (2019) conducted an observational study on 1124 Japanese patients with LQTS and various pathogenic variants (e.g., nonpore membrane-spanning variants, pore site and segment 5 to segment 6 [S5-pore-S6] variants, and N/C-terminus variants) for LQT1, LQT2, and LQT3. For patients with LQT1, the membrane-spanning pathogenic variant was associated with a higher risk of arrhythmic events compared to the N/C-terminus variant in female patients (HR, 1.60; 95% CI, 1.19 to 2.17; p=.002). Patients with LQT2 S5-pore-S6 variants were found to have a higher risk of arrhythmic events compared to others (HR, 1.88; 95% CI, 1.44 to 2.44; p<.001). In patients with LQT3, S5-pore-S6 variants were associated with lethal arrhythmic events compared with other (HR, 4.2; 95% CI, 2.09 to 8.36; p<.001). While these findings suggest that risk stratification of arrhythmic events may potentially be informed by specific pathogenic gene variants in LQTS, the study is limited by its retrospective analysis.

Short QT Syndrome

Limited data on the clinical validity of short QT syndrome (SQTS) were identified in the peer-reviewed literature due to the rarity of the condition. A precise genetic testing yield is unknown.

No studies were identified that provide evidence for the clinical utility of genetic testing for SQTS, consistent with the clinical rarity of the condition. Clinical sensitivity for the test is low, with laboratory test providers estimating a yield as low as 15%.

Summary of Evidence

Brugada Syndrome

For individuals with suspected Brugada Syndrome (BrS) who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields. The clinical validity of testing for BrS is low: a genetic variant can only be identified in approximately 15% to 35% of BrS. Management changes, primarily use of ICDs, are directed by clinical symptoms. It is not clear that a genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known Brugada Syndrome (BrS) variant who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields. Brugada syndrome management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on the effect of changes in management based on genetic testing in an individual with family members who have a known variant. However, a negative test would allow family members to defer further testing. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Catecholaminergic Polymorphic Ventricular Tachycardia

For individuals with suspected CPVT who receive genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia (CPVT), the evidence includes observational studies reporting on testing yields. A genetic variant can be identified in approximately 60% of CPVT patients. There is a chain of evidence to suggest that testing for variants associated with CPVT in individuals who are suspected to have these disorders. Confirming the diagnosis of CPVT is likely to lead to a health outcome benefit by initiating changes in management that reduce the risk of ventricular arrhythmias and sudden cardiac death (SCD). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known catecholaminergic polymorphic ventricular tachycardia (CPVT) variant who receive genetic testing for variants associated with CPVT, the evidence includes observational studies reporting testing yields. For close relatives of patients with known CPVT variants who are found to have a pathogenic variant, preventive treatment can be initiated. Also, a negative test in the setting of a known familial variant should have a high negative predictive value. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Long QT Syndrome

For individuals with suspected congenital long QT syndrome (LQTS) who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on the testing yield. A genetic variant can be identified in

approximately 70% of those with LQTS. The clinical utility of genetic testing for LQTS is high when there is a moderate-to-high pretest probability. There is a chain of evidence to suggest that testing for variants associated with LQTS in individuals who are suspected to have these disorders leads to improved outcomes. A definitive diagnosis of LQTS leads to treatment with β-blockers in most cases, and sometimes to treatment with an ICD. As a result, confirming the diagnosis is likely to lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and sudden cardiac death (SCD). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known long QT syndrome (LQTS) variant who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on changes in management. A positive genetic test for an LQTS variant leads to treatment with β-blockers in most cases, and sometimes to treatment with an ICD; a negative test would allow family members to defer further testing. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Short QT Syndrome

For individuals with suspected short QT syndrome (SQTS) who receive genetic testing for variants associated with SQTS, the evidence includes limited data on testing yields. The yield of genetic testing in SQTS is not well-characterized. Management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on changes in management based on genetic testing in a symptomatic proband without a definitive diagnosis. It is not clear that a genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic to determine future risk of short QT syndrome (SQTS) with a close relative(s) (i.e., first-, second-, or third-degree relative) with a known short QT syndrome (SQTS) variant who receive genetic testing for variants associated with SQTS, the evidence includes observational studies reporting on testing yields. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management, which improve net health outcomes. Changes in management may include periodic clinical and cardiovascular evaluations to detect the earliest signs of disease, as well as genetic counseling. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close family member(s) (i.e., first-, second-, or third-degree relative) who experienced sudden cardiac death (SCD) and a specific diagnosis has been made who receive genetic testing for variants associated with cardiac ion channelopathies, the evidence includes cohort studies that describe the genetic testing yield. In all studies identified, genetic testing was obtained only after a specific diagnosis

was suspected based on history or ancillary testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Genetic Testing for Idiopathic Dilated Cardiomyopathy
Dilated cardiomyopathy (DCM) is defined as the presence of left ventricular enlargement and dilatation in conjunction with significant systolic dysfunction. Dilated cardiomyopathy has an estimated prevalence of 1 in 2700 in the United States. The age of onset for DCM is variable, ranging from infancy to the eighth decade, with most individuals developing symptoms in the fourth through sixth decade. Primary clinical manifestations of DCM are heart failure and arrhythmias. Symptoms of heart failure, such as dyspnea on exertion and peripheral edema, are the most common presentation of DCM. These symptoms are generally gradual in onset and slowly progressive over time. Progressive myocardial dysfunction also may lead to electrical instability and arrhythmias. Symptoms of arrhythmias may include light-headedness, syncope, or sudden cardiac arrest.

There are a variety of causes of dilated cardiomyopathy (DCM), including genetic and nongenetic conditions. Genetic forms of DCM are heterogeneous in their molecular basis and clinical expression. Genetic testing for DCM has potential utility for confirming a diagnosis of genetic DCM and as a prognostic test in family members when familial DCM is present.

Idiopathic Dilated Cardiomyopathy
When an individual presents with dilated cardiomyopathy (DCM), a workup is performed to identify underlying causes, especially those treatable. The standard workup consists of a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for coronary artery disease as warranted by risk factors. An extensive workup including cardiac magnetic resonance imaging (MRI), exercise testing, right-sided catheterization with biopsy, and 24-hour electrocardiography monitoring will uncover only a small number of additional etiologies for DCM. Approximately 35% to 40% of DCM cases are thus determined to be idiopathic after a negative workup for the secondary causes listed above. This has traditionally been termed idiopathic dilated cardiomyopathy (IDC).

Clustering of IDC within families has been reported, leading to the conclusion that at least some cases of DCM have a genetic basis. Familial DCM is diagnosed when 2 closely related family members have IDC in the absence of underlying causes. Penetrance of familial DCM is variable and age-dependent, often leading to a lack of appreciation of the familial component.

Genetic Dilated Cardiomyopathy
Genetic dilated cardiomyopathy (DCM) has been proposed as a newer classification that includes both familial DCM and some cases of sporadic idiopathic dilated cardiomyopathy (IDC). The percentage of patients with sporadic DCM that has a genetic basis is not well characterized. Most disease-associated variants are inherited in an

autosomal dominant fashion, but some autosomal recessive, X-linked, and mitochondrial patterns of inheritance also are present. Expanded numbers of genotyped individuals facilitate genotype-phenotype correlations and studies of natural disease history. Recognition of high-risk variant carriers is important as these individuals would be expected to have the most to gain from pre-emptive interventions.
In general, genotype-phenotype correlations in the inherited cardiomyopathies are either not present or not well characterized. There have been some purported correlations between certain disease-associated variants and the presence of arrhythmias. For example, individuals with conduction system disease and/or a family history of sudden cardiac death (SCD) may be more likely to have disease-associated variants in the lamin A/C (LM), SCN5A, and desmin genes. Kayvanpour et al (2017) performed a meta-analysis of genotype-phenotype associations in DCM. The analysis included 48 studies (N=8097 patients) and found a higher prevalence of sudden cardiac death, cardiac transplantation, and ventricular arrhythmias in the LM and phospholamban (PLN) disease-associated variant carriers and increasing penetrance with age of DCM phenotype in subjects with titin (TTN)-truncating variants.

There may be interactions between genetic and environmental factors that lead to the clinical manifestations of DCM. A genetic variant may not in itself be sufficient to cause DCM but may predispose to developing DCM in the presence of environmental factors such as nutritional deficiencies or viral infections. It also has been suggested that DCM genetics may be more complex than single-gene variants, with low-penetrance variants that are common in the population contributing to a cumulative risk of DCM that includes both genetic and environmental factors.

Diagnosis and Management of Dilated Cardiomyopathy
Primary clinical manifestations of dilated cardiomyopathy (DCM) are heart failure and arrhythmias. Symptoms of heart failure, such as dyspnea on exertion and peripheral edema, are the most common presentations of DCM. These symptoms are generally gradual in onset and slowly progressive over time. Progressive myocardial dysfunction also may lead to electrical instability and arrhythmias. Symptoms of arrhythmias may include light-headedness, syncope, or sudden cardiac arrest.

Many underlying conditions can cause DCM, including:

- Ischemic coronary artery disease
- Toxins
- Metabolic conditions
- Endocrine disorders
- Inflammatory and infectious diseases
- Infiltrative disorders
- Tachycardia-mediated cardiomyopathy.

Treatment of DCM is similar to that for other causes of heart failure. This includes medications to reduce fluid overload and relieve strain on the heart, and lifestyle modifications such as salt restriction. Patients with clinically significant arrhythmias also

may be treated with antiarrhythmic medications, pacemaker implantation, and/or an automatic implantable cardiac defibrillator (AICD). AICD placement for primary prevention also may be performed if criteria for low ejection fraction and/or other clinical symptoms are present. End-stage DCM can be treated with cardiac transplantation.

Genetic Testing for Dilated Cardiomyopathy

Approximately 30% to 40% of patients with dilated cardiomyopathy (DCM) referred for genetic testing will have a disease-associated variant identified. Disease-associated variants linked to DCM have been identified in more than 40 genes of various types and locations. The most common genes involved are those that code for TTN, myosin heavy chain (MYH7), troponin T (TNNT2), and alpha-tropomyosin (TPM1). These 4 genes account for approximately 30% of disease-associated variants identified in cohorts of patients with DCM. A high proportion of the identified disease-associated variants are rare, or novel, variants, thus creating challenges in assigning the pathogenicity of discovered variants. Some individuals with DCM will have more than 1 DCM-associated variant. The frequency of multiple disease-associated variants is uncertain, as is the clinical significance.

Testing Patients with Signs and/or Symptoms of Dilated Cardiomyopathy

Clinical Context and Test Purpose

The purpose of genetic testing in patients who have signs and/or symptoms of dilated cardiomyopathy (DCM) is to confirm a diagnosis and inform treatment decisions such as the decision on when to implant a cardioverter-defibrillator. Because DCM presents with nonspecific symptoms and can be caused by various disorders, it has been proposed that genetic testing can confirm a DCM diagnosis in borderline cases or idiopathic DCM. Decisions on medical therapy in symptomatic DCM patients are generally based on cardiac phenotype, although the prophylactic placement of a pacemaker and/or implantable cardioverter-defibrillator is sometimes considered in patients with DCM and lamin A/C (LM) or desmin disease-associated variants.

Populations

The relevant population of interest is patients with signs and/or symptoms of DCM (ie, heart failure or arrhythmias, frequently presenting as dyspnea on exertion and peripheral edema), which is considered idiopathic DCM after a negative workup for secondary causes.

Interventions

Genetic testing can be performed on any number of candidate genes, individually or collectively. Lists of genes that may lead to inherited cardiomyopathies and testing laboratories in the United States are provided at the GeneTests website funded by BioReference Laboratories and the Genetic Testing Registry of the National Center for Biotechnology Information website.

Evaluation and genetic testing of cardiomyopathy are complex. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators
The comparator of interest is standard clinical care without genetic testing such that decisions regarding medical therapy in symptomatic dilated cardiomyopathy (DCM) patients are being made based on cardiac phenotype.

Outcomes
The outcomes of interest for individuals with symptomatic dilated cardiomyopathy (DCM):

Outcomes	Details
Overall survival	2-year survival
Change in disease status	New York Heart Association heart failure class
Symptoms	KCCQ or other validated symptom assessment tools
Functional outcomes	KCCQ; timed walk; exercise testing
Quality of Life	KCCQ, Minnesota Living with Heart Failure or other validated QOL assessment tools
Treatment-related morbidity	Adverse events of implantable cardioverter-defibrillator

KCCQ: Kansas City Cardiomyopathy Questionnaire; QOL: quality of life.

The potentially beneficial outcomes of primary interest would be an improvement in overall survival and change in disease status because changes in management in symptomatic DCM are initiated to prevent sudden cardiac death and slow or reverse the progression of heart failure. Improvement in symptoms, functioning, and quality of life are also important.
The potentially harmful outcomes are those resulting from a false test result. False-positive test results can lead to the initiation of unnecessary treatment and adverse events from that treatment. In this case, placement of an implantable cardioverter-defibrillator.

Trials of genetic testing or treatment strategies in this population were not found. Two trials of implantable cardioverter-defibrillator use in other nonischemic cardiomyopathies have reported that changes in the 2- and 5-year overall survival are meaningful for interventions for cardiomyopathies. Therefore, 2-year survival and changes in other outcomes over the same period should be considered meaningful in this review.

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Numerous studies have evaluated the proportion of patients with clinically diagnosed DCM who have disease-associated variants. These studies vary in the genes examined and methods used to detect these variants. A common type of study describes the presence of 1 type of disease-associated variant in probands with DCM or family members of the proband. Fewer studies have evaluated multiple genes in cohorts of patients with DCM. In addition, only a limited number of studies have used next-generation sequencing (NGS), which is expected to have higher sensitivity than other methods and is expected to have higher rates of variants of uncertain significance

Next Generation Sequencing (NGS)
The largest study to date, the Integrated Heart Research in Translational Genetics of Dilated Cardiomyopathies in Europe (INHERITANCE) project, examined a comprehensive set of disease-associated variants and used NGS as the testing method. A total of 639 patients with sporadic (51%) or familial (49%) DCM were enrolled in 8 clinical centers in Europe between 2009 and 2011. Secondary DCM was ruled out by excluding patients with hypertension, valve disease, and other loading conditions; coronary artery disease was ruled out by coronary angiography in 53% of patients. Next generation sequencing was used to sequence 84 genes. Pathogenicity of variants was classified as known (included in the Human Genome Mutation Database for heart muscle diseases and channelopathies); likely (frameshift insertions or deletions, stop-gain or stop-loss variants, and splice-site variants); potential (not common, nonsynonymous variants associated with "disease" prediction according to an online calculator, SNPs&GO[26,]); or benign (identified in the SNP database[8,] with allele frequency ≥1%). Known DCM-associated variants were found in 101 (16%) patients, most commonly in the PKP2, MYBPC3, and DSP genes. Additionally, 117 likely pathogenic variants were found in 26 genes in 147 (23%) patients, most commonly in TTN, PKP2, MYBPC3, DSP, RYR2, DSC2, DSG2, and SCN5A. Eighty-two (13%) patients carried more than 1 DCM-associated variant, and there was considerable overlap of identified disease-causing variants with other cardiac diseases: 31% of patients had variants associated with arrhythmogenic right ventricular cardiomyopathy; 16% with hypertrophic cardiomyopathy; 6% with channelopathies; and 6% with other cardiac diseases.

Dalin et. al. (2017) used next generation sequencing (NGS) to sequence the coding regions of 41 DCM-associated genes in 176 unrelated patients with idiopathic DCM, which were compared with 503 healthy reference individuals in the European ancestry cohort of the 1000 Genomes project. Fifty-five (31%) patients had 1 variant in the analyzed genes, and 24 (14%) patients had 2 or more variants. Genetic variants in any

gene, or variants in LM, MYH7, or TTN alone, were all associated with early disease onset and reduced transplant-free survival. Lamin A/C variants had the strongest association with transplant-free survival. There was no difference in the prevalence of familial DCM between patients with and without variants. Patients with more than 1 variant were more likely to have familial DCM or potential familial DCM compared with patients with only 1 variant (p=.046). Stop-gain and frameshift variants were more common in DCM patients (12%) than in the healthy reference individuals (0.6%). However, the prevalence of missense variants was 35% in DCM patients and 37% in healthy reference individuals; conservation and pathogenicity scores and localization of missense variants were also similar in the 2 groups.

Other Methods and Clinical Outcomes

Ebert et. al., (2020) evaluated the frequency of (likely) pathogenic variants among 98 patients with DCM referred for ventricular tachycardia ablation. All patients underwent electroanatomical mapping and testing of ≥55 cardiomyopathy-related genes. Likely pathogenic/pathogenic variant-positive patients were compared with likely pathogenic/pathogenic variant negative patients and followed for ventricular tachycardia recurrence. In 37 (38%) patients, likely pathogenic/pathogenic variants were identified, most frequently LMNA (30%), TTN (16%), SCN5A (8%), RBM20 (5%), and DSP (5%). Likely pathogenic/pathogenic variant-positive carriers had a lower left ventricular ejection fraction as compared to likely pathogenic/pathogenic variant-negative carriers (35% vs. 42%; p=.005). After a median follow-up of 2.4 years, 63 (64%) patients had ventricular tachycardia recurrence (81% pathogenic variant-positive vs. 54% pathogenic variant-negative; p=.007) and 28 (29%) patients died (51% pathogenic variant-positive vs. 15% pathogenic variant-negative; p<.001).

Myers et. al., (2018) evaluated the presence of Bcl2-associated anthanogene 3 (BAG3) variants in African Americans with DCM and the association of the variants on event-free survival. Genetic testing for BAG3 variants was performed on African American patients from 3 independent trials (African American Heart Failure Trial, Intervention in Myocarditis and Acute Cardiomyopathy Trial-2, and Genetic Risk Assessment of Cardiac Events study). Among 402 patients with idiopathic DCM, 4 BAG3 variants were detected in 42 (10%) patients. In a population of 359 patients of European ancestry with idiopathic DCM, the prevalence of BAG3 variants was zero. Among the 402 patients with idiopathic DCM, those with BAG3 variants experienced significantly lower event-free survival compared with patients that did not have BAG3 variants (p=.02).

Verdonschot et. al., (2018) compared long-term outcomes among DCM patients with (n=38) and without (n=265) truncating titin variants (TTNtv). Patients were followed for a median of 45 months (interquartile range, 20 to 77 months). Outcomes of interest included cardiac death, heart transplantation, life-threatening ventricular arrhythmias, and unscheduled heart failure hospitalizations. None of the outcomes was significantly different among patients with and without TTNtv except for life-threatening ventricular arrhythmias. Patients with TTNtv experienced significantly more life-threatening ventricular arrhythmias compared with patients without TTNtv (hazard ratio [HR]: 2.8;

95% confidence interval [CI]: 1.2 to 6.3). Combining the 4 outcomes into a composite endpoint was not statistically significant, possibly due to the small number of patients with TTNtv (HR: 1.5; 95% CI: 0.7 to 3.1).

Van der Linde et. al. (2017) published a retrospective analysis of 80 individuals (15 probands, 65 family members) in the Netherlands who had a variant in the MYH7 gene identified through whole-exome sequencing.[28,] Cardiomyopathy was observed in 47.7% of individuals with the variant gene, and the majority (63%) of those with cardiomyopathy also showed a reduced left ventricular ejection fraction. A higher proportion of individuals with the variant gene had a congenital heart defect compared with the likelihood observed in the general Dutch population (8.8% vs. 1%). Following haplotype analysis, the investigators concluded that the variant observed appeared to be a founder mutation in MYH7, acknowledging the sample size and length of follow-up were not optimal and could not account for other potential genetic factors

There are no randomized controlled trials (RCTs) assessing clinical utility. Below information is related to 2 prospective observational studies.

Although researchers have investigated pharmacogenetic associations in DCM, the absence of prospective, randomized trials to compare standard treatment with genotype-guided treatment precludes the findings being clinically useful. Reddy et. al., (2015) evaluated the impact of adrenergic receptor genotype on hemodynamic status in 2 cohorts of pediatric patients (age <22 years) who had DCM and stable (n=44) or advanced (ie, listed for transplantation; n=91) heart failure. Three adrenergic receptor variants associated with heart failure in adults were genotyped: ADRA2C del322-325, ADRB1 Gly389Arg, and ADRB2 Gly16Arg. At a mean follow-up of 2.2 years, patients with stable or advanced heart disease who had at least 1 variant showed greater response to ß-blocker treatment than patients who had no variant (genotype ß-blocker interaction p-values ≤.05 for several hemodynamic parameters). Wasielewski et al (2014) reported on a descriptive study investigating whether familial DCM may predispose to anthracycline-associated cardiomyopathy.[39,] Genotyping of 48 cardiomyopathy-associated genes in patients with DCM who also had anthracycline-associated cardiomyopathy (n=5) and in patients with anthracycline-associated cardiomyopathy alone who met criteria for familial DCM based on family history (n=6) identified 2 known pathogenic variants and 9 VUS.

In an observational prospective study, Hasselberg et. al., (2017) followed 79 individuals with an LM variant who were either symptomatic probands (n=48) or asymptomatic genotype-positive family members (n=31). By the end of 4 years of follow-up, 37% of the patients were pacemaker-dependent due to third-degree atrioventricular blockage. During an average of 8 years of follow-up, 15 of the 79 probands received heart transplantations. Asymptomatic family members experienced a 9% annual incidence of newly documented cardiac phenotype and 61% (19/31) cardiac penetrance during an average of 4 years of follow-up. Given the combined likelihood of morbidity and mortality, the requirement for heart transplantation, and the considerable frequency of other cardiac events observed during follow-up in both symptomatic and asymptomatic

groups, the investigators recommended that relatives of probands with known LM variant be screened due to increased risk.

Genetic Testing for Asymptomatic Individuals to Determine Future Risk

Clinical Context and Test Purpose
The purpose of genetic testing for patients who are asymptomatic with a close relative who has dilated cardiomyopathy (DCM) and a known genetic variant is to inform decisions regarding the frequency of screening and timing of initiation of treatment such as when to implant a cardioverter-defibrillator or start therapy with β-blockers or angiotensin-converting enzyme inhibitors.

It has been proposed that early initiation of therapy with angiotensin-converting enzyme inhibitors or β-blockers may slow progression of heart failure, but there is no evidence to support their use in asymptomatic patients.

Populations
The relevant population of interest is individuals who are asymptomatic with a close relative who has dilated cardiomyopathy (DCM) and a known pathogenic variant.

Interventions
The genetic testing for dilated cardiomyopathy (DCM) is performed using tests that should be primarily focused on the variant(s) identified in the relative with DCM. Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators
The comparator of interest is standard clinical care without genetic testing such that decisions on screening and medical therapy are based on guidelines for patients with a relative with dilated cardiomyopathy (DCM).

Outcomes
Outcomes of interest for asymptomatic individuals with a relative with dilated cardiomyopathy (DCM):

Outcomes	Details
Morbid events	Incidence of heart failure or tachycardia
Symptoms	KCCQ or other validated symptom assessment tools
Functional outcomes	KCCQ; timed walk; exercise testing
QOL	KCCQ, Minnesota Living with Heart Failure or other validated QOL assessment tools
Treatment-related morbidity	Adverse effects of ICD, ACE inhibitors, or β-blockers

ACE: angiotensin-converting enzyme; ICD: implantable cardioverter-defibrillator; KCCQ: Kansas City Cardiomyopathy Questionnaire; QOL: quality of life.
The potentially beneficial outcome of primary interest would be a reduction in the incidence of morbid events because changes in management in symptomatic DCM are initiated to prevent the development of heart failure and tachycardia. Prevention of symptoms, maintenance of function, and quality of life are also important.

The potentially harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse events from that treatment. In this case, placement of an implantable cardioverter-defibrillator or treatment with angiotensin-converting enzyme inhibitors or β-blockers. False-negative test results could lead to delay in diagnosis and treatment.

Review of Evidence
Several studies have described the prevalence of dilated cardiomyopathy (DCM) in family members of patients diagnosed with idiopathic DCM, with estimates ranging from 20% to 35%.

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

In family members of patients with DCM, genetic testing can be used to determine whether a known pathogenic variant has been inherited. Several issues in predictive testing for DCM create challenges for establishing that genetic testing is clinically useful. This first requires confidence that the variant identified in the proband causes DCM (clinically valid). If there is uncertainty about the pathogenicity of the variant, then genetic testing may provide misleading information. Because of the high number of novel variants and VUS identified in DCM, the confidence that a variant causes the disorder is less than for many other cardiac conditions.
Uncertain penetrance and variable clinical expression also need to be considered in determining the utility of predictive testing. Because of heterogeneity in clinical expression, it may not be possible to adequately counsel an asymptomatic patient on the precise likelihood of developing DCM, even when an inherited variant has been identified.

Predictive testing may lead to changes in screening and surveillance, particularly for patients who test negative in whom surveillance might be discontinued. However, it is uncertain whether this approach leads to improved outcomes because of the uncertain clinical validity of testing. For example, a proband may be identified with a variant that is possibly pathogenic. A close family member may test negative for that variant and be falsely reassured they are not at-risk for DCM when they still may have another undiscovered variant.

While there is general agreement that early treatment for DCM is optimal, no trials demonstrated improved outcomes with presymptomatic treatment compared with delaying treatment until the onset of symptoms, although at least 1 such trial is in progress. If early treatment is based primarily on genetic testing, then additional concerns of false-positive (initiating unnecessary treatment and adverse events of those treatments) and false-negative test results (delay of treatment initiation) need to be considered.

In the observational prospective study by Hasselberg et al (2017) described above, 31 of the 79 individuals were asymptomatic family members with an LM variant. The asymptomatic family members experienced a 9% annual incidence of newly documented cardiac phenotype and 61% (19/31) cardiac penetrance during an average of 4 years of follow-up. Ten (31%) experienced atrioventricular blockage, 12 experienced ventricular tachycardia, and 7 experienced atrial fibrillation during follow-up. Given the combined likelihood of morbidity and mortality, and the considerable frequency of other cardiac events observed during follow-up in the initially asymptomatic group, the investigators recommended that relatives of probands with known LM variant be screened.

Summary of Evidence

For individuals who have signs and/or symptoms of dilated cardiomyopathy (DCM) who receive comprehensive genetic testing, the evidence includes large case series reporting clinical validity and prospective observational studies reporting clinical utility. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 40%. Additional studies assessed clinical outcomes of patients with DCM and at least 1 known variant compared with patients with DCM and no known variants. The studies reported that patients with DCM and known variants experienced lower event-free survival, earlier onset of symptoms, lower transplant-free survival, and more life-threatening arrhythmias compared with patients with DCM and no known variants. A prospective observational study has reported that patients with DCM and known variants experienced high rates of morbidity and mortality during 4 to 8 years of follow-up. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management, which improve net health outcomes. Changes in management may include earlier implantation of cardiac defibrillators or increased surveillance to detect worsening of symptoms, as well as cascade genetic testing of asymptomatic family members. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a first-degree relative who has dilated cardiomyopathy (DCM) and a known familial variant who receive targeted genetic testing for a known familial variant, the evidence includes case series reporting clinical value and a prospective observational study reporting clinical utility. Relevant outcomes are test validity, symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. For an individual at-risk due to genetic DCM in the family, genetic testing can identify whether a familial variant has been inherited. A prospective

observational study with 4 to 8 years of follow-up reported the development of cardiac symptoms among patients initially asymptomatic who had DCM-related variants. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management, which improve net health outcomes. Changes in management may include periodic clinical and cardiovascular evaluations to detect the earliest signs of disease, as well as genetic counseling. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy
Familial hypertrophic cardiomyopathy (HCM) is an inherited condition that is caused by a variation in 1 or more of the cardiac sarcomere genes. HCM is associated with numerous cardiac abnormalities, the most serious of which is sudden cardiac death (SCD). Genetic testing for HCM-associated variations is currently available through several commercial laboratories.

Due to the complexity of genetic testing for hypertrophic cardiomyopathy (HCM) and the potential for misinterpretation of results, the decision to test and the interpretation of test results should be performed by, or in consultation with, an expert in the area of medical genetics and/or hypertrophic cardiomyopathy.

To inform and direct genetic testing for at-risk individuals, genetic testing should initially be performed in at least 1 close relative with definite hypertrophic cardiomyopathy (index case), if possible

Because there are varying degrees of penetrance for different hypertrophic cardiomyopathy variants, consideration for testing of second- or third-degree relatives may be appropriate in certain circumstances. Some judgment should be allowed for these decisions (e.g., in the case of a small family pedigree). Consultation with an expert in medical genetics and/or the genetics of hypertrophic cardiomyopathy, in conjunction with a detailed pedigree analysis, is appropriate when testing of second- or third-degree relatives is considered.

Familial Hypertrophic Cardiomyopathy
Familial hypertrophic cardiomyopathy is the most common genetic cardiovascular condition, with a phenotypic prevalence of approximately 1 (0.2%) in 500 adults. It is the most common cause of sudden cardiac death (SCD) in adults younger than 35 years of age and is probably the most common cause of death in young athletes. The overall mortality rate for patients with hypertrophic cardiomyopathy is estimated to be 1% per year in the adult population.

The genetic basis for hypertrophic cardiomyopathy is a defect in the cardiac sarcomere, which is the basic contractile unit of cardiac myocytes and is composed of different protein structures. Around 1400 disease-associated variants in at least 18 different genes have been identified. About 90% of pathogenic variants are missense (i.e., 1 amino acid is replaced for another), and the strongest evidence for pathogenicity is available for 11

genes coding for thick filament proteins (*MYH7*, *MYL2*, *MYL3*), thin filament proteins (TNNt2, TNNI3, TNNC1, TPM1, ACTC), intermediate filament proteins (*MYBPC3*), and the Z-disc adjoining the sarcomere (*ACTN2*, *MYOZ2*). Variants in myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) are the most common and account for roughly 80% of sarcomeric hypertrophic cardiomyopathy. These genetic defects are inherited in an autosomal dominant pattern with rare exceptions. In patients with clinically documented hypertrophic cardiomyopathy, genetic abnormalities can be identified in approximately 60%. Most patients with clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo variants

Diagnosis and Management

The clinical diagnosis of hypertrophic cardiomyopathy depends on the presence of left ventricular hypertrophy, measured by echocardiography or magnetic resonance imaging (MRI), in the absence of other known causative factors such as valvular disease, long-standing hypertension, or another myocardial disease. In addition to primary cardiac disorders, there are systemic diseases that can lead to left ventricular hypertrophy and thus mimic hypertrophic cardiomyopathy. These include infiltrative diseases such as amyloidosis, glycogen storage diseases (e.g., Fabry disease, Pompe disease), and neuromuscular disorders (e.g., Noonan syndrome, Friedreich ataxia). These disorders need to be excluded before a diagnosis of familial hypertrophic cardiomyopathy is made. Hypertrophic cardiomyopathy is a very heterogeneous disorder. Manifestations range from subclinical, asymptomatic disease to severe, life-threatening disease. Wide phenotypic variability exists among individuals, even when an identical variant is present, including among affected family members. This variability in clinical expression may be related to environmental factors and modifier genes. A large percentage of patients with hypertrophic cardiomyopathy, perhaps the majority, are asymptomatic or have minimal symptoms. These patients do not require treatment and are not generally at high-risk for sudden cardiac death. A subset of patients has severe disease that causes a major impact on quality of life and life expectancy. Severe disease can lead to disabling symptoms, as well as complications of hypertrophic cardiomyopathy, including heart failure and malignant ventricular arrhythmias. Symptoms and presentation may include sudden cardiac death due to unpredictable ventricular tachyarrhythmias, heart failure, or atrial fibrillation, or some combination.

Management of patients with hypertrophic cardiomyopathy involves treating cardiac comorbidities, avoiding therapies that may worsen obstructive symptoms, treating obstructive symptoms with β-blockers, calcium channel blockers, and (if symptoms persist) invasive therapy with surgical myectomy or alcohol ablation, optimizing treatment for heart failure, if present, and sudden cardiac death risk stratification. Implantable cardioverter-defibrillator implantation may be indicated if there is a family history of sudden cardiac death.

Diagnostic screening of first-degree relatives and other family members is an important component of hypertrophic cardiomyopathy management. Guidelines have been

established for screening clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals aged 12 to 18 years and every 3 to 5 years for adults. Additional screening is recommended for any change in symptoms that might indicate the development of hypertrophic cardiomyopathy

Genetic Testing
Genetic testing has been proposed as a component of screening at-risk individuals to determine predisposition to hypertrophic cardiomyopathy (HCM) among those individuals at-risk. Individuals at-risk for hypertrophic cardiomyopathy (HCM) are defined as individuals who have a close relative with established hypertrophic cardiomyopathy. Results of genetic testing may influence the management of at-risk individuals, which may, in turn, lead to improved outcomes. Furthermore, results of genetic testing may have implications for decision making in the areas of reproduction, employment, and leisure activities. However, the likelihood of obtaining a positive genetic test in the proband is only about 50% because all genes causing hypertrophic cardiomyopathy (HCM) have not yet been identified or are absent from testing panels. Failure to identify the causative variant in the proband is an indeterminate result that provides no useful information and precludes predictive testing in 33% to 67% of cases. Commercial testing has been available since 2003, and numerous companies offer genetic testing for hypertrophic cardiomyopathy (HCM). Testing is performed either as a comprehensive or targeted gene test. Comprehensive testing, which is done for an individual without a known genetic variant in the family, analyzes the genes most commonly associated with genetic variants for hypertrophic cardiomyopathy and evaluates whether any potentially pathogenic variants are present. Some available panels include testing for multisystem storage diseases that may include cardiac hypertrophy, such as Fabry disease (*GLA*), familial transthyretin amyloidosis (*TTR*), and X-linked Danon disease (*LAMP2*).

Other panels include testing for genes related to hypertrophic cardiomyopathy (HCM) and those associated with other cardiac disorders. For example, the Pan Cardiomyopathy panel (Laboratory for MolecularMedicine) is a next-generation sequencing panel of 62 genes associated with hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, left ventricular noncompaction syndrome, Danon syndrome, Fabry disease, Brugada syndrome, and transthyretin amyloidosis.
For a patient with a known variant in the family, targeted testing is performed. Targeted variant testing evaluates for the presence or absence of a single variant known to exist in a close relative.

It can be difficult to determine the pathogenicity of genetic variants associated with hypertrophic cardiomyopathy (HCM). Some studies have reported that assignment of pathogenicity has a relatively high error rate and that classification changes over time. With next-generation sequencing, the sensitivity of identifying variants on the specified genes has increased substantially. At the same time, the number of variants of

uncertain significance is also increased with next-generation sequencing. Also, the percentage of individuals who have more than 1 variant that is thought to be pathogenic is increasing.

Testing for a Specific Hypertrophic Cardiomyopathy Related Variant

Clinical Context and Test Purpose
The purpose of targeted genetic testing of individuals who are asymptomatic but at-risk of hypertrophic cardiomyopathy (HCM) is to inform management decisions. Genetic testing for hypertrophic cardiomyopathy (HCM) would play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals and genetic testing for reproductive decision making.

Populations
The relevant population of interest is asymptomatic individuals with a close relative who has hypertrophic cardiomyopathy and a known pathogenic variant.
This population of patients would also include the following:
Arrhythmogenic Cardiomyopathy (ACM)/Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)/ Arrhythmogenic Right Ventricular Dysplasia (ARVD)
ARVC/ARVD is a rare type of cardiomyopathy that occurs if the muscle tissue in the right ventricle dies and is replaced by fat or scar tissue:

- This process disrupts the heart's electrical system, causing arrhythmias.
- It usually affects teens and young adults.
- Symptoms include heart palpitations and fainting after physical activity.
- It can cause sudden cardiac arrest in young athletes.
- It may require implantation of a device to prevent death from an arrhythmia

Non-Compacted Left Ventricular Cardiomyopathy
Variations in several genes have been found to cause left ventricular noncompaction. Mutations in the MYH7 and MYBPC3 genes have been estimated to cause up to 30 percent of cases; mutations in other genes are each responsible for a small percentage of cases. However, the cause of the condition is often unknown. It is unclear how genetic mutations cause left ventricular noncompaction. During normal development before birth, cardiac muscle gets condensed (compacted), becoming smooth and firm. Mutations in certain genes likely lead to changes in this process, resulting in a left ventricular cardiac muscle that is not compacted but is thick and spongy, leading to left ventricular noncompaction.

Interventions
The test being considered is targeted genetic testing for the variant(s) identified in the relative with hypertrophic cardiomyopathy (HCM).

Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators
The comparator of interest is standard clinical management without genetic testing such that decisions related to surveillance and medical therapy are based on guidelines for individuals with a relative with hypertrophic cardiomyopathy (HCM).

Outcomes
If the test has a high, negative predictive value, the main beneficial outcome would be to safely reduce or eliminate the need for routine clinical surveillance for signs and symptoms of hypertrophic cardiomyopathy (HCM).

Potentially harmful outcomes are those resulting from a false test result. False-positive results can lead to initiation of unnecessary treatment and adverse events from that treatment. False-negative results could lead to delay in diagnosis and treatment.

The appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, children) and variation in age of onset of hypertrophic cardiomyopathy (HCM) from genetic causes. Changes in outcomes due to increased surveillance or early initiation of treatment in asymptomatic individuals would take many years to become evident.

Review of the Evidence

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing. When an individual tests positive for a specific hypertrophic cardiomyopathy (HCM) related variant, the clinical validity of a test to detect that specific variant in an asymptomatic first-degree relative relies on 2 factors: the analytic validity of the test itself and the penetrance (the probability that an individual with an identified pathogenic variant already has hypertrophic cardiomyopathy (HCM) or will develop hypertrophic cardiomyopathy (HCM) in the near future). A negative test indicates that the individual is free of the variant, while a positive test indicates that the patient has the variant and is at a higher risk for developing hypertrophic cardiomyopathy in the future.

Multiple studies have been published on the phenotypic penetrance of hypertrophic cardiomyopathy, which ranges from 50% to 100% and is briefly summarized below.

- Variants in the *MYBPC3* gene are the most common cause (14% to 26%) of hypertrophic cardiomyopathy (HCM). Approximately 40% of adults under the age

of 50 with *MYBPC3* variants do not have cardiac hypertrophy, and disease penetrance may remain incomplete through the age of 60.

- Variants in the *MYH7* gene are found in 13% to 25% of individuals with hypertrophic cardiomyopathy (HCM) and are associated with a high penetrance of disease, younger age at diagnosis, and more severe hypertrophy. However, there is substantial clinical heterogeneity in the phenotypic expression of hypertrophic cardiomyopathy in such individuals. Survival in those with hypertrophic cardiomyopathy (HCM) due to variants in the *MYH7* gene varies considerably despite nearly complete disease penetrance and significant hypertrophy.
- Variants in the *TNNI3* gene are found in 2% to 7% of individuals with hypertrophic cardiomyopathy (HCM) with a disease penetrance of approximately 50%.
- Variants in the *TNNT2, ACTC1, MYL2, MYL3,* and *TPM1* genes encode 1 of the myocardial sarcomeric proteins and are found in ≤4% of individuals with hypertrophic cardiomyopathy (HCM) with definitive evidence for their pathogenicity

Systematic Reviews

In 2017, Sedaghat-Hamedani et. al., conducted a systematic review and meta-analysis of studies assessing the genotype-phenotype associations in patients with hypertrophic cardiomyopathy (HCM) and variants in the following genes: *MYBPC3, MYH7, TNNT2*, and *TNNI3*. The literature search included studies from 1998 through 2015 and identified 51 studies with a total of 7675 patients with hypertrophic cardiomyopathy. The authors state that a quality assessment of the studies was performed but do not provide details on this assessment. Several studies reported heart transplantation rates among patients with hypertrophic cardiomyopathy and either *MYBPC3* or *MYH7*. Patients with the *MYH7* variant underwent significantly more heart transplantations compared with patients with the *MYBPC3* variant (p=.006). An analysis was also conducted comparing sudden cardiac deaths among patients with and without *MYBPC3, MYH7*, and *TNNT2* variants. Sudden cardiac death (SCD) occurred more frequently among patients with 1 of the variants compared with patients with no variants (p<.001).

Observational Studies

Lorenzini et. al., (2020) evaluated the incidence of new hypertrophic cardiomyopathy (HCM) diagnoses in sarcomere protein mutation carriers in a retrospective analysis. A total of 583 pathogenic/likely pathogenic variant carriers from 307 families were evaluated, with 267 (45.8%) diagnosed with hypertrophic cardiomyopathy at the initial evaluation and thereby excluded from the remainder of the study. An additional 31 subjects underwent a screening visit and were also excluded. This left a final study cohort of 285 subjects (median age: 14.2 years; 49.5% male). The frequency of causal genes was: MYBPC3 (43.2%), MYH7 (24.2%), TNNI3 (13.7%), TNNT2 (11.9%), TPM1 (3.2%), MYL2 (2.1%), ACTC1 (0.4%), and multiple mutations (1.4%). At a median follow-up of 8 years, 86 (30.2%) subjects developed hypertrophic cardiomyopathy and the estimated penetrance at 15 years of follow-up was 46%.

van Velzen et. al. (2018) conducted a retrospective analysis of asymptomatic relatives of 209 patients with hypertrophic cardiomyopathy. Genetic testing and counseling had been offered to all probands. In the cohort, 196 (94%) of the probands underwent genetic testing. Among the patients who were identified as variant-positive (149 of 196), 626 (80%) of the asymptomatic relatives underwent genetic testing. Results from testing of the relatives found 356 variant-negative and 264 variant-positive relatives. Cardiac screening was performed on the 264 relatives who were variant-positive and on the 157 relatives who did not undergo genetic testing (n=421). Based on the cardiac evaluation, hypertrophic cardiomyopathy was diagnosed in 126 (30%) of the relatives who were variant-positive and in 98 (37%) of the relatives who did not undergo genetic testing. After a median follow-up of 9 years of relatives with hypertrophic cardiomyopathy at baseline, all-cause mortality was 0.7% and cardiac mortality was 0.3%. After a median of 7 to 8 years of follow-up of relatives without hypertrophic cardiomyopathy at baseline, all-cause mortality was 0.1% and hypertrophic cardiomyopathy developed in 29 (16%).

Ko et. al., (2018) conducted a survey of patients with hypertrophic cardiomyopathy with and without variants and assessed first-degree family members for development of hypertrophic cardiomyopathy-related adverse events. Patients were recruited from a registry of patients with hypertrophic cardiomyopathy who had genetic testing. A total of 120 patients completed the survey: 56 had pathogenic variants; 49 had no variants; 11 had variants of undetermined significance; 4 had benign variants. A positive genetic test was associated with younger age at diagnosis, greater wall thickness, and absence of hypertension. Among patients with either a positive genetic test or family history, 34 of 203 first degree relatives (17%) reported a hypertrophic cardiomyopathy diagnosis. Among patients without genetic variants and no prior family history, 2 of 64 first degree relatives who were screened reported a hypertrophic cardiomyopathy diagnosis.

Lopes et. al., (2018) conducted genotype-phenotype analyses of probands and relatives (N=424) in the Portuguese registry of hypertrophic cardiomyopathy. The mean time of follow-up after diagnosis was 5.7 years (median of 3 years). Patients with a known variant were significantly more likely to have a family history of hypertrophic cardiomyopathy, a family history of sudden cardiac death, and no history of hypertension. Patients with a known variant were significantly more likely to have an American Heart Association/American College of Cardiology risk factor for sudden cardiac death compared with patients without a known variant. Genotype-positive status was associated with sudden cardiac death but was not associated with overall or cardiovascular mortality.

Cardoso et. al., (2017) reported on the outcomes of 17 first-degree relatives of 3 probands. Of the 17 tested, 14 child relatives were variant carriers (70%; median age, 8 years) of whom 7 (50%) were diagnosed with hypertrophic cardiomyopathy at initial assessment. After 3.5 years of follow-up, 2 of the phenotype negative genotype positive children developed hypertrophic cardiomyopathy at 10 and 15 years of age (28% penetrance rate).

Direct Evidence
No studies comparing outcomes for at-risk asymptomatic individuals managed with and without genetic testing were identified. Some studies have reported on cross-sectional or long-term follow-up of outcomes in single cohorts. These studies also showed that multiple pathogenic variants may occur in 1% to 10% of individual with hypertrophic cardiomyopathy (HC) and are associated with more severe disease and a worse prognosis. For these individuals, the targeted analysis might miss variants other than for the one tested. For this reason, some experts recommend comprehensive testing of all individuals; however, it is not known whether the presence of multiple pathogenic variants influences management decisions such that health outcomes might be improved.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

There is a range of benefits to genetic testing for at-risk individuals when there is a known disease-associated variant in the family.

- A positive test would imply that the individual has inherited the variant from the proband and can be placed under hypertrophic cardiomyopathy (HCM) surveillance using cardiac imaging to detect the development of the phenotype and adoption of therapy and lifestyle adaptations. However, it is important to underscore that because of variable penetrance, an individual with a positive test may not develop clinical disease in the future and, as such, all adopted interventions may not have an impact.
- A negative test would imply that the individual has not inherited the variant from the proband and clinical surveillance for hypertrophic cardiomyopathy (HCM) can be discontinued. Additionally, the individual can be reassured that the risk of developing the disease may be no greater than that of the general population. However, it is important to underscore that because of suboptimal clinical sensitivity relating to the less-than-perfect variant detection, an individual with a negative test could still develop clinical disease due to unidentified or de novo variants. Furthermore, misinterpretation of uninformative genetic test results may be high in the hypertrophic cardiomyopathy (HCM) community.

Nonspecific Testing for a Hypertrophic Cardiomyopathy Related Variant

Clinical Context and Test Purpose
The purpose of nonspecific genetic testing of individuals who are asymptomatic but at-risk of hypertrophic cardiomyopathy (HCM) is to inform management decisions. Genetic testing for hypertrophic cardiomyopathy (HCM) could play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals and genetic testing for reproductive decision making.

Populations
The relevant population of interest is individuals who are asymptomatic with a close relative who has hypertrophic cardiomyopathy (HCM) and an unknown pathogenic variant.

Interventions
The test being considered is nontargeted genetic testing.
Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators
The comparator of interest is standard clinical management without genetic testing such that decisions on surveillance and medical therapy are based on guidelines for individuals with a relative with hypertrophic cardiomyopathy (HCM).

Outcomes
The potential beneficial outcome of primary interest would be a reduction in surveillance for the development of hypertrophic cardiomyopathy (HCM). Maintenance of functioning and quality of life (QOL) are also important.

Potentially harmful outcomes are those resulting from a false result. False-positive test results can lead to initiation of unnecessary treatment and adverse events from that treatment. False-negative test results could lead to delay in diagnosis and treatment. The appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, children) and variation in age of hypertrophic cardiomyopathy (HCM) onset from genetic causes. Changes in outcomes due to increased surveillance or early initiation of treatment in asymptomatic individuals would take many years to become evident.

Review of Evidence

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing. Robyns et. al., (2019) conducted genotype-phenotype analyses of hypertrophic cardiomyopathy (HCM) patients to construct a score to predict the genetic yield and improve counseling. Unrelated patients with hypertrophic cardiomyopathy (N=378) underwent genetic testing for a panel of genes including at minimum *MYBPC3, MYH7,* and *TNNT2*. Multivariate logistic regression was utilized to identify clinical and electrocardiogram variables that predicted a positive genetic test. In total, 141 patients

carried a mutation (global yield 37%), 181 were variant-negative, and 56 carried a variant of uncertain significance. *MYBPC3* variants accounted for 21.6% of the genetic yield. Age at diagnosis of <45 years, familial hypertrophic cardiomyopathy, familial sudden death, arrhythmic syncope, maximal wall thickness ≥20 mm, asymmetrical hypertrophy, and the absence of negative T waves on lateral electrocardiogram were significant predictors of a positive genetic test. *MYBPC3* mutation carriers more frequently suffered sudden cardiac death (SCD) compared to troponin complex mutation carriers (p=.01). Maurizi et. al., (2018) assessed long-term outcomes of pediatric-onset hypertrophic cardiomyopathy (HCM) and age-specific risk factors for lethal arrhythmic events. Of 1644 patients with hypertrophic cardiomyopathy at 2 national referral centers for cardiomyopathies in Italy, 100 (6.1%) were aged 1 to 16 years at diagnosis. Forty-two of the 100 patients were symptomatic (42%) according to New York Heart Association classification >1 or Ross score >2. The yield of sarcomere gene testing was 55 of 70 patients (79%). During a median follow-up period of 9.2 years, 24 of 100 patients (24.0%) experienced cardiac events (1.9% per year), which included 19 lethal arrhythmic events and 5 heart failure-related events. Risk of lethal arrhythmic event was associated with symptoms at onset (hazard ratio [HR] 8.2; 95% confidence interval [CI], 1.5 to 68.4; p=.02). A trend toward an association between lethal arrhythmic event and Troponin I or Troponin T gene mutations was also detected (HR 4.1; 95% CI, 0.9 to 36.5; p=.06) but did not reach statistical significance.

Data from patients diagnosed with hypertrophic cardiomyopathy in the Sarcomeric Human Cardiomyopathy Registry (SHaRe) (N=4591; 12% with affected relatives; 35% with a family history of hypertrophic cardiomyopathy) indicates that for patients harboring 1 or more sarcomeric pathogenic/likely pathogenic variants, median age at diagnosis was 13.6 years younger than in those with no pathogenic variants (median, 37.5 years; interquartile range, 23.6 to 49.8 years vs. 51.1 years; interquartile range, 38.3 to 61.8 years; p<.001). Furthermore, patients with pathogenic/likely pathogenic sarcomere mutations had a 2-fold greater risk for adverse outcomes compared with patients without these mutations and a higher rate of hypertrophic cardiomyopathy family history (58% vs. 25%; p<.001).

A study conducted by Restrepo-Cardoba et. al., (2017) assessed the utility of genetic testing in patients with diagnosed hypertrophic cardiomyopathy classified with poor (Group A) or favorable (Group B) clinical course. Poor clinical course was defined as occurrence of a sudden cardiac death event, an appropriate implantable cardioverter-defibrillator discharge, and/or a required heart transplant for end-stage heart failure. Forty-five pathogenic mutations were identified in 28 (56%) patients in Group A and in 23 (46%) from Group B (p=.317). Only 40 patients (40%) demonstrated pathogenic mutations that were previously reported in the literature and only 15 (15%) had pathogenic mutations that were reported in ≥10 individuals. Four out of the 46 pathogenic mutations identified (8%) could have been considered as associated with poor prognosis based on published information. Pathogenic mutations associated with poor prognosis were detected in only 5 patients in Group A (10%). Additionally, mutations considered to confer a benign prognosis were detected in 3 patients (6%). By contrast, pathogenic

mutations were identified in 3 patients (6%) and mutations considered to confer a benign prognosis were detected in 4 patients (8%) with a favorable clinical course in Group B. Therefore, study authors concluded that genetic findings were not useful to predict prognosis in most hypertrophic cardiomyopathy patients.

Summary of Evidence
For individuals who are asymptomatic with risk for hypertrophic cardiomyopathy (HCM) because of a positive family history who receive testing for a specific hypertrophic cardiomyopathy (HCM) related variant identified in affected family member(s), the evidence includes studies reporting on the clinical validity of testing. For individuals at-risk for hypertrophic cardiomyopathy (HCM) (first-degree relatives), genetic testing is most useful when there is a known disease-associated variant in the family. In this situation, genetic testing will establish the presence or absence of the same variant in a close relative with a high degree of certainty. Presence of the variant indicates that the relative should undergo a cardiac evaluation upon receiving the variant-positive results. If a hypertrophic cardiomyopathy diagnosis is not made at that time, the patient should be monitored for development of symptoms. Absence of this variant will establish that the individual has not inherited the familial predisposition to hypertrophic cardiomyopathy (HCM) and thus has a similar risk of developing hypertrophic cardiomyopathy (HCM) as the general population. Such patients will no longer need ongoing surveillance for the presence of clinical signs of hypertrophic cardiomyopathy (HCM). Although no direct evidence comparing outcomes for at-risk individuals managed with and without genetic testing was identified, there is a strong chain of evidence that management changes can improve outcomes with genetic testing when there is a known familial variant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with risk for hypertrophic cardiomyopathy (HCM) because of a positive family history who receive nonspecific testing for a hypertrophic cardiomyopathy-related variant, the evidence includes studies reporting on the clinical validity of testing. Given the wide genetic variation in hypertrophic cardiomyopathy (HCM) and the likelihood that not all causative variants have been identified, there is imperfect clinical sensitivity. Therefore, a negative test is not sufficient to rule out a disease-associated variant in patients without a known family variant. For at-risk individuals without a known variant in the family, there is no clear relation between testing and improved outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Other Cardiac Conditions

Inherited Atrial Fibrillation
Inherited or familial atrial fibrillation is characterized by uncoordinated electrical activity in the atria. Symptoms of familial atrial fibrillation are indistinguishable from atrial fibrillation from non-genetic causes and include dizziness, chest pain, a sensation of fluttering or pounding in the chest (palpitations), shortness of breath, syncope and an

increased risk of stroke and sudden death. Some individuals with inherited atrial fibrillation do not experience these symptoms.

The incidence of the familial form of atrial fibrillation is unknown. The majority of atrial fibrillation can be attributed to underlying structural heart disease. Variations in three genes have been identified (i.e., KCNE2, KCNJ2, KCNQ1) and genetic testing for these variants is clinically available (National Institutes of Health, 2017); however, the majority of cases of atrial fibrillation are not caused by a gene variant. Standard treatment includes history and physical, electrocardiography and rhythm monitoring. Although genetic risk scores are highly associated with atrial fibrillation, genetic information currently affords small improvements in discrimination of risk (Lubitz et. al., 2017). Such testing is not yet considered the standard of care for the treatment or management of atrial fibrillation and the role of genetic testing for this indication is not supported by published consensus guidelines.

Genetic Testing for Cardiac Conditions in the General Population
The clinical utility of genetic testing in the general population for familial cardiac conditions is unknown and the role of such testing has not been established. Rather, confirmatory testing for affected individuals and predictive testing for at-risk individuals may assist in establishing a plan for monitoring or other targeted treatment if a specific variant has been identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome in this population of patients.

Coronary Artery Disease Risk
The expression levels of various genes in circulating white blood cell or whole blood samples have been reported to discriminate between cases of obstructive coronary artery disease (CAD) and healthy controls. Multiplex gene expression testing can be combined with other risk factors to predict the likelihood of obstructive CAD in patients who present with chest pain or other suggestive symptoms, or in asymptomatic patients who are at high risk of CAD.

Heart disease is the leading cause of mortality in the U.S. Individuals with signs and symptoms of obstructive coronary artery disease (CAD), the result of a chronic inflammatory process that ultimately results in progressive luminal narrowing and acute coronary syndromes, may be evaluated with a variety of tests according to prior risk. Coronary angiography is the gold standard for diagnosing obstructive CAD, but it is invasive and associated with a low but finite risk of harm. Thus, coronary angiography is recommended for patients at a high prior risk of CAD according to history, physical findings, electrocardiogram, and biomarkers of cardiac injury. For patients initially assessed at low-to-intermediate risk, observation, and noninvasive diagnostic methods, which may include imaging methods such as coronary computed tomographic angiography, may be recommended. Nevertheless, even noninvasive imaging methods have potential risks of exposure to radiation and contrast material. In addition, coronary angiography has a relatively low yield despite risk stratification recommendations. In one study of nearly 400,000 patients without known CAD undergoing elective coronary

angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter; result was 41% if using the broader definition, stenosis of 50% or more in any coronary vessel). Thus, methods of improving patient risk prediction prior to diagnostic testing are needed.

A CAD classifier has been developed based on the expression levels, in whole blood samples, of 23 genes plus patient age and sex. This information is combined in an algorithm to produce a score from 1 to 40, with higher values associated with a higher likelihood of obstructive CAD. The test is marketed as Corus CAD (CardioDx, Inc.). The intended population is stable, nondiabetic patients suspected of CAD either because of symptoms, a high-risk history, or a recent positive or inconclusive test result by conventional methods.

Summary of Evidence
At this time based on the peer reviewed medical literature the evidence on CAD classifiers the evidence is insufficient to determine that this technology results in an improvement in the net health outcome that results in changes in patient management over current standard of care. Further studies are needed.

Multigene Panel Testing for Hereditary Cardiomyopathies and Arrhythmias
Laboratories offer panel testing using next generation sequencing (NGS) for multiple genes at the same time to increase the likelihood of finding a causative gene mutation in a more efficient manner. Such testing may be performed for diagnostic or predictive purposes.

- Diagnostic genetic testing is performed in individuals with clinical signs or symptoms of a genetic condition. The genetic test may confirm or rule out a clinical diagnosis.
- Predictive genetic testing is performed in individual's known to be at increased risk of developing an inherited condition based on their family history.

Tests should be chosen to:

- Maximize the likelihood of identifying mutations in the genes of interest.
- Contribute to alterations in patient management.
- Minimize the change of finding variants of uncertain significance.

With the addition of multiple gene panels available for cardiology, the number of panel tests, and number of gene variations examined have continued to expand. The use of panel testing in cardiology includes, but not limited, to the following:

- Arrhythmia Panels or Channelopathies Panels (multiple labs)
- Arrhythmia Panel (Blueprint Genetics)
- Blueprint Cardiomyopathy Panel (Blueprint Genetics)
- Cardiac DNA Insight (Pathway Genomics)

- CardioNext (Ambry Genetics)
- CardioGXOne (Admera)
- Cardiomyopathy Panel (Knight Diagnostic Laboratories)
- Cardiomyopathy (Panel GeneDx)
- Cardiomyopathy and Arrhythmia Panel (ARUP Labratories)
- Cardiomyopathy Comprehensive Panel (Invitae)
- Cardiomyopathy NGS Panel (Allele Diagnostics)
- Cardio Familial Arrhythmia or Cardiomyopathy Panels (GenSeq)
- Cardiomyopathies, Channelopathies, Arrhythmias, and Aortic Panels (HealthinCode)
- Combined Cardiac Panel (GeneDx)
- Comprehensive Arrythmia Panel (GeneDx)
- Comprehensive Cardiology Panel (Blueprint Genetics)
- Comprehensive Cardiomyopathy Multi-Gene Panel (Mayo Clinic)
- Comprehensive Cardiomyopathy Panel (Invitae)
- Comprehensive Cardiovascular Deletion/Duplication Panel (EGL Genetic Diagnostics)
- Dilated Cardiomyopathy (DCM) Left Ventricular Non-Compaction (LVNC) (GeneDx)
- GeneSeq: Cardio Familial Cardiomyopathy Profile (Labcorp)
- Familion (Transgenomics)
- HCMNext (Ambry Genetics)
- Invitae Arrhythmia & Cardiomyopathy Comprehensive Panel (Invitae)
- Pan Cardiomyopathy Panel
- RhythmNext/Rhythm First/RhythmNext Reflex (Ambry Genetics)

Based on review of the peer reviewed medical literature over 30 gene variants have been identified related to cardiomyopathy. Single gene analysis or a panel focused on gene(s) associated with cardiomyopathy may be clinically useful and appropriate for an individual who has been diagnosed with cardiomyopathy to aid in treatment planning. Cardiomyopathy predisposes a small subset of individuals to an increased risk of sudden cardiac death (SCD) which may be the first symptom of cardiomyopathy.

Coverage determinations related to panel testing generally rely on the medical necessity component of a panel. A panel approach to testing is most compelling when:

- Multiple genes are known to cause the same condition and a limited subset of genes does not account for the majority of disease-causing mutations.
- The clinical presentation is highly suspicious for a genetic disorder, but the constellation of findings in the personal or family history does not suggest a specific diagnosis or limited set of conditions.

There are several variations of panels for use in diagnosis or risk assessment of genetic or hereditary conditions. For our purposes, panels will be divided into the following types:

- *Panels containing variants associated with a single condition:* These panels generally include all known pathogenic variants for a defined disease and do not include variants associated with other diseases. An example of such a panel would be one that includes pathogenic variants for hypertrophic cardiomyopathy but does not include variants associated with other cardiovascular disorders. These panels can be used for diagnostic or risk assessment purposes.
- *Panels containing variants associated with multiple related conditions:* These panels include all known pathogenic variants for a defined disease and variants associated with other related disorders. An example of such a panel would be a pan cardiomyopathy panel that includes pathogenic variants for hypertrophic cardiomyopathy and other types of cardiomyopathies (e.g., dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy). These panels can be used for diagnostic or risk assessment purposes.

The 2018 practice guideline by the Heart Failure Society states molecular genetic testing for multiple genes with the use of a multigene panel is now the standard of practice for cardio-vascular genetic medicine.

Summary of Evidence

Based on review of the peer reviewed medical literature there are over 30 gene variants that have been identified related to cardiomyopathy. Single gene analysis or a panel focused on gene(s) associated with cardiomyopathy may be clinically useful and appropriate for an individual who has been diagnosed with cardiomyopathy to aid in treatment planning (surveillance or treatment). Cardiomyopathy predisposes a small subset of individuals to an increased risk of sudden cardiac death (SCD) which may be the first symptom of cardiomyopathy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Based on review of the peer reviewed medical literature at this time multigene panels for cardiac ion channelopathies/arrhythmias are available and when at least 5 genes related to the condition being evaluated is part of the panel and no prior genetic testing has been completed the panel may be clinically useful in changing patient management in which subset of individuals may have increased risk of sudden cardiac death (SCD) which may be the first symptom. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Based on review of the peer reviewed medical literature multigene panels for any other indications not meeting the above the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American College of Cardiology and American Heart Association

In 2020, the American College of Cardiology Foundation and the American Heart Association issued updated joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy. The below table lists the recommendations on genetic testing:

Recommendations	COR	LOE
In patients with HCM, evaluation of familial inheritance, including a 3-generation family history, is recommended as part of the initial assessment.	1	B-NR
In patients with HCM, genetic testing is beneficial to elucidate the genetic basis to facilitate the identification of family members at risk for developing HCM (cascade testing).	1	B-NR
In patients with an atypical presentation of HCM or when another genetic condition is suspected to be the cause, a work-up including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended.	1	B-NR
In patients with HCM who choose to undergo genetic testing, pre- and posttest genetic counseling by an expert in the genetics of cardiovascular disease is recommended so that risks, benefits, results, and their clinical significance can be reviewed and discussed with the patient in a shared decision-making process.	1	B-NR
When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM.	1	B-NR
In first-degree relatives of patients with HCM, both clinical screening (ECG and 2D echocardiogram) and cascade genetic testing (when a pathogenic/likely pathogenic variant has been identified in the proband) should be offered.	1	B-NR
In families where a sudden unexplained death has occurred with a postmortem diagnosis of HCM, postmortem genetic testing is beneficial to facilitate cascade genetic testing and clinical screening in first-degree relatives.	1	B-NR
In patients with HCM who have undergone genetic testing, serial reevaluation of the clinical significance of the variant(s) identified is recommended to	1	B-NR

assess for variant reclassification, which may impact diagnosis and cascade genetic testing in family members.		
In affected families with HCM, preconception and prenatal reproductive and genetic counseling should be offered.	1	B-NR
In individuals who are genotype-positive, phenotype-negative for HCM, serial clinical assessment, ECG, and cardiac imaging are recommended at periodic intervals depending on age (every 1 to 2 years in children and adolescents, and every 3 to 5 years in adults) and change in clinical status.	1	B-NR
In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive athletics of any intensity is reasonable.	2a	C-LD
In patients with HCM, the usefulness of genetic testing in the assessment of risk of sudden cardiac death is uncertain.	2b	B-NR
In patients with HCM who harbor a variant of uncertain significance, the usefulness of clinical genetic testing of phenotype-negative relatives for the purpose of variant reclassification is uncertain.	2b	B-NR
For patients with HCM who have undergone genetic testing and were found to have no pathogenic variants (ie, harbor only benign/likely benign variants), cascade genetic testing of the family is not useful.	3	B-NR
Ongoing clinical screening is not indicated in genotype-negative relatives in families with genotype-positive HCM, unless the disease-causing variant is downgraded to variant of uncertain significance, likely benign, or benign variant during follow-up.	3	B-NR
In individuals who are genotype-positive, phenotype-negative for HCM, ICD is not recommended for primary prevention.	3	B-NR

COR: class of recommendation; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; LOE: level of evidence.

American College of Medical Genetics and Genomics (ACMG)
In 2018, the American College of Medical Genetics and Genomics (ACMG) published clinical practice recommendations for the genetic evaluation of cardiomyopathy. The following recommendations were made for all types of cardiomyopathies:

a. Genetic testing is recommended for the most clearly affected family member.
b. Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
c. In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.

The ACMG also provided information on specific variants, noting that TTNtv represents the most common genetic variant found in DCM (10% to 20% of cases), with LMNA being the second most common variant identified (diagnostic yield of 5.5%).

When a cardiovascular phenotype has been identified, the ACMG recommends family-based genetic evaluations and surveillance screening.

American Heart Association
In 2021, the American Heart Association published a scientific statement on genetic testing for heritable cardiovascular diseases (including channelopathies) in children. The statement recommends that genetic testing be performed when a cardiac channelopathy is likely to be present, including after a variant has been found in a family member. Testing to identify at-risk relatives can be considered. Brugada syndrome is difficult to identify since not all adults' express genetic variants; therefore, identifying at-risk children may require clinical evaluation, electrocardiogram (ECG) testing, and/or pharmacologic challenge of all of the child's first-degree relatives. Genetic testing should also be performed in children who are resuscitated from cardiac arrest with no clear cause. Several factors can be considered when deciding the appropriate age for genetic testing of an individual child, including whether the disease is expected to present during childhood, whether the channelopathy can be fatal, whether therapies exist to mitigate mortality risk, and family preferences. Ongoing follow-up genetic testing can confirm pathogenicity of the variant over time.

In 2020, the American Heart Association authored a scientific statement on genetic testing for inherited cardiovascular disease. Prior guidelines from several international cardiovascular clinical organizations and published studies were reviewed. For BrS, the authors concluded that genetic testing supports the clinical diagnosis. For patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (LQTS), genetic testing is needed for diagnosis and subtype classification. Management of LQTS may also differ depending on the causative gene. Genetic testing for all these conditions facilitates identifying at-risk family members. Specific genes with the strongest causative evidence for cardiac channelopathies are listed in below table

Specific Genes for Testing in Cardiac Channelopathies

Channelopathy	Genes with Definitive Evidence of a Casual Role in the Disease
LQTS	*KCNQ1, KCNH2, SCN5A*
SQTS	*KCNH2, KCNQ1, KCNJ2*
BrS	*SCN5A*
CPVT	*RYR2, CASQ2*

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; SQTS: short QT syndrome.

American Heart Association, American College of Cardiology, and the Heart Rhythm Society

In 2017, the American Heart Association, American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. The recommendations relating to cardiac ion channelopathies are summarized as follows (2017):

- In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended. Class of Recommendation: I (strong) Level of Evidence B-NR- moderate level of evidence
- In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information. Class of Recommendation: I (strong) Level of Evidence B-NR- moderate level of evidence
- In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable. Genetic testing may confirm a diagnosis; however, therapy for these patients is not guided by genotype status. Class of Recommendation: Iia (moderate) Level of Evidence B-NR- moderate level of evidence
- In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives, allowing for lifestyle modification and potential treatment. Class of Recommendation: IIb (weak) Level of Evidence C-EO- consensus of expert opinion based on clinical experience
- In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives. IIb (weak) Level of Evidence C-EO- consensus of expert opinion based on clinical experience

The Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

The Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) jointly published an expert consensus statement on genetic testing for channelopathies

and cardiomyopathies. This document made the following specific recommendations concerning testing for LQTS, CPVT, Brugada Syndrome, and SQTS.

LQTS Class I

- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.
- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., ie, otherwise idiopathic) on serial 12-lead ECGs defined as QTc .480 ms (prepuberty) or .500 ms (adults).
- Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

LQTS Class II

- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values .460 ms (prepuberty) or .480 ms (adults) on serial 12-lead ECGs.

CPVT Class I

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

BrS Class I

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

BrS Class IIa

- Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and

expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.

BrS Class III

- Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern

SQTS Class I

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.

SQTS Class IIb

- Comprehensive or SQT1-3 (KCNH2, KCNQ1, and KCNJ2) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient's clinical history, family history, and electrocardiographic phenotype.

*Class I: "is recommended" when an index case has a sound clinical suspicion for the presence of a channelopathy with a high PPV for the genetic test (>40%) with a signal to noise ratio of >10 AND/OR the test may provide diagnostic or prognostic information or may change therapeutic choices.; Class Iia: "can be useful"; Class IIb: "may be considered"; Class III ("is not recommended"): The test fails to provide any additional benefit or could be harmful in the diagnostic process.

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

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

Heart Failure Society (HFS)/European Heart Rhythm Association (EHRA) and Asia Pacific Heart Rhythm Society

In 2013, the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society issued an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. The consensus statement refers to the 2011 guidelines on genetic testing for channelopathies and cardiomyopathies discussed next for the indications for genetic testing in patients

affected by inherited arrhythmias and their family members and for diagnostic, prognostic, and therapeutic implications of the results of genetic testing. The 2013 consensus statement provided guidance for the evaluation of patients with idiopathic ventricular fibrillation, sudden unexplained death syndrome, and sudden unexplained death in infancy. Guidance on genetic testing for these patients was included in the below table. Idiopathic ventricular fibrillation is defined as a resuscitated cardiac arrest victim, preferably with documentation of ventricular fibrillation, in whom known cardiac, respiratory, metabolic, and toxicologic etiologies have been excluded through clinical evaluation.

The guidelines defined several terms related to specific types of SCD, including sudden unexplained death syndrome, which refers to an unexplained sudden death in an individual older than 1 year of age, sudden arrhythmic death syndrome, which refers to a sudden unexplained death syndrome case with negative pathologic and toxicologic assessment, and sudden unexplained death in infancy, which refers to an unexplained sudden death in an individual younger than 1 year of age with negative pathologic and toxicologic assessment.

Recommendations for Genetic Testing in IVF, SUDS and SUDI

Indication	**Consensus Recommendations**	**Class**
IVF		
	Genetic testing in IVF can be useful when there is suspicion of a specific genetic disease following clinical evaluation of the IVF patient and/or family members.	
	Genetic screening of a large panel of genes in IVF patients in whom there is no suspicion of an inherited arrhythmogenic disease after clinical evaluation should not be performed.	
SUDS		
	Collection of blood and/or suitable tissue for molecular autopsy/postmortem genetic testing is recommended in all SUDS victims.	
	Genetic screening of the first-degree relatives of a SUDS victim is recommended whenever a	

	pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDS victim.	
SUDI		
	Collection of blood and/or suitable tissue for molecular autopsy is recommended in all SUDI victims.	
	An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing can be useful for all SUDI victims.	
	Genetic screening of the first-degree relatives of a SUDI victim is recommended whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDI victim. Obligate mutations carriers should be prioritized.	

IVF: idiopathic ventricular fibrillation; SUDI: sudden unexplained death in infancy; SUDS: sudden unexplained death syndrome.

Heart Failure Society

In 2018, the Heart Failure Society of America published practice guidelines on the genetic evaluation of cardiomyopathy. The following recommendations for genetic testing for cardiomyopathy were made:

Guideline 4:

- Genetic testing is recommended for patients with cardiomyopathy (level of evidence A)
    - Genetic testing is recommended for the most clearly affected family member.
    - Cascade genetic testing of at-risk family members is recommended for pathogenic and like pathogenic variants

Genetic testing is recommended to determine if pathogenic variant can be identified to facilitate patient management and family screening.

Testing should ideally be initiated on the person in a family with the most definitive diagnosis and most serve manifestations. This approach would maximize the likelihood of obtaining diagnosis and most severe manifestations. This approach would maximize the likelihood of obtaining diagnostic results and detection whether multiple pathogenic variants may be present and contributing to variable disease expression or severity.

Molecular genetic testing for multiple genes with the use of a multigene panel is now the standard of practice for cardio-vascular genetic medicine.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policy

- 02.04.83 Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections and Related Disorders

Genetic Testing for Cardiac Ion Channelopathies

Brugada Syndrome (BrS)
Note: *BrS gene include SCN5A (81407)*

Genetic testing for Brugada Syndrome (BrS) may be considered **medically necessary** for the one of the following indications:

- To confirm a diagnosis of Brugada syndrome (BrS) when signs and/or symptoms consistent with Brugada syndrome (BrS) are present (see below), but a definitive diagnosis cannot be made without genetic testing; **or**
- In asymptomatic individuals to determine future risk of Brugada syndrome (BrS) when patient has a close relative (first, second or third degree relative*) with a known Brugada syndrome (BrS) variant.

*A first-degree relative is defined as a close blood relative which includes the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative which includes individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

*A third-degree relative is defined as a blood relative which includes the individual's first cousins, great-grandparents, or great grandchildren

***Note**: Signs and symptoms suggestive of Brugada syndrome (BrS) include the presence of a characteristic electrocardiographic pattern, documented ventricular arrhythmia, sudden cardiac death in a family member younger than 45 years old, a characteristic electrocardiographic pattern in a family member, inducible ventricular arrhythmias on electrophysiologic studies, syncope, or nocturnal agonal respirations.*

Genetic testing for Brugada Syndrome (BrS) is considered **investigational** not meeting the above criteria and for all other indications because the evidence is insufficient to determine the effects of this technology on net health outcomes.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
***Note:** CPVT genes include RYR2 (81408) and CASQ2 (81405)*

Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered **medically necessary** for the following indications:

- An asymptomatic individual to determine future risk of CPVT when at least one of the following criteria are met:
    - A close relative (i.e., first, second, or third-degree relative*) with a known CPTV variant; **or**
    - A close relative (i.e., first, second, or third-degree relative*) diagnosed with CPVT by clinical means whose genetic status is unavailable.
- To confirm a diagnosis of CPVT when signs and/or symptoms are present, but a definitive diagnosis cannot be made without genetic testing; **or**
- The individual being tested exhibits clinical features suggestive of CPTV including unexplained exercise or catecholamine-induced polymorphic ventricular arrhythmias (PVTs) and syncope during physical activity or emotional stress occurring in an individual with structurally normal heart.

*A first-degree relative is defined as a close blood relative which includes the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative which includes individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

*A third-degree relative is defined as a blood relative which includes the individual's first cousins, great-grandparents, or great grandchildren

***Note:** CPVT individuals generally present with syncope or cardiac arrest during the first or second decade of life. The symptoms are nearly always triggered by exercise or emotional stress. The resting ECG of patients with CPVT is typically normal, but exercise stress testing can induce a ventricular arrhythmia in most cases (75%-100%). Premature ventricular contractions (PVT), couplets, bigeminy, or polymorphic ventricular tachycardia (VT) are possible outcomes to the ECG stress test. For individuals who are unable to exercise, an infusion of epinephrine may induce ventricular arrhythmia, but this is less effective than exercise testing.*

Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) is considered **investigational** not meeting the above criteria and for all other indications because the evidence is insufficient to determine the effects of this technology on net health outcomes.

Long QT Syndrome (LQTS)
Note: *Long QT Syndrome genes include KCNQ1 (81406/81479), KCNH2 (81406/81479), and SCN5A (81407)*

Genetic testing to confirm a diagnosis of congenital long QT syndrome (LQTS) may be considered **medically necessary** when signs and/or symptoms of long QT syndrome (LQTS) are present, but a definitive diagnosis cannot be made without genetic testing which includes the following:

- Individual does not meet clinical criteria for long QT syndrome (LQTS) (i.e., those with Schwartz score < 4), but have a moderate-to-high pretest probability based on the Schwartz score and/or other clinical criteria.

Note: *Determining the pretest probability of long QT syndrome (LQTS) is not standardized. An example of a patient with a moderate-to-high pretest probability of LQTS is a patient with a Schwartz score of 2 or 3.*

Schwartz Score Diagnostic Criteria for LQTS

	Points
Electrocardiographic findings* (* In the absence of medications or disorders known to affect these electrocardiographic features)	
G. QTc	
• ≥480 ms	3
• 460 to 479 ms	2
• 450 to 459 ms (in males)	1
H. QTc fourth minute of recovery from exercise stress test ≥ 480 ms	1
I. Torsades de points	2
J. T-wave alternans	1
K. Notched T wave in 3 leads	1

L. Low heart rate for age (resting heart rate below the second percentile for age)	0.5
Clinical history	
C. Syncope • With stress • Without stress D. Congenital deafness	 2 1 0.5
Family History	
C. Family members with definite LQTS (the same family member cannot be counted in A or B) D. Unexplained sudden cardiac death below age 30 among immediate family members (the same family member cannot be counted in A or B)	1 0.5

SCORE:

- ≤1 point = low probability of long QT syndrome (LQTS)
- 1.5 to 3 points = intermediate probability of LQTS
- ≥3.5 points = high probability of LQTS

Genetic testing to determine future risk of long QT syndrome (LQTS) may be considered **medically necessary** when at least one of the following are met:

- A close relative (first, second or third degree relative*) with a known long QT syndrome (LQTS) variant; **or**
- A close relative (first, second or third degree relative*) diagnosed with long QT syndrome (LQTS) by clinical means whose genetic status is unavailable.

*A first-degree relative is defined as a close blood relative which includes the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative which includes individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

*A third-degree relative is defined as a blood relative which includes the individual's first cousins, great-grandparents, or great grandchildren

Genetic testing for long QT syndrome (LQTS) not meeting the above criteria and for all other indications, including but not limited to determining prognosis and/or directing therapy in patients with known LQTS because the evidence is insufficient to determine the effects of this technology on net health outcomes.

Short QT Syndrome (SQTS)
***Note**: Short QT Syndrome genes include KCNH2 (81406/81479), KCNQ1 (81406/81479), KCNJ2(81403))*

Genetic testing to determine future risk of Short QT Syndrome (SQTS) may be considered **medically necessary** when the patient has a close relative (first, second or third degree relative*) with known Short QT Syndrome (SQTS) variant.

*A first-degree relative is defined as a close blood relative which includes the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative which includes individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

*A third-degree relative is defined as a blood relative which includes the individual's first cousins, great-grandparents, or great grandchildren

***Note**: A patient with suspected short QT syndrome (SQTS) would be expected to have a shortened (<2 standard deviation below from the mean) rate-corrected shortened QT interval (QTc). Cutoffs below 350 ms for men and 360 ms for women have been derived from population normal values. The presence of a short QTc interval alone does not make the diagnosis of SQTS. Clinical history, family history, other electrocardiographic findings, and genetic testing may be used to confirm the diagnosis.*

Genetic Testing for Short QT Syndrome (SQTS) is considered **investigational** not meeting the above criteria and for all other indications because the evidence is insufficient to determine the effects of this technology on net health outcomes.

Genetic Testing for Cardiomyopathy and Other Cardiac Conditions

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy
***Note:** HCM genes include ACTC1(81405), MYL2 (81405), MYL3 (81405), MYH7 (81407), MYBPC3 (81407), TNNT2 (81406), and TNNI3 (81405)*

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered **medically necessary** for individuals who are at risk for development of hypertrophic cardiomyopathy (HCM) when the following is met:

- The individual has a first-degree relative **(**a close blood relative which includ**es** the patient's parents, full siblings, and children**)** with established hypertrophic cardiomyopathy (HCM), when there is a known pathogenic gene variation present in that affected relative.
- Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered **not medically necessary** for individuals with a family history of hypertrophic cardiomyopathy (HCM) in which a first-degree relative with

established hypertrophic cardiomyopathy (HCM) has tested negative for pathogenic variants.

Note:

- *To inform and direct genetic testing for at-risk individuals, genetic testing should initially be performed in at least 1 close relative with definite hypertrophic cardiomyopathy (HCM) (index case), if possible.*
- *Because there are varying degrees of penetrance for different hypertrophic cardiomyopathy (HCM) variants, consideration for testing of second- or third-degree relatives may be appropriate in certain circumstances. Some judgment should be allowed for these decisions (e.g., in the case of a small family pedigree). Consultation with an expert in medical genetics and/or the genetics of hypertrophic cardiomyopathy, in conjunction with a detailed pedigree analysis, is appropriate when testing of second- or third-degree relatives is considered.*

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered **investigational** not meeting the above criteria and for all other indications, including but not limited to following, because the evidence is insufficient to determine the effects of this technology on net health outcomes:

- Left ventricular noncompaction cardiomyopathies
- Restrictive cardiomyopathy

Genetic Testing for Idiopathic Dilated Cardiomyopathy (DCM)
Note: *Idiopathic dilated cardiomyopathy genes include ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CRYAB, CSRP3, DES, DMD, DSG2, EYA4, GATAS1, LAMA4, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYPN, PLN, PSEN1, PSEN2, RBM20, SCN5A, SGDC, TAZ, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, VCL*

Genetic testing for dilated cardiomyopathy (DCM) may be considered **medically necessary** when the individual meets one of the following:

- Individual with signs and symptoms of dilated cardiomyopathy (DCM), which is considered idiopathic after a negative workup for secondary causes; **or**
- Asymptomatic individual with a first-degree relative* who has dilated cardiomyopathy (DCM) and a known familial variant; or
- Patient has a significant cardiac conduction disorder (first, second or third-degree heart block) and/or a family history of premature cardiac death (< 50 years of age) in one or more first or second degree relative*; **or**
- Individual is a candidate for an implantable or wearable cardioverter defibrillator.

*A first-degree relative is defined as a close blood relative which includes the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative which includes individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

Genetic testing for dilated cardiomyopathy (DCM) is considered **investigational** when the above criteria is not met and for all other indications.

Genetic Testing for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)/ Arrhythmogenic Right Ventricular Dysplasia (ARVD)
Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC)/ arrhythmogenic right ventricular dysplasia (ARVD) including but not limited to the following genes DSC2 (81406), DSG2 (81406), DSP (81406), JUP (81406), PKP2 (81406), and TMEM43 (81406) may be considered **medically necessary** for one of the following indications:

- When signs and/or symptoms consistent with ARVC/AVRD are present, but a definitive diagnosis cannot be made without genetic testing; **or**
- Patient has a close relative (first, second or third degree relative*) with a known ARVC/ARVD variant.

*A first-degree relative is defined as a close blood relative which includes the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative which includes individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

**A third-degree relative is defined as a blood relative which includes the individual's first cousins, great-grandparents, or great grandchildren

Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC)/ arrhythmogenic right ventricular dysplasia (ARVD) is considered **investigational** when the above criteria is not met and for all other indications because the evidence is insufficient to determine the effects of this technology on net health outcomes.

Multigene Panels
Multigene panels specific to diagnosis and management of cardiomyopathies and cardiac ion channelopathies/arrhythmias using next generation sequencing (NGS) may be considered **medically necessary** when the **ALL** the following criteria are met:

- No previous genetic testing for cardiomyopathies or cardiac ion channelopathies/arrhythmias; **and**
- The individual meets the medical necessity criteria above for the cardiomyopathy or cardiac ion channelopathies/arrhythmias being evaluated; **and**
- The results of the test will directly impact the diagnostic and treatment options that are recommended for the patient; **and**
- Including but not limited to one of the following multigene panels:
    - Arrhythmia Panels or Channelopathies Panels (multiple labs)
    - Blueprint Cardiomyopathy Panel (Blueprint Genetics)
    - Cardiomyopathy Panel (Knight Diagnostic Laboratories)
    - Cardiomyopathy (Panel GeneDx)
    - Cardiomyopathy and Arrhythmia Panel (ARUP Labratories)

- Cardiomyopathy Comprehensive Panel (Invitae)
- Cardiomyopathy NGS Panel (Allele Diagnostics)
- Cardio Familial Arrhythmia or Cardiomyopathy Panels (GenSeq)
- Cardiomyopathies, Channelopathies, Arrhythmias, and Aortic Panels (HealthinCode)
- Comprehensive Cardiomyopathy Multi-Gene Panel (Mayo Clinic)
- Comprehensive Cardiomyopathy Panel (Invitae)
- Dilated Cardiomyopathy (DCM) Left Ventricular Non-Compaction (LVNC) (GeneDx)
- GeneSeq: Cardio Familial Cardiomyopathy Profile (Labcorp)
- Familion (Transgenomics)
- HCMNext (Ambry Genetics)
- Invitae Arrhythmia & Cardiomyopathy Comprehensive Panel (Invitae)
- Pan Cardiomyopathy Panel

Multigene panels not meeting the above criteria and for all other indications is considered **investigational** because the evidence is insufficient to determine the effects of this technology on net health outcomes.

Genetic Testing for Miscellaneous Cardiac Conditions
Gene expression testing to predict coronary artery disease including but not limited to the following is considered **investigational** because the evidence is insufficient to determine the effects of this technology on net health outcomes:

- Corus CAD (CardioDX, Inc)

Genetic testing for the following cardiac conditions including but not limited to the following is considered **investigational** because the evidence is insufficient to determine the effects of this technology on net health outcomes:

- Atrial fibrillation
- Early Repolarization “J-wave” Syndrome,
- Sinus Node Dysfunction (SND)

Policy Guidelines

Definitions
Arrhythmogenic Cardiomyopathy (ACM)/Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)/ Arrhythmogenic Right Ventricular Dysplasia (ARVD)
ARVC/ARVD is a rare type of cardiomyopathy that occurs if the muscle tissue in the right ventricle dies and is replaced by fat or scar tissue:

- This process disrupts the heart's electrical system, causing arrhythmias.
- It usually affects teens and young adults.
- Symptoms include heart palpitations and fainting after physical activity.
- It can cause sudden cardiac arrest in young athletes.
- It may require implantation of a device to prevent death from an arrhythmia

Brugada Syndrome (BrS): A genetic cardiac channelopathy manifested by abnormal EKG findings and an increased risk of SCD.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): An inherited cardiac channelopathy characterized by irregular heart rhythms brought on by physical exertion or intense emotion. CPVT may cause syncope (fainting), cardiac arrest, or SCD in affected individuals, resulting from a gene mutation.

Channelopathy: A heterogeneous group of disorders resulting from the dysfunction of ion channels located in the membranes of all cells and many cellular organelles. In cardiac cells, these channels play an integral role in repolarization during the heartbeat cycle and thus, enable the regular contractions of the healthy pumping heart.

Familial dilated cardiomyopathy (FDC): A form of dilated cardiomyopathy (DCM) which is associated with specific genetic mutations and is characterized by an enlargement of the left ventricle (that is, hypertrophy) with systolic dysfunction and a reduction in the force of contraction. Symptoms at initial presentation of DCM often include heart failure, arrhythmias and/or conduction system disease, and/or thromboembolic disease.

Familial hypertrophic cardiomyopathy (FHCM): A form of HCM (see below) which is associated with specific genetic mutations and is characterized by left ventricular hypertrophy (enlargement/thickening of the ventricle wall and/or interventricular septum), in the absence of another cardiac condition or systemic disease capable of producing significant hypertrophy. It is the most common inherited cardiac disorder, affecting 1 in 500 adults.

Hypertrophic cardiomyopathy (HCM): This myocardial disorder is caused by mutation in one of the genes currently known to encode different components of the sarcomere. The disorder is characterized by left ventricular hypertrophy (LVH) in the absence of predisposing cardiac conditions, (for example, aortic stenosis) or cardiovascular conditions, (for example, long-standing hypertension). The clinical manifestations of HCM range from asymptomatic to progressive heart failure to sudden cardiac death and vary from individual to individual even within the same family. Common symptoms include shortness of breath (particularly with exertion), chest pain, palpitations, orthostasis, presyncope, and syncope. Most often the LVH of HCM becomes apparent during adolescence or young adulthood, although it may also develop late in life, in infancy, or in childhood.

Long QT Syndrome (LQTS): An inherited or acquired cardiac disorder which is characterized as a "channelopathy." This refers to abnormalities in the sodium and potassium channels that control the excitability of the cardiac cells (myocytes), which can lead to episodes of syncope (dizziness/fainting) and SCD in affected individuals.

Non-Compacted Left Ventricular Cardiomyopathy
Variations in several genes have been found to cause left ventricular noncompaction. Mutations in the MYH7 and MYBPC3 genes have been estimated to cause up to 30 percent of cases; mutations in other genes are each responsible for a small percentage of cases. However, the cause of the condition is often unknown.

It is unclear how genetic mutations cause left ventricular noncompaction. During normal development before birth, cardiac muscle gets condensed (compacted), becoming smooth and firm. Mutations in certain genes likely lead to changes in this process, resulting in a left ventricular cardiac muscle that is not compacted but is thick and spongy, leading to left ventricular noncompaction.

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left ventricular cardiac muscle that is not compacted but is thick and spongy, leading to left ventricular noncompaction.

Panel testing: Involves the analysis of multiple genes for multiple mutations simultaneously.

Proband: A term used in medical genetics to refer to the first affected family member with a known pathogenic genetic mutation, which, in this document, refers to a family member with a known diagnosis of LQTS.

QT Interval: Period of time, as indicated on an electrocardiograph, associated with ventricular repolarization.

Short QT Syndrome (SQTS): An autosomal dominant channelopathy characterized by a shortened QT interval and action potential on EKG findings and an increased risk for adverse cardiac events including arrhythmias and SCD.

Sudden cardiac death (also called sudden death [SCD]): Death resulting from an abrupt loss of heart function (cardiac arrest).

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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
- 81403 Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) (Specific gene(s) tested for cardiac conditions may be included in the following molecular pathology procedure codes, including but are not limited to the following *KCNJ2)*
- 81404 Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) (Specific gene(s) tested for cardiac conditions may be

included in the following molecular pathology procedure codes, including but are not limited to the following *SCN1B)*

- 81405 Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) ABCD1 (ATP-binding cassette, sub-family D [ALD], member 1) (Specific gene(s) tested for cardiac conditions may be included in the following molecular pathology procedure codes, including but are not limited to the following *CASQ2,* ACTA2, TGFBR1 or 2, *TNNI3)*
- 81406 Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) (Specific gene(s) tested for cardiac conditions may be included in the following molecular pathology procedure codes, including but are not limited to the following: KCNH2 (potassium voltage-gated channel, subfamily H [ead-related], member 2) (e.g., short QT syndrome, long QT syndrome), full gene sequence; KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (e.g., short QT syndrome, long QT syndrome), full gene sequence; DSC2; DSG2; DSP; JUP; KCNH2, KCNQ1, LMNA, PKP2, TMEM43, TNNT2)
- 81407 Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) (Specific gene(s) tested for cardiac conditions may be included in the following molecular pathology procedure codes, including but are not limited to the following: SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (e.g., familial dilated cardiomyopathy), full gene sequence; MYH6; MYH7; MYBPC3)
  81408 Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) (Specific gene(s) tested for cardiac conditions may be included in the following molecular pathology procedure codes, including but are not limited to the following: RYR2 (ryanodine receptor 2 [cardiac]); FBN1 (fibrillin 1); MYH11)
- 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 Inherited 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 (DSG2, MYBPC3, MYH7, PKP2, and TTN) (Corus CAD [CardioDX, Inc])

- 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
- 81599 Unlisted multianalyte assay with algorithmic analysis
- 84999- Unlisted Chemistry Procedure
- S3861 Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome
- S3865 Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
- S3866 Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

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POLICY HISTORY

Date	Reason	Action
June 2022	Annual Review	Policy Revised
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Revised
June 2019	Annual Review	Policy Revised
June 2018	Annual Review	Policy Revised
June 2017	Annual Review	Policy Revised
June 2016	Annual Review	Policy Revised
June 2015	Annual Review	Policy Revised
July 2014	Annual Review	Policy Revised
September 2013	Annual Review	Policy Renewed
October 2012	Literature Review	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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