MEDICAL POLICY

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Medical Policy Title	**Genetic Testing for Cardiac Ion Channelopathies**
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Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Genetic testing for congenital long QT syndrome (LQTS) is considered **medically appropriate** for **ANY** of the following:

   A. Patients who meet the clinical criteria for congenital LQTS when **ALL** the following are met:

      1. The signs or symptoms of LQTS are present, but a definitive diagnosis cannot be made without genetic testing; **and**
      2. The test results will influence decisions concerning disease treatment.

   B. Individuals at risk for congenital LQTS who do not meet the clinical criteria for LQTS, when **ALL** the following are met:

      1. The test results will influence decisions concerning disease treatment; **and**
      2. Individual has **ANY** of the following:
         a. A first-, second-, or third-degree relative with a known LQTS variant;
         b. A first-, second-, or third-degree relative diagnosed with LQTS by clinical means, whose genetic status is unavailable; **or**
         c. Signs and/or symptoms indicating a moderate-to-high pretest probability of LQTS. Determining the pretest probability of 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 2-3).

II. Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) is considered **medically appropriate** for **ANY** of the following:

   A. Patients who meet the clinical criteria for CPVT when **ALL** the following are met:

      1. The signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing; **and**
      2. The test results will influence decisions concerning disease treatment.

   B. Individuals at risk for CPVT who do not meet the clinical criteria for CPVT, when **ALL** the following are met:

      1. The test results will influence decisions concerning disease treatment; **and**

2. Individual has **ANY** of the following:
    a. A first-, second-, or third-degree relative with a known CPVT mutation; **or**
    b. A first-, second-, or third-degree relative diagnosed, by clinical means, with CPVT whose genetic status is unavailable;

III. Genetic testing for Brugada syndrome (BrS) is considered **medically appropriate** for **ANY** of the following:
  A. Patients who meet the clinical criteria for BrS when **ALL** the following are met:
    1. The signs or symptoms of BrS are present, but a definitive diagnosis cannot be made without genetic testing; **and**
    2. The test results will influence decisions concerning disease treatment.
  B. Individuals at risk for BrS who do not meet the clinical criteria for BrS, when **ALL** the following are met:
    1. A first-, second-, or third-degree relative with a known BrS mutation; **and**
    2. The test results will influence decisions concerning disease treatment.

IV. Genetic testing to determine future risk of short QT syndrome (SQTS) is considered **medically appropriate** for **ALL** the following:
  A. Asymptomatic patients who have a first-, second-, or third-degree relative with a known SQTS variant.

RELATED POLICIES

Corporate Medical Policy

2.02.03 Genetic Testing for Inherited Disorders

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting documentation required:

The following factors will be considered when determining the medical appropriateness of a genetic test:

A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.

B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.

C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).

D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.

E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented.

DESCRIPTION

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, however a correct diagnosis is essential.

Congenital Long QT Syndrome (LQTS)

LQTS is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential. This lengthening increases the risk for arrhythmic events, such as torsade's de pointes, which may in turn result in syncope and sudden cardiac death. Management has focused on the use of beta blockers as first-line treatment, with pacemakers or implantable cardioverter defibrillators (ICD) as second-line therapy.

LQTS usually manifests itself before the age of 40 years and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult; this history may prompt additional testing in family members. It is estimated that more than one half of the 8,000 sudden unexpected deaths in children may be related to LQTS. The mortality of untreated patients with LQTS is estimated at one percent to two percent per year, although this figure will vary with the genotype. Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and thus LQTS has received some publicity regarding evaluation of adolescents for participation in sports.

In addition, LQTS may be considered when a long QT interval is incidentally observed on an electrocardiogram (EKG). Diagnostic criteria for LQTS have been established, which focus on EKG findings and clinical and family history (e.g., Schwartz criteria). However, measurement of the QT interval is not well standardized, and in some cases, patients may be considered borderline.

In addition to identifying the locus name of the genes involved in LQTS, there are several syndrome names that identify forms of LQTS, depending on the genes responsible and the features associated with the condition. Most forms of LQTS are carried in an autosomal dominant manner, with the exception of Jervell and Lange-Nielsen syndrome (JLNS), which is inherited in an autosomal recessive manner.

The Romano-Ward syndrome (RWS) is the most common form of inherited LQTS, with an estimated prevalence of 1:7000. A syncopal event is the most common symptom and typically occurs without warning. About 50 to 70 percent of individuals with a disease-causing mutation in one of the genes associated with RWS have symptoms. Cardiac events may occur from infancy through middle age but are most common from the preteen years through the 20s. Most individuals diagnosed with RWS have an affected parent. The proportion of cases caused by de novo mutations is small. Each child of an individual with RWS has a 50 percent risk of inheriting the disease-causing mutation. However, about 30 percent of families known to be clinically affected with RWS do not have detectable mutations in any one of the known genes. Clinical methods of genetic testing for this condition include mutation scanning and sequence analysis. The known genes, along with the locus name, which are responsible for this form include: KCNQ1 (LQT1), KCNH2 (LQT2), HERG, SCN5A (LQT3), KCNE1 (LQT5), MiRP1, CAV3, SCN4B, SNTAI, KCNJ5 and KCNE2 (LQT6).

Other less common and more severe forms of LQTS include Jervell and Lange-Nielsen Syndrome (JLNS), Andersen-Tawil syndrome (ATS), Ankyrin B syndrome, and Timothy syndrome or Syndactyly-Related LQTS.

Clinical Diagnosis of LQTS

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS. The most recent version of this scoring system is shown below (Schwartz 2011). A score of 3.5 or greater indicates a high probability that LQTS is present; a score of 1.5 to 3 indicates an intermediate probability; and a score of 1 or lower indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; therefore, the accuracy of this scoring system is ill-defined.

Diagnostic Scoring System for LQTS

Schwartz Criteria	Points
Electrocardiographic findings:	
$QT_c \geq 480$ msec	3
QT_c 460-479 msec	2
QT_c 450-459 msec	1

Schwartz Criteria	Points
QTc fourth minute of recovery from exercise stress test ≥ 480 msec	1
History of torsade's de pointes	2
T-wave alternans	1
Notched T-waves in three leads	1
Low heart rate for age	0.5
Clinical history: Syncope brought on by stress Syncope without stress Congenital deafness	 2 1 0.5
Family history: Family members with definite LQTS Unexplained sudden cardiac death in immediate family members younger than 30 years of age	 1 0.5

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Variants in four genes are known to cause CPVT, and investigators believe that other unidentified loci are involved as well. Currently, only 55 percent to 65 percent of patients with CPVT have an identified causative variant. Variants of the RYR2, the gene encoding the cardiac ryanodine receptor or KCNJ2 result in an autosomal dominant form of CPVT. CASQ2 (cardiac calsequestrin) and TRDN-related CPVT exhibit autosomal recessive inheritance. Some investigators have reported heterozygotes for CASQ2, as well as TRDN variants for rare, benign arrhythmias. RYR2 variants represent most CPVT cases (50%-55%), with CASQ2 accounting for one percent to two percent and TRDN accounting for an unknown proportion of cases. The penetrance of RYR2 variants is approximated at 83 percent. An estimated 50 percent to 70 percent 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 a patient this treatment because Anderson-Tawil syndrome is rarely fatal.

Clinical Diagnosis of CPVT

Giudicessi et al. (2019) published a diagnostic scoring system for CPVT shown below, which professional societies incorporated into their recommendations (Wilde 2022). A CPVT score, which does require an exercise stress test/ambulator Holter finding, of 3.5-12 points indicates a high pretest probability of CPVT. A CPVT score of 2-3 points indicates an intermediate pretest probability of CPVT. A CPVT score of 0.5-1.5 points indicates a low pretest probability of CPVT (nondiagnostic), while a score of 0 points indicates there is no evidence of CPVT.

Diagnostic Scoring System for CPVT

Clinical Criteria	Points
Symptoms:	
Exercise/activity-associated ACA/SCA	2
Exercise/activity-associated syncope or generalized seizures	1
Exercise stress test or Holter monitoring during exertional activity (REQUIRES ≥1 exercise stress test/ambulatory Holter finding)	
Inducible bidirectional ventricular tachycardia at HR >100 bpm	4
Inducible PVCs in bigeminy and bidirectional couplets at HR >100 bpm	2
Inducible PVCs at HR >100 bpm	1
Baseline HR QTc	
QTc≤420 ms	0.5
421<QTc<460 ms	0
QTc≥460 ms	-0.5
CPVT genetic test:	
Positive for ACMG-graded pathogenic variant	4
Positive for ACMG-graded likely pathogenic variant	2
Positive for a variant of uncertain significance	0
Negative CPVT genetic test (RYR2, CASQ2, TRDN, and CALM1-3)	-1
Holter:	
Ambulatory ventricular ectopy (>2% of total beats)	-1

Clinical Criteria	Points
Imaging (TTE or cardiac MRI/CT): Evidence of ischemic or structural heart disease	 -2
Age: ≥50 y of age at time of sentinel event	 -1
Family History: First-degree relative with definite CPVT Suspicious autopsy-negative SCD (exertional, near drowning, etc.) in a first- or second-degree relative ≤45 y. Unexplained autopsy-negative SCD in a first- or second-degree relative ≤age 45y	 1.5 1 0.5

Brugada Syndrome (BrS)

BrS is typically inherited in an autosomal dominant manner with incomplete penetrance. The proportion of cases that are inherited, versus de novo variants, is uncertain. Although some investigators have reported that up to 50 percent of cases are sporadic, others have reported that the instance of de novo variants is very low and is estimated to be only one percent of cases. 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 percent of cases; SCN10A has also been implicated. The other genes are of minor significance and account together for approximately five percent of cases. The absence of a positive test does not indicate the absence of BrS, with more than 65 percent of cases not having an identified genetic cause. Penetrance of BrS among persons with an SCN5A variant is 80 percent when undergoing electrocardiogram with sodium-channel blocker challenge and 25 percent when not using the electrocardiogram challenge.

Signs and symptoms suggestive of Brugada syndrome (BrS) include the presence of a characteristic electrocardiographic pattern, documented ventricular arrhythmia, sudden cardiac death (SCD) 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.

Short QT Syndrome (SQTS)

SQTS has been linked predominantly to variants in three 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. SQTS 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 sudden cardiac death (SCD).

Clinical Diagnosis of SQTS

Gollob et al. (2011) published a diagnostic scoring system for SQTS shown below, which professional societies incorporated into their recommendations (Wilde 2022) . A SQTS score of >4 points indicate a high probability of SQTS. A SQTS score of 3 points indicates an intermediate probability of SQTS. A SQTS score of <2 points indicate a low probability of SQTS. A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points

Diagnostic Scoring System for SQTS

Clinical Criteria	Points
Electrocardiographic findings:	
QT_c <370 msec	1
QT_c <350 msec	2
QT_c <330 msec	3
Jpoint-Tpeak interval <120 msec	1
Clinical history:	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history:	
First or second degree relative with high probability SGTS	2
First or second degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype:	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

SUPPORTIVE LITERATURE

Asatryan et al. (2019) 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. 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.

Chiu et al. (2022) performed genetic tests on 36 survivors of pediatric cardiac arrest (median age, 13.3 years). 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.

Long QT Syndrome

Tester DJ, et al. (2006) completed the largest study to evaluate the percentage of individuals with a clinical diagnosis of LQTS found to have a genetic variant. The sample was 541 consecutive patients referred for evaluation of LQTS. Clinical assessments of the patients were made while blinded to the genetic testing results. Among the 123 patients with a high probability of LQTS based on clinical assessments, defined as a Schwartz score of 4 or more, 72% (89/123) had a genetic variant. Among patients with a QTc greater than 480 ms, 62% had a genetic variant. Characteristics and results of selected studies are shown in Tables 6 and 7 below.

Bai R, et al. (2009) conducted a consecutive, prospective trial including patients from a sample of 1,394 consecutive probands with either a clinically confirmed or suspected diagnosis of LQTS, BrS, or CPVT or a personal or family history of idiopathic ventricular fibrillation/cardiac arrest/SCD referred for molecular diagnosis. The authors concluded the study showed genotyping can be performed at reasonable cost in individuals with conclusive diagnosis of long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia, and in patients with type I Brugada syndrome ECG with atrioventricular block.

Catecholaminergic Polymorphic Ventricular Tachycardia

Studies reporting the yield of RyR2 testing in CPVT have been conducted in patients with clinically diagnosed CPVT.

Priori SG, et al. (2002) conducted a retrospective study including patients with documented polymorphic ventricular arrhythmias occurring during physical or emotional stress with a normal heart. The clinical phenotype of the 30 probands and of 118 family members was evaluated, and mutation screening on the RyR2 gene was performed. Arrhythmias documented in probands were: 14 of 30 bidirectional ventricular tachycardia, 12 of 30 polymorphic ventricular tachycardia, and 4 of 30 catecholaminergic idiopathic ventricular fibrillation; RyR2 mutations were identified in 14 of 30 probands (36% bidirectional ventricular tachycardia, 58% polymorphic ventricular tachycardia, 50% catecholaminergic idiopathic ventricular fibrillation) and in 9 family members (4 silent gene carriers). Genotype-phenotype analysis showed that patients with RyR2 CPVT have events at a younger age than do patients with nongenotyped CPVT and that male sex is a risk factor for syncope in RyR2-CPVT (relative risk=4.2). The authors concluded the study showed patients with nongenotyped CPVT are predominantly women and become symptomatic later in life; patients with RyR2 CPVT become symptomatic earlier, and men are at higher risk of cardiac events. These data provide a rationale for prompt evaluation and treatment of young men with RyR2 mutations.

Medeiros-Domingo A, et al. (2009) published a retrospective study to determine the prevalence of mutations in the RYR2-encoded cardiac ryanodine receptor in cases with exertional syncope and normal corrected QT interval (QTc). Mutational analysis of all RYR2 exons was performed using polymerase chain reaction, high-performance liquid chromatography, and deoxyribonucleic acid sequencing on 155 unrelated patients (49% females, 96% Caucasian, age at diagnosis 20 +/- 15 years, mean QTc 428 +/- 29 ms), with either clinical diagnosis of CPVT (n = 110) or an initial diagnosis of exercise-induced long QT syndrome but with QTc <480 ms and a subsequent negative long QT syndrome genetic test (n = 45). Sixty-three (34 novel) possible CPVT1-associated mutations, absent in 400 reference alleles, were detected in 73 unrelated patients (47%). Thirteen new mutation-containing exons were identified. Two-thirds of the CPVT1-positive patients had mutations that localized to 1 of 16 exons. The authors concluded the study showed possible CPVT1 mutations in RYR2 were identified in nearly one-half of this cohort; 45 of the 105 translated exons are now known to host possible mutations. Considering that approximately 65% of CPVT1-positive cases would be discovered by selective analysis of 16 exons, a tiered targeting strategy for CPVT genetic testing should be considered.

Walsh et al. (2022) conducted an evidence-based reappraisal of genes that have been reported to cause CPVT and short QT syndrome (SQTS). The authors curated all published evidence for 11 CPVT implicated genes. The results were reviewed by a Channelopathy Expert Panel of 10 individuals with extensive experience, who provided the final classifications. Seven genes had definitive to moderate evidence for disease causation in CPVT, with either autosomal dominant (RYR2, CALM1, CALM2, CALM3) or autosomal recessive (CASQ2, TRDN, TECRL) inheritance. Three of the four disputed genes for CPVT (KCNJ2, PKP2, SCN5A) were deemed by the Expert Panel to be reported for phenotypes that were not representative of CPVT, while reported variants in a fourth gene (ANK2) were too common in the population to be disease-causing. The authors concluded the analysis showed seven CPVT genes have valid evidence for disease causation and should be included in genetic testing panels. Additional genes associated with conditions that may mimic clinical features of CPVT have

potential utility for differential diagnosis.

Brugada Syndrome

Chen et al. (2020) conducted a meta-analysis of 17 studies involving 1,780 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 [OR], 1.78; 95% confidence interval [CI], 1.19 to 2.26; p=.005), Asian (OR, 1.82; 95% CI, 1.07 to 3.11; p=.03), and Caucasian (OR, 2.24; 95% CI, 1.02 to 4.90; p=.04) patient populations. Doundoulakis et al (2024) conducted a meta-analysis of the SCN5A gene variant and arrhythmic risk in BrS.40, A total of 17 observational studies with 3568 patients were included. Four studies consisted of an Asian population, 12 studies of a White population, and 1 mixed population. Most patients were male (72%), and 24.7% were SCN5A(+). Meta-analysis of the ECG and electrophysiologic parameters showed prolonged P wave, PR interval, QRS, and QTc durations as well as larger abnormal substrate size before and after provocation test in the SCN5A(+) group compared with the SCN5A(-) group. Major arrhythmic events were significantly greater in SCN5A(+) patients (OR, 2.15; 95% CI, 1.53 to 2.99).

Sacilotto et al. (2020) reported data from the Genetics of Brazillian Arrhythmias (GenBra) registry. From 1999 to 2020, patients with spontaneous and drug-induced type-1 BrS were classified into two groups, asymptomatic (n = 116, 84.1%) and symptomatic (n = 22, 15.9%; 13 with arrhythmogenic syncope, 9 with aborted sudden cardiac death). Genetic testing for SCN5A mutation status, electrophysiologic study (EPS) parameters, and electrocardiogram (ECG) parameters were analyzed. A total of 138 consecutive patients were eligible, 101 men (73.2%), mean 41.4 years, mostly probands (79%). Spontaneous pattern, observed in 77.5% of the patients, was associated with symptoms only if expressed in V1 and V2 standard position (not high precordial leads; p = .014). The presence of right ventricular outflow tract conduction delay (RVOTcd) signs, positive EPS, and SCN5A status was similar between symptomatic and asymptomatic subjects. RVOTcd occurred more frequently in SCN5A carriers (QRS-f 33.3% vs. 7.7%; p = .005, AVR sign 58.3% vs. 13.6%; p < .001; deep S in lead I 75% vs. 48.5%, p = .025%), as well as longer HV interval (66 vs. 49 ms; p < .001). The authors concluded the study showed spontaneous type-1 Brugada pattern in standard leads and proband status were more frequent in symptomatic subjects. RVOTcd, more common in SCN5A carriers, did not predict symptoms in BrS patients. EPS exhibited limited prognostic value for this low-risk population.

Milman et al. (2021) 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 (OR, 5.41; 95% CI, 2.8 to 11.19; p<.001) and family history of SCD (OR, 2.73; 95% CI, 1.28 to 5.82; p=.009) were associated with having a pathogenic/likely pathogenic genotype.

Wang et al. (2022) published an observational study of 79 patients in China who had BrS, 59 of whom underwent genetic testing.44, Abnormal genetic results occurred in 25 (42.37%) patients, with pathogenic or likely pathogenic mutations in 8 (13.56%) patients. The genes most commonly associated with genetic mutations were SCN5A (44%), SCN10A (20%), and DSP (16%). Genetic carriers were more likely to have prolonged P-wave duration, QRS duration, QTc interval, decreased QRS amplitude, and T-wave or R-wave axis deviation than individuals without abnormal genetic findings.

Short QT Syndrome

Walsh et al. (2022) conducted an evidence-based reappraisal of genes that have been reported to cause CPVT and short QT syndrome (SQTS). The authors curated all published evidence for 9 SQTS implicated genes. The results were reviewed by a Channelopathy Expert Panel of 10 individuals with extensive experience, who provided the final classifications. For SQTS, only one gene (KCNH2) was classified as definitive, with three others (KCNQ1, KCNJ2, SLC4A3) having strong to moderate evidence. The majority of genetic evidence for SQTS genes was derived from very few variants (five in KCNJ2, two in KCNH2, one in KCNQ1/SLC4A3). The authors concluded the analysis showed four SQTS genes have valid evidence for disease causation and should be included in genetic testing panels. Additional genes associated with conditions that may mimic clinical features of SQTS have potential utility for differential diagnosis.

PROFESSIONAL GUIDELINE(S)

The European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) published an expert consensus statement on the state of genetic testing for cardiac diseases (Wilde 2022). Their recommendations include:

I. Genetic testing in patients with a potential cardiogenetic condition is performed only with appropriate genetic counselling.

II. In patients with a clear specific phenotype, it is appropriate to perform genetic testing analyzing genes with definite or strong evidence supporting disease causation.

III. In patients with a clear specific phenotype, it may be appropriate to analyze genes with moderate evidence supporting disease causation.

IV. In selected cases with a definite phenotype and no genetic diagnosis after testing of the genes with definite or strong evidence supporting disease causation, broader genetic testing may be considered. Such selected cases may include familial cases, those with atypical features, such as

extracardiac manifestations and those with unusual early disease onset.

V. Variant interpretation in the clinical setting is greatly enhanced by the use of disease specific, multidisciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists.

VI. Variant interpretation is best performed using standard guidelines for interpretation and can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration.

VII. Reported Variants of Uncertain Clinical Significance (VUS) may be reclassified, i.e., 'upgraded' [Likely Pathogenic/ Pathogenic (LP/P)] or 'downgraded' (Likely Benign/Benign), in multi-disciplinary clinics with access to molecular genetics laboratories, according to robustness of clinical phenotype and/or familial segregation evidence.

VIII. Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting.

IX. In families where a LP/P variant has been identified, detailed genetic counselling and guidance regarding inheritance patterns, variant penetrance, and risk should be offered, and cascade testing facilitated.

X. In patients with a high probability of a specific inherited cardiac disease and a molecular screening performed in a pre-NGS era or with an incomplete NGS panel, repetition of the testing should be considered.

<u>For Long QT Syndrome the recommendations include</u>:

I. Molecular genetic testing for definitive disease associated genes (currently KCNQ1, KCNH2, KCNE1, SCN5A, CALM1, CALM2, CACNA1C, and CALM3) should be offered to all index patients with a high probability diagnosis of LQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score > 3.5)

II. Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causing variant.

III. Predictive genetic testing in related children is recommended from birth onward (any age).

<u>For CPVT the recommendations include</u>:

I. In any patient satisfying the diagnostic criteria for CPVT (such as Class 1 clinical diagnosis [Priori 2013] or CPVT diagnostic score >3.5 [Giudicessi 2019]), molecular genetic testing is recommended for the currently established definite/strong evidence CPVT-susceptibility genes: RYR2, CASQ2, CALM1-3, TRDN, and TECRL.

II. In phenotype-positive CPVT patients who are negative for those established CPVT susceptibility genes, genetic testing may be considered for CPVT phenocopies resulting from pathogenic variants in the KCNJ2, SCN5A, and PKP2 genes.

III. In patients with a modest phenotype for CPVT (i.e., CPVT diagnostic score > 2 but , <3.5),

genetic testing may be considered for the established definite/strong evidence CPVT-susceptibility genes: RYR2, CASQ2, CALM1-3, TRDN, and TECRL.

IV. Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.

V. Predictive genetic testing in related children at risk of inheriting a P/LP variant is recommended from birth onward (any age).

For Brugada Syndrome the recommendations include:

I. Genetic testing with sequencing of SCN5A is recommended for an index case diagnosed with BrS with a type I ECG in standard or high precordial leads occurring either (i) spontaneously, or (ii) induced by sodium-channel blockade in presence of supporting clinical features or family history.

II. Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant

III. Predictive genetic testing (of pathogenic SCN5A variants) in related children is recommended from birth onward (any age).

For Short QT Syndrome the recommendations include:

I. In any patient satisfying the diagnostic criteria for SQTS (such as Class 1 clinical diagnosis [Priori 2013] or SQTS diagnostic score >4b [Gollob 2011]), molecular genetic testing is recommended for the definitive disease associated genes (currently KCNH2, KCNQ1).

II. Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.

III. Predictive genetic testing in related children may be considered in specific settings.

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 (Priori 2013). 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. 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 Heart Rhythm Society and European Heart Rhythm Association jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies (Ackerman 2011). This document made the following specific recommendations on testing for LQTS, BrS, CPVT, and SQTS shown below:

	Consensus Recommendation	Class	LOE
LQTS	• Comprehensive or LQT1-3 (KCNQ1, KCNH2, 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, 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.	I	C
	Comprehensive or LQT1-3 (KCNQ1, KCNH2, 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.	IIb	C
BrS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.	I	C
	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.	IIa	C
	Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.	III	C
CPVT	Comprehensive or CPVT1 and CVPT2 (RYR2, 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	I	C

	appropriate relatives following the identification of the CPVT-causative mutation in an index case.		
SQTS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.	I	C
	Comprehensive or SQT1-3 (KCNH2, KCNQ1, 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.	IIb	C

The American Heart Association published a scientific statement on interpreting incidentally identified genes associated with heritable cardiovascular diseases (including cardiac ion channelopathies) (Landstrom 2023). The statement notes that: "In partnership with a specialized inherited cardiovascular disease (CVD) center, individuals found to have an incidentally identified variant should undergo a comprehensive clinical evaluation for the CVD in question. This pretest probability of having the CVD in question should be modified by the strength of the gene variant with CVD to arrive at a posttest probability that the variant in question places the patient at risk of developing disease. This determines the need for additional clinical evaluation, management, and follow-up." In their proposed framework for the evaluation of a patient with incidental findings of genetic variants associated with channelopathies, the American Heart Association suggests that an electrocardiogram (ECG) testing, a 24-hour or longer Holter monitor, and an exercise stress test (if possible) should be performed.

The American Heart Association published a scientific statement on genetic testing for heritable cardiovascular diseases (including channelopathies) in children (Landstrom 2021). 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, 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.

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 (Musunuru 2020). For Brugada syndrome, the authors concluded that genetic testing supports the clinical diagnosis. For patients with CPVT and 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 of these conditions facilitates identifying at-risk family members. Specific genes with the strongest causative evidence for cardiac

channelopathies are listed in below:

Specific Genes for Testing in Cardiac Channelopathies

Channelopathy	Genes with definitive evidence of a causal role in the disease
LQTS	KCNQ1, KCNH2, SCN5A
SQTS	KCNH2, KCNQ1, KCNJ2
BrS	SCN5A
CPVT	RYR2, CASQ2

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 (SCD) (Al-Khatib 2017). Their recommendations for genetic testing in cardiac channelopathies are shown below:

Consensus Recommendation	COR	LOE
In first-degree relatives of patients who have a causative mutation for LQTS, CPVT, SQTS, or BrS, genetic counseling and mutation-specific genetic testing are recommended.	I (strong)	B-NR
In patients with clinically diagnosed LQTS, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information.	I (strong)	B-NR
In patients with CPVT 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.	IIa (moderate)	B-NR
In patients with suspected or established BrS, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives, allowing for lifestyle modification and potential treatment.	IIb (weak)	C-EO
In patients with SQTS, genetic testing may be considered to facilitate screening of first-degree relatives.	IIb (weak)	C-EO

The Heart Rhythm Society and Asia Pacific Heart Rhythm Society authored an expert consensus statement on investigation of individuals who have died from sudden unexplained death, patients with sudden cardiac arrest (SCA), and their families (Stiles 2020). Suspicion for a genetic cause of SCD or a resuscitated SCA warrants genetic testing and counseling. Genetic testing should include

the most likely genes for the suspected phenotype and should include clinical and genetic evaluation of family members to identify other at-risk individuals. Testing of many genes can lead to uncertainty and misinterpretation of results and is generally discouraged. Genetic investigation should only be undertaken by multidisciplinary teams with expertise in cardiology, genetics, and pathology. The document provides detailed guidance on specific scenarios for which genetic testing is warranted but does not describe specific genes that should be tested.

The European Society of Cardiology (ESC) issued guidelines for the management of patients with ventricular arrhythmias and prevention of SCD (Zeppenfeld 2022). Their recommendations include:

IV. In patients with clinically diagnosed LQTS, genetic testing, and genetic counselling are recommended.

V. Genetic testing for SCN5A gene is recommended for probands with BrS.

VI. Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT.

VII. Genetic testing is indicated in patients diagnosed with SQTS.

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 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.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
81403	Molecular pathology procedure, Level 4; Includes: KCNJ2 (potassium inwardly rectifying channel, subfamily J, member 2) (e.g., Andersen-Tawil syndrome), full gene sequence.
81405	Molecular pathology procedure, Level 6; Includes: CASQ2 (calsequestrin 2 [cardiac muscle]) (e.g., catecholaminergic polymorphic ventricular tachycardia), full gene sequence.

Code	Description
81406	Molecular pathology procedure, Level 7; Includes: KCNH2 (potassium voltage-gated channel, subfamily H[ead-related], member 2) (e.g., short QT syndrome, long QT syndrome), full gene sequence and KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (e.g., short QT syndrome, long QT syndrome), full gene sequence
81407	Molecular pathology procedure, Level 8; Includes: SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (e.g., familial dilated cardiomyopathy), full gene sequence.
81408	Molecular pathology procedure, Level 9; Includes: RYR2 (ryanodine receptor 2 [cardiac]) (e.g., catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of > 50 exons.
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
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 (Genomic Unity® Cardiac Ion Channelopathies Analysis, Variantyx Inc.)

HCPCS Codes

Code	Description
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome

ICD10 Codes

Code	Description
I45.81	Long QT syndrome

Code	Description
I46.9	Cardiac arrest, cause unspecified
I47.2 -.29	Ventricular tachycardia code range
I49.01	Ventricular fibrillation
I49.8	Other specified cardiac arrhythmias [Brugada Syndrome]
I49.9	Cardiac arrhythmia, unspecified
R94.31	Abnormal electrocardiogram [ECG] [EKG]
Z13.6	Encounter for screening for cardiovascular disorders
Z13.79	Encounter for other screening for genetic and chromosomal anomalies
Z82.41	Family history of sudden cardiac death
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system

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SEARCH TERMS

Andersen-Tawil syndrome, Brugada syndrome, Jervell and Lange-Nielsen syndrome, Long QT syndrome, Romano-Ward syndrome, Syndactyly-related LWTS, Timothy syndrome.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Molecular Pathology Procedures (LCD L35000) [accessed 2025 Apr 4]

Billing and Coding: Molecular Pathology Procedures (Article A56199) [accessed 2025 Apr 4]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
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- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

04/17/08, 04/16/09, 04/22/10, 04/21/11, 03/15/12, 03/21/13, 02/20/14, 03/19/15, 03/17/16, 03/16/17, 03/15/18, 03/21/19, 04/16/20, 05/20/21, 05/19/22, 05/18/23, 05/16/24, 05/22/25	
Date	**Summary of Changes**
05/22/25	• Annual review, code edit, added diagnosis codes. Policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
04/17/08	• Original effective date