# Genetic Testing for Cardiac Ion Channelopathies

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*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

## When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

**LONG QT SYNDROME**

Based on review of available data, the Company may consider genetic testing to confirm a diagnosis of congenital long QT syndrome (LQTS) when signs and/or symptoms of LQTS are present but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage.**** This includes:

- Individuals who do not meet the clinical criteria for LQTS (ie, those with a Schwartz score <4): but have a moderate-to-high pretest probability based on the Schwartz score and/or other clinical criteria.

Based on review of available data, the Company may consider Genetic testing of asymptomatic individuals to determine future risk of LQTS to be **eligible for coverage**** when at least one of the following is present:

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

## When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for LQTS for all other situations not meeting the criteria outlined above, including but not limited to determining prognosis and/or directing therapy in patients with known LQTS to be **investigational.***

**BRUGADA SYNDROME**

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing to confirm a diagnosis of Brugada Syndrome (BrS) when signs and/or symptoms consistent with BrS are present but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage.****

Based on review of available data, the Company may consider genetic testing of asymptomatic individuals to determine future risk of BrS when patients have a close relative (ie, first-, second-, or third-degree relative) with a known BrS variant to be **eligible for coverage.****

# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for BrS for all other situations not meeting the criteria above to be **investigational.***

**CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA**

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing to confirm a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) when signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage**.**

Based on review of available data, the Company may consider genetic testing of asymptomatic individuals to determine future risk of CPVT to be **eligible for coverage**** when at least one of the following criteria is present:

- A close relative (ie, first-, second-, or third-degree relative) with a known CPVT variant; or
- A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable.

# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for CPVT for all other situations not meeting the above criteria are not met to be **investigational.***

**SHORT QT SYNDROME**

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing of asymptomatic individuals to determine future risk of short QT syndrome (SQTS) when patients have a close

relative (ie, first-, second- or third-degree relative) with a known SQTS variant to be **eligible for coverage.****

# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for SQTS for all other situations not meeting the criteria outlined above to be **investigational.***

# Policy Guidelines

Genetic testing should be performed by an expert in genetic testing and/or cardiac ion channelopathies.

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.

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. An index 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 (Tristani-Firouzi, 2014). 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.

**Testing Strategy**

In general, testing for patients with suspected congenital LQTS, catecholaminergic polymorphic ventricular tachycardia (CPVT), or BrS should begin with a known familial variant, if one has been identified.

In cases where the family member's genetic diagnosis is unavailable, testing is available through either single-gene testing or panel testing. Panels for cardiac ion channelopathies are diagnostic test panels that may fall into one of several categories: panels that include variants for a single condition; panels that include variants for multiple conditions (indicated plus nonindicated conditions); and panels that include variants for multiple conditions (clinical syndrome for which clinical diagnosis not possible).

For situations in which a relative of a proband with unexplained cardiac death or unexplained sudden cardiac arrest (SCA) *or* an individual with unexplained SCA is being evaluated, genetic testing may be part of a diagnostic strategy that includes a comprehensive history and physical exam and 12-lead electrocardiogram (ECG), along with exercise stress test, transthoracic echocardiography, and additional evaluation as guided by the initial studies. Studies have suggested that, in such cases, a probable diagnosis of an inherited cardiac condition can be made following a nongenetic evaluation in 50% to 80% of cases (Behr et al, 2008; Krahn et al, 2009; Kumar et al, 2013; Wong et al, 2014). If, after a comprehensive evaluation, a diagnosis of CPVT, LQTS, or BrS is suspected but not definitive (ie, if there is a moderate-to-high pretest probability of either condition), genetic testing could be considered.

**Genetic Counseling**
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

# Background/Overview

**Cardiac Ion Channelopathies**
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. Data about the individual prevalences of long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome (SQTS) are presented in Table 1.

**Table 1. Epidemiology of Cardiac Ion Channelopathies**

| Variables | LQTS | BrS | CPVT | SQTS |
|---|---|---|---|---|
| Prevalence | 1:2000-5000 | 1:6000 | 1:7000-10,000 | Unidentified |
| Annual mortality rate | 0.3% (LQT1)<br>0.6% (LQT2)<br>0.56% (LQT3) | 4%[a] | 3.1% | Unidentified |
| Mean age at first event, y | 14 | 42[a] | 15 | 40 |

Adapted from Modell et al (2012).
BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; SQTS: short QT syndrome.
[a] Type 1 electrocardiographic pattern.

**Long QT Syndrome**

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 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 varies with the genotype.

**Brugada Syndrome**
Brugada syndrome is characterized by cardiac conduction abnormalities that increase the risk of syncope, ventricular arrhythmia, and 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. Males are more likely to be affected than females (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 death.[4,] Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.

**Catecholaminergic Polymorphic Ventricular Tachycardia**
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 years 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.

**Short QT Syndrome**
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.

**Sudden Cardiac Arrest or Sudden Cardiac Death**
Sudden cardiac arrest (SCA) and SCD refer to the sudden interruption of cardiac activity with circulatory collapse. The most common cause is coronary artery disease. Approximately 5% to 10% of SCA and SCD is due to arrhythmias without structural cardiac disease and are related to the primary electrical disease syndromes. The previously described cardiac ion channelopathies are among the primary electrical disease syndromes.

The evaluation and management of a survivor of SCA include an assessment of the circumstances of the event as well as a comprehensive physical examination emphasizing cardiovascular and neurologic systems, laboratory testing, ECG, and more advanced cardiac imaging or electrophysiologic testing as may be warranted. Genetic testing might be considered when, after completion of a comprehensive evaluation, there are findings consistent with a moderate-to-high likelihood of a primary electrical disease. Postmortem protocols for evaluation of a fatal SCA should be implemented when possible.

**Genetics of Cardiac Ion Channelopathies**

***Long QT Syndrome***

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.

Another factor complicating interpretation of the genetic analysis is the penetrance of a given variant or the presence of multiple phenotypic expressions. For example, approximately 50% of variant carriers never have any symptoms. There is variable penetrance for LQTS, and penetrance may differ for the various subtypes. While linkage studies in the past have indicated that penetrance was 90% or greater, a 1999 analysis using molecular genetics challenged this estimate and suggested that penetrance may be as low as 25% for some families.

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. A summary of clinical syndromes associated with hereditary LQTS is shown in Table 2. A 2021 analysis of 49 patients with channelopathies identified 3 rare variants that were pathogenic for LQTS and 8 rare variants that were likely pathogenic for LQTS, all involving *KCNQ1* or *KCNH2*.

**Table 2. Genetics of Long QT Syndrome**

| Type | Other Names | Chromosome Locus | Mutated Gene | Ion Current(s) Affected | Associated Findings |
|---|---|---|---|---|---|
| LQT1 | RWS | 11p15.5-p.15.4 | *KCNQ1* | Potassium | |
| LQT2 | RWS | 7qq36.1 | *KCNH2* | Potassium | |
| LQT3 | RWS | 3p22.2 | *SCN5A* | Sodium | |
| LQT4 | Ankyrin B syndrome | 4q25-26 | *ANK2* | Sodium, potassium, calcium | Catecholaminergic polymorphic ventricular arrhythmias, sinus node dysfunction, AF |
| LQT5 | RWS | 21q22.12 | *KCNE1* | Potassium | |
| LQT6 | RWS | 21q22.11 | *KNCE2* | Potassium | |
| LQT7 | Andersen-Tawil syndrome | 17.qq2432 | *KCNJ2* | Potassium | Episodic muscle weakness, congenital anomalies |
| LQT8 | Timothy syndrome | 12q13.33 | *CACNA1C* | Calcium | Congenital heart defects, hand/foot syndactyly, ASD |
| LQT9 | RWS | 3p25.3 | *CAV3* | Sodium | |
| LQT10 | RWS | 11q23.3 | *SCN4B* | Sodium | |
| LQT11 | RWS | 7q21.2 | *AKAP9* | Potassium | |
| LQT12 | RWS | 20q11.21 | *SNTAI* | Sodium | |
| LQT13 | RWS | 11q24.3 | *KCNJ5* | Potassium | |

| | | | | | |
|---|---|---|---|---|---|
| LQT14 | | 14q32.11 | *CALM1* | Calmodulin | |
| LQT15 | | 2p21 | *CALM2* | Calmodulin | |
| LQT16 | | 19q13.32 | *CALM3* | Calmodulin | |
| JLNS1 | JLNS | 11p15.5-11p15.4 | *KCNQ1* (homozygotes or compound heterozygotes) | Potassium | Congenital sensorineural hearing loss |
| JLNS2 | JLNS | 21q22.12 | *KCNE1* (homozygotes or compound heterozygotes) | Potassium | Congenital sensorineural hearing loss |

Adapted from Beckmann et al (2021), Arking et al (2014), and Alders (2015). AF: atrial fibrillation; ASD: autism spectrum disorder; LQT: long QT; LQTS: long QT syndrome; JLNS: Jervell and Lange-Nielsen syndrome; RWS: Romano-Ward syndrome.

***Brugada Syndrome***

Brugada syndrome 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 have reported that up to 50% of cases are sporadic, others have reported that the instance of de novo variants is very low and is estimated to be only 1% of cases.

Variants in 16 genes have been identified as causative of BrS, all of which lead 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.

***Catecholaminergic Polymorphic Ventricular Tachycardia***

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*. 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 have the dominant form of CPVT with a disease-causing variant. Most variants (90%) of*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.

***Short QT Syndrome***

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.

# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

Genetic Testing for Cardiac Ion Channelopathies

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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.

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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 (SCD). 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.

**Summary of Evidence**

***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. Relevant outcomes are overall survival (OS), test validity, changes in reproductive decision making, and morbid events. 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 implantable cardioverter-defibrillator (ICD). As a result, confirming the diagnosis is likely to lead to a health outcome benefit by reducing the risk for

ventricular arrhythmias and 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 LQTS variant who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on changes in management. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. 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.

***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. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. 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 BrS variant who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. 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 catecholaminergic polymorphic ventricular tachycardia (CPVT) who receive genetic testing for variants associated with CPVT, the evidence includes observational studies reporting on testing yields. Relevant outcomes are OS, test validity, changes in reproductive

decision making, and morbid events. 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 CPVT variant who receive genetic testing for variants associated with CPVT, the evidence includes observational studies reporting testing yields. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. 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.

***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. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. 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 with a close relative(s) with a known SQTS variant who receive genetic testing for variants associated with SQTS, the evidence includes observational studies reporting on testing yields. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. For patients with SQTS, management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on changes in management based on genetic testing in an individual with family members who have a known variant. 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 family member(s) who experienced 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.

**Additional Information**
Given the limited available evidence on genetic testing for BrS, clinical input was obtained in 2015. There was a consensus among the specialty societies and academic medical centers providing clinical input that genetic testing for BrS is medically necessary to establish a definitive diagnosis in patients with BrS symptoms and to evaluate family members of an individual with a known genetic variant of BrS. A review of guidelines from American and international cardiac specialty societies (American Heart Association, Heart Rhythm Society, European Heart Rhythm Association, Asia Pacific Heart Rhythm Society) was also conducted. The guidelines acknowledged that although the evidence is weak, genetic testing is recommended for both individuals with a suspected but not a definitive diagnosis of BrS and asymptomatic family members of individuals with known BrS variants.

Given the limited available evidence on genetic testing for SQTS, clinical input was obtained. Among the specialty societies and academic medical centers providing input, there was no consensus on the use of genetic testing for variants associated with SQTS; however, there was consensus that genetic testing to predict future risk of disease in individuals with close relatives who have a known variant associated with SQTS is useful in management that may lead to improved outcomes. A review of guidelines was also conducted. The use of genetic testing for patients with suspected SQTS was not addressed in many guidelines; however, one stated that testing may be considered if a cardiologist has established a strong clinical index of suspicion. Additionally, the guidelines acknowledged that although the evidence is weak, genetic testing may be considered for asymptomatic family members of individuals with known SQTS variants.

# Supplemental Information

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

***2015 Input***

In response to requests, input was received from 3 specialty societies (4 reviewers) and 4 academic medical centers (9 reviewers) while this policy was under review in 2015. Input was limited to the use of genetic testing for Brugada syndrome (BrS) and short QT syndrome (SQTS). There was a consensus that genetic testing for BrS is medically necessary to establish the diagnosis of BrS in an individual with a suspected but not definitive diagnosis of BrS and to evaluate family members of an individual with a known pathogenic genetic variant for BrS. There was less consensus on whether genetic testing for variants associated with SQTS is medically necessary to establish the diagnosis of SQTS in an individual with a suspected but not definitive diagnosis of SQTS, but there was consensus that testing for SQTS to evaluate family members of an individual with a known pathogenic genetic variant for SQTS is medically necessary. However, reviewers acknowledged that the rarity of SQTS somewhat limited conclusions that could be made.

**Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

***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 of these conditions facilitates identifying at-risk family members. Specific genes with the strongest causative evidence for cardiac channelopathies are listed in Table 3.

**Table 3. 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* |

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

***American Heart Association, American College of Cardiology, and 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 (SCD). Table 4 summarizes the recommendations relating to cardiac ion channelopathies.

**Table 4. Recommendations for Genetic Testing in Cardiac Channelopathies**

| 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 |

B-NR: moderate level of evidence, nonrandomized studies; BrS: Brugada syndrome; C-EO: consensus of expert opinion based on clinical experience; COR: class of recommendation; CPVT: catecholaminergic polymorphic ventricular tachycardia; LOE: level of evidence; LQTS: long QT syndrome; SQTS: short QT syndrome; VT: ventricular tachycardia.

***Heart Rhythm Society and Asia Pacific Heart Rhythm Society***

In 2020, 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. 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.

***Heart Rhythm Society, European Heart Rhythm Association, 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 (see Table 5). 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.

**Table 5. Recommendations for Genetic Testing in Idiopathic Ventricular Fibrillation, Sudden Unexplained Death Syndrome, and Sudden Unexplained Death in Infancy**

| | Consensus Recommendation | 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. | IIa |
| | 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. | III |
| SUDS | Collection of blood and/or suitable tissue for molecular autopsy/postmortem genetic testing is recommended in all SUDS victims. | I |
| | 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. | I |
| SUDI | Collection of blood and/or suitable tissue for molecular autopsy is recommended in all SUDI victims. | I |
| | An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing can be useful for all SUDI victims. | IIa |
| | 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. | I |

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

In 2011, the Heart Rhythm Society and European Heart Rhythm Association jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies. This document made the following specific recommendations on testing for LQTS, BrS, CPVT, and SQTS (see Table 6).

**Table 6. Cardiac Ion Channelopathy Testing Recommendations**

| | Consensus Recommendation | Class[a] | LOE[b] |
|---|---|---|---|
| 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.<br>• 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).<br>• 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 |

| | Consensus Recommendation | Class[a] | LOE[b] |
|---|---|---|---|
| | 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 appropriate relatives following the identification of the CPVT-causative mutation in an index case. | I | C |
| 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 |

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; ECG: electrocardiogram; LOE: level of evidence; LQTS: long QT syndrome; QTc: corrected QT; SQTS: short QT syndrome.

[a] Class I: "is recommended" when an index case has a sound clinical suspicion for the presence of a channelopathy with a high positive predictive value 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).
[b] Only consensus opinion of experts, case studies or standard of care.

**U.S. Preventive Services Task Force** Recommendations
Not applicable.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 7.

**Table 7. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT04832126 | Genetic Analysis of Heart Channelopathies in Brazilian Patients and Their Relatives | 100 | Jul 2024 (recruiting) |
| NCT03783975 | A Community-Based Approach to Overcoming Barriers to Cascade Screening for Long QT Syndrome | 500 | Dec 2021 (recruiting) |
| NCT02439658 | Genetics of QT Prolongation With Antiarrhythmics (DOFEGEN) | 1000 | Jul 2022 (recruiting) |
| NCT04232787 | Discovering the Genetic Causes of Brugada Syndrome in Thais and Southeast Asian Population (SEA-BrS) | 750 | Jan 2023 (recruiting) |

| | | | |
|---|---|---|---|
| NCT02824822 | Genetic Markers of Cardiovascular Diseases and the Potential Role in Sudden Unexpected Death in Epilepsy | 600 | Dec 2023 (recruiting) |
| NCT02014961 | Worm Study: Identification of Modifier Genes in a Unique Founder Population With Sudden Cardiac Death | 223 | Apr 2025 (recruiting) |
| NCT03880708 | China Inherited Ventricular Arrhythmias Registry, a Multicenter, Observational and Prospective Study | 500 | Oct 2027 (recruiting) |
| ***Unpublished*** | | | |
| NCT01705925[a] | Multicenter Evaluation of Children and Young Adults With Genotype Positive Long QT Syndrome | 92 | Dec 2018 (completed) |
| NCT02425189 | The Canadian National Long QT Syndrome Registry (LQTSREG) | 1051 | Aug 2020 (completed) |

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Genetic Testing for Cardiac Ion Channelopathies

Policy # 00408
Original Effective Date: 04/23/2014
Current Effective Date: 02/12/2024

# Policy History

Original Effective Date: 04/23/2014
Current Effective Date: 02/12/2024

| | |
|---|---|
| 04/03/2014 | Medical Policy Committee review |
| 04/23/2014 | Medical Policy Implementation Committee approval. New policy. |
| 01/01/2015 | Coding Update |
| 10/08/2015 | Medical Policy Committee review |
| 10/21/2015 | Medical Policy Implementation Committee approval. Added INV statement that genetic testing for LQTS or CPVT is investigational for all situations when criteria are not met, rationale and references updated |
| 01/07/2016 | Medical Policy Committee review |
| 01/22/2016 | Medical Policy Implementation Committee approval. Added eligibility statements for diagnostic testing for Brugada syndrome and testing of an asymptomatic individual with a known familial variant associated with Brugada syndrome or SQTS. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update |
| 01/05/2017 | Medical Policy Committee review |
| 01/18/2017 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/04/2018 | Medical Policy Committee review |
| 01/17/2018 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/10/2019 | Medical Policy Committee review |
| 01/23/2019 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/03/2020 | Medical Policy Committee review |
| 01/08/2020 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/07/2021 | Medical Policy Committee review |
| 01/13/2021 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/06/2022 | Medical Policy Committee review |
| 01/12/2022 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/05/2023 | Medical Policy Committee review |
| 01/11/2023 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/04/2024 | Medical Policy Committee review |
| 01/10/2024 | Medical Policy Implementation Committee approval. No change to coverage. |

Next Scheduled Review Date: 01/2025

Genetic Testing for Cardiac Ion Channelopathies

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Original Effective Date: 04/23/2014
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# Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|
| CPT | 0237U, 81403, 81405, 81406, 81407, 81408 , 81413, 81414 |
| HCPCS | S3861 |
| ICD-10 Diagnosis | All related diagnoses |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.