Introduction

Variants in certain genes in the DNA have been linked to some electrical abnormalities in the heart. These abnormalities cause heart rhythm problems which can make you faint or even cause sudden death. This policy describes when genetic testing may be medically necessary to help diagnose these heart rhythm problems.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT syndrome (LQTS)</td>
<td>Genetic testing to confirm a diagnosis of congenital long QT syndrome (LQTS) may be considered medically necessary when signs and/or symptoms of LQTS are present, but a definitive diagnosis cannot be made without genetic testing. This</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>includes:</td>
</tr>
<tr>
<td></td>
<td>• Individuals who do not meet the clinical criteria for LQTS (ie, those with a Schwartz score &lt;4): but have a moderate-to-high pretest probability (see Additional Guidelines section) based on the Schwartz score and/or other clinical criteria.</td>
</tr>
<tr>
<td></td>
<td>Genetic testing of asymptomatic individuals to determine future risk of LQTS may be considered medically necessary when at least one of the following criteria is met:</td>
</tr>
<tr>
<td></td>
<td>• A close relative (ie, first-, second-, or third-degree relative) has a known LQTS mutation</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>• A close relative has been diagnosed with LQTS by clinical means but their genetic status is unavailable</td>
</tr>
<tr>
<td></td>
<td>Genetic testing for LQTS gene variants in index patients with confirmed clinical LQTS may be considered medically necessary when used to assist unaffected first-degree family members (see Benefit Application section).</td>
</tr>
<tr>
<td></td>
<td>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, is considered investigational.</td>
</tr>
<tr>
<td>Brugada syndrome (BrS)</td>
<td>Genetic testing to confirm a diagnosis of Brugada syndrome (BrS) may be considered medically necessary when signs and/or symptoms consistent with BrS (see Additional Guidelines section) are present, but a definitive diagnosis cannot be made without genetic testing.</td>
</tr>
<tr>
<td></td>
<td>Genetic testing of asymptomatic individuals to determine future risk of BrS may be considered medically necessary when patients have a close relative (ie, first-, second-, or third-degree relative) with a known BrS variant.</td>
</tr>
<tr>
<td></td>
<td>Genetic testing for BrS for all other situations not meeting the criteria outlined above is considered investigational.</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Catecholaminergic polymorphic ventricular tachycardia (CPVT) | Genetic testing to confirm a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered medically necessary when signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing.  
Genetic testing of asymptomatic individuals to determine future risk of CPVT may be considered medically necessary when at least one of the following criteria is met:  
- A close relative (ie, first-, second-, or third-degree relative) has a known CPVT variant  
OR  
- A close relative has been diagnosed with CPVT by clinical means but their genetic status is unavailable  
Genetic testing for CPVT for all other situations not meeting the criteria outlined above is considered investigational. |
| Short QT syndrome (SQTS)                       | Genetic testing of asymptomatic individuals to determine future risk of short QT syndrome (SQTS) may be considered medically necessary when patients have a close relative (ie, first-, second-, or third-degree relative) with a known SQTS variant.  
Genetic testing for SQTS for all other situations not meeting the criteria outlined above is considered investigational. |

**Additional Guidelines**

Genetic testing should be performed by an individual with adequate expertise 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 in a family member younger than 45 years old, a characteristic electrocardiographic pattern
Additional Guidelines

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 the mean) rate-corrected 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 mutation, 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. The evaluation of the clinical utility of panel testing is outlined in a separate medical policy (See Related Policies). 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 is not possible).

For situations in which a relative of a proband with unexplained cardiac death or unexplained sudden cardiac arrest or an individual with unexplained sudden cardiac arrest is being evaluated, genetic testing may be part of a diagnostic strategy that includes a comprehensive history and physical exam and 12-lead electrocardiogram, 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, 200868; Krahn et al, 200964; Kumar et al, 201365; Wong et al, 201470). 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.
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81403</td>
<td>KCNJ2 (potassium inwardly-rectifying channel, subfamily J, member 2) (eg, Andersen-Tawil syndrome), full gene sequence</td>
</tr>
<tr>
<td>81405</td>
<td>CASQ2 (calsequestrin 2 [cardiac muscle]) (eg, catecholaminergic polymorphic ventricular tachycardia), full gene sequence</td>
</tr>
</tbody>
</table>
| 81406 | KCNH2 (potassium voltage-gated channel, subfamily H [ead-related], member 2) (eg, short QT syndrome, long QT syndrome), full gene sequence  
KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (eg, short QT syndrome, long QT syndrome), full gene sequence |
| 81407 | SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (eg, familial dilated cardiomyopathy), full gene sequence |
| 81408 | RYR2 (ryanodine receptor 2 [cardiac]) (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of > 50 exons |
| 81413 | Cardiac ion channelopathies (eg, 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 (eg, 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 |

**HCPCS**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3861</td>
<td>Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
Definition of Terms


1st-, 2nd-, or 3rd-degree relative: Includes the blood relatives on the same side of the family (mother or father). The mother’s and father’s sides of the family should be considered individually.

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins

Brugada syndrome: A genetic cardiac channelopathy characterized by abnormal electrocardiogram (EKG) results and an increased risk of sudden cardiac death (SCD).

Catecholaminergic polymorphic ventricular tachycardia (CPVT): A genetic cardiac channelopathy characterized by an extremely fast and irregular heartbeat in response to exercise or emotional stress. CPVT may cause syncope (fainting), cardiac arrest, or sudden cardiac death (SCD).

Channelopathy: A varied group of disorders resulting from the dysfunction/abnormalities in the sodium and potassium ion channels that control the excitability of the cardiac cells (myocytes). These channels play an integral role in repolarization during the heartbeat cycle and thus, enable the regular contractions of the healthy pumping heart muscle.

Index patient: The first patient in a family who has a disease or disorder. Also see proband.

Long QT syndrome: A genetic cardiac channelopathy where the heart muscle takes more time than usual to recharge between beats. This shows as a prolonged QT interval on an electrocardiogram (EKG). This abnormal heartbeat pattern can lead to episodes of dizziness/fainting, cardiac arrest and sudden cardiac death (SCD) in affected individuals.

Proband: A term used in medical genetics to refer to the first affected family member with a known pathogenic genetic mutation which, in this document, refers to a family member with a known diagnosis of LQTS.
**QT Interval:** Period of time, as detected on an electrocardiograph, associated with ventricular repolarization.

**Schwartz Score:** A set of diagnostic criteria for long QT syndrome (LQTS). The criteria are divided into 3 main categories with a maximum score of 9; however scores of greater than 3 indicate a high probability of LQTS. (See Table 2)

**Short QT Syndrome (SQTS):** An autosomal dominant channelopathy where the heart muscle takes less time than usual to recharge between beats. This shows as a shortened QT interval on an electrocardiogram (EKG). This abnormal heartbeat pattern may cause symptoms of dizziness/fainting and may increase the risk for adverse cardiac events.

**Sudden cardiac death (SCD):** Death resulting from an abrupt stop of heart function or cardiac arrest.

**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.

**Benefit Application**

Professional societies recommend that people who are affected by long QT syndrome undergo genetic testing. Genetic testing of unaffected, at-risk family members can then be focused only on the variant found in the affected family member.

The member’s contract may cover testing the non-covered index case if knowing the results of the genetic tests will benefit the covered family member who is at risk.
Evidence Review

Description

Genetic testing is available for patients suspected of having cardiac ion channelopathies, including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and short QT syndrome (SQTS). These disorders are clinically heterogeneous and may range from asymptomatic to presenting with sudden cardiac death. Testing for variants associated with these channelopathies may assist in diagnosis, risk-stratify prognosis, and/or identify susceptibility for the disorders in asymptomatic family members.

Background

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 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 pertaining to 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. The channelopathies discussed herein are genetically heterogeneous with hundreds of identified variants, but the group of disorders share basic clinical expression. The most common presentation is spontaneous or exercise-triggered syncope due to ventricular dysrhythmia. These can be self-limiting or potentially lethal cardiac events. The electrocardiographic features of each channelopathy are characteristic, but the electrocardiogram (EKG) is not diagnostic in all cases. Some secondary events (eg, electrolyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an EKG similar to those observed in a cardiac channelopathy.
Table 1. Epidemiology of Cardiac Ion Channelopathies

<table>
<thead>
<tr>
<th>Variables</th>
<th>LQTS</th>
<th>Brugada Syndrome</th>
<th>CPVT</th>
<th>SQTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>1:2000-5000</td>
<td>1:6000</td>
<td>1:7000-10,000</td>
<td>Unidentified</td>
</tr>
<tr>
<td>Annual mortality rate</td>
<td>0.3% (LQT1)</td>
<td>0.6% (LQT2)</td>
<td>4%</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>0.56% (LQT3)</td>
<td></td>
<td></td>
<td>Unidentified</td>
</tr>
<tr>
<td>Mean age at first event, y</td>
<td>14</td>
<td>42a</td>
<td>15</td>
<td>40</td>
</tr>
</tbody>
</table>

Adapted from Modell et al.\(^{2}\)
CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; SQTS: short QT syndrome.

\(^{a}\) Type 1 EKG pattern.

**Long QT Syndrome**

Congenital LQTS is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential. It increases the risk for arrhythmic events such as torsades de pointes, a type of ventricular tachycardia that can result in syncope and SCD. Management has focused on the use of β-blockers as first-line treatment, with pacemakers or implantable cardioverter defibrillator (ICD) as second-line therapy.

Congenital 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 family members to be tested. It is estimated that more than half of the 8000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1% to 2% per year, although this figure will vary with the genotype.

Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and thus LQTS has received 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 EKG. Diagnostic criteria for LQTS have been established, which focus on EKG findings and clinical and family history (ie, Schwartz criteria; see the Clinical Diagnosis subsection next). However, measurement of the QT interval is not well standardized and, in some instances, patients may be considered borderline cases.\(^{3}\)

In recent years, LQTS has been characterized as an “ion channel disease,” with abnormalities in the sodium and potassium channels that control the excitability of the cardiac myocytes. A genetic basis for LQTS has also emerged, with 7 different subtypes recognized, each
corresponding to variants in different genes. Also, typical ST-T wave patterns are also suggestive of specific subtypes. Some genetic subtypes are associated with abnormalities outside the cardiac conduction system.

**Brugada Syndrome**

BrS is characterized by cardiac conduction abnormalities that increase the risk of syncope, ventricular arrhythmia, and SCD. The disorder primarily manifests during adulthood, although it has been reported in infants as young as 2 days of age. BrS is an autosomal dominant disorder with an unexplained male predominance. Males are more likely to be affected than females (approximately an 8:1 ratio). BrS 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. Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.

**Catecholaminergic Polymorphic Ventricular Tachycardia**

CPVT 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 (VT) precipitated by exercise or emotional stress. The prevalence of CPVT is estimated between 1 in 7000 and 1 in 10,000 persons. CPVT has a mortality rate of 30% to 50% by age 35 and is responsible for 13% of cardiac arrests in structurally normal hearts. CPVT was previously believed to manifest only during childhood, but studies have now identified presentation between infancy and 40 years of age.

**Short QT Syndrome**

SQTS is characterized by a shortened QT interval on the EKG 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 sudden cardiac death (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 are due to arrhythmias without structural cardiac disease and are related to one of the primary electrical disease (PED) syndromes. The previously described cardiac ion channelopathies are among the PED 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, electrocardiogram, 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 PED. 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. This may be the case in up to 5% of total cases of LQTS. These types of variants may not be identified by gene sequence analysis. They can be more reliably identified by chromosomal microarray analysis, also known as array comparative genomic hybridization. Some laboratories that test for LQTS now offer detection of LQTS-associated deletions and duplications by this testing method. This type of test may be offered separately and may need to be ordered independently of gene sequence analysis when testing for LQTS.

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 mutation identified in a family member and targeted testing for this mutation is negative. Other laboratories have investigated different testing strategies. For example, Napolitano et al (2005) propose a 3-tiered approach, first testing for a core group of 64 codons that have a high incidence of variants, followed by additional testing of less frequent variants.
Another factor complicating interpretation of the genetic analysis is the penetrance of a given mutation or the presence of multiple phenotypic expressions. For example, approximately 50% of variant carriers never have any symptoms. There is variable penetrance for the LQTS, and penetrance may differ for the various subtypes. While linkage studies in the past 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.\textsuperscript{26}

The most commonly detected variants in patients with genetically confirmed LQTS involve KCNQ1, KCNH2, and SCN5A. 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.

### Table 2. Genetics of Long QT Syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Other Names</th>
<th>Chromosome Locus</th>
<th>Mutated Gene</th>
<th>Ion Current(s) Affected</th>
<th>Associated Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>RWS</td>
<td>11p15.5</td>
<td>KVLQT1 or KCNQ1 (heterozygotes)</td>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>LQT2</td>
<td>RWS</td>
<td>7q35-36</td>
<td>HERG, KCNH2</td>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>LQT3</td>
<td>RWS</td>
<td>3p21-24</td>
<td>SCN5A</td>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>LQT4</td>
<td>Ankyrin B syndrome</td>
<td>4q25-27</td>
<td>ANK2, ANKB</td>
<td>Sodium, potassium, calcium</td>
<td>Catecholaminergic polymorphic ventricular arrhythmias, sinus node dysfunction, AF</td>
</tr>
<tr>
<td>LQT5</td>
<td>RWS</td>
<td>21q22.1-22.2</td>
<td>KCNE1 (heterozygotes)</td>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>LQT6</td>
<td>RWS</td>
<td>21q22.1-22.2</td>
<td>MiRP1, KNCE2</td>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>LQT7</td>
<td>Andersen-Tawil syndrome</td>
<td>17q23.1-q24.2</td>
<td>KCNJ2</td>
<td>Potassium</td>
<td>Episodic muscle weakness, congenital anomalies</td>
</tr>
<tr>
<td>LQT8</td>
<td>Timothy syndrome</td>
<td>12q13.3</td>
<td>CACNA1C</td>
<td>Calcium</td>
<td>Congenital heart defects, hand/foot syndactyly, ASD</td>
</tr>
<tr>
<td>LQT9</td>
<td>RWS</td>
<td>3p25.3</td>
<td>CAV3</td>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>LQT10</td>
<td>RWS</td>
<td>11q23.3</td>
<td>SCN4B</td>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Other Names</td>
<td>Chromosome Locus</td>
<td>Mutated Gene</td>
<td>Ion Current(s) Affected</td>
<td>Associated Findings</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>LQT11</td>
<td>RWS</td>
<td>7q21-q22</td>
<td>AKAP9</td>
<td>Potassium</td>
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<tr>
<td>LQT12</td>
<td>RWS</td>
<td>20q11.21</td>
<td>SNTAI</td>
<td>Sodium</td>
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<tr>
<td>LQT13</td>
<td>RWS</td>
<td>11q24.3</td>
<td>KCNJ5</td>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>JLN1</td>
<td>JLNS</td>
<td>11p15.5</td>
<td>KVLQT1 or KCNQ1 (homozygotes or compound heterozygotes)</td>
<td>Potassium</td>
<td>Congenital sensorineural hearing loss</td>
</tr>
<tr>
<td>JLN2</td>
<td>JLNS</td>
<td>21q22.1-22.2</td>
<td>KCNE1 (homozygotes or compound heterozygotes)</td>
<td>Potassium</td>
<td>Congenital sensorineural hearing loss</td>
</tr>
</tbody>
</table>


AF: atrial fibrillation; ASD: autism spectrum disorder; LQT: long QT; JLNS: Jervell and Lange-Nielsen syndrome; RWS: Romano-Ward syndrome.

**Brugada Syndrome**

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 authors report up to 50% of cases are sporadic in nature, others report that the instance of de novo variants is very low and is estimated to be only 1% of cases.9

Variants in 16 genes have been linked to BrS, all of which lead to either a decrease in the inward sodium or calcium current or an increase in one of the outward potassium currents. Of these genes, SCN5A is the most important, estimated to account for more than 20% of cases15; SCN10A has also been implicated. The other genes are of minor significance and together they account for approximately 5% of cases.14 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.9

**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. Some have reported heterozygotes for CASQ2 and TRDN variants for rare, benign arrhythmias. Ryr2 variants represent most CPVT cases (50%-55%), with CASQ2 accounting for 1% to 2% and TRDN accounting for an unknown proportion of cases. The penetrance of Ryr2 variants is approximated at 83%.

An estimated 50% to 70% of patients will have the dominant form of CPVT with a disease-causing variant. Most variants (90%) to Ryr2 are missense variants, but in a small proportion of unrelated CPVT patients, large gene rearrangements or exon deletions have been reported. Additionally, nearly a third of patients diagnosed as LQTS with normal QT intervals have CPVT due to identified Ryr2 variants. Another misclassification, CPVT mistakenly 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**

SQTS has been linked predominantly to variants in 3 s 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 SCD.

**Genetic Testing for Cardiac Ion Channelopathies**

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

| Class I | Deleterious and probable deleterious mutations. They are mutations that have either previously been identified as pathologic (deleterious mutations), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious mutations). |
Class II
Possible deleterious mutations. These variants encode changes to protein(s) but occur in regions that are not considered critical. Approximately 5% of unselected patients without LQTS will exhibit mutations in this category.

Class III
Variants not generally expected to be deleterious. These variants encode modified protein(s); however, they are considered more likely to represent benign polymorphisms. Approximately 90% of unselected patients without LQTS will have one or more of these variants; therefore patients with only class III variants are considered “negative”.

Class IV
Non-protein-altering variants. These variants are not considered to have clinical significance and are not reported in the results of the Familion test.

Genetic Testing for Specific Cardiac Ion Channelopathies

Genetic testing for specific disorders, which may include 1 or more specific genes, is available from multiple academic and commercial laboratories, generally by next-generation sequencing or Sanger sequencing. In addition, panel testing for 1 or more cardiac ion channelopathies is available from a number of genetic diagnostics laboratories (see Table 3). The John Welsh Cardiovascular Diagnostic Laboratory, GeneDX, and Transgenomic all offer panels that genotype LQTS, BrS, CPVT, and SQTS, but there is some variation among manufacturers as to which genes are included.

Table 3. Examples of Cardiac Ion Channelopathy Genetic Testing Panels

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>LQTS</th>
<th>BrS</th>
<th>CPVT</th>
<th>SQTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambry Genetics (Aliso Viejo, CA)</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td></td>
</tr>
<tr>
<td>GeneDX (Gaithersburg, MD)</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>John Welsh Cardiovascular Diagnostic Laboratory, Baylor College of Medicine (Houston, TX)</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Prevention Genetics (Marshfield, WI)</td>
<td></td>
<td></td>
<td>•</td>
<td></td>
</tr>
<tr>
<td>Transgenomic/Familion (New Haven, CT)</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
</tbody>
</table>

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

Indicates multigene panel available for sudden cardiac death.

There are also commercially available panels that include genetic testing for cardiac ion channelopathies along with other hereditary cardiac disorders, such as hypertrophic.
cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (eg, iGene Cardiac Panel; ApolloGen, Irvine, CA).

Summary of Evidence

Long QT Syndrome

For individuals with suspected congenital 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, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 72% to 80% of LQTS. Most are point mutations identified by gene sequencing analysis; however, a small number are deletions/duplications best identified by chromosomal microarray analysis. The clinical validity of testing in LQTS is high, in the range of 70% to 80%. The clinical utility of genetic testing for LQTS is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. There is a strong chain of evidence to suggest that testing for variants associated with LQTS in individuals who are suspected to have these disorders, but in whom the diagnosis cannot be made by other methods, 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 cardiac 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 sudden cardiac death. While there is evidence suggesting that different genotypes are associated with varying risk of sudden cardiac death, there is insufficient evidence on the effects of changes in clinical management based on different genotypes. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with close relative(s) with a known LQTS variant who receive genetic testing for variants associated with congenital LQTS, the evidence includes studies reporting on changes in management. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. The studies conducted cardiologic and genetic evaluations of surviving family members of probands and determined whether the family members had the genetic variant. For close relatives of patients with known LQTS variants who were found to have a pathologic variant, preventive treatment was initiated. The studies did not provide follow-up information on the family members with the variant who received preventive treatment. The
evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Brugada Syndrome**

For individuals with suspected BrS who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields and a meta-analysis. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, 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 25% to 35% of BrS. BrS management changes, primarily use of ICDs, are directed by clinical symptoms. A meta-analysis reported that the presence of an SCN5A variant in patients with BrS was not predictive of the occurrence of a cardiac event, while a registry study published after the meta-analysis reported that the presence of the variant was related to a higher rate of cardiac events. 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 the effects of the technology on health outcomes.

For individuals who are asymptomatic with a close relative(s) with a known BrS variant who receive genetic testing for variants associated with congenital BrS, the evidence includes observational studies reporting on testing yields. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. BrS 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 a meaningful improvement in the net health outcome.

Given the limited available evidence on genetic testing for BrS, clinical input was obtained. 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.

**Catecholaminergic Polymorphic Ventricular Tachycardia**

For individuals with suspected CPVT who receive genetic testing for variants associated with congenital CPVT, the evidence includes observational studies reporting on testing yields. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 51% to 75% of CPVT patients. The clinical validity of testing in CPVT is moderate, in the range of 50% to 75%. The clinical utility of genetic testing for CPVT is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. There is a strong chain of evidence to suggest that testing for variants associated with CPVT in individuals who are suspected to have these disorders, but in whom the diagnosis cannot be made by other methods, leads to improved outcomes. 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. The evidence is sufficient to determine that the technology results in a meaningful 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 congenital CPVT, the evidence includes observational studies reporting testing yields. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. For close relatives of patients with known CPVT variants who are found to have a pathologic 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 a meaningful improvement in the net health outcome.

**Short QT Syndrome**

For individuals with suspected SQTS who receive genetic testing for variants associated with SQTS, the evidence includes limited data on testing yields. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. The clinical validity of testing for SQTS is low: a genetic
variant can only be identified in approximately 15% to 20% of SQTS patients. 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 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 the effects of the technology on health outcomes.

For individuals who are asymptomatic with a close relative(s) with a known SQTS variant who receive genetic testing for variants associated with congenital SQTS, the evidence includes observational studies reporting on testing yields. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, 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 the effects of the technology on health outcomes.

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 did state 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.

For individuals who are asymptomatic with a close family member(s) who experienced sudden cardiac death where no 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 the effects of the technology on health outcomes.
Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01705925&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Multicenter Evaluation of Children and Young Adults With Genotype Positive Long QT Syndrome</td>
<td>500</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT02876380</td>
<td>Prospective Identification of Long QT Syndrome in Fetal Life</td>
<td>600</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02425189</td>
<td>The Canadian National Long QT Syndrome Registry (LQTSREG)</td>
<td>600</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT02014961</td>
<td>Worm Study: Modifier Genes in Sudden Cardiac Death</td>
<td>223</td>
<td>Apr 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

<sup>a</sup> Denotes industry-sponsored or cosponsored trial

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

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

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 consensus that genetic testing for BrS is medically necessary to establish the diagnosis of BrS in an individual with a suspected but not definite diagnosis of BrS and to evaluate family members of an individual with a known pathogenic genetic mutation 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 definite diagnosis of SQTS, but there was consensus that testing for SQTS to evaluate family
members of an individual with a known pathogenic genetic mutation 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

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

In 2017, the American Heart Association, American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Table 5 summarizes the recommendations relating to cardiac ion channelopathies.

Table 5. Recommendations for Genetic Testing in Cardiac Channelopathies

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended.</td>
<td>I (strong)</td>
<td>B-NR</td>
</tr>
<tr>
<td>In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information.</td>
<td>I (strong)</td>
<td>B-NR</td>
</tr>
<tr>
<td>In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable. Genetic testing may confirm a diagnosis; however, therapy for these patients is not guided by genotype status.</td>
<td>IIA (moderate)</td>
<td>B-NR</td>
</tr>
<tr>
<td>In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives, allowing for lifestyle modification and potential treatment.</td>
<td>IIb (weak)</td>
<td>C-EO</td>
</tr>
<tr>
<td>In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives.</td>
<td>IIb (weak)</td>
<td>C-EO</td>
</tr>
</tbody>
</table>

B-NR: moderate level of evidence, nonrandomized studies; C-EO: consensus of expert opinion based on clinical experience; COR: class of recommendation; LOE: level of evidence; VT: ventricular tachycardia.
Heart Rhythm Society, European Heart Rhythm Association, et al.

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. This consensus statement refers to the 2011 guidelines on genetic testing for channelopathies and cardiomyopathies 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 6). 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 define several terms related to specific types of sudden cardiac death, including:

- sudden unexplained death syndrome: an unexplained sudden death in an individual older than 1 year of age

- sudden arrhythmic death syndrome: a sudden unexplained death syndrome case with negative pathologic and toxicologic assessment

- sudden unexplained death in infancy: an unexplained sudden death in an individual younger than 1 year of age with negative pathologic and toxicologic assessment.

Table 6. Recommendations for Genetic Testing in IVF, SUDS, and SUDI

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IVF</strong></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>IIa</td>
</tr>
<tr>
<td>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.</td>
<td>III</td>
</tr>
<tr>
<td><strong>SUDS</strong></td>
<td></td>
</tr>
<tr>
<td>Collection of blood and/or suitable tissue for molecular autopsy/postmortem genetic testing is recommended in all SUDS victims.</td>
<td>I</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
</tr>
</tbody>
</table>
Consensus Recommendation | Class
--- | ---
**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 concerning testing for QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome (see Table 7).

### Table 7. Cardiac Ion Channelopathy Testing Recommendations

<table>
<thead>
<tr>
<th>HRS and EHRA Consensus Recommendation</th>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
</table>
| **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 EKGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype. | I | C |

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 EKGs defined as QTc $\geq$ 480 ms (prepuberty) or $\geq$ 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.

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

**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 |
<table>
<thead>
<tr>
<th>HRS and EHRA Consensus Recommendation</th>
<th>Class(^a)</th>
<th>LOE(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 EKGs and/or provocative drug challenge testing) phenotype.</td>
<td>IIa</td>
<td></td>
</tr>
<tr>
<td>Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada EKG pattern.</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>CPVT</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQTS</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>IIb</td>
<td></td>
</tr>
</tbody>
</table>

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; EKG: electrocardiogram; EHRA: European Heart Rhythm Association; HRS: Heart Rhythm Society; 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.

**American College of Cardiology et al**

The American College of Cardiology/American Heart Association/European Society of Cardiology issued guidelines in 2006 on the management of patients with ventricular arrhythmias and the prevention of sudden death.\(^74\) These guidelines made a general statement that “In patients affected by LQTS, genetic analysis is useful for risk stratification and therapeutic decisions.” These guidelines did not address the use of genetic testing for the diagnosis of LQTS. The guidelines also state that genetic testing for CPVT, BrS, or SQTS may identify silent carriers for clinical monitoring but does not assist with risk stratification.
Canadian Cardiovascular Society and Canadian Hearth Rhythm Society

The Canadian Cardiovascular Society and Canadian Hearth Rhythm Society published a joint position paper in 2011. Genetic testing was recommended for cardiac arrest survivors with LQTS for the purpose of familial screening, as well as those with syncope with corrected QT (QTc) prolongation, as well as asymptomatic patients with QTc prolongation with a high clinical suspicion of LQTS. For clinically suspect catecholaminergic polymorphic ventricular tachycardia, testing is recommended for the purpose of familial screening. Genetic testing was also recommended for cardiac arrest survivors with a type I Brugada electrocardiogram pattern for the purpose of familial screening, as well as in patients with syncope and type I Brugada electrocardiogram pattern or asymptomatic patients with type I Brugada electrocardiogram pattern and a high clinical suspicion. No recommendations are given for short QT syndrome.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

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

References


18. Wilders R. Cardiac ion channelopathies and the sudden infant death syndrome. ISRN Cardiol. 2012;2012:846171. PMID 23304551

19. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. Aug 2011;8(8):1308-1339. PMID 21787999


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/11/05</td>
<td>Add Policy to Medicine Section, Pathology/Laboratory subsection - New Policy</td>
</tr>
<tr>
<td>07/11/06</td>
<td>Replace Policy - Policy updated with literature search; reference added; no change to policy statement.</td>
</tr>
<tr>
<td>02/12/08</td>
<td>Replace Policy - Policy updated with literature search; Policy statement changed to state that some indications of genetic testing for long QT syndrome may be considered medically necessary. References and code added.</td>
</tr>
<tr>
<td>08/12/08</td>
<td>Code Updates - Added S3860, S3861, S3862 (effective 10/1/08), no other changes.</td>
</tr>
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<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>02/10/09</td>
<td>Replace Policy - Policy updated with literature search; no change to the policy statement. References added.</td>
</tr>
<tr>
<td>04/13/10</td>
<td>Cross Reference Update - No other changes.</td>
</tr>
<tr>
<td>09/14/10</td>
<td>Replace Policy - Policy updated with literature search; policy statements unchanged. Reference numbers 28 to 32 added.</td>
</tr>
<tr>
<td>09/13/11</td>
<td>Replace Policy – Policy updated with literature search; policy statement changed: Genetic testing for patients with known LQTS to assist other at-risk family members, previously considered medically necessary, is now considered not medically necessary. Ten references removed, list renumbered; references 17, 22, 23, 25 and 26 added. Approved with 90-day hold; effective 2/8/12.</td>
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<tr>
<td>01/24/12</td>
<td>Codes 81280 – 81282 added.</td>
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<tr>
<td>03/13/12</td>
<td>Replace policy. Policy statement changed: Genetic testing for index patients with known LQTS to assist other at-risk family members, previously considered not medically necessary, is now considered medically necessary as a plan variance.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.43 (previously 2.04.43) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>09/11/12</td>
<td>Replace policy. Policy updated with literature search, references 14, 25-27, 29, 30 added. No change to policy statement.</td>
</tr>
<tr>
<td>01/10/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT code 81200 – 81479 and 81599, effective 1/1/13, added to the policy.</td>
</tr>
<tr>
<td>05/14/13</td>
<td>Update Related Policy. Add 12.04.91.</td>
</tr>
<tr>
<td>12/09/13</td>
<td>Replace policy. Policy updated with literature search, reference 33 added. No change to the policy statement. CPT Codes 81200-81479 and 81599 removed; there are codes specific to this policy. Deleted codes 83890-83912 also removed.</td>
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<tr>
<td>02/10/14</td>
<td>Replace policy. Policy updated with literature search through November 1, 2013, references 2, 3, 8-18, 20, 29-32, and 49. Policy title changed to “Genetic Testing for Cardiac Ion Channelopathies”. Background and rationale extensively rewritten to incorporate Brugada syndrome, CPVT, and short QT syndrome. Medically necessary statement added for CPVT when criteria are met and testing of index patient with CPVT. Investigational statements added for Brugada syndrome and short QT syndrome. HCPCS codes S3860 and S3862 removed from the policy; these codes were deleted in 2012.</td>
</tr>
<tr>
<td>03/21/14</td>
<td>Update Related Policies. Add 12.04.114.</td>
</tr>
<tr>
<td>12/17/14</td>
<td>Annual Review. Policy updated with literature search; policy statements unchanged. ICD-9 and ICD-10 diagnosis and procedure codes removed; these do not relate to policy adjudication.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>02/25/15</td>
<td>Annual Review. Policy updated with literature review through October 30, 2014. References 1-4, 13, 29-30, 39, 54, and 58-59 added. Background section reorganized. Language added to Policy Guidelines section to clarify testing strategy in family members of proband with sudden cardiac arrest. Additional policy statement added that genetic testing for LQTS or CPVT is investigational for all other situations when criteria are not met. Plan variance policy statements regarding testing of unaffected first degree family members retained.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Coding update; added new CPT codes 81413 and 81414 effective 1/1/17.</td>
</tr>
<tr>
<td>09/22/17</td>
<td>Policy moved to new format. No changes to policy statements.</td>
</tr>
<tr>
<td>01/01/18</td>
<td>Coding update, removed CPT codes 81280, 81281, and 81282 as these codes terminated 1/1/17.</td>
</tr>
<tr>
<td>04/01/18</td>
<td>Annual Review, approved March 20, 2018. Policy updated with literature review through November 2017; references 2, 61, 63, 67, and 72 added; references 9, 17, and 29 updated. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98110
Toll free 855-332-4535, Fax 425-918-5952. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filling a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan Iadann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pren kék akson avan sèten dat limit pou ka tenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Italiano (Italian):
Rusский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการประนายหรือการต่ออายุสิทธิของการดูแลสุขภาพของคุณผ่าน Premera Blue Cross และคุณอาจต้องการการติดต่อในหน้าที่มีความต้องการในการกำหนดเวลาที่แน่นอนเพื่อให้สามารถทราบข้อมูลเกี่ยวกับสิทธิของการดูแลสุขภาพที่คุณมีไม่ว่าคุณจะใช้สิทธินี้หรือไม่ โดยการติดต่อกับ Premera Blue Cross.

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):