Genetic Testing for Cardiac Ion Channelopathies

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for genetic testing for cardiac ion channelopathies when it is determined to be medically necessary because the criteria shown below are met.

Note: This is a type of genetic testing that may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Statements Topic is covered
Long QT Syndrome
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 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 (see Considerations) based on the Schwartz score and/or other clinical criteria.

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:

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

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.
Brugada Syndrome
Genetic testing to confirm a diagnosis of Brugada syndrome (BrS) may be considered medically necessary when signs and/or symptoms consistent with BrS (see Considerations) are present but a definitive diagnosis cannot be made without genetic testing.

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 mutation.

Genetic testing for BrS for all other situations not meeting the criteria outlined above is considered investigational.

Catecholaminergic Polymorphic Ventricular Tachycardia
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) with a known CPVT mutation; or
- A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable.

Genetic testing for CPVT for all other situations not meeting the criteria outlined above is considered investigational.

Short QT Syndrome
Genetic testing of asymptomatic individuals to determine future risk of SQTS may be considered medically necessary when patients have a close relative (ie, first-, second-, or third-degree relative) with a known SQTS mutation.

Genetic testing for SQTS for all other situations not meeting the criteria outlined above is considered investigational.

When Policy Topic is not covered
See above

Considerations
Genetic testing should be performed by an individual with adequate expertise in genetic testing and/or cardiac ion channelopathies.
Determining the pretest probability of LQTS is not standardized. An example of a patient with a moderate-to-high pretest probability of LQTS is a patient with a Schwartz score of 2 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 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 or 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 policy. Panels for cardiac ion channelopathies are diagnostic test panels that may fall into one of several categories: panels that include mutations for a single condition; panels that include mutations for multiple conditions (indicated plus nonindicated conditions); panels that include mutations 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 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 suggest 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.

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
- With suspected congenital long QT syndrome | Interventions of interest are:  
- Genetic testing for variants associated with congenital long QT syndrome | Comparators of interest are:  
- Standard management without genetic testing | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
- Other test performance measures  
- Changes in reproductive decision making  
- Morbid events |
| Individuals:  
- Who are asymptomatic with close relative(s) with a known long QT syndrome variant | Interventions of interest are:  
- Genetic testing for variants associated with congenital long QT syndrome | Comparators of interest are:  
- Standard management without genetic testing | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
- Other test performance measures  
- Changes in reproductive decision making  
- Morbid events |
| Individuals:  
- With suspected Brugada syndrome | Interventions of interest are:  
- Genetic testing for variants associated with Brugada syndrome | Comparators of interest are:  
- Standard management without genetic testing | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
- Other test performance measures  
- Changes in reproductive decision making  
- Morbid events |
| Individuals:  
- Who are asymptomatic with close relative(s) with a known Brugada syndrome variant | Interventions of interest are:  
- Genetic testing for variants associated with Brugada syndrome | Comparators of interest are:  
- Standard management without genetic testing | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
- Other test performance measures  
- Changes in reproductive decision making  
- Morbid events |
| Individuals:  
- With suspected catecholaminergic polymorphic ventricular tachycardia | Interventions of interest are:  
- Genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia | Comparators of interest are:  
- Standard management without genetic testing | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
- Other test performance measures  
- Changes in reproductive decision making  
- Morbid events |
| Individuals:  
- With suspected catecholaminergic polymorphic ventricular tachycardia | Interventions of interest are:  
- Genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia | Comparators of interest are:  
- Standard management without genetic testing | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
- Other test performance measures  
- Changes in reproductive decision making  
- Morbid events |
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 mutations associated with these channelopathies may assist in diagnosis, risk stratify prognosis, and/or identify susceptibility for the disorders in asymptomatic family members.

**Long QT Syndrome**

For individuals with suspected congenital LQTS who receive genetic testing for variants associated with congenital LQTS, the evidence includes studies reporting on the yield of testing among patients with clinically suspected or clinically diagnosed disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. 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

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Who are asymptomatic with close relative(s) with a known catecholaminergic polymorphic ventricular tachycardia variant</td>
<td>Genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia</td>
<td>Standard management without genetic testing</td>
<td>Overall survival</td>
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<tr>
<td></td>
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<td>Test accuracy</td>
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<td></td>
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<td>Test validity</td>
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<td>Other test performance measures</td>
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<td></td>
<td></td>
<td></td>
<td>Changes in reproductive decision making</td>
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<td></td>
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<td>Morbid events</td>
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</tbody>
</table>

Genetic Testing for Cardiac Ion Channelopathies 2.04.43
72% to 80% of LQTS. Most are point variants identified by gene sequencing analysis; however, a small number are deletions and duplications best identified by chromosomal microarray (CMA) analysis. The analytic validity of testing for point variants by sequence analysis is high, while the analytic validity of testing for deletions/duplications by CMA analysis is less certain. 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. A definitive diagnosis of either channelopathy 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. 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. Although for LQTS there is evidence suggesting that different genotypes are associated with varying risk of sudden cardiac death, there is insufficient evidence to conclude that the information from genetic testing on risk assessment leads to changes in clinical management. 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 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 that resulted from diagnosing LQTS by testing relatives of affected patients with known LQTS and studies reporting testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. The clinical utility of testing is high for close relatives of patients with known LQTS variants, because these individuals should also be treated if they are found to have a pathologic variant. In addition, 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.

**Brugada Syndrome**
For individuals with suspected BrS who receive genetic testing for variants associated with BrS, the evidence includes studies reporting on testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. Although the analytic validity of testing for is likely to be high, the clinical validity is lower: a genetic variant can be identified in approximately 25% to 35% of BrS. For BrS management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in a symptomatic proband without a definitive diagnosis. It is not
clear that 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 close relative(s) with a known BrS variant who receive genetic testing for variants associated with congenital BrS, the evidence includes studies reporting on testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. For BrS, management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in an individual with family members with 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 studies reporting on testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. 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 analytic validity of testing for point variants by sequence analysis is high, while the analytic validity of testing for deletions/duplications by CMA analysis is less certain. 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. Confirming the diagnosis of CPVT is likely to lead to a health outcome benefit by initiating changes in management that reduce the risk for ventricular arrhythmias and sudden cardiac death. 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. 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 close relative(s) with a known CPVT variant who receive genetic testing for variants associated with congenital CPVT, the evidence includes studies reporting testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. The clinical utility of testing is high for close relatives of patients with known CPVT variants, because these individuals should also be treated if they are found to have a pathologic variant. In addition, 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 among patients with clinically suspected disorders and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. Although the analytic validity of testing for is likely to be high, the clinical validity is lower: a genetic variant can be identified in approximately 15% to 20% of SQTS patients. For SQTS, management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in a symptomatic proband without a definitive diagnosis. It is not clear that that 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 close relative(s) with a known with a known SQTS variant who receive genetic testing for variants associated with congenital SQTS, the evidence includes studies reporting on testing yields among patients with clinically suspected disorders and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. For SQTS, management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in an individual with family members with a known variant. It is not clear that that 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 BrS and SQTS, clinical input was obtained. There was consensus that genetic testing for the diagnosis of BrS in individuals with suspected BrS in whom a definitive diagnosis cannot be made by other means is useful in making a diagnosis and subsequent management that may lead to improved outcomes. In addition, there was consensus that genetic testing to predict future risk of disease in individuals with close relatives with known variant associated with SQTS or BrS is useful in management that may lead to improved outcomes.

For individuals who are asymptomatic with a close family member(s) who experienced sudden cardiac death 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.

**Background**

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.1 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. 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 (ECG) is not diagnostic in all cases, and some secondary events (e.g., electrolyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an ECG similar to those observed in a cardiac channelopathy.

<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>4%a</td>
<td>3.1%</td>
<td>Unidentified</td>
</tr>
<tr>
<td></td>
<td>0.6% (LQT2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.56% (LQT3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mean age at first event, y | 14 | 42<sup>a</sup> | 15 | 40

Adapted from Modell et al (2012).<sup>2</sup>

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

<sup>a</sup> 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 sudden cardiac death. Management has focused on the use of β-blockers as first-line treatment, with pacemakers or ICD as second-line therapy.

Congenital LQTS usually manifests before the age of 40 years and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult; this history may prompt additional testing in family members. It is estimated that more than 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 ECG. Diagnostic criteria for LQTS have been established, which focus on ECG findings and clinical and family history (ie, Schwartz criteria, see following subsection, Clinical Diagnosis). However, measurement of the QT interval is not well-standardized, and, in some instances, patients may be considered borderline cases.<sup>(3)</sup>

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 mutations in different genes as indicated here.<sup>(4)</sup> In addition, typical ST-T wave patterns are also suggestive of specific subtypes.<sup>(5)</sup> Some of the genetic subtypes are associated with abnormalities outside the cardiac conduction system.

**Clinical Diagnosis**

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS.<sup>6</sup> The most recent version is shown in Table 2. A score of 3.5 or higher indicates a high probability that LQTS is present; a score of 1.5 to 3, an intermediate probability; and a score of 1 or less indicates a low probability of the disorder. Before the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; and because there is still no perfect criterion standard for diagnosing LQTS, the accuracy of this scoring system remains ill-defined.
### Table 2. Diagnostic Scoring System for Long QT Syndrome

<table>
<thead>
<tr>
<th>Schwartz Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrocardiographic findings</strong></td>
<td></td>
</tr>
<tr>
<td>QT corrected &gt;480 ms</td>
<td>3</td>
</tr>
<tr>
<td>QT corrected 460-470 ms</td>
<td>2</td>
</tr>
<tr>
<td>QT corrected &lt;450 ms</td>
<td>1</td>
</tr>
<tr>
<td>History of torsades de pointes</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T waves in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Syncope brought on by stress</td>
<td>2</td>
</tr>
<tr>
<td>Syncope without stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>Family members with definite long QT syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained sudden death in immediate family members &lt;30 y of age</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Adapted from Perrin and Gollob (2012).

### 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 ages between 2 days and 85 years have been reported. BrS is an autosomal dominant disorder with an unexplained male predominance. Males are more likely to be affected than females (approximate ratio, 8:1). 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.

### Clinical Diagnosis

The diagnosis of BrS is made by the presence of a type 1 Brugada pattern on the ECG in addition to other clinical features. This ECG pattern includes a coved ST-segment and a J-point elevation of 0.2 mV or higher followed by a negative T wave. This pattern should be observed in 2 or more of the right precordial ECG leads (V₁-V₃). This pattern may be concealed and can be revealed by administering a sodium-channel-blocking agent (eg, ajmaline or flecainide). Two additional ECG patterns have been described (type 2, type 3) but are less specific for the disorder. The diagnosis of BrS is considered definitive when the characteristic ECG pattern is present with at least one of the following clinical features: documented ventricular arrhythmia, SCD in a family member younger than 45 years old, characteristic ECG pattern in a family member, inducible ventricular arrhythmias on electrophysiology studies, syncope, or nocturnal agonal respirations.

### Clinical Management

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

CPVT is a rarely 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.

**Clinical Diagnosis**

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

**Clinical Management**

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

**Short QT Syndrome**

SQTS is characterized by a shortened QT interval on the 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.

**Clinical Diagnosis**

Patients generally present with syncope, pre-syncope, or cardiac arrest. An ECG with a corrected QT interval less than 330 ms, sharp T wave at the end of the QRS complex, and a brief or absent ST-segment are characteristic of the syndrome. However, higher QT intervals on ECG might also indicate SQTS, and the clinician has to determine if this is within the normative range of QT values. An index patient with suspected SQTS would be expected to have a shortened (<2 standard deviations below from the mean) rate-corrected shortened QT interval (QTc). Cutoffs below 350 ms for men and 360 ms for women have been derived from population normal values. The length of the QT interval was not associated with severity of symptoms in a 2006 series of 29 patients with SQTS. Electrophysiologic studies may be used to diagnose SQTS if the diagnosis is uncertain to evaluate for short refractory periods and inducible VT. However, in the series of 29 patients with SQTS described above, VT was inducible in only 3 of
6 subjects who underwent an electrophysiologic study. In 2011, a diagnostic scoring system was proposed by Gollob et al to help decision making after a review of 61 SQTS cases (see Table 3).

**Table 3. Diagnostic Scoring System for Short QT Syndrome**

<table>
<thead>
<tr>
<th>Gollob Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
</tr>
<tr>
<td>QT corrected &lt;370 ms</td>
<td>1</td>
</tr>
<tr>
<td>QT corrected &lt;350 ms</td>
<td>2</td>
</tr>
<tr>
<td>QT corrected &lt;330 ms</td>
<td>3</td>
</tr>
<tr>
<td>J point-T peak interval &lt;120 ms</td>
<td>1</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>History of sudden cardiac death</td>
<td>2</td>
</tr>
<tr>
<td>Documented polymorphic ventricular fibrillation or ventricular tachycardia</td>
<td>2</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>First- or second-degree relative with high probability short QT syndrome</td>
<td>2</td>
</tr>
<tr>
<td>First- or second-degree relative with autopsy-negative sudden cardiac death</td>
<td>1</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
</tr>
<tr>
<td>Genotype positive</td>
<td>2</td>
</tr>
<tr>
<td>Mutation of undetermined significance in a culprit gene</td>
<td>1</td>
</tr>
</tbody>
</table>

Adapted from Perrin and Gollob (2012).

**Clinical Management**

The primary management of SQTS is with ICD therapy. ICD decisions are based on the degree to which SQTS is considered likely, which depends on ECG features, family history, personal history of cardiac arrest or ventricular arrhythmias, and the ability to induce ventricular tachycardia on electrophysiologic studies.

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

**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 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 independent 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 variant identified in a family member and targeted testing for this variant is negative. Other laboratories have investigated different testing strategies. For example, Napolitano et al (2005) proposed 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 variant 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 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 4.

<table>
<thead>
<tr>
<th>Table 4. Genetics of Long QT Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
</tbody>
</table>

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 4.
<table>
<thead>
<tr>
<th>LQT</th>
<th>RWS</th>
<th>Chromosome</th>
<th>Gene(s)</th>
<th>Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RWS</td>
<td>11p15.5</td>
<td>KVLQT1 or KCNQ1 (heterozygotes)</td>
<td>Potassium</td>
</tr>
<tr>
<td>2</td>
<td>RWS</td>
<td>7q35-36</td>
<td>HERG, KCNH2</td>
<td>Potassium</td>
</tr>
<tr>
<td>3</td>
<td>RWS</td>
<td>3p21-24</td>
<td>SCN5A</td>
<td>Sodium</td>
</tr>
<tr>
<td>4</td>
<td>Ankyrin B syndrome</td>
<td>4q25-27</td>
<td>ANK2, ANKB</td>
<td>Sodium, potassium, calcium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Catecholaminergic polymorphic ventricular arrhythmias, sinus node dysfunction, AF</td>
</tr>
<tr>
<td>5</td>
<td>RWS</td>
<td>21q22.1-22.2</td>
<td>KCNE1 (heterozygotes)</td>
<td>Potassium</td>
</tr>
<tr>
<td>6</td>
<td>RWS</td>
<td>21q22.1-22.2</td>
<td>MiRP1, KNCE2</td>
<td>Potassium</td>
</tr>
<tr>
<td>7</td>
<td>Andersen-Tawil syndrome</td>
<td>17q23.1-q24.2</td>
<td>KCNJ2</td>
<td>Potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Episodic muscle weakness, congenital anomalies</td>
</tr>
<tr>
<td>8</td>
<td>Timothy syndrome</td>
<td>12q13.3</td>
<td>CACNA1C</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Congenital heart defects, hand/foot syndactyly, ASD</td>
</tr>
<tr>
<td>9</td>
<td>RWS</td>
<td>3p25.3</td>
<td>CAV3</td>
<td>Sodium</td>
</tr>
<tr>
<td>10</td>
<td>RWS</td>
<td>11q23.3</td>
<td>SCN4B</td>
<td>Sodium</td>
</tr>
<tr>
<td>11</td>
<td>RWS</td>
<td>7q21-q22</td>
<td>AKAP9</td>
<td>Potassium</td>
</tr>
<tr>
<td>12</td>
<td>RWS</td>
<td>20q11.21</td>
<td>SNTAI</td>
<td>Sodium</td>
</tr>
<tr>
<td>13</td>
<td>RWS</td>
<td>11q24.3</td>
<td>KCNJ5</td>
<td>Potassium</td>
</tr>
<tr>
<td>14</td>
<td>JLNS</td>
<td>11p15.5</td>
<td>KVLQT1 or KCNQ1 (homozygotes or compound heterozygotes)</td>
<td>Potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Congenital sensorineural hearing loss</td>
</tr>
<tr>
<td>15</td>
<td>JLNS</td>
<td>21q22.1-22.2</td>
<td>KCNE1 (homozygotes or compound heterozygotes)</td>
<td>Potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Congenital sensorineural hearing loss</td>
</tr>
</tbody>
</table>


**Brugada Syndrome**

BrS is typically inherited in an autosomal dominant manner with incomplete penetrance. The proportion of cases that are inherited, vs de novo variants, is uncertain. Although some have reported 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.9

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.

**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 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 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 in Table 5.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Deleterious and probable deleterious mutations. They are mutations that have either</td>
</tr>
</tbody>
</table>
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).

**II**  Possible deleterious mutations. These variants encode changes to protein(s) but occur in regions that are not considered critical. Approximately 5% of unselected patients without LQTS will exhibit mutations in this category.

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

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

**Genetic Testing for Specific Cardiac Ion Channelopathies**

Genetic testing for specific disorders, which may include one or more specific genes, is available from multiple academic and commercial laboratories, generally by next-generation sequencing or Sanger sequencing. Also, panel testing for one or more cardiac ion channelopathies is available from a number of genetic diagnostics laboratories (see Table 6). 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 on the included genes.

**Table 6. 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><strong>Ambry Genetics (Aliso Viejo, CA)</strong></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>GeneDX (Gaithersburg, MD)</strong></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>John Welsh Cardiovascular Diagnostic Laboratory, Baylor College of Medicine</strong>&lt;sup&gt;a&lt;/sup&gt; (Houston, TX)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>Prevention Genetics (Marshfield, WI)</strong></td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>Transgenomic/Familion&lt;sup&gt;a&lt;/sup&gt; (New Haven, CT)</strong></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.

<sup>a</sup> 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).

**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.
**Rationale**
This evidence review was created in June 2005 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 6, 2017. (see Appendix Table 1 for genetic testing categories).

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Genetic testing for variants associated with cardiac ion channelopathies**

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

The question addressed in this evidence review is: Does genetic testing for cardiac ion channelopathies (eg, long QT syndrome [LQTS], Brugada syndrome [BrS], catecholaminergic polymorphic ventricular tachycardia [CPVT], short QT syndrome [SQTS]) improve health outcomes in individuals with suspected channelopathies or in individuals with a close relative with known or suspected channelopathies?

The following PICOTS were used to select literature to inform this review.

**Patients**
The populations of interest are patients with suspected cardiac ion channelopathies or individuals with a close relative with known or suspected cardiac ion channelopathies.

**Interventions**
The intervention of interest is genetic testing for cardiac ion channelopathies.

**Comparators**
The comparator of interest is standard management without genetic testing.
Outcomes
Outcomes of interest include overall survival and test accuracy and validity. Positive results may also influence reproductive decisions.

A positive diagnosis of LQTS or CPVT in symptomatic patients may lead to treatment with β-blockers or with implantable cardioverter defibrillators (ICDs), which can reduce the risk for ventricular arrhythmias and sudden cardiac death (SCD).

A positive test for BrS in symptomatic patients may influence the decision for treatment with an ICD.

It is unknown how a positive SQTS test in symptomatic patients would influence treatment decisions.

Positive tests in asymptomatic family members can inform lifestyle changes and prevention treatment decisions.

Timing
The genetic assays may be recommended as part of a diagnostic strategy for patients who exhibit clinical symptoms that are not considered definitive.

The tests may also be recommended for asymptomatic family members of patients with known cardiac ion channel variants.

Setting
Genetic tests are conducted in clinical laboratories.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.
Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

The evidence related to the clinical validity and utility of genetic testing for the cardiac channelopathies consists primarily of studies that evaluate the yield of genetic testing and the impact of genetic testing on the diagnosis and subsequent management of a specific cardiac channelopathy. Many cardiac channelopathies lead to a common clinical outcome—increased risk of ventricular arrhythmias leading to an increased risk of SCD. Studies that evaluate the role of genetic testing for cardiac channelopathies as part of a diagnostic strategy in the evaluation of ventricular fibrillation or SCD from an unknown cause are discussed separately.

The evidence is presented as follows. first, for patients who are candidates for testing of specific channelopathies (LQTS, BrS, CPVT, SQTS) and asymptomatic family members of variant-positive probands. Next, evidence for genetic testing of survivors of unexpected cardiac arrest is presented; these individuals have the potential to have genetic testing for one of the specific channelopathies reviewed in this policy. Finally, the evidence is presented for genetic testing of family members in cases of SCD when a specific clinical diagnosis has not been made.

**Genetic Testing for the Diagnosis of Specific cardiac ion Channelopathies**

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.

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

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

**Long QT Syndrome**
Hofman et al (2007) compared clinical methods (Schwartz score, Keating criteria, and length of corrected QT [QTc]) with genetic testing results in 513 relatives of 77 LQTS probands with known variants. The diagnostic predictive powers of the
clinical method were calculated using the genetic assay results as a reference. The sensitivity and specificity of a Schwartz score of 4 or higher were 19% and 99%, respectively. The sensitivity and specificity of the Keating criteria were 36% and 99%. The best overall accuracy was obtained by using the length of the QTc as the sole criterion. Using a cutoff of 430 ms or longer for the QT interval, a sensitivity of 72% and a specificity of 86% were obtained.

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

The evidence on clinical specificity focuses on the frequency and interpretation of variants identified but not known to be pathologic. If a variant identified is known to be pathologic, then the specificity of this finding is high. However, many variants are not known to be pathologic, and the specificity for these variants is lower. The rate of identification of variants is estimated at 5% for patients who do not have LQTS.

A 2012 publication from the National Heart, Lung, and Blood Institute GO Exome Sequencing Project (ESP) reported on the rate of sequence variants in a large number of patients without LQTS. The ESP sequenced all genome regions of protein-coding in a sample of 5400 persons drawn from various populations, none of whom specifically had heart disease and/or channelopathies. Exome data were systematically searched to identify sequence variants previously associated with LQTS, including both nonsense variants, which are generally pathologic, and missense variants, which are less likely to be pathologic. Thirty-three such sequence variants were identified in the total population—all missense variations. The percentage of the population that had at least one of these missense variants was 5.2%. No nonsense variants were associated with LQTS found among the entire population.

**Brugada Syndrome**

The yield using SCN5A variant testing in BrS is low. Analyses of patients with a high clinical suspicion of BrS provided a yield between 25% and 35%, for a documented pathologic variant. The most commonly identified of the 8 known genes for BrS is SCN4A, which is found in 20% of genotype-positive cases.

The National Heart, Lung, and Blood Institute ESP data identified a BrS prevalence of 4.7% when considering the maximal number of identified genes and variants, which is far higher than in the general population. Forty-seven percent of the variants found in the published literature were determined to be pathogenic, whereas 75% of the variants in ESP were determined to be pathogenic.
In 2014, Hu et al evaluated the prevalence of SCN10A variants in 120 probands with BrS in more than 200 healthy controls. SCN10A encodes a voltage-gated sodium channel located adjacent to SCN5A on chromosome 3p21-22, which had previously been associated with pain perception but more recently was found in genome-wide association studies to be linked to cardiac conduction abnormalities. Seventeen SCN10A variants were identified in 25 probands, with a variant detection rate of 16.7% in BrS probands. Behr et al (2015) evaluated 7 candidate genes (SCN10A, HAND1, PLN, CASQ2, TKT, TBX3, TBX5) among 156 patients negative for SCN5A variants with symptoms indicative of BrS (64%) and/or a family history of sudden death (47%) or BrS (18%). Candidate genes had been selected based on a previous genome-wide association study based on the strength of association and biologic plausibility. Eighteen (11.5%) patients were found to have variants, most often in SCN10A (12/18 [67%]). Inquiry into other variants associated with BrS is ongoing, and expanded testing for variants other than SCN5A may improve the testing yield for BrS. Bezzina et al (2013) performed a genome-wide association study of 312 European individuals with BrS and 1115 controls from the 1000 Genomes Project. Two significant association signals were identified: one at the SCN10A locus (rs10428132) and another near the HEY2 gene (rs9388451).

**Catecholaminergic Polymorphic Ventricular Tachycardia**
Transgenomic’s 4-gene panel is expected to identify between 65% and 75% of patients who have a high clinical suspicion of CPVT. A lower yield is obtained by GeneDX for its 3-gene panel that estimates more than 51% of CPVT-positive individuals having a variant identified. Yield is affected if the patient’s ventricular tachycardia is bidirectional, which has a high yield, versus the more atypical presentation of idiopathic ventricular fibrillation, which has a lower (15%) yield. Disease penetrance has been estimated at 60% to 70%. The specificity of known pathologic variants for CPVT is uncertain but is likely high. A 2013 publication from the National Heart, Lung, and Blood Institute ESP reported on sequence variants in a large number of patients without CPVT. ESP sequenced all genome regions of protein coding in a sample of 6503 persons drawn from various populations who did not specifically have CPVT or other cardiac ion channelopathies. Exome data were systematically searched to identify missense variants previously associated with CPVT. Authors identified 11% previously described variants in the ESP population in 41 putative CPVT cases. These data suggested that false-positive results are low, but authors cautioned against attributing clinical CPVT to a single missense variant.

**Short QT Syndrome**
Limited data on the clinical validity of SQTS were identified in the peer-reviewed literature due to the rarity of the condition. A precise genetic testing yield is unknown but was previously reported by Transgenomic as between 15% and 20% of cases with a high clinical suspicion for SQTS.
Section Summary: Clinical Validity of Genetic Testing for the Diagnosis of a Specific Channelopathy

The evidence indicates that genetic testing will identify more individuals with possible cardiac ion channelopathies than clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic variant have the true clinical syndrome of the disorder. None of the clinical sensitivity estimates for the assays reported was above 80%, suggesting there are additional unidentified variants associated with the channelopathies. Therefore, a negative genetic test is not definitive for excluding LQTS, BrS, CPVT, or SQTs.

Data on the clinical specificity are available for LQTS but there are limited data for CPVT. The specificity varies according to the type of variant identified. For LQTS nonsense variants, which have the highest rate of pathogenicity, there are very few false positives among patients without LQTS, and therefore a high specificity. However, for missense variants, the rate is approximately 5% among patients without LQTS; therefore, the specificity for these types of variants is lower, and false-positive results do occur.

Because a low percentage of patients with BrS have the SCN5A variant, genetic testing for BrS has low sensitivity. Genetic testing for BrS is primarily confirmatory in persons with documented BrS.

Clinically Useful

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

Long QT Syndrome

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

Treatment with β-blockers has been demonstrated to decrease the likelihood of cardiac events, including sudden cardiac arrest. Although there are no controlled trials of β-blockers, there are pre-post studies from registry data that provide evidence on this question. Two such studies have reported large decreases in cardiovascular events and smaller decreases in cardiac arrest and/or sudden death after starting treatment with β-blockers. These studies reported a statistically significant reduction in cardiovascular events of more than 50% following initiation of β-blocker therapy. There was a reduction of similar magnitude in cardiac arrest/sudden death, which was also statistically significant.
Sodium-channel blockers (eg, mexiletine) are sometimes used, particularly in those with SCN5A variants. In a 2016 retrospective cohort study of 34 LQT3 patients with a pretherapy median QTc interval of 509 ms, mexiletine treatment for a median 36 months was associated with a statistically significant reduction in QTc (by 63 ms, p<0.001), and percentage and rate of arrhythmic events. The annual rate of arrhythmic events was 10.3% before treatment and 0.7% after treatment initiation (p<0.001).

Treatment with an ICD is available for patients who fail or cannot take β-blockers. One 2003 study reported on outcomes of treatment with ICDs. This study identified patients in the LQTS registry who had been treated with an ICD at the discretion of their treating physician. Patients in the registry who were not treated with an ICD, but had the same indications, were used as a control group. The authors reported that patients treated with an ICD had a greater than 60% reduction in cardiovascular outcomes.

A 2010 study by Hofman et al reported on changes in management that resulted from diagnosing LQTS by testing relatives of affected patients with known LQTS (cascade testing). Cascade testing of 66 index patients with LQTS led to the identification of 308 variant carriers. After a mean follow-up of 69 months, treatment was initiated in 199 (65%) of 308 carriers. Beta-blockers were started in 163 patients, a pacemaker was inserted in 26 patients, and an ICD was inserted in 10 patients. All carriers received education on lifestyle issues and avoidance of drugs that can cause QT prolongation.

Two studies evaluated the psychologic effects of genetic testing for LQTS. Hendriks et al (2008) studied 77 patients with an LQTS variant and their 57 partners. Psychologic testing was performed after the diagnosis of LQTS had been made and repeated twice over an 18-month period. Disease-related anxiety scores were increased in the index patients and their partners. This psychologic distress decreased over time but remained elevated at 18 months. Andersen et al (2008) conducted qualitative interviews with 7 individuals with LQTS variants. They reported that affected patients had excess worry and limitations in daily life associated with the increased risk of sudden death, which was partially alleviated by acquiring knowledge about LQTS. The greatest concern was expressed for their family members, particularly children and grandchildren.

For determining LQTS subtype or specific variant, the clinical utility is less certain. The evidence suggests that different LQTS subtypes may have variable prognoses, thus indicating that genetic testing may assist in risk stratification. Several reports have compared rates of cardiovascular events in subtypes of LQTS. These studies have reported that rates of cardiovascular events differ among subtypes, but there is no common pattern across all studies. Three of the 4 studies reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba et al (1998) reported that patients with LQT1 have higher event rates than patients with LQT2.
More recent research has identified specific sequence variants that might be associated with higher risk of adverse outcomes. Albert et al (2010) examined genetic profiles from 516 cases of LQTS included in 6 prospective cohort studies. Authors identified 147 sequence variants found in 5 specific cardiac ion channel genes and tested the association of these variants with SCD. Two common intronic variants, one in the Kcnq1 gene and one in the Scn5a gene, were most strongly associated with sudden death. Migdalovich et al (2011) correlated gender-specific risks for adverse cardiac events with the specific location of variants (pore-loop vs non-pore-loop) on the Kcnh2 gene in 490 males and 676 females with LQTS. They reported that males with pore-loop variants had a greater risk of adverse events (hazard ratio, 2.18; p=0.01) than males without pore-loop variants, but that this association was not present in females. Costa et al (2012) combined information on variant location and function with age and sex to risk-stratify patients with LQT1 by life-threatening events. Ruwald et al (2016) evaluated differences in outcomes associated with nonsense variants (vs missense variants) among 1090 patients with genetically confirmed type 1 LQTS (Kcnq1 variants). Cardiac events were comprised of the composite outcome of syncope, aborted cardiac arrest, SCD, or shock from an ICD. Non-missense stop codon variants were associated with the lowest risk of a cardiac event (40-year event rate, 27%), while non-c-loop, frameshift, splice, and all other non-missense variants had intermediate risk (40-year event rate, 44%, 46%, 43%, and 39%, respectively), and missense c-loop variants had the highest risk (40-year event rate, 70%).

Other research has reported that the presence of genetic variants at different locations can act as disease “promoters” in patients with LQTS variants. Amin et al (2012) reported that 3 single nucleotide variants (SNVs) in the untranslated region of the Kcnq1 were associated with alterations in the severity of disease. Patients with these SNVs had less severe symptoms and a shorter QT interval than patients without the SNVs. Park et al (2012) examined a large LQTS kindred that had a variable clinical expression of the disorder. Patients were classified into phenotypes of mild and severe LQTS. Two SNVs identified were associated with severity of disease, and all patients classified as having a severe phenotype also had one of these 2 SNVs present. Earle et al (2014) identified 4 SNVs at 2 risk loci (Nos1ap, Kcnq1) that were associated with increased risk of death or resuscitated cardiac death in a cohort of 273 patients with LQTS. In an analysis of 639 patients with Kcnh2 variants, Kolder et al (2015) also identified 3 SNVs at the Nos1ap locus as being associated with the QTc interval.

Some studies that have reported outcomes of treatment with β-blockers have also reported outcomes by specific subtypes of LQTS. Priori et al (2004) reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of β-blocker therapy. There was a decrease in event rates in all LQTS subtypes, with a similar magnitude of decrease in each subtype. Moss et al (2000) also reported pre-post event rates for patients treated with β-blocker therapy. This study indicated a significant reduction in event rates for patients with LQT1 and LQT2 but not for LQT3. This analysis was limited by the small number of patients with LQT3 and cardiac events before β-blocker treatment (4/28). Sauer et al (2007) evaluated differential response to β-blocker therapy in a Cox proportional hazards
analysis. They reported an overall risk reduction in the first cardiac event of approximately 60% (hazard ratio, 0.41; 95% confidence interval, 0.27 to 0.64) in adults treated with β-blockers and an interaction effect by genotype. Efficacy of β-blocker treatment was worse in those with LQT3 genotype (p=0.04) than in those with LQT1 or LQT2. There was no difference in efficacy between LQT1 and LQT2 genotypes.

There is also evidence on differential response to β-blockers according to the specific type and/or location of variants. Barsheshet et al (2012) examined 860 patients with documented variants in the KCNQ1 gene and classified the variants by type and location. Patients with missense variants in the cytoplasmic loop (c-loop variants) had a more marked risk reduction for cardiac arrest following treatment with β-blockers than patients with other variants (hazard ratio, 0.12; 95% confidence interval, 0.02 to 0.73; p=0.02).

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

In 2006, Gehi et al published a meta-analysis, calculating relative risks for events (SCD, syncope, or internal defibrillator shock) for a variety of potential predictors in patients with BrS. A total of 30 prospective studies including 1545 patients with BrS were analyzed. The overall event rate after an average of 32 months follow-up was 10% (95% confidence ratio, 8.5% to 11.5%). Patients with a history of syncope and male gender were at increased risk. Patients with the SCN5A variant were not at increased risk of an event (p=0.2).

In 2017, Yamagata et al published a study investigating the correlation between SCN5A variants and cardiac events, using data from a multicenter registry that enrolled patients with BrS whose SCN5A gene was analyzed. Of the 415 patients in the registry, 60 had an SCN5A variant, and 355 did not have an SCN5A variant. Mean follow-up was 72 months. Patients with the SCN5A variant experienced a first cardiac event at a significantly younger age and experienced a significantly higher rate of cardiac events compared with patients without the SCN5A variant.

Risk stratification criteria based on genetics are currently being investigated. Studies have compared 2 variants in patients with BrS. One variant leads to premature truncation of the protein (T), and the other is a missense variant (M). Meregalli et al (2009) evaluated whether the type of SCN5A variant is related to the severity of disease and found that those variants causing more severe reductions in peak sodium current had more severe phenotype. Patients with the
T-variant of SCN5A experienced significantly more syncope (19/75) compared with patients with the M-variant (2/35).

Van Malderen et al (2017) conducted a cross-sectional study to evaluate whether type of SCN5A variant was related to prolonged right ventricular ejection delay in patients with BrS. Right ventricular ejection delay was measured in 3 BrS patient populations: (1) those with a SCN5A T-variant (n=13), (2) those with a SCN5A M-variant (n=21), and (3) those without a SCN5A variant (n=66). Patients with T-variant had significantly longer right ventricular ejection delay compared with patients M-variant and patients without a SCN5A variant.

**Catecholaminergic Polymorphic Ventricular Tachycardia**
The clinical utility for genetic testing in CPVT follows a similar chain of logic as that for LQTS. In patients for whom the clinical diagnosis can be made with certainty, there is a limited utility for genetic testing. However, there are some patients in whom signs and symptoms of CPVT are present, but for whom the diagnosis cannot be made with certainty. In this case, documentation of a pathologic variant that is known to be associated with CPVT confirms the diagnosis. When the diagnosis is confirmed, treatment with β-blockers is indicated, and lifestyle changes are recommended. Although high-quality outcome studies are lacking to demonstrate a benefit of medication treatment, it is very likely that treatment reduces the risk of SCD. Therefore, there is a clinical utility.

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

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

**Section Summary: Clinical Utility of Genetic Testing for the Diagnosis of a Specific Channelopathy**
The clinical utility of genetic testing for LQTS or CPVT is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. A definitive diagnosis of either channelopathy leads to treatment with β-blockers in most cases, and sometimes to treatment with an ICD. As a result, confirming the diagnosis is likely to lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and SCD. The clinical utility of testing is also high for close relatives of patients with known cardiac ion channel variants because these individuals should also be treated if they have a pathologic variant.
For BrS, the clinical utility is less certain, but there is potential for genetic testing to change treatment decisions by stratifying patients for the need for ICD. A meta-analysis reported that the presence of SCN5A variants could not predict cardiac events; however, a registry study published after the meta-analysis reported that patients with the SCN5A variant experienced more cardiac events and experienced the first event at a younger age than patients who did not have the SCN5A variant. Studies have been conducted to further determine risk level by type of variant, but the studies have small sample sizes, so interpretation is limited.

For SQTS, the clinical utility is uncertain because there is no clear link between the establishment of a definitive diagnosis and a change in management that will improve outcomes.

**Genetic Testing for the Diagnosis of Cardiac Ion Channelopathy in Survivors of Unexpected Cardiac Arrest**

Several studies have been identified which evaluated patients who have survived unexplained cardiac arrest and who are suspected of having a cardiac ion channelopathy.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**

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

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

**Clinically Useful**

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

Krahn et al (2009) reported outcomes from a systematic assessment of patients with apparently unexplained cardiac arrest and no evidence of cardiac disease, which included cardiac magnetic resonance imaging (MRI), signal-averaged electrocardiogram (ECG), exercise testing, drug challenge, and selective
electrophysiologic testing, with targeted genetic testing as indicated based on disease phenotype. Sixty-three patients were evaluated, and 35 (56%) received a specific diagnosis after evaluation. Among the 35 diagnosed patients, LQTS was diagnosed in 8 (23%) patients, CPVT in 8 (23%), and BrS in 3 (9%); the remainder had arrhythmogenic right ventricular cardiomyopathy, coronary spasm, or myocarditis. Targeted genetic testing was performed by phenotype detection in patients after systematic clinical testing. Genetic testing was performed on suspected genes (for LQTS: KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2; for BrS: SCN5A; for arrhythmogenic right ventricular cardiomyopathy: Pkp2, Dsp; for CPVT: RyR2-selected exons 2 to 4, 6 to 15, 17 to 20, 39 to 49, 83, 84, 87 to 97, and 99 to 105). Targeted genetic testing revealed causative variants in 9 (47%) of 19 patients tested. The genetic testing yield in unselected patients with unexplained cardiac arrest is likely lower.

In the Kumar et al (2013) study, the authors evaluated the yield of a comprehensive evaluation, including targeted genetic testing, in a cohort of 52 families (including 91 relatives) with a proband with unexplained cardiac arrest. Probands were comprehensively evaluated with ECG, echocardiography, coronary angiography, and Holter monitoring, with provocation testing in one-third. A clinical diagnosis was made in 32 (62%) families with unexplained cardiac arrest, most commonly LQTS (n=11), followed by BrS (n=9), CPVT (n=3), early repolarization (n=3), hypertrophic cardiomyopathy (n=3), and SQTS (n=1). Targeted genetic evaluation of family members with a proven or suspected clinical phenotype led to a molecular diagnosis in 48%.

Jimenez-Jaimez et al (2015) reported on the results of a sequential testing protocol among 35 unexplained cardiac arrest survivors. Selected patients had a history of VF with no diagnostic findings on ECG, no pathologic findings on echocardiogram, and no angiographic lesions with 50% or more stenosis on coronary catheterization. Sequential testing included pharmacologic studies with flecainide and epinephrine with or without exercise stress testing, followed by familial evaluation with echocardiogram and ECG if pharmacologic studies were negative, and then by genetic testing with a next-generation sequencing panel of 126 genes related to cardiomyopathies and channelopathies if other testing was negative. A firm diagnosis was made in 18 (51.4%) cases, with 5 cases (4 cases of CPVT, 1 case of SQTS) made by genetic testing. All diagnoses of LQTS (n=3) and BrS (n=7) were made by pharmacologic testing or familial evaluation.

In 2017, Mellor et al published results from genetic testing on patients in the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry. Among 375 unexplained cardiac arrest survivors in the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry from 2006 to 2015, 174 underwent genetic testing at physicians’ discretion, based on guidelines and availability. A pathogenic variant was detected in 29 (17%) of patients tested. By clinical phenotype, the number of patients for whom a variant was detected was: 5 of 25 patients with an LQTS clinical phenotype; 2 of 7 patients with a BrS clinical phenotype; and 2 of 8 patients with a CPVT clinical phenotype.
Section Summary: Genetic Testing for the Diagnosis of Cardiac Ion Channelopathy in Patients Surviving Unexplained Cardiac Arrest

The evidence on genetic testing for cardiac ion channelopathies in individuals or family members who have survived unexplained cardiac arrest consists of cohort studies that describe the testing yield in patients who have a suspected clinical diagnosis based on history and preliminary testing. In all studies identified, genetic testing was performed only after a specific diagnosis was suspected based on other findings. In most studies, the yield was less than 50%.

There is potential for the utility of genetic testing of individuals or family members in the setting of unexplained cardiac arrest potentially due to a cardiac ion channelopathy. However, identified studies related to testing yields in this setting used testing only after a specific channelopathy was suspected based on history or ancillary testing. Genetic testing can be part of a diagnostic strategy for patients with unexplained cardiac arrest, but it should be preceded by thorough clinical evaluation.

Genetic testing in family members of probands experiencing SCD with unknown diagnosis

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist.

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

A small body of evidence exists on the testing yield for one or more cardiac ion channelopathies in family members of probands experiencing SCD where a specific clinical diagnosis has not been made.

In the largest study identified, Kumar et al (2013) assessed the yield of a comprehensive evaluation, including targeted genetic testing, in a cohort of 109 families (including 411 relatives) with autopsy-negative sudden unexplained death syndrome (SUDS), termed sudden arrhythmic death syndrome (SADS)\(^6\). SADS was defined as a sudden unexpected death in an individual with no known history of cardiac disease for whom death occurred within 1 hour of symptom onset or within 24 hours of the individual being seen alive and well and for whom a full postmortem examination, including toxicologic investigations, could not identify the cause of death. All families of SADS probands underwent a systematic protocol that included a review of the history of the proband and family members, along with physical exam, 12-lead ECG, exercise stress test, and transthoracic echocardiography for family members, with additional evaluation guided by the initial studies. If a clinical phenotype was proven or suspected during the cardiologic evaluation of the family members, targeted genetic testing of the
candidate gene(s) was performed on genomic DNA extracted from the deceased individual or the closest surviving affected relative of the deceased individual. A clinical diagnosis was made in 20 (18%) families, most commonly LQTS (15%), followed by BrS (3%) and CPVT (1%). Patients with suspected LQTS underwent candidate gene testing with Sanger sequencing of \( KCNQ1 \), \( KCNH2 \), \( SCN5A \), \( KCNE1 \), \( KCNE2 \), and \( KCNJ2 \) for LQTS, while those with suspected BrS underwent sequencing of \( SCN5A \) and those with suspected CPVT underwent sequencing of \( RYR2 \) and \( CASQ2 \). Molecular genetic testing was performed in 17 of 20 families and a pathogenic variant found in 6 families (yield, 35%).

Behr et al (2008) assessed the yield of comprehensive evaluation, including genetic testing, if indicated, of families of individuals with SADS. SADS cases were defined when sudden and unexpected deaths occurred in apparently healthy adults, and a coroner’s postmortem exam, toxicologic screen, and an expert cardiac autopsy failed to reveal any underlying cause of death. Fifty-seven SADS probands and their families were evaluated. In 30 (53%) of 57 families, definite and possible or probable inherited heart disease was identified, with definite LQTS in 13, possible/probable LQTS in 3, and BrS in 5. For inherited arrhythmia syndromes, genetic testing was performed using polymerase chain reaction of published exons and flanking introns for the following genes: all exons of \( KCNQ1 \), \( KCNE1 \), \( KCNH2 \), \( KCNE2 \), \( SCN5A \), \( ANK2 \), \( KCNJ2 \), \( CAV3 \), and \( CASQ2 \), and selected exons of \( hRyR2 \). Genetic testing was obtained in 24 SADS probands, 5 (21%) of whom were found to have a disease-causing variant. Disease-causing variants that cosegregated with phenotype in a pedigree were detected in 2 (33%) of 6 probands, with a subsequent familial diagnosis of definite or possible/probable LQTS.

Tan et al (2005) assessed the yield of cardiologic and genetic evaluations in surviving relatives of individuals with SUDS in a cohort of 43 families with at least 1 SUDS victim who died at the age of 40 or younger. SUDS was defined as death in a person with no family history of known heart disease that occurred suddenly (1 hour after complaints or within 12 hours of the victim being seen alive) and was unexplained because a relevant documented medical history (eg, syncope, seizures, palpitations) and antemortem cardiologic tests (eg, ECG) were absent and detailed postmortem macroscopic and microscopic examinations of the heart and its vessels either were not performed or were performed but initially did not provide an explanation. All surviving relatives underwent testing with a 12-lead resting ECG, an exercise ECG, and Doppler echocardiography; additional investigations in the surviving family members were determined by the relevant circumstances of the index patients. In 17 of 43 families, inherited disease and likely cause of death in the SUDS victim was identified. In 12 families, the diagnosis involved a primary electrical disease, with diagnosis based on resting ECG, exercise ECG, or flecainide challenge. Among those 12 families, 5 were found to have CPVT, 4 had LQTS, 2 had BrS, and 1 had a mixed phenotype of LQTS and BrS. Molecular genetic testing was positive in 10 families, with a clinical diagnosis of a primary electrical disease.
Wong et al (2014) assessed the yield of clinical history and cardiac and genetic evaluations in 112 pediatric relatives of 61 probands with SADS. All subjects underwent initial cardiac investigations including a 12-lead ECG, transthoracic 2-dimensional echocardiogram, exercise ECG when possible, and 24-hour Holter monitoring, with additional investigations, including signal-averaged ECG, cardiac MRI, and ajmaline provocation tests as indicated. A probable diagnosis of an inherited cardiac condition was made in 18 (29.5%) of 61 families, most often (15/18 [83%]) after evaluation of an adult relative of the proband. BrS was the most common diagnosis, affecting 13 (72%) families, with LQTS in 3 (17%) families and CPVT in 2 (11%). The targeted genetic diagnosis was undertaken in 14 (78%) of 18 families with an inherited cardiac condition diagnosis. Two (20%) of 10 families with BrS were identified with an SCN5A variant. The testing yield was 50% for both LQTS (1 KCNH2 variant detected) and CPVT (1 RyR2 variant detected).

Bagnall et al (2016) reported on prospectively collected data for cases of SCD in children and young adults (up to age 35) in Australia and New Zealand from 2010 to 2012. Of the 490 cases of SCD, 198 (40%) were unexplained after the autopsy. Of the unexplained deaths, 113 underwent genetic analysis of at least 59 cardiac arrhythmia and cardiomyopathy genes. Thirty-six pathogenic and probably pathogenic variants were found in 31 cases of unexplained SCD. Screening of families was performed in 91 of the 198 families in which an unexplained SCD occurred. A clinical diagnosis was established in 12 of the 91 families; inherited arrhythmogenic diseases were identified in 7 families.

Section Summary: Genetic Testing in Family Members of Probands Experiencing SCD
The evidence on the clinical validity of genetic testing for cardiac ion channelopathies in family members of probands with unexplained cardiac death or individuals with unexplained cardiac arrest consists of 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 other findings. In most studies, the yield was less than 50%.

There is potential for the utility of genetic testing of family members in the setting of a proband with SCD or unexplained cardiac arrest. However, identified studies related to testing yields in this setting used testing only after a specific channelopathy was suspected based on history or ancillary testing. Genetic testing can be part of a diagnostic strategy for patients with family members who experienced unexplained sudden cardiac arrest, but it should be preceded by thorough clinical evaluation.

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 those with LQTS. Most are point mutations identified by gene sequencing analysis; however, a small number are deletions and duplications are 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 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 observational 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 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.

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.

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

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.22 Table 7 summarizes the recommendations relating to cardiac ion 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</td>
<td>I (strong)</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

Table 7. Recommendations for Genetic Testing in Cardiac Channelopathies
Consensus Recommendation | COR | LOE
---|---|---
syndrome, genetic counseling and mutation-specific genetic testing are recommended. | I (strong) | B-NR
In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information. | IIa (moderate) | B-NR
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. | IIa (moderate) | B-NR
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. | IIb (weak) | C-EO
In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives. | IIb (weak) | C-EO

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. 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 8). 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 sudden cardiac death, 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 8. Recommendations for Genetic Testing in IVF, SUDS, and SUDI**

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing in IVF can be useful when there is suspicion of a specific</td>
<td>IIA</td>
</tr>
</tbody>
</table>
In 2011, 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 long QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome (see Table 9).

### Table 9. Cardiac Ion Channelopathy Testing Recommendations

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LQTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>• 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).</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>• 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.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td><strong>BrS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
**Consensus Recommendation**

<table>
<thead>
<tr>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td></td>
</tr>
</tbody>
</table>

- **the BrS-causative mutation in an index case.**
  - 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.
  - Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

- **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.

- **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.
  - 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.

---

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.

**American College of Cardiology et al**
The American College of Cardiology, American Heart Association, and European Society of Cardiology issued joint guidelines in 2006 on the management of patients with ventricular arrhythmias and the prevention of sudden death. 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 stated that genetic testing for catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, or short QT syndrome might identify silent carriers for clinical monitoring but does not assist with risk stratification.

**Canadian Cardiovascular Society and Canadian Heart Rhythm Society**
The Canadian Cardiovascular Society and Canadian Heart 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 was recommended for familial screening. Genetic testing was also recommended for cardiac arrest survivors with a type I Brugada electrocardiogram pattern for 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 high clinical suspicion. No recommendations are given for short QT syndrome.

**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 10.

### Table 10. 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>NCT01705925a</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.

* Denotes industry-sponsored or cosponsored trial.

**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


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81280</td>
<td>Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); full sequence analysis (Deleted code 1/1/2017)</td>
</tr>
<tr>
<td>81281</td>
<td>Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); known familial sequence variant (Deleted code 1/1/2017)</td>
</tr>
<tr>
<td>81282</td>
<td>Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); duplication/deletion variants (Deleted code 1/1/2017)</td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>81407</td>
<td>Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of &gt;50 exons, sequence analysis of multiple genes on one platform)</td>
</tr>
<tr>
<td>81408</td>
<td>Molecular pathology procedure, Level 9 (eg, analysis of &gt;50 exons in a single gene by DNA sequence analysis)</td>
</tr>
<tr>
<td>81413</td>
<td>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, KCN1,</td>
</tr>
</tbody>
</table>
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 (new code 1/1/2017)

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

ICD-10 Codes

I45.81  Long QT syndrome
Z13.6   Encounter for screening for cardiovascular disorders
Z13.79  Encounter for other screening for genetic and chromosomal anomalies

Effective in 2017, there are CPT genomic sequencing procedure codes for this testing:

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 \textit{ANK2}, \textit{CASQ2}, \textit{CAV3}, \textit{KCNE1}, \textit{KCNE2}, \textit{KCNH2}, \textit{KCNJ2}, \textit{KCNQ1}, \textit{RYR2}, and \textit{SCN5A}

81414: ; duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including \textit{KCNH2} and \textit{KCNQ1}

Other analyses related to this testing are listed under the following CPT tier 2 molecular pathology codes:

Under code 81403:

\textit{KCNJ2 (potassium inwardly-rectifying channel, subfamily J, member 2)} (eg, Andersen-Tawil syndrome), full gene sequence

Under code 81405:

\textit{CASQ2 (calsequestrin 2 [cardiac muscle])} (eg, catecholaminergic polymorphic ventricular tachycardia), full gene sequence

Under code 81406:

\textit{KCNH2 (potassium voltage-gated channel, subfamily H[ead-related], member 2)} (eg, short QT syndrome, long QT syndrome), full gene sequence

\textit{KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1)} (eg, short QT syndrome, long QT syndrome), full gene sequence

Under code 81407:
**SCN5A (sodium channel, voltage-gated, type V, alpha subunit)** (eg, familial dilated cardiomyopathy), full gene sequence

Under code 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

There is a HCPCS S code for testing for suspected Brugada syndrome:

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

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- 6/1/07 New policy; considered investigational.
- 6/1/08 Policy statement revised to state some indications of genetic testing for long QT syndrome may be considered medically necessary.
- 6/1/09 No policy statement changes.
- 6/1/10 No policy statement changes.
- 6/1/11 No policy statement changes.
- 6/1/12 No policy statement changes.
- 6/1/13 No policy statement changes.
- 11/1/13 No policy statement changes.
- 11/1/14 Policy title changed to “Genetic Testing for Cardiac Ion Channelopathies”. Medically necessary statement added for CPVT when criteria are met. Investigational statements added for Brugada syndrome and short QT syndrome. Added CPT codes.
- 11/1/15 Additional policy statement added that genetic testing for LQTS or CPVT is investigational for all other situations when criteria are not met.
- 11/1/16 Medically necessary statements added for diagnostic testing for Brugada syndrome and testing of an asymptomatic individual with a known familial mutation associated with Brugada syndrome or SQTS.
- 11/1/17 No policy statement changes.
- 11/1/18 No policy statement changes.

**Appendix**

**Appendix Table 1. Categories of Genetic Testing Addressed in Policy No. 2.04.43**

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td>X</td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
</tbody>
</table>
2. Testing cancer cells from an affected individual to benefit the individual
   2a. Diagnostic
   2b. Prognostic
   2c. Therapeutic

3. Testing an asymptomatic individual to determine future risk of disease

4. Testing of an affected individual’s germline to benefit family members

5. Reproductive testing
   5a. Carrier testing: preconception
   5b. Carrier testing: prenatal
   5c. In utero testing: aneuploidy
   5d. In utero testing: familial variants
   5e. In utero testing: other
   5f. Preimplantation testing with in vitro fertilization

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.