The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

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

**Background**

Cardiac ion channelopathies are the result of mutations in genes that code for protein subunits of the cardiac ion channels. These channels are essential cell membrane components that open or close to allow ions to flow into or out of the cell. The 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 1:2,000 – 1:3,000 persons in the general population. (1) Data pertaining to the individual prevalences of LQTS, CPVT, BrS and SQTS are presented in Table I. The channelopathies discussed in this Protocol are genetically heterogeneous with hundreds of identified mutations, 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 EKG 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 I. Epidemiology of Cardiac Ion Channelopathies**

<table>
<thead>
<tr>
<th></th>
<th>LQTS</th>
<th>CPVT</th>
<th>BrS</th>
<th>SQTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>1:2000-5000</td>
<td>1:7000-10,000</td>
<td>1:6000</td>
<td>Unidentified</td>
</tr>
<tr>
<td>Annual mortality rate</td>
<td><strong>0.3% (LQT1)</strong></td>
<td>3.1%</td>
<td><strong>4%</strong> $^a$</td>
<td>Unidentified</td>
</tr>
<tr>
<td>Mean age at first event, y</td>
<td>14 (12)</td>
<td>15 (10)</td>
<td>42 (16)$^b$</td>
<td>40 (24)</td>
</tr>
</tbody>
</table>
Adapted from Modell et al. (2)

BrS: Brugada syndrome; CPVT: Catecholaminergic polymorphic ventricular tachycardia; LQTS: Long QT syndrome; SQTS: Short QT syndrome.

a Type 1 EKG pattern.
b Type 1 EKG pattern

**Long QT Syndrome**

Congenital long QT syndrome 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 beta blockers as first-line treatment, with pacemakers or implantable cardiac defibrillators (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 one half of the 8,000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1–2% per year, although this figure will vary with the genotype (The channelopathies discussed in this Protocol are genetically heterogeneous with hundreds of identified mutations, 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 EKG 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.

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 electrocardiogram (EKG). Diagnostic criteria for LQTS have been established, which focus on EKG findings and clinical and family history (i.e., Schwartz criteria, see following section, “Clinical Diagnosis”). (4) However, measurement of the QT interval is not well-standardized, and in some instances, patients may be considered borderline cases. (5)

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 seven different subtypes recognized, each corresponding to mutations in different genes as indicated here. (6) In addition, typical ST-T wave patterns are also suggestive of specific subtypes. (7)

**Clinical Diagnosis**

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS. (4) The most recent version of this scoring system is shown Table II. A score of 4 or greater indicates a high probability that LQTS is present; a score of 2–3, a moderate-to-high probability; and a score of 1 or less indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; and since there is still no perfect gold standard for diagnosing LQTS, the accuracy of this scoring system remains ill-defined.

**Table II. Diagnostic Scoring System for LQTS (8)**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
</tr>
<tr>
<td>QTc &gt; 480 msec</td>
<td>3</td>
</tr>
<tr>
<td>QTc 460-470 msec</td>
<td>2</td>
</tr>
<tr>
<td>QTc &lt; 450 msec</td>
<td>1</td>
</tr>
</tbody>
</table>
Brugada Syndrome

BrS is characterized by cardiac conduction abnormalities which increase the risk of syncope, ventricular arrhythmia, and sudden cardiac death. Inheritance occurs in an autosomal dominant manner with patients typically having an affected parent. Children of affected parents have a 50% chance of inheriting the mutation. The instance of \textit{de novo} mutations is very low and is estimated to be only 1\% of cases. (9)

The disorder primarily manifests during adulthood although ages between two days and 85 years have been reported. (10) Males are more likely to be affected than females (approximately an 8:1 ratio). BrS is estimated to be responsible for 12\% of SCD cases. (1) For both genders there is an equally high risk of ventricular arrhythmias or sudden death. (9) Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life. (11) Management has focused on the use of implantable cardiac defibrillators (ICD) 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.

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. (12) This ECG pattern includes a coved ST-segment and a J-point elevation of \( \geq 0.2 \) mV followed by a negative T wave. This pattern should be observed in two or more of the right precordial ECG leads (V1 through V3). This pattern may be concealed and can be revealed by administering a sodium-channel-blocking agent (e.g., ajmaline or flecainide). (13) Two additional ECG patterns have been described (type 2 and type 3) but are less specific for the disorder. (14) The diagnosis of BrS is considered definite when the characteristic EKG pattern is present with at least one of the following clinical features: documented ventricular arrhythmia, sudden cardiac death in a family member < 45 years old, characteristic EKG pattern in a family member, inducible ventricular arrhythmias on EP studies, syncope, or nocturnal agonal respirations.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a rare inherited channelopathy which has an autosomal dominant mode of inheritance. The disorder manifests as a bidirectional or polymorphic VT precipitated by exercise or emotional stress. (3) The prevalence of CPVT is estimated between one in 7,000 to one in 10,000 persons. CPVT has a mortality rate of 30-50\% by age 35 and is responsible for 13\% of cardiac arrests in structurally normal hearts. (3) CPVT was previously believed to be only manifest during childhood but studies have now identified presentation between infancy and 40 years of age. (15)

Management of CPVT is primarily with the beta-blockers nadolol (1-2.5 mg/kg/day) or propranolol (2-4 mg/kg/day). If protection is incomplete (i.e., recurrence of syncope or arrhythmia), then flecainide (100-300 mg/day) may be added. If recurrence continues an ICD may be necessary with optimized pharmacologic
management continued post implantation. (16) Lifestyle modification with the avoidance of strenuous exercise is recommended for all CPVT patients.

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 ventricular arrhythmia in the majority of cases (75-100%). (8) 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. (17)

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. (18) 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. (3)

The mode of inheritance for SQTS is autosomal dominant. Management of the disease is complicated because the binding target for QT-prolonging drugs (e.g., sotalol) is Kv11.1 which is coded for by KCNH2, the most common site for mutations 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 who recur while on quinidine, an ICD is recommended. (8)

Clinical Diagnosis

Patients generally present with syncope, pre-syncope or cardiac arrest. An ECG with a corrected QT interval < 330 ms, sharp T-wave at the end of the QRS complex, and a brief or absent ST-segment is characteristic of the syndrome. (19) However, higher QT intervals on ECG might also indicate SQTS and the clinician has to determine if this is within the normal range of QT values. Recently a diagnostic scoring system has been proposed by Gollob and colleagues to aid in decision-making after a review of 61 SQTS cases (Table III). (20)

Table III. Diagnostic Scoring System for SQTS (8)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
</tr>
<tr>
<td>*QTc &lt; 370 msec</td>
<td>1</td>
</tr>
<tr>
<td>*QTc &lt; 350 msec</td>
<td>2</td>
</tr>
<tr>
<td>*QTc &lt; 330 msec</td>
<td>3</td>
</tr>
<tr>
<td>J point-T peak interval &lt; 120 msec</td>
<td>1</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>History of SCD</td>
<td>2</td>
</tr>
<tr>
<td>Documented polymorphic VT or VF</td>
<td>2</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>First or second degree relative with high probability SQTS</td>
<td>2</td>
</tr>
<tr>
<td>First or second degree relative with autopsy-negative SCD</td>
<td>1</td>
</tr>
<tr>
<td>SIDS</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>

QTc: QT corrected; SCD: Sudden cardiac death; SQTS: Short QT syndrome; VF: Ventricular fibrillation; VT: Ventricular tachycardia
Genetic Testing

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Deleterious and probable deleterious mutations. These are either mutation that have 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).</td>
</tr>
<tr>
<td>Class II</td>
<td>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.</td>
</tr>
<tr>
<td>Class III</td>
<td>Variants not generally expected to be deleterious. These variants encode modified protein(s); however, these 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.’</td>
</tr>
<tr>
<td>Class IV</td>
<td>Non-protein-altering variants. These are not considered to have clinical significance and are not reported in the results of the Familion® test.</td>
</tr>
</tbody>
</table>

Genetic testing is available from a number of genetic diagnostics laboratories. The John Welsh Cardiovascular Diagnostic Laboratory, GeneDX, and Transgenomic each offer panels which genotype LQTS, CPVT, BrS and SQTS, but there is some variation between the manufacturers on which genes to include in the assays.

Table 4. Examples of Cardiac Ion Channelopathy Genetic Testing Laboratories in the United States

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

LQTS: Long QT Syndrome; CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia; BrS: Brugada Syndrome; SQTS: Short QT Syndrome

*L阐明genetics cardiovascular NGS panel which included testing for LQTS and BrS is no longer being offered as of June, 2013. A subsequent version will be released which will include testing for duplications and deletions.

*Indicates multi-gene panel available for sudden cardiac death

Long QT Syndrome

There are more than 1,200 unique mutations on at least 13 genes that have been associated with LQTS. In addition to single mutations, some cases of LQTS are associated with deletions or duplications of genes. (21) This may be the case in up to 5% of total cases of LQTS. These types of mutations may not be identified by gene sequence analysis. They can be more reliably identified by chromosomal microarray analysis (CMA), also known as array comparative genomic hybridization (aCGH). Some laboratories that test for LQTS are now offering detection of LQTS-associated deletions and duplications by this testing method. This type of test may be offered as a separate test and may need to be ordered independently of gene sequence analysis when testing for LQTS.
The absence of a mutation does not imply the absence of LQTS; it is estimated that mutations are only identified in 70-75% of patients with a clinical diagnosis of LQTS. A negative test is only definitive when there is a known mutation identified in a family member and targeted testing for this mutation is negative. Other laboratories have investigated different testing strategies. For example, Napolitano and colleagues propose a three-tiered approach, first testing for a core group of 64 codons that have a high incidence of mutations, followed by additional testing of less frequent mutations.

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

Catecholaminergic Polymorphic Ventricular Tachycardia

Mutations in four genes are known to cause CPVT, and investigators believe other unidentified loci are involved as well. Currently, only 55-65% of patients with CPVT have an identified causative mutation. Mutations to \textit{RYR2} or \textit{KCNJ2} result in an autosomal dominant form of CPVT with \textit{CASQ2} and \textit{TRDN-related CPVT} exhibiting autosomal recessive inheritance. Some authors have reported heterozygotes for \textit{CASQ2} and \textit{TRDN} mutations rare, benign arrhythmias. \textit{RYR2} mutations represent the majority of CPVT cases (50-55%) with \textit{CASQ2} accounting for 1-2% and \textit{TRDN} accounting for an unknown proportion of cases. The penetrance of \textit{RYR2} mutations is approximated at 83%.

An estimated 50-70% of patients will have the dominant form of CPVT with a disease-causing mutation. Most mutations (90%) to \textit{RYR2} are missense mutations, 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 \textit{RYR2} mutations. Another misclassification, CPVT diagnosed as Anderson-Tawil syndrome may result in more aggressive prophylaxis for CPVT whereas a correct diagnosis can spare this treatment as Anderson-Tawil syndrome is rarely lethal.

Brugada syndrome

\textit{BrS} is typically inherited in an autosomal dominant manner with incomplete penetrance, although some authors report up to 50% of cases are sporadic in nature. Mutations in 16 genes have been identified as causative of \textit{BrS}, but of these \textit{SCN5A} is the most important accounting for more than an estimated 20% of cases. 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 \textit{BrS} with more than 65% of cases not having an identified genetic cause. Penetrance of \textit{BrS} among persons with a \textit{SCN5A} mutation is 80% when undergoing ECG with sodium channel blocker challenge and 25% when not using the ECG challenge.

Short QT syndrome

\textit{SQTS} has been linked predominantly to mutations in three genes \textit{KCNH2}, \textit{KCNJ2}, and \textit{KCNO1}. Some individuals with \textit{SQTS} do not have a mutation in these genes suggesting changes in other genes may also cause this disorder. \textit{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.

Policy (Formerly Corporate Medical Guideline)

Genetic testing in patients with suspected congenital long QT syndrome may be considered \textbf{medically necessary} for the following indications:
Individuals who do not meet the clinical criteria for LQTS (i.e., those with a Schwartz score less than four), but who have:

- a close relative (i.e., 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; or
- signs and/or symptoms indicating a moderate-to-high pretest probability* of LQTS.

*Determining the pretest probability of LQTS is not standardized. An example of a patient with a moderate to high pretest probability of LQTS is a patient with a Schwartz score of two to three.

Genetic testing for LQTS to determine prognosis and/or direct therapy in patients with known LQTS is considered investigational.

Genetic testing for CPVT may be considered medically necessary for patients who do not meet the clinical criteria for CPVT but who have:

- a close relative (i.e. 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; or
- signs and/or symptoms indicating a moderate-to-high pretest probability of CPVT.

Genetic testing for Brugada syndrome is considered investigational.

Genetic testing for short QT syndrome is considered investigational.

Refer also to Protocol General Approach for Genetic Testing for Benefit Application information.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


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: the official Journal of the Heart Rhythm Society 2011; 8(8):1308-39.


42. Albert CM, MacRae CA, Chasman DI et al. Common variants in cardiac ion channel genes are associated with sudden cardiac death. Circulation Arrhythmia and Electrophysiology 2010; 3(3):222-9.


50. 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), Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2011; 13(8):1077-109.