Medical Policy

Genetic Testing for Cardiac Ion Channelopathies

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Information Pertaining to All Policies
- Policy History
- References

Policy Number: 082
BCBSA Reference Number: 2.04.43

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing in patients with suspected congenital long QT syndrome may be considered MEDICALLY NECESSARY for the following indications:

Individuals who do not meet the clinical criteria for LQTS (ie, those with a Schwartz score less than 4), but who have:
- 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; 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 2 or 3.

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 (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; or
- Signs and/or symptoms indicating a moderate-to-high pretest probability of CPVT.

Genetic testing for Brugada syndrome is INVESTIGATIONAL.
Genetic testing for short QT syndrome is **INVESTIGATIONAL**.

**Prior Authorization Information**
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
<td>n/a</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
<td>n/a</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
<td>No</td>
<td>n/a</td>
</tr>
<tr>
<td>Medicare PPO Blue℠</td>
<td>No</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD-9 Codes**
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81280</td>
<td>Long QT syndrome gene analyses; full sequence analysis</td>
</tr>
<tr>
<td>81281</td>
<td>Long QT syndrome gene analyses; known familial sequence variant</td>
</tr>
<tr>
<td>81282</td>
<td>Long QT syndrome gene analyses; duplication/deletion variants</td>
</tr>
</tbody>
</table>

**HCPCS Codes**

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

**ICD-9 Diagnosis Codes**

<table>
<thead>
<tr>
<th>ICD-9-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>426.82</td>
<td>Long QT Syndrome</td>
</tr>
</tbody>
</table>

**ICD-10 Diagnosis Codes**

<table>
<thead>
<tr>
<th>ICD-10-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I45.81</td>
<td>Long QT Syndrome</td>
</tr>
</tbody>
</table>

**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.

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 1:2000 and 1:3000 persons in the general population. (1) The channelopathies discussed in this policy 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 electrocardiogram (EKG) is not diagnostic in all cases, and some secondary events (eg, electrolyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an EKG similar to those observed in a cardiac channelopathy.

**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 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 (The channelopathies discussed in this policy 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 (eg, electrolyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an EKG 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 (ie, 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 7 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) A score of 4 or greater indicates a high probability that LQTS is present; a score of 2 to 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.

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 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 EKG in addition to other clinical features.(12) This EKG 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 two or more of the right precordial EKG leads (V1-V3). This pattern may be concealed and can be revealed by administering a sodium-channel-blocking agent (eg, ajmaline or flecainide).(13) Two additional EKG 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 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.(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/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 postimplantation.(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 EKG 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 EKG 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 EKG and, at the cellular level, a shortening of the action potential. The clinical manifestations are an increased risk of atrial and/or ventricular arrhythmias. Because of the disease’s rarity the prevalence and risk of sudden death are currently unknown.

The mode of inheritance for SQTS is autosomal dominant. 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 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.

Clinical Diagnosis
Patients generally present with syncope, presyncope or cardiac arrest. An EKG 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 is characteristic of the syndrome. However, higher QT intervals on EKG might also indicate SQTS and the clinician has to determine if this is within the normative range of QT values.

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.

Long QT Syndrome
There are more than 1200 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. 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% to 75% of patients with a clinical diagnosis of LQTS. A negative test is only definitive when there is a known mutation identified in a family member and targeted testing for this mutation is negative. Other laboratories have investigated different testing strategies. For example, Napolitano et al propose a 3-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 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 mutation. Mutations to RYR2 or KCNJ2 result in an autosomal dominant form of CPVT with CASQ2 and TRDN-related CPVT exhibiting autosomal recessive inheritance. Some authors have reported heterozygotes for
CASQ2 and TRDN mutations rare, benign arrhythmias.(16) RYR2 mutations represent the majority of CPVT cases (50%-55%) with CASQ2 accounting for 1% to 2% and TRDN accounting for an unknown proportion of cases. The penetrance of RYR2 mutations is approximated at 83%.(16)

An estimated 50% to 70% of patients will have the dominant form of CPVT with a disease-causing mutation. Most mutations (90%) to RYR2 are missense mutations, but in a small proportion of unrelated CPVT patients large gene rearrangements or exon deletions have been reported.(15) Additionally, nearly a third of patients diagnosed as LQTS with normal QT intervals have CPVT due to identified 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
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 BrS, but of these SCN5A is the most important accounting for more than an estimated 20% of cases.(15) The other genes are of minor significance and account together for approximately 5% of cases.(3) 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 a SCN5A mutation is 80% when undergoing EKG with sodium channel blocker challenge and 25% when not using the EKG challenge.(9)

Short QT syndrome
SQTS has been linked predominantly to mutations in 3 genes KCNH2, KCNJ2, and KCNQ1. Some individuals with SQTS do not have a mutation 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.

Summary
A genetic mutation can be identified in approximately 72% to 80% of long QT syndrome (LQTS), 51% to 75% of catecholaminergic polymorphic ventricular tachycardia (CPVT), 25% to 35% of Brugada syndrome (BrS), and 15% to 20% of short QT syndrome (SQTS) patients. The majority of these are point mutations that are identified by gene sequencing analysis; however a small number are deletions/duplications that are best identified by chromosomal microarray analysis (CMA). The analytic validity of testing for point mutations by sequence analysis is high, while the analytic validity of testing for deletions/duplications by CMA is less certain. The clinical validity varies by condition. For LQTS, it is relatively high in the range of 70% to 80%, while for CPVT it is moderate in the range of 50% to 75%. For BrS and SQTS, the clinical validity is lower, in the range of 15% to 35%.

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 beta 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 sudden cardiac death. The clinical utility of testing is also high for close relatives of patients with known cardiac ion channel mutations, since these individuals should also be treated if they are found to have a pathologic mutation. For BrS and SQTS, the clinical utility is uncertain because there is not a clear link between the establishment of a definitive diagnosis and a change in management that will improve outcomes.

Therefore, genetic testing for the diagnosis of LQTS and CPVT may be considered medically necessary for the following individuals who do not have a definite clinical diagnosis but who have: (1) a close relative (ie, first-, second-, or third-degree relative) with a known pathologic mutation, (2) a close relative with a clinical diagnosis whose genetic status is unavailable, or (3) signs and/or symptoms indicating a moderate-to-high pretest probability of LQTS or CPVT, but in whom a definitive diagnosis cannot be
made clinically. For all other indications genetic testing for cardiac channelopathies is considered investigational.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/2014</td>
<td>References from BCBSA National medical policy.</td>
</tr>
<tr>
<td>5/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
<tr>
<td>2/2013</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
<tr>
<td>11/10</td>
<td>No changes to policy statements.</td>
</tr>
<tr>
<td>4/09</td>
<td>Reviewed - Medical Policy Group – Cardiology. No changes to policy statements.</td>
</tr>
<tr>
<td>3/09</td>
<td>No changes to policy statements.</td>
</tr>
<tr>
<td>3/01/09</td>
<td>New policy effective 3/01/09 created.</td>
</tr>
</tbody>
</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References

18. Wilders R. Cardiac ion channelopathies and the sudden infant death syndrome. ISRN Cardiol 2012; 2012:846171.
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. Circ Arrhythm Electrophysiol 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 Eur Soc Cardiol 2011;13(8):1077-109.