Genetic Testing for Cardiac Ion Channelopathies

Description of Procedure or Service

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

Cardiac ion channelopathies are the result of variants in genes that code for protein subunits of the cardiac ion channels. These channels are essential cell membrane components that open or close to allow ions to flow into or out of the cell. 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. The channelopathies discussed in this policy 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 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.

**Long QT Syndrome**

Congenital long QT syndrome (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 syncpe 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 itself before the age of 40 years, and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult; this history may prompt 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 of untreated
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patients with LQTS is estimated at 1%–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 some 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 (i.e., Schwartz criteria, see following section, “Clinical Diagnosis”). However, measurement of the QT interval is not well standardized, and in some cases, patients may be considered borderline cases.

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 variants recognized, each corresponding to variants in different genes as indicated here. In addition, typical ST-T-wave patterns are also suggestive of specific subtypes. 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. The most recent version of this scoring system is shown below. A score of 4 or greater indicates a high probability that LQTS is present, a score of 2–3 indicates a moderate 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; therefore, the accuracy of this scoring system is ill-defined.

Diagnostic Scoring System for LQTS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
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<tr>
<td>QT corrected &gt;480 msec</td>
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<td>QT corrected 460-470 msec</td>
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<td>QT corrected &lt;450 msec</td>
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<td>T-wave alternans</td>
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<tr>
<td>Notched T-waves in three leads</td>
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<tr>
<td>Low heart rate for age</td>
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<tr>
<td>Clinical history</td>
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<tr>
<td>Syncope brought on by stress</td>
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<tr>
<td>Syncope without stress</td>
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<tr>
<td>Congenital deafness</td>
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<td>Family history</td>
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<td>Family members with definite LQTS</td>
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<tr>
<td>Unexplained sudden death in immediate family members</td>
<td>0.5</td>
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<tr>
<td>&lt; 30 y of age</td>
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**Brugada Syndrome**

Brugada Syndrome (BrS) is characterized by cardiac conduction abnormalities which increase the risk of syncope, ventricular arrhythmia, and sudden cardiac death. The disorder primarily manifests during adulthood although ages between two days and 85 years have been reported. Males are more likely to be affected than females (approximately an 8:1 ratio). BrS is estimated to be responsible for 12% of SCD cases. For both genders 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. 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. This ECG pattern includes a coved ST-segment and a J-point elevation of \( \geq 0.2 \) mV or higher 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). Two additional ECG patterns have been described (type 2 and type 3) but are less specific for the disorder. The diagnosis of BrS is considered definite when the characteristic ECG 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 ECG pattern in a family member, inducible ventricular arrhythmias on electrophysiology studies (EP) studies, syncope, or nocturnal agonal respirations.

**Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)**

CPVT is a rare inherited channelopathy which may present with an autosomal dominant or autosomal recessive inheritance. The disorder manifests as a bidirectional or polymorphic VT precipitated by exercise or emotional stress. 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. CPVT was previously believed to manifest only during childhood, but studies have now identified presentation between infancy and 40 years of age.

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. 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%). 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.

**Short QT Syndrome (SQTS)**

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, presyncope, 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
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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 (less than 2 SD 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 series of 29 patients with SQTS. Electrophysiologic (EP) studies may be used to diagnose SQTS if the diagnosis is uncertain to evaluate for short refractory periods and inducible ventricular tachycardia. However, in the series of 29 patients with SQTS described above, VT was inducible in only 3 of 6 subjects who underwent an EP study. In 2011, a diagnostic scoring system was proposed by Gollob et al to aid in decision making after a review of 61 SQTS cases.

Clinical Management

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

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 who recur while on quinidine, an ICD is recommended.

Genetics of Cardiac Ion Channelopathies

Long QT Syndrome

There are more than 1,200 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 (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 variant does not imply the absence of LQTS; it is estimated that variants 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 variant identified in a family member and targeted testing for this variant is negative. Other laboratories have investigated different testing strategies. For example, Napolitano and colleagues propose a 3-tiered approach, first testing for a core group of 64 codons that have a high incidence of variants, followed by additional testing of less frequent variants.

Another factor complicating interpretation of the genetic analysis is the penetrance of a given variant or the presence of multiple phenotypic expressions. For example, approximately 50% of carriers of variants 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.

Variants involving KCNQ1, KCNH2, and SCN5A are the most commonly detected in patients with genetically confirmed LQTS. Some variants are associated with extracardiac abnormalities in addition to the cardiac ion channel abnormalities.
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Brugada syndrome
BrS is typically inherited in an autosomal dominant manner with incomplete penetrance. The proportion of cases that are inherited, versus de novo variants, is uncertain. Although some authors report up to 50% of cases are sporadic in nature, others report that the instance of de novo variants is very low and is estimated to be only 1% of cases.

Variants 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. 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 a 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 55-65% of patients with CPVT have an identified causative variant. Variants to the gene encoding the cardiac ryanodine receptor (RYR2) or to KCNJ2 result in an autosomal dominant form of CPVT with CASQ2 (cardiac calsequestrin) and TRDN-related CPVT exhibit autosomal recessive inheritance. Some authors have reported heterozygotes for CASQ2 and TRDN variants are rare, benign arrhythmias. RYR2 variants represent the majority of CPVT cases (50-55%) with CASQ2 accounting for 1-2% and TRDN accounting for an unknown proportion of cases. The penetrance of RYR2 mutations 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 as Anderson-Tawil syndrome is rarely lethal.

Short QT syndrome
SQTS has been linked predominantly to variants in three genes, KCNH2, KCNJ2, and KCNQ1. Variants in gene 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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for Cardiac Ion Channelopathies when the medical criteria and guidelines shown below are met.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.
Genetic Testing for Cardiac Ion Channelopathies

When Genetic Testing for Cardiac Ion Channelopathies 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 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 variant; or
- A close relative diagnosed with LQTS by clinical means whose genetic status is unavailable.

*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 2–3.

**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 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 variant.

**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 variant; or
- A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable.

**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 (i.e., first-, second-, third-degree relative) with a known SQTS variant.

When Genetic Testing for Cardiac Ion Channelopathies is not covered

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

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

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

Policy Guidelines

Long QT Syndrome
Evidence for genetic testing in individuals with suspected congenital long QT syndrome (LQTS) for variants associated with congenital LQTS, 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 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 long QT (LQTS) syndrome 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, 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

Brugada Syndrome
The evidence for genetic testing in individuals with suspected Brugada syndrome (BrS) for variants associated with BrS, 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.
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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 if 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 the technology results in a meaningful improvement in the net health outcome.

Catecholaminergic Polymorphic Ventricular Tachycardia
The evidence for genetic testing for individuals with suspected catecholaminergic polymorphic ventricular tachycardia (CPVT) for variants associated with congenital CPVT, 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
The evidence for genetic testing for individuals with suspected short QT syndrome (SQTS) for variants associated with SQTS, 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 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
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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 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 if 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: S3861, 81403, 81405, 81406, 81407, 81408, 81413, 81414

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy titled Genetic Testing for Long QT Syndrome


BCBSA TEC Assessment [Electronic Version]. February 2008


Genetic Testing for Cardiac Ion Channelopathies


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 2011; 13(8):1077-109. Retrieved from http://europace.oxfordjournals.org/content/13/8/1077.long


Medical Director review 1/2013

Specialty Matched Consultant Advisory Panel review 4/2013

For policy re-titled Genetic Testing for Cardiac Ion Channelopathies


Medical Director review 1/2014


Medical Director review 4/2014
Genetic Testing for Cardiac Ion Channelopathies

Specialty Matched Consultant Advisory Panel review 4/2015
Medical Director review 4/2015


Medical Director review 4/2016


Medical Director review 1/2017
Specialty Matched Consultant Advisory Panel review 4/2017
Medical Director review 4/2017

Policy Implementation/Update Information

For Policy titled Genetic Testing for Long QT Syndrome

11/17/08 New policy issued. Coverage is provided for genetic testing for long QT syndrome when the medical criteria and guidelines outlined in the policy are met. (adn)

12/7/09 Specialty Matched Consultant Advisory Panel review meeting 10/30/09. No change to policy statement. Policy approved as written. (adn)

6/22/10 Policy Number(s) removed (amw)

7/20/10 Description section extensively revised to include the Schwartz Diagnostic Scoring System for LQTS. Policy Guidelines updated. References updated. No change to Policy Statement. (mco)
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8/30/11  References updated. No changes to Policy Statements. (mco)

12/30/11 Added new codes 81280, 81281, 81282 to “Billing/Coding” section. Effective date 1/1/2012. (mco)

3/30/12  Deleted the following codes from the “Billing/Coding” section: S3860, S3862. (mco)


1/29/13  Added the following statement to the Policy Statement section: “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 2–3.” Replaced the word “intermediate” with “moderate” in the Description section for consistency. Medical Director review 1/2013. (mco)


For policy re-titled Genetic Testing for Cardiac Ion Channelopathies

1/28/14  Policy re-titled from “Genetic Testing for Long QT Syndrome” to “Genetic Testing for Cardiac Ion Channelopathies”. Description section and Policy Guidelines section extensively revised. Added the following criteria to the “When Covered” section: “Genetic testing for catecholaminergic polymorphic ventricular tachycardia (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. Added the following statements to the “When not Covered” section: “Genetic testing for Brugada syndrome is considered investigational. Genetic testing for short QT syndrome is considered investigational.” References updated. Medical Director review 1/2014. Policy noticed on 1/28/2014 for effective date 4/1/2014. (mco)


9/9/14  Deleted codes S3860 and S3862 from the Billing/Coding section. (mco)


4/1/16  Description section updated. When covered section updated to include medically necessary statements for diagnostic testing for Brugada syndrome and testing of an asymptomatic individual with a known familial mutation associated with Brugada syndrome or SQTS. Policy Guidelines section updated. References updated. (td)
Genetic Testing for Cardiac Ion Channelopathies


12/30/16 Billing/Coding section revised; deleted 81280, 81281, 81282, and added codes 81413 and 81414. (jd)

2/24/17 Policy Guidelines and references updated. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.