Genetic Testing for Cardiac Ion Channelopathies

File Name: genetic_testing_for_cardiac_ion_channelopathies
Origination: 10/2008
Last CAP Review: 4/2018
Next CAP Review: 4/2019
Last Review: 4/2018

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 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 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 3.5 or greater indicates a high probability that LQTS is present, a score of 1.5–3 indicates an intermediate 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>
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</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
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<tr>
<td>QT corrected &gt;480 msec</td>
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<tr>
<td>QT corrected 460-470 msec</td>
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<td>QT corrected &lt;450 msec</td>
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<td>History of torsades de pointes</td>
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<tr>
<td>T-wave alternans</td>
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</tr>
<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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<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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<tr>
<td>Family members with definite LQTS</td>
<td>1</td>
</tr>
<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 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 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 (2-4mg/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 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 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 1 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 and colleagues 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 include, 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 with recurrence 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 extra-cardiac 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 variants.

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.
Genetic Testing for Cardiac Ion Channelopathies

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 observational studies reporting on the yield of testing. 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 that are best identified by chromosomal microarray (CMA) 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 genotype. 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 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
The evidence for genetic testing in individuals with suspected Brugada syndrome (BrS) for variants associated with BrS, includes observational studies reporting on yields of testing 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. Management changes for BrS, primarily the 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 presence of the variant was related to a higher rate of cardiac events. There is limited evidence about changes in management based on genetic testing in a
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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 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. Management changes for BrS, primarily ICD implantation, 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 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.

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, and the 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**

The evidence for genetic testing for individuals with suspected catecholaminergic polymorphic ventricular tachycardia (CPVT) for variants associated with congenital CPVT, includes observational studies reporting on yields of testing. 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 for 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 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. 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 yields of testing. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in
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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. Management changes for SQTS, primarily ICDs, 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 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 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 with 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 guideline stated 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.

The evidence for genetic testing for variants associated with cardiac ion channelopathies in individuals who are asymptomatic with a close family member(s) who experienced sudden cardiac death and a specific diagnosis has been made includes, cohort studies that describe the genetic yield of testing. 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.

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

Genetic Testing for Cardiac Ion Channelopathies

BCBSA TEC Assessment [Electronic Version]. February 2008


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
Genetic Testing for Cardiac Ion Channelopathies

For policy re-titled Genetic Testing for Cardiac Ion Channelopathies


Medical Director review 1/2014
Medical Director review 4/2014
Specialty Matched Consultant Advisory Panel review 4/2015
Medical Director review 4/2015
Medical Director review 4/2016
Medical Director review 1/2017
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Medical Director review 1/2018

Specialty Matched Consultant Advisory Panel review 4/2018

Medical Director review 4/2018

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)


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)

Genetic Testing for Cardiac Ion Channelopathies

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)


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)


2/9/18  Policy Guidelines and references updated. Medical Director reviewed 1/2018. (jd)


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