

(20443)

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|-------------------------|-----|--|--------------------------------|
| <b>Medical Benefit</b>  |     | <b>Effective Date:</b> 04/01/18  | <b>Next Review Date:</b> 11/19 |
| <b>Preauthorization</b> | Yes | <b>Review Dates:</b> 05/09, 05/10, 03/11, 03/12, 03/13, 03/14, 03/15, 11/15, 11/16, 11/17, 11/18 |                                |

**Preauthorization is required.**

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

| Populations  | Interventions   | Comparators  | Outcomes   |
|--|---|--|--|
| Individuals: <ul style="list-style-type: none"> <li>With suspected congenital long QT syndrome</li> </ul>  | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with congenital long QT syndrome</li> </ul>                           | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |
| Individuals: <ul style="list-style-type: none"> <li>Who are asymptomatic with close relative(s) with a known long QT syndrome variant</li> </ul> | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with congenital long QT syndrome</li> </ul>                           | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |
| Individuals: <ul style="list-style-type: none"> <li>With suspected Brugada syndrome</li> </ul>   | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with Brugada syndrome</li> </ul>                                      | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |
| Individuals: <ul style="list-style-type: none"> <li>Who are asymptomatic with close relative(s) with a known Brugada syndrome variant</li> </ul> | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with Brugada syndrome</li> </ul>                                      | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |
| Individuals: <ul style="list-style-type: none"> <li>With suspected catecholaminergic polymorphic ventricular tachycardia</li> </ul>              | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia</li> </ul> | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |

| Populations   | Interventions   | Comparators  | Outcomes   |
|---|---|--|--|
| Individuals: <ul style="list-style-type: none"> <li>Who are asymptomatic with close relative(s) with a known catecholaminergic polymorphic ventricular tachycardia variant</li> </ul> | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia</li> </ul> | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |
| Individuals: <ul style="list-style-type: none"> <li>With suspected short QT syndrome</li> </ul>   | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with short QT syndrome</li> </ul>                                     | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |
| Individuals: <ul style="list-style-type: none"> <li>Who are asymptomatic with close relative(s) with a known short QT syndrome variant</li> </ul>                                     | Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for variants associated with short QT syndrome</li> </ul>                                     | Comparators of interest are: <ul style="list-style-type: none"> <li>Standard management without genetic testing</li> </ul> | Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Test validity</li> <li>Changes in reproductive decision making</li> <li>Morbid events</li> </ul> |

## 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 variants associated with these channelopathies may assist in diagnosis, risk-stratify prognosis, and/or identify susceptibility for the disorders in asymptomatic family members.

## SUMMARY OF EVIDENCE

### LONG QT SYNDROME

For individuals with suspected congenital LQTS who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on the testing yield. The relevant outcomes are overall survival (OS), test validity, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 70% of those with LQTS. The clinical utility of genetic testing for LQTS is high when there is a moderate-to-high pretest probability. There is a chain of evidence to suggest that testing for variants associated with LQTS in individuals who are suspected to have these disorders, leads to improved outcomes. A definitive diagnosis of LQTS leads to treatment with  $\beta$ -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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with close relative(s) with a known LQTS variant who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on changes in management. The relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. A positive genetic test for an LQTS variant leads to treatment with  $\beta$ -blockers in most cases, and sometimes to treatment with an ICD and a negative test would allow family members to defer further test-

ing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

#### BRUGADA SYNDROME

For individuals with suspected Brugada Syndrome (BrS) who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields. The relevant outcomes are OS, test validity, 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 15% to 35% of BrS. BrS management changes, primarily use of ICDs, are directed by clinical symptoms. It is not clear that a genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic with a close relative(s) with a known BrS variant who receive genetic testing for variants associated with congenital BrS, the evidence includes observational studies reporting on testing yields. The relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. BrS management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on the effect of changes in management based on genetic testing in an individual with family members who have a known variant. However, a negative test would allow family members to defer further testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Given the limited available evidence on genetic testing for BrS, clinical input was obtained. There was a consensus among the specialty societies and academic medical centers providing clinical input that genetic testing for BrS is medically necessary to establish a definitive diagnosis in patients with BrS symptoms and to evaluate family members of an individual with a known genetic variant of BrS. A review of guidelines from American and international cardiac specialty societies (American Heart Association, Heart Rhythm Society, European Heart Rhythm Association, Asia Pacific Heart Rhythm Society) was also conducted. The guidelines acknowledged that although the evidence is weak, genetic testing is recommended for both individuals with a suspected but not a definitive diagnosis of BrS and asymptomatic family members of individuals with known BrS variants.

#### CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

For individuals with suspected Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) who receive genetic testing for variants associated with congenital CPVT, the evidence includes observational studies reporting on testing yields. The relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 60% of CPVT patients. There is a chain of evidence to suggest that testing for variants associated with CPVT in individuals who are suspected to have these disorders. Confirming the diagnosis of CPVT is likely to lead to a health outcome benefit by initiating changes in management that reduce the risk of ventricular arrhythmias and sudden cardiac death. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known CPVT variant who receive genetic testing for variants associated with congenital CPVT, the evidence includes observational studies reporting testing yields. The relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. For close relatives of patients with known CPVT variants who are found to have a pathologic variant, preventive treatment can be initiated. Also, a negative test in the setting of a known familial variant should have a high negative predictive value. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

#### SHORT QT SYNDROME

For individuals with suspected Short QT Syndrome (SQTS) who receive genetic testing for variants associated with SQTS, the evidence includes limited data on testing yields. The relevant outcomes are OS, test validity,

changes in reproductive decision making, and morbid events. The yield of genetic testing in SQTS is not well-characterized. SQTS management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on changes in management based on genetic testing in a symptomatic proband without a definitive diagnosis. It is not clear that a genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic with a close relative(s) with a known SQTS variant who receive genetic testing for variants associated with congenital SQTS, the evidence includes observational studies reporting on testing yields. The relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. For patients with SQTS, management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on changes in management based on genetic testing in an individual with family members who have a known variant. It is not clear that a genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Given the limited available evidence on genetic testing for SQTS, clinical input was obtained. Among the specialty societies and academic medical centers providing input, there was no consensus on the use of genetic testing for variants associated with SQTS; however, there was consensus that genetic testing to predict future risk of disease in individuals with close relatives who have a known variant associated with SQTS is useful in management that may lead to improved outcomes. A review of guidelines was also conducted. The use of genetic testing for patients with suspected SQTS was not addressed in many guidelines; however, one did state that testing may be considered if a cardiologist has established a strong clinical index of suspicion. Additionally, the guidelines acknowledged that although the evidence is weak, genetic testing may be considered for asymptomatic family members of individuals with known SQTS variants.

## POLICY

### 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 (i.e., those with a Schwartz score less than four): but have a moderate-to-high pretest probability (see Policy Guidelines) 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 (i.e., 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.

Genetic testing for LQTS for all other situations not meeting the criteria outlined above, including but not limited to determining prognosis and/or directing therapy in patients with known LQTS, is considered **investigational**.

### BRUGADA SYNDROME

Genetic testing to confirm a diagnosis of Brugada syndrome (BrS) may be considered **medically necessary** when signs and/or symptoms consistent with BrS (see Policy Guidelines) 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 (i.e., first-, second-, or third-degree relative) with a known BrS variant.

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

#### CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Genetic testing to confirm a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered **medically necessary** when signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing.

Genetic testing of asymptomatic individuals to determine future risk of CPVT may be considered **medically necessary** when at least one of the following criteria is met:

- a close relative (i.e. 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.

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

#### SHORT QT SYNDROME

Genetic testing of asymptomatic individuals to determine future risk of short QT syndrome (SQTS) may be considered **medically necessary** when patients have a close relative (i.e., first-, second-, or third-degree relative) with a known SQTS variant.

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

#### POLICY GUIDELINES

Genetic testing should be performed by an expert in genetic testing and/or cardiac ion channelopathies.

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

Signs and symptoms suggestive of BrS include the presence of a characteristic electrocardiographic pattern, documented ventricular arrhythmia, sudden cardiac death in a family member younger than 45 years old, a characteristic electrocardiographic pattern in a family member, inducible ventricular arrhythmias on electrophysiologic studies, syncope, or nocturnal agonal respirations. An index patient with suspected SQTS would be expected to have a shortened (less than two 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 (Tristani-Firouzi, 2014). The presence of a short QTc interval alone does not make the diagnosis of SQTS. Clinical history, family history, other electrocardiographic findings, and genetic testing may be used to confirm the diagnosis.

#### TESTING STRATEGY

In general, testing for patients with suspected congenital LQTS, CPVT or BrS should begin with a known familial variant, if one has been identified.

In cases where the family member's genetic diagnosis is unavailable, testing is available through either single-gene testing or panel testing. The evaluation of the clinical utility of panel testing is outlined in the General Approach to Evaluating the Utility of Genetic Panels Protocol. Panels for cardiac ion channelopathies are diag-

nostic test panels that may fall into one of several categories: panels that include variants for a single condition; panels that include variants for multiple conditions (indicated plus nonindicated conditions); and panels that include variants for multiple conditions (clinical syndrome for which clinical diagnosis not possible).

For situations in which a relative of a proband with unexplained cardiac death or unexplained sudden cardiac arrest or an individual with unexplained sudden cardiac arrest is being evaluated, genetic testing may be part of a diagnostic strategy that includes a comprehensive history and physical exam and 12-lead electrocardiogram, along with exercise stress test, transthoracic echocardiography, and additional evaluation as guided by the initial studies. Studies have suggested that in such cases, a probable diagnosis of an inherited cardiac condition can be made following a nongenetic evaluation in 50% to 80% of cases (Behr et al, 2008; Krahn et al, 2009; Kumar et al, 2013; Wong et al, 2014). If, after a comprehensive evaluation, a diagnosis of CPVT, LQTS or BrS is suspected but not definitive (i.e., if there is a moderate-to-high pretest probability of either condition), genetic testing could be considered.

#### GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

#### MEDICARE ADVANTAGE

For Medicare Advantage genetic testing procedures for Cardiac Ion Channelopathies (e.g., Brugada Syndrome, Long QT Syndrome, Short QT Syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia) submitted under the following panels are considered **not medically necessary** as they are unlikely to impact therapeutic decision-making in the clinical management of the patient:

- genomic sequence analysis panel
- duplication/deletion gene analysis panel.

For Medicare Advantage the following individual genetic tests are unlikely to impact therapeutic decision-making, directly impact treatment, outcome and/or clinical management in the care of the patient and will be denied as **not medically necessary**:

- SCN5A
- RYR2

#### BACKGROUND

##### CARDIAC ION CHANNELOPATHIES

Cardiac ion channelopathies result from variants in genes that code for protein subunits of the cardiac ion channels. These channels are essential to cell membrane components that open or close to allow ions to flow into or out of the cell. Regulation of these ions is essential for the maintenance of a normal cardiac action potential. This group of disorders is associated with ventricular arrhythmias and an increased risk of sudden cardiac death (SCD). These congenital cardiac channelopathies can be difficult to diagnose, and the implications of an incorrect diagnosis could be catastrophic.



The prevalence of any cardiac channelopathy is still ill-defined but is thought to be between one in 2000 and one in 3000 persons in the general population.<sup>1</sup> Data about the individual prevalences of LQTS, BrS, CPVT, and SQTS are presented in Table 1.

Table 1. Epidemiology of Cardiac Ion Channelopathies

| Variables                      | LQTS                                       | Brugada Syndrome | CPVT          | SQTS         |
|--------------------------------|--|------------------|---------------|--------------|
| Prevalence                     | 1:2000-5000                                | 1:6000           | 1:7000-10,000 | Unidentified |
| Annual mortality rate          | 0.3% (LQT1)<br>0.6% (LQT2)<br>0.56% (LQT3) | 4% <sup>a</sup>  | 3.1%          | Unidentified |
| Mean age at first event, years | 14   | 42 <sup>a</sup>  | 15            | 40           |

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

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

<sup>a</sup>Type 1 electrocardiographic pattern.

### Long QT Syndrome

Congenital LQTS is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential, increasing the risk for arrhythmic events, such as torsades de pointes, which may, in turn, result in syncope and SCD.

Congenital LQTS usually manifests before the age of 40 years. 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.

### Brugada Syndrome

BrS is characterized by cardiac conduction abnormalities that increase the risk of syncope, ventricular arrhythmia, and SCD. The disorder primarily manifests during adulthood, although ages between two days and 85 years have been reported.<sup>3</sup> BrS is an autosomal dominant disorder with an unexplained male predominance. Males are more likely to be affected than females (approximate ratio, 8:1). BrS is estimated to be responsible for 12% of SCD cases.<sup>1</sup> For both sexes, there is an equally high-risk of ventricular arrhythmias or sudden death.<sup>4</sup> Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.<sup>5</sup>

### Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a rare, inherited channelopathy that may present with autosomal dominant or autosomal recessive inheritance. The disorder manifests as a bidirectional or polymorphic ventricular tachycardia precipitated by exercise or emotional stress.<sup>6</sup> The prevalence of CPVT is estimated between one in 7000 and one in 10000 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.<sup>6</sup> CPVT was previously believed to manifest only during childhood, but studies have now identified presentation between infancy and 40 years of age.<sup>7</sup>

### Short QT Syndrome

SQTS is characterized by a shortened QT interval on the electrocardiogram and, at the cellular level, a shortening of the action potential.<sup>8</sup> 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.<sup>6</sup>

### Sudden Cardiac Arrest or Sudden Cardiac Death

Sudden Cardiac Arrest (SCA) and SCD refer to the sudden interruption of cardiac activity with circulatory collapse. The most common cause is coronary artery disease. Approximately 5% to 10% of SCA and SCD are due to arrhythmias without structural cardiac disease and are related to the primary electrical disease syndromes. The previously described cardiac ion channelopathies are among the primary electrical disease syndromes.

The evaluation and management of a survivor of SCA include an assessment of the circumstances of the event as well as a comprehensive physical examination emphasizing cardiovascular and neurologic systems, laboratory testing, electrocardiogram, and more advanced cardiac imaging or electrophysiologic testing as may be warranted. Genetic testing might be considered when, after completion of a comprehensive evaluation, there are findings consistent with a moderate-to-high likelihood of a primary electrical disease. Postmortem protocols for evaluation of a fatal SCA should be implemented when possible.

## GENETICS OF CARDIAC ION CHANNELOPATHIES

### Long QT Syndrome

There are more than 1200 unique variants on at least 13 genes encoding potassium-channel proteins, sodium-channel proteins, calcium channel-related factors, and membrane adaptor proteins that have been associated with LQTS. In addition to single variants, some cases of LQTS are associated with deletions or duplications of genes.<sup>9</sup>

The absence of a variant does not imply the absence of LQTS; it is estimated that variants are only identified in 70% to 75% of patients with a clinical diagnosis of LQTS.<sup>10</sup> 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.

Another factor complicating interpretation of the genetic analysis is the penetrance of a given variant or the presence of multiple phenotypic expressions. For example, approximately 50% of variant carriers never have any symptoms. There is variable penetrance for the LQTS, and penetrance may differ for the various subtypes. While linkage studies in the past have indicated that penetrance was 90% or greater, a 1999 analysis using molecular genetics challenged this estimate and suggested that penetrance may be as low as 25% for some families.<sup>11</sup>

Variants involving KCNQ1, KCNH2, and SCN5A are the most commonly detected in patients with genetically confirmed LQTS. Some variants are associated with extra-cardiac abnormalities in addition to the cardiac ion channel abnormalities. A summary of clinical syndromes associated with hereditary LQTS is shown in Table 2.

Table 2. Genetics of Long QT Syndrome

| Type  | Other Names             | Chromosome Locus | Mutated Gene                    | Ion Current(s) Affected    | Associated Findings   |
|-------|-------------------------|------------------|---------------------------------|----------------------------|---|
| LQT1  | RWS                     | 11p15.5          | KVLQT1 or KCNQ1 (heterozygotes) | Potassium                  |   |
| LQT2  | RWS                     | 7q35-36          | HERG, KCNH2                     | Potassium                  |   |
| LQT3  | RWS                     | 3p21-24          | SCN5A                           | Sodium                     |   |
| LQT4  | Ankyrin B syndrome      | 4q25-27          | ANK2, ANKB                      | Sodium, potassium, calcium | Catecholaminergic polymorphic ventricular arrhythmias, sinus node dysfunction, AF |
| LQT5  | RWS                     | 21q22.1-22.2     | KCNE1 (heterozygotes)           | Potassium                  |   |
| LQT6  | RWS                     | 21q22.1-22.2     | MiRP1, KNCE2                    | Potassium                  |   |
| LQT7  | Andersen-Tawil syndrome | 17.q23.1-q24.2   | KCNJ2                           | Potassium                  | Episodic muscle weakness, congenital anomalies                                    |
| LQT8  | Timothy syndrome        | 12q13.3          | CACNA1C                         | Calcium                    | Congenital heart defects, hand/foot syndactyly, ASD                               |
| LQT9  | RWS                     | 3p25.3           | CAV3                            | Sodium                     |   |
| LQT10 | RWS                     | 11q23.3          | SCN4B                           | Sodium                     |   |
| LQT11 | RWS                     | 7q21-q22         | AKAP9                           | Potassium                  |   |



| Type  | Other Names | Chromosome Locus | Mutated Gene   | Ion Current(s) Affected | Associated Findings                   |
|-------|-------------|------------------|--|-------------------------|---------------------------------------|
| LQT12 | RWS         | 20q11.21         | SNTA1  | Sodium                  |                                       |
| LQT13 | RWS         | 11q24.3          | KCNJ5  | Potassium               |                                       |
| JLN1  | JLNS        | 11p15.5          | KVLQT1 or KCNQ1<br>(homozygotes or compound heterozygotes) | Potassium               | Congenital sensorineural hearing loss |
| JLN2  | JLNS        | 21q22.1-22.2     | KCNE1<br>(homozygotes or compound heterozygotes)           | Potassium               | Congenital sensorineural hearing loss |

Adapted from Beckmann et al (2013)<sup>12</sup> Arking et al (2014)<sup>13</sup>, and Alders (2015)<sup>14</sup>

AF: atrial fibrillation; ASD: autism spectrum disorder; LQT: long QT; JLNS: Jervell and Lange-Nielsen syndrome; RWS: Romano-Ward syndrome.

### 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 have reported up to 50% of cases are sporadic, others have reported that the instance of de novo variants is very low and is estimated to be only 1% of cases.<sup>4</sup>

Variants in 16 genes have been identified as causative of BrS, all of which lead to a decrease in the inward sodium or calcium current or an increase in one of the outward potassium currents. Of these, SCN5A is the most important, accounting for more than an estimated 20% of cases<sup>7</sup>; SCN10A has also been implicated. The other genes are of minor significance and account together for approximately 5% of cases.<sup>6</sup> The absence of a positive test does not indicate the absence of BrS, with more than 65% of cases not having an identified genetic cause. Penetrance of BrS among persons with an SCN5A variant is 80% when undergoing electrocardiogram with sodium-channel blocker challenge and 25% when not using the electrocardiogram challenge.<sup>4</sup>

### Catecholaminergic Polymorphic Ventricular Tachycardia

Variants in four genes are known to cause CPVT, and investigators believe other unidentified loci are involved as well. Currently, only 55% to 65% of patients with CPVT have an identified causative variant. Variants of the gene encoding the cardiac ryanodine receptor (RYR2) or to KCNJ2 result in an autosomal dominant form of CPVT. CASQ2 (cardiac calsequestrin) and TRDN-related CPVT exhibit autosomal recessive inheritance. Some have reported heterozygotes for CASQ2 and TRDN variants for rare, benign arrhythmias.<sup>15</sup> RYR2 variants represent most CPVT cases (50%-55%), with CASQ2 accounting for 1% to 2% and TRDN accounting for an unknown proportion of cases. The penetrance of RYR2 variants is approximated at 83%.<sup>15</sup>

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.<sup>7</sup> Additionally, nearly a third of patients diagnosed as LQTS with normal QT intervals have CPVT due to identified RYR2 variants. Another misclassification, CPVT diagnosed as Anderson-Tawil syndrome may result in more aggressive prophylaxis for CPVT whereas a correct diagnosis can spare this treatment because Anderson-Tawil syndrome is rarely fatal.

### Short QT Syndrome

SQTS has been linked predominantly to variants in three genes (KCNH2, KCNJ2, KCNQ1).<sup>13</sup> Variants in genes encoding alpha- and beta-subunits of the L-type cardiac calcium channel (CACNA1C, CACNB2) have also been associated with SQTS. Some individuals with SQTS do not have a variant in these genes, suggesting changes in other genes may also cause this disorder. SQTS is believed to be inherited in an autosomal dominant pattern.

Although sporadic cases have been reported, patients frequently have a family history of the syndrome or SCD.

## REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

## RELATED PROTOCOL

General Approach to Evaluating the Utility of Genetic Panels

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

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

## REFERENCES

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

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