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Medical Benefit		Effective Date: 01/01/16	Next Review Date: 11/17
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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"> With suspected congenital long QT syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for mutations associated with congenital long QT syndrome 	Comparators of interest are: <ul style="list-style-type: none"> Standard management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Test accuracy Test validity Other test performance measures Changes in reproductive decision making Morbid events
Individuals: <ul style="list-style-type: none"> Who are asymptomatic with close relative(s) with a known long QT syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for mutations associated with congenital long QT syndrome 	Comparators of interest are: <ul style="list-style-type: none"> Standard management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Test accuracy Test validity Other test performance measures Changes in reproductive decision making Morbid events
Individuals: <ul style="list-style-type: none"> With suspected Brugada syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for mutations associated with Brugada syndrome 	Comparators of interest are: <ul style="list-style-type: none"> Standard management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Test accuracy Test validity Other test performance measures Changes in reproductive decision making Morbid events
Individuals: <ul style="list-style-type: none"> Who are asymptomatic with close relative(s) with a known Brugada syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for mutations associated with Brugada syndrome 	Comparators of interest are: <ul style="list-style-type: none"> Standard management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Test accuracy Test validity Other test performance measures Changes in reproductive decision making Morbid events

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

Description

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

Summary of Evidence

The evidence for genetic testing for mutations associated with congenital LQTS and CPVT in individuals with suspected LQTS or CPVT, or in individuals who are asymptomatic with close relatives with a known mutation associated with LQTS or CPVT, includes studies reporting on the yield of testing 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 mutation can be identified in approximately 72% to 80% of LQTS and 51% to 75% of CPVT patients. Most are point mutations identified by gene sequencing analysis; however, a small number are deletions/duplications best identified by chromosomal microarray analysis (CMA).

The analytic validity of testing for point mutations by sequence analysis is high, while the analytic validity of testing for deletions/duplications by CMA is less certain. The clinical validity of testing in LQTS is high, in the range of 70% to 80%; for CPVT, it is moderate, in the range of 50% to 75%. The clinical utility of genetic testing for LQTS or CPVT is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. A definitive diagnosis of either channelopathy leads to treatment with 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 indirect evidence to suggest that testing for mutations associated with LQTS or 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 clinical utility of testing is also high for close relatives of patients with known cardiac ion channel mutations, because these individuals should also be treated if they are found to have a pathologic mutation. In addition, a negative test in the setting of a known familial mutation should have a high negative predictive value. 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for mutations associated with BrS and SQTS in individuals with suspected BrS or SQTS, or in individuals who are asymptomatic with close relatives with a known mutation associated with BrS or SQTS, includes studies reporting on the yield of testing 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 mutations is likely to be high, the clinical validity is lower: a genetic mutation can be identified in approximately 25% to 35% of BrS and 15% to 20% of SQTS patients. For BrS and SQTS, management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing, either in a symptomatic proband without a definitive diagnosis or in an individual with family members with a known mutation. 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.

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 mutation; 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 mutation.

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 mutation; 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 SQTs may be considered **medically necessary** when patients have a close relative (i.e., first-, second-, or third-degree relative) with a known SQTs mutation.

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 individual with adequate expertise 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.

An index patient with suspected SQTs would be expected to have a shortened (shorter than two 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 (Tristani-Firouzi, 2004). 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.

Signs and symptoms suggestive of BrS include the presence of characteristic electrocardiographic (ECG) 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.

Testing Strategy

In general, testing for patients with suspected congenital LQTS, CPVT or BrS should begin with a known familial mutation, 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 diagnostic test panels that may fall into one of several categories: panels that include mutations for a single condition; panels that include mutations for multiple conditions (indicated plus nonindicated conditions); panels that include mutations 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 (ECG), along with exercise stress test, transthoracic echocardiography, and additional evaluation as guided by the initial studies. Studies suggest 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, or 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.

Background

Cardiac ion channelopathies result from mutations in genes that code for protein subunits of the cardiac ion channels. These channels are essential cell membrane components that open or close to allow ions to flow into or out of the cell. 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.¹ Data pertaining to the individual prevalences of LQTS, CPVT, BrS, and SQTs are presented in Table 1. The channelopathies discussed herein are genetically heterogeneous with hundreds of identified mutations, but the group of disorders share basic clinical expression. The most common presentation is spontaneous or exercise-triggered syncope due to ventricular dysrhythmia. These can be self-limiting or potentially lethal cardiac events. The electrocardiographic features of each channelopathy are characteristic, but the electrocardiogram (ECG) is not diagnostic in all cases, and some secondary events (e.g., electro-

lyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an ECG similar to those observed in a cardiac channelopathy.

Table 1. Epidemiology of Cardiac Ion Channelopathies

	LQTS	CPVT	Brugada Syndrome	SQTS
Prevalence	1:2000-5000	1:7000-10,000	1:6000	Unidentified
Annual mortality rate	0.3% (LQT1) 0.6% (LQT2) 0.56% (LQT3)	3.1%	4% ^a	Unidentified
Mean age at first event, y	14	15	42 ^b	40

Adapted from Modell et al.

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

^a Type 1 ECG pattern.

^b Type 1 ECG 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. Management has focused on the use of β -blockers as firstline treatment, with pacemakers or implantable cardioverter defibrillator (ICD) as second-line therapy.

Congenital LQTS usually manifests before the age of 40 years and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult; this history may prompt additional testing in family members. It is estimated that more than half of the 8000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1% to 2% per year, although this figure will vary with the genotype.

Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and thus LQTS has received publicity regarding evaluation of adolescents for participation in sports. In addition, LQTS may be considered when a long QT interval is incidentally observed on an ECG. Diagnostic criteria for LQTS have been established, which focus on ECG findings and clinical and family history (i.e., Schwartz criteria, see the Clinical Diagnosis subsection next). However, measurement of the QT interval is not well-standardized and, in some instances, patients may be considered borderline cases.²

In recent years, LQTS has been characterized as an “ion channel disease,” with abnormalities in the sodium and potassium channels that control the excitability of the cardiac myocytes. A genetic basis for LQTS has also emerged, with seven different subtypes recognized, each corresponding to mutations in different genes as indicated here.³ In addition, typical ST-T wave patterns are also suggestive of specific subtypes.⁴ Some 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.⁵ The most recent version is shown in Table 2. A score of four or greater indicates a high probability that LQTS is present; a score of two to three, a moderate-to-high probability; and a score of one or less indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; and because there is still no perfect criterion standard for diagnosing LQTS, the accuracy of this scoring system remains ill-defined.

Table 2. Diagnostic Scoring System for Long QT Syndrome⁶

Schwartz Criteria	Points
Electrocardiographic findings QT corrected > 480 ms	3

Schwartz Criteria	Points
QT corrected 460-470 ms	2
QT corrected < 450 ms	1
History of torsades de pointes	2
T-wave alternans	1
Notched T-waves in three leads	1
Low heart rate for age	0.5
Clinical history	
Syncope brought on by stress	2
Syncope without stress	1
Congenital deafness	0.5
Family history	
Family members with definite long QT syndrome	1
Unexplained sudden death in immediate family members < 30 y of age	0.5

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.⁷ Males are more likely to be affected than females (approximately an 8:1 ratio). BrS is estimated to be responsible for 12% of SCD cases.¹ For both sexes, there is an equally high risk of ventricular arrhythmias or sudden death.⁸ Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.⁹ Management has focused on the use of ICDs 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.¹⁰ 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-V3). This pattern may be concealed and can be revealed by administering a sodium-channel-blocking agent (e.g., ajmaline or flecainide).¹¹ Two additional ECG patterns have been described (type 2, type 3) but are less specific for the disorder.¹² The diagnosis of BrS is considered definitive when the characteristic ECG pattern is present with at least one of the following clinical features: documented ventricular arrhythmia, SCD in a family member younger than 45 years old, characteristic ECG pattern in a family member, inducible ventricular arrhythmias on electrophysiology studies, syncope, or nocturnal agonal respirations.

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 (VT) precipitated by exercise or emotional stress.¹³ The prevalence of CPVT is estimated between one in 7000 and one in 10,000 persons. CPVT has a mortality rate of 30% to 50% by age 35 and is responsible for 13% of cardiac arrests in structurally normal hearts.¹³ CPVT was previously believed to manifest only during childhood, but studies have now identified presentation between infancy and 40 years of age.¹⁴

Management of CPVT is primarily with the β -blockers nadolol (1-2.5 mg/kg/d) or propranolol (2-4 mg/kg/d). If protection is incomplete (i.e., recurrence of syncope or arrhythmia), then flecainide (100-300 mg/d) may be added. If recurrence continues, an ICD may be necessary with optimized pharmacologic management continued postimplantation.¹⁵ 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 most cases (75%-100%).⁶ 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.¹⁶

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.¹⁷ 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.¹³

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-segment are characteristic of the syndrome.¹⁸ 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 two 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.¹⁹ The length of the QT interval was not associated with severity of symptoms in one series of 29 patients with SQTS.²⁰ 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 three of six subjects who underwent an EP study.²⁰ In 2011, a diagnostic scoring system was proposed by Gollob et al to aid in decision making after a review of 61 SQTS cases (see Table 3).²¹

Table 3. Diagnostic Scoring System for Short QT Syndrome⁶

Gollob Criteria	Points
Electrocardiographic findings	
QT corrected < 370 ms	1
QT corrected < 350 ms	2
QT corrected < 330 ms	3
J point-T peak interval < 120 ms	1
Clinical history	
History of sudden cardiac death	2
Documented polymorphic ventricular fibrillation or ventricular tachycardia	2
Unexplained syncope	1
Atrial fibrillation	1
Family history	
First- or second-degree relative with high probability short QT syndrome	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

Clinical Management

The primary management of SQTS is with ICD therapy. The degree to which SQTS is considered likely, based 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 (e.g., sotalolol) is Kv11.1, which is coded for by *KCNH2*, the most common site for mutations in SQTS (subtype 1). Treatment with quinidine (which is able to bind to both open and inactivated states of Kv11.1) is an appropriate QT-prolonging treatment. This treatment has been reported to reduce the rate of arrhythmias from 4.9% to 0% per year. For those who recur while on quinidine, an ICD is recommended.⁶

Genetics of Cardiac Ion Channelopathies

Long QT Syndrome

There are more than 1200 unique mutations 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 mutations, some cases of LQTS are associated with deletions or duplications of genes.²² This may be the case in up to 5% of total cases of LQTS. These types of mutations may not be identified by gene sequence analysis. They can be more reliably identified by chromosomal microarray analysis (CMA), also known as array comparative genomic hybridization (aCGH). Some laboratories that test for LQTS now offer detection of LQTS-associated deletions and duplications by this testing method. This type of test may be offered separately and may need to be ordered independent of gene sequence analysis when testing for LQTS.

The absence of a mutation does not imply the absence of LQTS; it is estimated that mutations are only identified in 70% to 75% of patients with a clinical diagnosis of LQTS.²³ A negative test is only definitive when there is a known mutation identified in a family member and targeted testing for this mutation is negative. Other laboratories have investigated different testing strategies. For example, Napolitano et al propose a three-tiered approach, first testing for a core group of 64 codons that have a high incidence of mutations, followed by additional testing of less frequent mutations.²⁴

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

Mutations involving *KCNQ1*, *KCNH2*, and *SCN5A* are the most commonly detected in patients with genetically confirmed LQTS. Some mutations are associated with extracardiac abnormalities in addition to the cardiac ion channel abnormalities. A summary of clinical syndromes associated with hereditary LQTS is shown in Table 4.

Table 4: Genetics of Long QT Syndrome

Type	Other Names	Chromosome Locus	Mutated Gene	Ion Current(s) Affected	Associated Findings
LQT1	RWS	11p15.5	<i>KVLQT1</i> or <i>KCNQ1</i> (heterozygotes)	Potassium	
LQT2	RWS	7q35-36	<i>HERG</i> , <i>KCNH2</i>	Potassium	
LQT3	RWS	3p21-24	<i>SCN5A</i>	Sodium	
LQT4	Ankyrin B syndrome	4q25-27	<i>ANK2</i> , <i>ANKB</i>	Sodium, potassium, and calcium	Catecholaminergic polymorphic ventricular arrhythmias, sinus node dysfunction, AF
LQT5	RWS	21q22.1-22.2	<i>KCNE1</i> (heterozygotes)	Potassium	
LQT6	RWS	21q22.1-22.2	<i>MIRP1</i> , <i>KNCE2</i>	Potassium	
LQT7	Andersen-Tawil syndrome	17.q23.1-q24.2	<i>KCNJ2</i>	Potassium	Episodic muscle weakness, congenital anomalies
LQT8	Timothy	12q13.3	<i>CACNA1C</i>	Calcium	Congenital heart defects,

Type	Other Names	Chromosome Locus	Mutated Gene	Ion Current(s) Affected	Associated Findings
	syndrome				hand/foot syndactyly, ASD
LQT9	RWS	3p25.3	<i>CAV3</i>	Sodium	
LQT10	RWS	11q23.3	<i>SCN4B</i>	Sodium	
LQT11	RWS	7q21-q22	<i>AKAP9</i>	Potassium	
LQT12	RWS	20q11.21	<i>SNTA1</i>	Sodium	
LQT13	RWS	11q24.3	<i>KCNJ5</i>	Potassium	
JLN1	JLNS	11p15.5	<i>KVLQT1</i> or <i>KCNQ1</i> (homozygotes or compound heterozygotes)	Potassium	Congenital sensorineural hearing loss
JLN2	JLNS	21q22.1-22.2	<i>KCNE1</i> (homozygotes or compound heterozygotes)	Potassium	Congenital sensorineural hearing loss

Adapted from Beckmann et al²⁶ and Alders and Mannens.²⁷

AF: atrial fibrillation; ASD: autism spectrum disorder; LQT: long QT; LQTS: long QT syndrome; 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 mutations, is uncertain. Although some authors report up to 50% of cases are sporadic in nature, others report that the instance of de novo mutations is very low and is estimated to be only 1% of cases.⁸

Mutations in 16 genes have been identified as causative of BrS, all of which lead to either 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.¹⁴ The other genes are of minor significance and account together for approximately 5% of cases.¹³ 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* mutation is 80% when undergoing ECG with sodium channel blocker challenge and 25% when not using the ECG challenge.⁸

Catecholaminergic Polymorphic Ventricular Tachycardia

Mutations in four genes are known to cause CPVT, and investigators believe other unidentified loci are involved as well. Currently, only 55% to 65% of patients with CPVT have an identified causative mutation. Mutations to 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 authors have reported heterozygotes for *CASQ2* and *TRDN* mutations for rare, benign arrhythmias.¹⁵ *RYR2* mutations represent most of CPVT cases (50%-55%), with *CASQ2* accounting for 1% to 2% and *TRDN* accounting for an unknown proportion of cases. The penetrance of *RYR2* mutations is approximated at 83%.¹⁵

An estimated 50% to 70% of patients will have the dominant form of CPVT with a disease-causing mutation. Most mutations (90%) to *RYR2* are missense mutations, but in a small proportion of unrelated CPVT patients, large gene rearrangements or exon deletions have been reported.¹⁴ Additionally, nearly a third of patients diagnosed as LQTS with normal QT intervals have CPVT due to identified *RYR2* mutations. Another misclassification, CPVT diagnosed as Anderson-Tawil syndrome, may result in more aggressive prophylaxis for CPVT whereas a correct diagnosis can spare this treatment because Anderson-Tawil syndrome is rarely lethal.

Short QT Syndrome

SQTS has been linked predominantly to mutations in three genes (*KCNH2*, *KCNJ2*, *KCNQ1*). Mutations 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 mutation in these genes, suggesting changes in other genes may also cause this disorder. SQTS is believed to be inherited in an autosomal dominant pattern. Although sporadic cases have been reported, patients frequently have a family history of the syndrome or SCD.

Genetic Testing for Cardiac Ion Channelopathies

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

Class I	Deleterious and probable deleterious mutations. They are either mutations that have previously been identified as pathologic (deleterious mutations), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious mutations).
Class II	Possible deleterious mutations. These variants encode changes to protein(s) but occur in regions that are not considered critical. Approximately 5% of unselected patients without LQTS will exhibit mutations in this category.
Class III	Variants not generally expected to be deleterious. These variants encode modified protein(s); however, they are considered more likely to represent benign polymorphisms. Approximately 90% of unselected patients without LQTS will have one or more of these variants; therefore patients with only class III variants are considered “negative.”
Class IV	Non-protein-altering variants. These variants are not considered to have clinical significance and are not reported in the results of the Familion [®] test.

Genetic testing for specific disorders, which may include one or more specific genes, is available from multiple academic and commercial laboratories, generally by next-generation sequencing or Sanger sequencing. In addition, panel testing for one or more cardiac ion channelopathies is available from a number of genetic diagnostics laboratories (see Table 5). The John Welsh Cardiovascular Diagnostic Laboratory, GeneDX, and Transgenomic all offer panels that genotype LQTS, CPVT, BrS, and SQTS, but there is some variation among manufacturers on the included genes.

Table 5. Examples of Cardiac Ion Channelopathy Genetic Testing Panels

Laboratory	LQTS	CPVT	BrS	SQTS
AmbryGenetics (Aliso Viejo, CA)	•	•	•	
GeneDX (Gaithersburg, MD)	•	•	•	•
John Welsh Cardiovascular Diagnostic Laboratory, Baylor College of Medicine ^a (Houston, TX)	•	•	•	•
Prevention Genetics (Marshfield, WI)		•		
Transgenomic/FAMILION ^a (New Haven, CT)	•	•	•	•

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

^a Indicates multigene panel available for sudden cardiac death.

There are also commercially available panels that include genetic testing for cardiac ion channelopathies along with other hereditary cardiac disorders, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (e.g., iGene Cardiac Panel; ApolloGen, Irvine, CA).

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 Act (CLIA). Laboratories that offer LDTs must be licensed by 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

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.**

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

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