



Louisiana

Genetic Testing for Cardiac Ion Channelopathies

Policy # 00408

Original Effective Date: 04/23/2014

Current Effective Date: 01/17/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

LONG QT SYNDROME

Based on review of available data, the Company may consider genetic testing to confirm a diagnosis of congenital long QT syndrome (LQTS) when signs and/or symptoms of LQTS are present but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage**. 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.

Based on review of available data, the Company may consider Genetic testing of asymptomatic individuals to determine future risk of LQTS to be **eligible for coverage** when at least one of the following is present:

- 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.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers 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 to be **investigational**.*

BRUGADA SYNDROME

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

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Based on review of available data, the Company may consider genetic testing to confirm a diagnosis of Brugada Syndrome (BrS) when signs and/or symptoms consistent with BrS are present but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage**.

Based on review of available data, the Company may consider Genetic testing of asymptomatic individuals to determine future risk of BrS when patients have a close relative (ie, first-, second-, or third-degree relative) with a known BrS variant to be **eligible for coverage**.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for BrS for all other situations not meeting the criteria above to be **investigational**.*

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing to confirm a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) when signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage**.

Based on review of available data, the Company may consider genetic testing of asymptomatic individuals to determine future risk of CPVT to be **eligible for coverage** when at least one of the following criteria is present:

- 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.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for CPVT for all other situations not meeting the above criteria are not met to be **investigational**.*

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SHORT QT SYNDROME

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing of asymptomatic individuals to determine future risk of short QT syndrome (SQTS) when patients have a close relative (ie, first-, second- or third-degree relative) with a known SQTS variant to be **eligible for coverage**.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for SQTS for all other situations not meeting the criteria outlined above to be **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 2 or 3.

An index patient with suspected SQTS would be expected to have a shortened (<2 SD below from the mean) rate-corrected shortened QT interval (QTc). Cutoffs below 350 ms for men and 360 ms for women have been derived from population normal values (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.

Signs and symptoms suggestive of BrS include the presence of 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.

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.

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In cases where the family member's genetic diagnosis is unavailable, testing is available through either single-gene testing or panel testing. Panels for cardiac ion channelopathies are diagnostic 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 (ie, 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/Overview

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 SCD. These congenital cardiac channelopathies can be difficult to diagnose, and the implications of an incorrect diagnosis could be catastrophic.

The prevalence of any cardiac channelopathy is still ill-defined but is thought to be between 1:2000 and 1:3000 persons in the general population. Data pertaining to the individual prevalences of LQTS, CPVT, BrS, and SQTs are presented in Table 1. 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 electrocardiogram (ECG) is

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not diagnostic in all cases, and some secondary events (eg, electrolyte 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 (12)	15 (10)	42 (16) ^b	40 (24)

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 first-line 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 (ie, Schwartz criteria, see following subsection, Clinical Diagnosis). However, measurement of the QT interval is not well-standardized, and, in some instances, 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 subtypes 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.

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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 in Table 2. A score of 4 or greater indicates a high probability that LQTS is present; a score of 2 to 3, a moderate-to-high probability; and a score of 1 or less indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; and because there is still no perfect gold standard for diagnosing LQTS, the accuracy of this scoring system remains ill-defined.

Table 2. Diagnostic Scoring System for Long QT Syndrome

Schwartz Criteria	Points
Electrocardiographic findings	
QT corrected >480 ms	3
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 3 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 2 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 sexes 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 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. 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 2 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 (eg, ajmaline or flecainide). Two additional ECG patterns have been described (type

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2, type 3) but are less specific for the disorder. 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

Catecholaminergic polymorphic ventricular tachycardia 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. The prevalence of CPVT is estimated between 1 in 7000 and 1 in 10,000 persons. Catecholaminergic polymorphic ventricular tachycardia has a mortality rate of 30% to 50% by age 35 and is responsible for 13% of cardiac arrests in structurally normal hearts. Catecholaminergic polymorphic ventricular tachycardia was previously believed to be only manifest during childhood, but studies have now identified presentation between infancy and 40 years of age.

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 (ie, recurrence of syncope or arrhythmia), then flecainide (100-300 mg/d) may be added. If recurrence continues, an ICD may be necessary with optimized pharmacologic management continued postimplantation. 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

Short QT syndrome 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-segment is 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

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SQTS would be expected to have a shortened (less than 2 SD below from the mean) rate-corrected shortened QT interval (QTc). Cutoffs below 350 ms for men and 360 ms for women have been derived from population normal values. The length of the QT interval was not associated with severity of symptoms in 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 et al to aid in decision-making after a review of 61 SQTS cases (see Table 3).

Table 3. Diagnostic Scoring System for Short QT Syndrome

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
Variant 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 (eg, sotalol) is Kv11.1, which is coded for by KCNH2, the most common site for variants in SQTS (subtype 1). Treatment with quinidine (which is able to bind to both open and inactivated states of Kv11.1) is an appropriate QT-prolonging treatment. This treatment has been reported to reduce the rate of arrhythmias from 4.9% to 0% per year. For those who recur while on quinidine, an ICD is recommended.

Genetics of Cardiac Ion Channelopathies

Long QT Syndrome

There are more than 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

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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% to 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 et al propose a 3-tiered approach, first testing for a core group of 64 codons that have a high incidence of variants, followed by additional testing of less frequent variants.

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

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

Table 4: Genetics of Long QT Syndrome

Type of Long QT Syndrome	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	

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LQT6	RWS	21q22.1-22.2	<i>MIRP1, KNCE2</i>	Potassium	
LQT7	Andersen-Tawil syndrome	17.q23.1-q24.2	<i>KCNJ2</i>	Potassium	Episodic muscle weakness, congenital anomalies
LQT8	Timothy syndrome	12q13.3	<i>CACNA1C</i>	Calcium	Congenital heart defects, 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 al and Alders et al.

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 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, 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, 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 an *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% to 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. *CASQ2* (cardiac calsequestrin) and *TRDN*-related CPVT exhibit autosomal recessive

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inheritance. Some authors have reported heterozygotes for *CASQ2* and *TRDN* variants for rare, benign arrhythmias. *RYR2* variants represent the majority of CPVT cases (50%-55%), with *CASQ2* accounting for 1% to 2% and *TRDN* accounting for an unknown proportion of cases. The penetrance of *RYR2* variants 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 because Anderson-Tawil syndrome is rarely lethal.

Short QT syndrome

Short QT syndrome has been linked predominantly to variants in 3 genes (*KCNH2*, *KCNJ2*, *KCNQ1*). 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.

Genetic Testing for Cardiac Ion Channelopathies

Genetic testing can be comprehensive (testing for all possible variants in multiple gene) or targeted (testing for a single variant identified in a family member). For comprehensive testing, the probability that a specific variant is pathophysiologically significant is greatly increased if the same variant has been reported in other cases. A variant 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 variants. They are either variant that have previously been identified as pathologic (deleterious variants), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious variants).

Class II Possible deleterious variants. 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 variants 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

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Genetic Testing for Cardiac Ion Channelopathies

Policy # 00408

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Class I Deleterious and probable deleterious variants. They are either variant that have previously been identified as pathologic (deleterious variants), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious variants).

and are not reported in the results of the Familion test.

Genetic testing for specific disorders, which may include 1 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 1 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 each 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 Laboratories in the United States

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/Famillion(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 (eg, iGene Cardiac Panel [ApolloGen Inc., Irvine, CA]).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD).

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Rationale/Source

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) the analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) the clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) the clinical utility of the test, ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The evidence related to the clinical validity and utility of genetic testing for the cardiac channelopathies consists primarily of studies that evaluate yield of genetic testing and the impact of genetic testing on the diagnosis and subsequent management of a specific cardiac channelopathy. Many of the cardiac channelopathies lead to a common clinical outcome--increased risk of ventricular arrhythmias leading to an increased risk of SCD. Studies that evaluate the role of genetic testing for cardiac channelopathies as part of a diagnostic strategy in the evaluation of ventricular fibrillation or sudden cardiac death from an unknown cause are discussed separately.

Genetic Testing for the Diagnosis of a Specific Channelopathy

Analytic Validity

Commercially available genetic testing for cardiac channelopathies involves a variety of methods such as chip-based oligonucleotide hybridization, direct sequencing of protein-coding portions, and flanking regions of targeted exons, and next-generation sequencing. The analytic sensitivity of these methods for each condition is between 95% and 99%.

Clinical Validity

The true clinical sensitivity and specificity of genetic testing for specific cardiac ion channelopathies cannot be determined with certainty, as there is no independent gold standard for the diagnosis. The clinical diagnosis can be compared to the genetic diagnosis, and vice versa, but neither the clinical diagnosis nor the results of genetic testing can be considered an adequate gold standard.

Long QT Syndrome

Hofman et al performed the largest study, comparing clinical methods with genetic diagnosis using registry data. This study compared multiple methods for making the clinical diagnosis, including the Schwartz score, the Keating criteria, and the absolute length of the QTc with genetic testing. These data indicate that only a minority of patients with a genetic variant will meet the clinical criteria for LQTS. Using the most common clinical definition of LQTS (a Schwartz score of 4 or greater) only 19% of patients with a genetic variant met the clinical criteria. Even at lower cutoffs of the Schwartz score, the percentage of patients with a genetic variant who met clinical criteria was still relatively low, improving to only 48% when a cutoff of 2 or greater was used. When the Keating criteria were used for clinical diagnosis, similar results were obtained. Only 36% of patients with a genetic variant met the Keating criteria for LQTS. The best overall accuracy was obtained by using the length of the QTc as the sole criterion; however, even this criterion achieved only

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modest sensitivity at the expense of lower specificity. Using a cutoff of 430 ms or longer for the QT interval, a sensitivity of 72% and a specificity of 86% were obtained.

Tester et al completed the largest study to evaluate the percentage of individuals with a clinical diagnosis of LQTS that are found to have a genetic variant. The population in this study was 541 consecutive patients referred for evaluation of LQTS. A total of 123 patients had definite LQTS on clinical grounds, defined as a Schwartz score of 4 or greater, and 274 patients were found to have a LQTS variant. The genetic diagnosis was compared with the clinical diagnosis, defined as a Schwartz score of 4 or greater. Of the 123 patients with a clinical diagnosis of LQTS, 72% (89/123) were found to have a genetic variant.

The evidence on clinical specificity focuses on the frequency and interpretation of variants that are identified that are not known to be pathologic. If a variant is identified that is previously known to be pathologic, then the specificity of this finding is high. However, many variants are discovered on gene sequencing that are not known to be pathologic, and the specificity of these types of findings are lower. The rate of identification of variants is estimated to be in the range of 5% for patients who do not have LQTS.

A publication from the National Heart, Lung, and Blood Institute (NHLBI) GO Exome Sequencing Project (ESP) reported on the rate of sequence variations in a large number of patients without LQTS. The ESP sequenced all genome regions of protein coding in a sample of 5400 persons drawn from various populations, none of which included patients specifically with heart disease and/or channelopathies. Exome data were systematically searched to identify sequence variations that had previously been associated with LQTS, including both nonsense variations that are generally pathologic and missense variations, which are less likely to be pathological. A total of 33 such sequence variations were identified in the total population, all of them being missense variations. The percentage of the population that had at least one of these missense variations was 5.2%. No nonsense variations were associated with LQTS found among the entire population.

Brugada Syndrome

The yield of genetic testing using SCN5A variant testing in BrS is low.¹⁸ Analyses of patients with a high clinical suspicion of BrS provided a yield, between 25% and 35%, for a documented pathologic variant. Variant analysis of 27 SCN5A exons on cases from BrS databases at 9 international centers resulted in yields of 11% to 28%. The most commonly identified of the 8 known genes for BrS is SCN5A, which is found more in than 20% of genotype-positive cases. Variant analysis of 27 SCN5A exons on cases from BrS databases at 9 international centers resulted in yields of 11% to 28%.

National Heart, Lung, and Blood Institute ESP data identified a BrS prevalence of 4.7% when considering the maximal number of identified genes and variants, which is far higher than in the general population. Forty-seven percent of the variants found in the published literature were determined to be pathogenic, whereas 75% of the variants in ESP were determined to be pathogenic.

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In 2014, Hu et al evaluated the prevalence of *SCN10A* variants in 120 probands with BrS in more than 200 healthy controls. *SCN10A* encodes a voltage-gated sodium channel located adjacent to *SCN5A* on chromosome 3p21-22, which had previously been associated with pain perception but more recently was found in genome-wide association studies to be linked to cardiac conduction abnormalities. Seventeen *SCN10A* variants were identified in 25 probands, with a variant detection rate of 16.7% in BrS probands. Behr et al (2015) evaluated 7 candidate genes (*SCN10A*, *HAND1*, *PLN*, *CASQ2*, *TKT*, *TBX3*, *TBX5*) among 156 patients negative for *SCN5A* variants with symptoms indicative of BrS (64%) and/or a family history of sudden death (47%) or BrS (18%).³⁶ Candidate genes had been selected based on a previous genome-wide association study based on strength of association and biologic plausibility. Eighteen (11.5%) patients were found to have variants, most often in *SCN10A* (12/18 [67%]). Inquiry into other variants associated with BrS is ongoing, and expanded testing for variants in addition to *SCN5A* may improve the yield of genetic testing for BrS. Bezzina et al (2013) performed a genome-wide association study of 312 European individuals with BrS and 1115 controls from the 1000 Genomes Project.³⁷ Two significant association signals were identified: one at the *SCN10A* locus (rs10428132) and another near the *HEY2* gene (rs9388451).

Catecholaminergic Polymorphic Ventricular Tachycardia

Transgenomic's 4 gene panel is expected to identify between 65% and 75% of patients who have a high clinical suspicion of CPVT. A lower yield is obtained by GeneDX for their 3 gene panel that estimates more than 51% of CPVT positive individuals having a variant identified. Yield is affected if the patient's VT is bidirectional, which has a high yield, versus the more atypical presentation of IVF, which has a lower (15%) yield. Penetrance of the disease has been estimated at 60% to 70%.

The specificity of known pathologic variants for CPVT is not certain, but is likely to be high. A publication from the NHLBI ESP reported on sequence variations in a large number of patients without CPVT. The ESP sequenced all genome regions of protein coding in a sample of 6503 persons drawn from various populations who did not specifically have CPVT or other cardiac ion channelopathies. Exome data were systematically searched to identify missense variations that had previously been associated with CPVT. The authors identified 11% of the previously described variants in the ESP population in 41 putative CPVT cases. These data suggest that false-positive results are low, but the authors caution against attributing clinical CPVT to a single missense variant.

Short QT Syndrome

Limited data on the clinical validity of SQTs were identified in the peer reviewed literature due to the rarity of the condition. A precise genetic testing yield is unknown, but has been reported by Transgenomic as between 15% to 20% of cases with a high clinical suspicion for SQTs.

Section Summary

This evidence indicates that genetic testing will identify more individuals with possible cardiac ion channelopathies compared with clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic variant have the true clinical syndrome of the disorder. None of the

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clinical sensitivities for the assays in this policy are above 80%, suggesting there are additional variants associated with the channelopathies that have not been identified to date. Therefore, a negative genetic test is not definitive for excluding LQTS, CPVT, BrS, or SQTS.

Data on the clinical specificity were available for LQTS and very limited data for CPVT. The specificity varies according to the type of variant identified. For LQTS nonsense variants, which have the highest rate of pathogenicity, there are very few false positives among patients without LQTS, and therefore a high specificity. However, for missense variants, there is a rate of approximately 5% among patients without LQTS; therefore the specificity for these types of variant is lower and false-positive results do occur.

Clinical Utility

Long QT Syndrome

LQTS is a disorder that may lead to catastrophic outcomes, ie, sudden cardiac death in otherwise healthy individuals. Diagnosis using clinical methods alone may lead to underdiagnosis of LQTS, thus exposing undiagnosed patients to the risk of sudden cardiac arrest. For patients in whom the clinical diagnosis of LQTS is uncertain, genetic testing may be the only way to further clarify whether LQTS is present. Patients who are identified as genetic carriers of LQTS variants have a non-negligible risk of adverse cardiac events even in the absence of clinical signs and symptoms of the disorder. Therefore, treatment is likely indicated for patients found to have a LQTS variant, with or without other signs or symptoms.

Treatment with β -blockers has been demonstrated to decrease the likelihood of cardiac events, including sudden cardiac arrest. Although there are no controlled trials of β -blockers, there are pre-post studies from registry data that provide evidence on this question. Two such studies reported large decreases in cardiovascular events and smaller decreases in cardiac arrest and/or sudden death after starting treatment with beta-blockers. These studies reported a statistically significant reduction in cardiovascular events of more than 50% following initiation of β -blocker therapy. There was a reduction of similar magnitude in cardiac arrest/sudden death, which was also statistically significant.

Sodium-channel blockers (eg, mexiletine) are sometimes used, particularly in those with *SCN5A* variants. In a 2016 retrospective cohort study of 34 LQT3 patients with a pretherapy median QTc interval of 509 ms, mexiletine treatment for a median 36 months was associated with a statistically significant reduction in QTc (by 63 ms, $p < 0.001$), as well as percentage and rate of arrhythmic events. The annual rate of arrhythmic events was 10.3% before treatment and 0.7% after treatment initiation ($p < 0.001$).

Treatment with an ICD is available for patients who fail or cannot take β -blockers. One published study reported on outcomes of treatment with ICDs. This study identified patients in the LQTS registry who had been treated with an ICD at the discretion of their treating physician. Patients in the registry who were not treated with an ICD, but had the same indications, were used as a control group. The authors reported that patients treated with an ICD had a greater than 60% reduction in cardiovascular outcomes.

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One study reported on changes in management that resulted from diagnosing LQTS by testing relatives of affected patients with known LQTS (cascade testing). Cascade testing of 66 index patients with LQTS led to the identification of 308 variant carriers. After a mean follow-up of 69 months, treatment was initiated in 199 of 308 (65%) of carriers. Beta-blockers were started in 163 patients, a pacemaker was inserted in 26 patients, and an ICD was inserted in 10 patients. All carriers received education on lifestyle issues and avoidance of drugs that can cause QT prolongation.

Two studies evaluated the psychologic effects of genetic testing for LQTS. Hendriks et al studied 77 patients with an LQTS variant and their 57 partners. Psychologic testing was performed after the diagnosis of LQTS had been made and repeated twice over an 18-month period. Disease-related anxiety scores were increased in the index patients and their partners. This psychologic distress decreased over time but remained elevated at 18 months. Andersen et al conducted qualitative interviews with 7 individuals found to have LQTS variants. They reported that affected patients had excess worry and limitations in daily life associated with the increased risk of sudden death, which was partially alleviated by acquiring knowledge about LQTS. The greatest concern was expressed for their family members, particularly children and grandchildren.

For determining LQTS subtype or specific variant, the clinical utility is less certain. The evidence suggests that different subtypes of LQTS may have variable prognosis, thus indicating that genetic testing may assist in risk stratification. Several reports have compared rates of cardiovascular events in subtypes of LQTS. These studies report that rates of cardiovascular events differ among subtypes, but there is no common pattern across all studies. Three of the 4 studies reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba et al reported that patients with LQT1 have higher event rates than patients with LQT2.

More recent research has identified specific sequence variants that might be associated with higher risk of adverse outcomes. Albert et al examined genetic profiles from 516 cases of LQTS included in 6 prospective cohort studies. The authors identified 147 sequence variations found in 5 specific cardiac ion channel genes and tested the association of these variations with SCD. Two common intronic variations, one in the *KCNQ1* gene and one in the *SCN5A* gene, were most strongly associated with sudden death. Migdalovich et al correlated gender-specific risks for adverse cardiac events with the specific location of variants (pore-loop vs non-pore-loop) on the *KCNH2* gene in 490 males and 676 females with LQTS. They reported that males with pore-loop variants had a greater risk of adverse events (hazard ratio [HR], 2.18; $p=0.01$) than males without pore-loop variants, but that this association was not present in females. Costa et al combined information on variant location and function with age and sex to risk-stratify patients with LQT1 by life-threatening events. Ruwald et al evaluated differences in outcomes associated with nonsense variants (compared with missense variants) among 1090 patients with genetically confirmed type 1 LQTS (*KCNQ1* variants). Cardiac events were comprised of the composite outcome of syncope, aborted cardiac arrest, SCD, or shock from an ICD. Non-missense stop codon variants were associated with the lowest risk of a cardiac event (40-year event rate, 27%), while non-c-loop, frameshift, splice, and all other non-missense

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variants had intermediate risk (40-year event rate, 44%, 46%, 43%, and 39%, respectively), and missense c-loop variants had the highest risk (40-year event rate, 70%).

Other research has reported that the presence of genetic variants at different locations can act as disease “promoters” in patients with LQTS variants. Amin et al reported that 3 single-nucleotide polymorphisms (SNPs) in the untranslated region of the *KCNQ1* were associated with alterations in the severity of disease. Patients with these SNPs had less severe symptoms and a shorter QT interval compared with patients without the SNPs. Park et al examined a large LQTS kindred that had variable clinical expression of the disorder. Patients were classified into phenotypes of mild and severe LQTS. Two SNPs were identified that were associated with severity of disease, and all patients classified as having a severe phenotype also had one of these 2 SNPs present. Earl et al identified 4 SNPs at 2 risk loci, *NOS1AP* and *KCNQ1*, which were associated with increased risk of death or resuscitated cardiac death in a cohort of 273 patients with LQTS. In an analysis of 639 patients with *KCNH2* variants, Kolder et al also identified 3 SNPs at the *NOS1AP* locus as being associated with the QTc interval.

Some studies that report outcomes of treatment with β -blockers also report outcomes by specific subtypes of LQTS. Priori et al reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of β -blocker therapy. There was a decrease in event rates in all LQTS subtypes, with a similar magnitude of decrease in each subtype. Moss et al also reported pre-post event rates for patients treated with β -blocker therapy. This study indicated a significant reduction in event rates for patients with LQT1 and LQT2 but not for LQT3. This analysis was also limited by the small number of patients with LQT3 and cardiac events prior to β -blocker treatment (4/28). Sauer et al evaluated differential response to β -blocker therapy in a Cox proportional hazards analysis. They reported an overall risk reduction in first cardiac event of approximately 60% (HR=0.41; 95% confidence interval [CI], 0.27 to 0.64) in adults treated with β -blockers and an interaction effect by genotype. Efficacy of β -blocker treatment was worse in those with LQT3 genotype ($p=0.04$) compared with LQT1 or LQT2. There was no difference in efficacy between genotypes LQT1 and LQT2.

There is also some evidence on differential response to β -blockers according to different specific type and/or location of variants. Barsheset et al examined 860 patients with documented variants in the *KCNQ1* gene and classified the variants according to type and location. Patients with missense variants in the cytoplasmic loop (c-loop variants) had a more marked risk reduction for cardiac arrest following treatment with β -blockers than patients with other variants (HR=0.12; 95% CI, 0.02 to 0.73; $p=0.02$).

Brugada Syndrome

The diagnostic yield of genetic testing for BrS limits its diagnostic capability. A finding of a genetic variant is not diagnostic of the disorder but is an indicator of high risk for development of BrS. The diagnostic criteria for BrS do not presently include the presence of a genetic variant. Furthermore, treatment is based on the presence of symptoms such as syncope or documented ventricular arrhythmias. Treatment is primarily with an implantable ICD, which is reserved for high-risk patients. However, for family members of patients with a known BrS variant, a negative test can rule out the disorder.

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Risk stratification criteria are currently inadequate, and the contribution of genetic sequencing is limited to identification of *SCN5A* variants that occur in less than 25% of cases. Meregalli et al investigated whether type of *SCN5A* variant is related to severity of disease and found that those variants that caused more severe reductions in peak sodium current had the most severe phenotype. However, a meta-analysis of 30 BrS prospective studies found family history of SCD and presence of an *SCN5A* variant were insufficient to predict risk for cardiac events in BrS.

Catecholaminergic Polymorphic Ventricular Tachycardia

The clinical utility for genetic testing in CPVT follows a similar chain of logic as that for LQTS. In patients for whom the clinical diagnosis can be made with certainty, there is limited utility for genetic testing. However, there are some patients in whom signs and symptoms of CPVT are present, but for whom the diagnosis cannot be made with certainty. In this case, documentation of a pathologic variant that is known to be associated with CPVT confirms the diagnosis. When the diagnosis is confirmed, treatment with β -blockers is indicated, and lifestyle changes are recommended. Although high-quality outcome studies are lacking to demonstrate a benefit of medication treatment, it is very likely that treatment reduces the risk of sudden cardiac death. Therefore, there is clinical utility.

There is currently no direct method of genotype-based risk stratification for management or prognosis of CPVT. However, testing can have important implications for all family members for presymptomatic diagnosis, counseling, or therapy. Asymptomatic patients with confirmed CPVT should also be treated with β -blockers and lifestyle changes. In addition, CPVT has been associated with sudden infant death syndrome and some investigators have considered testing at birth for prompt therapy in infants who are at risk due to CPVT in close family members.

Short QT Syndrome

No studies were identified that provide evidence for the clinical utility of genetic testing for SQTs. Clinical sensitivity for the test is low, with laboratory testing providers estimating a yield as low as 15%.

Section Summary: Clinical Utility of Genetic Testing for the Diagnosis of a Specific Cardiac Ion Channelopathy

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 ICD. As a result, confirming the diagnosis is likely to lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and SCD. The clinical utility of testing is also high for close relatives of patients with known cardiac ion channel variants, because these individuals should also be treated if they are found to have a pathologic variant. For BrS, the clinical utility is less certain, but there is potential for genetic testing to change treatment decisions by stratifying patients for need for ICD. For SQTs, the clinical utility is uncertain because there is no clear link between the establishment of a definitive diagnosis and a change in management that will improve outcomes.

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Strategy for Genetic Testing in the Setting of Sudden Cardiac Arrest or Ventricular Fibrillation

In addition to studies reporting the yield of testing for specific syndromes, a smaller body of evidence exists on the yield of a diagnostic strategy that may include genetic testing for 1 or more cardiac ion channelopathies in cases of SCD, sudden cardiac arrest, or ventricular fibrillation (VF) where a specific clinical diagnosis has not been made.

Evaluation of Family Members of Probands with SCD

In the largest study identified, Kumar et al assessed the yield of a comprehensive evaluation, including targeted genetic testing, in a cohort of 109 families (including 411 relatives) with autopsy-negative sudden unexplained death syndrome (SUDS), termed sudden arrhythmic death syndrome (SADS). Sudden arrhythmic death syndrome was defined as a sudden unexpected death in an individual with no known history of cardiac disease for whom death occurred within 1 hour of symptom onset or within 24 hours of the individual being seen alive and well and for whom a full postmortem examination, including toxicologic investigations, could not identify the cause of death. All families of SADS probands underwent a systematic protocol that included a review of the history of the proband and family members, along with physical exam, 12-lead ECG, exercise stress test, and transthoracic echocardiography for family members, with additional evaluation guided by the initial studies. If a clinical phenotype was proven or suspected during the cardiologic evaluation of the family members, targeted genetic testing of the candidate gene(s) was performed on genomic DNA extracted from the deceased individual or the closest surviving affected relative of the deceased individual. A clinical diagnosis was made in 20 families (18%), most commonly LQTS (15%), followed by BrS (3%) and CPVT (1%). Patients with suspected LQTS underwent candidate gene testing with Sanger sequencing of *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ2* for LQTS, while those with suspected BrS underwent sequencing of *SCN5A* and those with suspected CPVT underwent sequencing of *RYR2* and *CASQ2*. Molecular genetic testing was performed in 17 of 20 families and a pathogenic variant found in 6 families (yield, 35%).

Behr et al assessed the yield of comprehensive evaluation, including genetic testing, if indicated, of families of individuals with SADS. Sudden arrhythmic death syndrome cases were defined when sudden and unexpected deaths occurred in apparently healthy adults, and a coroner's postmortem exam, toxicologic screen, and an expert cardiac autopsy failed to reveal any underlying cause of death. Fifty-seven SADS probands and their families were evaluated. In 30 of 57 (53%) families, definite and possible or probable inherited heart disease was identified, with definite LQTS in 13, possible/probable LQTS in 3, and BrS in 5. For inherited arrhythmia syndromes, genetic testing was performed via PCR of published exons and flanking introns for the following genes: all exons of *KCNQ1*, *KCNE1*, *KCNH2*, *KCNE2*, *SCN5A*, *ANK2*, *KCNJ2*, *CAV3*, and *CASQ2*, and selected exons of hRyR2. Genetic testing was obtained in 24 SADS probands, 5 of whom (21%) were found to have a disease-causing variant. Disease-causing variants that cosegregated with phenotype in a pedigree were detected in 2 of 6 (33%) probands, with a subsequent familial diagnosis of definite or possible/probable LQTS.

Tan et al assessed the yield of cardiologic and genetic evaluations in surviving relatives of individuals with SUDS in a cohort of 43 families with at least 1 SUDS victim who died at the age of 40 or younger. Sudden

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unexplained death syndrome was defined as death in a person with no family history of known heart disease that occurred suddenly (1 hour after complaints or within 12 hours of the victim being seen alive) and was unexplained because a relevant documented medical history (eg, syncope, seizures, palpitations) and antemortem cardiologic tests (eg, ECG) were absent and detailed postmortem macroscopic and microscopic examinations of the heart and its vessels either were not performed or were performed but initially did not provide an explanation. All surviving relatives underwent testing with a 12-lead resting ECG, an exercise ECG, and Doppler echocardiography; additional investigations in the surviving family members were determined by the relevant circumstances of the index patients. In 17 of 43 families, an inherited disease and likely cause of death in the SUDS victim was identified. In 12 families, the diagnosis involved a primary electrical disease, with diagnosis based on resting ECG, exercise ECG, or flecanide challenge. Among those 12 families, 5 were found to have CPVT, 4 had LQTS, 2 had BrS, and 1 had a mixed phenotype of LQTS and BrS. Molecular genetic testing was positive in 10 families, with a clinical diagnosis of a primary electrical disease.

Wong et al assessed the yield of clinical history and cardiac and genetic evaluations in 112 pediatric relatives of 61 probands with SADS. All subjects underwent initial cardiac investigations included a 12-lead ECG, transthoracic 2-dimensional echocardiogram, exercise ECG when possible, and 24-hour Holter monitoring, with additional investigations, including signal averaged ECG, cardiac MRI, and ajmaline provocation tests as indicated. A probable diagnosis of an inherited cardiac condition was made in 18 of 61 families (29.5%), most often (15/18 [83%]) after evaluation of an adult relative of the proband. BrS was the most common diagnosis, affecting 13 families (72%), with LQTS in 3 families (17%) and CPVT in 2 (11%). Targeted genetic diagnosis was undertaken in 14 of 18 (78%) families with an inherited cardiac condition diagnosis. Two of 10 families (20%) with BrS were identified with an SCN5A variant. The yield of genetic testing was 50% for both LQTS (1 *KCNH2* variant detected) and CPVT (1 *RyR2* variant detected).

Bagnall et al (2016) reported prospectively collected data on all cases of SCD in children and young adults (up to age 35) in Australia and New Zealand from 2010 to 2012. Of the 490 cases of SCD, 198 (40%) were unexplained after autopsy. Of the unexplained deaths, 113 underwent genetic analysis of at least 59 cardiac arrhythmia and cardiomyopathy genes. Thirty-six pathogenic and probably pathogenic variants were found in 31 cases of unexplained SCD. Screening of families was performed in 91 of the 198 families in which an unexplained SCD occurred. A clinical diagnosis was established in 12 of the 91 families; inherited arrhythmogenic diseases were identified in 7 families.

Evaluation of Individuals with Cardiac Arrest

Krahn et al reported outcomes from a systematic assessment of patients with apparently unexplained cardiac arrest and no evidence of cardiac disease, which included cardiac magnetic resonance imaging (MRI), signal-averaged ECG, exercise testing, drug challenge, and selective electrophysiologic testing, with targeted genetic testing as indicated based on disease phenotype. Sixty-three patients were evaluated, of whom 35 (56%) received a specific diagnosis after evaluation. Among the 35 diagnosed patients, LQTS was detected in 8 patients (23%), CPVT in 8 (23%), and BrS in 3 (9%); the remainder had arrhythmogenic right ventricular cardiomyopathy, coronary spasm, or and myocarditis. Targeted genetic testing was

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performed on the basis of phenotype detection in patients after systematic clinical testing. Genetic testing was performed on suspected culprit genes (for LQTS: *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*; for BrS: *SCN5A*; for arrhythmogenic right ventricular cardiomyopathy: *Pkp2*, *Dsp*; for CPVT: *RyR2*-selected exons 2 to 4, 6 to 15, 17 to 20, 39 to 49, 83, 84, 87 to 97, and 99 to 105). Targeted genetic testing demonstrated evidence of causative variants in 9 of 19 patients tested (47%). The yield of genetic testing in unselected patients with unexplained cardiac arrest is likely lower.

In the Kumar et al study described above, the authors also evaluated the yield of a comprehensive evaluation, including targeted genetic testing, in a cohort of 52 families (including 91 relatives) with a proband with unexplained cardiac arrest. Proband was comprehensively evaluated with ECG, echocardiography, coronary angiography, and Holter monitoring, with provocation testing in one-third. A clinical diagnosis was made in 32 (62%) families with unexplained cardiac arrest, most commonly LQTS (n=11), followed by BrS (n=9), CPVT (n=3), early repolarization (n=3), hypertrophic cardiomyopathy (n=3), and SQTS (n=1). Targeted genetic evaluation of family members with a proven or suspected clinical phenotype led to a molecular diagnosis in 48%.

Jimenez-Jaimez et al reported the results of a sequential testing protocol among 35 unexplained cardiac arrest survivors. Included patients had a history of VF with no diagnostic findings on ECG, no pathologic findings on echocardiogram, and no angiographic lesions with 50% or more stenosis on coronary catheterization. Sequential testing included pharmacologic studies with flecainide and epinephrine with or without exercise stress testing, followed by familial evaluation with echocardiogram and ECG if pharmacologic studies were negative, and then by genetic testing with a next-generation sequencing panel of 126 genes related to cardiomyopathies and channelopathies if other testing was negative. A firm diagnosis was made in 18 cases (51.4%), with 5 cases (4 cases of CPVT, 1 case of SQTS) made on the basis of genetic testing. All diagnoses of LQTS (n=3) and BrS (n=7) were made on the basis of pharmacologic testing or familial evaluation.

Section Summary: Strategy for Genetic Testing in the Setting of Sudden Cardiac Arrest or VF

The evidence on the clinical validity of genetic testing for cardiac ion channelopathies in evaluating family members of probands with unexplained cardiac death or individuals with unexplained cardiac arrest consists of cohort studies that describe the yield of genetic testing in patients who have a suspected clinical diagnosis based on history and preliminary testing. These studies generally describe the yield of an approach to diagnostic testing that includes genetic testing. In all of the studies identified, genetic testing was obtained only after a specific diagnosis was suspected based on other findings; no evidence on the yield of genetic testing in unselected families with a family history of unexplained cardiac death or cardiac arrest was identified. The yield of targeted genetic testing ranged from 20% to 80%, although in most studies the yield was less than 50%.

There is potential for utility of genetic testing of individuals or family members in the setting of a proband with sudden cardiac death or unexplained cardiac arrest potentially due to a cardiac ion channelopathy. However, all identified studies related to the yield of testing in the setting used testing only after a specific

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channelopathy was suspected based on history or ancillary testing. Genetic testing can be part of a diagnostic strategy for patients with unexplained sudden cardiac arrest, but it should be preceded a thorough clinical evaluation of the survivor, if available, and family members to support suspicion of a specific clinical diagnosis.

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 studies reporting on the yield of testing among patients with clinically suspected or clinically diagnosed disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 72% to 80% of LQTS. Most are point variants identified by gene sequencing analysis; however, a small number are deletions and duplications best identified by CMA analysis. The analytic validity of testing for point variants by sequence analysis is high, while the analytic validity of testing for deletions/duplications by CMA analysis is less certain. The clinical validity of testing in LQTS is high, in the range of 70% to 80%. The clinical utility of genetic testing for LQTS is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. A definitive diagnosis of either channelopathy leads to treatment with β -blockers in most cases, and sometimes to treatment with an ICD. As a result, confirming the diagnosis is likely to lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and sudden cardiac death. There is a strong chain of evidence to suggest that testing for variants associated with LQTS in individuals who are suspected to have these disorders, but in whom the diagnosis cannot be made by other methods, leads to improved outcomes. Although for LQTS there is evidence suggesting that different genotypes are associated with varying risk of sudden cardiac death, there is insufficient evidence to conclude that the information from genetic testing on risk assessment leads to changes in clinical management. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with close relative(s) with a known LQTS variant who receive genetic testing for variants associated with congenital LQTS, the evidence includes studies reporting on changes in management that resulted from diagnosing LQTS by testing relatives of affected patients with known LQTS and studies reporting testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. The clinical utility of testing is high for close relatives of patients with known LQTS variants, because these individuals should also be treated if they are found to have a pathologic variant. In addition, a negative test in the setting of a known familial variant should have a high negative predictive value. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Brugada Syndrome

For individuals with suspected BrS who receive genetic testing for variants associated with BrS, the evidence includes studies reporting on testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. Although the analytic validity of testing for is likely to be high, the clinical validity is lower: a genetic variant can be identified in approximately 25% to 35% of BrS. For BrS management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in a symptomatic proband without a definitive diagnosis. It is not clear that that genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic with close relative(s) with a known BrS variant who receive genetic testing for variants associated with congenital BrS, the evidence includes studies reporting on testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. For BrS, management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in an individual with family members with a known variant. However, a negative test would allow family members to defer further testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Catecholaminergic Polymorphic Ventricular Tachycardia

For individuals with suspected CPVT who receive genetic testing for variants associated with congenital CPVT, the evidence includes studies reporting on testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 51% to 75% of CPVT patients. The analytic validity of testing for point variants by sequence analysis is high, while the analytic validity of testing for deletions/duplications by CMA analysis is less certain. The clinical validity of testing in CPVT is moderate, in the range of 50% to 75%. The clinical utility of genetic testing for CPVT is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. Confirming the diagnosis of CPVT is likely to lead to a health outcome benefit by initiating changes in management that reduce the risk for ventricular arrhythmias and sudden cardiac death. There is a strong chain of evidence to suggest that testing for variants associated with CPVT in individuals who are suspected to have these disorders, but in whom the diagnosis cannot be made by other methods, leads to improved outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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For individuals who are asymptomatic with close relative(s) with a known CPVT variant who receive genetic testing for variants associated with congenital CPVT, the evidence includes studies reporting testing yields among patients with clinically suspected disorders, a history of sudden cardiac arrest, and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. The clinical utility of testing is high for close relatives of patients with known CPVT variants, because these individuals should also be treated if they are found to have a pathologic variant. In addition, a negative test in the setting of a known familial variant should have a high negative predictive value. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Short QT Syndrome

For individuals with suspected SQTs who receive genetic testing for variants associated with SQTs, the evidence includes limited data on testing yields among patients with clinically suspected disorders and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. Although the analytic validity of testing for is likely to be high, the clinical validity is lower: a genetic variant can be identified in approximately 15% to 20% of SQTs patients. For SQTs, management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in a symptomatic proband without a definitive diagnosis. It is not clear that that genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic with close relative(s) with a known with a known SQTs variant who receive genetic testing for variants associated with congenital SQTs, the evidence includes studies reporting on testing yields among patients with clinically suspected disorders and/or family members with sudden cardiac death. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. For SQTs, management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about changes in management based on genetic testing in an individual with family members with a known variant. It is not clear that 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.

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Policy History

Original Effective Date: 04/23/2014

Current Effective Date: 01/17/2018

04/03/2014 Medical Policy Committee review

04/23/2014 Medical Policy Implementation Committee approval. New policy.

01/01/2015 Coding Update

10/08/2015 Medical Policy Committee review

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Louisiana

Genetic Testing for Cardiac Ion Channelopathies

Policy # 00408

Original Effective Date: 04/23/2014

Current Effective Date: 01/17/2018

- 10/21/2015 Medical Policy Implementation Committee approval. Added INV statement that genetic testing for LQTS or CPVT is investigational for all situations when criteria are not met, rationale and references updated
 - 01/07/2016 Medical Policy Committee review
 - 01/22/2016 Medical Policy Implementation Committee approval. Added eligibility statements for diagnostic testing for Brugada syndrome and testing of an asymptomatic individual with a known familial variant associated with Brugada syndrome or SQTS.
 - 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
 - 01/05/2017 Medical Policy Committee review
 - 01/18/2017 Medical Policy Implementation Committee approval. No change to coverage.
 - 01/04/2018 Medical Policy Committee review
 - 01/17/2018 Medical Policy Implementation Committee approval. No change to coverage.
- Next Scheduled Review Date: 01/2019

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Code Type	Code
CPT	81403, 81405, 81406, 81407, 81408 , 81413, 81414
HCPCS	S3861
ICD-10 Diagnosis	I45.81 Q23.8 Q23.9 Q24.8 Z13.79 Z13.89

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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