

Medical Policy



Title: Genetic Testing for Cardiac Ion Channelopathies

Professional

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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.

Cardiac ion channelopathies are the result of 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. The regulation of these ions is essential for the maintenance of a normal cardiac action potential. This group of disorders is associated with ventricular arrhythmias and an increased risk of sudden cardiac death (SCD). These congenital cardiac channelopathies can be difficult to diagnose, and the implications of an incorrect diagnosis could be catastrophic.

The prevalence of any cardiac channelopathy is still ill-defined but is thought to be between 1:2000 and 1:3000 persons in the general population.⁵ 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 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 (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	BrS	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.⁶

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

^aType 1 ECG pattern

^bType 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 sudden cardiac death. Management has focused on the use of β -blockers as first-line treatment, with pacemakers or implantable cardiac defibrillators (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 one 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 1–2% 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).⁷ However, measurement of the QT interval is not well-standardized, and, in some instances, patients may be considered borderline cases.⁸

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 mutations in different genes as indicated here.⁹ In addition, typical ST-T wave patterns are also suggestive of specific subtypes.¹⁰ Some of the genetic subtypes are associated with abnormalities outside the cardiac conduction system.

Clinical Diagnosis

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS.⁷ The most recent version of this scoring system is shown 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 LQTS¹¹

Schwartz Criteria	Points
Electrocardiographic findings	
-QT _c >480 ms	3
-QT _c 460-470 ms	2
-QT _c <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 LQTS	1
-Unexplained sudden death in immediate family members <30 y of age	0.5

LQTS: long QT syndrome; QT_c: QT corrected.

Brugada Syndrome

BrS is characterized by cardiac conduction abnormalities that increase the risk of syncope, ventricular arrhythmia, and sudden cardiac death. The disorder primarily manifests during adulthood, although ages between 2 days and 85 years have been reported.¹² 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.⁵ For both sexes there is an equally high risk of ventricular arrhythmias or sudden death.¹³ Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.¹⁴ Management has focused on the use of

implantable cardiac defibrillators (ICD) in patients with syncope or cardiac arrest and isoproterenol for electrical storms. Patients who are asymptomatic can be closely followed to determine if ICD implantation is necessary.

Clinical Diagnosis

The diagnosis of BrS is made by the presence of a type 1 Brugada pattern on the ECG in addition to other clinical features.¹⁵ 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).¹⁶ Two additional ECG patterns have been described (type 2, type 3) but are less specific for the disorder.¹⁷ The diagnosis of BrS is considered definite when the characteristic ECG pattern is present with at least one of the following clinical features: documented ventricular arrhythmia, sudden cardiac death in a family member ←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 VT precipitated by exercise or emotional stress.¹⁸ The prevalence of CPVT is estimated between 1 in 7000 and 1 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.¹⁸ CPVT was previously believed to be only manifest during childhood but studies have now identified presentation between infancy and 40 years of age.¹⁹

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/day) may be added. If recurrence continues, an ICD may be necessary with optimized pharmacologic management continued postimplantation.²⁰ 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%).¹¹ 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.²¹

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.²² 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.¹⁸

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 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.¹¹

Clinical Diagnosis

Patients generally present with syncope, presyncope or cardiac arrest. An ECG with a corrected QT interval <330 ms, sharp T-wave at the end of the QRS complex, and a brief or absent ST-segment is characteristic of the syndrome.²³ 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. Recently a diagnostic scoring system has been proposed by Gollob et al to aid in decision-making after a review of 61 SQTS cases (Table 3).²⁴

Table 3. Diagnostic Scoring System for SQTS¹¹

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

QT_c: QT corrected; SCD: sudden cardiac death; SQTS: short QT syndrome; VF: ventricular fibrillation; VT: ventricular tachycardia

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.²⁵ 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 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 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.²⁶ 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 3-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.²⁷

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.²⁸

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 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	
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 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	

Type of Long QT Syndrome	Other Names	Chromosome Locus	Mutated Gene	Ion Current(s) Affected	Associated Findings
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 al²⁹ and Alders et al.³⁰

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 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.¹³ 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, but of these *SCN5A* is the most important, accounting for more than an estimated 20% of cases.¹⁹ The other genes are of minor significance and account together for approximately 5% of cases.¹⁸ The absence of a positive test does not indicate the absence of BrS with more than 65% of cases not having an identified genetic cause. Penetrance of BrS among persons with a *SCN5A* mutation is 80% when undergoing ECG with sodium channel blocker challenge and 25% when not using the ECG challenge.¹³

Catecholaminergic Polymorphic Ventricular Tachycardia

Mutations 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 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.²⁰ *RYR2* mutations 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* mutations is approximated at 83%.²⁰

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.¹⁹ 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 as Anderson-Tawil syndrome is rarely lethal.

Short QT syndrome

SQTS has been linked predominantly to mutations in 3 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 genes) 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 as to 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. These 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 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 which genes to include in the assays.

Table 5. Examples of Cardiac Ion Channelopathy Genetic Testing Laboratories in the United States

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

^a AmbryGen's NGS cardiovascular panel, which included testing for LQTS and BrS, is no longer being offered as of November 2014. A subsequent version will be released and it will include testing for duplications and deletions.

^b Indicates multigene panel available for sudden cardiac death.

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

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]).

Regulatory Status

There are no assay kits approved by the U.S. Food and Drug Administration (FDA) for genetic testing for cardiac ion channelopathies. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

POLICY

- A. Genetic testing in patients with suspected congenital long QT syndrome (LQTS) may be considered **medically necessary** for the following indications:

Individuals who do not meet the clinical criteria for LQTS (i.e., those with a Schwartz score less than 4), but who have:

1. a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation

OR

2. a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable

OR

3. signs and/or symptoms indicating a moderate-to-high pretest probability* of LQTS.

*Determining the pretest probability of LQTS is not standardized. An example of a patient with a moderate-to-high pretest probability of LQTS is a patient with a Schwartz score of 2–3.

- B. Genetic testing for LQTS to determine prognosis and/or direct therapy in patients with known LQTS is considered **not medically necessary**.
- C. Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered **medically necessary** for patients who do not meet the clinical criteria for CPVT but who have:
 - 1. a close relative (i.e. first-, second-, or third-degree relative) with a known CPVT mutation
OR
 - 2. a close relative diagnosed with CPVT by clinical means whose genetic status is unavailable
OR
 - 3. signs and/or symptoms indicating a moderate-to-high pretest probability of CPVT
- D. Genetic testing for Brugada syndrome is considered **experimental / investigational**.
- E. Genetic testing for short QT syndrome is considered **experimental / investigational**.

Policy Guidelines

Testing Strategy

- 1. In general, testing for patients with suspected congenital LQTS or CPVT should begin with a known familial mutation, if one has been identified.
- 2. 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 BCBSKS medical policy titled General Approach to Evaluating the Utility of Genetic Panels. 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).
- 3. 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.¹⁻⁴ If, after a comprehensive evaluation, a diagnosis of CPVT or LQTS is suspected but not definitive (ie, if there is a moderate-to-high pretest probability of either condition), genetic testing could be considered.

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RATIONALE

The most recent update covers the period through October 30, 2014.

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 mutation that is present or in excluding a mutation 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 sudden cardiac death. 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% to 99%.¹⁴

Clinical Validity

The true clinical sensitivity and specificity of genetic testing for 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 al³¹ 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 corrected QT (QTc) with genetic testing. These data indicate that only a minority of patients with a genetic

mutation 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 mutation met the clinical criteria. Even at lower cutoffs of the Schwartz score, the percentage of patients with a genetic mutation 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 mutation 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 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% was obtained.

Tester et al³² completed the largest study to evaluate the percent of individuals with a clinical diagnosis of LQTS that are found to have a genetic mutation. 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 mutation. The genetic diagnosis was compared to the clinical diagnosis, defined as a Schwartz score of 4 or greater. Of all 123 patients with a clinical diagnosis of LQTS, 72% (89/123) were found to have a genetic mutation.

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 mutation 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.³³

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.³⁴ 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 that 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 percent 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.

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 mutation 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%.³⁵

The specificity of known pathologic mutations for CPVT is not certain, but likely to be high. A publication from the NHLBI ESP reported on sequence variations in a large number of patients without CPVT.³⁶ 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.

Brugada Syndrome

The yield of genetic testing in BrS is low.²³ Analyses of patients with a high clinical suspicion of BrS provided a yield of between 25% to 35% for a documented pathologic mutation.¹⁴ Mutational analysis of 27 *SCN5A* exons on cases from BrS databases at 9 international centers resulted in yields of 11% to 28%.³⁷ The most commonly identified of the 8 identified genes for BrS is *SCN45* which is found in more than 20% of genotype positive cases.

NHLBI ESP data identified a BrS prevalence of 4.7% when considering the maximal number of identified genes and mutations 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.³⁸

In 2014, Hu et al evaluated the prevalence of *SCN10A* variants in 120 probands with BrS in more than 200 healthy controls.³⁹ *SCN10A* encodes a voltage-gated sodium channel located adjacent to *SCN5A* on chromosome 3p21-22, and had previously been associated with pain perception but more recently was found in genome-wide association studies to be associated with cardiac conduction abnormalities. Seventeen *SCN10A* mutations were identified in 25 probands, with a mutation detection rate of 16.7% in BrS probands. Expanded testing for mutations in addition to *SCN5A* may improve the yield of genetic testing for BrS.

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.³⁷

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 mutation have the true clinical syndrome of the disorder. None of the clinical sensitivities for the assays in this policy are above 80% suggesting that there are additional mutations 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 at the present time.

Data on the clinical specificity was available for LQTS and very limited data for CPVT. The specificity varies according to the type of mutation identified. For LQTS nonsense mutations, 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 mutations, there is a rate

of approximately 5% among patients without LQTS; therefore the specificity for these types of mutation 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 mutations 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 mutation, 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 β -blockers.⁴⁰⁻⁴¹ 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.

Treatment with an implantable cardioverter-defibrillator (ICD) is available for patients who fail or cannot take β -blockers. One published study reported on outcomes of treatment with ICDs.⁴² 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.

One study reported on changes in management that resulted from diagnosing LQTS by testing relatives of affected patients with known LQTS (cascade testing).⁴³ Cascade testing of 66 index patients with LQTS led to the identification of 308 mutation 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 psychological effects of genetic testing for LQTS. Hendriks et al studied 77 patients with a LQTS mutation and their 57 partners.⁴⁴ 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 mutations.⁴⁵ 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 mutation, 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.^{41,46-48} These studies report that rates of cardiovascular events differ among subtypes, but there is not a common pattern across all studies. Three of the 4 studies^{41,46,47} reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba et al⁴⁸ 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 al⁴⁹ 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 sudden cardiac death. Two common intronic variations, one in the *KCNQ1* gene and one in the *SCN5A* gene were most strongly associated with sudden death. Migdalovich et al⁵⁰ correlated gender-specific risks for adverse cardiac events with the specific location of mutations (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 mutations had a greater risk of adverse events (hazard ratio [HR], 2.18; $p=0.01$) than males without pore-loop mutations but that this association was not present in females. Costa et al⁵¹ combined information on mutation location and function with age and gender to risk-stratify patients with LQTS 1 by life-threatening events.

Other research has reported that the presence of genetic variants at different locations can act as disease “promoters” in patients with LQTS mutations.^{52,53} Amin et al⁵² 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 to patients without the SNPs. Park et al⁵³ 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.⁵⁴

There is not sufficient evidence to conclude that the information obtained from genetic testing on risk assessment leads to important changes in clinical management. Most patients will be treated with β -blocker therapy and lifestyle modifications, and it has not been possible to identify a group with low enough risk to forego this conservative treatment. Conversely, for high-risk patients, there is no evidence suggesting that genetic testing influences the decision to insert an ICD and/or otherwise intensify treatment.

Some studies that report outcomes of treatment with β -blockers also report outcomes by specific subtypes of LQTS.^{41,47} Priori et al⁴¹ 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 al⁴⁰ 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 al⁵⁵ 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 mutations. Barsheset et al⁵⁶ examined 860 patients with documented mutations in the *KCNQ1* gene and classified the mutations according to type and location. Patients with missense mutations in the cytoplasmic loop (c-loop mutations) had a more marked risk reduction for cardiac arrest following treatment with β -blockers than patients with other mutations (HR=0.12; 95% CI, 0.02 to 0.73; p=0.02).

This evidence suggests that knowledge of the specific mutation present may provide some prognostic information but is not sufficient to conclude that knowledge of the specific mutation improves outcomes for a patient with known LQTS. These data suggest that there may be differences in response to β -blocker therapy, according to LQTS subtype and the type/location of the specific mutation. However, the evidence is not consistent in this regard; eg, one of the 3 studies demonstrated a similar response to β -blockers for LQT3 compared to other subtypes. Although response to β -blocker therapy may be different according to specific features of LQTS, it is unlikely that this evidence could be used in clinical decision making, because it is not clear how this information would influence management.

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 mutation 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.

Brugada Syndrome

The low clinical sensitivity of genetic testing for BrS limits its diagnostic capability. A finding of a genetic mutation is not diagnostic of the disorder but is an indicator of high risk for development

of BrS. The diagnostic criteria for BrS does not presently include the presence of a genetic mutation. Furthermore, treatment is based on the presence of symptoms such as syncope or documented ventricular arrhythmias. Treatment is primarily with a implantable ICD, which is reserved for high-risk patients. The presence or absence of a genetic mutation is unlikely to change treatment decisions for patients with suspected or confirmed BrS.

Risk stratification criteria are currently inadequate and the contribution of genetic sequencing is limited to identification of *SCN5A* mutations that occur in less than 25% of cases. Meregalli et al investigated if type of *SCN5A* mutation is related to severity of disease and found that those mutations that caused more severe reductions in peak sodium current had the most severe phenotype.⁵⁷ However, a meta-analysis of 30 BrS prospective studies found family history of SCD and presence of an *SCN5A* mutation as insufficient to predict risk for cardiac events in BrS.⁶

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%.³⁷

Section Summary

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 sudden cardiac death. 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. For BrS and 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.

Testing Strategy for the Use of 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 Proband 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 (SUDES), termed sudden arrhythmic death syndrome (SADS).³ SADS 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 mutation 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.¹ SADS 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 mutation. Disease-causing mutations 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.⁵⁸ SUDS 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 flecainide 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.⁴ 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* mutation. The yield of genetic testing was 50% for both LQTS (1 *KCNH2* mutation detected) and CPVT (1 *RyR2* mutation detected).

Evaluation of Cardiac Arrest Survivors

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.² 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 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 mutations 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.³ Probands were 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%.

Section Summary

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 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.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in November 2014 found 1 ongoing trial related to genetic testing for cardiac ion channelopathies that is currently enrolling patients:

- Multicenter Evaluation of Children and Young Adults With Genotype Positive Long QT Syndrome (NCT01705925) – This is an observational cohort study to assess genotype-phenotype correlations in patients under age 20 with genotype-positive LQTS. Enrollment is planned for 500 subjects; the estimated study completion date is December 2019.

Summary of Evidence

A genetic mutation can be identified in approximately 72% to 80% of long QT syndrome (LQTS), 51% to 75% of catecholaminergic polymorphic ventricular tachycardia (CPVT), 25% to 35% of Brugada syndrome (BrS), and 15% to 20% of short QT syndrome (SQTS) patients. The majority of these are point mutations that are identified by gene sequencing analysis; however, a small number are deletions/duplications that are best identified by chromosomal microarray (CMA) analysis. 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 varies by condition. For LQTS, it is relatively high, in the range of 70% to 80%, while for CPVT, it is moderate, in the range of 50% to 75%. For BrS and SQTS, the clinical validity is lower, in the range of 15% to 35%.

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 sudden cardiac death. The clinical utility of testing is also high for close relatives of patients with known cardiac ion channel mutations, since these individuals should also be treated if they are found to have a pathologic mutation. For BrS and 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.

Therefore, genetic testing for the diagnosis of LQTS and CPVT may be considered medically necessary for the following individuals who do not have a definite clinical diagnosis but who have: (1) a close relative (ie, first-, second-, or third-degree relative) with a known pathologic mutation, (2) a close relative with a clinical diagnosis whose genetic status is unavailable, or (3) signs and/or symptoms indicating a moderate-to-high pretest probability of LQTS or CPVT, but in whom a definitive diagnosis cannot be made clinically. For all other indications genetic testing for cardiac channelopathies is considered investigational.

Practice Guidelines and Position Statements

In 2013, the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society (APHRS) issued ~~jointly published~~ an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes.⁵⁹ These guidelines refer to the 2011 guidelines on genetic testing for channelopathies

and cardiomyopathies referenced below for the indications for genetic testing in patients affected by inherited arrhythmias and their family members and for diagnostic, prognostic, and therapeutic implications of the results of genetic testing. The 2013 guidelines provide guidance for the evaluation of patients with idiopathic ventricular fibrillation (IVF), sudden unexplained death syndrome (SUDS), and sudden unexplained death in infancy (SUDI), which includes genetic testing; they are outlined in Table 6. IVF is defined as a resuscitated cardiac arrest victim, preferably with documentation of ventricular fibrillation (VF), in whom known cardiac, respiratory, metabolic, and toxicologic etiologies have been excluded through clinical evaluation.

The guidelines define several terms related to specific types of sudden cardiac death, including SUDS, which refers to an unexplained sudden death in an individual older than 1 year of age, sudden arrhythmic death syndrome, which refers to a SUDS case with negative pathologic and toxicologic assessment, and SUDI, which refers to an unexplained sudden death in an individual younger than 1 year of age with negative pathologic and toxicologic assessment.

Table 6. HRS/EHRA/APHRS Recommendations for Genetic Testing in IVF, SUDS, and SUDI

	Class	HRS/EHRA/APHRS Consensus Recommendation
IVF	IIa	Genetic testing in IVF can be useful when there is suspicion of a specific genetic disease following clinical evaluation of the IVF patient and/or family members.
	III	Genetic screening of a large panel of genes in IVF patients in whom there is no suspicion of an inherited arrhythmogenic disease after clinical evaluation should not be performed.
SUDS	I	Collection of blood and/or suitable tissue for molecular autopsy/postmortem genetic testing is recommended in all SUDS victims.
	I	Genetic screening of the first-degree relatives of a SUDS victim is recommended whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDS victim.
SUDI	I	Collection of blood and/or suitable tissue for molecular autopsy is recommended in all SUDI victims.
	IIa	An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing can be useful for all SUDI victims.
	I	Genetic screening of the first-degree relatives of a SUDI victim is recommended whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDI victim. Obligate mutations carriers should be prioritized.

APHRS: Asia Pacific Heart Rhythm Society; IVF: idiopathic ventricular fibrillation; EHRA: European Heart Rhythm Association; HRS: Heart Rhythm Society; SUDI: sudden unexplained death in infancy; SUDS: sudden unexplained death syndrome.

In 2011, HRS and EHRA jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies.²³ This document made the following specific recommendations concerning testing for LQTS, CPVT, BrS, and SQTs (Table 7).

Table 7. HRS and EHRA Cardiac Ion Channelopathy Testing Recommendations

	Class	HRS and EHRA Consensus Recommendation
LQTS	I	<ul style="list-style-type: none"> Comprehensive or LQT1-3 (<i>KCNQ1, KCNH2, SCN5A</i>) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype. Comprehensive or LQT1-3 (<i>KCNQ1, KCNH2, SCN5A</i>) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., ie, otherwise idiopathic) on serial 12-lead ECGs defined as QTc .480 ms (prepuberty) or .500 ms (adults). Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.
	IIb	<ul style="list-style-type: none"> Comprehensive or LQT1-3 (<i>KCNQ1, KCNH2, SCN5A</i>) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values .460 ms (prepuberty) or .480 ms (adults) on serial 12-lead ECGs.
CPVT	I	<ul style="list-style-type: none"> Comprehensive or <i>CPVT1</i> and <i>CVPT2 (RYR2, CASQ2)</i> targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.
BrS	I	<ul style="list-style-type: none"> Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.
	IIa	<ul style="list-style-type: none"> Comprehensive or BrS1 (<i>SCN5A</i>) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.
	III	<ul style="list-style-type: none"> Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.
SQTS	I	<ul style="list-style-type: none"> Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.
	IIb	<ul style="list-style-type: none"> Comprehensive or SQT1-3 (<i>KCNH2, KCNQ1, KCNJ2</i>) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient's clinical history, family history, and electrocardiographic phenotype.

EHRA: European Heart Rhythm Association; HRS: Heart Rhythm Society; LQTS: long QT syndrome; QTc: QT corrected; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

- Class I: "is recommended" when an index case has a sound clinical suspicion for the presence of a channelopathy with a high positive predictive value for the genetic test (>40%) with a signal-to-noise ratio of >10 AND/OR the test may provide diagnostic or prognostic information or may change therapeutic choices; Class IIa: "can be useful"; Class IIb: "may be considered"; Class III ("is not recommended"): The test fails to provide any additional benefit or could be harmful in the diagnostic process.
- The level of evidence of all recommendations is C (only consensus opinion of experts, case studies or standard of care).

The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) issued guidelines in 2006 on the management of patients with ventricular arrhythmias and the prevention of sudden death.⁶⁰ These guidelines made a general statement that "In patients affected by LQTS, genetic analysis is useful for risk stratification and therapeutic decisions." These guidelines did not address the use of genetic testing for the diagnosis of LQTS.

The guidelines also state that for genetic testing for CPVT, BrS, or SQTs may identify silent carriers for clinical monitoring but does not assist with risk stratification.

The Canadian Cardiovascular Society and Canadian Heart Rhythm Society published a joint position paper in 2011.²⁴ Genetic testing was recommended for cardiac arrest survivors with LQTS for the purpose of familial screening as well as those with syncope with QTc prolongation as well as asymptomatic patients with QTc prolongation with a high clinical suspicion of LQTS. For clinically suspect CPVT, testing is recommended for the purpose of familial screening. Genetic testing is also recommended for cardiac arrest survivors with a Type I Brugada electrocardiograph (ECG) pattern for the purpose of familial screening as well as in patients with syncope and Type I Brugada ECG pattern or asymptomatic patients with Type I Brugada ECG pattern and a high clinical suspicion. No recommendations are given regarding SQTs.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force has not addressed the treatment of genetic testing for cardiac ion channelopathies.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- 81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
- 81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
- 81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
- 81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
- 81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
- 81413 Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
- 81414 Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication / deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1

S3861 Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome

- Effective in 2012, there are CPT codes for this testing: 81280, 81281, 81282.
- Other analyses related to this testing are listed under the following CPT Tier 2 molecular pathology codes:
 - Under code 81403 - *KCNJ2* (potassium inwardly-rectifying channel, subfamily J, member 2) (eg, Andersen-Tawil syndrome), full gene sequence
 - Under code 81405 - *CASQ2* (calsequestrin 2 [cardiac muscle]) (eg, catecholaminergic polymorphic ventricular tachycardia), full gene sequence
 - Under code 81406 - *KCNH2* (potassium voltage-gated channel, subfamily H [lead-related], member 2) (eg, short QT syndrome, long QT syndrome), full gene sequence and *KCNQ1* (potassium voltage-gated channel, KQT-like subfamily, member 1) (eg, short QT syndrome, long QT syndrome), full gene sequence
 - Under code 81407 - *SCN5A* (sodium channel, voltage-gated, type V, alpha subunit) (eg, familial dilated cardiomyopathy), full gene sequence
 - Under code 81408 - *RYR2* (ryanodine receptor 2 [cardiac]) (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of > 50 exons
- There is a HCPCS S code for testing for suspected Brugada syndrome: S3861.

ICD-9 Diagnoses

- 426.82 Long QT syndrome
 746.89 Congenital anomalies; other specified anomalies of the heart
 V82.79 Genetic screening; Other genetic screening

ICD-10 Diagnoses (Effective October 1, 2015)

- I45.81 Long QT syndrome
 Q24.8 Other specified congenital malformations of heart
 Z13.79 Encounter for other screening for genetic and chromosomal anomalies

REVISIONS

12-07-2012	Description section updated
	Rationale section updated
	References updated
03-31-2014	Title changed from: "Genetic Testing for Congenital Long QT Syndrome" to: "Genetic Testing for Cardiac Ion Channelopathies"
	Description section updated In Policy section: <ul style="list-style-type: none"> ▪ In Item A revised wording of "with a Schwartz score of 4 or more" to read, "(i.e., those with a Schwartz score less than 4)" ▪ In Item A 3 added an asterisk reference to read, "signs and/or symptoms indicating a moderate-to-high pretest probability* of LQTS. *Determining the pretest probability of LQTS is not standardized. An example of a patient with a moderate-to-high pretest probability of LQTS is a patient with a Schwartz score of 2–3." <ul style="list-style-type: none"> ▪ Added Items C 1 – C 3 to reflect indications for catecholaminergic polymorphic ventricular tachycardia (CPVT), "Genetic testing for CPVT may be considered medically necessary for patients who do not

	<p>meet the clinical criteria for CPVT but who have:</p> <ol style="list-style-type: none"> 1. a close relative (i.e. first-, second-, or third-degree relative) with a known CPVT mutation; or 2. a close relative diagnosed with CPVT by clinical means whose genetic status is unavailable; or 3. signs and/or symptoms indicating a moderate-to-high pretest probability of CPVT." <ul style="list-style-type: none"> ▪ Added Item D: "Genetic testing for Brugada syndrome is considered experimental / investigational." ▪ Added Item E: "Genetic testing for short QT syndrome is considered experimental / investigational."
	Rationale section updated
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT codes: 81403, 81405, 81406, 81407, 81408 ▪ Updated Coding information ▪ Added ICD-10 Diagnoses codes
	References updated
02-16-2015	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A added "(LQTS)" abbreviation to read, "Genetic testing in patients with suspected congenital long QT syndrome (LQTS) may be considered..." ▪ In Item C added "catecholaminergic polymorphic ventricular tachycardia" nomenclature to read, "Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered..." ▪ The above revisions have no impact to the policy position and are considered maintenance updates. ▪ Added Policy Guidelines <p>"Testing Strategy</p> <ol style="list-style-type: none"> 1. In general, testing for patients with suspected congenital LQTS or CPVT should begin with a known familial mutation, if one has been identified. 2. 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 BCBSKS medical policy titled General Approach to Evaluating the Utility of Genetic Panels. 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). 3. 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.1-4 If, after a comprehensive evaluation, a diagnosis of CPVT or LQTS is suspected but not definitive (ie, if there is a moderate-to-high pretest probability of either condition), genetic testing could be considered."
	Rationale section updated
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated Coding instructions
	<p>In Revision section:</p> <ul style="list-style-type: none"> ▪ Removed revision details for: 08-12-2009, 10-26-2010, 12-01-2011, 02-14-2012, 04-10-2012
	References updated

01-01-2017	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT Codes: 81413, 81414 (Effective January 1, 2017) ▪ Removed CPT Codes: 81280, 81281, 81282 (Effective December 31, 2016)
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