Medical Policy

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Title: Genetic Testing for Cardiac Ion Channelopathies

Related Policies:	▪ *General Approach to Evaluating the Utility of Genetic Panels*

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected congenital long QT syndrome	Interventions of interest are: • Genetic testing for variants associated with congenital long QT syndrome	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive decision making • Morbid events
Individuals: • Who are asymptomatic with close relative(s) with a known long QT	Interventions of interest are: • Genetic testing for variants associated with congenital long QT	Comparators of interest are: • Standard management without genetic	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive

Populations	Interventions	Comparators	Outcomes
syndrome variant	syndrome	testing	decision making • Morbid events
Individuals: • With suspected Brugada syndrome	Interventions of interest are: • Genetic testing for variants associated with Brugada syndrome	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive decision making • Morbid events
Individuals: • Who are asymptomatic with close relative(s) with a known Brugada syndrome variant	Interventions of interest are: • Genetic testing for variants associated with Brugada syndrome	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive decision making • Morbid events
Individuals: • With suspected catecholaminergic polymorphic ventricular tachycardia	Interventions of interest are: • Genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive decision making • Morbid events
Individuals: • Who are asymptomatic with close relative(s) with a known catecholaminergic polymorphic ventricular tachycardia variant	Interventions of interest are: • Genetic testing for variants associated with catecholaminergic polymorphic ventricular tachycardia	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive decision making • Morbid events
Individuals: • With suspected short QT syndrome	Interventions of interest are: • Genetic testing for variants associated with short QT syndrome	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive decision making • Morbid events
Individuals: • Who are asymptomatic with close relative(s) with a known short QT syndrome variant	Interventions of interest are: • Genetic testing for variants associated with short QT syndrome	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test validity • Changes in reproductive decision making • Morbid events

DESCRIPTION

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

OBJECTIVE

The objective of this evidence review is to examine whether genetic testing for cardiac ion channelopathies (e.g., long QT syndrome, short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia) improves health outcomes in individuals with suspected channelopathies or individuals with a close relative with known or suspected channelopathies.

BACKGROUND

Cardiac Ion Channelopathies

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

The prevalence of any cardiac channelopathy is still ill-defined but is thought to be between 1 in 2000 and 1 in 3000 persons in the general population.[1,] Data about the individual prevalences of long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome (SQTS) are presented in Table 1.

Table 1. Epidemiology of Cardiac Ion Channelopathies

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

Adapted from Modell et al (2012).[2,]
BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; SQTS: short QT syndrome.
[a] Type 1 electrocardiographic pattern.

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

Congenital LQTS usually manifests before the age of 40 years. It is estimated that more than half of the 8000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1% to 2% per year, although this figure varies with the genotype.

Brugada Syndrome
Brugada syndrome 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.[3,] Brugada syndrome is an autosomal dominant disorder with an unexplained male predominance. Males are more likely to be affected than females (approximate ratio, 8:1). Brugada syndrome is estimated to be responsible for 12% of SCD cases.[1,] For both sexes, there is an equally high risk of ventricular arrhythmias or sudden death.[4,] Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.[5,]

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 precipitated by exercise or emotional stress.[6,] 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 years and is responsible for 13% of cardiac arrests in structurally normal hearts.[6,] Catecholaminergic polymorphic ventricular tachycardia was previously believed to manifest only during childhood, but studies have now identified presentation between infancy and 40 years of age.[7,]

Short QT Syndrome
Short QT syndrome is characterized by a shortened QT interval on the electrocardiogram (ECG) and, at the cellular level, a shortening of the action potential.[8,] 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.[6,]

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

The evaluation and management of a survivor of SCA include an assessment of the circumstances of the event as well as a comprehensive physical examination emphasizing cardiovascular and neurologic systems, laboratory testing, ECG, and more advanced cardiac imaging or electrophysiologic testing as may be warranted. Genetic testing might be considered

when, after completion of a comprehensive evaluation, there are findings consistent with a moderate-to-high likelihood of a primary electrical disease. Postmortem protocols for evaluation of a fatal SCA should be implemented when possible.

GENETICS OF CARDIAC ION CHANNELOPATHIES

Long QT Syndrome

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

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.[10,] A negative test is only definitive when there is a known variant identified in a family member and targeted testing for this variant is negative.

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

Variants involving *KCNQ1*, *KCNH2*, and *SCN5A* are the most commonly detected in patients with genetically confirmed LQTS. Some variants are associated with extra-cardiac abnormalities in addition to the cardiac ion channel abnormalities. A summary of clinical syndromes associated with hereditary LQTS is shown in Table 2. A 2021 analysis of 49 patients with channelopathies identified 3 rare variants that were pathogenic for LQTS and 8 rare variants that were likely pathogenic for LQTS, all involving *KCNQ1* or *KCNH2*.[12,]

Table 2. Genetics of Long QT Syndrome

Type	Other Names	Chromosome Locus	Mutated Gene	Ion Current(s) Affected	Associated Findings
LQT1	RWS	11p15.5-p.15.4	*KCNQ1*	Potassium	
LQT2	RWS	7qq36.1	*KCNH2*	Potassium	
LQT3	RWS	3p22.2	*SCN5A*	Sodium	
LQT4	Ankyrin B syndrome	4q25-26	*ANK2*	Sodium, potassium, calcium	Catecholaminergic polymorphic ventricular arrhythmias, sinus node dysfunction, AF
LQT5	RWS	21q22.12	*KCNE1*	Potassium	
LQT6	RWS	21q22.11	*KNCE2*	Potassium	
LQT7	Andersen-	17.qq2432	*KCNJ2*	Potassium	Episodic muscle

Type	Other Names	Chromosome Locus	Mutated Gene	Ion Current(s) Affected	Associated Findings
	Tawil syndrome				weakness, congenital anomalies
LQT8	Timothy syndrome	12q13.33	*CACNA1C*	Calcium	Congenital heart defects, hand/foot syndactyly, ASD
LQT9	RWS	3p25.3	*CAV3*	Sodium	
LQT10	RWS	11q23.3	*SCN4B*	Sodium	
LQT11	RWS	7q21.2	*AKAP9*	Potassium	
LQT12	RWS	20q11.21	*SNTAI*	Sodium	
LQT13	RWS	11q24.3	*KCNJ5*	Potassium	
LQT14		14q32.11	*CALM1*	Calmodulin	
LQT15		2p21	*CALM2*	Calmodulin	
LQT16		19q13.32	*CALM3*	Calmodulin	
JLNS1	JLNS	11p15.5-11p15.4	*KCNQ1* (homozygotes or compound heterozygotes)	Potassium	Congenital sensorineural hearing loss
JLNS2	JLNS	21q22.12	*KCNE1* (homozygotes or compound heterozygotes)	Potassium	Congenital sensorineural hearing loss

Adapted from Beckmann et al (2021),[13,] Arking et al (2014),[14,] and Alders (2015).[15,]
AF: atrial fibrillation; ASD: autism spectrum disorder; LQT: long QT; JLNS: Jervell and Lange-Nielsen syndrome; RWS: Romano-Ward syndrome.

Brugada Syndrome

Brugada syndrome is typically inherited in an autosomal dominant manner with incomplete penetrance. The proportion of cases that are inherited, versus de novo variants, is uncertain. Although some have reported that up to 50% of cases are sporadic, others have reported that the instance of de novo variants is very low and is estimated to be only 1% of cases.[4,]

Variants in 16 genes have been identified as causative of BrS, all of which lead to a decrease in the inward sodium or calcium current or an increase in one of the outward potassium currents. Of these, *SCN5A* is the most important, accounting for more than an estimated 20% of cases[7,]; *SCN10A* has also been implicated. The other genes are of minor significance and account together for approximately 5% of cases.[6,] 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.[4,] A 2021 analysis of 49 patients with channelopathies identified 1 rare variant that was pathogenic for BrS and 3 rare variants that were likely pathogenic for BrS, all involving the *SCN5A* gene.[12,]

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 of the gene encoding the cardiac ryanodine receptor (*RYR2*) or to *KCNJ2* result in an autosomal dominant form of CPVT. *CASQ2* (cardiac calsequestrin) and *TRDN*-related CPVT exhibit autosomal recessive inheritance. A channelopathy expert panel review has also found moderate to definitive evidence for an autosomal dominant inheritance of *CALM1*, *CALM2*, and *CALM3* and an autosomal recessive inheritance of *TECRL*.[16,] Some have reported heterozygotes for *CASQ2* and *TRDN* variants for rare, benign arrhythmias.[17,] *RYR2* variants represent most CPVT cases (50% to 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%.[17,]

An estimated 50% to 70% of patients have the dominant form of CPVT with a disease-causing variant. Most variants (90%) of *RYR2* are missense variants, but in a small proportion of unrelated CPVT patients, large gene rearrangements or exon deletions have been reported.[7,] Additionally, nearly a third of patients diagnosed as LQTS with normal QT intervals have CPVT due to identified *RYR2* variants. Another misclassification, CPVT diagnosed as Anderson-Tawil syndrome may result in more aggressive prophylaxis for CPVT whereas a correct diagnosis can spare this treatment because Anderson-Tawil syndrome is rarely fatal.

Short QT Syndrome

Short QT syndrome has been linked predominantly to variants in 3 genes (*KCNH2*, *KCNJ2*, *KCNQ1*).[14,] 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. A channelopathy expert panel concluded that only *KCNH2* had a definitive relationship with SQTS and *KCNQ1*, *KCNJ2*, and *SLC4A3* had strong to moderate causative evidence.[16,] Short QT syndrome is believed to be inherited in an autosomal dominant pattern. Although sporadic cases have been reported, patients frequently have a family history of the syndrome or SCD.

REGULATORY STATUS

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

POLICY

Long QT Syndrome

A. Genetic testing to confirm a diagnosis of congenital long QT syndrome (LQTS) may be considered **medically necessary** when signs and/or symptoms of LQTS are present, but a definitive diagnosis cannot be made without genetic testing. This includes:

   1. Individuals who do not meet the clinical criteria for LQTS (i.e., those with a Schwartz score <4): but have a moderate-to-high pretest probability (see Policy Guidelines section) based on the Schwartz score and/or other clinical criteria.

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

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

   OR

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

C. 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 individuals with known LQTS, is considered **experimental / investigational**.

Brugada Syndrome

D. Genetic testing to confirm a diagnosis of Brugada syndrome (BrS) may be considered **medically necessary** when signs and/or symptoms consistent with BrS (see Policy Guidelines section) are present, but a definitive diagnosis cannot be made without genetic testing.

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

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

Catecholaminergic Polymorphic Ventricular Tachycardia

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

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

1. A close relative (i.e., first-, second-, or third-degree relative) with a known CPVT variant;

OR

2. A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable.

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

Short QT Syndrome

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

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

POLICY GUIDELINES

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

Determining the pretest probability of long QT syndrome (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.

Signs and symptoms suggestive of Brugada syndrome (BrS) include the presence of a characteristic electrocardiographic pattern, documented ventricular arrhythmia, sudden cardiac death in a family member younger than 45 years old, a characteristic electrocardiographic pattern in a family member, inducible ventricular arrhythmias on electrophysiologic studies, syncope, or nocturnal agonal respirations. An index patient with suspected short QT syndrome (SQTS) would be expected to have a shortened (<2 standard deviation below from the mean) rate-corrected shortened QT interval (QTc). Cutoffs below 350 ms for men and 360 ms for women have been derived from population normal values (Tristani-Firouzi, 2014). The presence of a short QTc interval alone does not make the diagnosis of SQTS. Clinical history, family

history, other electrocardiographic findings, and genetic testing may be used to confirm the diagnosis.

Testing Strategy

A. In general, testing for individuals with suspected congenital LQTS or catecholaminergic polymorphic ventricular tachycardia (CPVT), or BrS should begin with a known familial variant, if one has been identified.

B. 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 variants for a single condition; panels that include variants for multiple conditions (indicated plus nonindicated conditions); panels that include variants for multiple conditions (clinical syndrome for which clinical diagnosis not possible).

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

Genetic Counseling

Genetic counseling is primarily aimed at individuals 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.

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through November 9, 2023.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

GENETIC TESTING FOR VARIANTS ASSOCIATED WITH CARDIAC ION CHANNELOPATHIES

Clinical Context and Test Purpose

The purpose of genetic testing in individuals with unexplained cardiac arrhythmias and/or other conduction abnormalities is to confirm the presence or absence of a cardiac ion channelopathy and inform clinical management.

The following PICO was used to select literature to inform this review.

Populations

The population of interest are individuals with suspected cardiac ion channelopathies (e.g., long QT syndrome [LQTS], Brugada syndrome [BrS], catecholaminergic polymorphic ventricular tachycardia [CPVT], short QT syndrome [SQTS]) or asymptomatic individuals with a close relative(s) with a known cardiac ion channelopathy variants.

The channelopathies discussed herein are genetically heterogeneous with hundreds of identified variants, but the group of disorders shares basic clinical expression. The most common presentation is spontaneous or exercise-triggered syncope due to ventricular dysrhythmia. These can be self-limiting or potentially lethal cardiac events. The electrocardiographic features of each channelopathy are characteristic, but the electrocardiogram (ECG) is not diagnostic in all cases, and some secondary events (e.g., electrolyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an ECG similar to those observed in a cardiac channelopathy.

Interventions

The intervention being considered is genetic testing for variants associated with cardiac ion channelopathies. Genetic tests are conducted in clinical laboratories. Genetic testing should be accompanied by genetic counseling including discussions with the individuals or guardians about

the importance and interpretation of genetic information and sharing of information with potentially affected family members as appropriate.

Genetic testing can be comprehensive (testing for all possible variants in multiple genes) 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 associated with a disorder and therefore may or may not be pathogenic. Variants are classified by their pathogenic potential; an example of such a classification system used in the Familion assay is as follows in Table 3.

Table 3. Familion Assay Classification System

Class	Description
I	Deleterious and probable deleterious mutations. They are mutations that have either previously been identified as pathogenic (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).
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.
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."
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.

LQTS: long QT syndrome.

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. Also, panel testing for 1 or more cardiac ion channelopathies is available from a number of genetic diagnostics laboratories, but there is some variation among manufacturers in the included genes.

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.

Comparators

The following practice is currently being used: standard management without genetic testing. Diagnosis and management are described in the following sections by the condition.

Long QT Syndrome Diagnosis

The Schwartz criteria are commonly used as a diagnostic scoring system for long QT syndrome (LQTS).[18,] The most recent version is shown in Table 4. A score of 3.5 or higher indicates a high probability that LQTS is present; a score of 1.5 to 3, an intermediate probability; and a score of 1 or less indicates a low probability of the disorder. Before the availability of genetic testing, it was

not possible to test the sensitivity and specificity of this scoring system, and because there is still no perfect criterion standard for diagnosing LQTS, the accuracy of this scoring system remains ill-defined.

Table 4. Diagnostic Scoring System for Long QT Syndrome

Schwartz Criteria	Points
Electrocardiographic findings QT corrected >480 ms QT corrected 460-470 ms QT corrected <450 ms	 3 2 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 Syncope without stress Congenital deafness	 2 1 0.5
Family history Family members with definite LQTS Unexplained sudden death in immediate family members <30 y of age	 1 0.5

Adapted from Perrin and Gollob (2012).[19,]
LQTS: long QT syndrome.

Long QT Standard Management

Primary management of asymptomatic or symptomatic long QT is β-blocker treatment with an intensification of therapy, if necessary due to recurrent arrhythmic events or intolerable side effects, including additional medication, left cardiac sympathetic denervation or placement of an implantable cardioverter-defibrillator (ICD). Avoidance of medications known to prolong the QT interval and the aggressive treatment of electrolyte imbalances are also advised.

Brugada Diagnosis

The diagnosis of Brugada syndrome (BrS) is made by the presence of a type 1 Brugada pattern on the ECG in addition to other clinical features.[20,] 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 (V_1-V_3). This pattern may be concealed and can be revealed by administering a sodium-channel-blocking agent (e.g., flecainide).[21,] Two additional ECG patterns have been described (type 2, type 3) but are less specific for the disorder.[22,] The diagnosis of BrS is considered definitive when the characteristic ECG pattern is present with at least 1 of the following clinical features: documented ventricular arrhythmia, sudden cardiac death (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.

Brugada Standard Management
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.

Catecholaminergic Polymorphic Ventricular Tachycardia 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 catecholaminergic polymorphic ventricular tachycardia (CPVT) is typically normal, but exercise stress testing can induce a ventricular arrhythmia in most cases (75% to 100%).[19,] Premature ventricular contractions, couplets, bigeminy, or polymorphic ventricular tachycardia (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.[23,]

Catecholaminergic Polymorphic Ventricular Tachycardia Standard Management
Management of CPVT is primarily with the β-blockers nadolol (1 to 2.5 mg/kg/d) or propranolol (2 to 4 mg/kg/d). If protection is incomplete (i.e., recurrence of syncope or arrhythmia), then flecainide (100 to 300 mg/d) may be added. If recurrence continues, an ICD may be necessary with optimized pharmacologic management continued post-implantation.[17,] Lifestyle modification with the avoidance of strenuous exercise is recommended for all CPVT patients.

Short QT Diagnosis
Patients generally present with syncope, pre-syncope, or cardiac arrest. An ECG with a corrected QT interval less than 330 ms, sharp T wave at the end of the QRS complex, and a brief or absent ST-segment are characteristic of the syndrome.[24,] 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 short QT syndrome (SQTS) would be expected to have a shortened (<2 standard deviations below from the mean) rate-corrected shortened QT interval (QTc). Cutoffs below 350 ms for men and 360 ms for women have been derived from population normal values.[25,] The length of the QT interval was not associated with severity of symptoms in a 2006 series of 29 patients with SQTS.[26,] Electrophysiologic studies may be used to diagnose SQTS if the diagnosis is uncertain to evaluate for short refractory periods and inducible VT. However, in the series of 29 patients with SQTS described above, VT was inducible in only 3 of 6 subjects who underwent an electrophysiologic study.[26,] A diagnostic scoring system was proposed by Gollob et al (2011) to help decision making after a review of 61 SQTS cases (see Table 5).[27,]

Table 5. 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 SCD	2
Documented polymorphic ventricular fibrillation or VT	2

Gollob Criteria	Points
Unexplained syncope AF	1 1
Family history First- or second-degree relative with high probability SQTS First- or second-degree relative with autopsy-negative SCD Sudden infant death syndrome	 2 1 1
Genotype Genotype positive Mutation of undetermined significance in a culprit gene	 2 1

Adapted from Perrin and Gollob (2012).[19,]
AF: atrial fibrillation; SCD: sudden cardiac death; SQTS: short QT syndrome; VT: ventricular tachycardia.

Short QT Standard Management
The primary management of SQTS is with ICD therapy. Decisions about ICD therapy are based on the degree to which SQTS is considered likely, which depends on ECG features, family history, personal history of cardiac arrest or ventricular arrhythmias, and the ability to induce VT on electrophysiologic studies.

Anti-arrhythmic drug management of the disease is complicated because the binding target for QT-prolonging drugs (e.g., sotalol) is Kv11.1, which is coded for by *KCNH2*, the most common site for variants in SQTS (subtype 1). Treatment with quinidine (which is able to bind to both open and inactivated states of Kv11.1) is an appropriate QT-prolonging treatment. This treatment has been reported to reduce the rate of arrhythmias from 4.9% to 0% per year. For those with recurrence while on quinidine, an ICD is recommended.[19,]

Outcomes
The general outcomes of interest are overall survival (OS), test validity, changes in reproductive decision making, and morbid events (e.g., cardiac events).

A positive diagnosis of LQTS or CPVT in symptomatic patients may lead to treatment with β-blockers or with ICDs, which can reduce the risk for ventricular arrhythmias and SCD.

A positive test for BrS in symptomatic patients may influence the decision for treatment with an ICD.

It is unknown how a positive SQTS test in symptomatic patients would influence treatment decisions.

Positive tests in asymptomatic family members can inform lifestyle changes and prevention treatment decisions.

The genetic assays may be recommended as part of a diagnostic strategy for patients who exhibit clinical symptoms that are not considered definitive.

The tests may also be recommended for asymptomatic family members of patients with known cardiac ion channel variants.

The evidence related to the clinical validity and utility of genetic testing for the cardiac channelopathies consists primarily of studies that evaluate the yield of genetic testing and the impact of genetic testing on the diagnosis and subsequent management of a specific cardiac channelopathy. Many 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 SCD from an unknown cause are discussed separately.

The evidence is presented as follows. First, for patients who are candidates for testing of specific channelopathies (LQTS, BrS, CPVT, SQTS) and asymptomatic family members of variant-positive probands. Finally, the evidence is presented for the genetic testing of family members in cases of SCD when a specific clinical diagnosis has not been made.

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for specific cardiac ion channelopathies, studies that meet the following eligibility criteria were considered:

- Reported on the yield of genetic testing in patients with suspected or confirmed channelopathy;
- Included clinical diagnosis;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

In addition, studies reporting on the clinical specificity will be discussed briefly when available.

GENETIC TESTING FOR THE DIAGNOSIS OF SPECIFIC CARDIAC ION CHANNELOPATHIES

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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

Survivors of Sudden Cardiac Arrest
Asatryan et al (2019) evaluated the diagnostic validity and clinical utility of genetic testing in sudden cardiac arrest (SCA) survivors (n=60) with or without previous clinical evidence of heart disease.[28,] Patients without coronary artery disease were included; 24 (40%) with clear detectable cardiac phenotype [Ph(+)SCA] and 36 (60%) with no clear cardiac phenotype [Ph(-)SCA]. Targeted exome sequencing was performed using the TruSight-One Sequencing Panel (Illumina). A total of 32 pathogenic or likely pathogenic gene variants were found in 27 (45%) patients: 17 (71%) in the Ph(+)SCA group and 10 (28%) in the Ph(-)SCA group. Mutations in 16 (67%) Ph(+)SCA patients were congruent with the suspected phenotype, consisting of 12 (50%) cardiomyopathies and 4 (17%) channelopathies. Mutations in 6 (17%) Ph(-)SCA patients

revealed a cardiac ion channelopathy explaining their SCA event. An additional 4 (11%) mutations in this group could not explain the phenotype and require additional studies. Overall, cardiac genetic testing was positive in 2/3 of the Ph(+)SCA group and 1/6 of the Ph(-)SCA group. The study was limited in its description of clinical criteria for establishing a diagnostic clinical phenotype. While the authors suggest the testing was useful to identify or confirm an inherited heart disease, with important impact on patient care and first-degree relatives at risk, health outcomes pertaining to clinical management of patients or asymptomatic familial probands were not reported.

Chiu et al (2022) performed genetic tests on 36 survivors of pediatric cardiac arrest (median age, 13.3 years).[29,] The yield rate of genetic testing in the study cohort was 84.6%, including 14 pathogenic and 8 likely pathogenic variants. Long QT syndrome, CPVT, and BrS were diagnosed in 25%, 16.7%, and 6% of patients, respectively; genetic testing led to a change in diagnosis from CPVT to LQTS in 1 patient. Assessment of long-term outcomes showed that 10-year transplant-free survival was higher among patients who received genetic testing soon after the cardiac arrest event. Subsequent testing of family members of 15 probands identified 8 family members with positive genetic tests, but information on subsequent management of these patients was lacking.

Long QT Syndrome

Tester et al (2006) completed the largest study to evaluate the percentage of individuals with a clinical diagnosis of LQTS found to have a genetic variant.[30,] The sample was 541 consecutive patients referred for evaluation of LQTS. Clinical assessments of the patients were made while blinded to the genetic testing results. Among the 123 patients with a high probability of LQTS based on clinical assessments, defined as a Schwartz score of 4 or more, 72% (89/123) had a genetic variant. Among patients with a QTc greater than 480 ms, 62% had a genetic variant. Characteristics and results of selected studies are shown in Tables 6 and 7 below.

Table 6. Characteristics of Clinical Validity Studies of Genetic Testing for Long QT Syndrome

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors
Tester et al (2006)[30,]	Unrelated patients referred to Mayo Clinic's Sudden Death Genomics Laboratory for LQTS genetic testing from 1997 to 2004	Consecutive; prospective	Schwartz and Moss score (≥4 suggests strong probability for LQTS)	Unclear but described as 'comprehensive mutational analysis'	Yes
Bai et al (2009)[31,]	Patients from a sample of 1394 consecutive probands with either a clinically confirmed or suspected diagnosis of LQTS, BrS, or CPVT or a personal or family history of idiopathic ventricular	Consecutive; prospective	Diagnosed clinically as conclusive or possible; criteria not specified	*KCNQ1, KCNH2, SCN5A, KCNE1,* and *KCNE2*	NR

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors
	fibrillation/cardiac arrest/SCD referred for molecular diagnosis				

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; NR: not reported; SCD: sudden cardiac death.

Table 7. Yield of Genetic Testing for Long QT Syndrome

Study	N	Excluded Samples	Yield of Genetic Testing
Tester et al (2006)[30,]	541	None	NR
Schwartz and Moss ≥4	123	Unknown Schwartz/Moss (n=124)	72%
Schwartz and Moss <4	294	Unknown Schwartz/Moss (n=124)	44%
Bai et al (2009)[31,]	546	NR	40%
Conclusive Dx	304	NR	64%
Possible Dx	160	NR	14%

Dx: diagnosis; NR: not reported.

The purpose of limitations tables (see Tables 8 and 9) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 8. Study Relevance Limitations of Clinical Validity Studies of Genetic Testing for Long QT Syndrome

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Tester et al (2006)[30,]		1: Not clear which genes were tested			
Bai et al (2009)[31,]	3: Criteria for clinical diagnosis unclear				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 9. Study Design and Conduct Limitations of Clinical Validity Studies of Genetic Testing for Long QT Syndrome

Study	Selection[a]	Blinding[b]	Test Delivery[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Tester et al (2006)[30,]					2: Insufficient data for clinical score in 23% of samples that had genetic testing	
Bai et al (2009)[31,]		1: Blinding not described			1: No description of exclusions or indeterminate results	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

The evidence on clinical specificity focuses on the frequency and interpretation of variants identified but not known to be pathogenic. If a variant identified is known to be pathogenic, then the specificity of this finding is high. However, many variants are not known to be pathogenic, and the specificity for these variants is lower. The rate of identification of variants is estimated at 5% for patients who do not have LQTS.[32,]

A 2012 publication from the National Heart, Lung, and Blood Institute GO Exome Sequencing Project (ESP) reported on the rate of sequence variants in a large number of patients without LQTS.[33,] The ESP sequenced all genome regions of protein-coding in a sample of 5400 persons drawn from various populations, none of whom specifically had heart disease and/or channelopathies. Exome data were systematically searched to identify sequence variants previously associated with LQTS, including both nonsense variants, which are generally pathogenic, and missense variants, which are less likely to be pathogenic. Thirty-three such sequence variants were identified in the total population (all missense variations). The percentage of the population that had at least 1 of these missense variants was 5.2%. No nonsense variants were associated with LQTS found among the entire population.

Brugada Syndrome

Priori et al (2000) reported an early paper to describe the yield of genetic testing for BrS.[34,] In 58 probands with a clinical diagnosis of BrS, the yield of *SCN5A* testing was 15%.

Kapplinger et al (2010) reported results from an international compendium of *SCN5A* variants of more than 2000 patients referred for BrS genetic testing which yielded almost 300 distinct mutations in 438 of 2111 (21%) patients, ranging from 11% to 28% across the 9 testing centers.[35,]

Hu et al (2014) evaluated the prevalence of *SCN10A* variants in 120 probands with BrS.[36,] 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%).[37,] Eighteen (11.5%) patients were found to have variants, most often in *SCN10A* (12/18 [67%]).

Andorin et al (2016) described the yield of *SCN5A* genetic testing in 75 patients younger than 19 years of age from 62 families who had a Brugada type I ECG pattern; only 20% were symptomatic.[38,] The ECG pattern was spontaneous in 34% and drug-induced in 66%. The yield was very high compared to previous studies at 77%. The authors hypothesized that the high yield might have been due to the inclusion of only a pediatric population.

Chen et al (2019) conducted a meta-analysis of 17 studies involving 1780 unrelated and consecutive patients with BrS to assess the relationship between *SCN5A* mutation status and phenotypic features.[39,] A history of syncope and spontaneous type 1 ECG pattern were observed in 31% and 59% of BrS patients, respectively. A total of 52% of patients had ICD implantation. The average frequency of *SCN5A* mutations was 20%, which ranged from 11% to 43% across studies. The onset of symptoms was found to occur at a younger age in the *SCN5A*(+) group (34 ± 17 vs. 42 ± 16 years; p=.0003). The presence of a spontaneous type 1 ECG pattern was associated with an increased risk of cardiac events in BrS patients based on a pooled analysis of 12 studies (71% vs. 57%; p=.0002). *SCN5A*(+) patients had a higher proportion of sick sinus syndrome (43% vs. 5%; p<.001) and atrial ventricular block (71% vs. 30%; p=.01). However, there was a lower rate of VT/ventricular fibrillation inducibility during electrophysiology study (41% vs. 51%; p=.01), which may partially be explained by heterogeneity in electrophysiology study protocols. The *SCN5A* mutation was associated with an increased risk of major adverse events in the overall BrS (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.19 to 2.26; p=.005), Asian (OR, 1.82; 95% CI, 1.07 to 3.11; p=.03), and Caucasian (OR, 2.24; 95% CI, 1.02 to 4.90; p=.04) patient populations.

Monasky et al (2019) evaluated 15 BrS-associated genes (*CACNA1C, CACNA2D1, CACNB2, GPD1L, HCN4, KCND2, KCND3, PKP2, RANGRF, SCN10A, SCN1B, SCN2B, SCN3B, SCN5A,* and *TRPM4*) with the TruSight One sequencing kit and NextSeq platform in 297 BrS patients screened for study enrollment.[40,] The 2 most common mutations were *SCN5A* (84 [28.3%]) followed by *SCN10A* (8 [2.7%]). Clinical characteristics of BrS patients harboring *SCN5A* or *SCN10A* mutations were not found to be significantly different between probands, although patients with a variety of type I-III ECG patterns were represented in both cohorts.

Sacilotto et al (2020) reported data from the Genetics of Brazillian Arrhythmias (GenBra) registry.[41,] From 1999 to 2020, 138 (22 symptomatic) consecutive patients with type-1 BrS were assessed for invasive and noninvasive parameters and *SCN5A* mutation status. No difference in the rate of *SCN5A*-positive patients was found between asymptomatic and symptomatic groups (20/76 [26.3%] vs. 5/17 [29.4%]; p=.770). *SCN5A* carriers had significantly higher frequencies of aVR sign, S wave, and QRS-f.

Milman et al (2021) published an observational study of 678 patients from 14 countries with a first arrhythmic event due to BrS.[42,] Of the 392 probands, 23.5% were *SCN5A*(+) with 44 pathogenic/likely pathogenic variants and 48 variants of unknown significance. The remaining probands were *SCN5A*(-). Patients with pathogenic/likely pathogenic variants were more likely to be aged <16 years (p=.023), female (p=.013), and have a family history of SCD (p<.001) compared to patients who were *SCN5A*(-). Logistic regression found that White ethnicity (OR, 5.41; 95% CI, 2.8 to 11.19; p<.001) and family history of SCD (OR, 2.73; 95% CI, 1.28 to 5.82; p=.009) were associated with having a pathogenic/likely pathogenic genotype.

Wang et al (2022) published an observational study of 79 patients in China who had BrS, 59 of whom underwent genetic testing.[43,] Abnormal genetic results occurred in 25 (42.37%) patients, with pathogenic or likely pathogenic mutations in 8 (13.56%) patients. The genes most commonly associated with genetic mutations were *SCN5A* (44%), *SCN10A* (20%), and *DSP* (16%). Genetic carriers were more likely to have prolonged P-wave duration, QRS duration, QTc interval, decreased QRS amplitude, and T-wave or R-wave axis deviation than individuals without abnormal genetic findings.

The description of the studies are below in Table 10 and results are shown in Table 11.

Table 10. Characteristics of Clinical Validity Studies of Genetic Testing for Brugada Syndrome

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors
Priori et al (2000)[34,]	Patients with the typical Brugada ECG pattern, without structural heart disease	Retrospective	Clinical and ECG diagnosis, criteria not specified	*SCN5A*	Unclear
Bai et al (2009)[31,]	Patients from a sample of 1394 consecutive probands with either a clinically confirmed or suspected diagnosis of LQTS, BrS, or CPVT or a personal or family history of idiopathic ventricular fibrillation/cardiac arrest/SCD referred for molecular diagnosis	Consecutive; prospective	Diagnosed clinically as conclusive or possible; criteria not specified	*SCN5A*	NR
Kapplinger et al (2010)[35,]	Unrelated cases of clinically suspected BrS from international BrS databases (5 Europe, 3 United States, 1 Japan)	Retrospective; unclear whether the samples were consecutive	Referring physician made a clinical diagnosis of either possible or definite BrS, criteria not specified	27 translated exons in *SCN5A*	Unclear
Hu et al (2014)[36,]	Unrelated patients with	Retrospective;	2005 Consensus	*SCN10A*	Unclear

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors
	BrS referred to a single-center for genetic testing	not clear if selection was consecutive	Conference diagnostic criteria (Heart Rhythm Society and the European Heart Rhythm Association)		
Behr et al (2015)[37,]	Unrelated BrS Caucasian patients negative for *SCN5A* variants with symptoms and/or a family history of sudden death or BrS from 8 centers in Europe and U.S.	Retrospective; not clear if selection was consecutive	Locally diagnosed, criteria not specified	*SCN10A, HAND1, CASQ2, TKT, PLN, TBX5, TBX3*	Unclear
Andorin et al (2016)[38,]	Patients (some from same family) <19 years of age at "diagnosis" of BrS (based on ECG pattern alone) in 16 European hospitals; 20% were symptomatic	Retrospective; not clear if selection was consecutive	Brugada type 1 ECG pattern either spontaneously or after challenge with a sodium channel blocker	*SCN5A*	Unclear
Chen et al (2019)[39,]	Unrelated BrS patients >16 years of age with spontaneous or drug-induced type 1 ECG pattern from 17 studies in Japan, Europe, China, and others; 59% were spontaneously symptomatic	Meta-analysis; consecutive	Spontaneous or induced Brugada type 1 ECG pattern	*SCN5A*	NR
Monasky et al (2019)[40,]	BrS patients (some from same family) with spontaneous or inducible arrhythmia	Prospective; not clear if selection was consecutive	Clinical diagnosis with EPS study and substrate ablation; unclear requirements for ECG pattern type	*SCN5A, SCN10A*	NR
Sacilotto et al (2020)[41,]	BrS patients in Brazillian registry with type 1 ECG pattern	Prospective; consecutive	Spontaneous or induced Brugada type 1 ECG pattern	*SCN5A, GPD1L, SCN10A, SCN18, SCN28, SCN38, CACNA1C, CACNB2, KCND3,*	Unclear

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors
				CACNAD2, KCNJ8, KCNE3, SLMAP, RANGRF	
Milman et al (2021)[42,]	BrS patients from 14 countries with a first arrhythmic event	Observational cohort (Survey on Arrhythmic Events in Brugada Syndrome); selection not reported	NR	*SCN5A*	None
Wang et al (2022)[43,]	Patients with suspected BrS	Retrospective	One of 3 characteristic ECG patterns and one of the following: family history of BrS or SCD, documented ventricular arrhythmia, or arrhythmic syncope or paroxysmal nocturnal dsypnea	*ABCC9, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CASQ2, DSG2, DSP, GPD1L, HCN4, KCND3, KCNE3, KCNE5, KCNJ8, KCNH2, PLN, PKP2, RANGRF, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4A, SCN5A, SCNN1A, TRPM4, TTN*	None

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; ECG: electrocardiogram; EPS: electrophysiological study; LQTS: long QT syndrome; NR: not reported; SCD: sudden cardiac death.

Table 11. Yield of Genetic Testing for Brugada Syndrome

Study	N	Excluded Samples	Yield of Genetic Testing (Range)
Priori et al (2000)[34,]	52	NR	15%
Bai et al (2009)[31,]	798		8%
Conclusive Dx	405		13%
Possible Dx	248		4%
Kapplinger et al (2010)[35,]	2111	NR	21% (11% to 28%)
Hu et al (2014)[36,]	150	NR	17%
Behr et al (2015)[37,]	156	*SCN5A* re-sequencing (n=2) revision of the diagnosis (n=4), non-European ancestry (n=3)	11.5%
Andorin et al (2016)[38,]	75 (from 62 families)	Only 75/106 had genetic analysis; reasons for lack of genetic analysis unclear	77%
Chen et al (2019)[39,]	1780	NR	20% (11% to 43%)
Monasky et al (2019)[40,]	294	NR	28.3% (*SCN5A*) 2.7% (*SCN10A*)
Sacilotto et al (2020)[41,]	138 (109 probands; 22/138 symptomatic)	Genetic analysis was only performed in 93/138 patients (76 asymptomatic, 17 symptomatic)	26.3% (*SCN5A*, asymptomatic) 29.4% (*SCN5A*, symptomatic)
Milman et al (2021)[42,]	678 (392 probands)	NR	23.5%
Wang et al (2022)[43,]	79 probands	Genetic testing was performed in only 59 probands	13.56% with pathogenic/likely pathogenic variants

Dx: diagnosis; NR: not reported.

The purpose of limitations tables (see Tables 12 and 13) is to display notable limitations identified in selected primary studies. This information is synthesized as a summary of the body

of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 12. Study Relevance Limitations of Clinical Validity Studies of Genetic Testing for Brugada Syndrome

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Priori et al (2000)[34,]	3: Criteria for clinical diagnosis unclear				
Bai et al (2009)[31,]	3: Criteria for clinical diagnosis unclear				
Kapplinger et al (2010)[35,]	3: Criteria for clinical diagnosis unclear				
Hu et al (2014)[36,]					
Behr et al (2015)[37,]	3: Criteria for clinical diagnosis unclear				
Andorin et al (2016)[38,]	4: Majority of probands had only Brugada pattern ECG without symptoms				
Monasky et al (2019)[40,]	3: Criteria for clinical diagnosis unclear; patients had variety of type I-III ECG patterns			1: Study does not directly address a key health outcome	
Sacilotto et al (2020)[41,]	4: Majority of probands had only Brugada type 1 ECG pattern without symptoms				
Milman et al (2021)[42,]	3: Criteria for clinical diagnosis unclear			1: Study does not directly address a key health outcome	
Wang et al (2022)[43,]				1: Study does not directly address a key health outcome	

ECG: electrocardiogram.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding

minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 13. Study Design and Conduct Limitations of Clinical Validity Studies of Genetic Testing for Brugada Syndrome

Study	Selection [a]	Blinding [b]	Test Delivery [c]	Selective Reporting [d]	Data Completeness [e]	Statistical [f]
Priori et al (2000)[34],	1: Not clear if all eligible patients were included	1: Blinding not described			1: No description of exclusions or indeterminate results	
Bai et al (2009)[31],		1: Blinding not described			1: No description of exclusions or indeterminate results	
Kapplinger et al (2010)[35],	1: Not clear if all eligible patients were included	1: Blinding not described			1: No description of exclusions or indeterminate results	
Hu et al (2014)[36],	1, 2: Not clear if all eligible patients were included; not clear how samples were selected	1: Blinding not described			1: No description of exclusions or indeterminate results	
Behr et al (2015)[37],	1, 2: Not clear if all eligible patients were included; not clear how samples were selected	1: Blinding not described				
Andorin et al	1, 2: Not clear if all	1: Blinding			1: Unclear why ~30% of patients did not	

Study	Selection [a]	Blinding [b]	Test Delivery [c]	Selective Reporting [d]	Data Completeness [e]	Statistical [f]
(2016)[38,]	eligible patients were included; not clear how samples were selected	not described			have genetic analysis	
Monasky et al (2019)[40,]	1, 2: Not clear if all eligible patients were included; not clear how samples were selected	1: Blinding not described		1: Not registered; 2: Evidence of selective reporting; detailed outcomes for *SCN5A* cohort not reported		
Sacilotto et al (2020)[41,]		1: Blinding not described			1: Unclear why ~33% of patients did not have genetic analysis	
Milman et al (2021)[42,]	1: Selection not described	1: Blinding not described				
Wang et al (2022)[43,]	1, 2: Not clear if all eligible patients were included; not clear how samples were selected	1: Blinding not described				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples

excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Catecholaminergic Polymorphic Ventricular Tachycardia

Studies reporting the yield of *RyR2* testing in CPVT have been conducted in patients with clinically diagnosed CPVT.[31,44,45,46,]

Characteristics are shown in Table 14 and results are shown in Table 15. The yield in cases with a 'strong' diagnosis of CPVT is around 60%.

Table 14. Characteristics of Clinical Validity Studies of Genetic Testing for Catecholaminergic Polymorphic Ventricular Tachycardia

Study	Study Population	Design	Clinical Diagnosis	Genes included	Blinding of Assessors
Priori et al (2002)[44,]	Patients with documented polymorphic ventricular arrhythmias occurring during physical or emotional stress with a normal heart	Retrospective; unclear whether samples were consecutive	Ventricular fibrillation elicited by physical or emotional stress in the absence of identifiable precipitating factors and in the absence of VT documented at Holter and/or exercise stress testing	*RyR2*	NR
Medeiros-Domingo et al (2009)[45,]	Patients referred for genetic testing with "strong" diagnosis of CPVT	Retrospective; unclear whether samples were consecutive	Exertional syncope plus documentation of bidirectional or polymorphic VT	*RyR2*	NR
Bai et al (2009)[31,]	Patients from a sample of 1394 consecutive probands with either a clinically confirmed or suspected diagnosis of LQTS, BrS, or CPVT or a personal or family history of idiopathic ventricular fibrillation/cardiac arrest/SCD referred for molecular diagnosis	Consecutive; prospective	Diagnosed clinically as conclusive or possible; criteria not specified	*RyR2*	NR
Kapplinger et al (2018)[46,]	Patients referred for commercial genetic testing with well-phenotyped	Retrospective; unclear whether samples were consecutive	History of exertional syncope with documentation of exercise-related	*RyR2*	NR

Study	Study Population	Design	Clinical Diagnosis	Genes included	Blinding of Assessors
	cases and "strong" diagnosis of CPVT		bidirectional or polymorphic VT		

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; NR: not reported; SCD: sudden cardiac death; VT: ventricular tachycardia.

Table 15. Yield of Genetic Testing for Catecholaminergic Polymorphic Ventricular Tachycardia

Study	N	Excluded Samples	Yield of Genetic Testing
Priori et al (2002)[44,]	30	NR	47%
Medeiros-Domingo et al (2009)[45,]	78	NR	60%
Bai et al (2009)[31,]	175	NR	35%
Conclusive Dx	81	NR	62%
Possible Dx	21	NR	5%
Kapplinger et al (2018)[46,]	78	NR	59%

Dx: diagnosis; NR: not reported.

The purpose of the limitations tables (see Tables 16 and 17) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 16. Study Relevance Limitations of Clinical Validity Studies of Genetic Testing for Catecholaminergic Polymorphic Ventricular Tachycardia

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Priori et al (2002)[44,]					
Medeiros-Domingo et al (2009)[45,]					
Bai et al (2009)[31,]	3: Criteria for clinical diagnosis unclear				
Kapplinger et al (2018)[46,]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4.

Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 17. Study Design and Conduct Limitations of Clinical Validity Studies of Genetic Testing for Catecholaminergic Polymorphic Ventricular Tachycardia

Study	Selection [a]	Blinding [b]	Test Delivery [c]	Selective Reporting [d]	Data Completeness [e]	Statistical [f]
Priori et al (2002)[44,]	1,2: Not clear if all eligible patients were included	1: Blinding not described			1: No description of exclusions or indeterminate results	
Medeiros-Domingo et al (2009)[45,]	1,2: Not clear if all eligible patients were included	1: Blinding not described			1: No description of exclusions or indeterminate results	
Bai et al (2009)[31,]		1: Blinding not described			1: No description of exclusions or indeterminate results	
Kapplinger et al (2018)[46,]	1,2: Not clear if all eligible patients were included	1: Blinding not described			1: No description of exclusions or indeterminate results	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

The specificity of known pathogenic variants for CPVT is uncertain but is likely high. A 2013 publication from the National Heart, Lung, and Blood Institute ESP reported on sequence variants

in a large number of patients without CPVT.[47,] 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 variants previously associated with CPVT. Authors identified 11% previously described variants in the ESP population in 41 putative CPVT cases. These data suggested that false-positive results are low, but authors cautioned 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.

Section Summary: Clinical Validity of Genetic Testing for the Diagnosis of a Specific Channelopathy
In probands with LQTS and CPVT, genetic testing has a yield for identifying a disease-causing variant of approximately 70% and 60%, respectively. In probands with BrS, genetic testing has a much lower yield probably ranging from about 15% to 30% depending on the genes included. The yield of genetic testing is not well established in SQTS.

Data on the clinical specificity are available for LQTS but there are 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, the rate is approximately 5% among patients without LQTS; therefore, the specificity for these types of variants is lower, and false-positive results do occur.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Long QT Syndrome
Long QT syndrome may lead to catastrophic outcomes (i.e., SCD) in otherwise healthy individuals. Diagnosis using clinical methods alone may lead to underdiagnosis of LQTS, thus exposing undiagnosed patients to the risk of SCA. For patients in whom the clinical diagnosis of LQTS is uncertain, genetic testing may be necessary to 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 an LQTS variant, with or without other signs or symptoms.

Treatment with β-blockers has been demonstrated to decrease the likelihood of cardiac events, including SCA.

Sodium-channel blockers (e.g., mexiletine) are sometimes used, particularly in those with *SCN5A* variants. Preliminary modeling studies by Zhu et al (2018) designed to predict LQT3 mutations with enhanced mexiletine sensitivity have been successfully validated in a small initial cohort of patients.[48,]

Treatment with an ICD is available for patients who fail or cannot take β-blockers.

Two studies evaluated the psychological effects of genetic testing for LQTS. Hendriks et al (2008) studied 77 patients with an LQTS variant and their 57 partners.[49,] 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 psychological distress decreased over time but remained elevated at 18 months. Andersen et al (2008) conducted qualitative interviews with 7 individuals with LQTS variants.[50,] 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.

The evidence suggests that different LQTS subtypes may have variable prognoses, thus indicating that genetic testing may assist in risk stratification. Several reports have compared rates of cardiovascular events in subtypes of LQTS.[51,52,53,54,] These studies have reported that rates of cardiovascular events differ among subtypes, but there is no common pattern across all studies. Three of the 4 studies[51,52,53,] reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba et al (1998)[54,] reported that patients with LQT1 have higher event rates than patients with LQT2.

Some studies that have reported outcomes of treatment with β-blockers have also reported outcomes by specific subtypes of LQTS.[51,53,] Priori et al (2004) reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of β-blocker therapy.[51,] There was a decrease in event rates in all LQTS subtypes, with a similar magnitude of decrease in each subtype. Moss et al (2000) also reported pre-post event rates for patients treated with β-blocker therapy.[55,] This study indicated a significant reduction in event rates for patients with LQT1 and LQT2 but not for LQT3. This analysis was limited by the small number of patients with LQT3 and cardiac events before β-blocker treatment (4/28). Sauer et al (2007) evaluated differential response to β-blocker therapy in a Cox proportional hazards analysis.[56,] They reported an overall risk reduction in the first cardiac event of approximately 60% (hazard ratio [HR], 0.41; 95% 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=.04) than in those with LQT1 or LQT2. There was no difference in efficacy between LQT1 and LQT2 genotypes.

Shimizu et al (2019) conducted an observational study on 1124 Japanese patients with LQTS and various pathogenic variants (e.g., nonpore membrane-spanning variants, pore site and segment

5 to segment 6 [S5-pore-S6] variants, and N/C-terminus variants) for LQT1, LQT2, and LQT3.[57,] For patients with LQT1, the membrane-spanning pathogenic variant was associated with a higher risk of arrhythmic events compared to the N/C-terminus variant in female patients (HR, 1.60; 95% CI, 1.19 to 2.17; p=.002). Patients with LQT2 S5-pore-S6 variants were found to have a higher risk of arrhythmic events compared to others (HR, 1.88; 95% CI, 1.44 to 2.44; p<.001). In patients with LQT3, S5-pore-S6 variants were associated with lethal arrhythmic events compared with other (HR, 4.2; 95% CI, 2.09 to 8.36; p<.001). While these findings suggest that risk stratification of arrhythmic events may potentially be informed by specific pathogenic gene variants in LQTS, the study is limited by its retrospective analysis.

Biton et al (2019) studied LQTS patients (n=212) enrolled in the Rochester LQTS ICD registry who underwent ICD implantation for primary prevention of SCD.[58,] During median follow-up duration of 9.2 ± 4.9 years, 42 patients experienced at least 1 appropriate shock. The cumulative probability of appropriate shock at 8 years was 22%. QT_c ≥550 ms (HR, 3.94; 95% CI, 2.08 to 7.46; p<.001) and prior syncope on β-blockers (HR, 1.92 ; 95% CI, 1.01 to 3.65; p=.047) were associated with an increased risk of appropriate shock. Importantly, LQT2 genotype (HR, 2.10; 95% CI, 1.22 to 3.61; p=.008) and the presence of multiple mutations (HR, 2.87; 95% CI, 1.49 to 5.53; p=.002) were associated with an increased risk of recurrent shocks compared to LQT1 genotype, suggesting that both clinical and genetic variables may have utility in the risk stratification of high-risk patients undergoing evaluation for an ICD.

Cuneo et al (2020) conducted a multicenter retrospective analysis of 148 pregnancies from 103 families with the 3 most common heterozygous pathogenic LQTS genotypes (*KCNQ1*, *KCNH2*, or *SCN5A*).[59,] Fetal death at >20 weeks gestation was 8 times more frequent compared to the general population. The likelihood of fetal death was found to be significantly greater with maternal versus paternal LQTS (24.4% vs. 3.5%; p=.36).

Brugada Syndrome

The diagnostic testing yield for BrS limits its clinical usefulness. 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 decisions are 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.

Rattanawong et al (2019) conducted a systematic review and meta-analysis of 7 cohort and case-control studies investigating the association of *SCN5A* mutations with major arrhythmic events (e.g., VT, ventricular fibrillation, appropriate implantable ICD shocks, aborted cardiac arrest, and SCD) in patients with BrS (n=1049).[60,] *SCN5A* mutations were associated with major arrhythmic events in Asian patients (risk ratio, 2.03; 95% CI, 1.37 to 3.00; p=.0004; I^2=0.0%), symptomatic patients (risk ratio, 2.66; 95% CI, 1.62 to 4.36; p=.0001; I^2=23.0%), and patients with spontaneous Brugada type 1 ECG pattern (risk ratio, 1.84; 95% CI, 1.05 to 3.23; p=.03; I^2=0.0%). The inclusion criteria did not specify criteria for establishing a clinical diagnosis of BrS, and therefore, the analysis was limited by heterogeneity in clinical, genetic, and outcome reporting among included studies. Reporting on specific major arrhythmic events relevant to health outcomes such as delivery of appropriate ICD shocks and aborted cardiac arrests was not

individually reported. Therefore, the clinical utility of *SCN5A* genetic variant risk stratification in this population remains unclear.

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 a 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 pathogenic 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 SCD. Therefore, there is a 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. Also, 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, consistent with the clinical rarity of the condition. Clinical sensitivity for the test is low, with laboratory test providers estimating a yield as low as 15%.

Section Summary: Clinical Utility of Genetic Testing for the Diagnosis of a Specific 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 have a pathogenic variant.

For BrS, the clinical utility is less certain, but there is potential for genetic testing to change treatment decisions by stratifying patients for the need for ICD. A meta-analysis reported that the presence of *SCN5A* variants could not predict cardiac events; however, a registry study published after the meta-analysis reported that patients with the *SCN5A* variant experienced more cardiac events and experienced the first event at a younger age than patients who did not have the *SCN5A* variant. Studies have been conducted to further determine risk level by type of variant, but the studies have small sample sizes, so interpretation is limited.

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.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input

In response to requests, input was received from 3 specialty societies (4 reviewers) and 4 academic medical centers (9 reviewers) while this policy was under review in 2015. Input was limited to the use of genetic testing for Brugada syndrome (BrS) and short QT syndrome (SQTS). There was a consensus that genetic testing for BrS is medically necessary to establish the diagnosis of BrS in an individual with a suspected but not definitive diagnosis of BrS and to evaluate family members of an individual with a known pathogenic genetic variant for BrS. There was less consensus on whether genetic testing for variants associated with SQTS is medically necessary to establish the diagnosis of SQTS in an individual with a suspected but not definitive diagnosis of SQTS, but there was consensus that testing for SQTS to evaluate family members of an individual with a known pathogenic genetic variant for SQTS is medically necessary. However, reviewers acknowledged that the rarity of SQTS somewhat limited conclusions that could be made.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association

In 2023, the American Heart Association published a scientific statement on interpreting incidentally identified genes associated with heritable cardiovascular diseases (including cardiac ion channelopathies).[61,] The statement notes that: "In partnership with a specialized inherited cardiovascular disease (CVD) center, individuals found to have an incidentally identified variant should undergo a comprehensive clinical evaluation for the CVD in question. This pretest probability of having the CVD in question should be modified by the strength of the gene variant with CVD to arrive at a posttest probability that the variant in question places the patient at risk of developing disease. This determines the need for additional clinical evaluation, management, and follow-up." In their proposed framework for the evaluation of a patient with incidental findings of genetic variants associated with channelopathies, the American Heart Association suggests that a electrocardiogram (ECG) testing, a 24-hour or longer Holter monitor, and an exercise stress test (if possible) should be performed.

In 2021, the American Heart Association published a scientific statement on genetic testing for heritable cardiovascular diseases (including channelopathies) in children.[62,] The statement recommends that genetic testing be performed when a cardiac channelopathy is likely to be

present, including after a variant has been found in a family member. Testing to identify at-risk relatives can be considered. Brugada syndrome is difficult to identify since not all adults express genetic variants; therefore, identifying at-risk children may require clinical evaluation, ECG testing, and/or pharmacologic challenge of all of the child's first-degree relatives. Genetic testing should also be performed in children who are resuscitated from cardiac arrest with no clear cause. Several factors can be considered when deciding the appropriate age for genetic testing of an individual child, including whether the disease is expected to present during childhood, whether the channelopathy can be fatal, whether therapies exist to mitigate mortality risk, and family preferences. Ongoing follow-up genetic testing can confirm pathogenicity of the variant over time.

In 2020, the American Heart Association authored a scientific statement on genetic testing for inherited cardiovascular disease.[63,] Prior guidelines from several international cardiovascular clinical organizations and published studies were reviewed. For BrS, the authors concluded that genetic testing supports the clinical diagnosis. For patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (LQTS), genetic testing is needed for diagnosis and subtype classification. Management of LQTS may also differ depending on the causative gene. Genetic testing for all of these conditions facilitates identifying at-risk family members. Specific genes with the strongest causative evidence for cardiac channelopathies are listed in Table 18.

Table 18. Specific Genes for Testing in Cardiac Channelopathies

Channelopathy	Genes with definitive evidence of a causal role in the disease
LQTS	*KCNQ1*, *KCNH2*, *SCN5A*
SQTS	*KCNH2, KCNQ1, KCNJ2*
BrS	*SCN5A*
CPVT	*RYR2, CASQ2*

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

American Heart Association, American College of Cardiology, and Heart Rhythm Society

In 2017, the American Heart Association, American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (SCD).[64,] Table 19 summarizes the recommendations relating to cardiac ion channelopathies.

Table 19. Recommendations for Genetic Testing in Cardiac Channelopathies

Consensus Recommendation	COR	LOE
In first-degree relatives of patients who have a causative mutation for LQTS, CPVT, SQTS, or BrS, genetic counseling and mutation-specific genetic testing are recommended.	I (strong)	B-NR
In patients with clinically diagnosed LQTS, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic	I (strong)	B-NR

Consensus Recommendation	COR	LOE
information.		
In patients with CPVT and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable. Genetic testing may confirm a diagnosis; however, therapy for these patients is not guided by genotype status.	IIa (moderate)	B-NR
In patients with suspected or established BrS, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives, allowing for lifestyle modification and potential treatment.	IIb (weak)	C-EO
In patients with SQTS, genetic testing may be considered to facilitate screening of first-degree relatives.	IIb (weak)	C-EO

B-NR: moderate level of evidence, nonrandomized studies; BrS: Brugada syndrome; C-EO: consensus of expert opinion based on clinical experience; COR: class of recommendation; CPVT: catecholaminergic polymorphic ventricular tachycardia; LOE: level of evidence; LQTS: long QT syndrome; SQTS: short QT syndrome; VT: ventricular tachycardia.

Heart Rhythm Society and Asia Pacific Heart Rhythm Society

In 2020, the Heart Rhythm Society and Asia Pacific Heart Rhythm Society authored an expert consensus statement on investigation of individuals who have died from sudden unexplained death, patients with sudden cardiac arrest (SCA), and their families.[65,] Suspicion for a genetic cause of SCD or a resuscitated SCA warrants genetic testing and counseling. Genetic testing should include the most likely genes for the suspected phenotype and should include clinical and genetic evaluation of family members to identify other at-risk individuals. Testing of many genes can lead to uncertainty and misinterpretation of results and is generally discouraged. Genetic investigation should only be undertaken by multidisciplinary teams with expertise in cardiology, genetics, and pathology. The document provides detailed guidance on specific scenarios for which genetic testing is warranted but does not describe specific genes that should be tested.

Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society

In 2013, the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society issued an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes.[66,] The consensus statement refers to the 2011 guidelines on genetic testing for channelopathies and cardiomyopathies discussed next 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 consensus statement provided guidance for the evaluation of patients with idiopathic ventricular fibrillation, sudden unexplained death syndrome, and sudden unexplained death in infancy. Guidance on genetic testing for these patients was included (see Table 20). Idiopathic ventricular fibrillation is defined as a resuscitated cardiac arrest victim, preferably with documentation of ventricular fibrillation, in whom known cardiac, respiratory, metabolic, and toxicologic etiologies have been excluded through clinical evaluation.

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

Table 20. Recommendations for Genetic Testing in Idiopathic Ventricular Fibrillation, Sudden Unexplained Death Syndrome, and Sudden Unexplained Death in Infancy

	Consensus Recommendation	Class
IVF	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.	IIa
	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.	III
SUDS	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.	I
SUDI	Collection of blood and/or suitable tissue for molecular autopsy is recommended in all SUDI victims.	I
	An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing can be useful for all SUDI victims.	IIa
	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.	I

IVF: idiopathic ventricular fibrillation; SUDI: sudden unexplained death in infancy; SUDS: sudden unexplained death syndrome.

In 2011, the Heart Rhythm Society and European Heart Rhythm Association jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies.[24,] This document made the following specific recommendations on testing for LQTS, BrS, CPVT, and SQTS (see Table 21).

Table 21. Cardiac Ion Channelopathy Testing Recommendations

	Consensus Recommendation	Class[a]	LOE[b]
LQTS	• Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) 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 (*KCNQ1*, *KCNH2*, *SCN5A*) 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., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults).	I	C

	Consensus Recommendation	Class[a]	LOE[b]
	• 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.		
	Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) 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.	IIb	C
BrS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.	I	C
	Comprehensive or BrS1 (*SCN5A*) 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.	IIa	C
	Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.	III	C
CPVT	Comprehensive or *CPVT1* and *CVPT2* (*RYR2*, *CASQ2*) 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.	I	C
SQTS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.	I	C
	Comprehensive or SQT1-3 (*KCNH2*, *KCNQ1*, *KCNJ2*) 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.	IIb	C

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; ECG: electrocardiogram; LOE: level of evidence; LQTS: long QT syndrome; QTc: corrected QT; SQTS: short QT syndrome.
[a] 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).
[b] Only consensus opinion of experts, case studies or standard of care.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 22.

Table 22. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04832126	Genetic Analysis of Heart Channelopathies in Brazilian Patients and Their Relatives	100	Jul 2024 (recruiting)
NCT03783975	A Community-Based Approach to Overcoming Barriers to Cascade Screening for Long QT Syndrome	500	Dec 2022 (recruiting)
NCT02439658	Genetics of QT Prolongation With Antiarrhythmics (DOFEGEN)	1000	April 2023 (recruiting)
NCT04232787	Discovering the Genetic Causes of Brugada Syndrome in Thais and Southeast Asian Population (SEA-BrS)	750	Jan 2023 (recruiting)
NCT02824822	Genetic Markers of Cardiovascular Diseases and the Potential Role in Sudden Unexpected Death in Epilepsy	600	Dec 2029 (recruiting)
NCT02014961	Worm Study: Identification of Modifier Genes in a Unique Founder Population With Sudden Cardiac Death	223	Apr 2025 (recruiting)
NCT03880708	China Inherited Ventricular Arrhythmias Registry, a Multicenter, Observational and Prospective Study	500	Oct 2027 (recruiting)
Unpublished			
NCT01705925[a]	Multicenter Evaluation of Children and Young Adults With Genotype Positive Long QT Syndrome	92	Dec 2018 (completed)
NCT02425189	The Canadian National Long QT Syndrome Registry (LQTSREG)	1051	Aug 2020 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81403	Molecular pathology procedure, Level 4 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
81413	Cardiac ion channelopathies (e.g., 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 (e.g., 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
0237U	Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome

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: ▪ 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." ▪ 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 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." ▪ 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
	In Coding section: ▪ Added CPT codes: 81403, 81405, 81406, 81407, 81408 ▪ Updated Coding information ▪ Added ICD-10 Diagnoses codes
	References updated
02-16-2015	Description section updated
	In Policy section: ▪ 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 "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

REVISIONS	
	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 (i.e., if there is a moderate-to-high pretest probability of either condition), genetic testing could be considered."
	Rationale section updated
	In Coding section: ▪ Updated Coding instructions
	In Revision section: ▪ Removed revision details for: 08-12-2009, 10-26-2010, 12-01-2011, 02-14-2012, 04-10-2012
	References updated
01-01-2017	In Coding section: ▪ Added CPT Codes: 81413, 81414 (Effective January 1, 2017) ▪ Removed CPT Codes: 81280, 81281, 81282 (Effective December 31, 2016)
03-29-2021	Updated Description section
	In Policy Section: • Added: <u>Long QT Syndrome</u> A. Genetic testing to confirm a diagnosis of congenital long QT syndrome (LQTS) may be considered medically necessary when signs and/or symptoms of LQTS are present, but a definitive diagnosis cannot be made without genetic testing. This includes: 1. Individuals who do not meet the clinical criteria for LQTS (i.e., those with a Schwartz score <4): but have a moderate-to-high pretest probability (see Policy Guidelines section) based on the Schwartz score and/or other clinical criteria. B. Genetic testing of asymptomatic individuals to determine future risk of LQTS may be considered medically necessary when at least one of the following criteria is met: 1. A close relative (i.e., first-, second-, or third-degree relative) with a known LQTS variant; OR 2. A close relative diagnosed with LQTS by clinical means whose genetic status is unavailable. C.Genetic testing for LQTS for all other situations not meeting the criteria outlined above, including but not limited to determining prognosis and/or directing therapy in patients with known LQTS, is considered experimental / investigational. <u>Brugada Syndrome</u> D.Genetic testing to confirm a diagnosis of Brugada syndrome (BrS) may be considered medically necessary when signs and/or symptoms consistent with BrS (see Policy Guidelines section) are present, but a definitive diagnosis cannot be made without genetic testing. E.Genetic testing of asymptomatic individuals to determine future risk of BrS may be considered medically necessary when patients have a close relative (i.e., first-, second-, or third-degree relative) with a known BrS variant. F.Genetic testing for BrS for all other situations not meeting the criteria outlined above is considered experimental / investigational.

REVISIONS	
	Catecholaminergic Polymorphic Ventricular Tachycardia G.Genetic testing to confirm a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered medically necessary when signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing. H.Genetic testing of asymptomatic individuals to determine future risk of CPVT may be considered medically necessary when at least one of the following criteria is met: 1. A close relative (i.e., first-, second-, or third-degree relative) with a known CPVT variant; OR 2. A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable. I.Genetic testing for CPVT for all other situations not meeting the criteria outlined above is considered experimental / investigational. Short QT Syndrome J.Genetic testing of asymptomatic individuals to determine future risk of short QT syndrome (SQTS) may be considered medically necessary when patients have a close relative (i.e., first-, second-, or third-degree relative) with a known SQTS variant. K.Genetic testing for SQTS for all other situations not meeting the criteria outlined above is considered experimental / investigational. • Deleted Long QT Syndrome 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 Brugada Syndrome D.Genetic testing for Brugada syndrome is considered experimental / investigational. 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 mutationOR 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
	Updated Rationale section
	In Coding section • Added: CPT code 0237U and ICD10 Z13.6 • Removed: all ICD-9 diagnosis codes and ICD-10 diagnosis code Q24.8
	Updated Reference section
	Added Appendix section
03-08-2022	Updated Description Section
	Updated Rationale Section

REVISIONS	
	Updated References Section
02-28-2023	Updated Description Section
	Updated Rationale Section
	Updated References Section
	Removed Appendix Section
03-12-2024	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes
	Updated References Section

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