Medical Policy

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Title: Genetic Testing for Cardiac Ion Channelopathies (e.g., Congenital Long QT Syndrome, Brugada Syndrome, etc.)

Description/Background

CARDIAC ION CHANNELOPATHIES

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

The prevalence of any cardiac channelopathy is still ill-defined but is thought to be between 1:2000 and 1:3000 persons in the general population.[1] Data pertaining to the individual prevalence of LQTS, CPVT, BrS, and 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 (LQTS)
Congenital LQTS is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential, increasing the risk for arrhythmic events, such as torsades de pointes, which may in turn result in syncope and sudden cardiac death.

Congenital LQTS usually manifests before the age of 40 years. It is estimated that more than one half of the 8,000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1–2% per year, although this figure will vary with the genotype.

Brugada Syndrome (BrS)
BrS is characterized by cardiac conduction abnormalities that increase the risk of syncope, ventricular arrhythmia, and sudden cardiac death. The disorder primarily manifests during adulthood, although ages between 2 days and 85 years have been reported.[3] BrS is an autosomal dominant disorder with an unexplained male predominance. Males are more likely to be affected than females (approximately an 8:1 ratio). BrS is estimated to be responsible for 12% of SCD cases.[1] For both sexes there is an equally high risk of ventricular arrhythmias or sudden death.[4] Penetrance is highly variable, with phenotypes ranging from asymptomatic expression to death within the first year of life.[5]

Catecholaminergic Polymorphic Ventricular Tachycardia
CPVT is a rare inherited channelopathy that may present with autosomal dominant or autosomal recessive inheritance. The disorder manifests as a bidirectional or polymorphic VT precipitated by exercise or emotional stress. The prevalence of CPVT is estimated between 1 in 7000 and 1 in 10,000 persons. CPVT has a mortality rate of 30% to 50% by age 35 and is responsible for 13% of cardiac arrests in structurally normal hearts.[6] CPVT was previously believed to be only manifest during childhood, but studies have now identified presentation between infancy and 40 years of age.[7]

Short QT Syndrome (SQTS)
SQTS is characterized by a shortened QT interval on the 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 sudden cardiac death (SCD) refer to the sudden interruption of cardiac activity with circulatory collapse. The most common cause is coronary artery disease. Approximately 5% to 10% of SCA and SCD are due to arrhythmias without structural cardiac disease and are related to the primary electrical disease (PED) syndromes. The previously described cardiac ion channelopathies are among the PED syndromes.

The evaluation and management of a survivor of SCA include an assessment of the circumstances of the event as well as a comprehensive physical examination emphasizing cardiovascular and neurologic systems, laboratory testing, electrocardiogram, and more advanced cardiac imaging or electrophysiologic testing as may be warranted. Genetic testing might be considered when, after completion of a comprehensive evaluation, there are findings consistent with a moderate-to-high likelihood of a PED. 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 mutations on at least 13 genes encoding potassium-channel proteins, sodium-channel proteins, calcium channel-related factors, and membrane adaptor proteins that have been associated with LQTS. In addition to single mutations, some cases of LQTS are associated with deletions or duplications of genes.[9]

The absence of a mutation does not imply the absence of LQTS; it is estimated that mutations are only identified in 70% to 75% of patients with a clinical diagnosis of LQTS.[10] A negative test is only definitive when there is a known mutation identified in a family member and targeted testing for this mutation is negative.

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

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

Table 2. Genetics of Long QT Syndrome

Type	Other Names	Chromosome Locus	Mutated Gene	Ion Current(s) Affected	Associated Findings
LQT1	RWS	11p15.5-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-Tawil syndrome	17.qq2432	*KCNJ2*	Potassium	Episodic muscle 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; LQTS: long QT syndrome; JLNS: Jervell and Lange-Nielsen syndrome; RWS: Romano-Ward syndrome.

Brugada Syndrome

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

Variants in 16 genes have been identified as causative of BrS, all of which lead to either a decrease in the inward sodium or calcium current or an increase in one of the outward potassium currents, but of these *SCN5A* is the most important, accounting for more than an estimated 20% of cases,[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* mutation 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 mutation. Mutations to the gene encoding the cardiac ryanodine receptor (*RYR2)* or to *KCNJ2* result in an autosomal dominant form of CPVT. *CASQ2* (cardiac calsequestrin) and *TRDN*-related CPVT exhibit autosomal recessive inheritance. 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 authors have reported heterozygotes for *CASQ2* and *TRDN* mutations for rare, benign arrhythmias. *RYR2* mutations represent the majority of CPVT cases (50%-55%), with *CASQ2* accounting for 1% to 2% and *TRDN* accounting for an unknown proportion of cases. The penetrance of *RYR2* mutations is approximated at 83%.[17]

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

Short QT Syndrome
SQTS has been linked predominantly to mutations in 3 genes (*KCNH2*, *KCNJ2*, *KCNQ1*).[14] Mutations in genes encoding alpha- and beta-subunits of the L-type cardiac calcium channel (*CACNA1C*, *CACNB2*) have also been associated with SQTS. Some individuals with SQTS do not have a mutation in these genes, suggesting changes in other genes may also cause this disorder. 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] SQTS is believed to be inherited in an autosomal dominant pattern. Although sporadic cases have been reported, patients frequently have a family history of the syndrome or SCD.

Regulatory Status

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

Medical Policy Statement

The safety and effectiveness of genetic testing for cardiac ion channelopathies have been established. It may be considered a useful diagnostic option when indicated for patients meeting specified guidelines.

Inclusionary and Exclusionary Guidelines

NOTE: If the treating physician feels strongly that a patient is exhibiting signs and symptoms of a cardiac channelopathy but is unsure of its specific etiology (LQTS vs. Brugada vs. CPVT vs. SQT), genetic testing using a comprehensive panel to test for all four channelopathies is appropriate.

GENETIC TESTING FOR LQTS SYNDROME

- **Inclusions:**
- When signs and/or symptoms of LQTS are present but a definitive diagnosis cannot be made without genetic testing. This includes:

    - Individuals who do not meet the clinical criteria for LQTS (i.e., those with a Schwartz score <4): but have a moderate-to-high pretest probability based on the Schwartz score and/or other clinical criteria.
- Genetic testing of asymptomatic individuals to determine future risk of LQTS when at least one of the following criteria is met:
    - A close relative (i.e., first-, second-, or third-degree relative) with a known LQTS variant; or
    - A close relative diagnosed with LQTS by clinical means whose genetic status is unavailable.
- Genetic testing for LQTS for all other situations not meeting the criteria outlined above, including but not limited to determining prognosis and/or directing therapy in patients with known LQTS, is considered **experimental/investigational**.

Exclusions:
All other situations when the above criteria are not met

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GENETIC TESTING FOR BRUGADA SYNDROME

Inclusions:
- Genetic testing to confirm a diagnosis of Brugada syndrome (BrS) when signs and/or symptoms consistent with BrS are present but a definitive diagnosis cannot be made without genetic testing (signs and symptoms suggestive of Brugada syndrome (BrS) include the presence of characteristic electrocardiographic pattern, documented ventricular arrhythmia, sudden cardiac death in a family member younger than 45 years old, a characteristic electrocardiographic pattern in a family member, inducible ventricular arrhythmias on electrophysiologic studies, syncope, or nocturnal agonal respirations).
- Genetic testing of asymptomatic individuals to determine future risk of BrS when patients have a close relative (i.e., first-, second-, or third-degree relative) with a known BrS variant.

Exclusions:
All other situations when the above criteria are not met

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GENETIC TESTING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT):

Inclusions:
- Genetic testing to confirm a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered established when signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing.
- Genetic testing of asymptomatic individuals to determine future risk of CPVT may be considered established when at least one of the following criteria are met:
    - A close relative (i.e., first or second-, or third degree relative) with a known CPVT mutation; ***OR***
    - A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable

Exclusions:
All other situations when the above criteria are not met.

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GENETIC TESTING FOR SHORT QT SYNDROME

Inclusions:
- Individual is the index case and also a plan member; **OR**
- Genetic testing of asymptomatic individuals to determine future risk of SQTS when patients have a close relative (i.e., first-, second-, or third-degree relative) with a known SQTS mutation.

Exclusions:
Genetic testing for SQTS for all other situations not meeting the criteria outlined above.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

S3861 81405 81408 81413 81414 81479

Other codes (investigational, not medically necessary, etc.):

0237U*

*This code is not reimbursable, use the established laboratory codes for covered services

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Rationale

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.

GENETIC TESTING FOR VARIANTS ASSOCIATED WITH CARDIAC ION CHANELOPATHIES

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 **PICOs** were used to select literature to inform this review.

Populations

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

The channelopathies discussed herein are genetically heterogeneous with hundreds of identified variants, but the group of disorders share basic clinical expression. The most common presentation is spontaneous or exercise-triggered syncope due to ventricular dysrhythmia. These can be self-limiting or potentially lethal cardiac events. The electrocardiographic features of each channelopathy are characteristic, but the electrocardiogram (ECG) is 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 of interest is genetic testing for cardiac ion channelopathies. Genetic tests are conducted in clinical laboratories. Genetic testing should be accompanied by genetic counseling including discussions with the individual 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 pathologic. Variants are classified by their pathologic 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 one or more specific genes, is available from multiple academic and commercial laboratories, generally by next-generation sequencing or Sanger sequencing. Also, panel testing for one or more cardiac ion channelopathies is available from a number of genetic diagnostics laboratories but there is some variation among manufacturers on 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 comparator of interest is diagnosis and management without genetic testing. Diagnosis and management are described in the following sections by condition.

Long QT Syndrome Diagnosis

The Schwartz criteria are commonly used as a diagnostic scoring system for 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	3
QT corrected 460-470 ms	2
QT corrected <450 ms	1
History of torsades de pointes	2
T-wave alternans	1
Notched T waves in 3 leads	1
Low heart rate for age	0.5
Clinical history	
Syncope brought on by stress	2
Syncope without stress	1
Congenital deafness	0.5
Family history	
Family members with definite long QT syndrome	1
Unexplained sudden death in immediate family members <30 y of age	0.5

Adapted from Perrin and Gollob (2012)[17]

Long QT Standard Management

Primary management of asymptomatic or symptomatic long QT is beta-blocker treatment with 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 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 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 one of the following clinical features: documented ventricular arrhythmia, SCD in a family member younger than 45 years old, characteristic ECG pattern in a family member, inducible ventricular arrhythmias on electrophysiology studies, syncope, or nocturnal agonal respirations.

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 CPVT is typically normal, but exercise stress testing can induce a ventricular arrhythmia in most cases (75%-100%).[19] Premature ventricular contractions, couplets, bigeminy, or polymorphic VT are possible outcomes to the ECG stress test. For patients who are unable to exercise, an infusion of epinephrine may induce ventricular arrhythmia, but this is less effective than exercise testing.[23]

Catecholaminergic Polymorphic Ventricular Tachycardia
Standard Management of CPVT is primarily with the β-blockers nadolol (1-2.5 mg/kg/d) or propranolol (2-4 mg/kg/d). If protection is incomplete (i.e., recurrence of syncope or arrhythmia), then flecainide (100-300 mg/d) may be added. If recurrence continues, an ICD may be necessary with optimized pharmacologic management continued 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 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] In 2011, a

diagnostic scoring system was proposed by Gollob et al 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
Unexplained syncope	1
AF	1
Family history	
First- or second-degree relative with high probability SQTS	2
First- or second-degree relative with autopsy-negative SCD	1
Sudden infant death syndrome	1
Genotype	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

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. ICD decisions 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 ventricular tachycardia on electrophysiologic studies.

Antiarrhythmic 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 implantable cardioverter defibrillators (ICD), which can reduce the risk for ventricular arrhythmias and sudden cardiac death (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 which 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 yield of genetic testing and the impact of genetic testing on the diagnosis and subsequent management of a specific cardiac channelopathy. Many of the cardiac channelopathies lead to a common clinical outcome—increased risk of ventricular arrhythmias leading to an increased risk of sudden cardiac death. Studies that evaluate the role of genetic testing for cardiac channelopathies as part of a diagnostic strategy in the evaluation of ventricular fibrillation or sudden cardiac death from an unknown cause are discussed separately.

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 genetic testing of family members in cases of SCD when a specific clinical diagnosis has not been made.

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, as there is no independent gold standard for the diagnosis. The clinical diagnosis can be compared to the genetic diagnosis, and vice versa, but neither the clinical diagnosis nor the results of genetic testing can be considered an adequate 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 was 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.

Table 6. Characteristics of Clinical Validity Studies of Genetic Testing for LQTS

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors
Tester (2006)	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 (2009)	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	KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2	NR

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 LQTS

Study	N	Excluded Samples	Yield of Genetic Testing
Tester (2006)			
Overall	541	None	NR
Schwartz and Moss ≥4	123	Unknown Schwartz/Moss (n=124)	72%
Bai (2009)			
Overall	546	NR	40%
Conclusive dx	304	NR	64%
Possible dx	160	NR	14%

Dx: diagnosis; LQTS: long QT syndrome; NR: not reported.

The purpose of the 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. Relevance Limitations of Clinical Validity Studies of Genetic Testing for LQTS

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

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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 LQTS

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Tester (2006)					2.Insufficient data for clinical score in 23% of samples that had genetic testing	
Bai (2009)		1.Blinded not described				

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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 to other tests not reported.

The evidence on clinical specificity focuses on the frequency and interpretation of variants identified but not known to be pathologic. If a variant identified is known to be pathologic, then the specificity of this finding is high. However, many variants are not known to be pathologic, 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 pathologic, and missense variants, which are less likely to be pathologic. Thirty-three such sequence variants were identified in the total population-all missense variations. The percentage of the population that had at least one of these missense variants was 5.2%. No nonsense variants were associated with LQTS found among the entire population.

Brugada Syndrome
Priori (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]

In 2014, Hu et al 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 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 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=0.0003). 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=0.0002). *SCN5A*(+) patients had a higher proportion of sick sinus syndrome (43% vs. 5%; p<0.001) and atrial ventricular block (71% vs. 30%; p=0.01). However, there was a lower rate of ventricular tachycardia/ventricular fibrillation inducibility during electrophysiology study (EPS) (41% vs. 51%; p=0.01), which may partially be explained by heterogeneity in EPS protocols. The *SCN5A* mutation was associated with an increased risk of major adverse events in the overall BrS (odds ratio [OR] 1.78; 95% CI, 1.19 to 2.26; p=0.005), Asian (OR 1.82; 95% CI, 1.07 to 3.11; p=0.03), and Caucasian (OR 2.24; 95% CI, 1.02 to 4.90; p=0.04) patient population.

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 two 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*=0.770). *SCN5A* carriers had a significantly higher frequency 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 (odds ratio, 5.41; 95% CI, 2.8 to 11.19; p<.001) and family history of SCD (odds ratio, 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 Grugada

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors
Priori (2000)	Patients with the typical Brugada ECG pattern, without structural heart disease	Retrospective	Clinical and ECG diagnosis, criteria not specified	*SCN5A*	Unclear
Bai (2009)	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 (2010)	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 (2014)	Unrelated patients with BrS referred to a single center for genetic testing	Retrospective; not clear if selection was consecutive	2005 Consensus Conference diagnostic criteria (Heart Rhythm Society and the European Heart Rhythm Association)	*SCN10A*	Unclear
Behr (2015)	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 US	Retrospective; not clear if selection was consecutive	Locally diagnosed, criteria not specified	*SCN10A, HAND1, CASQ2, TKT, PLN, TBX5, TBX3*	Unclear
Andorin (2016)	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 (2019)	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 (2019)	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)	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, CACNAD2, KCNJ8, KCNE3, SLMAP, RANGRF*	Unclear
Milman et al (2021)	BrS patients from 14 countries with a first arrhythmic event	Observational cohort; selection not reported	NR	*SCN5A*	None
Wang et al (2022)	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

Study	N	Excluded Samples	Yield of Genetic Testing
Priori (2000)	52	NR	15%
Bai (2009)			
Overall	798		8%
Conclusive dx	405		13%
Possible dx	248		4%
Kapplinger (2010)	2111	NR	21% (range 11% to 28%)
Hu (2014)	150	NR	17%
Behr (2015)	156	SCN5A re-sequencing (n=2) revision of the diagnosis (n=4), non-European ancestry (n=3)	11.5%
Andorin (2016)	75 (from 62 families)	Only 75/106 have genetic analysis; reasons for lack of genetic analysis unclear	77%
Chen (2019)	1780	NR	20% (11% to 43%)
Monasky (2019)	294	NR	28.3% (*SCN5A*) 2.7% (*SCN10A*)
Sacilotto et al (2020)	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)	678 (392 probands)	NR	23.5%
Wang et al (2022)[4]	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 the limitations tables (see Tables 12 and 13) 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 12. Relevance Limitations of Clinical Validity Studies of Genetic Testing for Brugada

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up
Priori (2000)	3.Criteria for clinical diagnosis unclear				
Bai (2009)	3.Criteria for clinical diagnosis unclear				
Kapplinger (2010)	3.Criteria for clinical diagnosis unclear				
Hu (2014)					
Behr (2015)	3.Criteria for clinical diagnosis unclear				
Andorin (2016)	4.Majority of probands had only Brugada pattern ECG without symptoms				
Chen (2019)					

Monasky (2019)	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)	4: Majority of probands had only Brugada type 1 ECG pattern without symptoms				
Milman et al (2021)	3: criteria for clinical diagnosis unclear			1:study does not directly address a key health outcome	
Wang et al (2022)				1: Study does not directly address a key health outcome	

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Priori (2000)	1.Not clear if all eligible patients were included	1.Blinded not described			1.No description of exclusions or indeterminate results	
Bai (2009)		1.Blinded not described			1.No description of exclusions or indeterminate results	
Kapplinger (2010)	1.Not clear if all eligible patients were included	1.Blinded not described			1.No description of exclusions or indeterminate results	
Hu (2014)	1,2.Not clear if all eligible patients were included; not clear how samples were selected	1.Blinded not described			1.No description of exclusions or indeterminate results	

Behr (2015)	1,2.Not clear if all eligible patients were included; not clear how samples were selected	1.Blinded not described				
Andorin (2016)	1,2.Not clear if all eligible patients were included; not clear how samples were selected	1.Blinded not described			1.Unclear why ≈30% of patients did not have genetic analysis	
Chen (2019)						
Monasky (2019)	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)		1: Blinding not described			1: Unclear why ~33% of patients did not have genetic analysis	
Milman et al (2021)	1:Selection not described	1:Blinding not described				
Wang et al (2022)	1, 2: Not clear if all eligible patients were included; not clear how samples were selected	1: Blinding not described				

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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 to 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.[31,44-46] 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 CPVT

Study	Study Population	Design	Clinical Diagnosis	Genes Included	Blinding of Assessors

Priori (2002)	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 in the absence of ventricular tachycardia documented at Holter and/or exercise stress testing	*RyR2*	NR
Medeiros-Domingo (2009)	Patients referred for genetic testing with "strong" diagnosis of CPVT	Retrospective; unclear whether samples were consecutive	Exertional syncope plus documentation of bidirectional or polymorphic ventricular tachycardia	*RyR2*	NR
Bai (2009)	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 (2018)	Patients referred for commercial genetic testing with well-phenotyped cases and "strong" diagnosis of CPVT	Retrospective; unclear whether samples were consecutive	History of exertional syncope with documentation of exercise-related bidirectional or polymorphic ventricular tachycardia	*RyR2*	NR

Table 15. Yield of Genetic Testing for CPVT

Study	N	Excluded Samples	Yield of Genetic Testing
Priori (2002)	30	NR	47%
Medeiros-Domingo (2009)	78	NR	60%
Bai (2009)			
Overall	175	NR	35%
Conclusive dx	81	NR	62%
Possible dx	21	NR	5%
Kapplinger (2018)	78	NR	59%

The purpose of the gaps tables (see Tables 16 and 17) is to display notable gaps 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. Relevance Gaps of Clinical Validity Studies of Genetic Testing for CPVT

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

The evidence gaps 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 Gaps of Clinical Validity Studies of Genetic Testing for CPVT

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Priori (2002)	1,2.Not clear if all eligible patients were included	1.Blinded not described			1.No description of exclusions or indeterminate result	
Medeiros-Domingo (2009)	1,2.Not clear if all eligible patients were included	1.Blinded not described			1.No description of exclusions or indeterminate result	
Bai (2009)		1.Blinded not described			1.No description of exclusions or indeterminate result	
Kapplinger	1,2.Not clear if all eligible patients were included	1.Blinded not described			1.No description of exclusions or indeterminate result	

The evidence gaps 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 to 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.

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

Clinically Useful
A test is clinically useful if use of the results inform 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
LQTS is a disorder that may lead to catastrophic outcomes, i.e., sudden cardiac death in otherwise healthy individuals. Diagnosis using clinical methods alone may lead to under-diagnosis of LQTS, thus exposing undiagnosed patients to the risk of sudden cardiac arrest. For patients in whom the clinical diagnosis of LQTS is uncertain, genetic testing may be necessary to further clarify whether LQTS is present. Patients who are identified as genetic carriers of LQTS mutations have a non-negligible risk of adverse cardiac events even in the

absence of clinical signs and symptoms of the disorder. Therefore, treatment is likely indicated for patients found to have a LQTS mutation, with or without other signs or symptoms.

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

Sodium-channel blockers such as mexiletine are sometimes used, particularly in those with *SCN5A* mutations.[48]

Treatment with an implantable cardioverter-defibrillator (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 studied 77 patients with a LQTS mutation 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 psychologic distress decreased over time but remained elevated at 18 months. Andersen et al+ conducted qualitative interviews with 7 individuals found to have LQTS mutations.[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 subtypes of LQTS may have variable prognosis, thus indicating that genetic testing may assist in risk stratification. Several reports have compared rates of cardiovascular events in subtypes of LQTS.[51-54]These studies report that rates of cardiovascular events differ among subtypes, but there is not a common pattern across all studies. Three of the 4 studies[51-53] reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba et (1998) alreported that patients with LQT1 have higher event rates than patients with LQT2.[54]

Some studies that report outcomes of treatment with beta blockers also report outcomes by specific subtypes of LQTS.[51,53] Priori et al reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of beta 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 also reported pre-post event rates for patients treated with beta 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 also limited by the small number of patients with LQT3 and cardiac events prior to beta blocker treatment (4/28). Sauer et al evaluated differential response to beta blocker therapy in a Cox proportional hazards analysis.[56] They reported an overall risk reduction in first cardiac event of approximately 60% (HR=0.41; 95% confidence interval [CI], 0.27 to 0.64) in adults treated with beta blockers and an interaction effect by genotype. Efficacy of beta blocker treatment was worse in those with LQT3 genotype (p=0.04) compared with LQT1 or LQT2. There was no difference in efficacy between genotypes LQT1 and LQT2.

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=0.002). 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<0.001). 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<0.001). 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%. $QT_c \geq 550$ ms (HR 3.94; 95%CI 2.08 to 7.46; p<0.001) and prior syncope on β-blockers (HR 1.92, 95% CI 1.01 to 3.65; p=0.047) were associated with an increased risk of appropriate shock. Importantly, LQT2 genotype (HR 2.10, 95% CI 1.22 to 3.61; p=0.008) and the presence of multiple mutations (HR 2.87, 95% CI 1.49 to 5.53; p=0.002) 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 vs paternal LQTS (24.4% vs. 3.5%; *P*=0.36).

Brugada Syndrome

The diagnostic testing yield for BrS limits its clinical usefulness. A finding of a genetic mutation is not diagnostic of the disorder but is an indicator of high risk for development of BrS. The diagnostic criteria for BrS does not presently include the presence of a genetic mutation. Furthermore, treatment 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 sudden cardiac death) 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=0..0004; I^2=0.0%), symptomatic patients (risk ratio 2.66; 95% CI, 1.62 to 4.36; p=0.0001; 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=0.03; 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 limited utility for genetic testing. However, there are some patients in whom signs and symptoms of CPVT are present, but for whom the diagnosis cannot be made with certainty. In this case, documentation of a pathologic mutation that is known to be associated with CPVT confirms the diagnosis. When the diagnosis is confirmed, treatment with beta blockers is indicated, and lifestyle changes are recommended. Although high-quality outcome studies are lacking to demonstrate a benefit of medication treatment, it is very likely that treatment reduces the risk of sudden cardiac death. Therefore, there is clinical utility.

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

Short QT Syndrome

No studies were identified that provide evidence for the clinical utility of genetic testing for SQTS in a comprehensive literature review, consistent with the clinical rarity of the condition. Clinical sensitivity for the test is low, with laboratory testing providers estimating a yield as low as 15%.

Section Summary: Clinical Utility of Genetic Testing for the Diagnosis of a Specific 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 beta blockers in most cases, and sometimes to treatment with an ICD. As a result, confirming the diagnosis is likely to lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and sudden cardiac death. The clinical utility of testing is also high for close relatives of patients with known cardiac ion channel mutations, because these individuals should also be treated if they are found to have a pathologic variant.

For BrS the clinical utility is less certain, but there is potential for genetic testing to change treatment decisions in stratifying patients for 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 compared with 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.

SUMMARY OF EVIDENCE

Long QT Syndrome

For individuals with suspected congenital long QT syndrome who receive genetic testing for mutations associated with congenital LQTS, the evidence includes observational studies reporting on the yield of testing. Relevant outcomes are overall survival, changes in reproductive decision making, and morbid events. A genetic mutation can be identified in approximately 70% of LQTS. The clinical utility of genetic testing for LQTS is high when there is a moderate-to-high pretest probability. There is a chain of evidence to suggest that testing for variants associated with LQTS in individuals who are suspected to have these disorders, leads to improved outcomes. A definitive diagnosis LQTS leads to treatment with β-blockers in most cases, and sometimes to treatment with an implantable cardiac defibrillator (ICD). As a result, confirming the diagnosis is likely to lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and sudden cardiac death. There is evidence suggesting that different genotypes are associated with varying risk of sudden cardiac death. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with close relative(s) with a known long QT (LQTS) variant who receive genetic testing for mutations associated with congenital LQTS, the evidence includes observational studies reporting on changes in management. Relevant outcomes are overall survival, changes in reproductive decision making, and morbid events. A positive genetic test for an LQTS variant leads to treatment with β-blockers in most cases, and sometimes to treatment with an implantable cardiac defibrillator (ICD) and a negative test would allow family members to defer further testing. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Brugada Syndrome

For individuals with suspected BrS who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields Relevant outcomes are overall survival, changes in reproductive decision making, and morbid events. The clinical validity of testing for BrS is low: a genetic variant can only be identified in approximately 15% to 35% of BrS. BrS management changes, primarily use of ICDs, are directed by clinical symptoms. It is not clear that that genetic diagnosis in the absence of other clinical signs and symptoms leads to a change in management that improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic with close relative(s) with a known BrS mutation who receive genetic testing for mutations associated with congenital BrS, the evidence includes observational studies reporting on the yield of testing. Relevant outcomes are overall survival, changes in reproductive decision making, and morbid events. BrS management changes, primarily ICD implantation, are directed by clinical symptoms. There is limited evidence about the effect of changes in management based on genetic testing in an individual with family members with a known mutation. However, a negative test would allow family members to defer further testing. The evidence is sufficient to determine the effects of the technology on health outcomes.

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

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

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

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

Given the limited available evidence on genetic testing for SQTS, clinical input was obtained. Among the specialty societies and academic medical centers providing input, there was not consensus on the use of genetic testing for variants associated with SQTS; however, there was consensus that genetic testing to predict future risk of disease in individuals with close relatives with a known variant associated with SQTS is useful in management that may lead to

improved outcomes. A review of guidelines was also conducted. The use of genetic testing for patients with suspected SQTS was not addressed in many guidelines; however one guideline stated that testing may be considered if a cardiologist has established a strong clinical index of suspicion. Additionally, the guidelines acknowledged that although the evidence is weak, genetic testing may be considered for asymptomatic family members of individuals with known SQTS variants.

For individuals who are asymptomatic with a close family member(s) who experienced sudden cardiac death specific diagnosis has been made who receive genetic testing for variants associated with cardiac ion channelopathies, the evidence includes cohort studies that describe the genetic testing yield. In all studies identified, genetic testing was obtained only after a specific diagnosis was suspected based on history or ancillary testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 18.

Table 18. 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
NCT03783975	A Community-Based Approach to Overcoming Barriers to Cascade Screening for Long QT Syndrome	500	Dec 2022
NCT02439658	Genetics of QT Prolongation With Antiarrhythmics (DOFEGEN)	500	Apr 2023
NCT04232787	Discovering the Genetic Causes of Brugada Syndrome in Thais and Southeast Asian Population (SEA-BrS)	750	Jan 2023
NCT02824822	Genetic Markers of Cardiovascular Diseases and the Potential Role in Sudden Unexpected Death in Epilepsy	600	Dec 2029
NCT02014961	Worm Study: Identification of Modifier Genes in a Unique Founder Population With Sudden Cardiac Death	223	Apr 2025
NCT03880708	China Inherited Ventricular Arrhythmias Registry, a Multicenter, Observational and Prospective Study	500	Oct 2027
Unpublished			
NCT01705925[a]	Multicenter evaluation of children and young adults with genotype positive long QT syndrome	500	Dec 2018
NCT02425189	The Canadian National Long QT Syndrome Registry (LQTSREG)	1051	Aug 2020

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

SUPPLEMENTAL INFORMATION

Input Received 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.

In response to requests, Blue Cross Blue Shield Association received input from 4 academic medical centers (9 reviewers) and 3 specialty societies (4 reviewers).The review was limited to input related to the use of genetic testing for Brugada syndrome and short QT syndrome. There was consensus that genetic testing for Brugada syndrome is medically necessary to establish the diagnosis of Brugada syndrome in an individual with a suspected but not definite diagnosis of Brugada syndrome, and to evaluate family members of an individual with a known pathogenic genetic mutation for BrS. There was less consensus on whether genetic testing is medically necessary to establish the diagnosis of SQTS in an individual with a suspected but not definite diagnosis of SQTS, but there was consensus that testing for SQTS to evaluate family members of an individual with a known pathogenic genetic mutation 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

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.[61] 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, electrocardiogram (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.[62] 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 19.

Table 19. Specific Genes for Testing in Cardiac Channelopathies

Channelopathy	Genes with Definitive Evidence of 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 the Heart Rhythm Society[63]

In 2017, the American Heart Association (AHA), American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Table 20 summarizes the recommendations relating to cardiac ion channelopathies included in the guidelines:

Table 20. AHA/ACC/HRS 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 information.	I (strong)	B-NR
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, non-randomized studies; C-EO: consensus of expert opinion based on clinical experience; COR: class of recommendation; LOE: level of evidence.

Heart Rhythm Society and Asia Pacific Heart Rhythm Society[64]

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. 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 et al[65]

In 2013, the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society (APHRS) issued an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. These guidelines refer to the 2011 guidelines on genetic testing for channelopathies and cardiomyopathies referenced below for the indications for genetic testing in patients affected by inherited arrhythmias and their family members and for diagnostic, prognostic, and therapeutic implications of the results of genetic testing. The 2013 guidelines provide guidance for the evaluation of patients with idiopathic ventricular fibrillation (IVF), sudden unexplained death syndrome (SUDS), and sudden unexplained death in infancy (SUDI), which includes genetic testing; they are outlined in Table 21. IVF is defined as a resuscitated cardiac arrest victim, preferably with documentation of ventricular fibrillation (VF), in whom known cardiac, respiratory, metabolic, and toxicologic etiologies have been excluded through clinical evaluation.

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

Table 21. HRS/EHRA/APHRS Recommendations for genetic testing in IVF, SUDS, and SUDI

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

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

In 2011, HRS and EHRA jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies.[24] This document made the following specific recommendations concerning testing for LQTS, BrS, CPVT, and SQTS (see Table 22).

Table 22. HRS and EHRA Cardiac Ion Channelopathy Testing Recommendations

	Class[a]	HRS and EHRA Consensus Recommendations	LOE[b]
LQTS	I	• 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 s (such as electrolyte abnormalities, hypertrophy, bundle branch block, i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc. 480 ms (prepuberty) or 0.500 ms(adults). • Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.	C
	IIb	Comprehensive or LQT1-3 (KCNQ1, KCNH2, SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values 0.460 ms (prepuberty) or 0.480 ms (adults) on serial 12-lead ECGs.	C
BrS	I	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.	C
	IIa	Comprehensive or BrS1 (SCH5A) 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-leading ECGs and/or provocative drug challenge testing) phenotype.	C
	III	Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern	C
CPVT	I	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	C
SQTS	I	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.	C
	IIb	Comprehensive or SQT1-3 (KCHNH2, 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	C

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; ECG: electrocardiogram; EHRA: European Heart Rhythm Association; HRS: Heart Rhythm Society; 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 or care.

Government Regulations National/Local:

Medicare does not have a policy specifically addressing genetic testing for cardiac ion channelopathies. However, the current codes being used to bill for this testing are payable if the ordering physician determines that they are medically necessary. CPT code, S3861, is not covered by Medicare.

Local

Wisconsin Physician's Service (WPS) (MI) has an LCD called, "Molecular Diagnostic Testing" (L36807), effective for services performed on or after 04/27/23, which only addresses testing for patients with a possible genetic predisposition to developing cancer. It does not address molecular testing for non-cancer conditions.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing for Inherited Hypertrophic Cardiomyopathy
- Genetic Testing for ARVC/D

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/08	3/5/08	4/27/08	Joint policy established
11/1/08	8/19/08	9/23/08	New S codes (effective 10/1/08) added to policy
1/1/09	10/13/08	12/30/08	Inclusionary/exclusionary guidelines clarified to mirror BCBSA.
3/1/11	1/4/11	1/4/11	Changed title of policy from “Genetic Testing for Long QT Syndrome” to “Genetic Testing for Cardiac Channelopathies”. References updated.
11/1/11	8/16/11	8/16/11	Clarified description of Brugada syndrome and the inclusionary guidelines for testing for the syndrome. Added exclusion for comparative genomic hybridization testing (chromosomal microarray analysis) for LQTS-considered experimental and investigational. References updated
5/1/12	2/21/12	2/21/12	Added new genetic testing CPT codes 81280, 81281 and 81283
11/1/13	8/22/13	8/27/13	Routine update of established service. Updated references and rationale. No change in policy status.
9/1/15	6/16/15	7/16/15	Routine maintenance. Added information regarding short QTS. Updated criteria, rationale and references
9/1/16	6/21/16	6/21/16	Routine maintenance. Updated rationale and references. Investigational status for short QTS changed to established w/criteria.
5/1/17	4/3/17	4/18/17	Deleted codes 81280, 81281, and 81282. Added codes 81413 and 81414. Updated rationale and references, no change in policy status.
5/1/18	2/20/18	2/20/18	Updated medical policy statement language. Updated rationale section, added references 29, 33, 66, 68 and 73.

5/1/19	2/19/19		Rationale reformatted, references 27, 30-31, and 34-37 added. Policy statements unchanged.
5/1/20	2/18/20		Routine policy maintenance, no change in policy status.
5/1/21	2/16/21		Updated rationale, reference # 26, 36-38, 52-55 added. Code 0237U added to policy as not reimbursable, asterisk added to use established laboratory codes. No change in policy status.
5/1/22	2/15/22		Updated rationale, added references 12, 16, 29 and 42. No change in policy status.
5/1/23	2/21/23		Updated rationale, added reference 43. No change in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR CARDIAC ION CHANNELOPATHIES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.