FEP Medical Policy Manual

FEP 2.04.43 Genetic Testing for Cardiac Ion Channelopathies

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Related Policies:

None

Genetic Testing for Cardiac Ion Channelopathies

Description

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

OBJECTIVE

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

POLICY STATEMENT

Long QT Syndrome

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

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

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

- A close relative (ie, first-, second-, or third-degree relative) with a known LQTS variant; or
- A close relative diagnosed with LQTS by clinical means whose genetic status is unavailable.

Genetic testing for LQTS for all other situations not meeting the criteria outlined above, including but not limited to determining prognosis and/or directing therapy in individuals with known LQTS, is considered **investigational**.

Brugada Syndrome

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

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

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

Catecholaminergic Polymorphic Ventricular Tachycardia

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

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

- A close relative (ie, first-, second-, or third-degree relative) with a known CPVT variant; or
- A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable.

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

Short QT Syndrome

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

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

POLICY GUIDELINES

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

Determining the pretest probability of long QT syndrome (LQTS) is not standardized. An example of a patient with a moderate-to-high pretest probability of LQTS is a patient with a Schwartz score of 2 or 3.

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

Testing Strategy

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

In cases where the family member's genetic diagnosis is unavailable, testing is available through either single-gene testing or panel testing. The evaluation of the clinical utility of panel testing is outlined in evidence review 2.04.92 (on a general approach to evaluating the utility of genetic panels). Panels for cardiac ion channelopathies are diagnostic test panels that may fall into one of several categories: panels that include variants for a single condition; panels that include variants for multiple conditions (indicated plus nonindicated conditions); and panels that include variants for multiple conditions (clinical syndrome for which clinical diagnosis not possible).

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

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual"s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Recommendations indicate that, when possible, genetic testing for long QT syndrome be performed in an affected family member so that testing in unaffected, at-risk family members can focus on the variant found in the affected family member. However, coverage for testing of the affected index case (proband) is dependent on contract benefit language.

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

RATIONALE

Summary of Evidence

Long QT Syndrome

For individuals with suspected congenital long QT syndrome (LQTS) who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on the testing yield. Relevant outcomes are overall survival (OS), test validity, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 70% of those with 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 of LQTS leads to treatment with β-blockers in most cases, and sometimes to treatment with an implantable cardioverter-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 (SCD). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known LQTS variant who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on changes in management. Relevant outcomes are OS, test validity, 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 ICD; a negative test would allow family members to defer further testing. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Brugada Syndrome

For individuals with suspected Brugada syndrome (BrS) who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields. Relevant outcomes are OS, test validity, 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. Management changes, primarily use of ICDs, are directed by clinical symptoms. 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 that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known BrS variant who receive genetic testing for variants associated with BrS, the evidence includes observational studies reporting on testing yields. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. Brugada syndrome management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on the effect of changes in management based on genetic testing in an individual with family members who have a known variant. However, a negative test would allow family members to defer further testing. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Catecholaminergic Polymorphic Ventricular Tachycardia

For individuals with suspected catecholaminergic polymorphic ventricular tachycardia (CPVT) who receive genetic testing for variants associated with CPVT, the evidence includes observational studies reporting on testing yields. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. A genetic variant 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 of ventricular arrhythmias and sudden cardiac death (SCD). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known CPVT variant who receive genetic testing for variants associated with CPVT, the evidence includes observational studies reporting testing yields. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. For close relatives of patients with known CPVT variants who are found to have a pathogenic variant, preventive treatment can be initiated. Also, a negative test in the setting of a known familial variant should have a high negative predictive value. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Short QT Syndrome

For individuals with suspected short QT syndrome (SQTS) who receive genetic testing for variants associated with SQTS, the evidence includes limited data on testing yields. Relevant outcomes are OS, test validity, changes in reproductive decision making, and morbid events. The yield of genetic testing in SQTS is not well-characterized. Management changes, primarily use of ICDs, are directed by clinical symptoms. There is limited evidence on changes in management based on genetic testing in a symptomatic proband without a definitive diagnosis. 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 that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative(s) with a known SQTS variant who receive genetic testing for variants associated with SQTS, the evidence includes observational studies reporting on testing yields. Relevant outcomes are OS, test validity, 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 that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close family member(s) who experienced SCD and a 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American Heart Association

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

In 2021, the American Heart Association published a scientific statement on genetic testing for heritable cardiovascular diseases (including channelopathies) in children.[62,] The statement recommends that genetic testing be performed when a cardiac channelopathy is likely to be present, including after a variant has been found in a family member. Testing to identify at-risk relatives can be considered. Brugada syndrome is difficult to identify since not all adults express genetic variants; therefore, identifying at-risk children may require clinical evaluation, ECG testing, and/or pharmacologic challenge of all of the child"s first-degree relatives. Genetic testing should also be performed in children who are resuscitated from cardiac arrest with no clear cause. Several factors can be considered when deciding the appropriate age for genetic testing of an individual child, including whether the disease is expected to present during childhood, whether the channelopathy can be fatal, whether therapies exist to mitigate mortality risk, and family preferences. Ongoing follow-up genetic testing can confirm pathogenicity of the variant over time.

In 2020, the American Heart Association authored a scientific statement on genetic testing for inherited cardiovascular disease.[63,] Prior guidelines from several international cardiovascular clinical organizations and published studies were reviewed. For BrS, the authors concluded that genetic testing supports the clinical diagnosis. For patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (LQTS), genetic testing is needed for diagnosis and subtype classification. Management of LQTS may also differ depending on the causative gene. Genetic testing for all of these conditions facilitates identifying at-risk family members. Specific genes with the strongest causative evidence for cardiac channelopathies are listed in Table 1.

Table 1. Specific Genes for Testing in Cardiac Channelopathies

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

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

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

In 2017, the American Heart Association, American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (SCD).[64,] Table 2 summarizes the recommendations relating to cardiac ion channelopathies.

Table 2. 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, nonrandomized studies; BrS: Brugada syndrome; C-EO: consensus of expert opinion based on clinical experience; COR: class of recommendation; CPVT: catecholaminergic polymorphic ventricular tachycardia; LOE: level of evidence; LQTS: long QT syndrome; SQTS: short QT syndrome; VT: ventricular tachycardia.

Heart Rhythm Society and Asia Pacific Heart Rhythm Society

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

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

In 2013, the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society issued an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes.[66,] The consensus statement refers to the 2011 guidelines on genetic testing for channelopathies and cardiomyopathies discussed next for the indications for genetic testing in patients affected by inherited arrhythmias and their family members and for diagnostic, prognostic, and therapeutic implications of the results of genetic testing. The 2013 consensus statement provided guidance for the evaluation of patients with idiopathic ventricular fibrillation, sudden unexplained death syndrome, and sudden unexplained death in infancy. Guidance on genetic testing for these patients was included (see Table 3). Idiopathic ventricular fibrillation is defined as a resuscitated cardiac arrest victim, preferably with documentation of ventricular fibrillation, in whom known cardiac, respiratory, metabolic, and toxicologic etiologies have been excluded through clinical evaluation.

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

Table 3. Recommendations for Genetic Testing in Idiopathic Ventricular Fibrillation, Sudden Unexplained Death Syndrome, and Sudden Unexplained Death in Infancy

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

	An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing can be useful for all SUDI victims.	IIa
	Genetic screening of the first-degree relatives of a SUDI victim is recommended whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDI victim. Obligate mutations carriers should be prioritized.	I

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

In 2011, the Heart Rhythm Society and European Heart Rhythm Association jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies.[24,] This document made the following specific recommendations on testing for LQTS, BrS, CPVT, and SQTS (see Table 4).

Table 4. Cardiac Ion Channelopathy Testing Recommendations

	Consensus Recommendation	**Class[a]**	**LOE[b]**
LQTS	• Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient"s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype. • Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., ie, otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults). • Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.	I	C
	Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs.	IIb	C
BrS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.	I	C
	Comprehensive or BrS1 (*SCN5A*) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient"s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.	IIa	C
	Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.	III	C
CPVT	Comprehensive or *CPVT1* and *CVPT2* (*RYR2*, *CASQ2*) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient"s clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion. Mutation-specific genetic testing is	I	C

	recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.		
SQTS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.	I	C
	Comprehensive or SQT1-3 (*KCNH2*, *KCNQ1*, *KCNJ2*) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient"s clinical history, family history, and electrocardiographic phenotype.	IIb	C

BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; ECG: electrocardiogram; LOE: level of evidence; LQTS: long QT syndrome; QTc: corrected QT; SQTS: short QT syndrome.

[a] Class I: "is recommended" when an index case has a sound clinical suspicion for the presence of a channelopathy with a high positive predictive value for the genetic test (>40%) with a signal-to-noise ratio of >10 and/or the test may provide diagnostic or prognostic information or may change therapeutic choices; Class IIa: "can be useful"; Class IIb: "may be considered"; Class III: "is not recommended" (the test fails to provide any additional benefit or could be harmful in the diagnostic process).

[b] Only consensus opinion of experts, case studies or standard of care.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
December 2012	Replace policy	Policy updated with literature search and references, no change in policy statement.
December 2013	Replace policy	Policy updated with literature search, references add, no change to policy statement. Language in Description section on the Schwartz score of 2-3 for pretest probability revised to sate "moderate-to-high, probability to make it consistent with policy statement language.
March 2014	Replace policy	Policy updated with literature search, numerous references added, Policy title changed to "Genetic Testing for Cardiac Ion Channelopathies,. Background and rationale extensively rewritten to incorporate Brugada syndrome, CPVT, and Short QT Syndrome. Medically necessary statement added for CPVT when criteria are met. Investigational statements added for Brugada syndrome and short QT syndrome.
March 2015	Replace policy	Policy updated with literature review. References 1-4, 13, 29- 30, 39, 54, and 58-59 added. Background section reorganized. Language added to Policy Guidelines section. Additional policy statement added that genetic testing for LQTS or CPVT is investigational for all other situations when criteria are not met. Policy statements otherwise unchanged.
December 2015	Replace policy	Policy updated with literature review through September 14, 2015; references 25, 42, 55, 59, and 64 added. Clinical input reviewed; medically necessary statements added for diagnostic testing for Brugada syndrome Policy statement also revised to align with FEP benefit, with the removal of genetic testing for asymptomatic individuals.
March 2017	Replace policy	Policy updated with literature review; references 27, 37, 42, and 66 added. Policy statements unchanged.
March 2018	Replace policy	Policy updated with literature review through November 6, 2017; references 2, 61, 63, 67, and 72 added; references 9, 17, and 29 updated. Policy statements unchanged.
March 2019	Replace policy	Policy updated with literature review through October 30, 2018; references 27, 30-31, and 34-37 added. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through October 31, 2019; references added. Policy statements unchanged. Policy updated with diagnostic testing for asymptomatic individuals as this may impact treatment decisions.
March 2021	Replace policy	Policy updated with literature review through October 19, 2020; references added. Policy statements unchanged.
March 2022	Replace policy	Policy updated with literature review through December 1, 2021; references added. Policy statements unchanged.
March 2023	Replace policy	Policy updated with literature review through November 16, 2022; reference added. Policy statements unchanged.
March 2024	Replace policy	Policy updated with literature review through November 9, 2023; reference added. Minor editorial refinements to policy statements; intent unchanged.