BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.43 Genetic Testing for Cardiac Ion Channelopathies

Annual Effective Policy Date: April 1, 2026

Original Policy Date: December 2011

Related Policies:

None

Genetic Testing for Cardiac Ion Channelopathies

Description

Description

Genetic testing is available for individuals 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

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

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. 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 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.

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).[63,] 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.[64,] 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.[65,] 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).[66,] 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.[67,] 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.[68,] 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.[25,] 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	I	C

	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.		
	Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, *SCN5A*) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs.	IIb	C
BrS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.	I	C
	Comprehensive or BrS1 (*SCN5A*) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient"s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.	IIa	C
	Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.	III	C
CPVT	Comprehensive or *CPVT1* and *CVPT2* (*RYR2*, *CASQ2*) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient"s clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.	I	C
SQTS	Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.	I	C
	Comprehensive or SQT1-3 (*KCNH2*, *KCNQ1*, *KCNJ2*) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient"s clinical history, family history, and electrocardiographic phenotype.	IIb	C

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

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

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

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.

REFERENCES

1. Abriel H, Zaklyazminskaya EV. Cardiac channelopathies: genetic and molecular mechanisms. Gene. Mar 15 2013; 517(1): 1-11. PMID 23266818
2. Modell SM, Bradley DJ, Lehmann MH. Genetic testing for long QT syndrome and the category of cardiac ion channelopathies. PLoS Curr. May 03 2012; 4: e4f9995f69e6c7. PMID 22872816
3. Huang MH, Marcus FI. Idiopathic Brugada-type electrocardiographic pattern in an octogenarian. J Electrocardiol. Apr 2004; 37(2): 109-11. PMID 15127377
4. Brugada R, Campuzano O, Sarquella-Brugada G, et al. Brugada Syndrome. In: Adam MP, Feldman J, Mirza GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2025. https://www.ncbi.nlm.nih.gov/books/NBK1517/. Updated August 2022. Accessed November 2025.
5. Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. Circulation. Mar 08 2011; 123(9): 1021-37. PMID 21382904
6. Bennett MT, Sanatani S, Chakrabarti S, et al. Assessment of genetic causes of cardiac arrest. Can J Cardiol. Jan 2013; 29(1): 100-10. PMID 23200097
7. Ackerman MJ, Marcou CA, Tester DJ. Personalized medicine: genetic diagnosis for inherited cardiomyopathies/channelopathies. Rev Esp Cardiol. Apr 2013;66(4):298-307. PMID 23484907
8. Wilders R. Cardiac ion channelopathies and the sudden infant death syndrome. ISRN Cardiol. 2012; 2012: 846171. PMID 23304551
9. Eddy CA, MacCormick JM, Chung SK, et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. Heart Rhythm. Sep 2008; 5(9): 1275-81. PMID 18774102
10. Chiang CE. Congenital and acquired long QT syndrome. Current concepts and management. Cardiol Rev. 2004; 12(4): 222-34. PMID 15191637
11. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. Circulation. Feb 02 1999; 99(4): 529-33. PMID 9927399
12. Sarquella-Brugada G, Fernandez-Falgueras A, Cesar S, et al. Clinical impact of rare variants associated with inherited channelopathies: a 5-year update. Hum Genet. Oct 2022; 141(10): 1579-1589. PMID 34546463
13. Beckmann BM, Scheiper-Welling S, Wilde AAM, et al. Clinical utility gene card for: Long-QT syndrome. Eur J Hum Genet. Dec 2021; 29(12): 1825-1832. PMID 34031550
14. Arking DE, Pulit SL, Crotti L, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet. Aug 2014; 46(8): 826-36. PMID 24952745
15. Alders M, Christiaans I. Long QT Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2015.
16. Walsh R, Adler A, Amin AS, et al. Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. Eur Heart J. Apr 14 2022; 43(15): 1500-1510. PMID 34557911
17. Napolitano C, Manzzanti A, Bloise R, Priori SG. Catecholaminergic Polymorphic Ventricular Tachycardia. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2025. https://www.ncbi.nlm.nih.gov/books/NBK1289// Updated June 2022. Accessed November 2025.
18. Schwartz PJ, Moss AJ, Vincent GM, et al. Diagnostic criteria for the long QT syndrome. An update. Circulation. Aug 1993; 88(2): 782-4. PMID 8339437
19. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation. Nov 15 2011; 124(20): 2181-4. PMID 22083145
20. Wilde AA, Behr ER. Genetic testing for inherited cardiac disease. Nat Rev Cardiol. Oct 2013; 10(10): 571-83. PMID 23900354
21. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. Feb 08 2005; 111(5): 659-70. PMID 15655131
22. Benito B, Brugada J, Brugada R, et al. Brugada syndrome. Rev Esp Cardiol. Nov 2009; 62(11): 1297-315. PMID 19889341
23. Perrin MJ, Gollob MH. The genetics of cardiac disease associated with sudden cardiac death: a paper from the 2011 William Beaumont Hospital Symposium on molecular pathology. J Mol Diagn. Sep 2012; 14(5): 424-36. PMID 22749884
24. Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart. Jan 2003; 89(1): 66-70. PMID 12482795
25. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. Aug 2011; 8(8): 1308-39. PMID 21787999
26. Tristani-Firouzi M. The Long and Short of It: Insights Into the Short QT Syndrome. J Am Coll Cardiol. Apr 08 2014; 63(13): 1309-1310. PMID 24333498
27. Giustetto C, Di Monte F, Wolpert C, et al. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. Eur Heart J. Oct 2006; 27(20): 2440-7. PMID 16926178

28. Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. J Am Coll Cardiol. Feb 15 2011; 57(7): 802-12. PMID 21310316
29. Asatryan B, Schaller A, Seiler J, et al. Usefulness of Genetic Testing in Sudden Cardiac Arrest Survivors With or Without Previous Clinical Evidence of Heart Disease. Am J Cardiol. Jun 15 2019; 123(12): 2031-2038. PMID 30975432
30. Chiu SN, Juang JJ, Tseng WC, et al. Impact of genetic tests on survivors of paediatric sudden cardiac arrest. Arch Dis Child. Jan 2022; 107(1): 41-46. PMID 34127479
31. Tester DJ, Will ML, Haglund CM, et al. Effect of clinical phenotype on yield of long QT syndrome genetic testing. J Am Coll Cardiol. Feb 21 2006; 47(4): 764-8. PMID 16487842
32. Bai R, Napolitano C, Bloise R, et al. Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing. Circ Arrhythm Electrophysiol. Feb 2009; 2(1): 6-15. PMID 19808439
33. Kapa S, Tester DJ, Salisbury BA, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. Circulation. Nov 03 2009; 120(18): 1752-60. PMID 19841300
34. Refsgaard L, Holst AG, Sadjadieh G, et al. High prevalence of genetic variants previously associated with LQT syndrome in new exome data. Eur J Hum Genet. Aug 2012; 20(8): 905-8. PMID 22378279
35. Priori SG, Napolitano C, Gasparini M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: A prospective evaluation of 52 families. Circulation. Nov 14 2000; 102(20): 2509-15. PMID 11076825
36. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm. Jan 2010; 7(1): 33-46. PMID 20129283
37. Hu D, Barajas-Martnez H, Pfeiffer R, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. J Am Coll Cardiol. Jul 08 2014; 64(1): 66-79. PMID 24998131
38. Behr ER, Savio-Galimberti E, Barc J, et al. Role of common and rare variants in SCN10A: results from the Brugada syndrome QRS locus gene discovery collaborative study. Cardiovasc Res. Jun 01 2015; 106(3): 520-9. PMID 25691538
39. Andorin A, Behr ER, Denjoy I, et al. Impact of clinical and genetic findings on the management of young patients with Brugada syndrome. Heart Rhythm. Jun 2016; 13(6): 1274-82. PMID 26921764
40. Chen C, Tan Z, Zhu W, et al. Brugada syndrome with SCN5A mutations exhibits more pronounced electrophysiological defects and more severe prognosis: A meta-analysis. Clin Genet. Jan 2020; 97(1): 198-208. PMID 30963536
41. Doundoulakis I, Pannone L, Chiotis S, et al. SCN5A gene variants and arrhythmic risk in Brugada syndrome: An updated systematic review and meta-analysis. Heart Rhythm. Oct 2024; 21(10): 1987-1997. PMID 38614189
42. Monasky MM, Micaglio E, Vicedomini G, et al. Comparable clinical characteristics in Brugada syndrome patients harboring SCN5A or novel SCN10A variants. Europace. Oct 01 2019; 21(10): 1550-1558. PMID 31292628
43. Sacilotto L, Scanavacca MI, Olivetti N, et al. Low rate of life-threatening events and limitations in predicting invasive and noninvasive markers of symptoms in a cohort of type 1 Brugada syndrome patients: Data and insights from the GenBra registry. J Cardiovasc Electrophysiol. Nov 2020; 31(11): 2920-2928. PMID 32870538
44. Milman A, Behr ER, Gray B, et al. Genotype-Phenotype Correlation of SCN5A Genotype in Patients With Brugada Syndrome and Arrhythmic Events: Insights From the SABRUS in 392 Probands. Circ Genom Precis Med. Oct 2021; 14(5): e003222. PMID 34461752
45. Wang LL, Chen YH, Sun Y, et al. Genetic Profile and Clinical Characteristics of Brugada Syndrome in the Chinese Population. J Cardiovasc Dev Dis. Oct 28 2022; 9(11). PMID 36354768
46. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation. Jul 02 2002; 106(1): 69-74. PMID 12093772
47. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. J Am Coll Cardiol. Nov 24 2009; 54(22): 2065-74. PMID 19926015
48. Kapplinger JD, Pundi KN, Larson NB, et al. Yield of the RYR2 Genetic Test in Suspected Catecholaminergic Polymorphic Ventricular Tachycardia and Implications for Test Interpretation. Circ Genom Precis Med. Feb 2018; 11(2): e001424. PMID 29453246
49. Jabbari J, Jabbari R, Nielsen MW, et al. New exome data question the pathogenicity of genetic variants previously associated with catecholaminergic polymorphic ventricular tachycardia. Circ Cardiovasc Genet. Oct 2013; 6(5): 481-9. PMID 24025405
50. Zhu W, Mazzanti A, Voelker TL, et al. Predicting Patient Response to the Antiarrhythmic Mexiletine Based on Genetic Variation. Circ Res. Feb 15 2019; 124(4): 539-552. PMID 30566038
51. Hendriks KS, Hendriks MM, Birnie E, et al. Familial disease with a risk of sudden death: a longitudinal study of the psychological consequences of predictive testing for long QT syndrome. Heart Rhythm. May 2008; 5(5): 719-24. PMID 18452877
52. Andersen J, yen N, Bjorvatn C, et al. Living with long QT syndrome: a qualitative study of coping with increased risk of sudden cardiac death. J Genet Couns. Oct 2008; 17(5): 489-98. PMID 18719982
53. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA. Sep 15 2004; 292(11): 1341-4. PMID 15367556
54. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med. May 08 2003; 348(19): 1866-74. PMID 12736279
55. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. Jan 02 2001; 103(1): 89-95. PMID 11136691
56. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of the genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. N Engl J Med. Oct 01 1998; 339(14): 960-5. PMID 9753711
57. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation. Feb 15 2000; 101(6): 616-23. PMID 10673253

58. Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. J Am Coll Cardiol. Jan 23 2007; 49(3): 329-37. PMID 17239714
59. Shimizu W, Makimoto H, Yamagata K, et al. Association of Genetic and Clinical Aspects of Congenital Long QT Syndrome With Life-Threatening Arrhythmias in Japanese Patients. JAMA Cardiol. Mar 01 2019; 4(3): 246-254. PMID 30758498
60. Biton Y, Rosero S, Moss AJ, et al. Primary prevention with the implantable cardioverter-defibrillator in high-risk long-QT syndrome patients. Europace. Feb 01 2019; 21(2): 339-346. PMID 29947754
61. Cuneo BF, Kaizer AM, Clur SA, et al. Mothers with long QT syndrome are at increased risk for fetal death: findings from a multicenter international study. Am J Obstet Gynecol. Mar 2020; 222(3): 263.e1-263.e11. PMID 31520628
62. Rattanawong P, Chenbhanich J, Mekraksakit P, et al. SCN5A mutation status increases the risk of major arrhythmic events in Asian populations with Brugada syndrome: systematic review and meta-analysis. Ann Noninvasive Electrocardiol. Jan 2019; 24(1): e12589. PMID 30126015
63. Landstrom AP, Chahal AA, Ackerman MJ, et al. Interpreting Incidentally Identified Variants in Genes Associated With Heritable Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. Apr 2023; 16(2): e000092. PMID 36970980
64. Landstrom AP, Kim JJ, Gelb BD, et al. Genetic Testing for Heritable Cardiovascular Diseases in Pediatric Patients: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. Oct 2021; 14(5): e000086. PMID 34412507
65. Musunuru K, Hershberger RE, Day SM, et al. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. Aug 2020; 13(4): e000067. PMID 32698598
66. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. Oct 2018; 15(10): e190-e252. PMID 29097320
67. Stiles MK, Wilde AAM, Abrams DJ, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm. Jan 2021; 18(1): e1-e50. PMID 33091602
68. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. Dec 2013; 10(12): 1932-63. PMID 24011539

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.

Date	Action	Description
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.
March 2025	Replace policy	Policy updated with literature review through December 5, 2024; reference added. Policy statements unchanged.
March 2026	Replace policy	Policy updated with literature review through November 13, 2025; reference added. Policy statements unchanged.