

FEP 2.04.43 Genetic Testing for Cardiac Ion Channelopathies

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Related Policies: None

Genetic Testing for Cardiac Ion Channelopathies

Description

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

FDA REGULATORY STATUS

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

POLICY 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 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 **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.

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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 for CPVT 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 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).

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 or an individual with unexplained sudden cardiac arrest is being evaluated, genetic testing may be part of a diagnostic strategy that includes a comprehensive history and physical exam and 12-lead electrocardiogram, 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

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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

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.

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

RATIONALE

Summary of Evidence

Long QT Syndrome

For individuals with suspected congenital 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, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 72% to 80% of those with LQTS. Most are point mutations identified by gene sequencing analysis; however, a small number are deletions and duplications are best identified by chromosomal microarray analysis. The clinical validity of testing in LQTS is high, in the range of 70% to 80%. The clinical utility of genetic testing for LQTS is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. There is a strong chain of evidence to suggest that testing for variants associated with LQTS in individuals who are suspected to have these disorders, but in whom the diagnosis cannot be made by other methods, 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 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. While there is evidence suggesting that different genotypes are associated with varying risk of sudden cardiac death, there is insufficient evidence on the effects of changes in clinical management based on different genotypes. The evidence is sufficient to determine 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 and a meta-analysis. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, 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 25% to 35% of BrS. BrS management changes, primarily use of ICDs, are directed by clinical symptoms. A meta-analysis reported that the presence of an *SCN5A* variant in patients with BrS was not predictive of the occurrence of a cardiac event, while a registry study published after the meta-analysis reported that the presence of the variant was related to a higher rate of cardiac events. 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

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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 BrS, clinical input was obtained. There was a 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, Asia Pacific Heart Rhythm Society) was also conducted. The guidelines acknowledged that although the evidence is weak, genetic testing is recommended for individuals with a suspected but not a definitive diagnosis of BrS.

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 testing yields. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, and morbid events. A genetic variant can be identified in approximately 51% to 75% of CPVT patients. The clinical validity of testing in CPVT is moderate, in the range of 50% to 75%. The clinical utility of genetic testing for CPVT is high when there is a moderate-to-high pretest probability and when the diagnosis cannot be made with certainty by other methods. There is a strong chain of evidence to suggest that testing for variants associated with CPVT in individuals who are suspected to have these disorders, but in whom the diagnosis cannot be made by other methods, leads to improved outcomes. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Heart Association, American College of Cardiology, and the 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.⁷² Table 1 summarizes the recommendations relating to cardiac ion channelopathies.

Table 1 Recommendations for Genetic Testing in Cardiac Channelopathies

| Consensus Recommendation | COR | LOE |
|--|----------------|------|
| In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended. | I (strong) | B-NR |
| In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information. | I (strong) | B-NR |
| In patients with catecholaminergic polymorphic ventricular tachycardia 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 Brugada syndrome, 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 short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives. | IIb (weak) | C-EO |

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B-NR: moderate level of evidence, nonrandomized studies; C-EO: consensus of expert opinion based on clinical experience; COR: class of recommendation; LOE: level of evidence; VT: ventricular tachycardia.

Heart Rhythm Society, European Heart Rhythm Association, et al

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.⁷³ 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 2). 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 sudden cardiac death, 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 2 Recommendations for Genetic Testing in IVF, SUDS, and SUDI

| | 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. | Ila |
| | 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. | Ila |
| | 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, Heart Rhythm Society and European Heart Rhythm Association jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies.¹⁹ This document made the following specific recommendations on testing for long QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome (see Table 3).

Table 3 Cardiac Ion Channelopathy Testing Recommendations

| | Consensus Recommendation | Class ^a | LOE ^b |
|------|--|--------------------|------------------|
| LQTS | • Comprehensive or LQT1-3 (<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i>) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical | I | C |

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

American College of Cardiology et al

The American College of Cardiology, American Heart Association, and European Society of Cardiology issued joint guidelines in 2006 on the management of patients with ventricular arrhythmias and the prevention of sudden death.⁷⁴ These guidelines made a general statement that "In patients affected by LQTS, genetic analysis is useful for risk stratification and therapeutic decisions." These guidelines did not address the use of genetic testing for the diagnosis of LQTS.

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The guidelines also stated that genetic testing for catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, or short QT syndrome might identify silent carriers for clinical monitoring but does not assist with risk stratification.

Canadian Cardiovascular Society and Canadian Heart Rhythm Society

The Canadian Cardiovascular Society and Canadian Heart Rhythm Society published a joint position paper in 2011.²² Genetic testing was recommended for cardiac arrest survivors with LQTS for the purpose of familial screening, as well as those with syncope with corrected QT (QTc) prolongation, as well as asymptomatic patients with QTc prolongation with a high clinical suspicion of LQTS. For clinically suspect catecholaminergic polymorphic ventricular tachycardia, testing was recommended for familial screening. Genetic testing was also recommended for cardiac arrest survivors with a type I Brugada electrocardiogram pattern for familial screening, as well as in patients with syncope and type I Brugada electrocardiogram pattern or asymptomatic patients with type I Brugada electrocardiogram pattern and high clinical suspicion. No recommendations are given for short QT syndrome.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

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POLICY HISTORY

| Date | Action | Description |
|---------------|---------------|---|
| December 2011 | New Policy | |
| December 2012 | Update Policy | Policy updated with literature search and references, no change in policy statement. |
| December 2013 | Update 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 state "moderate-to-high" probability to make it consistent with policy statement language |
| March 2014 | Update 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 |

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| | | 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 | Update 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 | Update 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 | Update Policy | Policy updated with literature review; references 27, 37, 42, and 66 added. Policy statements unchanged. |
| March 2018 | Update 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. |

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