FEP 2.04.43 Genetic Testing for Cardiac Ion Channelopathies

Effective Date: April 1, 2019  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 and risk-stratify prognosis.

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

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 (i.e., those with a Schwartz score <4): but have a moderate-to-high pretest probability (see Policy Guidelines section) based on the Schwartz score and/or other clinical criteria.

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**.

**Short QT Syndrome**

Genetic testing for individuals with suspected SQTS 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). 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 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
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comprehensive evaluation, a diagnosis of CPVT, LQTS, or BrS is suspected but not definitive (i.e., if there is a moderate-to-high pretest probability of either condition), genetic testing could be considered.

GENETIC COUNSELING
Genetic counseling is primarily aimed at 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
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).

FDA REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 LQTS who receive genetic testing for variants associated with congenital LQTS, the evidence includes observational studies reporting on the testing yield. The relevant outcomes are OS, 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 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 a meaningful 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. The relevant outcomes are OS, changes in reproductive decision making, and morbid events. A positive genetic test for an LQTS variant leads to treatment with β-
null
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Short QT Syndrome

For individuals with suspected SQTS who receive genetic testing for variants associated with SQTS, the evidence includes limited data on testing yields. The relevant outcomes are OS, changes in reproductive decision making, and morbid events. The yield of genetic testing in SQTS is not well-characterized. 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 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 the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
American Heart Association, American College of Cardiology, and the Heart Rhythm Society

The American Heart Association, American College of Cardiology, and the Heart Rhythm Society (2017) published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.49 Table 1 summarizes the recommendations relating to cardiac ion channelopathies.

Table 1. Recommendations for Genetic Testing in Cardiac Channelopathies

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
<td>I (strong)</td>
<td>B-NR</td>
</tr>
<tr>
<td>In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Genetic testing offers diagnostic, prognostic, and therapeutic information.</td>
<td>I (strong)</td>
<td>B-NR</td>
</tr>
<tr>
<td>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.</td>
<td>IIa (moderate)</td>
<td>B-NR</td>
</tr>
<tr>
<td>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.</td>
<td>IIb (weak)</td>
<td>C-EO</td>
</tr>
<tr>
<td>In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives.</td>
<td>IIb (weak)</td>
<td>C-EO</td>
</tr>
</tbody>
</table>

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

The Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society (2013) issued an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes.\(^50\). 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 one 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 one year of age with negative pathologic and toxicologic assessment.

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

IVF: idiopathic ventricular fibrillation; SUD: sudden unexplained death in infancy; SUDS: sudden unexplained death syndrome.
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The Heart Rhythm Society and European Heart Rhythm Association (2011) jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies. This document made the following specific recommendations on testing for long QT syndrome (LQTS), BrS, catecholaminergic polymorphic ventricular tachycardia (CPVT), and SQTS (see Table 3).

Table 3. Cardiac Ion Channelopathy Testing Recommendations

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>Classa</th>
<th>LOEb</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
<td>IIb</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>• Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.</td>
<td>III</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>Classa</th>
<th>LOEb</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>• 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.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

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.

- 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.

- 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

8. Wilders R. Cardiac ion channelopathies and the sudden infant death syndrome. ISRN Cardiol. 2012;2012:846171. PMID 23304551

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22. 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):1308-1339. PMID 21787999


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## POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2011</td>
<td>New Policy</td>
<td>Policy updated with literature search and references, no change in policy statement.</td>
</tr>
<tr>
<td>December 2012</td>
<td>Update Policy</td>
<td>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</td>
</tr>
<tr>
<td>December 2013</td>
<td>Update Policy</td>
<td>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.</td>
</tr>
<tr>
<td>March 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 1-4, 13, 29-30, 39, 54, and 58-59 added. Background section reorganized. 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.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Update Policy</td>
<td>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.</td>
</tr>
<tr>
<td>December 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 30, 2018; references 27, 30-31, and 34-37 added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

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