Clinical Policy Title: Genetic testing for long QT syndrome (LQTS)

Clinical Policy Number: 04.01.02

Effective Date: Dec. 1, 2013
Initial Review Date: June 19, 2013
Most Recent Review Date: July 20, 2016
Next Review Date: July 2017

Related policies:

CP# 05.01.05 Molecular targeted therapy

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage Policy

Prestige Health Choice considers the use of genetic testing for long QT syndrome (LQTS), also known as Familion testing, to be clinically proven and therefore medically necessary when the following criteria are met:

- The individual has a close relative (first-, second- or third-degree) with a known LQTS mutation.
- The individual has a close relative (first-, second- or third-degree) diagnosed with LQTS by clinical means and whose genetic status is unavailable.
- The individual has palpitations, syncope and/or dizziness with a history of a close relative (first-, second-, or third-degree) who experienced a sudden cardiac death.
- The individual has a prolonged QT interval on resting electrocardiogram (a corrected QTc) of greater than 440 msec without an identifiable acquired or external cause for the QTc prolongation (i.e., bradycardia, electrolyte imbalance or certain medications/drugs) (QTc values of ≥ 0.44 sec are treated as suspicious, CSANZ 2011.)
The individual has signs and/or symptoms indicating a moderate-to-high pretest probability of LQTS using the Schwartz criteria (score of 2 – 3).

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

A negative genetic test in a clinically normal individual of a well-characterized family should eliminate the need for future testing (for the same individual), as genetic testing for a particular disease is usually performed once per lifetime. All other uses of genetic testing for long QT syndrome/Familion testing are not medically necessary.

Alternative covered services

Physical examination, electric conductivity tests: electrocardiogram (ECG), echocardiography, genetic counseling.

Background

Long QT syndrome (LQTS) is caused by mutations in a set of genes that code the protein subunits of cardiac ion channels. These ion channels are important for the electrical conductivity and signals of the heart. The electrical signals may be recorded by an electrocardiogram (ECG) and produce a characteristic waveform. The different components of the waveform are identified by the letters P, Q, R, S and T. The distinctive feature of LQTS is the lengthening of the Q – T interval on an electrocardiogram (ECG). The Q – T interval on the waveform represents the duration of the electrical activation and deactivation of the heart ventricles, which are the lower, main pumping chambers of the heart. With the advent of genetic testing, there is evidence of an overlap of specific genotypes that cause the characteristic T wave shapes.

*LQTS genetic mutations may lead to an increase in the Q – T Interval on an electrocardiogram.*
In medical genetics, testing is done to diagnose individuals who possess chromosomal, genetic variations associated with a high risk of having or transmitting LQTS. The abnormal mutations and variations in DNA sequencing that cause LQTS are represented by abnormal allele configurations that are not found in the otherwise normal, healthy population. Genetic tests may be conducted for individuals who are asymptomatic or have a family member with this diagnosed genetic disorder. All first-degree relatives (i.e., siblings, parents and children) of an individual with an LQTS gene mutation have up to a 50 percent risk of harboring the same mutation. Typically, LQTS is inherited in an autosomal dominant pattern, in which a single mutation causes the disease. The genetic material (DNA) used for testing may be obtained from a blood sample or may be gathered by a mouth swab. Laboratories are able to offer multi-gene cardiomyopathy/cardiac panels that test many genes (may contain 50 or more) in an effort to diagnose several cardiac conditions at 1 time.

The importance of identifying individuals for an inherited cardiac arrhythmia is highlighted by the potential lethality of these syndromes, mostly due to ventricular tachyarrhythmias. LQTS usually affects children or young adults, although it may occur in otherwise healthy individuals of various ages. Most people with LQTS are diagnosed either by family history, an episode of syncope, or by surviving a severe ventricular arrhythmia. For some unfortunate symptomatic individuals, the initial presentation of LQTS symptoms leads to sudden cardiac death. The goal of genetic testing for LQTS is to prevent sudden death through medical therapy, to counsel the individual and their family, and to assist with lifestyle changes (CSANZ, 2011).

Literature suggests that LQTS may be responsible for as many as 3,000 unexpected deaths in children and young adults in the United States each year (Model, 2012). Younger individuals have a higher risk of unexpected sudden death than adults with a genetic cardiac disease. A family history of sudden death, possibly with genetic confirmation, may influence treatment decisions for those with suspected and ultimately confirmed LQTS. Because this disease is a primarily an electrical disorder, most individuals have no evidence of structural heart disease or LV dysfunction, making the long-term prognosis excellent if the arrhythmia is controlled. Treatment may involve beta blockers, permanent pacing, or left cervicothoracic sympathectomy (Tracy, et al, 2008).

Practice guideline statements from the American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and European Society of Cardiology (ESC) have noted an evolving role for genetic testing of LQTS in risk stratification and clinical decision-making (Zipes, et al., 2006). This stance pertaining to the use of risk stratification and data from genetic analysis becoming of increasing import to meaningful clinical decisionmaking was further addressed in the 2012 American College of Cardiology, American Heart Association Task Force, and European Society of Cardiology (ACCF/AHA/HRS) focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. Both independent reviews and professional society guidelines agree that genetic testing should not be used alone in making recommendations for a prognosis for LQTS, though testing may be used to support clinical diagnosis and early detection of at-risk relatives (Ackerman, et al., 2011; Antzelevitch, et al.,2005; Priori and Cerrone, 2005).
<table>
<thead>
<tr>
<th>Variant</th>
<th>Gene Name</th>
<th>Frequency</th>
<th>Current Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>30 – 35%</td>
<td>K+, alpha subunit</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2</td>
<td>25 – 30%</td>
<td>K+, alpha subunit</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>5 – 10%</td>
<td>Na+, alpha subunit</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK2</td>
<td>1 – 2%</td>
<td>Na+, targeting protein</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1</td>
<td>1%</td>
<td>K+, beta subunit</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>Rare</td>
<td>K+, subunit</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>Rare</td>
<td>K+, potassium channel</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1C</td>
<td>Rare</td>
<td>Ca++, alpha 1C subunit</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Rare</td>
<td>Na+, caveolin-3 protein</td>
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<table>
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<tr>
<th>Variant</th>
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<th>Frequency</th>
<th>Function</th>
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<tr>
<td>LQT10</td>
<td>SCN4B</td>
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<td>LQT11</td>
<td>AKAP9</td>
<td>Rare</td>
<td>K+, protein kinase</td>
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<td>LQT12</td>
<td>SNTA1</td>
<td>Rare</td>
<td>Na+, α1-syntrophin</td>
</tr>
<tr>
<td>LQT13</td>
<td>KCNJ5</td>
<td>Rare</td>
<td>potassium channel</td>
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</tbody>
</table>

**Searches**

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

Searches were conducted in June 13, 2016 using the terms “cardiac, genetic testing, Familion” and “long QT syndrome”.

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**
The genetics of cardiac ion channelopathies are extremely varied. The number of genes that have been associated with causing long-QT syndrome has risen to 10, and there are hundreds of possible mutations in these genes that appear to be harmful. The Familion genetic test includes just 5 of the genes that are known to be associated with cardiac ion channelopathies and therefore the number of symptomatic first-degree relatives of those with known LQTS mutations is high.

The use of the Familion genetic test may potentially have clinical utility in patients with LQTS. For first-degree relatives with known LQTS mutations in 1 of 5 genes included in the test, the Familion genetic test can confirm the presence of the familial mutation. A negative result is also instructive, as with the high analytical sensitivity and low probability of a sporadic mutation, a negative result would indicate a low probability of the patient having LQTS. Thus, use of the Familion genetic test in first-degree relatives of those with a known LQTS mutation may allow better use of prophylactic treatment for payers and avoidance of unnecessary restrictive activity for patients.

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. Premarketed approval from FDA is not required as long as the assay is performed in a laboratory facility that observes the CLIA regulations. The provider of the Familion genetic test has a current CLIA license.

**Policy updates:**

None.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Taggart NW, et. al. (2007)</td>
<td><strong>Key Points:</strong></td>
</tr>
<tr>
<td>Diagnostic miscues in congenital long-QT syndrome:</td>
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- **BACKGROUND:** Long-QT syndrome (LQTS) is a potentially lethal cardiac channelopathy that can be mistaken for palpitations, neurocardiogenic syncope and epilepsy. Because of increased physician and public awareness of warning signs suggestive of LQTS, there is the potential for LQTS to be overdiagnosed. The authors sought to determine the agreement between the dismissal diagnosis from an LQTS subspecialty clinic and the original referral diagnosis.

- **METHODS AND RESULTS:** Data from the medical record were compared with data from the outside evaluation for 176 consecutive patients (121 females, median age 16 years, average referral corrected QT interval [QTc] of 481 ms) referred with a diagnosis of LQTS. After evaluation at Mayo Clinic's LQTS Clinic, patients were categorized as having definite LQTS (D-LQTS), possible LQTS (P-LQTS), or no LQTS (No-LQTS). Seventy-three patients (41%) were categorized as No-LQTS, 56 (32%) as P-LQTS, and only 47 (27%) as D-LQTS. The yield of genetic testing among D-LQTS patients was 78% compared with 34% for P-LQTS and 0% among No-LQTS patients (P<0.0001). The average QTc was greater in either D-LQTS or P-LQTS than in No-LQTS (461 versus 424 ms, P<0.0001). Vasovagal syncope was more common among the No-LQTS subset (28%) than the P-LQTS/D-LQTS...
group (8%; P=0.04). Determinants for discordance (i.e., positive outside diagnosis versus No-LQTS) included overestimation of QTc, diagnosing LQTS on the basis of “borderline” QTc values and interpretation of a vasovagal fainting episode as an LQTS-precipitated cardiac event.

- Conclusion Diagnostic concordance was present for less than one-third of the patients who sought a second opinion. Two of every 5 patients referred with the diagnosis of LQTS departed without such a diagnosis. Miscalculation of the QTc, misinterpretation of the normal distribution of QTc values and misinterpretation of symptoms appear to be responsible for most of the diagnostic miscues.

Key Points:

- Mutations were classified according to their location in the KCNQ1, potassium channel position protein, i.e., N-terminus, transmembrane or C-terminus. Transmembrane mutations accounted for 66% of the mutations.
- In patients with transmembrane mutations, their QTc interval was longer, there was a higher incidence of cardiac events (syncope, aborted cardiac arrest or death) and the use of beta-blockers was more common.
- The QTc interval was also significantly longer in 19 patients who had 2 SCN5A mutations compared with those with a single mutation.
- In patients with KCNQ1 mutations that cause a > 50% increase in ion channel repolarizing current, the risk of cardiac events was approximately twice that of patients with mutations that cause a < 50% reduction in ion channel repolarizing current.
- The QTc was also significantly longer in patients with the worst impairment in ion channel function.

Glossary

**Electrocardiogram (ECG, EKG)** — A test that records the electrical activity of the heart and displays the results on a visual graph. It is used to evaluate cardiac function, arrhythmias and the diagnosis of other cardiac disorders.

**Chromosome** — Within a single cell, a strand of amino acids that carries genetic information.

**Gene** — An integral part of a chromosome that determines an individual organism’s hereditary physical characteristics.

**KCNQ1** — Approved symbol. Approved name potassium voltage-gated channel subfamily Q member 1.

**Mutation** — Any change in the inherited genetic structure.

**Relatives, first-, second-, and third-degree** — An individual’s close blood family members:
• **First-degree relative** — Parents, full siblings or children.
• **Second-degree relative** — Aunts, uncles, grandparents, grandchildren, nieces, nephews or half-siblings.
• **Third-degree relative** — Great-grandparents, great aunts, great uncles or first cousins.

**Subtype One** — Type or component that is included in the long QT syndrome type.

**References**

**Professional society guidelines/other:**


Ackerman MJ, Priori SG, Williams, 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). Europace. 2011; 13(8):1077-109.


Blue Cross Blue Shield Association (BCBSA), Technology Evaluation Center (TEC). Genetic testing for long QT syndrome. 2007 TEC Assessments 2008;22(9). Chicago, IL.


Peer-reviewed references:


Clinical trials:

Searched clinicaltrials.gov on June 13, 2016 using terms: long QT syndrome (LQTS), genetic testing | Open Studies. 22 studies found, one relevant.


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):


Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tr>
<td>81280</td>
<td>Long QT syndrome gene analyses (e.g., KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2). Full sequence analysis.</td>
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<td>81281</td>
<td>Long QT syndrome gene analyses (e.g., KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2). Known familial sequence variant.</td>
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<td>81282</td>
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<td>ICD-10 Code</td>
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<tr>
<td>I45.81</td>
<td>Long QT syndrome.</td>
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<tr>
<td>R55</td>
<td>Syncope and collapse.</td>
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<td>R42</td>
<td>Dizziness and giddiness.</td>
<td>Symptoms of syndrome.</td>
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<td>R00.2</td>
<td>Palpitations.</td>
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<td>R94.31</td>
<td>Abnormal electrocardiogram [ECG] [EKG].</td>
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<td>Z82.41</td>
<td>Family history of sudden cardiac death.</td>
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<td>Z84.81</td>
<td>Family history of carrier of genetic disease.</td>
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</tr>
<tr>
<td>Z13.89</td>
<td>Encounter for screening for other disorder</td>
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<tr>
<td>Z13.79</td>
<td>Encounter for other screening for genetic and chromosomal anomalies.</td>
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<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes.</td>
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