Clinical Policy Title: Genetic testing for long QT syndrome

Clinical Policy Number: 04.01.02

Effective Date: December 1, 2013
Initial Review Date: June 19, 2013
Most Recent Review Date: June 5, 2018
Next Review Date: June 2019

Policy contains:
- Familion testing.
- Long QT syndrome subtypes.

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, 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 long QT syndrome mutation.
- The individual has a close relative (first-, second- or third-degree) diagnosed with long QT syndrome 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 long QT syndrome 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 may be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of genetic testing for long QT syndrome/Familion testing are not medically necessary.
• 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.

Alternative covered services:

• Physical examination.
• Electric conductivity tests: electrocardiogram, echocardiography.
• Genetic counseling.

Background

Long QT syndrome is a heart rhythm condition that can cause rapid and irregular heartbeats, leading to fainting spells, seizures, and (when the condition is extended), sudden death. A genetic condition, an estimated 1 in 2000 newborns have the disorder, or roughly 2,000 cases per year in the U.S. (Schartz, 2009).

The syndrome 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 long QT syndrome 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.
Long QT syndrome 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 long QT syndrome. The abnormal mutations and variations in DNA sequencing that cause long QT syndrome 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 long QT syndrome gene mutation have up to a 50 percent risk of harboring the same mutation. Typically, long QT syndrome 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 one 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. Long QT syndrome usually affects children or young adults, although it may occur in otherwise healthy individuals of various ages. Most people with long QT syndrome 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 long QT syndrome symptoms leads to sudden cardiac death. The goal of genetic testing for long QT syndrome 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 long QT syndrome may be responsible for as many as 3,000 unexpected deaths in children and young adults in the United States each year (Modell, 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 long QT syndrome. 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, 2008).
Long QT syndrome can also be an acquired condition from cardiovascular medications administered to predisposed patients, often in the Intensive Care Unit. Treatment of acquired long QT syndrome, which is essentially fatal, is essentially awareness, identification, and discontinuation of QT prolonging drugs (Beitland, 2014).

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 long QT syndrome in risk stratification and clinical decision-making (Zipes, 2006). This stance pertaining to the use of risk stratification and data from genetic analysis becoming of increasing import to meaningful clinical decision making 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 long QT syndrome, though testing may be used to support clinical diagnosis and early detection of at-risk relatives (Ackerman, 2011).

<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>

<table>
<thead>
<tr>
<th>Variant</th>
<th>Gene Name</th>
<th>Frequency</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>Rare</td>
<td>Na+, beta subunit</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>Rare</td>
<td>K+, protein kinase</td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

Searches

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
Efforts were conducted on April 17, 2018 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 five 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 long QT syndrome mutations is high.

The use of the Familion genetic test may potentially have clinical utility in patients with long QT syndrome. For first-degree relatives with known long QT syndrome 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 long QT syndrome. Thus, use of the Familion genetic test in first-degree relatives of those with a known Long QT syndrome 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 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.

Long QT syndrome is a significant factor in certain fetal disorders. It accounted for 15 – 17 percent of fetal bradycardias of <110 beats per minute among fetuses with a normally structured heart; of patients
with a significant prenatal finding of long QT syndrome, 17 – 35 percent exhibited reduced baseline fetal heart rate of 110 – 120 beats per minute on electronic cardiotocography (Ishikawa, 2013).

Four articles on cost-effectiveness of genetic testing for long QT syndrome in infants and young adults were reviews. Testing in the early detection of long QT syndrome was cost-effective compared with no testing in symptomatic cases, and not cost-effective when compared with watchful waiting in asymptomatic first-degree relatives of patients with established long QT syndrome; in neonates, testing was highly cost-effective when compared with any screening strategy (Gonzalez, 2015).

Policy updates:

A total of no guidelines/other and three peer-reviewed references were added to this policy in 2017.

No new guidelines or clinical references were identified in 2018.

Summary of clinical evidence

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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</table>
| Taggart NW, et. al. (2007) Diagnostic miscues in congenital long-QT syndrome | **Key points:**
| | • BACKGROUND: Long-QT syndrome 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 long QT syndrome, there is the potential for long QT syndrome to be overdiagnosed. The authors sought to determine the agreement between the dismissal diagnosis from an long QT syndrome 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 long QT syndrome. After evaluation at Mayo Clinic's long QT syndrome Clinic, patients were categorized as having definite long QT syndrome, possible long QT syndrome, or no LQTS. Seventy-three patients (41%) were categorized as no-long QT syndrome, 56 (32%) as possible long QT syndrome, and only 47 (27%) as definite -long QT syndrome. The yield of genetic testing among definite long QT syndrome patients was 78% compared with 34% for possible long QT syndrome and 0% among no -long QT syndrome patients (p < 0.0001). The average QTc was greater in either D-long QT syndrome or P-long QT syndrome than in nolong QT syndrome (461 versus 424 ms, p < 0.0001). Vasovagal syncope was more common among the no-long QT syndrome subset (28%) than the possible -long QT syndrome/D-long QT syndrome group (8%; P=0.04). Determinants for discordance (i.e., positive outside diagnosis versus no-long QT syndrome) included overestimation of QTc, diagnosing long QT syndrome on the basis of "borderline" QTc values and interpretation of a vasovagal fainting episode as an long QT syndrome-precipitated cardiac event.
| | • CONCLUSIONS: 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 long QT syndrome departed without such a diagnosis. Miscalculation of the QTc, misinterpretation of the
new distribution of QTc values and misinterpretation of symptoms appear to be responsible for most of the diagnostic miscues.

Moss et. al. (2007)
The effects of 77 different KCNQ1 mutations on phenotype in 600 patients from 101 families from the United States, Japan and the Netherlands were investigated

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.

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.


April 17, 2018.


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**
No NCDs identified as of the writing of this policy.

Local Coverage Determinations


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>
</tr>
</thead>
<tbody>
<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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<tr>
<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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<tr>
<td>81282</td>
<td>Long QT syndrome gene analyses (e.g., KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2). Duplication/Deletion variants.</td>
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<tr>
<td>81414</td>
<td>Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1</td>
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<tr>
<td>81413</td>
<td>Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCN</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>I45.81</td>
<td>Long QT syndrome.</td>
<td></td>
</tr>
<tr>
<td>R55</td>
<td>Syncope and collapse.</td>
<td>Symptoms of syndrome.</td>
</tr>
<tr>
<td>R42</td>
<td>Dizziness and giddiness.</td>
<td></td>
</tr>
<tr>
<td>R00.2</td>
<td>Palpitations.</td>
<td></td>
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<tr>
<td>R94.31</td>
<td>Abnormal electrocardiogram [ECG] [EKG].</td>
<td></td>
</tr>
<tr>
<td>Z82.41</td>
<td>Family history of sudden cardiac death.</td>
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<tr>
<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>
<td></td>
</tr>
<tr>
<td>Z13.79</td>
<td>Encounter for other screening for genetic and chromosomal anomalies.</td>
<td></td>
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<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes.</td>
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</table>