The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

### Description

Congenital long QT syndrome (LQTS) is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential, increasing the risk for arrhythmic events, such as torsades de pointes, which may in turn result in syncope and sudden cardiac death. Management has focused on the use of beta blockers as first-line treatment, with pacemakers or implantable cardiac defibrillators (ICD) as second-line therapy.

Congenital LQTS usually manifests before the age of 40 years and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult; this history may prompt additional testing in family members. It is estimated that more than one half of the 8,000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1–2% per year, although this figure will vary with the genotype, discussed further here. (1) Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and thus LQTS has received publicity regarding evaluation of adolescents for participation in sports. In addition, LQTS may be considered when a long QT interval is incidentally observed on an electrocardiogram (EKG). Diagnostic criteria for LQTS have been established, which focus on EKG findings and clinical and family history (i.e., Schwartz criteria, see following section, “Clinical Diagnosis”). (2) However, measurement of the QT interval is not well-standardized, and in some cases, patients may be considered borderline cases. (3)

In recent years, LQTS has been characterized as an “ion channel disease,” with abnormalities in the sodium and potassium channels that control the excitability of the cardiac myocytes. A genetic basis for LQTS has also emerged, with seven different subtypes recognized, each corresponding to mutations in different genes as indicated here. (4) In addition, typical ST-T-wave patterns are also suggestive of specific subtypes. (5)

### Clinical Diagnosis

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS. (2) The most recent version of this scoring system is shown Table 1. A score of four or greater indicates a high probability that LQTS is present; a score of two to three, an intermediate probability; and a score of one or less indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; and since there is still no perfect gold standard for diagnosing LQTS, the accuracy of this scoring system remains ill-defined.
Table 1. Diagnostic Scoring System for LQTS (Adapted from reference 3)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
</tr>
<tr>
<td>*QTc &gt; 480 msec</td>
<td>3</td>
</tr>
<tr>
<td>*QTc 460-470 msec</td>
<td>2</td>
</tr>
<tr>
<td>*QTc &lt; 450 msec</td>
<td>1</td>
</tr>
<tr>
<td>History of torsades de pointes</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T-waves in three leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>*Syncope brought on by stress</td>
<td>2</td>
</tr>
<tr>
<td>*Syncope without stress</td>
<td>1</td>
</tr>
<tr>
<td>*Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>*Family members with definite LQTS</td>
<td>1</td>
</tr>
<tr>
<td>*Unexplained sudden death in immediate family members younger than 30 years of age</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Genetic Testing**

For example, if a family member has been diagnosed with LQTS based on clinical characteristics, complete analysis of all LQTS-associated genes can be performed to both identify the specific mutation and identify the subtype of LQTS. If a mutation is identified, then additional family members can undergo targeted genetic analysis for the identified mutation.

There are more than 1,200 unique mutations on at least 13 genes that have been associated with LQTS. The pathophysiologic significance of each of the discrete mutations is an important part of the interpretation of genetic analysis. Laboratories that test for LQTS keep a database of known pathologic mutations; however, these are mainly proprietary and may vary among different laboratories. The probability that a specific mutation is pathophysiologically significant is greatly increased if the same mutation has been reported in other cases of known LQTS. In other cases, a mutation may be found that has not definitely been associated with LQTS and therefore may or may not be pathologic. Variants are classified as to their pathologic potential; an example of such a classification system is as follows:

- **Class I** – Deleterious and probable deleterious mutations. These are either mutations that have previously been identified as pathologic (deleterious mutations), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious mutations).
- **Class II** – Possible deleterious mutations. These variants encode changes to protein(s) but occur in regions that are not considered critical. Approximately 5% of unselected patients without LQTS will exhibit mutations in this category.
- **Class III** – Variants not generally expected to be deleterious. These variants encode modified protein(s); however, these are considered more likely to represent benign polymorphisms. Approximately 90% of unselected patients without LQTS will have one or more of these variants; therefore patients with only Class III variants are considered ‘negative.’
• Class IV – Non-protein-altering variants. These are not considered to have clinical significance and are not reported in the results of the Familion® test.

In addition to single mutations, some cases of LQTS are associated with deletions or duplications of genes (6). This may be the case in up to 5% of total cases of LQTS. These types of mutations may not be identified by gene sequence analysis. They can be more reliably identified by chromosomal microarray analysis (CMA), also known as array comparative genomic hybridization (aCGH). Some laboratories that test for LQTS are now offering detection of LQTS-associated deletions and duplications by this testing method. This type of test may be offered as a separate test and may need to be ordered independently of gene sequence analysis when testing for LQTS. The absence of a mutation does not imply the absence of LQTS; it is estimated that mutations are only identified in 70-75% of patients with a clinical diagnosis of LQTS. (7) A negative test is only definitive when there is a known mutation identified in a family member and targeted testing for this mutation is negative. Other laboratories have investigated different testing strategies. For example, Napolitano and colleagues propose a three-tiered approach, first testing for a core group of 64 codons that have a high incidence of mutations, followed by additional testing of less frequent mutations. (8)

Another factor complicating interpretation of the genetic analysis is the penetrance of a given mutation or the presence of multiple phenotypic expressions. For example, approximately 50% of carriers of mutations never have any symptoms. There is variable penetrance for the LQTS, and penetrance may differ for the various subtypes. While linkage studies in the past indicated that penetrance was 90% or greater, more recent analysis by molecular genetics has challenged this number, (9) and suggested that penetrance may be as low as 25% for some families.

Corporate Medical Guideline

Genetic testing in patients with suspected congenital long QT syndrome may be considered medically necessary for the following indications:

Individuals who do not meet the clinical criteria for LQTS (i.e., those with a Schwartz score less than four), but who have:
• a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation; or
• a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable; or
• signs and/or symptoms indicating a moderate-to-high pretest probability* of LQTS.

* Determining the pretest probability of 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 two to three.

Genetic testing for LQTS to determine prognosis and/or direct therapy in patients with known LQTS is considered investigational.

Refer also to Protocol Genetic Testing for Inherited Disorders for Benefit Application information.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced
Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


