Status
Active

**Medical and Behavioral Health Policy**
Section: Laboratory
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# GENETIC TESTING FOR CONGENITAL LONG QT SYNDROME

**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 itself 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 of untreated patients with LQTS is estimated at 1%–2% per year, although this figure will vary with the genotype, discussed further here. Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and thus LQTS has received some 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 EKG. Diagnostic criteria for LQTS have been established, which focus on EKG findings and clinical and family history (e.g., Schwartz criteria, see following section, “Clinical Diagnosis”). However, measurement of the QT interval is not well standardized, and in some cases, patients may be considered borderline cases.

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 variants recognized, each corresponding to mutations in different genes as indicated here. In addition, typical ST-T-wave patterns are also suggestive of specific subtypes.

**LQT1** is associated with mutations in the gene KNQ1 located on chromosome 11. LQT1 is responsible for about 50% of all LQTS, and arrhythmic events prompted by exercise may occur most commonly in this subtype. Therefore, patients with LQT1 may be advised to minimize exercise.

**LQT2** is associated with mutations in the gene KCNH2 located on chromosome 7 and is seen in 45% of patients with LQTS. Arrhythmic events appear to be precipitated by auditory stimuli, and these patients may be advised to avoid clock alarms, etc.

**LQT3** is associated with mutations in the gene SCN5A located on chromosome 3. This subtype is seen in 3%–4% of patients with LQTS. In this subtype, the majority of cardiac events occur during sleep. LQT3 variant is also known as the Brugada syndrome.

**LQT 4-7** involve KCN genes located on chromosomes 21 and 17. These variants each account for less than 1% of LQTS.

## Clinical Diagnosis

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS. The most recent version of this scoring system is shown in the Table. A score of 4 or greater indicates a high probability that LQTS is present; a score of 2-3 an intermediate probability; and a score of 1 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; therefore, the accuracy of this scoring system is ill-defined.

**Table. Diagnostic Scoring System for LQTS**

| Criteria | Points |
|---|---|
| Electrocardiographic findings | |
| *$QT_c$ >480 msec | 3 |
| *$QT_c$ 460-470 msec | 2 |
| *$QT_c$ <450 msec | 1 |
| History of torsades de pointes | 2 |
| T-wave alternans | 1 |
| Notched T-waves in three leads | 1 |
| Low heart rate for age | 0.5 |
| Clinical history | |
| *Syncope brought on by stress | 2 |
| *Syncope without stress | 1 |
| *Congenital deafness | 0.5 |
| Family History | |
| *Family members with definite LQTS | 1 |
| **Unexplained sudden death in immediate family members younger than 30 years of age* | 0.5 |

**Genetic Testing**

The Familion® test describes the analysis of the genes responsible for subtypes LQT 1-5. The test is offered in a variety of ways. For example, if a family member has been diagnosed with LQTS based on clinical characteristics, complete analysis of all five 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 a focused genetic analysis for the identified mutation. If a specific type of LQTS is suspected based on the EKG abnormalities, genetic testing can focus on the individual gene.

All of the LQTS genes are large, and genetic testing has revealed multiple different mutations along their length. The pathophysiologic significance of each of the discrete mutations is an important part of the interpretation of genetic analysis. PGxHealth (New Haven, CT), the laboratory offering the Familion® test, compares the results to the PGxHealth Cardiac Ion Channel Variant Database, which includes data from over 750 individuals of diverse ethnic backgrounds. Therefore, the chance that a specific mutation is pathophysiologically significant is increased if it is the same mutation as that reported in several other cases of known LQTS. However, there may be many instances when the detected mutations are of unknown significance. Variants are placed into four classes, based on the probability that the variant identified represents an actual deleterious LQTS mutation:

- Class I – Deleterious and probable deleterious mutations. These are either mutations which have previously been identified (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 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 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.

The absence of a mutation does not imply the absence of LQTS; it is estimated that mutations are only identified in 60–70% of patients with

a clinical diagnosis of LQTS. For these reasons, the most informative result of testing would probably occur when a family member undergoes genetic testing for a specific genetic mutation that has been identified in symptomatic relatives known to have LQTS. Interpretation of the results will likely be improved as the database grows. 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.

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 mutation 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, and suggested that penetrance may be as low as 25% for some families.

**Policy:**

Genetic testing in patients with suspected Congenital Long QT Syndrome (LQTS) may be considered **MEDICALLY NECESSARY** for individuals who do not meet the clinical criteria for LQTS, but who have the following:

- 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 2-3.

Genetic testing for Long QT Syndrome (LQTS) to determine prognosis and/or direct therapy in patients with known LQTS is considered **INVESTIGATIVE** due to a lack of evidence demonstrating its impact on improved health outcomes.

**Coverage:**

Blue Cross and Blue Shield of Minnesota medical policies apply generally to all Blue Cross and Blue Plus plans and products. Benefit plans vary in coverage and some plans may not provide coverage for certain services addressed in the medical policies.

Medicaid products and some self-insured plans may have additional policies and prior authorization requirements. Receipt of benefits is subject to all terms and conditions of the member's summary plan description (SPD). As applicable, review the provisions relating to a specific coverage determination, including exclusions and limitations. Blue Cross reserves the right to revise, update and/or add to its medical policies at any time without notice.

For Medicare NCD and/or Medicare LCD, please consult CMS or National Government Services websites.

Refer to the Pre-Certification/Pre-Authorization section of the Medical Behavioral Health Policy Manual for the full list of services, procedures, prescription drugs, and medical devices that require Pre-certification/Pre-Authorization. Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.

**Coding:**

*The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.*

**CPT:**

81280 Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); full sequence analysis

81281 Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); known familial sequence variant

81282 Long qt syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); duplication/deletion variants

**HCPCS:**

S3861 Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome

**Policy History:**

**Developed September 10, 2008**

**Most recent history:**
Reviewed September 8, 2010
Reviewed September 14, 2011
Reviewed September 12, 2012
Reviewed September 11, 2013

**Cross Reference:**

Genetic Testing and Counseling for Heritable Disorders, VI-09