



# CIGNA HEALTHCARE COVERAGE POSITION

**Subject Genetic Testing for Long QT Syndrome (LQTS)**

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### INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Position

**CIGNA HealthCare covers genetic testing for long QT syndrome (LQTS) as medically necessary for EITHER of the following:**

- For confirmatory testing when the patient has been confirmed to have prolonged QT interval on electrocardiogram (ECG) or Holter monitor, and an acquired cause has been ruled out.
- For predictive testing when there is evidence of EITHER of the following situations in a first-degree relative\*:
  - There is a history of prolonged QT interval on ECG or Holter monitor, sudden death, or near sudden death and a genetic syndrome is suspected.
  - There is a positive genetic test for LQTS.

\*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes. First-degree relatives include the individual's parents, full siblings and children.

**All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.**

**CIGNA HealthCare does not cover genetic screening for LQTS in the general population, because such screening is considered not medically necessary or of unproven benefit.**

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## General Background

Long QT syndrome (LQTS) is a disorder of the heart's electrical system. It is characterized by prolongation of the QT interval. The QT interval is the section on the electrocardiogram (ECG) that represents the time it takes for the electrical system to fire an impulse through the ventricles and then recharge. The electrical activity of the heart is produced by the flow of ions in and out of the cells of the heart. LQTS is a defect in the ion channels, which causes a delay in the time it takes for the electrical system to recharge after each heartbeat. LQTS disorders are considered channelopathies, or diseases that affect cardiac ion channels. This condition predisposes the individual to cardiac events and arrhythmias including: torsades de pointes ventricular tachycardia, syncope episodes, ventricular fibrillation and cardiac arrest. LQTS may also be caused by acquired factors, most commonly by use of certain drugs that will cause prolongation of the QT interval.

LQTS is diagnosed by considering the clinical features, the family history and the ECG findings of the patient. Unexplained syncope or sudden cardiac death in a child or young adult should raise suspicion of the possibility of LQTS. Electrophysiological testing has not been demonstrated to be helpful in making this diagnosis. The clinical features are a result of the torsades, and may range from minor symptoms such as dizziness, to seizure, syncope and sudden death. Congenital LQTS will usually manifest before the age of 40 years, generally in childhood and adolescence. The age is usually dependent on the genotype. The prolongation of the QT interval is a risk factor independent of patient's age, history of myocardial infarction, heart rate and history of drug use. Patients with QT interval corrected by heart rate (QTc) of greater than 440 milliseconds are at two to three times higher risk for sudden cardiac death than those with QTc interval of under 440 milliseconds. The mortality rate of untreated patients with LQTS is in the range of 1% to 2% per year. Sudden cardiac death may be precipitated by a triggering event, such as physical exercise, swimming, sleep deprivation, auditory stimuli, and sudden intense sympathetic stimuli (Kahn, 2002). In an effort to enhance diagnostic reliability, an elaborate point score system has been proposed by Schwartz et al. (1993) that incorporates QTc duration, as well as other hallmarks such as syncope and a family history of this condition.

In approximately 6% to 12%, of patients, the QTc interval is within normal limits. Other ECG features which may assist in diagnosis include T-wave and U-wave abnormalities, sinus bradycardia with sinus pause, and increased QT interval dispersion. The T-wave may be larger, prolonged, and bizarre looking with notched, bifid, biphasic, or alternans appearance. In particular, genetic screening provides major and unique assistance in a family member with normal QT interval (Schwartz, 2005).

Long-term management of LQTS includes beta-adrenergic blockers. This medication has been shown to result in a significant reduction in the incidence of cardiac events in patients with congenital LQTS. Permanent pacemaker implantation has been used in patients who are symptomatic despite being on full dose of beta-adrenergic blockers, and bradycardia is a prominent feature of the syndrome. Implantable cardioverter defibrillators are used when the combination of beta-adrenergic blockers and pacing fails to prevent presyncope or syncope episodes.

More than 300 different mutations have thus far been identified in the known LQTS genes. However, it is thought that not all the genes responsible for LQTS have been identified. In addition, sporadic cases of LQTS may occur as a result of spontaneous mutations. It has been noted that only about 50% of clinically apparent LQTS patients can be genotyped to one of the known genes. This suggests that additional LQTS genes may exist that cause the disorder. A lack of family history does not entirely preclude the diagnosis of congenital LQTS (Kahn, 2002). The inability to identify a genetic mutation in some LQTS patients limits the utility of genetic testing for LQTS because a negative result does not exclude the disease (Vincent, 2000).

### Forms of LQTS

There are several forms of LQTS, depending on the genes responsible and the features associated with the condition. Most forms of LQTS are carried in an autosomal dominant manner, with the exception being Jervell and Lange-Nielsen syndrome (JLNS), which is inherited in an autosomal recessive manner.

Articles in the medical literature may use the terminology LQT1, LQT2, etc., to refer to the locus name of genes involved in LQTS, or the phenotype (Vincent, 2008).

**Romano-Ward Syndrome:** Romano-Ward syndrome (RWS) is the most common form of inherited LQTS. The estimated prevalence of RWS is 1:7000. A syncopal event is the most common symptom in RWS and typically occurs without warning. About 50–70% of individuals with a disease-causing mutation in one of the genes associated with RWS have symptoms; cardiac events may occur from infancy through middle age, but are most common from the preteen years through the 20s (Vincent, 2008).

RWS is inherited in an autosomal dominant manner. Most individuals diagnosed with RWS have an affected parent. The proportion of cases caused by de novo mutations is small. Each child of an individual with RWS has a 50% risk of inheriting the disease-causing mutation. About 30% of families known to be clinically affected with RWS do not have detectable mutations in any one of the known genes. Clinical methods of genetic testing for this condition include: mutation scanning and sequence analysis. The five known genes, along with the locus name, that are responsible for this form include (Vincent, 2008):

Gene	Locus name
KCNQ1	LQT1
KCNH2	LQT2
SCN5A	LQT3
KCNE1	LQT5
KCNE2	LQT6

**Jervell and Lange-Nielsen Syndrome:** Jervell and Lange-Nielsen syndrome (JLNS) is a more severe and rare form of LQTS. In addition to the prolongation of the QT interval, this diagnosis is accompanied by profound congenital sensorineural deafness. The prognosis is worse than that for RWS. It has been noted that over half of untreated children with JLNS die prior to age 15 years. JLNS is inherited in an autosomal recessive manner. Most of the mutations for this form are on the KCNQ1 and KCNE1 genes, both of which can also cause RWS. Parents of a child with JLNS may be heterozygotes; rarely, only one parent may be a carrier, and the other mutation may arise as a de novo mutation. Parents may or may not have the LQTS phenotype. At conception, the siblings of an affected individual may have a 25% chance of being affected with JLNS, a 50% chance of being carriers of a JLNS disease-causing mutation and at risk for LQTS, and a 25% chance of being unaffected and not carriers. Clinical methods of genetic testing for this condition include mutation scanning and sequence analysis (Daley, et al., 2007; Schwartz, et al., 2006).

**Andersen-Tawil Syndrome:** Andersen-Tawil syndrome (ATS), or Andersen syndrome, is a rare disorder that is characterized by a triad of distinctive dysmorphic features: episodic flaccid muscle weakness, ventricular arrhythmias and prolonged QT interval and common anomalies such as low-set ears, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis. In the first or second decade, affected individuals present with either cardiac symptoms (palpitations and/or syncope) or weakness that occurs spontaneously following prolonged rest or following rest after exertion. It is inherited in an autosomal dominant manner. The prevalence is not known. At least 50% of affected individuals have an affected parent, while up to 50% are caused by de novo mutations. The gene that is known to be responsible for this form is KCNJ2 (locus name LQT7). Clinical methods of genetic testing for this condition include mutation scanning and sequence analysis (Tawil and Venance, 2007).

**Timothy Syndrome or Syndactyly-Related LQTS:** Timothy syndrome, also known as syndactyly-related LQTS, or LQTS with syndactyly, is a rare form of LQTS that is a multisystem disorder characterized by cardiac, hand, facial and neurodevelopmental features. There are two forms described in the literature: classic (type 1) and a very rare second form (type 2). Timothy syndrome types 1 and 2 are usually the result of a de novo autosomal dominant mutation, although they have been reported to result from parental germline mosaicism. The only gene known to be associated with this condition is CACNA1C. To date, none of the individuals diagnosed with Timothy syndrome has had an affected parent. Testing of the CACNA1C gene is available on a clinical basis. Clinical method of genetic testing is targeted mutation analysis (Splawski, et al., 2008).

### **Genetic Screening in the General Population**

Genetic screening of all children, young athletes, or all young persons with unexplained syncope is not feasible for the following reasons: No commercial laboratories do these tests because the false-negatives and the false-positive test rate is not well-defined and would have to be extremely low for a screening test. Thus, population screening for LQTS by deoxyribonucleic acid (DNA) testing is neither recommended nor available (Vincent, 2001).

### **Prenatal Testing and Preimplantation Genetic Testing**

The optimal time for determination of genetic risk is before pregnancy. Review of the literature notes that prenatal genetic testing and preimplantation genetic testing for congenital LQTS has so far occurred only in the research setting. When the disease-causing mutation has been identified in an affected family member, testing may be available in research laboratories.

### **Familion<sup>®</sup> Test**

The Familion<sup>®</sup> test (Clinical Data, Inc., Newton, MA) is a patented genetic test that is intended to provide analysis of five major cardiac ion channel genes. According to the Clinical Data website, the analysis includes sequence determination and variant detection. It is noted at the website that the genes analyzed by this test include: KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. Testing for LQTS may be performed with one of following configurations:

- Comprehensive cardiac ion channel analysis: This will provide analysis for variants in all five genes and is appropriate when there is a high index of suspicion of disease such as stress-induced syncope, prolonged QT interval, family history of sudden cardiac death and unexplained ventricular arrhythmia.
- Family specific analysis: This test provides analysis of one or more mutations found in an index case using either one of the above test configurations or confirmed results from another laboratory and is appropriate for testing blood relatives.

### **Literature Review**

Priori et al. (2003) conducted an evaluation of 647 patients to define the cumulative probability of a first cardiac event (defined as syncope, cardiac arrest, or sudden death) before therapy (i.e., the natural history of the disease) and to analyze the complex interplay among the genetic locus, sex and the duration of repolarization, which determines the probability of cardiac events in the LQTS. In addition, the study looked at whether the available data might provide insights into risk stratification. The study involved 647 patients: 386 with mutation of LQT1 locus, 206 with mutation at LQT2 locus and 55 with mutation at LQT3 locus. The cumulative probability of a first cardiac event before the age of 40 years and before the initiation of therapy was determined according to genotype, sex, and the QT interval corrected for heart rate (QTc). Within each genotype, risk was assessed in the four categories derived from the combination of sex and QTc (<500 millisecond or ≥500 millisecond). The results noted that the incidence of a first cardiac event before the age of 40 years and before the initiation of therapy was lower among patients with a mutation at the LQT1 locus (30%) than among those with a mutation at the LQT2 locus (46%) or those with a mutation at the LQT3 locus (42%). In addition, it was noted that the genetic locus and the QTc, but not sex, were independent predictors of risk. Further analysis indicated that the QTc was an independent predictor of risk among patients with a mutation at the LQT1 locus and those with a mutation at the LQT2 locus but not among those with a mutation at the LQT3 locus, whereas sex was an independent predictor of events only among those with a mutation at the LQT3 locus. The authors concluded that “The locus of the causative mutation affects the clinical course of the LQTS and modulates the effects of the QTc and sex on clinical manifestations.” Based on these findings, the authors proposed a risk stratification for LQTS with possible implications for disease management.

A review of sudden cardiac deaths termed sudden arrhythmic death syndrome (SADS) was conducted by Behr et al. (2003). Of 147 relatives of 32 people who died of SADS, 109 underwent cardiological assessment. Seven (22%) of the 32 families were diagnosed with inherited cardiac disease—four with LQTS, one with nonstructural cardiac electrophysiological disease, one with myotonic dystrophy, and one with hypertrophic cardiomyopathy. The authors concluded that families of people who die from SADS should be offered assessment in centers with experience in inherited cardiac disease.

Imboden et al. (2006) conducted a retrospective study to investigate the distribution of alleles for LQTS in 484 nuclear families with type 1 disease and 269 nuclear families with type 2 disease. The mutation segregation, sex ratio and parental transmission were analyzed after correction for single ascertainment. Types 1 and 2 are caused by mutations in the potassium-channel genes, KCNQ1 and KCNH2, respectively. The subjects were recruited from five European referral centers for LQTS. The results indicated that classic Mendelian inheritance ratios were not observed in the offspring of either female carriers of LQTS type 1 or male and female carriers LQTS type 2. It was noted that 870 were carriers of a mutation (57%), and 664 were noncarriers (43%,  $p < 0.001$ ). Among the 870 carriers, the allele for LQTS was transmitted more often to female offspring (476 [55%]) than to male offspring (394 [45%],  $p = 0.005$ ). There was an increase in maternal transmission of LQTS mutations to daughters observed, which possibly contributed to the excess of female patients with autosomal dominant long-QT syndrome. The authors concluded that positive selection of the mutated alleles that cause LQTS leads to transmission distortion, with increased proportions of mutation carriers among the offspring of affected families.

A technology assessment was performed by Blue Cross Blue Shield Association (BCBSA), Technology Evaluation Center (TEC) (2008) to review evidence to determine if genetic testing for LQTS improves health outcomes for patients with known or suspected LQTS. Among the findings, the report noted that, "Despite uncertainties in the diagnostic accuracy of genetic testing, the clinical utility of testing is high. This is due to the catastrophic outcomes associated with LQTS and the availability of low-risk treatments that are efficacious in reducing adverse outcomes. The risk of undertreatment of such individuals is therefore likely to far outweigh the risk of overtreatment of such individuals." Regarding testing of individuals with a known LQTS mutation in the family but who do not themselves meet the clinical criteria for LQTS, the report noted that "genetic testing will improve outcomes. These individuals have a high pretest probability of disease and LQTS can be diagnosed with certainty if the test is positive. Treatment of these individuals with beta blockers will reduce the incidence of subsequent cardiovascular events. Furthermore, because the specific mutation is known prior to testing, the disease can be ruled out with certainty if results are negative."

The BCBSA TEC report included the following conclusions (2008):

- These situations met TEC criteria for establishing the diagnosis of LQTS in the following individuals:
  - Individuals who do not meet the clinical criteria for LQTS, but who have:
    - a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation
    - a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable
    - signs and/or symptoms indicating a moderate to high pretest probability of LQTS
  - An individual who meets the clinical criteria for LQTS and who has a close relative at risk for LQTS with an indication for genetic testing. In this circumstance, testing of the individual with LQTS is intended to inform genetic testing options for at-risk relatives.
- Genetic testing for LQTS does not meet the TEC criteria for determining prognosis and/or directing therapy in patients with known LQTS who do not have close relative(s) with indications for genetic testing.

### **Professional Societies/Organizations**

In 2006, evidenced-based practice guidelines were published by the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (ACC/AHA/ESC) regarding management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. The guidelines note that, "In patients affected by LQTS, genetic analysis is useful for risk stratification and for making therapeutic decisions. Although genetic analysis is not yet widely available, it is advisable to try to make it accessible to LQTS patients."

### **Summary**

Molecular diagnosis affords the potential to enhance diagnostic reliability in long QT syndrome (LQTS). The role for genetic diagnosis in this disease is substantial, given the number of inherent difficulties that exist in identifying the LQTS phenotype solely from measurement of QT interval duration on 12 lead electrocardiogram (ECG). Available genotype-phenotype correlations in LQTS show that a normal QT corrected for heart rate (QTc) does not exclude LQTS. Genetic testing for LQTS may be used to identify mutations in individuals or family members with suspected or confirmed LQTS.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

CPT®* Codes	Description
	Multiple/varied

HCPCS Codes	Description
S3860	Genetic testing, comprehensive cardiac ion channel analysis, for variants in 5 major cardiac ion channel genes for individuals with high index of suspicion for familial Long QT Syndrome (LQTS) or related syndromes
S3862	Genetic testing, family-specific ion channel analysis, for blood-relatives of individuals (index case) who have previously tested positive for a genetic variant of a cardiac ion channel syndrome using either one of the above test configurations (S3860 or S3861) or confirmed results from another laboratory

ICD-9-CM Diagnosis Codes	Description
426.82	Long QT syndrome

\*Current Procedural Terminology (CPT®) ©2007 American Medical Association: Chicago, IL.

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