



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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

**Effective Date ..... 10/15/2010**  
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### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer'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 Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. 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 benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

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

- confirmatory testing when there is confirmed prolonged QT interval on electrocardiogram (ECG) or Holter monitor, and an acquired cause has been ruled out
- predictive testing when there is evidence of EITHER of the following situations in a first-degree relative\*:
  - a history of prolonged QT interval on ECG or Holter monitor (i.e., corrected QT [QTc] interval of >470 msec [males] or >480 msec [females]), sudden death, or near sudden death and a genetic syndrome is suspected
  - a positive genetic test for LQTS
- prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when the disease-causing mutation has been identified in an affected parent

\*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.

**CIGNA does not cover comparative genomic hybridization testing (chromosomal microarray analysis) for LQTS with because it is considered experimental, investigational or unproven.**

**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 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 that 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. 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, syncopal 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. The QT interval increases with decreasing heart rate, which makes it necessary to use a rate-corrected QT interval termed QTc when assessing whether the interval is prolonged or normal QTC interval. LQTS may be diagnosed when the prolongation of the QTc interval is >470 msec (males) or >480 msec (females) (Vincent, 2009; Crotti, et al., 2008). Unexplained syncope or sudden cardiac death in a child or young adult should raise suspicion of the possibility of LQTS. The clinical features 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 with the age 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. 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, 2006). Long-term management of LQTS may include lifestyle modification, beta-adrenergic blockers, permanent pacemaker implantation, and implantable cardioverter defibrillators.

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. Not all patients meeting clinical criteria for LQTS have detectable mutations in one of the known associated 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).

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 subtype or locus name of genes involved in LQTS, or the phenotype. The genes associated with LQTS include (Vincent, 2009; Crotti, et al., 2008):

Gene	Subtype/Locus name
KCNQ1	LQT1
KCNH2	LQT2
SCN5A	LQT3
ANK2	LQT4
KCNE1	LQT5
KCNE2	LQT6
KCNJ2	LQT7
CACNA1	LQT8
CAV3	LQT9
SCN4B	LQT10

**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, 2009).

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 five known genes. The majority of these individuals have T-wave patterns consistent with the phenotype associated with one of the known genes, which suggests that undetected mutations of the known genes may be the cause of the negative genetic result. Clinical methods of genetic testing for this condition include: mutation scanning and sequence analysis. The genes that have been identified to be associated with this form include KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. In addition, it is thought that these genes have an association with LQTS: SCN4B, ANK2, KCNJ2, CAV3 (Vincent, 2009; Crotti, et al., 2008).

**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 (Tranebjaerg, et al., 2010; 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. A detectable mutation in KCNJ2 is found in approximately 60% of the individuals with ATS. The diagnosis of ATS can be confirmed with the presence of a pathogenic KCNJ2 mutation which is the gene known to be responsible for ATS is KCNJ2 (locus name LQT7) (Tawil and Venance, 2010).

**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 (Splawski, et al., 2009).

### **Genetic Testing for Long QT Syndrome**

The Familion<sup>®</sup> test (Clinical Data, Inc., Newton, MA) is a patented genetic test that provides analysis of 11 genes associated with LQTS. 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, KCNE2, KCNJ, CAV3, SCN4B, SNTA1, CACNA1C, and AKAP9. Testing may be performed with sequence analysis in the following configurations:

- Comprehensive cardiac ion channel analysis: provides analysis for variants in the 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: 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

An additional genetic test for LQTS became commercially available in 2009 from GeneDx (Gaithersburg, MD). It is noted at the website that they perform sequence analysis of the following genes: KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ, CAV3, SCN4B, SNTA1, CACNA1C, and AKAP9. According to the GeneDx website, this testing is available for:

- LQTS panel in a new patient
- Testing for a relative for a single known mutation
- Prenatal diagnosis for a known mutation
- LQTS Deletion/Duplication Testing

Chromosomal microarray analysis (CMA), a method of genetic testing, has been proposed to be used in genetic testing for LQTS. CMA is an emerging method of genetic testing that is also referred to as array comparative genomic hybridization, array CGH, or aCGH. The testing method can identify small deletions and duplications of the subtelomeres, each pericentromeric region and other chromosome regions. The LQTS ExonArrayDx test (Gaithersburg, MD) is a microarray test that, according to the provider's website, utilizes a custom-designed oligonucleotide array for comparative genomic hybridization for the purpose of detecting a deletion or duplication in the LQTS genes. There are few studies published in the scientific literature that examine the use of this testing for these conditions. A cohort study evaluated whether deletions and/or duplications of one or more exons of the main LQTS genes were present in an LQTS mutation-negative cohort of 26 probands (Eddy, et al., 2008). It was found that in three patients an altered exon copy number was detected. The clinical utility and the specific patients who are appropriate for this type of testing have not yet been determined. The use of this testing method in patients with suspected LQTS is still preliminary and is not yet recommended.

### **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. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cell obtained by amniocentesis or chorionic villus sampling. Preimplantation genetic testing (PGD) may also be performed. The disease-causing mutation must be identified before prenatal testing of fetus or PGD is performed. Prenatal testing requests for conditions

such as LQTS that do not affect intellect and have treatment options available is not common (Vincent, 2009; Tranebjaerg, et al., 2010; Tawil, et al., 2010; Splawski, et al., 2009).

### **Literature Review**

Several studies have been published that indicate that genetic testing for LQTS may offer early identification of those patients at high risk to develop LQTS and may provide the opportunity for early intervention (Priori, et al., 2003; Behr, et al., 2003; Imboden, et al., 2006).

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 when used to report genetic testing for long QT syndrome as outlined as covered in this policy:**

<b>CPT®* Codes</b>	<b>Description</b>
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83893	Molecular diagnostics; dot/slot blot production, each nucleic acid preparation
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88291	Cytogenetics and molecular cytogenetics, interpretation and report

<b>HCPCS Codes</b>	<b>Description</b>
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

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
426.82	Long QT syndrome
427.0-427.69	Cardiac dysrhythmias
780.2	Syncope and collapse
780.4	Dizziness and giddiness
V12.53	Personal history of sudden cardiac arrest
V17.41	Family history of sudden cardiac death (SCD)
V17.49	Family history of other cardiovascular diseases
V18.9	Family history of genetic disease carrier

**Experimental/Investigational/Unproven and Not Covered when used to report comparative hybridization (chromosomal microarray analysis) testing for LQTS:**

<b>CPT®* Codes</b>	<b>Description</b>
88386	Array-based evaluation of multiple molecular probes; 251 through 500 probes

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	10/15/2008	0193	Genetic Testing for Long QT Syndrome (LQTS)

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