Kansas City

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Genetic Testing for Congenital Long QT Syndrome

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for genetic testing for congenital Long QT Syndrome (LQTS) when it is determined to be medically necessary because the criteria shown below are met.

Some plans may have contract or benefit exclusions for genetic testing.

When Policy Topic is covered

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, 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 2-3.

When Policy Topic is not covered

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

Description of Procedure or Service

Long QT syndrome (LQTS) is caused by a mutation in one of the genes that controls cellular sodium and potassium ion channels. Testing for this mutation may assist in the diagnosis of LQTS and/or may identify patients at risk for LQTS when there is a family member diagnosed with the disorder.

Congenital long QT syndrome 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 instances, 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 7 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 4 or greater indicates a high probability that LQTS is present; a score of 2–3, a moderate-to-high 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; 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)

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

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 3-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.

Rationale

The following discussion of the evidence is based on a 2007 TEC Assessment, "Genetic Testing for Long QT Syndrome." (10)

Validation of the clinical use of any genetic test focuses on 3 main principles: 1) the analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent; 2) the clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and 3) the clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Analytic Validity

Information on analytic sensitivity and specificity for gene sequence analysis was obtained from the website of Transgenomics (formerly PGxHealth) (New Haven, CT). Additional unpublished data were supplied by Transgenomics in response to a list of structured questions.

The website states that the analytic sensitivity of the test is greater than 99%: This analytic sensitivity is based on an independent analysis of 21 “unknown” samples, which had been previously characterized and supplied to the company by a research lab at the University of Rochester, NY. Of these 21 samples, 20 contained various types of mutations, including nonsense, missense, splice site, and insertions/deletions, and one sample was a “wild type,” containing no mutations. According to the manufacturer, all of the mutations were correctly identified, thus leading to their reporting of analytic sensitivity of greater than 99%.

The website states the following concerning the analytic specificity of the test: “The chance of a falsely detected genetic variant is minimized by requiring that each variant be seen in sequence traces for both forward and reverse directions and that two trained technicians independently examine each trace. Chances of false positives are minimized by the use of a validated sample tracking system that uses robotics and barcodes. For each positive finding of a Class I or Class II variant, a second round of PCR amplification and sequencing is performed to confirm the initial finding.”

Abnormal results from the commercial test are reported as Class I or Class II mutations, and the analytic specificity for each class of mutations will differ. Approximately 75% of all reported deleterious mutations are Class I, and the remaining 25% are Class II mutations. For Class I mutations, data from the validation sample reported by the manufacturer indicate that false positive results are expected to be extremely uncommon, so that analytic specificity will approach 100%. For Class II mutations, false positive results are more likely to occur. Analysis of non-long QT syndrome (LQTS) patients revealed that variants reported as Class II mutations are found in approximately 5% of patients without LQTS. Therefore, the analytic specificity of Class II mutations is expected to be approximately 95%.

Kapa et al. (11) examined the likelihood that sequence variations were benign versus pathogenic mutations by comparing variations found in patients with definite LQTS with those from normal patients. This study compared gene sequence variations found in 388 definite cases of LQTS with sequence variations from approximately 1,300 unaffected individuals. Sequence variations in unaffected individuals, which presumably represent non-pathologic changes, were missense mutations in more than 99% of cases. Therefore, variations that were not missense mutations had a very high predictive value for pathologic mutations. For missense mutations, the location appeared to be critical in predicting whether they are pathogenic. Missense mutations in certain areas of the KCNQ1 gene, such as the transmembrane, linker and pore regions, had a high probability of being pathogenic.

Clinical Validity

The true clinical sensitivity and specificity of genetic testing for LQTS cannot be determined with certainty, as there is no independent gold standard for the diagnosis of LQTS. The clinical diagnosis can be compared to the genetic diagnosis, and vice versa, but neither the clinical diagnosis nor the results of genetic testing can be considered an adequate gold standard.

Hofman et al. (12) performed the largest study, comparing clinical methods with genetic diagnosis using registry data. This study compared multiple methods for making the clinical diagnosis, including the Schwartz score, the Keating criteria, and the absolute length of the corrected QT (QTc) with genetic testing. These data indicate that only a minority of patients with a genetic mutation will meet the clinical criteria for LQTS. Using the most common clinical definition of LQTS, a Schwartz score of 4 or greater, only 19% of patients with a genetic mutation met the clinical criteria. Even at lower cutoffs of the Schwartz score, the percentage of patients with a genetic mutation who met clinical criteria was still relatively low, improving to only 48% when a cutoff of 2 or greater was used. When the Keating criteria were used for clinical diagnosis, similar results were obtained. Only 36% of patients with a genetic mutation met the Keating criteria for LQTS.

The best overall accuracy was obtained by using the length of the QTc as the sole criterion; however, even this criterion achieved only modest sensitivity at the expense of lower specificity. Using a cutoff of 430 msec or longer for the QT interval, a sensitivity of 72% and a specificity of 86% was obtained.

Tester et al. (13) completed the largest study to evaluate the percent of individuals with a clinical diagnosis of LQTS that are found to have a genetic mutation. The population in this study was 541 consecutive patients referred for evaluation of LQTS. A total of 123 patients had definite LQTS on clinical grounds, defined as a Schwartz score of 4 or greater, and 274 patients were found to have a LQTS mutation. The genetic diagnosis was compared to the clinical diagnosis, defined as a Schwartz score of 4 or greater. Of all 123 patients with a clinical diagnosis of LQTS, 72% (89/123) were found to have a genetic mutation.

The evidence on clinical specificity focuses on the frequency and interpretation of variants that are identified that are not known to be pathologic. If a mutation is identified that is previously known to be pathologic, then the specificity of this finding is high. However, many variants are discovered on gene sequencing that are not known to be pathologic, and the specificity of these types of findings are lower. The rate of identification of variants is estimated to be in the range of 5% for patients who do not have LQTS. (11)

A publication from the National Heart, Lung, and Blood Institute (NHLBI) GO exome sequencing project (ESP) reported on the rate of sequence variations in a large number of patients without LQTS. (14) The ESP sequenced all genome regions of protein-coding in a sample of 5,400 persons drawn from various populations, none of which included patients specifically with heart disease and/or channelopathies. Exome data were systematically searched to identify sequence variations that had previously been associated with LQTS, including both nonsense variations that are generally pathologic and missense variations that are less likely to be pathological. A total of 33 such sequence variations were identified in the total population, all of them being missense variations. The percent of the population that had at least one of these missense variations was 5.2%. There were no nonsense variations associated with LQTS found among the entire population.

Conclusions. This evidence indicates that genetic testing will identify more individuals with possible LQTS compared with clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic mutation have the true clinical syndrome of LQTS. The data also demonstrate that approximately 30% of patients with a clinical diagnosis will not be found to have a known mutation, suggesting that there are additional mutations associated with LQTS that have not been identified to date. Therefore, a negative genetic test is not definitive for excluding LQTS at the present time.

The clinical specificity varies according to the type of mutation identified. For nonsense mutations, which have the highest rate of pathogenicity, there are very few false positives among patients without LQTS, and therefore a high specificity. However, for missense mutations, there is a rate of approximately 5% among patients without LQTS; therefore the specificity for these types of mutation is less and false positive results do occur.

Clinical Utility

Diagnosis. For diagnosing LQTS, the clinical utility of genetic testing is high. LQTS is a disorder that may lead to catastrophic outcomes, i.e., sudden cardiac death in otherwise healthy individuals. Diagnosis using clinical methods alone may lead to underdiagnosis of LQTS, thus exposing undiagnosed patients to the risk of sudden cardiac arrest. For patients in whom the clinical diagnosis of LQTS is uncertain, genetic testing may be the only way to further clarify whether LQTS is present. Patients who are identified as genetic carriers of LQTS mutations have a non-negligible risk of adverse cardiac events even in the absence of clinical signs and symptoms of the disorder. Therefore, treatment is likely indicated for patients found to have a LQTS mutation, with or without other signs or symptoms.

Treatment with beta blockers has been demonstrated to decrease the likelihood of cardiac events, including sudden cardiac arrest. Although there are no controlled trials of beta blockers, there are pre-post studies from registry data that provide evidence on this question. Two such studies reported large decreases in cardiovascular events and smaller decreases in cardiac arrest and/or sudden death after starting treatment with beta blockers. (15, 16) These studies reported a statistically significant reduction in cardiovascular events of greater than 50% following initiation of beta-blocker therapy. There was a reduction of similar magnitude in cardiac arrest/sudden death, which was also statistically significant.

Treatment with an implantable cardioverter-defibrillator (ICD) is available for patients who fail or cannot take beta-blocker therapy. One published study reported on outcomes of treatment with ICDs. (17) This study identified patients in the LQTS registry who had been treated with an ICD at the discretion of their treating physician. Patients in the registry who were not treated with an ICD, but had the same indications, were used as a control group. The authors reported that patients treated with an ICD had a greater than 60% reduction in cardiovascular outcomes.

One study reported on changes in management that resulted from diagnosing LQTS by testing relatives of affected patients with known LQTS (cascade testing). (18) Cascade testing of 66 index patients with LQTS led to the identification of 308 mutation carriers. After a mean follow-up of 69 months, treatment was initiated in 199/308 (65%) of carriers. Beta-blockers were started in 163 patients, a pacemaker was inserted in 26 patients, and an ICD was inserted in 10 patients. All carriers received education on lifestyle issues and avoidance of drugs that can cause QT prolongation.

Two studies evaluated the psychological effects of genetic testing for LQTS. Hendriks et al. studied 77 patients with a LQTS mutation and their 57 partners. (19) Psychologic testing was performed after the diagnosis of LQTS had been made and repeated twice over an 18-month period. Disease-related anxiety scores were increased in the index patients and their partners. This psychologic distress decreased over time but remained elevated at 18 months. Andersen et al. conducted qualitative interviews with 7 individuals found to have LQTS mutations. (20) They reported that affected patients had excess worry and limitations in daily life associated with the increased risk of sudden death, which was partially alleviated by acquiring knowledge about LQTS. The greatest concern was expressed for their family members, particularly children and grandchildren.

Prognosis. For determining LQTS subtype or specific mutation, the clinical utility is less certain. The evidence suggests that different subtypes of LQTS may have variable prognosis, thus indicating that genetic testing may assist in risk stratification. Several reports have compared rates of cardiovascular events in subtypes of LQTS. (1, 16, 21, 22) These studies report that rates of cardiovascular events differ among subtypes, but there is not a common pattern across all studies. Three of the 4 studies (16, 21, 22) reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba and colleagues (1) reported that patients with LQT1 have higher event rates than patients with LQT2.

More recent research has identified specific sequence variants that might be associated with higher risk of adverse outcomes. Albert et al. (23) examined genetic profiles from 516 cases of LQTS included in 6 prospective cohort studies. The authors identified 147 sequence variations found in 5 specific cardiac ion channel genes and tested the association of these variations with sudden cardiac death. Two common intronic variations, one in the KCNQ1 gene and one in the SCN5A gene were most strongly associated with sudden death. Migdalovich et al. (24) correlated gender-specific risks for adverse cardiac events with the specific location of mutations (pore-loop vs. non pore-loop) on the KCNH2 gene in 490 males and 676 females with LQTS. They reported that males with pore-loop mutations had a greater risk of adverse events (hazard ratio [HR]: 2.18, p=0.01) than males without pore-loop mutations but that this association was not present in females. Costa et al. (25) combined information on mutation location and function with age and gender to risk-stratify patients with LQTS 1 by life-threatening events.

Other research has reported that the presence of genetic variants at different locations can act as disease “promoters” in patients with LQTS mutations. (26, 27) Amin et al. (26) reported that 3 single-

nucleotide polymorphisms (SNPs) in the untranslated region of the KCNQ1 were associated with alterations in the severity of disease. Patients with these SNPs had less severe symptoms and a shorter QT interval compared to patients without the SNPs. Park et al. (27) examined a large LQTS kindred that had variable clinical expression of the disorder. Patients were classified into phenotypes of mild and severe LQTS. Two SNPs were identified that were associated with severity of disease, and all patients classified as having a severe phenotype also had one of these 2 SNPs present.

Conclusions. This evidence suggests that knowledge of the specific mutation present may provide some prognostic information but is not sufficient to conclude that knowledge of the specific mutation improves outcomes for a patient with known LQTS.

Management. There is not sufficient evidence to conclude that the information obtained from genetic testing on risk assessment leads to important changes in clinical management. Most patients will be treated with beta-blocker therapy and lifestyle modifications, and it has not been possible to identify a group with low enough risk to forego this conservative treatment. Conversely, for high-risk patients, there is no evidence suggesting that genetic testing influences the decision to insert an ICD and/or otherwise intensify treatment.

Some studies that report outcomes of treatment with beta blockers also report outcomes by specific subtypes of LQTS. (16, 22) Priori and colleagues (16) reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of beta-blocker therapy. There was a decrease in event rates in all LQTS subtypes, with a similar magnitude of decrease in each subtype. Moss and colleagues (15) also reported pre-post event rates for patients treated with beta-blocker therapy. This study indicated a significant reduction in event rates for patients with LQT1 and LQT2 but not for LQT3. This analysis was also limited by the small number of patients with LQT3 and cardiac events prior to beta-blocker treatment (4 of 28). Sauer and colleagues (28) evaluated differential response to beta-blocker therapy in a Cox proportional hazards analysis. These authors reported an overall risk reduction in first cardiac event of approximately 60% (HR: 0.41, 95% confidence interval [CI]: 0.27-0.64) in adults treated with beta blockers and an interaction effect by genotype. Efficacy of beta-blocker treatment was worse in those with LQT3 genotype (p=0.04) compared with LQT1 or LQT2. There was no difference in efficacy between genotypes LQT1 and LQT2.

There is also some evidence on differential response to beta blockers according to different specific type and/or location of mutations. Barsheset et al. (29) examined 860 patients with documented mutations in the KCNQ1 gene and classified the mutations according to type and location. Patients with missense mutations in the cytoplasmic loop (c-loop mutations) had a more marked risk reduction for cardiac arrest following treatment with beta blockers compared to patients with other mutations (HR: 0.12, 95% CI: 0.02-0.73, p=0.02).

Conclusions. These data suggest that there may be differences in response to beta-blocker therapy, according to LQTS subtype and the type/location of the specific mutation. However, the evidence is not consistent in this regard; for example, one of the 3 studies demonstrated a similar response to beta-blockers for LQT3 compared to other subtypes. Although response to beta-blocker therapy may be different according to specific features of LQTS, it is unlikely that this evidence could be used in clinical decision making, since it is not clear how this information would influence management.

Indications for Testing

Indications for testing will depend on a variety of factors, including family history, presence or absence of a known mutation in the family, symptoms, length of the QTc interval on electrocardiogram (EKG), etc. For diagnostic testing, patients with a moderate-to-high pretest probability of LQTS, but in whom the diagnosis cannot be made by clinical methods, will derive the most benefit from testing. Table 2 provides a framework for categorizing patients into testing categories; however, as indicated in the table, there may be substantial uncertainty on the benefit of testing for a number of these categories.

For individuals with a known LQTS mutation in the family but who do not themselves meet the clinical criteria for LQTS, 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.

For diagnosis of LQTS in other patient populations, there may be a benefit as well. For patients who have some signs and symptoms of LQTS but no known mutation in the family, testing may be beneficial. In this situation, LQTS can be diagnosed with reasonable certainty if a Class I mutation is identified; however, the likelihood of false positive results is higher than if a known mutation were present in the family. In patients with lower pretest probabilities of disease, the utility of testing declines, although precise risk/benefit thresholds cannot be established.

Table 2. Potential Patient Indications for Genetic Testing

	Meets clinical criteria for LQTS	**Some signs/symptoms of LQTS; does not meet clinical criteria**	**No signs/symptoms of LQTS**
FH positive and known mutation in family	- (?)	++	+
FH positive but family mutation status unknown	- (?)	+	+
FH negative	-	+ (?)	-

++ definite benefit of genetic testing
+ probable benefit of genetic testing
? uncertain benefit of genetic testing
- no benefit of genetic testing

Clinical criteria for LQTS – Schwartz score 4 or greater (other definitions possible as well)

FH+ – family history positive for sudden death at age younger than 30 years; or clinical diagnosis of LQTS in family (without known mutation)

Signs/symptoms of LQTS – long QT interval on EKG; syncope; aborted cardiac arrest

Genetic testing has also been proposed to determine LQTS subtype and/or the specific mutation present. For individuals who meet clinical criteria for LQTS, genetic testing for this purpose has not been demonstrated to improve the patient's health outcomes. Once diagnosed with LQTS, most, if not all patients, should be treated with beta-blocker therapy and lifestyle modifications. For patients with known LQTS, there is no evidence to suggest that genetic testing influences clinical decisions whether to treat with beta-blocker therapy, nor does the evidence indicate that knowledge of genetic testing results influences the decision to implant an automated implantable cardioverter-defibrillator (AICD). Therefore, it is not possible to conclude that genetic testing for LQTS improves outcomes when used to direct therapy or determine prognosis.

Based on the above evidence, it can be concluded that genetic testing for LQTS improves health outcomes for the following patient groups:

- 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; 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.

Summary
A genetic mutation can be identified in approximately 70-75% of patients with LQTS. The majority of these are point mutations that are identified by gene sequencing analysis; however a small number are deletions/duplications that are best identified by chromosomal microarray analysis (CMA). The clinical validity of testing for point mutations by sequence analysis is high, while the clinical validity of testing for deletions/duplications by CMA is less certain.

The clinical utility of genetic testing for LQTS is high when there is a moderate to high pre-test probability of LQTS and when the diagnosis cannot be made with certainty by other methods. A definitive diagnosis of LQTS leads to treatment of LQTS with beta blockers in most cases, and sometimes to treatment with an ICD. As a result, confirming the diagnosis of LQTS will lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and sudden cardiac death. The clinical utility of testing is also high for close relatives of patients with known LQTS, since these individuals should also be treated if they are found to have a pathologic LQTS mutation. Therefore, genetic testing for the diagnosis of LQTS is medically necessary for the following individuals who do not have a clinical diagnosis of LQTS but who have: 1) a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation, 2) a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable, or 3) signs and/or symptoms indicating a moderate-to-high pretest probability of LQTS. For all other indications, including prognosis and management of patients with known LQTS, genetic testing is considered investigational.

Practice Guidelines and Position Statements
The Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies. (30) This document made the following specific recommendations concerning testing for LQTS:

- Class I (is recommended) (level of evidence C)
    - Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.
    - Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc .480 ms (prepuberty) or .500 ms (adults).
    - Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.
- Class IIb (may be considered) (level of evidence C)
    - Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values .460 ms (prepuberty) or .480 ms (adults) on serial 12-lead ECGs.

The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) issued guidelines in 2006 on the management of patients with ventricular arrhythmias and the prevention of sudden death. (31) These guidelines made a general statement that "In patients affected by LQTS, genetic analysis is useful for risk stratification and therapeutic decisions." These guidelines did not address the use of genetic testing for the diagnosis of LQTS.

Medicare National Coverage
None

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Billing Coding/Physician Documentation Information

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

There is a CPT genetic testing code modifier specific to this syndrome: -8C: Long QT syndrome, KCN (Jervell and Lange-Nielsen syndromes, types 1, 2, 5 and 6) and SCN (Brugada syndrome, SIDS and type 3)

Between October 2008 and 2012, there were specific HCPCS S codes for this testing:

- 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
- S3861: Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome
- 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 or confirmed results from another laboratory.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

6/1/07 New policy; considered investigational.

6/1/08 Policy statement revised to state some indications of genetic testing for long QT syndrome may be considered medically necessary.

6/1/09 No policy statement changes.

6/1/10 No policy statement changes.

6/1/11	No policy statement changes.
6/1/12	No policy statement changes.
6/1/13	No policy statement changes.
11/1/13	No policy statement changes.

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