

MEDICAL POLICY



SUBJECT: GENETIC TESTING FOR CONGENITAL LONG QT SYNDROME	EFFECTIVE DATE: 04/17/08 REVISED DATE: 04/16/09, 04/22/10, 04/21/11, 03/15/12, 03/21/13, 02/20/14, 03/19/15, 03/17/16, 03/16/17, 03/15/18
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<ul style="list-style-type: none">• <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i>• <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i>• <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i>	

POLICY STATEMENT:

- I. Based upon our criteria and review of the peer-reviewed literature, genetic testing for congenital long QT syndrome (LQTS) is considered **medically necessary** for:
 - A. Patients who meet the clinical criteria for congenital LQTS when:
 1. The signs and/or symptoms of LQTS are present, but a definitive diagnosis cannot be made without genetic testing; and
 2. The test results will influence decisions concerning disease treatment.
 - B. Individuals at risk for congenital LQTS who do not meet the clinical criteria for LQTS, but who have:
 1. A first- (parent, sibling, children), second- (grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings), or third- (great-grandparents, great-grandchildren, great-aunts, great-uncles, first cousin, and grand-niece or - nephew) degree relative with a known LQTS mutation; or
 2. A first-, second-, or third-degree 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. 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.

POLICY GUIDELINES:

- I. Supporting documentation required:
 - A. Family history (pedigree) which includes first-, second-, and third-degree relatives, identifying family members affected; and
 - B. Genetic testing results from any other family members. If family member(s) have not been tested (and are more appropriate to be tested first), clear and distinct rationale as to why the family member(s) cannot be tested (i.e., specific reason why testing was declined); and
 - C. Documentation of discussion between the physician and member of rationale for genetic testing and treatment options for the individual patient based on test results.
- II. Genetic testing is appropriate only when offered in a setting with adequately trained health care professionals to provide appropriate pre and post-test counseling and performed by a qualified laboratory.
- III. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.
- IV. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).
- V. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

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DESCRIPTION:

Congenital long QT syndrome (LQTS) is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential. This lengthening increases 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 cardioverter 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. 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). 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 (LQT1- LQT7) recognized, each corresponding to mutations in different genes as indicated here. In addition, typical ST-T-wave patterns are also suggestive of specific subtypes. Some genetic subtypes are associated with abnormalities outside the cardiac conduction system.

In addition to identifying the locus name of the genes involved in LQTS, there are several syndrome names that identify 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.

The Romano-Ward Syndrome (RWS) is the most common form of inherited LQTS with an estimated prevalence of 1:7000. A syncopal event is the most common symptom 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. 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. However, 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: KCNQ1 (LQT1), KCNH2 (LQT2), HERG, SCN5A (LQT3), KCNE1 (LQT5), MiRP1, CAV3, SCN4B, SNTA1, KCNJ5 and KCNE2 (LQT6).

Other less common and more severe forms of LQTS include Jervell and Lange-Nielsen Syndrome (JLNS), Andersen-Tawil Syndrome (ATS), Ankyrin B syndrome, and Timothy Syndrome or Syndactyly-Related 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 below. A score of 3.5 or greater indicates a high probability that LQTS is present; a score of 1.5-3 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.

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Diagnostic Scoring System for LQTS (Schwartz criteria)

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

Genetic testing for Long QT syndrome is performed at multiple academic and commercial laboratories, generally by next-generation sequencing or Sanger sequencing. In addition, panel testing for one or more cardiac ion channelopathies is available from a number of genetic diagnostics laboratories. The John Welsh Cardiovascular Diagnostic Laboratory, GeneDX, and Transgenomic all offer panels that genotype LQTS, CPVT, BrS, and SQTS, but there is some variation among manufacturers on the included genes.

The Arrhythmia Panel at GeneDx includes sequence analysis of 30 genes that cause various arrhythmia syndromes. Many of these genes code for ion channel proteins of the heart muscle that help regulate the movement of sodium, potassium and calcium ions in and out of cardiac cells, as well as their associated regulatory factors and interaction partners. Disease-causing variants in genes that cause arrhythmia syndromes, including ARVC, BrS, CPVT, and LQTS, have been reported to exhibit reduced penetrance and variable expressivity, even among individuals in the same family. Four other tests are offered by GeneDx as part of the Long QT syndrome testing.

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 in symptomatic relatives known to have LQTS. Interpretation of the results will likely be improved as the databases grow. 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 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.

RATIONALE:

Indications for genetic 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 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. 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

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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.

Genetic testing to determine LQTS subtype and/or the specific mutation present has been recognized to be of clinical value. The literature reviewed suggests that different subtypes of LQTS may have variable prognoses, thus indicating that genetic testing may assist in risk stratification. This evidence is from case series and prospectively collected registry data. Among the syndromes, there appears to be relatively large differences in risk of clinical events. Because of the low prevalence of LQTS (1:7000) it is not possible to assess the benefit of suggested therapies through prospective randomized trials. The data regarding therapeutic efficacy in affected patients are based on observational long-term studies.

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.”

In 2011, the HRS and EHRA issued a joint expert consensus statement on genetic testing for channelopathies and cardiomyopathies with the following recommendations for LQTS testing. Individuals with a strong clinical index of suspicion for LQTS based on their clinical history, family history, and expressed ECG phenotype (Class I). Asymptomatic individuals with idiopathic QT prolongation on serial 12-lead ECGs defined as QTc longer than 480 ms (prepuberty) or longer than 500 ms (adults) (Class I); may be considered for QTc values above 460 ms (prepuberty) or over 480 ms (adults) (Class IIb).

The guidelines defined several terms related to specific types of sudden cardiac death, including sudden unexplained death syndrome, which refers to an unexplained sudden death in an individual older than 1 year of age, sudden arrhythmic death syndrome, which refers to a sudden unexplained death syndrome case with negative pathologic and toxicologic assessment, and sudden unexplained death in infancy, which refers to an unexplained sudden death in an individual younger than 1 year of age with negative pathologic and toxicologic assessment.

In 2017, the American Heart Association, American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

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 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, e.g., 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.

A BCBSA 2007 TEC Assessment determined that the commercially available genetic test for LQTS (Familion®) is accurate in identifying a mutation that is present, and in excluding mutations that are not present. The diagnostic accuracy of genetic testing for detecting the clinical syndrome of LQTS cannot be determined with certainty due to the lack of a true gold standard for clinical diagnosis. In patients with a known clinical diagnosis of LQTS, approximately 70% are found to have a deleterious mutation associated with LQTS, indicating that other genetic mutations may exist that have not been identified. For diagnosing LQTS, the clinical utility of genetic testing is high. LQTS is a disorder which may lead to catastrophic outcomes, e.g., sudden cardiac death, in otherwise healthy individuals. Diagnosis using

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clinical methods alone may lead to underdiagnoses 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 or not 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, whether or not other signs or symptoms exist. 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.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

CPT:	81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) <i>CASQ2 (calsequestrin 2 [cardiac muscle])</i> (eg, catecholaminergic polymorphic ventricular tachycardia), full gene sequence.
CPT:	81406	Molecular pathology procedure level (Includes <i>KCNH2 (potassium voltage-gated channel, subfamily H [eag-related], member 2)</i> (eg, short QT syndrome, long QT syndrome), full gene sequence and <i>KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1)</i> (eg, short QT syndrome, long QT syndrome), full gene sequence
	81407	Molecular pathology procedure level 8 (includes <i>SCN5A (sodium channel, voltage-gated, type V, alpha subunit)</i> (eg, familial dilated cardiomyopathy), full gene sequence
	81408	Molecular pathology procedure level 7 analysis of >50 exons in a single gene by DNA sequence analysis <i>RYR2 (ryanodine receptor 2 [cardiac])</i> (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of > 50 exons.
	81413	Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A (effective 1/1/2017)
	81414	Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A ; duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1 (effective 1/1/2017)

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HCPCS:	S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome
ICD10:	I45.81	Long QT syndrome
	Q23.8-Q23.9	Other or unspecified congenital malformations of aortic and mitral valves (code range)
	Q24.8	Other specified congenital malformations of heart

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* key article

KEY WORDS:

Andersen-Tawil syndrome, Brugada syndrome, ~~Family Test~~, Jervell and Lange-Nielsen syndrome, Long QT syndrome, Romano-Ward syndrome, Syndactyly-related LWTS, Timothy syndrome

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ContrId=298&ver=79&ContrVer=1&CtrctrSelected=298*1&Ctrctr=298&s=41&DocType=Active&bc=AAgAAAQAAAA&