Test Specific Guidelines

Long QT Syndrome Genetic Testing

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Introduction

Genetic testing for long QT syndrome is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Genomic Unity Cardiac Ion Channelopathies Analysis	0237U
Long QT Syndrome Deletion/Duplication Panel	81414
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What Is Long QT Syndrome?

Definition

Long QT syndrome (LQTS) is a disorder of heart rhythm with QT prolongation and T-wave abnormalities on electrocardiogram (ECG).[1] Several forms of LQTS exist. Some forms are purely cardiac and other forms have additional clinical findings such as hearing loss.[1] Testing may offer prognostic information in some cases, as specific genes and even specific mutations within those genes have some level of correlation to risk for sudden death, effectiveness of beta-blocker therapy, and preventive strategies.[1-5]

Prevalence

LQTS is seen in all ethnic groups and its prevalence is 1 in 2,500.[1,6,7]

Symptoms

Signs and symptoms of LQTS are variable, but may include a prolonged QT interval on an ECG, torsades de pointes, syncope, seizures, cardiac arrest, and sudden cardiac death, with or without family history.[1,2]

Symptoms typically occur in young individuals who are otherwise healthy.[1] Certain events — such as exercise, emotional stress, a startle, or sleep — can trigger arrhythmia in individuals with LQTS.[1] Individuals with LQTS are recommended to avoid these potential triggers when possible.[1]

Cause

LQTS is caused by mutations in a number of genes, most of which are related to the functioning of sodium or potassium ion channels in the heart.[1]

Genetic LQTS must be differentiated from acquired long QT intervals which can be caused by exposure to certain medications, certain heart conditions, bradycardia, electrolyte imbalances, dietary deficiencies, or intracranial disease.[1]

Inheritance

LQTS is inherited is an autosomal dominant disorder. The exception is LQTS associated with sensorineural deafness (Jervell and Lange-Nielsen syndrome) which is an autosomal recessive disorder.[1]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

LQTS may be considered when there is syncope, aborted cardiac arrest, or sudden death in a child or young adult.[1]

Screening for LQTS is by ECG, and sometimes includes an ambulatory ECG (Holter monitor), and/or an exercise- or medication-induced stress test.[1,3] In many cases, the diagnosis of LQTS can be made based on personal and family history and clinical findings.[1,2,4] However, approximately 25% of individuals with LQTS will not have diagnostic ECG changes.[2,6] A scoring system was developed which takes into consideration ECG findings, clinical history of syncope (with and without stress), and family history.[1] The diagnosis is established with one or more of the following:[1]

"A risk score of 3.5 or greater [on the scoring system] in the absence of a secondary cause for QT prolongation,

The presence of a corrected QT interval of 500 ms or greater in repeated ECGs in the absence of a secondary cause for QT prolongation

The identification of a pathogenic variant in one of the [genes] known to be associated with LQTS."

Genetic testing for LQTS is typically performed with a sequencing panel. Commercially available genetic testing exists and varies by laboratory. The 15 most common genes known to cause LQTS are on most panels: AKAP9, ANKB, CACNA1C, CALM1, CALM2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, and SNTA1.[1,8] Mutations in three genes (KCNQ1, KCNH2, and SCN5A) account for the majority of cases.[1,2] The remaining genes collectively contribute to 5% of LQTS.[8] Testing will find a mutation in approximately 75% of individuals with a clinical diagnosis of LQTS.[1,4]

Deletion/duplication testing for LQTS is also available. Laboratories often bundle sequencing and deletion/duplication analysis.

Management

The primary treatment for LQTS is beta-blocker medication.[1] Implantable cardioverter-defribrillators (ICD), left cardiac sympathetic denervation (LCSD) and/or sodium channel blockers may also be considered for individuals.[1]

Survival

Many individuals with LQTS can be largely asymptomatic, with cardiac arrest or sudden cardiac death as the first and only symptom in 6-8% of affected individuals. Of the individuals who die from complications of LQTS, death is the first sign 10-15% of the time.[1]

Pre-symptomatic diagnosis of LQTS has been shown to prevent symptoms and increase life expectancy. Screening with ECG starting in childhood is recommended for first degree relatives of individuals with LQTS.[6,7]

Test Information

Introduction

Testing for LQTS may include known familial mutation analysis, multigene panel testing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to LQTS testing.

American College of Cardiology, American Heart Association Task Force, and Heart Rhythm Society

A guideline from the American College of Cardiology, the American Heart Association Task Force and the Heart Rhythm Society (ACC/AHA/HRS, 2017) highlighted the ability to stratify risk based on genotype in LQTS and recommended genetic counseling and genetic testing in individuals with clinically diagnosed LQTS.[6]

In addition, “in patients and family members in whom genetic testing for risk stratification for SCA [sudden cardiac arrest] or SCD [sudden cardiac death] is recommended, genetic counseling is beneficial.” [6]

Asia Pacific Heart Rhythm Society and Heart Rhythm Society

A multidisciplinary group developed recommendations for evaluating individuals and descendants of family members with SCA. The Asia Pacific Heart Rhythm Society (APHRS, 2020) and the Heart Rhythm Society (HRS, 2020) stated the following regarding genetic testing:[9]

"Genetic evaluation of SCA survivors is recommended for those with a diagnosed or suspected genetic cardiac disease phenotype when the results are likely to influence diagnosis, management, or family screening." (Class 1, Level B)

"When genetic evaluation is performed in an SCA survivor with a suspected or diagnosed genetic cardiac disease phenotype, it is recommended that evaluations include only genes where there is robust gene–disease association." (Class 1, Level B)

"Family screening should include genetic testing and clinical evaluation when genetic testing of a proband with SUD [sudden unexplained death] detects a pathogenic or likely pathogenic variant." (Class 1, Level B)

"If a pathogenic or likely pathogenic variant that fits the phenotype has been identified in an SCD proband, first-degree relatives should be offered DNA testing, with ongoing clinical evaluation for those testing positive." (Class 1, Level C)

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Heart Rhythm Society

An expert consensus statement from the European Heart Rhythm Association, the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society and the Latin American Heart Rhythm Society (EHRA/HRS/APHR/LAHRS, 2022) addressed the

utility and appropriateness of genetic testing for inherited cardiovascular conditions. The consensus statements were categorized as follows:[10]

Supported by strong observational evidence and authors' consensus

Some evidence and general agreement favor the usefulness/ efficacy of a test

There is evidence or general agreement not to recommend a test

Regarding the choice of genetic testing and variant interpretation:

Genetic testing should occur with genetic counseling. [Supported by strong observational evidence and authors' consensus]

If an individual has a clear phenotype, it is appropriate to analyze genes with definite/strong evidence support disease causation [Supported by strong observational evidence and authors' consensus] and may be appropriate to analyze genes with moderate evidence for disease causation. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

In some cases with a clear phenotype and negative genetic testing of genes with definite/strong evidence for disease causation, broader genetic testing may be considered [Some evidence and general agreement favor the usefulness/ efficacy of a test].

"Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting." [There is evidence or general agreement not to recommend a test]

"Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multi-disciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists." Standard guidelines for variant interpretation should be used. Variant interpretation "can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration. [Supported by strong observational evidence and authors' consensus]

Variants of uncertain significance may be reclassified to likely pathogenic, pathogenic, likely benign or benign. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

When a likely pathogenic or pathogenic variant has been identified, genetic counseling should be offered. The inheritance pattern, penetrance, and associated risks can be discussed. Additionally, cascade testing for relatives can be facilitated. [Supported by strong observational evidence and authors' consensus]

"Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causing variant."

"Predictive genetic testing in related children is recommended from birth onward (any age)" [Supported by strong observational evidence and authors' consensus]

Some affected individuals may have had previous genetic testing that was not a comprehensive, such as prior to the use of next generation sequencing or with an incomplete testing panel. Repeat testing should be considered in these cases. [Supported by strong observational evidence and authors' consensus]

Regarding genetic testing for LQTS:

"Molecular genetic testing for definitive disease associated genes (currently KCNQ1, KCNH2, SCN5A, CALM1, CALM2, and CALM3) should be offered to all index patients with a high probability diagnosis of LQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score 3.5 or greater)." [Supported by strong observational evidence and authors' consensus]

"Analysis of specific genes should be offered to patients with a specific diagnosis as follows: KCNQ1 and KCNE1 in patients with Jervell and Lange-Nielsen syndrome, CACNA1C in Timothy syndrome, KCNJ2 in Andersen–Tawil syndrome, and TRDN in patients suspected to have triadin knockout syndrome." [Supported by strong observational evidence and authors' consensus]

"An analysis of CACNA1C and KCNE1 may be performed in all index patients in whom a cardiologist has established a diagnosis of LQTS with a high probability, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score 3.5 or greater)." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

European Society of Cardiology

The European Society of Cardiology (ESC, 2015) guidelines for the management of individuals with ventricular arrhythmias and the prevention of sudden cardiac death stated:[7]

“LQTS is diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration.” [Class I, Level C recommendation]

Heart Rhythm Society and European Heart Rhythm Association

An expert consensus statement from the Heart Rhythm Society (HRS, 2011) and the European Heart Rhythm Association (EHRA, 2011) made the following recommendations regarding genetic testing:[4]

“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."[4] [Class I, "is recommended"][4]

"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>480ms (prepuberty) or >500ms (adults)." [Class I, "is recommended"][4]

"Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values>460ms (prepuberty) or >480ms (adults) on serial 12-lead ECGs." [Class IIb "may be considered"][4]

"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 I, "is recommended"][4]

Older American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC, 2006) guidelines on the management of ventricular arrhythmias made no specific evidence-based recommendations about genetic testing for LQTS, but do state:

"[Genetic testing is] useful for risk stratification and for making therapeutic decisions," and they highlight the benefit for identifying family members for counseling and preventative management. They conclude: "Although genetic analysis is not yet widely available, it is advisable to try to make it accessible to LQTS patients." [3]

Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society

An expert consensus statement from the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS, 2013) incorporated genetic test results into the recommended diagnostic criteria:[5]

"LQTS is diagnosed:

In the presence of an LQTS risk score ≥3.5 in the absence of a secondary cause for QT prolongation and/or

In the presence of an unequivocally pathogenic mutation in one of the LQTS genes or

In the presence of a corrected QT interval for heart rate using Bazett's formula (QTc) ≥500 ms in repeated 12- lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.

LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation."

Criteria

Introduction

Requests for genetic testing for LQTS are reviewed using these criteria.

Long QT Syndrome Known Familial Mutation Analysis

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No previous genetic testing for Long QT Syndrome that would detect the familial mutation, AND

Diagnostic and Predisposition Testing:

Long QT Syndrome family mutation identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND

Rendering laboratory is a qualified provider of service per the Health Plan policy

Long QT Syndrome Sequencing or Multigene Panel

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No previous genetic testing for Long QT Syndrome, AND

Diagnostic Testing for Symptomatic Individuals:

Clinical signs indicating moderate to high pre-test probability of Long QT syndrome, but diagnosis cannot be made with certainty by other methods (i.e. Schwartz criteria of 2-3), or

Confirmation of prolonged QTc or T-wave abnormalities [>460ms (prepuberty) or >480ms (adults)on serial 12-lead ECGs] on exercise or ambulatory ECG, or during pharmacologic provocation testing and acquired cause has been ruled out, or

A prolonged or borderline prolonged QT interval on ECG or Holter monitor and acquired cause has been ruled out, or

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Profound congenital bilateral sensorineural hearing loss and prolonged QTc, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Long QT Syndrome Deletion/Duplication Analysis

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No mutation identified with long QT full gene sequence analysis, or

Neither or only one mutation in KCNQ1 or KCNE1 identified in an individual with profound congenital bilateral sensorineural hearing loss and prolonged QTc, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy

Billing and Reimbursement Considerations

When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, eviCore will redirect to the panel code(s).

If the laboratory will not accept redirection to a panel code, the medical necessity of each billed component procedure will be assessed independently.

In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement:

KCNQ1

KCNH2

SCN5A

References

Introduction

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