## Long QT Syndrome Testing

### Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT Syndrome Sequencing Multigene Panel</td>
<td>81413</td>
</tr>
<tr>
<td>Long QT Syndrome Deletion/Duplication Panel</td>
<td>81414</td>
</tr>
<tr>
<td>Long QT Syndrome Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>ANK2 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CASQ2 Sequencing</td>
<td>81405</td>
</tr>
<tr>
<td>CAV3 Sequencing</td>
<td>81404</td>
</tr>
<tr>
<td>KCNE1 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>KCNE2 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>KCNH2 Sequencing</td>
<td>81406</td>
</tr>
<tr>
<td>KCNJ2 Sequencing</td>
<td>81403</td>
</tr>
<tr>
<td>KCNQ1 Sequencing</td>
<td>81406</td>
</tr>
<tr>
<td>RYR2 Sequencing</td>
<td>81408</td>
</tr>
<tr>
<td>SCN5A Sequencing</td>
<td>81407</td>
</tr>
<tr>
<td>SCN4B Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>AKAP9 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>SNTA1 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>KCNJ5 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CALM1 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CALM2 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CACNA1C Sequencing</td>
<td>81479</td>
</tr>
</tbody>
</table>
What is Long QT syndrome

Definition

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.\textsuperscript{1} Testing may offer prognostic information in some cases, as specific genes and even specific mutations within those genes may have some correlation to risk for sudden death, effectiveness of beta-blocker therapy, and preventive strategies.\textsuperscript{1,3,4}

- Signs and symptoms of long QT syndrome (LQTS) are variable, but may include a prolonged QT interval on an electrocardiogram, torsades de pointes, syncope, seizures, cardiac arrest, and sudden cardiac death.\textsuperscript{1,2}
- Symptoms typically occur in young individuals who are otherwise healthy.\textsuperscript{1} Certain events — such as exercise, emotional stress, a startle, or sleep — can trigger arrhythmia in individuals with LQTS.\textsuperscript{1} Patients are recommended to avoid these activities when possible.\textsuperscript{1}
- Screening for LQTS is by electrocardiography (ECG or EKG), and sometimes includes an ambulatory ECG (Holter monitor), and/or an exercise- or medication-induced stress test.\textsuperscript{1,3} In many cases, the diagnosis of LQTS can be made based on personal and family history and clinical findings.\textsuperscript{1} However, approximately 10-40% of LQTS patients will not have diagnostic ECG changes.\textsuperscript{4}
- Several forms of LQTS exist. The autosomal dominant Romano-Ward syndrome is the most common form, with a prevalence of 1 in 3000 to 1 in 5000.\textsuperscript{1,2} It affects all ethnic groups.\textsuperscript{1} All forms of LQTS are estimated to affect at least 1 in 2500 people.\textsuperscript{4}
- Genetic LQTS must be differentiated from acquired LQTS, which can be caused by exposure to certain medications, certain heart conditions, bradycardia, electrolyte imbalances, dietary deficiencies, or intracranial disease.\textsuperscript{1}

Test information

- Genetic testing for LQTS is typically performed with a sequencing panel. Commercially available genetic testing exists for the AKAP9, ANK2, CACNA1C, CAV3, CALM1, CALM2, CALM3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1, and TRDN genes associated with LQTS.\textsuperscript{1} Mutations in three genes (KCNQ1, KCNH2, and SCN5A) account for the majority of cases.\textsuperscript{1,2} Testing will find a mutation in approximately 75% of patients with a clinical diagnosis of LQTS.\textsuperscript{4} Composition of test panels varies by laboratory.
- Deletion/duplication testing for the AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, SCN4B, SCN5A, SNTA1 genes is also available.
• Once the causative mutation has been identified in a family member, other at-risk relatives only need to be tested for that mutation — not a panel of genes. Testing by known familial mutation analysis is greater than 99% accurate.\(^1\)

Guidelines and evidence

A 2013 expert consensus statement from the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society incorporates genetic test results into the recommended diagnostic criteria:\(^5\)

• LQTS is diagnosed:
  o In the presence of an LQTS risk score ≥3.5 in the absence of a secondary cause for QT prolongation and/or
  o In the presence of an unequivocally pathogenic mutation in one of the LQTS genes or
  o 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.

A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) makes 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.” [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 (2006) guidelines on the management of ventricular arrhythmias made no specific evidence-based recommendations about genetic testing for LQTS, but do state:
  
  o “[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

The 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death state:⁶

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

Criteria

Known Familial Mutation Analysis

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

• Previous Genetic Testing:
  
  o No previous genetic testing for Long QT Syndrome inclusive of known family mutation, AND

• Diagnostic Testing for Symptomatic Individuals:
  
  o 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

Sequencing or Multigene Panel

• Genetic Counseling:
  
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous genetic testing for Long QT Syndrome, AND

• Diagnostic Testing for Symptomatic Individuals:
  o 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
  o 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
  o A prolonged or borderline prolonged QT interval on ECG or Holter monitor and acquired cause has been ruled out, or
  o Profound congenital bilateral sensorineural hearing loss and prolonged QTc, AND

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

Deletion/Duplication Analysis

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

• Previous Genetic Testing:
  o No mutation identified with long QT full gene sequence analysis, or
  o 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:
  o KCNQ1
  o KCNH2
  o SCN5A

Benefit exclusion

Exclusions and other considerations

Testing unaffected individuals (e.g. carrier testing, predictive testing, presymptomatic testing, etc) is a BCBSAZ benefit exclusion and, therefore, not eligible for reimbursement.

References


