

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of long QT syndrome (LQTS)

Establishing a diagnosis of a LQTS, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Identifying variants within genes known to be associated with increased risk for disease features and allowing for predictive testing of at-risk family members

Genetics Test Information

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate the genes on this panel.

[Prior Authorization](#) is available for this assay; see Special Instructions.

Highlights

This test uses next-generation sequencing to test for variants in the *AKAP9*, *ANK2*, *CACNA1C*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*, *SCN4B*, *SCN5A*, and *SNTA1* genes.

This test may aid in the diagnosis of long QT syndrome.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Long QT Syndrome Multi-Gene Panel Prior Authorization Ordering Instructions](#)
- [Hereditary Cardiomyopathies and Arrhythmias: Patient Information](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing Followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Whole Blood EDTA

Advisory Information

[Targeted testing for familial variants \(also called site-specific or known mutations testing\) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.](#)

Necessary Information

1. [Hereditary Cardiomyopathies and Arrhythmias: Patient Information \(T725\)](#) is required, see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.
2. Include physician name and phone number with specimen.

Specimen Required

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions: Send specimen in original tube.

Additional Information: Prior Authorization is available for this test. **Submit the required form with the specimen.**

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-[Informed Consent for Genetic Testing \(T576\)](#)

-[Informed Consent for Genetic Testing-Spanish \(T826\)](#)

2. [Long QT Syndrome Multi-Gene Panel Prior Authorization Ordering Instructions](#) in Special Instructions

3. If not ordering electronically, complete, print, and send a [Cardiovascular Test Request Form \(T724\)](#) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

No specimen should be rejected.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Ambient (preferred)		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Long QT syndrome (LQTS) is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on electrocardiogram (EKG), which may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant

inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS.

RWS has an estimated prevalence of 1 in 3,000 individuals. Of the families who meet clinical diagnostic criteria for RWS, approximately 75% have known genetic causes, while approximately 25% have no detectable pathogenic variants in any of the genes known to cause RWS. Approximately 3% of RWS cases are the result of large deletions or duplications in *KCNQ1* or *KCNH2*. Deletions/duplications have not been reported in the other genes implicated in RWS.

Only about half of the individuals with a pathogenic gene variant associated with RWS have symptoms, usually one to a few syncopal spells, and thus many patients with this condition unfortunately present with sudden cardiac death as their first symptom. Cardiac events may occur any time from infancy through adulthood, but are most common from the preteen years through the 20s. Additionally, RWS is believed to account for approximately 10% to 15% of sudden infant death syndrome (SIDS) cases. In some cases, LQTS may be associated with congenital profound bilateral sensorineural hearing loss, known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either *KCNQ1* or *KCNE1*.

Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies that may include hand/foot syndactyly, structural heart defects, facial dysmorphism, and neurodevelopmental features. Ventricular tachyarrhythmia is the leading cause of death with an average age of death of 2.5 years. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the *CACNA1C* gene.

Management strategies for LQTS include pharmacologic therapies, implantable cardioverter defibrillators (ICD), or other surgical interventions, and lifestyle restrictions such as avoidance of competitive sports or other triggers for cardiac events. In some cases, knowledge of the LQTS genotype may assist in tailoring an individual's treatment plan. For example, patients with an *SCN5A* pathogenic variant may not respond well to the typical first-line therapy of beta-blockers and may have a lower threshold for consideration of an ICD.

Genetic testing in LQTS is recommended and supported by multiple consensus statements to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members. Even individuals with a normal QT interval may still be at risk for a cardiac event and sudden cardiac death and, thus, EKG analysis alone is insufficient to rule out the diagnosis and genetic testing is necessary to confirm the presence or absence of disease in at-risk family members. Pre- and posttest genetic counseling is an important factor in the diagnosis and management of LQTS and is supported by expert consensus statements.

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of long QT syndrome (LQTS) or a related disorder.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a family history of LQTS or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual allows for more informative testing of at-risk individuals.

Technical Limitations:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false-negative or false-positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, less than 6 weeks from time of sample collection) heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with a genetics professional should be considered for interpretation of this result.

A list of benign and likely benign variants detected for this patient is available from the lab upon request.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient's results.

Clinical Reference

1. Online Mendelian Inheritance in Man. Retrieved June 2018. Available at www.omim.org/search?index=entry&sort=score+desc%2C+prefix_sort+desc&start=1&limit=10&search=Long+QT
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3. Alders M, Bikker H, Christiaans I: Long QT Syndrome. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al: University of Washington, Seattle. 1993-2018. 2003 Feb 20 (Updated 2018 Feb 8). Accessed June 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1129/
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5. Napolitano C, Splawski I, Timothy KW, et al: Timothy Syndrome. In GeneReviews. Edited by RA Pagon, MP

Adam, HH Ardinger, et al: University of Washington, Seattle. 1993-2018. 2006 Feb 15 (Updated 2015 Jul 16). Accessed June 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1403/

6. Barc J, Briec F, Schmitt S, et al: Screening for copy number variation in genes associated with the long QT syndrome: clinical relevance. *J Am Coll Cardiol* 2011;57(1):40-47

7. Priori SG, Wilde AA, Horie M, et al: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm* 2013;10:12:1932-1963

8. Ackerman MJ, Priori SG, Willems S, et al: HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm* 2011;8:1308-1339

9. Pazoki R, Wilde AA, Bezzina CR: Genetic basis of ventricular arrhythmias. *Curr Cardiovasc Risk Rep* 2010;4:454-460

10. Wilde AA: Is there a role for implantable cardioverter defibrillators in long QT syndrome? *J Cardiovasc Electrophysiol* 2002;13(Suppl 1):S110-S113

Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline. Supplemental and/or confirmatory Sanger sequencing is performed when necessary.(Unpublished Mayo method)

The following genes are evaluated in this multigene panel: *AKAP9*, *ANK2*, *CACNA1C*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*, *SCN4B*, *SCN5A*, and *SNTA1*.

PDF Report

No

Day(s) and Time(s) Test Performed

Monday; Varies

Analytic Time

4 weeks after prior authorization approved

Maximum Laboratory Time

6 weeks

Specimen Retention Time

Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81403

81404

81406 x 2

81407

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
LQTGP	Long QT Syndrome Multi-Gene Panel,B	In Process

Result ID	Test Result Name	Result LOINC Value
36826	Gene(s) Evaluated	48018-6
36827	Result Summary	50397-9
36828	Result Details	82939-0
36829	Interpretation	59462-2
36956	Additional Information	48767-8
36957	Method	85069-3
36958	Disclaimer	62364-5
36830	Reviewed by	18771-6

Prior Authorization

Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.