Prior Authorization Review Panel
MCO Policy Submission

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Plan: Keystone First Community HealthChoices	**Submission Date**: 8/1/24
Policy Number: ccp.1037	**Effective Date:** 12/2023 **Revision Date:** July 1, 2024
Policy Name: Genetic testing for long QT syndrome	

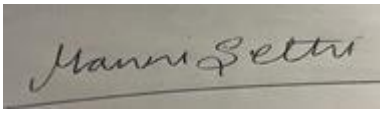
Type of Submission – Check all that apply:

- **New Policy**
- **x Revised Policy***
- **Annual Review – No Revisions**
- **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Genetic testing for long QT syndrome

Clinical Policy ID: CCP. 1037

Recent review date: 7/2024

Next review date: 11/2025

Policy contains: Cardiac channelopathy; Familion test; genetic testing; long QT syndrome; sudden cardiac death.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Genetic testing (comprehensive or targeted) for long QT syndrome is clinically proven and, therefore, may be medically necessary for any of the following indications (Ackerman, 2011):

- The member has a close relative (first-, second- or third-degree) with a known long QT syndrome mutation.
- The member has a close relative (first-, second- or third-degree) diagnosed with long QT syndrome by clinical means and whose genetic status is unavailable.
- The member has palpitations, syncope, or dizziness with a history of a close relative (first-, second-, or third-degree) who experienced a sudden cardiac death.
- The member has a prolonged corrected QT interval on resting electrocardiogram of greater than 440 msec without an identifiable acquired or external cause for the prolongation (i.e., bradycardia, electrolyte imbalance, cardiac pacemaking, or certain medications/drugs) (Skinner, 2011).
- The member has signs or symptoms indicating a moderate-to-high pretest probability of long QT syndrome using the Schwartz criteria (Appendix table 2).

Genetic counseling is recommended for ordering and interpretation of genetic tests.

Limitations

All other uses of genetic testing for long QT syndrome are not medically necessary.

A negative genetic test in a clinically normal member of a well-characterized family should eliminate the need for future testing (for the same member), as genetic testing for a particular disease is usually performed once per lifetime.

Alternative covered services

- Physical examination.
- Electric conductivity tests: electrocardiogram, echocardiography.
- Genetic counseling.

Background

Long QT syndrome is a cardiac condition that can cause rapid and irregular heartbeats, leading to fainting spells, seizures, and sudden death (National Heart, Lung, and Blood Institute, 2021). Long QT syndrome is an electrical conduction disorder corresponding to the electrical activation and deactivation of the heart ventricles, which is exhibited on an electrocardiogram. The two major forms are known as Jervell and Lange-Nielsen syndrome, and Romano-Ward syndrome. It is a known risk factor for lethal ventricular dysrhythmias, and can be difficult to see on an electrocardiogram in the setting of ventricular pacing. In the United States, this condition causes an estimated 3,000 to 4,000 sudden deaths annually in children and young adults of all ethnicities, but when diagnosed and controlled, the long-term prognosis is excellent (Schurr, 2022).

Long QT syndrome can be inherited or acquired disorder. The acquired form may be drug-induced or caused by medical conditions that result in potassium or sodium ion deficiencies in the bloodstream, certain underlying heart conditions, and pacemakers can also prolong QT and ventricular response (National Heart, Lung, and Blood Institute, 2021).

The inherited form has variations in the encoding genes that influence cardiac ion channels, accessory ion channel subunits, or proteins used for modulating ion channel function. These variations have been the primary identifying causes in 75% of all cases; but 25% still are unidentified genotypically, which hinders the discovery of family members at risk. Long QT syndrome is inherited in an autosomal dominant pattern, in which a single mutation causes the disease. Therefore, all first-degree relatives of an index case have up to a 50% risk of harboring the same mutation, but asymptomatic family members with a normal QT interval may still be at risk for cardiac events (Wilde, 2022).

Seventeen genes are known to be associated with long QT syndrome (Skinner, 2019; Appendix table 1). LQT subtypes 1, 2, and 3 contribute approximately 75% of all cases (Alders, 2018). The potential lethality of these syndromes, mostly due to ventricular tachy-dysrhythmias, highlights the importance of identifying individuals with an inherited cardiac arrhythmia and clarifying risk to asymptomatic first-degree relatives (Alders, 2018). Schwartz (1993; Appendix table 2) diagnostic criteria incorporate family history, clinical history, and electrocardiogram findings to determine the probability of an inherited long QT syndrome, and genetic testing is used to establish the diagnosis.

The goals of genetic testing are to prevent sudden death through medical therapy, to counsel the individual and their family, and to assist with lifestyle changes. Molecular genetic testing approaches consist of multigene panel testing, single-gene testing, and more comprehensive exomic or genomic testing. Single-gene testing consists of sequence analysis followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found. Methods used in a multigene panel may include sequence analysis, deletion/duplication analysis, or other non-sequencing-based tests, and some panels may apply customized phenotype-focused exome analysis (Alders, 2018).

Choice of testing will depend on many factors such as family history, clinical presentation, differential diagnosis, and diagnostic test sensitivity. However, approximately 20% of patients meeting clinical diagnostic criteria will not have a causative variant identified after comprehensive genetic testing, and some subtypes are associated with other inherited phenotypes. The optimal choice is the test(s) most likely to both identify the genetic cause

of the condition at the most reasonable cost and limit identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype (Alders, 2018).

A limited number of U.S. laboratories perform genetic testing for inherited long QT syndrome (Genetic Testing Registry, 2021). Commercially available genetic testing for long QT syndrome involves direct sequencing of protein-coding portions and flanking regions of targeted exons following polymerase chain reaction amplification (Modell, 2012). This testing is conducted in laboratories regulated under the Clinical Laboratory Improvement Amendments Act of 1988 and does not require U.S. Food and Drug Administration approval for commercial use.

Findings

Clinical Guidelines:

The Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) issued an expert consensus statement with the following recommendations for genetic testing in long QT syndrome (Ackerman, 2011):

- Comprehensive or targeted LQT 1, 2, or 3 genetic testing is recommended for patients with a strong clinical suspicion of long QT syndrome based on clinical history, family history, and electrocardiogram findings.
- Comprehensive or targeted LQT 1, 2, or 3 genetic testing is recommended for asymptomatic patients with Q-T interval prolongation on serial electrocardiograms in the absence of known contributing factors.
- Mutation-specific genetic testing is recommended for family members and relatives after identification of a causative mutation in an index case.
- Comprehensive or targeted LQT 1, 2, or 3 genetic testing may be considered for asymptomatic patients with idiopathic Q-T interval prolongation on serial electrocardiograms.

The American College of Medical Genetics and Genomics (ACMG) guideline includes KCNQ1, KCNH2, and SCN5A for the Romano-Ward long QT syndrome subtypes 1, 2, and 3 in its list of 59 medically actionable genes recommended for return as secondary findings during clinical genomic sequencing (Kalia, 2017).

The Canadian Cardiovascular Society's clinical practice updated its management of patients with prolonged QT interval, genetic testing is useful for diagnosing congenital long QT syndrome, especially among asymptomatic relatives of an individual who has tested positive for a genetic variant associated with congenital long QT syndrome. The guideline recommends that when an affected individual has a causative variant identified, first-degree relatives should be offered genetic testing coupled with clinical screening. However, the guideline also notes that relying exclusively on genetic data can lead to over- or underdiagnosis, because approximately 15% of congenital long QT syndrome cases do not have a currently recognized genetic variant, and recent data show that the role of rare variants causing the syndrome on their own is weak (Davies, 2023).

Other Evidence:

A systematic review found genetic testing for early detection of long QT syndrome to be cost-effective compared to no testing in symptomatic cases, but not cost-effective compared to watchful waiting in asymptomatic first-degree relatives (Gonzalez, 2015). Testing was highly cost-effective in neonates compared to any screening strategy.

A systematic review that examined the role of genetic testing and cardiovascular screening in long QT syndrome to decrease the risk of sudden cardiac death in young athletes produced some promising findings. The review looked at six studies (n = 6,400) participants with an average age of 18.5 years. The review highlights that while electrocardiogram screening can identify long QT syndrome, genetic testing can reveal underlying mutations in 70% of affected individuals and, in conjunction with resting and exercise electrocardiograms (Longo, 2018).

The Clinical Genome Resource Channelopathy Clinical Domain Working Group found definitive gene-disease associations for only KCNQ1, KCNH2, and SCN5A (LQT subtypes 1-3). Four genes (CALM1, CALM2, CALM3, TRDN) had strong evidence for atypical long QT syndrome. Evidence was limited or disputed for many other commonly tested genes (Adler, 2020).

Two large database studies suggested minor long QT syndrome genes may be overrepresented in study populations and associated with weakly penetrant, mild disease (Giudicessi, 2020; Roberts, 2020). This casts uncertainty on the rationale for routine comprehensive genetic testing, as rare variants are often included in commercial panels despite lack of established clinical actionability. Evolving knowledge necessitates expert genetics input for appropriate testing and interpretation.

In 2024, we reorganized the findings section of the policy and added the Canadian Cardiovascular Society's practice update and the systematic review by Longo and colleagues. No policy changes were warranted.

References

On June 14, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "long QT syndrome" (MeSH) and "long QT syndrome," "inherited," and "congenital." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

6/2013: initial review date and clinical policy effective date: 12/2013

7/2016: Policy references updated.

5/2017: Policy references updated.

4/2018: Policy references updated.

5/2019: Policy references updated. The policy ID was changed.

4/2020: Policy references updated.

7/2021: Policy references updated.

7/2022: Policy references updated.

7/2023: Policy references updated.

7/2024: Policy references updated.

Appendix

Table 1. Long QT syndrome subtypes

Variant	Gene Name	Frequency	Current affected
LQT1	KCNQ1	30 – 35%	K+, alpha subunit
LQT2	KCNH2	25 – 30%	K+, alpha subunit
LQT3	SCN5A	5 – 10%	Na+, alpha subunit
LQT4	ANK2	1 – 2%	Na+, targeting protein
LQT5	KCNE1	1%	K+, beta subunit
LQT6	KCNE2	Rare	K+, subunit
LQT7	KCNJ2	Rare	K+, potassium channel
LQT8	CACNA1C	Rare	Ca++, alpha 1C subunit
LQT9	CAV3	Rare	Na+, caveolin-3 protein
LQT10	SCN4B	Rare	Na+, beta subunit
LQT11	AKAP9	Rare	K+, protein kinase
LQT12	SNTA1	Rare	Na+, α1-syntrophin
LQT13	KCNJ5	Rare	potassium channel
LQT14	CALM1	Rare	Many
LQT15	CALM2	Rare	Many
LQT16	CALM3	Rare	Many
LQT17	TRDN	Rare	Not reported

Sources: Alders (2018) and Skinner (2019).

Table 2. Schwartz clinical diagnostic criteria for long QT syndrome

Criteria	Points[1]
Electrocardiogram findings	
(In the absence of medications or disorders known to affect these findings)	
Corrected Q – T interval:	
> 480 msec	3
460 to 470 msec	2
450 msec (in males)	1
Torsades de pointes[2]	2
T-wave alternans	1
Notched T wave in three leads	1
Low heart rate for ages	0.5
Clinical history	
Syncope[2]	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family members with definite long QT syndrome	1
Unexplained sudden cardiac death	0.5

at under 30 years among immediate
family member(s)

[1]Scoring correlates with probability of low QT syndrome: < 1 point, low probability; 2 to 3 points, intermediate probability; and > 4 points, high probability.

[2]Torsades de pointes and syncope are mutually exclusive.

Source: Adapted from Schwartz (1993).