This document addresses genetic testing of cardiac ion channel mutations in persons with suspected channelopathies, such as long QT syndrome (LQTS), in order to determine the risk for sudden cardiac death (SCD). Congenital LQTS is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential (an abnormally long QT interval seen on electrocardiographic [EKG] tracings). This can increase the risk for arrhythmic events, such as torsades de pointes, and may result in syncope (fainting episodes) and SCD. Diagnostic criteria for LQTS have been established which focus on EKG findings, as well as clinical and family history.

**Position Statement**

**Medically Necessary:**

Genetic testing for LQTS is considered medically necessary in a potentially at-risk individual, to rule out significant increased risk of LQTS and sudden death, when all of the following are present:

A. Individual to be tested has a first-degree relative (proband) with a clinical diagnosis of LQTS; and

B. That proband has sustained one of the following:
   1. Sudden death, or
   2. Unexplained syncopal episode, or
   3. Ventricular fibrillation with successful resuscitation; and

C. A mutation confirmatory for LQTS has been identified in the proband that will be specifically tested for in this potentially at-risk individual; and

D. Genetic counseling, which encompasses all of the following components, has been performed:
   1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
   2. Education about inheritance, genetic testing, disease management, prevention and resources; and
   3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
   4. Counseling for the psychological aspects of genetic testing.

**Investigational and Not Medically Necessary:**

Genetic testing for all other cardiac ion channel mutations is considered investigational and not medically necessary, including, but not limited to, testing for:

- Brugada Syndrome (BrS);
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT);
- Short QT Syndrome (SQTS).

**Rationale**

Long QT syndrome (LQTS) is a phenotypic disease characterized by a prolonged QT interval and polymorphic ventricular tachycardia and may lead to life-threatening ventricular arrhythmias and sudden cardiac death (SCD). LQTS can be primary when inherited or genetic, or secondary when precipitated by numerous drugs, structural cardiac disease and other disease and clinical conditions. Primary or congenital/inherited LQTS has been associated with hundreds of mutations in more than 10 genes that affect ion channels contributing to the cardiac action potential. Disorders resulting from ion channel dysfunction are known as channelopathies. Approximately 75% of individuals presenting with LQTS have an identifiable gene mutation (Ackerman, 2011). Congenital LQTS usually manifests before the age of 40 and may be suspected when there is a history of seizure, syncope, or SCD in a child or young adult, with a prolonged QT interval, in the absence of structural cardiac disease, and may prompt genetic analysis to identify the presence of genetic mutations associated with cardiac channelopathies. A history of these occurrences or the confirmation of a gene mutation associated with cardiac channelopathies in a first-degree relative may prompt diagnostic scrutiny of other family members.

The European Society of Cardiology Task Force on Sudden Cardiac Death first published a guidance document in 2001 (Priori, et al) referring to genetic defects on one specific cardiac sodium channel gene (LQT3), associated with higher risk for SCD in LQTS. The Task Force acknowledged that much work is needed in larger population groups with less known or apparent heart disease than those reviewed for this paper, in order to achieve effective identification and risk stratification of at-risk population groups for the ultimate goal of substantial reductions in the rates of SCD in the general population (Priori, 2001). Subsequent research has identified specific sequence variants associated with LQTS. Migmalievich correlated gender-specific risks for adverse cardiac events with the specific location of mutations (pore-loop vs. non-pore-loop) on the KCNH2 gene in 490 males and 676 females with LQTS. They reported that males with pore-loop mutations had a greater risk of adverse events [hazard ratio [HR], 2.18; p=0.01] than males without pore-loop mutations but that this association was not present in females. Albert examined genetic profiles from 516 cases of LQTS included in 6 prospective cohort studies. The authors identified 147 sequence variations found in 5 specific cardiac ion channel genes and tested the association of these variations with SCD. Two common intrinsic variations, one in the KCNQ1 gene and one in the SCN5A gene, were most strongly associated with SCD in individuals of European ancestry. This research suggests that combined assessments of the individual's clinical information and mutation-specific data from a known proband may be used for improved risk stratification of individuals considered at risk for life-threatening cardiac events related to LQTS (Albert, 2010; Migmalievich, 2011).

At least 12 types of LQTS have been identified, varying in part based on their effect on the action potential, ion channel and genotype. There are three major types of LQTS: LQT1, LQT2 and LQT3, accounting for OVER 90% of LQTS (Schwarz, 2001). Gene specific therapy recommendations have been developed and gene testing can contribute to treatment choice (Ruan, 2008).

According to the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities:

- The clinical manifestations of a long-QT mutation may be influenced by the specific gene involved and the functional consequences of the mutation in that gene. Risk stratification for LQTS continues to evolve, with data from genetic analysis becoming increasingly useful for clinical decision making (Epstein, 2008).

In 2011, a Heart Failure Society of America/European Heart Rhythm Association (HRS/EHRA) Consensus Statement on the State of Genetic Testing for Channelopathies and Cardiomyopathies was issued (Ackerman, 2011) which included the following guidance:

- A Class I recommendation ("is recommended") was applied for genetic testing in index cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of
a genetic test is high (likelihood of positive result > 40% and signal/noise ratio > 10 AND/OR when the genetic test result provides either diagnostic or prognostic information, or when the genetic test result influences therapeutic choices);

- Screening of family members for the mutation identified in the proband of the family is recommended as a Class I when genetic testing leads to the adoption of therapy/protective measures/lifestyle adaptations;

- Conversely, the authors have assigned a Class III recommendation when results of genetic testing are not associated with use of therapeutic or protective measures but the results may be useful for reproductive counseling or instances in which genetic testing is requested by the patient who wants to know his/her mutation status.

Regarding the strength of the evidence currently available for genetic testing, this HRS/EHRA Consensus Statement provided the following additional information:

Documents produced by other scientific societies have acknowledged the need to define the criteria used to rank the strength of recommendation for genetic diseases. The most obvious difference is that randomized and/or blinded studies do not exist. Instead, most of the available data are derived from registries that have followed patients and recorded outcome information. Contrary to common misconception; genetic tests are probabilistic tests, not deterministic tests. Many positive test results contain the index case’s and his/her family’s definitive disease-causing mutation, the proverbial pathogenic “smoking gun.” However, many so-called “positive” test results are represented by less informative DNA variants currently annotated with the expression, “Variants of Uncertain Significance” (VUS). Only recently is the frequency of rare VUS among otherwise healthy volunteers across the exomes of various disease-causing genes being identified. Regardless of the disease in question or the specific genetic test pursued, treatment decisions should not rely solely on the patient’s genetic test result but should be based on results from his/her comprehensive clinical evaluation.

Regarding other channelopathies, such as short QT syndrome (SQTS) and Brugada syndrome (BrS), there are molecular genetic tests available for the targeted gene mutations most commonly associated with these conditions. However, the low prevalence of these rare conditions and confounding factors, such as varying penetrance, genotype-phenotype profiles, and risk stratification have resulted in inadequate data to demonstrate the clinical utility, validity, and sensitivity of this testing, to date. Gollob and colleagues (2011) proposed diagnostic criteria and risk stratification for subjects with SQTS. Mazzanti and colleagues (2014) studied 73 subjects with SQTS for a median follow-up period of 56 months, investigating, in part, whether the multiparametric risk score proposed by Gollob could identify individuals at risk of life-threatening events. When the modified Gollob score was applied to the study group, 5 of 8 subjects (63%) who experienced cardiac arrest had a score of less than 3, corresponding to a predicted low probability of arrhythmic events. The authors state, “Overall, we urge caution regarding the use of this scoring system for risk stratification.” Additionally, while 15 to 20% of index cases with known BrS have a genetic mutation at SCN5A with all individuals with known SCN5A mutations have BrS, and other less well studied genes are also involved with BrS (Miura, 2008). Treatment management for individuals exhibiting signs and symptoms suspicious for arrhythmias and SCD are not significantly changed, as a result of a confirmatory genetic test for BrS or SQTS (Gollob, 2011; Meregel, 2009; Nielsen, 2013). Similarly, genetic testing for suspected catecholaminergic polymorphic ventricular tachycardia (CPVT) currently lacks the support of large, well-designed trials demonstrating how risk stratification impacts treatment management or clinical outcomes (Jabbari, 2013; Napolitano, 2014).

The medical necessity criteria in this document have been formulated based on the evidence currently available demonstrating clinical benefit to testing for a select population group. Additional future studies are expected to further inform about the impact of genetic testing technology on risk stratification, preventive treatment management, and clinical outcomes for the channelopathies. The study evidence currently available has indicated the propensity for differing mutations all along the length of these large cardiac ion channel genes, making the clinical significance of each of these discrete mutations difficult to determine from current study evidence. Another factor confounding interpretation of this genetic analysis is the penetrance of a given mutational the is the multiplet phenotype expression. This explains why many carriers of genetic mutations never exhibit actual symptoms of the disease process, themselves.

### Background/Overview

Voltage-gated sodium channels play an important role in the initiation, propagation and maintenance of normal cardiac rhythm. In recent years, inherited mutations in the sodium channel genes have emerged as a genetic basis for LQTS with several variants identified corresponding to mutations in different genes. Additional genetic channelopathies include BrS, SQTS and CPVT. Multiple mutations in multiple genes have been associated with BrS with phenotypic variance also noted. SQTS is characterized by a shortened QT interval on EKG associated with genetic mutations in three genes, KCNH2, KCNJ2, and KCNQ1. However, SQTS has been diagnosed in individuals without mutations in known SCN5A mutations have BrS, and other less well studied genes are also involved with BrS (Miura, 2008). Treatment management for individuals exhibiting signs and symptoms suspicious for arrhythmias and SCD are not significantly changed, as a result of a confirmatory genetic test for BrS or SQTS (Gollob, 2011; Meregel, 2009; Nielsen, 2013). Similarly, genetic testing for suspected catecholaminergic polymorphic ventricular tachycardia (CPVT) currently lacks the support of large, well-designed trials demonstrating how risk stratification impacts treatment management or clinical outcomes (Jabbari, 2013; Napolitano, 2014).

An example of the genetic tests currently available is the FAMILION® Test (Transgenomic® Inc., New Haven, CT formerly manufactured by PGx Health™, a division of Clinical Data® Inc.). FAMILION is a family of genetic tests inclusive of several genetic blood tests that analyzes blood samples for the cardiac ion channel genes associated with cardiac channelopathies, such as LQTS, BrS or SQTS. According to the manufacturer, these tests can confirm the presence or absence of genetic mutations in multiple specific cardiac ion channel genes. This information may contribute to risk stratification for SCD in carriers of LQTS or other channelopathies and in treatment planning for individuals and family members.

The FAMILION test is currently performed exclusively at designated laboratory facilities provided by Transgenomics, Inc. (New Haven, CT) which purchased all rights to the genetic testing products under the FAMILION brand of PGx Health in December, 2010. According to information available online at the manufacturer’s website:

- FDA approval is not currently required for clinical use of this test. This test meets the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act (CLIA) and its implementing regulations. The test may use some reagents produced for research purposes only.

The test can be performed in three different configurations:

- Comprehensive Cardiac Ion Channel Analysis: provides analysis for variants in five cardiac ion genes and is considered appropriate by the manufacturer’s information (when there is a high index of suspicion of disease, such as stress-induced syncope, prolonged QT interval, family history of SCD and/or unexplained ventricular rhythms);

- Sodium Channel Analysis: provides analysis for variants only for the SCN5A gene and is appropriate (according to the manufacturer) in cases of suspected Brugada syndrome;

- Family Specific Analysis: provides analysis of one or more mutations found in an index case using either one of the above test configurations or confirmed results from another laboratory and is appropriate (according to the manufacturer) for testing blood relatives.

According to the National Society of Genetic Counselors (NSGC), genetic counseling is the process of assisting individuals to understand and adapt to the medical, psychological and familial ramifications of a genetic disease. This process typically includes the guidance of a specially trained professional who:

1. Integrates the interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
2. Provides education about inheritance, genetic testing, disease management, prevention and resources; and
3. Provides counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
4. Provides counseling for the psychological aspects of genetic testing (NSGC, 2006).

Definitions

https://www.anthem.com/medicalpolicies/policies/mp_pw_a050307.htm
Brugada Syndrome: A genetic cardiac channelopathy manifested by abnormal EKG findings and an increased risk of SCD.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): An inherited cardiac channelopathy characterized by irregular heart rhythms brought on by physical exertion or intense emotion. CPVT may cause syncope (fainting), cardiac arrest, or SCD in affected individuals, resulting from gene mutation.

Channelopathy: A heterogeneous group of disorders resulting from the dysfunction of ion channels located in the membranes of all cells and many cellular organelles. In cardiac cells, these channels play an integral role in repolarization during the heartbeat cycle and thus, enable the regular contractions of the healthy pumping heart.

Long QT Syndrome (LQTS): An inherited or acquired cardiac disorder which is characterized as a "channelopathy." This refers to abnormalities in the sodium and potassium channels that control the excitability of the cardiac cells (myocytes), which can lead to episodes of syncope (dizziness/fainting) and SCD in affected individuals.

Proband: A term used in medical genetics to refer to the first affected family member with a known pathogenic genetic mutation which, in this document, refers to a family member with a known diagnosis of LQTS.

QT Interval: Period of time, as indicated on an electrocardiograph, associated with ventricular repolarization.

Short QT Syndrome (SQTS): An autosomal dominant channelopathy characterized by a shortened QT interval and action potential on EKG findings and an increased risk for adverse cardiac events including arrhythmias and SCD.

Sudden cardiac death (also called sudden death [SCD]): Death resulting from an abrupt loss of heart function (cardiac arrest).

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When Services may be Medically Necessary when criteria are met for Long QT syndrome testing:

**CPT**

- 81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:
  - KCNH2 (potassium voltage-gated channel, subfamily H [eag-related], member 2) (eg, short QT syndrome, long QT syndrome), full gene sequence;
  - KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (eg, short QT syndrome, long QT syndrome), full gene sequence

- 81413 Cardiac ion channelopathies (eg, 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, KCNJ1, RYR2, and SCN5A

- 81414 Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1

**ICD-10 Diagnosis**

- I45.89 Other specified conduction disorders (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia)
- I45.89 Ventricular tachycardia

**Coding**

For the procedure and diagnosis codes listed above when criteria are not met, for testing for channelopathies other than Long QT syndrome, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When Services are Investigational and Not Medically Necessary:

- 81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [when specified as the following]:
  - SCN1B (sodium channel, voltage-gated, type 1, beta) (eg, Brugada syndrome), full gene sequence

- 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) [when specified as the following]:
  - CASQ2 (calsequestrin 2 [cardiac muscle]) (eg, catecholaminergic polymorphic ventricular tachycardia), full gene sequence

- 81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:
  - CACNB2 (calcium channel, voltage-dependent, beta 2 subunit) (eg, Brugada syndrome), full gene sequence;
  - KCNH2 (potassium voltage-gated channel, subfamily H [eag-related], member 2) (eg, short QT syndrome, long QT syndrome), full gene sequence;
  - KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (eg, short QT syndrome, long QT syndrome), full gene sequence

- 81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:
  - SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (eg, familial dilated cardiomyopathy), full gene sequence

- 81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:
  - RYR2 (ryanodine receptor 2 [cardiac]) (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of >50 exons

**HCPSCS**

- S3861 Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome

**ICD-10 Diagnosis**

- I45.89 Other specified conduction disorders [Brugada syndrome, short QT syndrome]
- I47.2 Ventricular tachycardia

https://www.anthem.com/medicalpolicies/policies/mp_pw_a050307.htm
Family history of sudden cardiac death

References

Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:


4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Genetic testing for long QT syndrome. TEC Assessment, 2008; 22(9).


**Websites for Additional Information**


**Index**

Brugada Syndrome
Cardiac Ion Channel Genetic Testing
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
Channeleoapathies
FAMILION
Genetic Testing
Long QT Syndrome, LQTS
Short QT Syndrome, SQTS
Therapeutic Diagnostics

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

**Document History**

<table>
<thead>
<tr>
<th>Status</th>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised</td>
<td>05/04/2017</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Updated the medically necessary statements to include criteria for genetic counseling. Updated Background/Overviews, References and History sections. Updated the formatting in the Position Statement section.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>02/02/2017</td>
<td>MPTAC review. References were updated.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>01/11/2017</td>
<td>Updated Coding section with 01/01/2017 CPT changes; removed codes 81280, 81281, 81282; deleted 12/31/2016.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>02/04/2016</td>
<td>MPTAC review. The Rationale, Background, Definitions and References sections were updated. Removed ICD-9 codes from Coding section.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>02/05/2015</td>
<td>MPTAC review. References were updated.</td>
</tr>
<tr>
<td>Revised</td>
<td>02/13/2014</td>
<td>MPTAC review. A position statement was added for clarification regarding genetic testing for additional channeleoapathies considered investigational and not medically necessary. The Rationale, Coding and References sections were updated.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>07/01/2013</td>
<td>Updated Coding section with 07/01/2013 CPT changes.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>02/24/2013</td>
<td>MPTAC review. References were updated.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>01/01/2013</td>
<td>Updated Coding section with 01/01/2013 CPT changes; removed 83890-83914 deleted 12/31/2012.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>02/26/2012</td>
<td>MPTAC review. Consultant input reviewed; along with the recommendations of the Heart Failure Society of America-European Heart Rhythm Association (HRS/EHRA) Consensus Statement on the State of Genetic Testing for Channeleoapathies and Cardiomyopathies (Ackerman, 2011). No change to criteria. The Rationale, Definitions and References were updated. Updated Coding section with 04/01/2012 HCPCS changes; removed codes S3890 and S3862 deleted 03/31/2012.</td>
</tr>
<tr>
<td>Reviewed</td>
<td>11/17/2011</td>
<td>MPTAC review. The Rationale, Definitions and References were updated. Updated Coding section with 01/01/2012 CPT and HCPCS changes; removed codes 83890-83914, 88261-88291; removed S3860, S3862 deleted 12/31/2011.</td>
</tr>
</tbody>
</table>