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Medical Policy Manual

Topic: Genetic Testing for Cardiac Ion Channelopathies

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Background

Genetic testing is available for patients suspected of having cardiac ion channelopathies including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and short QT syndrome (SQTS). These disorders may range from asymptomatic to presenting with sudden cardiac death (SCD). These congenital cardiac channelopathies can be difficult to diagnose, and the implications of an incorrect diagnosis could be catastrophic. Testing for mutations associated with these channelopathies may assist in diagnosis, prognostic risk stratification, medical management and/or identification of susceptibility for the disorders in asymptomatic family members.

The channelopathies discussed in this policy are genetically heterogeneous with hundreds of identified mutations, but the group of disorders share a basic clinical expression. The most common presentation is spontaneous or exercise-triggered syncope due to ventricular dysrhythmia. These can be self-limiting or potentially lethal cardiac events. The electrocardiographic features of each channelopathy are characteristic, but the electrocardiogram (ECG) is not diagnostic in all cases and some secondary events (e.g., electrolyte disturbance, cardiomyopathies, or subarachnoid hemorrhage) may result in an ECG similar to those observed in a cardiac channelopathy.

The circumstances surrounding cardiac arrest may often be insightful concerning which channelopathy is present. For example, cardiac arrest during exercise (especially swimming) occurs in 68% of patients with LQTS 1 but may also point to CPVT. Mental stress can trigger cardiac arrest in CPVT or it could be indicative of LQTS 2 if auditory stimuli or emotion are associated with the event. Cardiac arrest during sleep is suggestive of LQTS 3 or BrS while cardiac arrest during a fever, after a large meal, or if the patient is abusing cocaine are considered to be suspicious of BrS.[1]

Long QT Syndrome (LQTS)

Congenital LQTS is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential, increasing the risk for arrhythmic events which may in turn result in syncope and sudden cardiac death. LQTS is characterized as a mutation in one of the genes that controls cellular sodium and potassium ion channels. Management has focused on the use of beta blockers as first-line treatment, with pacemakers or implantable cardiac defibrillators (ICD) as second-line therapy.

Congenital LQTS usually manifests before the age of 40 years and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult. It is estimated that more than one half of the 8,000 sudden unexpected deaths in children may be related to LQTS. The mortality rate of untreated patients with LQTS is estimated at 1–2% per year, although this figure varies with the genotype.[2] Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and thus LQTS has received publicity regarding evaluation of adolescents for participation in sports.

Clinical Diagnosis

Diagnostic criteria for LQTS have been established which focus on ECG findings and clinical and family history.[3] However, measurement of the QT interval is not well-standardized, and in some instances, patients may be considered borderline cases.[4] The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS (see Policy Guidelines for scoring definitions).[3]

Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; and since there is still no perfect gold standard for diagnosing LQTS, the accuracy of this scoring system remains ill-defined.

Brugada Syndrome (BrS)

BrS is characterized by cardiac conduction abnormalities which increase the risk of syncope, ventricular arrhythmia, and sudden cardiac death. Inheritance occurs in an autosomal dominant manner with patients typically having an affected parent. Children of affected parents have a 50% chance of inheriting the mutation. The instance of de novo mutations is very low and is estimated to be only 1% of cases.[5]

The disorder primarily manifests during adulthood although ages between two days and 85 years have been reported.[6] Males are more likely to be affected than females (approximately an 8:1 ratio). BrS is estimated to be responsible for 12% of SCD cases,[7] and for both genders there is an equally high risk of ventricular arrhythmias or sudden death.[5] Penetrance is highly variable ranging from asymptomatic expression to death within the first year of life.[8] Management has focused on the use of implantable cardiac defibrillators (ICD) in patients with syncope or cardiac arrest and isoproterenol for electrical

storms. Patients who are asymptomatic can be closely followed to determine if ICD implantation is necessary.

Clinical Diagnosis

The diagnosis of BrS requires the presence of a type 1 Brugada pattern on the ECG in addition to other clinical features.[9] This ECG pattern includes a coved ST-segment and a J-point elevation of >= 0.2 mV followed by a negative T wave. This pattern should be observed in two or more of the right precordial ECG leads (V1 through V3). The pattern may be concealed and can be revealed by administering a sodium-channel-blocking agent (e.g., ajmaline or flecainide).[10] Although two additional ECG patterns (type 2 and type 3) are available, only type 1 is considered diagnostic for the disorder.[11] The diagnosis of BrS is considered definite when the characteristic ECG pattern is present with at least one of the following clinical features: documented ventricular arrhythmia, sudden cardiac death in a family member <45 years old, characteristic ECG pattern in a family member, inducible ventricular arrhythmias on EP studies, syncope, or nocturnal agonal respirations.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT is a rare inherited channelopathy which has an autosomal dominant mode of inheritance. The disorder manifests as a bidirectional or polymorphic ventricular tachycardia (VT) precipitated by exercise or emotional stress.[1] CPVT has a mortality rate of 30-50% by age 35 and is responsible for 13% of cardiac arrests in structurally normal hearts.[1] CPVT was believed to be only manifest during childhood but studies have now identified presentation between infancy and 40 years of age.[12]

Management of CPVT is primarily with the beta-blockers nadolol (1-2.5 mg/kg/day) or propranolol (2-4 mg/kg/day). If protection is incomplete (i.e., recurrence of syncope or arrhythmia), then flecainide (100-300 mg/day) may be added. If recurrence continues an ICD may be necessary with optimized pharmacologic management continued post implantation.[13] Lifestyle modification with the avoidance of strenuous exercise is recommended for all CPVT patients.

Clinical Diagnosis

Patients generally present with syncope or cardiac arrest during the first or second decade of life. The symptoms are always triggered by exercise or emotional stress. The resting ECG of patients with CPVT is typically normal, but exercise stress testing can induce ventricular arrhythmia in the majority of cases (75-100%).[13,14] Premature ventricular contractions, couplets, bigeminy, or polymorphic VT are possible outcomes to the ECG stress test. For patients who are unable to exercise, an infusion of epinephrine may induce ventricular arrhythmia, but this is less effective than exercise testing.[15]

Short QT Syndrome (SQTS)

SQTS is characterized by a shortened QT interval on the ECG and, at the cellular level, a shortening of the action potential.[16] The clinical manifestations are an increased risk of atrial and/or ventricular arrhythmias. Because of the disease's rarity the prevalence and risk of sudden death are currently unknown.[1]

The mode of inheritance for SQTS is autosomal dominant. Management of the disease is complicated because the binding target for QT-prolonging drugs (e.g., sotalol) is Kv11.1 which is coded for by KCNH2, the most common site for mutations in SQTS (subtype 1). Treatment with quinidine (which is

able to bind to both open and inactivated states of Kv11.1) is an appropriate QT-prolonging treatment. This treatment has been reported to reduce the rate of arrhythmias from 4.9% to 0% per year. For those who recur while on quinidine, an ICD is recommended.[14]

Clinical Diagnosis

Patients generally present with syncope, pre-syncope or cardiac arrest. An ECG with a corrected QT interval <330 ms, sharp T-wave at the end of the QRS complex, and a brief or absent ST-segment is characteristic of the SQTS.[17] However, higher QT intervals on ECG might also indicate SQTS, and the clinician has to determine if this is within the normal range of QT values. Recently a diagnostic scoring system has been proposed by Gollob and colleagues to aid in decision-making after a review of 61 SQTS cases.[18]

Genetic Testing

If a family member has been diagnosed with a cardiac channelopathy based on clinical characteristics; complete analysis of the specific channelopathy-associated genes can be performed to both identify the specific mutation and subtype. If a mutation is identified, then additional family members can undergo targeted genetic analysis for the identified mutation.

Currently, interpretation of cardiac ion channelopathy mutation testing is complicated by several factors. The pathophysiologic significance of each of the discrete mutations is an important part of the interpretation of genetic analysis. Laboratories that test for cardiac ion channelopathies keep a database of known pathologic mutations; however, these are mainly proprietary and may vary among different laboratories. In addition, the probability that a specific mutation is pathophysiologically significant is greatly increased if the same mutation has been reported in other cases. However, a mutation may also be found that has not definitely been associated with a disorder and therefore may or may not be pathologic. Variants are classified as to their pathologic potential; an example of such a classification system used in the Familion® assay is as follows:

- Class I – Deleterious and probable deleterious mutations. These are either mutations that have previously been identified as pathologic (deleterious mutations), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious mutations).
- Class II – Possible deleterious mutations. These variants encode changes to protein(s) but occur in regions that are not considered critical. Approximately 5% of unselected patients without LQTS will exhibit mutations in this category.
- Class III – Variants not generally expected to be deleterious. These variants encode modified protein(s); however, these are considered more likely to represent benign polymorphisms. Approximately 90% of unselected patients without LQTS will have one or more of these variants; therefore patients with only Class III variants are considered 'negative.'
- Class IV – Non-protein-altering variants. These are not considered to have clinical significance and are not reported in the results of the Familion® test.

Another factor complicating interpretation of the genetic analysis is the penetrance of a given mutation or the presence of multiple phenotypic expressions. For example, approximately 50% of carriers of mutations never have any symptoms.

<u>Long QT Syndrome</u>

In recent years, a genetic basis for LQTS has emerged, with seven different subtypes recognized, each corresponding to mutations in different genes.[19] In addition, typical ST-T wave patterns are also suggestive of specific subtypes.[20]

There are more than 1,200 unique mutations on at least 13 genes that have been associated with LQTS, and each mutation carries a unique pathophysiologic significance. In addition to single mutations, some cases of LQTS are associated with large gene deletions or duplications.[21] This may be the case in up to 5% of total cases of LQTS. These types of mutations may not be identified by gene sequence analysis. They can be more reliably identified by chromosomal microarray analysis (CMA), also known as array comparative genomic hybridization (aCGH). Some laboratories that test for LQTS are now offering detection of LQTS-associated deletions and duplications by this testing method. This type of test may be offered as a separate test and may need to be ordered independently of gene sequence analysis when testing for LQTS.

The absence of a mutation does not imply the absence of LQTS; it is estimated that mutations are only identified in 70% to 75% of patients with a clinical diagnosis of LQTS.[22] A negative test is only definitive when there is a known mutation identified in a family member and targeted testing for this mutation is negative. Other laboratories have investigated different testing strategies. For example, Napolitano et al. propose a 3-tiered approach, first testing for a core group of 64 codons that have a high incidence of mutations, followed by additional testing of less frequent mutations.[23] There is variable penetrance for the LQTS, and penetrance may differ for the various subtypes. While linkage studies in the past indicated that penetrance was 90% or greater, more recent analysis by molecular genetics has challenged this number, and suggested that penetrance may be as low as 25% for some families.[24]

Catecholaminergic Polymorphic Ventricular Tachycardia

Mutations in 4 genes are known to cause CPVT, and investigators believe other unidentified loci are involved as well. Currently, only 55% to 65% of patients with CPVT have an identified causative mutation. Mutations to RYR2 or KCNJ2 result in an autosomal dominant form of CPVT with CASQ2 and TRDN-related CPVT exhibiting autosomal recessive inheritance. Some authors have reported heterozygotes for CASQ2 and TRDN mutations rare, benign arrhythmias.[13] RYR2 mutations represent the majority of CPVT cases (50-55%) with CASQ2 accounting for 1-2% and TRDN accounting for an unknown proportion of cases. The penetrance of RYR2 mutations is approximated at 83%.[13]

An estimated 50% to 70% of patients will have the dominant form of CPVT with a disease-causing mutation. Most mutations (90%) to RYR2 are missense mutations, but in a small proportion of unrelated CPVT patients large gene rearrangements or exon deletions have been reported.(15) Additionally, nearly a third of patients diagnosed as LQTS with normal QT intervals have CPVT due to identified RYR2 mutations. Another misclassification, CPVT diagnosed as Anderson-Tawil syndrome may result in more aggressive prophylaxis for CPVT whereas a correct diagnosis can spare this treatment as Anderson-Tawil syndrome is rarely lethal.

Brugada Syndrome

BrS is typically inherited in an autosomal dominant manner with incomplete penetrance, although some authors report up to 50% of cases are sporadic in nature. Mutations in 16 genes have been identified as causative of BrS, but of these SCN5A is the most important accounting for more than an

estimated 20% of cases.[12] The other genes are of minor significance and account together for approximately 5% of cases.[1] The absence of a positive test does not indicate the absence of BrS with more than 65% of cases not having an identified genetic cause. Penetrance of BrS among persons with a SCN5A mutation is 80% when undergoing ECG with sodium channel blocker challenge and 25% when not using the ECG challenge.[5]

Short QT Syndrome

SQTS has been linked predominantly to mutations in three genesKCNH2, KCNJ2, and KCNQ1. Some individuals with SQTS do not have a mutation in these genes suggesting changes in other genes may also cause this disorder. SQTS is believed to be inherited in an autosomal dominant pattern. Although sporadic cases have been reported, patients frequently have a family history of the syndrome or SCD.

MEDICAL POLICY CRITERIA

I. Congenital Long QT Syndrome (LQTS)

Genetic testing for LQTS may be considered **medically necessary** in patients who do not meet the clinical criteria for LQTS (e.g., Schwartz score <4*) but meet one or more of the following criteria:

A A close blood relative* with a known LQTS mutation; or

B. A close blood relative* diagnosed with LQTS by clinical means whose genetic status is unavailable; or

C Signs or symptoms indicating a moderate pretest probability of LQTS (e.g., Schwarz score of 2-3)

II. Genetic testing for Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) may be considered **medically necessary** in patients who meet one or more of the following criteria:

A. A close blood relative* with a known CPVT mutation; or

B. A close blood relative* diagnosed with CPVT by clinical means whose genetic status is unavailable;

C. Clinical suspicion of CPVT based upon the presence of polymorphic ventricular arrhythmias as documented by electrocardiogram (ECG or EKG) induced by either of the following methods:

1. Graded exercise stress test; or

2. Infusion of epinephrine in patients where exercise is contraindicated.

III. Genetic testing for LQTS or CPVT is considered **investigational** for all other indications including but not limited to the following:

A. To determine prognosis and/or direct therapy in patients with known LQTS

B. For screening of the general population

IV. Genetic testing for all other cardiac ion channelopathies, including but not limited to Brugada syndrome or short QT syndrome, is considered **investigational**.

*See Policy Guidelines for:
- Schwartz scoring definitions, and
- Definition of *close blood relatives*

POLICY GUIDELINES

Schwartz Criteria (diagnostic scoring system for LQTS):

- ≥4 indicates a high probability of LQTS
- 2–3 indicates an intermediate probability of LQTS
- ≤1 indicates a low probability of LQTS.

Close blood relatives include first-, second-, and third-degree relatives from the same lineage:

- First-degree relatives: parents, siblings, and children of an individual
- Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent) of an individual
- Third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, and first-cousins

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Literature Appraisal

A BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment was completed in 2007 on, "Genetic Testing for Long QT Syndrome."[25] The following discussion of the evidence is based upon this assessment.

Analytic Validity

Commercially available genetic testing for cardiac channelopathies involves a variety of methods such as chip-based oligonucleotide hybridization, direct sequencing of protein-coding portions and flanking regions of targeted exons, and next generation sequencing. For each condition, the analytic sensitivity of these methods is between 95%-99%.[8]

Clinical Validity

The true clinical sensitivity and specificity of genetic testing for cardiac channelopathies cannot be determined with certainty, as there is no independent diagnostic gold standard. The clinical diagnosis can be compared to the genetic diagnosis, and vice versa, but neither the clinical diagnosis nor the results of genetic testing can be considered an adequate gold standard.

Long QT Syndrome (LQTS)

Ultimately, the evidence indicates that genetic testing will identify more individuals with possible LQTS compared with clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic mutation have the true clinical syndrome of LQTS. The data also demonstrate that approximately 30% of patients with a clinical diagnosis will not be found to have a known mutation, suggesting that there are additional mutations associated with LQTS that have not been identified to date. Therefore, a negative genetic test is not definitive for excluding LQTS at the present time.

Hofman et al. performed the largest study, comparing clinical methods with genetic diagnosis using registry data.[26] This study compared multiple methods for making the clinical diagnosis, including the Schwartz score, the Keating criteria, and the absolute length of the corrected QT (QTc) with genetic testing. These data indicate that only a minority of patients with a genetic mutation will meet the clinical criteria for LQTS. Using a Schwartz score of 4 or greater, the study found only 19% of patients with a genetic mutation met the clinical definition of LQTS. Even at lower cutoffs of the Schwartz score, the percentage of patients with a genetic mutation who met clinical criteria was still relatively low, improving to only 48% when a cutoff of 2 or greater was used. When the Keating criteria were used for clinical diagnosis, similar results were obtained. Only 36% of patients with a genetic mutation met the Keating criteria for LQTS.

The best overall accuracy was obtained by using the length of the QTc as the sole criterion; however, even this criterion achieved only modest sensitivity at the expense of lower specificity. Using a cutoff of 430 msec or longer for the QT interval, a sensitivity of 72% and a specificity of 86% was obtained.

Tester et al. completed the largest study to evaluate the percent of individuals with a clinical diagnosis of LQTS that are found to have a genetic mutation.[27] The population in this study was 541 consecutive patients referred for evaluation of LQTS. A total of 123 patients had definite LQTS on clinical grounds, defined as a Schwartz score of 4 or greater, and 274 patients were found to have a LQTS mutation. The genetic diagnosis was compared to the clinical diagnosis, defined as a Schwartz score of 4 or greater. Of all 123 patients with a clinical diagnosis of LQTS, 72% (89/123) were found to have a genetic mutation.

The evidence on clinical specificity focuses on the frequency and interpretation of variants that are identified that are not known to be pathologic. If a mutation is identified that is previously known to be pathologic, then the specificity of this finding is high. However, many variants are discovered on gene sequencing that are not known to be pathologic, and the specificity of these types of findings are lower.

The rate of identification of variants is estimated to be in the range of 5% for patients who do not have LQTS.[28]

A publication from the National Heart, Lung, and Blood Institute (NHLBI) GO exome sequencing project (ESP) reported on the rate of sequence variations in a large number of patients without LQTS.[29] The ESP sequenced all genome regions of protein-coding in a sample of 5,400 persons drawn from various populations, none of which included patients specifically with heart disease and/or channelopathies. Exome data were systematically searched to identify sequence variations that had previously been associated with LQTS, including both nonsense variations that are generally pathologic and missense variations that are less likely to be pathological. A total of 33 such sequence variations were identified in the total population, all of them being missense variations. The percent of the population that had at least one of these missense variations was 5.2%. There were no nonsense variations associated with LQTS found among the entire population.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

The Transgenomic® CPVT 4 gene panel (includes RYR2, KCNJ2, CASQ2 and ANK2 genes) is expected to identify between 65% and 75% of patients who have a high clinical suspicion of CPVT.[30] Sensitivity for the GeneDX® 3 gene CPVT panel is estimated to be between 50%-70% by the manufacturer. Yield is affected by the patient's VT. If the VT is bidirectional (BVT), the test will have a high yield versus the more atypical presentation of idiopathic ventricular fibrillation (IVF) which has a lower (15%) yield. The overall penetrance of CPTV has been estimated at 60%-70%.[31]

The specificity of known pathologic mutations for CPVT is not certain, but likely to be high. A publication from the National Heart, Lung, and Blood Institute Exome Sequencing Project (NHLBI ESP) reported on sequence variations in a large number of patients without CPVT.[32] The ESP sequenced all genome regions of protein-coding in a sample of 6503 persons drawn from various populations who did not specifically have CPVT or other cardiac ion channelopathies. Exome data were systematically searched to identify missense variations that had previously been associated with CPVT. The authors identified 11% of the previously described variants in the ESP population in 41 putative CPVT cases. This data suggests that false positive results are low; however, the presence of one of these variants may not always translate into the development of CPVT.

Brugada Syndrome (BrS)

The sensitivity of BrS genetic testing is low.[33] Analyses of patients with a high clinical suspicion of BrS provided a yield of approximately 25% for a documented pathologic mutation.[5] Of the eight identified genes for BrS, the most commonly identified is SCNA5 which is found in more than 20% of genotype positive cases.[5]

NHLBI ESP data identified a BrS prevalence of 4.7% when considering the maximal number of identified genes and mutations, which is far higher than in the general population.[34] In a prediction analysis using ≥ 3 prediction tools, the ESP determined that 47% of the BrS variants were determined to be pathogenic compared to 75% of the BrS variants found in the published literature.

Short QT Syndrome (SQTS)

Limited data on the clinical validity of SQTS were identified in the peer reviewed literature due to the rarity of the condition. A precise genetic testing yield is unknown, but has been reported by Transgenomic as between 15% to 20% of cases with a high clinical suspicion for SQTS.[35]

Conclusion

This evidence indicates that genetic testing will identify more individuals with possible cardiac ion channelopathies compared with clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic mutation have the true clinical syndrome of the disorder. None of the clinical sensitivities for the assays in this policy are above 80% suggesting that there are additional mutations associated with the channelopathies that have not been identified to date. Therefore, a negative genetic test is not definitive for excluding LQTS, CPVT, BrS or SQTS at the present time.

Data on the clinical specificity was available for LQTS and very limited data for CPVT. The specificity varies according to the type of mutation identified. For LQTS nonsense mutations, which have the highest rate of pathogenicity, there are very few false positives among patients without LQTS, and therefore a high specificity. However, for missense mutations, there is a rate of approximately 5% among patients without LQTS; therefore the specificity for these types of mutation is less and false positive results do occur.

Clinical Utility

Long QT Syndrome (LQTS)

Genetic Testing for LQTS to Determine Diagnosis

For diagnosing LQTS, the clinical utility of genetic testing is high. LQTS is a disorder that may lead to catastrophic outcomes, i.e., sudden cardiac death in otherwise healthy individuals. Diagnosis using clinical methods alone may lead to under-diagnosis of LQTS, thus exposing undiagnosed patients to the risk of sudden cardiac arrest. For patients in whom the clinical diagnosis of LQTS is uncertain, genetic testing may be the only way to further clarify whether LQTS is present. Patients who are identified as genetic carriers of LQTS mutations have a non-negligible risk of adverse cardiac events even in the absence of clinical signs and symptoms of the disorder. Therefore, treatment is likely indicated for patients found to have a LQTS mutation, with or without other signs or symptoms.

Treatment with beta blockers has been demonstrated to decrease the likelihood of cardiac events, including sudden cardiac arrest. Although there are no controlled trials of beta blockers, there are pre-post studies from registry data that provide evidence on this question. Two such studies reported large decreases in cardiovascular events and smaller decreases in cardiac arrest and/or sudden death after starting treatment with beta blockers.[36,37] These studies reported a statistically significant reduction in cardiovascular events of greater than 50% following initiation of beta-blocker therapy. There was a reduction of similar magnitude in cardiac arrest/sudden death, which was also statistically significant.

Treatment with an implantable cardioverter-defibrillator (ICD) is available for patients who fail or cannot take beta-blocker therapy. One published study reported on outcomes of treatment with ICDs.[38] This study identified patients in the LQTS registry who had been treated with an ICD at the discretion of their treating physician. Patients in the registry who were not treated with an ICD, but had the same

indications, were used as a control group. The authors reported that patients treated with an ICD had a greater than 60% reduction in cardiovascular outcomes.

One study reported on changes in management that resulted from diagnosing LQTS by testing relatives of affected patients with known LQTS (cascade testing).[39] Cascade testing of 66 index patients with LQTS led to the identification of 308 mutation carriers. After a mean follow-up of 69 months, treatment was initiated in 199/308 (65%) of carriers. Beta-blockers were started in 163 patients, a pacemaker was inserted in 26 patients, and an ICD was inserted in 10 patients. All carriers received education on lifestyle issues and avoidance of drugs that can cause QT prolongation.

Two studies evaluated the psychological effects of genetic testing for LQTS. Hendriks et al. studied 77 patients with a LQTS mutation and their 57 partners.[40] Psychologic testing was performed after the diagnosis of LQTS had been made and repeated twice over an 18-month period. Disease-related anxiety scores were increased in the index patients and their partners. This psychologic distress decreased over time but remained elevated at 18 months. Andersen et al. conducted qualitative interviews with 7 individuals found to have LQTS mutations.[41] They reported that affected patients had excess worry and limitations in daily life associated with the increased risk of sudden death, which was partially alleviated by acquiring knowledge about LQTS. The greatest concern was expressed for their family members, particularly children and grandchildren.

Genetic Testing for LQTS to Determine Prognosis

For determining LQTS subtype or specific mutation, the clinical utility is less certain. The evidence suggests that different subtypes of LQTS may have variable prognosis, thus indicating that genetic testing may assist in risk stratification. Several reports have compared rates of cardiovascular events in subtypes of LQTS.[2,37,42,43] These studies report that rates of cardiovascular events differ among subtypes, but there is not a common pattern across all studies. Three of the four studies[37,42,43] reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba and colleagues[2] reported that patients with LQT1 have higher event rates than patients with LQT2. Overall, the evidence suggests that knowledge of the specific mutation present may provide some prognostic information but is not sufficient to conclude that this information improves outcomes for a patient with known LQTS.

More recent research has identified specific sequence variants that might be associated with higher risk of adverse outcomes. Albert et al. examined genetic profiles from 516 cases of LQTS included in six prospective cohort studies.[44] The authors identified 147 sequence variations found in 5 specific cardiac ion channel genes and tested the association of these variations with sudden cardiac death. Two common intronic variations, one in the KCNQ1 gene and one in the SCN5A gene were most strongly associated with sudden death. Migdalovich et al. 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.[45] 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. Costa et al. combined information on mutation location and function with age and gender to risk-stratify patients with LQTS 1 by life-threatening events.[46]

Other research has reported that the presence of genetic variants at different locations can act as disease "promoters" in patients with LQTS mutations. Amin et al. reported that 3 single-nucleotide polymorphisms (SNPs) in the untranslated region of the KCNQ1 were associated with alterations in the severity of disease.[47] Patients with these SNPs had less severe symptoms and a shorter QT interval compared to patients without the SNPs. Park et al. examined a large LQTS kindred that had variable

clinical expression of the disorder.[48] Patients were classified into phenotypes of mild and severe LQTS. Two SNPs were identified that were associated with severity of disease, and all patients classified as having a severe phenotype also had one of these 2 SNPs present.

More recently, Mullally and colleagues conducted a study to determine whether multiple mutations ≥ 2 in ≥ 1 LQTS susceptibility gene would increase a patients risk for life-threatening cardiac events in 403 patients from a LQTS registry.[49] Patients with multiple mutations (n=57) were found to have a higher rate of life threatening cardiac events during follow-up periods (23% vs. 11%; p=0.031) In addition, patients with multiple mutations in a single LQTS gene were associated with a 3.2-fold increased risk for life threatening cardiac events (p=0.01). However authors noted that multiple mutations found in more than one LQTS gene were not associated with a greater risk when compared to patients with a single mutation.

Patient Management Based on Genetic Testing for LQTS

There is insufficient evidence to conclude that the information obtained from genetic testing on risk assessment leads to important changes in clinical management. Most patients will be treated with beta-blocker therapy and lifestyle modifications, and it has not been possible to identify a group with low enough risk to forego this conservative treatment. Conversely, for high-risk patients, there is no evidence suggesting that genetic testing influences the decision to insert an ICD and/or otherwise intensify treatment.

Some studies that reported outcomes of treatment with beta blockers also report outcomes by specific subtypes of LQTS.[37,43] Priori and colleagues reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of beta-blocker therapy.[37] There was a decrease in event rates in all LQTS subtypes, with a similar magnitude of decrease in each subtype. Moss and colleagues also reported pre-post event rates for patients treated with beta-blocker therapy.[36] This study indicated a significant reduction in event rates for patients with LQT1 and LQT2 but not for LQT3. This analysis was also limited by the small number of patients with LQT3 and cardiac events prior to beta-blocker treatment (4 of 28). Sauer and colleagues evaluated differential response to beta-blocker therapy in a Cox proportional hazards analysis.[50] These authors reported an overall risk reduction in first cardiac event of approximately 60% (HR: 0.41, 95% confidence interval [CI]: 0.27-0.64) in adults treated with beta blockers and an interaction effect by genotype. Efficacy of beta-blocker treatment was worse in those with LQT3 genotype (p=0.04) compared with LQT1 or LQT2. There was no difference in efficacy between genotypes LQT1 and LQT2.

There is also some evidence on differential response to beta blockers according to different specific type and/or location of mutations. Barsheset et al. examined 860 patients with documented mutations in the KCNQ1 gene and classified the mutations according to type and location.[51] Patients with missense mutations in the cytoplasmic loop (c-loop mutations) had a more marked risk reduction for cardiac arrest following treatment with beta blockers compared to patients with other mutations (HR: 0.12, 95% CI: 0.02-0.73, p=0.02).

These data suggest that there may be differences in response to beta-blocker therapy, according to LQTS subtype and the type/location of the specific mutation. However, the evidence is not consistent in this regard; for example, one of the 3 studies demonstrated a similar response to beta-blockers for LQT3 compared to other subtypes. Although response to beta-blocker therapy may be different according to specific features of LQTS, it is unlikely that this evidence could be used in clinical decision making, since it is not clear how this information would influence management.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

The clinical utility for genetic testing in CPVT follows a similar chain of logic as that for LQTS. In patients for whom the clinical diagnosis can be made with certainty, there is limited utility for genetic testing. However, without a validated diagnostic scoring system, such as the Schwartz criteria for LQTS, it is unclear how a non-genetic diagnosis of CPVT can be made with certainty. As in most cases of suspected CPVT, documentation of a pathologic mutation that is known to be associated with CPVT confirms the diagnosis. Once a diagnosis is confirmed, treatment with beta blockers and lifestyle changes are typically recommended. Although high-quality outcome studies are lacking to demonstrate a benefit of medication treatment in patients with CPVT, it is likely that treatment reduces the risk of sudden cardiac death.

There is currently no direct method of genotype-based risk stratification for management or prognosis of CPVT. However, testing can have important implications for all family members for presymptomatic diagnosis, counseling or therapy. Asymptomatic patients with confirmed CPVT should also be treated with beta-blockers and lifestyle changes. In addition, CPVT has been associated with SIDS and some investigators have considered testing at birth for prompt therapy in infants who are at risk due to a family history of CPVT.

Brugada Syndrome (BrS)

The low clinical sensitivity of genetic testing for BrS limits its diagnostic capability. A finding of a genetic mutation is not diagnostic of the disorder but is an indicator of high risk for development of BrS. The diagnostic criteria for BrS do not presently require genetic mutation testing in order to establish a clinical diagnosis of the disorder. Furthermore, treatment is based on the presence of symptoms such as syncope or documented ventricular arrhythmias. Treatment is primarily with an implantable ICD, which is reserved for high-risk patients. The presence or absence of a genetic mutation is unlikely to change treatment decisions for patients with suspected or confirmed BrS.

Risk stratification criteria are currently inadequate and the contribution of genetic sequencing is limited to identification of SCN5A mutations which occur in less than 25% of cases. Meregalli et al. investigated whether type of SCN5A mutation was related to severity of disease and found that those mutations that caused more severe reductions in peak sodium current had the most severe phenotype.[52] However, a meta-analysis of 30 BrS prospective studies found family history of SCD and presence of an SCN5A mutation insufficient to predict risk for cardiac events in BrS.[53]

Short QT Syndrome (SQTS)

No studies were identified that provide evidence for the clinical utility of genetic testing for SQTS. Clinical sensitivity for the test is low with laboratory testing providers estimating a yield as low as 15%.[35]

Clinical Practice Guidelines

Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)[17]

These two groups jointly published an expert consensus statement on genetic testing for channelopathies and cardiomyopathies.

The following recommendations are specific to LQTS testing:

- Class I (is recommended) (level of evidence C*)
    - 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.
    - 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 .480 ms (prepuberty) or .500 ms (adults).
    - 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 IIb (may be considered) (level of evidence C*)
    - Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values .460 ms (prepuberty) or .480 ms (adults) on serial 12-lead ECGs.

The following recommendations are specific to CPVT testing:

- Class I (is recommended) (level of evidence C*)
    - Comprehensive or CPVT1 and CVPT2 (RYR2 and CASQ2) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.

The following recommendations are specific to BrS testing:

- Class I (is recommended) (level of evidence C*)

    - Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

- Class IIa (can be useful) (level of evidence C*)
    - Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.

- Class III (is not recommended) (level of evidence C*)

- Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

The following recommendations are specific to SQTS testing:

- Class I (is recommended) (level of evidence C*)
  - Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.

- Class IIb (may be considered) (level of evidence C*)
  - Comprehensive or SQT1-3 (KCNH2, KCNQ1, and KCNJ2) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient's clinical history, family history, and electrocardiographic phenotype.

*Level C evidence is based upon expert consensus opinion or case studies.

American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC)[54]

These groups issued guidelines in 2006 on the management of patients with ventricular arrhythmias and the prevention of sudden death. These guidelines made a general statement that "In patients affected by LQTS, genetic analysis is useful for risk stratification and therapeutic decisions." These guidelines did not address the use of genetic testing for the diagnosis of LQTS. The guidelines also state that genetic testing for CPVT, Brugada syndrome, or SQTS may identify silent carriers for clinical monitoring but does not assist with risk stratification.

Summary

In the majority of cases, a definitive diagnosis of a cardiac ion channelopathy leads to treatment with beta-blockers, and in some cases an implantable cardiac defibrillator (ICD). As a result, confirmation of a suspected cardiac ion channelopathy is likely to lead to a health outcome benefit by reducing the risk for ventricular arrhythmias and sudden cardiac death. Therefore, the clinical utility of genetic testing for cardiac ion channelopathies lies in the sensitivity of any given test to detect a mutation in patients suspected of having a disorder. For these gene tests, clinical validity varies by condition.

Long QT Syndrome (LQTS)

For Long QT Syndrome (LQTS), clinical validity is relatively high, in the range of 70% to 80%. For mutations with high clinical validity, the identification of a mutation is likely to confirm a cardiac ion channelopathy disorder which cannot be made with certainty by other method. A definitive diagnosis may lead to improved health outcomes by reducing the risk for ventricular arrhythmias and sudden cardiac death. Therefore, genetic testing for the diagnosis of LQTS may be considered medically necessary in patients who meet the policy criteria and in who a clinical diagnosis is uncertain.

The current evidence is insufficient to permit conclusions related to the ability of genetic testing for LQTS to guide treatment decisions and improve health outcomes in patients who do not have known risk factors for LQTS, such as clinical signs or symptoms of LQTS or a family history of LQTS. Nor is there evidence to support conclusions regarding improved outcomes for gene testing in patients who

have a known clinical diagnosis of LQTS. Therefore, genetic testing for LQTS for purposes of general population screening or in patients with a known diagnosis of LQTS is considered investigational.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

For CPVT, the clinical validity is moderate, in the range of 50% to 75%. For mutations with moderate clinical validity, the identification of a mutation is likely to confirm a cardiac ion channelopathy disorder which cannot be made with certainty by other method. A definitive diagnosis may lead to improved health outcomes by reducing the risk for ventricular arrhythmias and sudden cardiac death. Therefore, genetic testing for the diagnosis of CPVT may be considered medically necessary in patients who meet the policy criteria and in who a clinical diagnosis is uncertain.

The current evidence is insufficient to permit conclusions related to the ability of genetic testing for CPVT to guide treatment decisions and improve health outcomes in patients who do not have known risk factors for LQTS, such as clinical signs or symptoms of CPVT or a family history of CPVT. Nor is there evidence to support conclusions regarding improved outcomes for gene testing in patients who have a known clinical diagnosis of CPVT. Therefore, genetic testing for CPVT for purposes of general population screening or in patients with a known diagnosis of CPVT is considered investigational.

Brugada Syndrome (BrS)

For BrS, the clinical validity is low, in the range of 15% to 35%. For mutations with low clinical validity, the diagnostic capability of genetic testing is limited as the identification of a mutation is not necessarily indicative of the disorder. Therefore, genetic testing for BrS is considered investigational.

Short QT Syndrome (SQTS)

For SQTS, the clinical validity is also low, in the range of 15% to 35%. For mutations with low clinical validity, the diagnostic capability of genetic testing is limited as the identification of a mutation is not necessarily indicative of the disorder. Therefore, genetic testing for SQTS is considered investigational.

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CROSS REFERENCES

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy, Genetic Testing, Policy No. 72

CODES	NUMBER	DESCRIPTION
CPT	81280	Long QT syndrome gene analyses (e.g., KCNQ1, KCNH2,

CODES	NUMBER	DESCRIPTION
		SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1 and ANK2); full sequence analysis
	81281	;known familial sequence variant
	81282	;duplication/deletion variants
HCPCS	S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome