Clinical Appropriateness Guidelines

Genetic Testing for Hereditary Cardiac Disease

EFFECTIVE SEPTEMBER 9, 2019
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Scope

This document addresses genetic testing for inherited arrhythmias and cardiomyopathies. Aortopathies and other connective tissue disorders with cardiac manifestations as well as congenital heart defects are NOT included in this document; see Clinical Appropriateness Guidelines: Genetic Testing for Single-Gene and Multifactorial Conditions. All tests listed in this guideline may not require prior authorization; please refer to the health plan.

Genetic Counseling Requirement

Genetic testing included in these guidelines is covered when:

1. The patient meets coverage criteria outlined in the guidelines
2. A recommendation for genetic testing has been made by one of the following:
   - An independent board-certified or board-eligible medical geneticist not employed by a commercial genetic testing laboratory*
   - An American Board of Medical Genetics or American Board of Genetic Counseling-certified genetic counselor not employed by a commercial genetic testing laboratory*
   - A genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory*

Who:

- Has evaluated the individual and performed pre-test genetic counseling
- Has completed a three-generation pedigree
- Intends to engage in post-test follow-up counseling

*A physician, genetic counselor or genetic nurse employed by a laboratory that operates within an integrated, comprehensive healthcare delivery system is not considered to be an employee of a commercial genetic testing laboratory for the purpose of these guidelines.

Appropriate Use Criteria

Confirmation/Diagnostic Testing

Confirmatory or diagnostic genetic testing for hereditary arrhythmias and cardiomyopathies is medically...
necessary when all of the following criteria are met:

- The individual is at risk for and/or has signs and symptoms of a hereditary cardiac disease
- The requested testing is as targeted as possible to a specific subset of genes related to the suspected condition (e.g. hypertrophic cardiomyopathy OR arrhythmogenic right ventricular cardiomyopathy/dysplasia)
- There are no additional relevant disease-specific criteria listed below

**Testing of Asymptomatic Individuals**

Single-site genetic testing for a known familial deleterious or suspected deleterious mutation is medically necessary for the following indications:

- Hypertrophic cardiomyopathy (HCM)
- Long QT syndrome (LQTS)
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Dilated cardiomyopathy (DCM)
- Brugada syndrome (BrS)
- Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)
- Left ventricular non-compaction cardiomyopathy (LVNC)
- Restrictive cardiomyopathy (RCM)

**Post-Mortem Testing**

Post-mortem cardiac genetic testing of an individual with sudden unexplained death, whose first degree family member is a covered member, is reasonable in the following circumstances:

- When the autopsy reveals evidence for a specific underlying heritable cardiac condition (e.g. ARVC, HCM, DCM, RCM) AND all of the following criteria are met:
  a. The corresponding targeted testing is ordered (e.g. HCM panel testing in cases where autopsy revealed evidence for HCM)
  b. No other living relative has clinical evidence for the suspected condition (e.g. should a living relative have evidence for HCM, then testing for the living relative is recommended)

- In ‘autopsy negative’ cases when all of the following criteria are met:
  a. The deceased individual meets one of the following:
     i. Age 40 years or younger at death
ii. Over 40 years at death and there is a documented family history of sudden death or cardiomyopathy

b. Cause for death remains unknown after completion of autopsy and toxicology testing (if completed)

c. The test requested is a single gene or targeted panel test for common genetic causes of sudden cardiac arrest/death and/or is as targeted as possible for the clinical indication

Long QT

Genetic testing for long QT syndrome (LQTS) is medically necessary when the individual meets general criteria for hereditary cardiac genetic testing (above) and one of the following indications:

- Confirmatory (i.e., diagnostic) testing when there is confirmed prolonged QT interval on electrocardiogram (ECG) or Holter monitor (i.e., corrected QT [QTc] interval of >470 msec [males] or >480 msec [females]), and an acquired cause has been ruled out

- Predictive testing, when there is evidence in a first-degree relative of either of the following:
  - A history of prolonged QT interval on ECG or Holter monitor (i.e., corrected QT [QTc] interval of >470 msec [males] or >480 msec [females]) and the affected individual is not available for testing
  - Sudden death of suspected cardiac diagnosis or near sudden death at age 40 or younger with no evidence of ischemia and no genetic testing was performed

Dilated Cardiomyopathy

Targeted single gene (DES, LMNA, SCN5A) OR multi-gene DCM panel genetic testing is medically necessary when the general criteria for hereditary cardiac genetic testing (above) are met in addition to one of the following:

- Individual has a clinical diagnosis of dilated cardiomyopathy (DCM)

- Individual has significant cardiac conduction disease (first-, second- or third-degree block) and/or family history of premature cardiac death (<50 years) in a first- or second-degree relative

- Individual is a candidate for an ICD

Tests Not Clinically Appropriate

- Broad “multi-condition” panel testing (e.g. pan-cardio panel, arrhythmia panel) is not medically necessary

- Genetic testing for short QT syndrome and atrial fibrillation is not medically necessary
CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive.

Covered when medical necessity criteria are met:

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<td>genes, including DSG2, MYPBC3, MYH7, PKP2, and TTN</td>
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Background

Most forms of arrhythmias and cardiomyopathies are multifactorial. There are, however, several forms of Mendelian hereditary cardiac disease that cause severe and early-onset symptoms. The hereditary arrhythmias and cardiomyopathies are primarily diagnosed clinically and symptoms can be variable within the same family. Although genetic test results may not guide medical management for those with a clinical diagnosis, identification of a mutation can allow for detection of asymptomatic family members who might benefit from life-saving treatment. Most hereditary cardiac conditions are associated with multiple genes. Targeted panel testing is reasonable in most cases.

Rationale for Genetic Counseling for Hereditary Cardiac Conditions

Pre-test genetic counseling provides individuals seeking genetic testing the opportunity to make informed decisions about their genetic testing and subsequent medical management options. Genetic counseling combines expertise in obtaining and interpreting family history information, the ability to identify the most beneficial individual in a family to initiate testing, identification of the most appropriate testing options, experience in obtaining informed consent for testing and proficiency in genetic variant interpretation, in order to maximize the genetic testing experience for patients and their healthcare providers. The genetic counseling informed consent process also educates and empowers patients to
consider the psychological, financial, employment, disability, and insurance implications of genetic testing and results (Al-Khatib et al. 2018). Patients who receive genetic counseling report increased knowledge, understanding, and satisfaction regarding their genetic testing experience (Armstrong et al. 2015; Harvey et al. 2007).

The advent of multi-gene panels and genome-scale sequencing have increased the complexity of the genetic testing landscape. Misuse of genetic testing increases the risk for adverse events and patient harm, including missed opportunities for diagnosis and disease prevention (Bellcross et al. 2011; Plon et al. 2011). Genetic information requires expert interpretation and ongoing re-evaluation to ensure the most accurate interpretation is utilized to inform medical management decision making. The multitude of genetic testing options as well as the complex information revealed by genetic testing can make choosing the most appropriate test and interpretation of results difficult for non-genetics healthcare providers (Ray 2011). Involvement of a clinical genetics provider has been shown to ensure the correct test is ordered, limit result misinterpretation and allow patients to make informed, evidence-based medical decisions with their healthcare providers (Cragun et al. 2015).

Genetic counseling not only improves patient outcomes but also reduces unnecessary healthcare spending. Pre-test genetic counseling has been shown to reduce inappropriate test ordering and prevent unnecessary medical procedures and interventions that follow from inaccurate result interpretation (DHHS 2011). While genetic testing is now available for almost all clinical specialties, correct use and interpretation is necessary to prevent adverse outcomes. While genetic counseling may benefit any patient considering or undergoing genetic testing, tests that offer predictive information or have a higher chance of identifying variants of uncertain significance often carry stronger recommendations in the form of consensus guidelines and professional statements recommending genetic counseling by trained genetics professionals.

Both the joint consortium of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (AHA/ACC/HRS) as well as the ACMG have issued strong recommendations for genetic counseling for individuals undergoing evaluation for inherited cardiac disease.

In their Task Force publication from 2017 (Al Khatib et al. 2018), the AHA/ACC/HRS provided this recommendation:

*The decision to proceed with genetic testing requires discussion, regarding the clinical use of genetic information to be obtained for both the proband and family members, as well as consideration of the important psychological, financial, employment, disability, and life insurance implications of positive genotyping. Balancing privacy of health care information for the proband with the “right to know” for family members, and the ability to provide appropriate communication of information to all potentially affected family members can be challenging on many levels, including family dynamics, geographic proximity, and access to healthcare. For these reasons, genetic counseling generally occurs before proceeding with genetic testing, and, from a patient’s perspective, is optimally provided by genetic counselors, if available, in collaboration with physicians. A combined approach of genetic counseling with medical guidance may appropriately balance the decision as to whether genetic testing would be beneficial on an individual basis.*
In the recent joint statement put forth by the ACMG and Heart Failure Society (Hershberger et al. 2018), genetic counseling performed by a board-certified or board-eligible genetic specialist or specialized physician in the absence of a genetics professional is recommended as a key component of the evaluation of individuals with suspected familial cardiomyopathies with a level of evidence of A, their strongest recommendation. In addition, this recommendation includes specific guidance regarding genetic counseling which notes that genetics professionals are specially trained to provide: review of medical records essential for phenotyping, obtaining a pedigree, patient and family education, evaluating genetic testing options, obtaining consent for genetic testing, facilitating family communication, and ordering and interpreting genetic test results while addressing psychosocial issues.

**Long QT**

Long QT syndrome (LQTS) is characterized by prolongation of the QT interval on electrocardiogram (ECG). LQTS disorders are considered channelopathies, or diseases that affect cardiac ion channels. This condition predisposes the individual to cardiac events and arrhythmias including: torsades de pointes, ventricular tachycardia, syncopal episodes, ventricular fibrillation and cardiac arrest.

LQTS is diagnosed by considering the clinical features, the family history, and the ECG findings of the patient. LQTS may be diagnosed when the prolongation of the QTc interval is >470 msec (males) or >480 msec (females) (Crotti 2008). The clinical features may range from minor symptoms such as dizziness, to more severe symptoms such as seizure, syncope and sudden death. Congenital LQTS will usually manifest before the age of 40 years, generally in childhood and adolescence with the age of onset associated with the genotype. Long-term management of LQTS may include lifestyle modification, beta-adrenergic blockers, permanent pacemaker implantation, and implantable cardioverter defibrillators.

At least 15 genes have been found to be associated with LQTS; however, mutations in 3 genes represent the most common causes: KCNQ1 (30-35%), KCNH2 (25-30%), and SCN5A (5-10%). Not all patients meeting clinical criteria for LQTS have detectable mutations in one of the known associated genes. The recommended testing approach includes either single gene sequencing or a multi-gene sequencing panel, which may be more cost effective given the multiple associated genes. Genetic screening may provide unique assistance to a family member with normal QT interval (Schwartz 2006), as at-risk individuals can be identified prior to the onset of symptoms.

**Dilated Cardiomyopathy**

Dilated cardiomyopathy (DCM) is characterized by enlargement of the left ventricle of the heart and systolic impairment, in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic dysfunction (Haas 2015). The symptoms of DCM are similar to heart failure including shortness of breath, chest pain/tightness, fainting episodes and cardiac arrhythmias. The most serious complication of DCM is sudden, irregular heart rhythms that can be life threatening. Some individuals with DCM will have no symptoms throughout their lifetime.

DCM is a heterogeneous condition caused by ischemia, systemic disease (e.g. mitochondrial or muscular dystrophy), toxins, or infection. Twenty to 50 percent of cases of idiopathic DCM are inherited. DCM can be inherited as an X-linked, autosomal recessive or autosomal dominant condition. Autosomal dominant is the most common form of inherited DCM. There are at least 38 different genes known to cause DCM and many more genes implicated as associated with the condition. Genetic testing is available for
multiple DCM genes, typically in large multi-gene panels. Genetic testing identifies a mutation in 22-50% of cases.

The 2011 HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies recommends comprehensive (testing all clinically available DCM genes) or targeted (LMNA and SCN5A) DCM genetic testing for patients with DCM and significant cardiac conduction disease (i.e. first, second or third degree heart block) and/or family history of premature unexplained death. In addition, they state that genetic testing can be useful for patients with familial DCM to confirm diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family and to help with family planning. Known familial mutation testing is recommended when a mutation has been identified in the family.

Although genetic testing is useful in differentiating between familial versus isolated DCM, and therefore facilitates identification of at-risk family members, management for the individual affected with DCM typically does not change once a diagnosis of familial DCM is established. The one exception to this is when a LMNA mutation is identified. In individuals identified with a LMNA mutation requiring pacemaker placement (i.e. history of arrhythmia or known risk of arrhythmia), the use of a pacing ICD rather than a pacemaker has been recommended due to the risk of ventricular arrhythmias and sudden death (Meune 2006).

In families where a mutation is not yet identified, clinical screening (physical exam, echocardiogram, and ECG) for DCM is recommended for asymptomatic at-risk relatives yearly in childhood and every 1-3 years in adults (Journal of Cardiac Failure Vol. 15 No. 2 2009). If there is a family history of early onset disease or family history of sudden death, increased frequency of screening may be more appropriate.

Once a familial mutation is identified, genetic testing for the known familial mutation in asymptomatic family members can differentiate between relatives who are at high risk of DCM and sudden death, versus relatives who did not inherit the familial mutation and for whom clinical screening is not warranted.

**Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is characterized by increased size of the left ventricle of the heart, typically caused by thickening of the walls of the heart. The symptoms of HCM can be variable, ranging from no symptoms to shortness of breath or irregular heart rhythms, or sudden death. The irregular heart rhythms can occur without warning and may be life threatening. HCM has a prevalence of 1/500 individuals, making it one of the most common cardiac genetic diseases. It is inherited as an autosomal dominant trait with reduced penetrance. Family history focused on history of sudden death and age of onset in family members can be helpful in risk stratification.

HCM is the most common cause of sudden death in athletes, accounting for 30% of cases of young sudden death during competition. Approximately 5%-10% of individuals with HCM progress to end-stage disease with impaired systolic function and, in some cases, left ventricular dilatation and regression of LVH. The annual mortality rate in individuals with end-stage disease is estimated at 11% and cardiac transplantation may be required. Current testing is estimated (depending on number of genes tested - from 10 to 31 genes) to detect a mutation in 60-80% of individuals with HCM. Most of the mutations are found in sarcomeric proteins that are involved with contraction of the heart muscle, but undiagnosed glycogen storage disease can also present as HCM, as can transthyretin amyloidosis; some panels
include these genes. Approximately 5% of patients will have two or more mutations identified (compound heterozygote); these patients often have an earlier age of onset and worse prognosis.

HCM is typically diagnosed clinically with cardiac imaging, physical exam, electrocardiogram, or based on histopathologic features at autopsy. Among persons with clinically diagnosed HCM, genetic testing is of unclear benefit for risk stratification, specifically sudden cardiac death (SCD) (Gersh et al. 2011). The major benefit of genetic testing in non-syndromic HCM lies in at-risk family member identification, prenatal testing, preimplantation genetic diagnosis, and, occasionally, distinguishing hereditary HCM from a secondary cause (e.g. uncontrolled hypertension, athlete’s heart).

In the absence of an identifiable pathogenic mutation in the family, medical management for individuals with a family history of HCM includes increased cardiac screening with physical examination, 12-lead EKG, annual two-dimensional echocardiography during adolescence, and in some cases cardiac MRI, with screening continuing every 5 years in adulthood. Given the possibility for late-onset disease, screening well into adulthood is recommended. Once a mutation has been identified, testing negative for a known familial mutation allows at-risk family members to discontinue all screening (which can be both costly and time-consuming) (Gersh et al. 2011).

**Brugada Syndrome**

The diagnosis of Brugada Syndrome (BrS) is based on symptoms, electrocardiogram (EKG) and family history. A diagnosis can be made based on EKG results and clinical history in approximately 75% of persons. Genetic testing can also be helpful to make a diagnosis of BrS.

BrS is characterized by a specific pattern of EKG (ST segment elevation in leads V1-V3). This can be associated with right bundle branch block, a defect in the heart’s conduction system that can also be seen on EKG. This pattern may be seen on resting EKG or may require an EKG while receiving a drug known as a sodium channel blocker. Symptoms of BrS can include arrhythmia or irregular heartbeats and fainting spells. These symptoms often occur at rest. Other triggers include high fever, large meals and excessive alcohol consumption. These BrS symptoms may be fatal if untreated.

Brugada syndrome typically presents in males in their 30s or 40s and is the second cause of death in men from Southeast Asia under the age of 40 years. Implantable cardioverter defibrillators (ICDs) are the only therapy currently known to be effective in persons with BrS with syncope or cardiac arrest. Avoidance of certain medications is recommended for persons with Brugada syndrome, as well as particular attention during a febrile state as this can be a risk factor for syncope.

At least sixteen genes are associated with Brugada syndrome. However, a recent study did not find a significant association between mutations in genes other than SCN5A and arrhythmia in a European population and warns about interpretation of variants in such other genes (Le Scouarnec 2015). Mutations in the SCN5A gene are the most common genetic cause for Brugada syndrome (20-30%) and account for >75% of BrS genotype positive persons. Targeted testing of SCN5A can be useful among persons with clinical suspicion for BrS, according to HRS guidelines (2011). Genetic testing is not indicated among persons with an isolated type 2 or 3 Brugada pattern on EKG. In most cases, the primary value of genetic testing for Brugada syndrome is to benefit at-risk family members.
Short QT Syndrome

Short QT syndrome (SQTS) is a congenital, inherited, primary electric disorder of the heart characterized by abnormally short QT intervals on the surface ECG (<360 ms) and an increased proclivity to develop atrial and/or ventricular tachyarrhythmias (Gussak 2005). SQTS is a genetically heterogeneous disease caused by mutations in five different genes (KCNH2, KCNQ1, KCNJ2, CACNA1C, and CACNB2B). All follow autosomal dominant inheritance; KCNH2 mutations are by far the most common cause in affected individuals (Patel 2010). However, mutation frequency and penetrance of these genes are uncertain.

HRS/EHRA guidelines regarding channelopathies and cardiomyopathies state that comprehensive or 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 (Class IIb-May be Useful) (HRS/EHRA 2011).

Atrial Fibrillation

Atrial fibrillation is characterized by uncoordinated electrical activity in the atria. Symptoms include dizziness, chest pain, palpitations, shortness of breath, syncope and an increased risk of stroke and sudden death. Some individuals with atrial fibrillation do not experience any symptoms. While the majority of cases of AF are not hereditary, familial clustering does occur. Familial cases of AF are indistinguishable from acquired cases. Although a number of genes have been associated with an increased risk of AF, the role of these common genetic variants in risk stratification, assessment of disease progression, and determination of clinical outcomes is limited. Routine genetic testing related to AF is not indicated (January; ACC/AHA/HRS Practice Guidelines 2014).

Post-Mortem Testing

When plans cover genetic testing for the benefit of family members, postmortem genetic testing to confirm a diagnosis and allow for early detection of other family members should be considered. Best practice guidelines describe appropriate testing scenarios that include young (<40) unexplained sudden death and cases of suspected cardiomyopathies. Recent evidence suggests that genetic testing can help identify inherited cardiac disease in 25-35% of cases of sudden cardiac deaths.

Examples of suspicious circumstances at the time of death include: drowning in an experienced swimmer, single motor vehicle accident when no other factors are present (negative toxicology screen), unexplained seizure in young person and sudden death during exercise or sleep.

Professional Society Guidelines


Selected References

Probes. 2015 Oct;29(5):308
PubMed PMID: 16336512.

Revision History
Medical Advisory Board Review:

v2.2019 05/23/2019: No Criteria Changes
v1.2018 03/31/2018: Reviewed

PROPRIETARY

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Clinical Steering Committee Review:

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v1.2018 02/28/2018: Approved
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Revisions:

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<td>Megan Czarniecki, MS, CGC</td>
<td>Revised general criteria language. Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Renumbered to v3.2017 and submitted to CSC for approval.</td>
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**Primary Author:** Tricia See, MS, CGC