Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Familial Hypertrophic Cardiomyopathy

Familial hypertrophic cardiomyopathy (HCM) is an inherited condition that is caused by a disease-associated variant in one or more of the cardiac sarcomere genes. HCM is associated with numerous cardiac abnormalities, the most serious of which is sudden cardiac death. Genetic testing for HCM-associated variants is currently available through a number of commercial laboratories.

Familial hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular condition, with a phenotypic prevalence of approximately 1 in 500 adults (0.2%). It is the most common cause of sudden cardiac death (SCD) in adults younger than 35 years of age, and is probably the most common cause of death in young athletes. The overall mortality rate for patients with HCM is estimated to be 1% per year in the adult population.

The genetic basis for HCM is a defect in the cardiac sarcomere, which is the basic contractile unit of cardiac myocytes composed of a number of different protein structures. Nearly 1,400 disease-associated variants in at least 18 different genes have been identified. Approximately 90% of pathogenic variants are missense (i.e., one amino acid is replaced for another), and the strongest evidence for pathogenicity is available for 11 genes coding for thick filament proteins (MYH7, MYL2, MYL3), thin filament proteins (TNNT2, TNNI3, TNNC1, TPM1, ACTC), intermediate filament proteins (MYBPC3), and the Z-disc adjoining the sarcomere (ACTN2, MYOZ2). Variants in myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3) are the most common and account for roughly 80% of sarcomeric HCM. These genetic defects are inherited in an autosomal dominant pattern with rare exceptions. In patients with clinically documented HCM, genetic abnormalities can be identified in approximately 60%. Most patients with clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo variants.

The clinical diagnosis of HCM depends on the presence of left ventricular hypertrophy (LVH), measured by echocardiography or MRI, in the absence of other known causative factors such as valvular disease, long-standing hypertension, or other myocardial disease. In addition to primary cardiac disorders, there are systemic diseases that can lead to LVH and thus “mimic” HCM. These include infiltrative diseases such as amyloidosis, glycogen storage diseases such as Fabry disease and Pompe disease, and neuromuscular disorders such as Noonan’s syndrome and Friedreich’s ataxia. These disorders need to be excluded before a diagnosis of familial HCM is made.

HCM is a very heterogeneous disorder. Manifestations range from subclinical, asymptomatic disease to severe life-threatening disease. Wide phenotypic variability exists among individuals, even when an identical variant is present, including among affected family members. This variability in clinical expression may be related to environmental factors and modifier genes. A large percentage of patients with HCM, perhaps the majority of all HCM patients, are asymptomatic or have minimal symptoms.
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These patients do not require treatment and are not generally at high risk for SCD. A subset of patients has severe disease that causes a major impact on quality of life and life expectancy. Severe disease can lead to disabling symptoms, as well as complications of HCM, including congestive heart failure (CHF) and malignant ventricular arrhythmias. Symptoms and presentation may include SCD due to unpredictable ventricular tachyarrhythmias, heart failure, or atrial fibrillation, or some combination. Management of patients with HCM involves treating cardiac comorbidities, avoiding therapies that may worsen obstructive symptoms, treating obstructive symptoms with β-blockers, calcium channel blockers, and (if symptoms persist), invasive therapy with surgical myectomy or alcohol ablation, optimizing treatment for heart failure, if present, and SCD risk stratification.

Diagnostic screening of first-degree relatives and other family members is an important component of HCM management. Guidelines have been established for screening in clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12-18 months for individuals between the ages of 12 to 18 years, and every 3 to 5 years for adults. Additional screening is recommended for any change in symptoms that might indicate the development of HCM.

Genetic Testing for Familial Hypertrophic Cardiomyopathy

Genetic testing has been proposed as a component of screening at-risk individuals, in order to determine predisposition to HCM among those patients at risk. Patients at risk for HCM are defined as individuals who have a close relative with established HCM. Results of genetic testing may influence management of at-risk individuals, which may in turn lead to improved outcomes. Furthermore, results of genetic testing may have implications for decision-making in the areas of reproduction, employment, and leisure activities. However, the potential of obtaining a positive genetic test in the proband is only about 50% since all genes causing HCM have not yet been identified or are absent from testing panels. Failure to identify the causative variant in the proband is an indeterminate result that provides no useful information and precludes predictive testing in 33% to 67% of cases.

Commercial testing has been available since 2003, and there are numerous companies that currently offer genetic testing for HCM. Testing is performed either as comprehensive testing or targeted gene testing. Comprehensive testing, which is done for an individual without a known genetic variant in the family, analyzes the genes that are most commonly associated with genetic variants for HCM and evaluates whether any potentially pathogenic variants are present. Some of the available panels include testing for multisystem storage diseases that may include cardiac hypertrophy, such as Fabry disease (GLA), familial transthyretin amyloidosis (TTR), and X-linked Danon disease (LAMP2).

Other panels include testing for genes that are related to HCM but also those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen) is a next-generation sequencing (NGS) panel of 44 genes associated with HCM, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, left ventricular noncompaction syndrome, Danon syndrome, Fabry disease, Barth syndrome, and transthyretin amyloidosis.

For a patient with a known variant in the family, targeted testing is performed. Targeted variant testing evaluates the presence or absence of a single variant known to exist in a close relative.

There can be difficulties in determining the pathogenicity of genetic variants associated with HCM. Some studies have reported that assignment of pathogenicity has a relatively high error rate and that classification changes over time. With next-generation (NGS) and whole-exome sequencing techniques, the sensitivity of identifying variants on the specified genes has increased substantially. At the same time, the number of variants of unknown significance is also increased with NGS. Also, the percent of individuals who have more than 1 variant that is thought to be pathogenic is increasing. A 2013 study reported that 9.5% (19/200) patients from China with HCM had multiple pathogenic variants and that the number of variants correlated with severity of disease.
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**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Sequencing tests for hypertrophic cardiomyopathy (HCM) are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing.

To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

There are no assay kits approved by FDA for genetic testing for HCM.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

BCBSNC will provide coverage for genetic testing for predisposition to inherited hypertrophic cardiomyopathy (HCM) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

**Benefits Application**

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**When Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy (HCM) is covered**

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered medically necessary for individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM, when there is a known pathogenic gene variant present in that affected relative. (See policy guidelines).

**When Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy (HCM) is not covered**

Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathologic variants.

Genetic testing for predisposition to HCM is considered investigational for all other patient populations, including but not limited to individuals who have a first-degree relative with clinical HCM, but in whom genetic testing is unavailable.

**Policy Guidelines**

The evidence for testing for a specific hypertrophic cardiomyopathy (HCM) –related variant identified in affected family member(s), in individuals who are asymptomatic with risk for HCM because of a positive family history, includes studies reporting on the clinical validity of testing. Relevant outcomes
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include overall survival, test accuracy and validity, changes in reproductive decision making, symptoms, and morbid events. For individuals at risk for HCM (first-degree relatives), genetic testing is most useful when there is a known disease-associated variant in the family. In this situation, genetic testing will establish the presence or absence of the same variant in a close relative with a high degree of certainty. Absence of this variant will establish that the individual has not inherited the familial predisposition to HCM and thus has a similar risk of developing HCM as the general population. These patients no longer need ongoing surveillance for the presence of clinical signs of HCM. Although no direct evidence comparing outcomes for at-risk individuals managed with and without genetic testing was identified, there is a strong chain of evidence that there are management changes that improve outcomes with genetic testing when there is a known familial variant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

The evidence for nonspecific testing for HCM-related variant(s) in individuals who are asymptomatic with risk for HCM because of a positive family history, includes studies reporting on the clinical validity of testing. Relevant outcomes include overall survival, test accuracy and validity, changes in reproductive decision making, symptoms, and morbid events. Given the wide genetic variation in HCM and the likelihood that not all causative variants have been identified, there is imperfect clinical sensitivity. Therefore, a negative test is not sufficient to rule out a disease-associated variant in patients without a known family variant. For at-risk individuals without a known variant in the family, there is not a clear relationship between testing and improved outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: S3865, S3866, 81403, 81405, 81406, 81407, 81439, 81479, G0452

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


BlueCross BlueShield Association Technology Evaluation Center (TEC). Genetic testing for predisposition to inherited hypertrophic cardiomyopathy. 2009 TEC Assessments; Volume 24, Tab 11.


Ackerman MJ, Priori SG, Willems S. et al. Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic
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testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011 Aug;13(8):1077-109. Retrieved from http://europace.oxfordjournals.org/content/13/8/1077.long#content-block

Specialty Matched Consultant Advisory Panel review 10/2012


Specialty Matched Consultant Advisory Panel review 10/2013


Senior Medical Director review 12/2014


Specialty Matched Consultant Advisory Panel review 10/2015

Medical Director review 10/2015


Medical Director review 10/2016


Medical Director review 3/2017

Specialty Matched Consultant Advisory Panel review 10/2017

Medical Director review 10/2017


Medical Director review 3/2018

Specialty Matched Consultant Advisory Panel review 10/2018
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Medical Director review 10/2018

**Policy Implementation/Update Information**

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<th>Date</th>
<th>Details</th>
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<td>1/24/11</td>
<td>New policy. “Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered medically necessary for individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM, when there is a known pathogenic gene mutation present in that affected relative. (See policy guidelines). Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative has tested negative for pathologic mutations. Genetic testing for predisposition to HCM is considered investigational for all other patient populations, including but not limited to individuals who have a first-degree relative with clinical HCM, but in whom genetic testing is unavailable.” Reviewed by Medical Director. (mco)</td>
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<td>10/30/12</td>
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<td>1/29/13</td>
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<td>2/10/15</td>
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<td>Description section revised. When Not Covered statement clarified to indicate that familial testing should be in a family member with established HCM; policy intent otherwise unchanged. Policy Guidelines section revised. References updated. (td)</td>
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<td>12/30/16</td>
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4/13/18   Minor revision to Description section. References updated. Medical Director review 3/2018. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.