Medical Policy

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

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Policy Number: 909
BCBSA Reference Number: 2.02.28
NCD/LCD: N/A

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

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.

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 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.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.
## Commercial Managed Care (HMO and POS)
<table>
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<th>No</th>
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## Commercial PPO and Indemnity
|                      | No |
## Medicare HMO BlueSM
|                      | No |
## Medicare PPO BlueSM
|                      | No |

### CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

### CPT Codes

There is no specific CPT code for this service.

### HCPCS Codes

<table>
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<th>HCPCS Codes</th>
<th>Code Description</th>
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<tr>
<td>S3866</td>
<td>Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family</td>
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### Description

**Familial Hypertrophic Cardiomyopathy**

Familial hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular condition, with a phenotypic prevalence of approximately 1 (0.2%) in 500 adults. 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 and is composed of different protein structures. Around 1400 disease-associated variants in at least 18 different genes have been identified. About 90% of pathogenic variants are missense (i.e., 1 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 the clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo variants.

### Diagnosis and Management

The clinical diagnosis of HCM depends on the presence of left ventricular hypertrophy, measured by echocardiography or magnetic resonance imaging, in the absence of other known causative factors such as valvular disease, long-standing hypertension, or another myocardial disease. In addition to primary cardiac disorders, there are systemic diseases that can lead to left ventricular hypertrophy and thus mimic HCM. They include infiltrative diseases such as amyloidosis, glycogen storage diseases (e.g., Fabry disease, Pompe disease), and neuromuscular disorders (e.g., Noonan syndrome, Friedreich 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, are asymptomatic or have minimal symptoms. 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 heart failure 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. Implantable cardioverter defibrillator implantation may be indicated if there is a family history of SCD.

Diagnostic screening of first-degree relatives and other family members is an important component of HCM management. Guidelines have been established for screening clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals ages 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
Genetic testing has been proposed as a component of screening at-risk individuals 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 the 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 likelihood of obtaining a positive genetic test in the proband is only about 50% because 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 numerous companies offer genetic testing for HCM. Testing is performed either as a comprehensive or targeted gene test. Comprehensive testing, which is done for an individual without a known genetic variant in the family, analyzes the genes most commonly associated with genetic variants for HCM and evaluates whether any potentially pathogenic variants are present. Some 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 related to HCM and those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen) is a next-generation sequencing 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 for the presence or absence of a single variant known to exist in a close relative.

It can be difficult to determine 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 sequencing 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 uncertain significance is also increased with next-generation sequencing. Also, the percentage 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.

**Summary**

For individuals who are asymptomatic with risk for HCM because of a positive family history who receive testing for a specific HCM-related variant identified in affected family member(s), the evidence includes studies reporting on the clinical validity of testing. Relevant outcomes are 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. Such patients will 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 management changes can 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.

For individuals who are asymptomatic with risk for HCM because of a positive family history who receive nonspecific testing for an HCM-related variant, the evidence includes studies reporting on the clinical validity of testing. Relevant outcomes are 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 no clear relation between testing and improved outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy History**

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<thead>
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<th>Date</th>
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<tr>
<td>4/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>2/2016</td>
<td>BCBSA National medical policy review. Clarification made to not medically necessary policy statement to indicate that familial testing should be in a family member with established HCM; policy statements otherwise unchanged. 2/1/2016</td>
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<tr>
<td>2/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>12/2013</td>
<td>Coding information clarified.</td>
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<tr>
<td>2/2013</td>
<td>New policy describing coverage and non-coverage.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


34. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic 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). Heart Rhythm. Aug 2011;8(8):1308-1339. PMID 21787999