Medical Policy
Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

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- Policy: Medicare
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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 Blue℠ and Medicare PPO Blue℠ 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.
### 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>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Code Description</th>
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<tbody>
<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>
</tr>
</tbody>
</table>

#### Description

**Familial Hypertrophic Cardiomyopathy**

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 also the most common cause of death in young athletes. The overall death 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 a number of different protein structures. Nearly 1400 individual mutations in at least 18 different genes have been identified to date. Approximately 90% of pathogenic mutations are missense (ie, 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). Mutations 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 mutations.

The clinical diagnosis of HCM depends on the presence of left ventricular hypertrophy (LVH), measured by echocardiography or magnetic resonance imaging, 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 syndrome and 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 mutation is present, including among affected family members.² This variability in clinical expression may be related to environmental factors and modifier genes.¹⁰ A large percentage of patients with HCM, perhaps the majority of all HCM patients, are asymptomatic or have minimal symptoms.⁹,¹⁰

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.¹¹ 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 to 18 months for individuals ages 12 to 18 years and every 3 to 5 years for adults.¹⁰ Additional screening is recommended for any change in symptoms that might indicate the development of HCM.¹⁰

**Genetic Testing for Familial Hypertrophic Cardiomyopathy**

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 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.

Commercial testing has been available since May 2003, and there are numerous commercial companies that currently offer genetic testing for HCM.¹²⁻¹⁵,⁶ Testing is performed either as comprehensive testing or targeted gene testing. Comprehensive testing, which is done for an individual without a known genetic mutation in the family, analyzes the genes that are most commonly associated with genetic mutations for HCM and evaluates whether any potentially pathogenic mutations are present. The number of HCM genes in the testing panel ranges between 9 and 52. Additional testing characteristics of some of the commercially available panels are presented in Table 1.₆ For a patient with a known mutation in the family, targeted testing is performed. Targeted mutation testing evaluates the presence or absence of a single mutation 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.¹⁶,¹⁷ 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 mutation 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 mutations and that the number of mutations correlated with severity of disease.¹⁸

**Table 1. Characteristics of Commercial Testing for HCM**

<table>
<thead>
<tr>
<th>Company</th>
<th>No. of HCM Genes in Panel</th>
<th>Testing Technique</th>
<th>Turnaround Time, wk</th>
<th>No. of Probability Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneDx (Gaithersburg, MD)</td>
<td>18</td>
<td>NGS and deletion/duplication analysis</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Panel Description</td>
<td>Cost Ranges</td>
<td>Remarks</td>
<td></td>
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</tr>
<tr>
<td>Transgenomic (Omaha, NE)</td>
<td>Direct (Sanger) sequencing</td>
<td>4-6 (comprehensive) 2-4 (targeted)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Partners (Cambridge MA)</td>
<td>NGS and Sanger sequencing</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>ApolloGen (Irvine, CA)</td>
<td>NGS</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Prevention Genetics (Marshfield, WI)</td>
<td>NGS, Sanger sequencing, and/or deletion/duplication analysis</td>
<td>5-7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Invitae (San Francisco, CA)</td>
<td>NGS and deletion/duplication/CNV analysis</td>
<td>2-3</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Maron et al6 and GeneTests.org.

Some of these panels include testing for multisystem storage diseases that may include cardiac hypertrophy, such as Fabry disease (GLA), familial transthyretin amyloidosis (TTR), X-linked Danon disease (LAMP2). Several academic centers, including Emory University School of Medicine and Washington University in St. Louis, also offer HCM genetic panels.

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, Irvine, CA) is an NGS panel of 44 genes that are 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.

CNV: copy number variant; HCM: hypertrophic cardiomyopathy; NGS: next-generation sequencing.

**Summary**

Familial hypertrophic cardiomyopathy (HCM) is an inherited condition that is caused by a mutation in 1 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 mutations is currently available through a number of commercial laboratories.

The evidence for testing for specific HCM-related mutation 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 analytic and clinical validity of testing. Relevant outcomes 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 mutation in the family. In this situation, genetic testing will establish the presence or absence of the same mutation in a close relative with a high degree of certainty. Absence of this mutation 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 indirect chain of evidence that there are management changes that improve outcomes with genetic testing when there is a known familial mutation. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</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>
</tr>
<tr>
<td>12/2013</td>
<td>Coding information clarified.</td>
</tr>
<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


37. Ackerman MJ, Priori SG, Willem 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