# Hypertrophic Cardiomyopathy Testing

## Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is hypertrophic cardiomyopathy

Definition

Hypertrophic cardiomyopathy (HCM) is a genetic condition associated with unexplained thickening of the heart wall surrounding the left ventricle (called left ventricular hypertrophy or LVH).\textsuperscript{1,2}

- A clinical diagnosis is suggested by a nondilated left ventricle with a wall thickness of 13-15mm or more in adults,\textsuperscript{3,4} or ≥2 standard deviations in children.\textsuperscript{5} However, some individuals with HCM have smaller LV measurements and variable patterns of LVH may be observed.\textsuperscript{4,5}
- Other causes of LVH should be ruled out, including underlying cardiac disease (e.g., chronic hypertension, aortic stenosis), extreme physiologic hypertrophy (“athlete's heart”), and other multisystem disorders that may have LVH as a feature (e.g., Fabry disease, Friedreich's ataxia, Noonan syndrome, LEOPARD syndrome, Danon disease, Barth syndrome, Pompe syndrome).\textsuperscript{4,6}
- Signs and symptoms are variable ranging from a lifelong asymptomatic course to progressive heart failure and sudden cardiac death.\textsuperscript{1,2}
- HCM affects about 1 in 500 people, and is the most common cause of sudden cardiac death among young people under 35 - especially athletes.\textsuperscript{4}
- HCM is an autosomal dominant condition. First-degree relatives (parents/siblings/children) of someone with HCM have up to a 50% chance of also being affected. Longitudinal clinical screening is recommended for at-risk relatives.\textsuperscript{2,5,7}
• HCM is caused by a mutation in one of at least 14 genes. Genetic testing can be useful to confirm a diagnosis of inherited HCM in a person with unexplained LVH. A family history of LVH, heart failure, or sudden cardiac death supports the diagnosis of HCM but is not required to make a diagnosis. The severity and likelihood of cardiac death may be associated with the gene mutation that causes HCM.

• Identifying a gene mutation does not significantly change management for someone diagnosed with HCM. However, once the disease-causing mutation is identified, at-risk relatives can have reliable genetic testing to define their risk and screening needs.

Test information

• HCM Sequencing Panels vary by laboratory but most laboratories test at least the eight genes most commonly linked to HCM. Mutations in the MYH7 and MYBC3 genes are most common. About 35-60% of people clinically diagnosed with HCM will have a mutation in one of the genes commonly tested.

• Once a mutation is identified in a family member, the family mutation can be specifically identified with >99% accuracy in asymptomatic family members, or those with equivocal symptoms.

Guidelines and evidence

Diagnostic testing

• Evidence-based guidelines from the European Society of Cardiology published in 2014 state:
  - “Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.” (Class 1, Level B)
  - “It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.” (Class 1, Level C)
  - “In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis.” (Class 1, Level B)
  - “Genetic testing in patients with a borderline diagnosis of HCM should be performed only after detailed assessment by specialist teams.” (Class IIa, Level C)
  - “Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.” (Class IIa, Level C)
• The Cardiac Society of Australia and New Zealand (2013) made the following recommendation regarding the use of diagnostic testing for HCM:\(^9\)
  o “Genetic testing may also help to discriminate between HCM and other causes of left ventricular hypertrophy, including hypertension and ‘athlete’s heart’.”

• A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)\(^10\) makes Class 1 recommendation that:
  o “Comprehensive or targeted (MYBPC3, MYH7, TNNI3, TNNT2, TPM1) HCM genetic testing is recommended for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient’s clinical history, family history, and electrocardiographic/echocardiographic phenotype.”

• Evidence-based guidelines from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published in 2011 state:
  o “Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to the cause.” (Class 1, Level of evidence B).\(^5\)
  o “Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM.” (Class IIa, Level of Evidence B).\(^5\)

• Evidence-based practice guidelines for the genetic evaluation of cardiomyopathies, including HCM, from the Heart Failure Society of America (HFSA, 2018) state:\(^6\)
  o Genetic testing is recommended for the most clearly affected family member (Level of evidence A)
    ▪ Genetic testing is recommended to determine if a pathogenic variant can be identified to facilitate patient management and family screening
    ▪ The level of evidence for testing in HCM is based on studies showing a high diagnostic yield of genetic testing in children and adults and prognostic value of genotype status
  o In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.

**Predictive testing**

• Evidence-based guidelines from the European Society of Cardiology published in 2014 state:\(^8\)
"It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations." (Class 1, Level C)

"Cascade genetic screening, after pre-test counseling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation." (Class I, Level B)

"Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives who have the same definite disease-causing mutation as the proband." (Class 1, Level C)

"First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family." (Class IIa, Level B)

- The Cardiac Society of Australia and New Zealand (2013) made the following recommendation regarding the use of predictive testing for HCM:
  - "Identifying the disease-causing gene mutation can be very valuable for a family, as it can allow earlier management of at-risk members and avoid unnecessary screening of non-carriers."

- A 2011 expert consensus statement from the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) makes Class 1 recommendation that:
  - "Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case."

- Evidence-based guidelines from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published in 2011 make the following Class I recommendations:
  - "Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM." (Level of Evidence: B)
  - "In individuals with pathogenic mutations who do not express the HCM phenotype, it is recommended to perform serial electrocardiogram (ECG), transthoracic echocardiogram (TTE), and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient’s age and change in clinical status." (Level of Evidence: B)

- Evidence-based practice guidelines for the genetic evaluation of cardiomyopathies, including HCM, from the Heart Failure Society of America (HFSA, 2018) state:
  - Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants (Level of evidence A).
Criteria
Known Familial Mutation(s) for Hypertrophic Cardiomyopathy

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous HCM-associated genetic testing inclusive of known family mutation, AND
- Diagnostic/Predisposition Testing for Presymptomatic/Asymptomatic Individuals:**
  - HCM known family mutation in 1st or 2nd degree biologic relative, OR
- Diagnostic Testing for Symptomatic Individuals:
  - HCM known family mutation in 1st or 2nd degree biologic relative
  - Echocardiogram demonstrating LVH without obvious cause (valvular disease, hypertension, infiltrative or neuromuscular disorder), and
  - Myocardial wall thickening of greater than or equal to 15mm (1.5cm), or
  - Presence of pathognomonic histopathologic features of HCM
    - Myocyte disarray
    - Hypertrophy
    - Increased myocardial fibrosis, and
  - The results of the test will directly impact the diagnostic and treatment options that are recommended for the patient, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**NOTE:** Since symptoms may occur in childhood, testing of children who are at-risk for a pathogenic mutation may be appropriate, but requires genetic counseling and careful consideration of ethical issues related to genetic testing in minors.³

Hypertrophic Cardiomyopathy Genetic Testing Panel

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing for HCM, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Echocardiogram demonstrating LVH without obvious cause (valvular disease, hypertension, infiltrative or neuromuscular disorder), and
  o Myocardial wall thickening of greater than or equal to 15mm (1.5cm), or
  o Presence of pathognomonic histopathologic features of HCM
    ▪ Myocyte disarray
    ▪ Hypertrophy
    ▪ Increased myocardial fibrosis, and
  o The results of the test will directly impact the diagnostic and treatment options that are recommended for the patient, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Billing and reimbursement considerations

• When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, eviCore will redirect to the panel code(s).
• If the laboratory will not accept redirection to a panel code, the medical necessity of each billed component procedure will be assessed independently.
  o In general, only a limited number of panel components that are most likely to explain the member’s presentation will be reimbursable. The remaining panel components will not be reimbursable.
  o When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement:
    ▪ MYH7
    ▪ MYBPC3
    ▪ TNNT2
    ▪ TNNI3
    ▪ TPM1

References


