Test Specific Guidelines

Hypertrophic Cardiomyopathy Genetic Testing

MOL.TS.189.A
v1.0.2023

Introduction

Hypertrophic cardiomyopathy genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Hypertrophic Cardiomyopathy Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Hypertrophic Cardiomyopathy Genetic Testing Panel (at least 5 cardiomyopathy- related genes)	81439
Hypertrophic Cardiomyopathy Genetic Testing Panel	S3865
Hypertrophic Cardiomyopathy Known Familial Mutation Analysis	81403

Procedures addressed by this guideline	Procedure codes
Hypertrophic Cardiomyopathy Known Familial Mutation Analysis	S3866

What Is Hypertrophic Cardiomyopathy?

Definition

Hypertrophic cardiomyopathy (HCM) is a genetic condition associated with thickening of the walls of the left ventricle (called left ventricular hypertrophy or LVH).[1,2]

Incidence

HCM affects about 1 in 500 people, and is the most common cause of sudden cardiac death (SCD) among young people under 35 - especially athletes.[3]

Symptoms

Signs and symptoms are variable ranging from a lifelong asymptomatic course to progressive heart failure and SCD.[1,2]

Cause

HCM is caused by a mutation in one of 29 currently known genes.[2] 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.[3,4]

Inheritance

HCM is an autosomal dominant disorder. Longitudinal clinical screening is recommended for at-risk relatives.[2,5,6]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

A clinical diagnosis is suggested by a non-dilated left ventricle with a wall thickness of 13-15mm or more in adults or ≥2 standard deviations in children.[4,7]

However, some individuals with HCM have smaller LV measurements and variable patterns of LVH may be observed.[3,5]

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).[3,4]

HCM sequencing panels vary by laboratory but most laboratories test at least the eight genes most commonly linked to HCM.[1] A mutation is detected in up to 60% of affected individuals with a family history of HCM and in up to 30% of affected individuals without a family history of HCM.[2] Mutations in the MYH7 and MYBC3 genes are most common, accounting for approximately 80% of mutations.[1,4]

Management

Identifying a gene mutation does not always change management for someone clinically diagnosed with HCM. However, if HCM is found to be caused by an underlying syndrome, it could significantly change management decisions.[4]

Once the disease-causing mutation is identified, at-risk relatives can have reliable genetic testing to define their risk and screening needs.[6] Identifying a gene mutation significantly changes medical management in individuals without a clinical diagnosis of HCM.[5,6,7]

Survival

The risk of SCD in individuals with HCM is 0.5-2% per year and can be the first presenting feature of HCM.[8]

Test Information

Introduction

Testing for HCM may include known familial mutation analysis or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and Evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to HCM testing.

American College of Cardiology Foundation and the American Heart Association

Evidence-based guidelines from the American College of Cardiology Foundation (ACCF, 2011) and the American Heart Association (AHA, 2011) Task Force stated:[5]

“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)

“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).

"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).

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2018) published a practice resource on genetic testing for cardiomyopathies. This practice resource is an abbreviated version of the Heart Failure Society Guidelines above, on which ACMG collaborated. They stated:[9]

“Recommendation 1. Genetic testing is recommended for patients with cardiomyopathy.”

“(a) Genetic testing is recommended for the most clearly affected family member.”

“(b) Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.”

“(c) In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.”

American Heart Association and the American College of Cardiology

A joint committee guideline from the American Heart Association (AHA, 2020) and American College of Cardiology (ACC, 2020) made the following class 1 recommendations:[10]

“When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM."

“In first-degree relatives of patients with HCM, both clinical screening (ECG and 2D echocardiogram) and cascade genetic testing (when a pathogenic/likely pathogenic variant has been identified in the proband) should be offered."

“In patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause, a work-up including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy (‘HCM phenocopies’) is recommended."

Cardiac Society of Australia and New Zealand

The Cardiac Society of Australia and New Zealand (CSANZ, 2013) made the following recommendations regarding testing for HCM:[11]

"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."

"Genetic testing may also help to discriminate between HCM and other causes of left ventricular hypertrophy, including hypertension and “athlete’s heart”."

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society and Latin American Heart Rhythm Society

An expert consensus statement from the European Heart Rhythm Association, the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society and the Latin American Heart Rhythm Society (EHRA/HRS/APHR/LAHRS, 2022) addressed the utility and appropriateness of genetic testing for inherited cardiovascular conditions.[12] The consensus statements were categorized as follows:

Supported by strong observational evidence and authors' consensus

Some evidence and general agreement favor the usefulness/ efficacy of a test

There is evidence or general agreement not to recommend a test

Regarding the choice of genetic testing and variant interpretation:

Genetic testing should occur with genetic counseling. [Supported by strong observational evidence and authors' consensus]

If an individual has a clear phenotype, it is appropriate to analyze genes with definite/strong evidence support disease causation [Supported by strong observational evidence and authors' consensus] and may be appropriate to analyze genes with moderate evidence for disease causation. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

In some cases with a clear phenotype and negative genetic testing of genes with definite/strong evidence for disease causation, broader genetic testing may be considered. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting." [There is evidence or general agreement not to recommend a test]

"Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multi-disciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists." Standard guidelines for variant interpretation should be used. Variant interpretation "can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration. [Supported by strong observational evidence and authors' consensus]

Variants of uncertain significance may be reclassified to likely pathogenic, pathogenic, likely benign or benign. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

When a likely pathogenic or pathogenic variant has been identified, genetic counseling should be offered. The inheritance pattern, penetrance, and associated risks can be discussed. Additionally, cascade testing for relatives can be facilitated. [Supported by strong observational evidence and authors' consensus]

Some affected individuals may have had previous genetic testing that was not a comprehensive, such as prior to the use of next generation sequencing or with an incomplete testing panel. Repeat testing should be considered in these cases. [Supported by strong observational evidence and authors' consensus].

Regarding genetic testing for hypertrophic cardiomyopathy:

"For genetic testing in a proband with HCM (including those cases diagnosed post-mortem), the initial tier of genes tested should include genes with definitive or strong evidence of pathogenicity (currently MYH7, MYBPC3, TNNI3, TPM1, MYL2, MYL3, ACTC1, and TNNT2)." [Supported by strong observational evidence and authors' consensus]

"For genetic testing in a proband with HCM, the initial tier of genes tested may include genes with moderate evidence of pathogenicity (CSRP3, TNNC1, JPH2)." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"In patients with HCM, genetic testing is recommended for identification of family members at risk of developing HCM." [Supported by strong observational evidence and authors' consensus]

"In patients with atypical clinical presentation of HCM, or when another genetic condition associated with unexplained hypertrophy is suspected (e.g. HCM phenocopy) genetic testing is recommended." [Supported by strong observational evidence and authors' consensus]

"Predictive genetic testing in related children is recommended in those aged >10–12 years." [Supported by strong observational evidence and authors' consensus]

"In patients with HCM who harbour a variant of uncertain significance, the usefulness of genetic testing of phenotype-negative relatives for the purpose of variant reclassification is uncertain." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"Predictive genetic testing in related children aged below 10–12 years may be considered, especially where there is a family history of early-onset disease." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"In patients with HCM who harbour a variant of uncertain significance, testing of affected family members for the purpose of variant classification may be considered." [Supported by strong observational evidence and authors' consensus]

"For patients with HCM in whom genetic testing found no LP/P [likely pathogenic/pathogenic] variants, cascade genetic testing of family relatives is not recommended." [There is evidence or general agreement not to recommend a test]

"Ongoing clinical screening is not recommended in genotype-negative relatives in most families with genotype-positive HCM." [There is evidence or general agreement not to recommend a test]

European Society of Cardiology

Evidence-based guidelines from the European Society of Cardiology (ESC, 2014) stated:[7]

"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)

“Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.” (Class 1, Level B)

“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)

Heart Failure Society of America

Evidence-based practice guidelines for the genetic evaluation of cardiomyopathies, including HCM, from the Heart Failure Society of America (HFSA, 2018) stated:[4]

"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."

"In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered."

"Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants." (Level of evidence A)

Criteria

Introduction

Request for HCM testing are reviewed using the following criteria:

Known Familial Mutation Analysis 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 that would detect the familial 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, and

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) in adults, or greater than 2 standard deviations for age in children, or

Presence of the following 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 individual, 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.

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:

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) in adults, or greater than 2 standard deviations for age in children, or

Presence of the following 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 individual, 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.

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.

When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement:

MYH7

MYBPC3

TNNT2

TNNI3

References

Introduction

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