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Medical Policy Manual

Topic: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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.

Background

Familial hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular condition, with a phenotypic prevalence of approximately 1 in 500 adults (0.2%).[1] 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 the most common cause of death in young athletes[2] The overall death rate for patients with HCM is estimated to be 1% per year in the adult population.[3,4]

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.[5] Nearly 1400 individual mutations in at least 18 different genes have been identified to date.[6-8] Approximately 90% of pathogenic mutations 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*). 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.[5] Genetic abnormalities can be identified in approximately 60% of patients with clinically documented HCM.[7,9] Most patients demonstrate a familial pattern of disease, although some exceptions are found, presumably due to *de novo* mutations.[9]

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.[7] 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.[9] These disorders need to be excluded before a diagnosis of familial HCM is made.

HCM is a very heterogenous 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.

Diagnostic screening of first-degree relatives and other family members is an important component of HCM management. Guidelines have been established for clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals between the ages of 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] Results of genetic testing may influence management of these 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.[6,11-14] 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 12 and 18.[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.[15,16] With next-generation 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 next-generation

sequencing. Also, the percent of individuals who have more than 1 mutation that is thought to be pathogenic is increasing. A study in 2013 reported that 9.5% (19/200) patients with HCM had multiple pathogenic mutations and that the number of mutations correlated with severity of disease.[17]

Regulatory Status

There are no assay kits approved by the U.S. Food and Drug Administration (FDA) for genetic testing for HCM, nor are any kits being actively manufactured and marketed for distribution. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. While FDA has technical authority to regulate home-brew tests, there is currently no active oversight or any known plans to begin oversight. Home-brew tests may be developed using reagents prepared in-house or, if available, commercially manufactured analyte-specific reagents (ASRs). ASRs are single reagents "intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens" and must meet certain FDA criteria but are not subject to premarket review.

MEDICAL POLICY CRITERIA

I. 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 and a known pathogenic HCM gene mutation.

II. 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.

III. 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.

*Note: First-degree relatives: parents, siblings, and children of an individual

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This policy is based primarily on a 2010 TEC Assessment[18] that considered whether genetic testing for patients at risk for hypertrophic cardiomyopathy (HCM) improves outcomes. The TEC report reviewed the evidence on the accuracy of genetic testing in identifying patients who will subsequently develop HCM. Seven studies were identified that met the inclusion criteria for review.[19-25]

Analytic and Clinical Validity

For predispositional genetic testing, the analytic validity (ability to detect or exclude a *specific* mutation identified in another family member) and clinical validity (ability to detect *any* pathologic mutation in a patient with HCM and exclude a mutation in a patient without HCM) were evaluated. The analytic validity is more relevant when there is a known mutation in the family, whereas the clinical validity is more relevant for individuals without a known mutation in the family.

The analytic sensitivity and specificity of sequence analysis for detecting mutations that cause HCM is estimated to be almost 100%; however this is based upon limited data provided by the manufacturer, from case series.[21,25-27] Therefore, in patients with a known mutation in the family, targeted genetic testing has high predictive value for both a positive (mutation detected) and a negative (mutation not detected) test result. A negative test indicates that the individual is free of the mutation, while a positive test indicates that the patient has the mutation and is at risk for developing HCM in the future.

The clinical validity of genetic testing for HCM is considerably lower than the analytic validity, ranging from 33-63%. Evidence on clinical sensitivity, also called the mutation detection rate, consists of several case series of patients with established HCM.[19,20,22-24] This low detection rate may be due to testing methods, not-yet-identified HCM gene mutations, and nongenetic factors that mimic HCM.

The use of next-generation sequencing and whole-exome sequencing has the potential to substantially increase this sensitivity. Increased detection of mutations have been demonstrated in small numbers of patients,[28,29] but larger studies are not yet available to determine the magnitude of the improvement in clinical sensitivity.

Penetrance

The exact penetrance of HCM is unknown, with one review noting that not everyone with a deleterious mutation will develop manifestations of HCM.[30] However, a recent review indicated disease penetrance at approximately 100% with advanced age.[27] In addition, penetrance varies among different mutations and may even vary among different families with an identical pathologic mutation.[31,32]
As a result, it is not possible to accurately estimate the penetrance for any given mutation in a specific family. Therefore, the identification of an HCM gene mutation does not always confer a diagnosis of HCM.

Clinical Predictors of a Mutation

A study by Ingles et al. included 265 unrelated individuals with HCM, in which a total of 52% (138/265) had a mutation identified.[33] Mutations were more frequent in patients with an established family history of HCM than in those without a family history (72% vs 29%, $p<0.001$), and in those with a family history of sudden cardiac death (SCD) (89% vs 59%, $p<0.001$). Other predictors of finding a pathogenic mutation were female gender and increased left ventricular (LV) wall thickness.

A second study by Gruner et al. derived a score for predicting the likelihood of finding a mutation, called the Toronto Hypertrophic Cardiomyopathy Genotype Score.[34] The score was developed using data from 471 consecutive patients referred for testing, of which 35% (163/471) were found to have a mutation. Independent predictors of a mutation that were incorporated into the model were age at diagnosis, female gender, arterial hypertension, positive family history, LV wall morphology, and LV posterior wall thickness.

Multiple HCM Mutations

Multiple pathologic mutations are found in 1% to 10% of patients with HCM and are associated with more severe disease and a worse prognosis.[7,17] For these patients, targeted mutation analysis may miss additional HCM mutations. Some experts recommend comprehensive testing of all individuals for this reason; however, it is not known whether the presence of multiple pathologic mutations influences management decisions such that health outcomes might be improved.

Conclusion

In patients without a known familial HCM mutation, genetic testing provides little value in determining whether HCM will develop. For these patients, a negative gene test is not sufficient to rule out HCM and a positive genetic test is not sufficient for establishing the presence of clinical disease. Given that HCM is almost always inherited in an autosomal dominant fashion and is rarely spontaneous, genetic testing is most beneficial in families where there is an established clinical diagnosis of HCM and a known HCM mutation.

Clinical Utility

The 2009 TEC Assessment did not identify any studies which evaluated the impact of genetic testing on treatment decisions or health outcomes. In addition, no studies since the publication of the TEC report have evaluated the use of HCM genetic tests to improve management decisions or health outcomes.

Despite this lack of evidence, there are some benefits to predisposition genetic testing of at-risk individuals when there is a known mutation in the family. Inheritance of the predisposition to HCM can be ruled out with near certainty when the genetic test is negative (mutation not detected) in this circumstance. A positive test result (mutation detected) is less useful. It confirms the presence of a pathologic mutation and an inherited predisposition to HCM but does not establish the presence of the disease. It is possible that surveillance for HCM may be increased after a positive test, but the changes in management are not standardized.

Knowledge of the results of genetic testing may aid in decision making on such issues as reproduction by providing information on the susceptibility to develop future disease. Direct evidence on the impact of genetic information on this type of decision making is lacking, and the effect of such decisions on health outcomes is uncertain.

Clinical Practice Guidelines and Position Statements

American College of Cardiology (ACC) Foundation/American Heart Association (AHA)[35]

In 2011, the ACC Foundation and the AHA issued joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy. The following recommendations were issued concerning genetic testing:

- Class I indications: Procedure/treatment should be performed/administered
    - Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM
    - Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient
    - Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM
    - 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 be the cause

- Class IIa indications: Additional studies with focused objectives are needed

  Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM

- Class IIb indications: Additional studies with broad objectives needed; additional registry data would be helpful.

  The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain

- Class III indications: No Benefit
    - Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation
    - Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM

All ACC/AHA recommendations were given a Level B recommendation, indicating limited populations were evaluated and the recommendation was based on a single randomized trial or nonrandomized studies.

Heart Rhythm Society and the European Heart Rhythm Association (HRS/EHRA)[36]

In 2011, the Heart Rhythm Society and the European Heart Rhythm Association published recommendations for genetic testing for cardiac channelopathies and cardiomyopathies based upon expert consensus. For hypertrophic cardiomyopathy, the following recommendations were made:

- 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.
- Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case.

Summary

For individuals at risk for hypertrophic cardiomyopathy (HCM), genetic testing is most useful when there is a known mutation in the family. For these patients, 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. Therefore, genetic testing may be considered medically necessary for first-degree relatives of individuals with a known pathologic mutation.

For at-risk individuals without a known mutation in the family, the evidence does not permit conclusions regarding the impact of HCM genetic testing on health outcomes because there is not a clear relationship between testing and improved outcomes. Therefore, genetic testing is considered investigational in patients where a familial HCM mutation is unknown.

For at-risk individuals who have a family member with HCM, who tests negative for pathologic mutations, genetic testing is considered not medically necessary because a positive mutation in an asymptomatic at-risk patient does not necessarily confer a diagnosis of HCM.

REFERENCES

1. Ramaraj, R. Hypertrophic cardiomyopathy: etiology, diagnosis, and treatment. *Cardiol Rev*. 2008;16:172-80. PMID: 18562807
2. Alcalai, R, Seidman, JG, Seidman, CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. *J Cardiovasc Electrophysiol*. 2008;19:104-10. PMID: 17916152
3. Marian, AJ. Genetic determinants of cardiac hypertrophy. *Curr Opin Cardiol*. 2008;23:199-205. PMID: 18382207
4. Roberts, R, Sigwart, U. Current concepts of the pathogenesis and treatment of hypertrophic cardiomyopathy. *Circulation*. 2005;112:293-6. PMID: 16009810
5. Keren, A, Syrris, P, McKenna, WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. *Nat Clin Pract Cardiovasc Med*. 2008;5:158-68. PMID: 18227814
6. Maron, BJ, Maron, MS, Semsarian, C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *J Am Coll Cardiol*. 2012;60:705-15. PMID: 22796258
7. Cirino AL HC. Hypertrophic Cardiomyopathy: the genetic determinants of clinical disease expression. GeneReviews 2008. [cited 01/2009]; Available from: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hyper-card
8. Ghosh, N, Haddad, H. Recent progress in the genetics of cardiomyopathy and its role in the clinical evaluation of patients with cardiomyopathy. *Curr Opin Cardiol*. 2011 Mar;26(2):155-64. PMID: 21297463
9. Elliott, P, McKenna, WJ. Hypertrophic cardiomyopathy. *Lancet*. 2004;363:1881-91. PMID: 15183628
10. Maron, BJ, McKenna, WJ, Danielson, GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42:1687-713. PMID: 14607462

11. Arya, A, Bode, K, Piorkowski, C, et al. Catheter ablation of electrical storm due to monomorphic ventricular tachycardia in patients with nonischemic cardiomyopathy: acute results and its effect on long-term survival. *Pacing Clin Electrophysiol*. 2010;33:1504-9. PMID: 20636312
12. GeneDx® Personal Communication 2010.
13. Correlagan® Personal Communication 2010.
14. PGxHealth® Personal Communication 2010.
15. Das, KJ, Ingles, J, Bagnall, RD, Semsarian, C. Determining pathogenicity of genetic variants in hypertrophic cardiomyopathy: importance of periodic reassessment. *Genet Med*. 2013. PMID: 24113344
16. Andreasen, C, Nielsen, JB, Refsgaard, L, et al. New population-based exome data are questioning the pathogenicity of previously cardiomyopathy-associated genetic variants. *Eur J Hum Genet*. 2013;21:918-28. PMID: 23299917
17. Zou, Y, Wang, J, Liu, X, et al. Multiple gene mutations, not the type of mutation, are the modifier of left ventricle hypertrophy in patients with hypertrophic cardiomyopathy. *Mol Biol Rep*. 2013 Jun;40(6):3969-76. PMID: 23283745
18. TEC Assessment 2009. "Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy." BlueCross BlueShield Association Technology Evaluation Center, Vol. 24, Tab 11.
19. Harvard CardioGenomics website. 2010. [cited 11/2013]; Available from: http://cardiogenomics.med.harvard.edu/home
20. Erdmann, J, Daehmlow, S, Wischke, S, et al. Mutation spectrum in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy. *Clin Genet*. 2003;64:339-49. PMID: 12974739
21. Niimura, H, Bachinski, LL, Sangwatanaroj, S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. *N Engl J Med*. 1998 Apr 30;338(18):1248-57. PMID: 9562578
22. Olivotto, I, Girolami, F, Ackerman, MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2008;83:630-8. PMID: 18533079
23. Richard, P, Charron, P, Carrier, L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation*. 2003;107:2227-32. PMID: 12707239
24. Van Driest, SL, Ellsworth, EG, Ommen, SR, Tajik, AJ, Gersh, BJ, Ackerman, MJ. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. *Circulation*. 2003;108:445-51. PMID: 12860912
25. Watkins, H, McKenna, WJ, Thierfelder, L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med*. 1995 Apr 20;332(16):1058-64. PMID: 7898523
26. Seidman, SN, Orr, G, Raviv, G, et al. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. *J Clin Psychopharmacol*. 2009;29:216-21. PMID: 19440073
27. Pinto, YM, Wilde, AA, van Rijsingen, IA, Christiaans, I, Deprez, RH, Elliott, PM. Clinical utility gene card for: hypertrophic cardiomyopathy (type 1-14). *Eur J Hum Genet*. 2011;19. PMID: 21267010
28. D'Argenio, V, Frisso, G, Precone, V, et al. DNA sequence capture and next-generation sequencing for the molecular diagnosis of genetic cardiomyopathies. *J Mol Diagn*. 2014 Jan;16(1):32-44. PMID: 24183960

29. Mook, OR, Haagmans, MA, Soucy, JF, et al. Targeted sequence capture and GS-FLX Titanium sequencing of 23 hypertrophic and dilated cardiomyopathy genes: implementation into diagnostics. *J Med Genet*. 2013;50:614-26. PMID: 23785128
30. Charron, P, Carrier, L, Dubourg, O, et al. Penetrance of familial hypertrophic cardiomyopathy. *Genet Couns*. 1997;8(2):107-14. PMID: 9219008
31. Fananapazir, L, Epstein, ND. Genotype-phenotype correlations in hypertrophic cardiomyopathy. Insights provided by comparisons of kindreds with distinct and identical beta-myosin heavy chain gene mutations. *Circulation*. 1994 Jan;89(1):22-32. PMID: 8281650
32. Page, SP, Kounas, S, Syrris, P, et al. Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. *Circ Cardiovasc Genet*. 2012;5:156-66. PMID: 22267749
33. Ingles, J, Sarina, T, Yeates, L, et al. Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy. *Genet Med*. 2013;15:972-7. PMID: 23598715
34. Gruner, C, Ivanov, J, Care, M, et al. Toronto hypertrophic cardiomyopathy genotype score for prediction of a positive genotype in hypertrophic cardiomyopathy. *Circ Cardiovasc Genet*. 2013;6:19-26. PMID: 23239831
35. Gersh, BJ, Maron, BJ, Bonow, RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:2761-96. PMID: 22068435
36. 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*. 2011;8:1308-39. PMID: 21787999

CROSS REFERENCES

Genetic Testing for Cardiac Ion Channelopathies, Genetic Testing, Policy No. 07

CODES	NUMBER	DESCRIPTION
CPT	81403	Tier 2 Molecular Pathology Procedures; Level 4
	81405	Tier 2 Molecular Pathology Procedures; Level 6
	81406	Tier 2 Molecular Pathology Procedures; Level 7
	81407	Tier 2 Molecular Pathology Procedures; Level 8
	81479	Unlisted molecular pathology procedure
HCPCS	S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
	S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family