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## Hypertrophic Cardiomyopathy Genetic Testing

### Background:

Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium that is characterized by unexplained left ventricular hypertrophy (LVH) in a non-dilated ventricle. Distinctive findings of myocardial hypertrophy with myocyte disarray are the histopathologic hallmarks of this disorder. The clinical spectrum of HCM is diverse, ranging from asymptomatic individuals to those with disabling symptoms of heart failure, exercise intolerance, and chest pain. HCM is also associated with an increased risk of sudden cardiac death.

Genetic studies have defined HCM as a disease of the sarcomere — caused by mutations in any of a dozen genes that encode different elements of the contractile apparatus in cardiac myocytes. To date, over 700 individual mutations have been identified. With a prevalence estimated to be ~1/500 in the general population, HCM is the most common monogenic cardiac disorder and is inherited in an autosomal dominant mode. In addition, defects in genes involved in storage diseases, such as *LAMP2*, *PRKAG2* and *GLA*, typically cause systemic disease but may also result in predominant cardiac manifestations, which can mimic hypertrophic cardiomyopathy (HCM).

Echocardiographic evidence of unexplained left ventricular hypertrophy typically forms the basis for establishing the clinical diagnosis of HCM, however this finding fails to identify all affected individuals. Although the gene mutation responsible for causing HCM is inherited at the time of conception, it may take decades before there is clinically evident expression of LVH. Therefore, making the clinical diagnosis of HCM early in life may be a particular challenge.

### HCM Testing

**Genes:** *MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC*, *MYL2*, *MYL3*, *LAMP2*, *PRKAG2*, *GLA*

**Methodology:** A combination of oligonucleotide hybridization-based DNA sequencing using the Affymetrix GeneChip® platform and dideoxy-based DNA sequencing of the coding regions and splice sites of all genes.

**Analytical Sensitivity:** 98%

**Clinical Sensitivity:** 51%

### Turnaround Times:

- HCM CardioChip: 5 weeks
- Any single gene test: 3 weeks
- Familial mutation testing: 2 weeks

**Sample Requirements:** 7cc's blood in a K<sub>3</sub>EDTA (purple top) tube

### Costs:

- HCM CardioChip: \$3,000
- *MYH7* Gene Sequencing: \$1,700
- *MYBPC3* Gene Sequencing: \$1,500
- *TNNT2* Gene Sequencing: \$1,000
- *TNNI3* Gene Sequencing: \$700
- *TPM1* Gene Sequencing: \$700
- *ACTC* Gene Sequencing: \$700
- *MYL2* Gene Sequencing: \$700
- *MYL3* Gene Sequencing: \$700
- Familial mutation test: \$250

In addition to confirming the diagnosis of HCM in patients with clinically evident disease, genetic testing allows for early identification and diagnosis of individuals at greatest risk for developing HCM, prior to the expression of typical clinical manifestations (e.g. LVH). If a mutation is identified in such a preclinical individual, regular and serial outpatient follow up is indicated. Referral to a cardiologist with specific expertise in the management of HCM is highly recommended for patients with established disease as well as family members who are found to have a positive genetic test. Long term follow-up is necessary to survey for the development of clinical manifestations as well as to optimize treatment. If clinically unaffected members of a family with an identified causal mutation for HCM are found not to carry that mutation (genotype negative), they can be definitively diagnosed as unaffected with HCM and reassured that neither they nor their children will be at higher risk compared to the general population to develop this disorder. Serial follow up is no longer needed.

Based on previous testing of the top 8 HCM genes (*MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*, *TPM1*, *ACTC*, *MYL2*, *MYL3*) in 750 cases in the Laboratory for Molecular Medicine, the likelihood of identifying an HCM mutation in a patient with features of HCM is approximately 51% (40% for isolated cases and 66% for cases with a positive family history of either HCM or sudden cardiac death). Our new test, the **HCM CardioChip**, sequences 11 genes (*MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*, *TPM1*, *ACTC*, *MYL2*, *MYL3*, *LAMP2*, *PRKAG2*, *GLA*) known to cause HCM using a novel method of DNA sequencing.

**Synonyms (OMIM#192600):**

- VENTRICULAR HYPERTROPHY, HEREDITARY
- ASYMMETRIC SEPTAL HYPERTROPHY; ASH
- HYPERTROPHIC SUBAORTIC STENOSIS, IDIOPATHIC; IHSS
- CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC; FHC
- CMH1, CMH2, CMH3, CMH4, CMH5, CMH6, CMH7, CMH8, CMH10

**HCM Genes**

Gene	Name	OMIM#	Locus
<i>MYH7</i>	myosin, heavy chain 7	160760	14q12
<i>MYBPC3</i>	myosin-binding protein c, cardiac	600958	11p11.2
<i>TNNT2</i>	troponin t2, cardiac	191045	1q32
<i>TNNI3</i>	troponin i, cardiac	191044	19q13.4
<i>TPM1</i>	tropomyosin 1	191010	15q22.1
<i>ACTC</i>	actin, alpha, cardiac muscle	102540	15q14
<i>MYL2</i>	myosin regulatory light chain	160781	12q23-q24.3
<i>MYL3</i>	myosin essential light chain, cardiac	160790	3p
<i>LAMP2</i>	lysosomal associated membrane protein 2	309060	Xq24
<i>PRKAG2</i>	5-AMP-activated protein kinase, gamma-2 subunit	602743	7q35-q36
<i>GLA</i>	alpha-galactosidase a	301500	Xq22

**Epidemiology:** Approximately 1/500

- Males and females are affected in equal frequency
- No known racial predilection

**Clinical Symptoms and Features (variable, and may not occur in every patient):**

- Left Ventricular Hypertrophy (LVH)
- Electrocardiographic (EKG) changes
- Shortness of breath, chest pain, exercise intolerance

- Increased risk of Sudden Cardiac Death (SCD)

**Inheritance Pattern:** Autosomal dominant

- The presence of a pathogenic mutation in one copy of the above listed genes is sufficient to cause HCM
- Children of an affected individual with an identified pathogenic mutation have a 50% risk of inheriting the same mutation

**Test Indications:**

- Patients with clinical features of HCM
- Parents, siblings, and possibly children of a patient diagnosed with a mutation in one of the HCM genes
- Prenatal testing when a parent or child is diagnosed with HCM and has an identified sarcomere gene mutation

**Test Outcomes:**

- The detection of a pathogenic mutation will offer a definitive diagnosis for an affected patient
- Referral to a cardiology center with expertise in the management of hypertrophic cardiomyopathy is highly recommended

**Turn-Around-Times:**

- HCM CardioChip: 5 weeks
- Any single gene test: 3 weeks
- Familial mutation testing: 2 weeks

**Methodology:** The HCM CardioChip Test is performed by a combination of oligonucleotide hybridization-based DNA sequencing of the coding regions and splice sites of the *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC*, *MYL2*, *MYL3*, *LAMP2*, *PRKAG2*, and *GLA* genes using a custom design on the Affymetrix GeneChip platform as well as dideoxy-based DNA sequencing of the coding regions and splice sites of *MYBPC3*. This test does not detect all mutations in non-coding regions that could affect gene expression or deletions encompassing a large portion of the gene.

**Analytical Sensitivity:** The HCM CardioChip Test detects over 98% of HCM-causing mutations in the 11 genes tested.

**Clinical Sensitivity:** Based on results from the first 750 cases tested in the Laboratory for Molecular Medicine, the likelihood of identifying an HCM mutation in one of the 8 sarcomere genes (*MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC*, *MYL2*, *MYL3*), in a patient with features of HCM, is approximately 51% (40% for isolated cases and 66% for cases with a positive family history of either HCM or sudden cardiac death).

**Cost and CPT Codes:**

HCM CardioChip (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC*, *MYL2*, *MYL3*, *LAMP2*, *PRKAG2*, *GLA*):

- Cost: \$3,000
- CPT codes: 83891(1), 83892(1), 83898(165), 83904(25), 83909(1), 83894(1), 88386(1)

*MYH7* Gene Sequencing

- Cost: \$1,700

- CPT codes: 83891(1), 83894(1), 83898(28), 83904(28), 83909(1), 83912(1)

*MYBPC3* Gene Sequencing

- Cost: \$1,500
- CPT codes: 83891(1), 83894(1), 83898(25), 83904(25), 83909(1), 83912(1)

*TNNT2* Gene Sequencing

- Cost: \$1,000
- CPT codes: 83891(1), 83894(1), 83898(15), 83904(15), 83909(1), 83912(1)

*TNNI3* Gene Sequencing

- Cost: \$700
- CPT codes: 83891(1), 83894(1), 83898(8), 83904(8), 83909(1), 83912(1)

*TPM1* Gene Sequencing

- Cost: \$700
- CPT codes: 83891(1), 83894(1), 83898(11), 83904(11), 83909(1), 83912(1)

*ACTC* Gene Sequencing

- Cost: \$700
- CPT codes: 83891(1), 83894(1), 83898(6), 83904(6), 83909(1), 83912(1)

*MYL2* Gene Sequencing

- Cost: \$700
- CPT codes: 83891(1), 83894(1), 83898(6), 83904(6), 83909(1), 83912(1)

*MYL3* Gene Sequencing

- Cost: \$700
- CPT codes: 83891(1), 83894(1), 83898(6), 83904(6), 83909(1), 83912(1)

Testing for Known Familial Mutation

- Cost: \$250
- CPT codes: 83891(1), 83894(1), 83898(1), 83904(1), 83909(1), 83912(1)