

## Overview

### Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hypertrophic cardiomyopathy (HCM)

Establishing a diagnosis of a hereditary HCM, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

### Genetics Test Information

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate the genes tested on this panel.

[Prior Authorization](#) is available for this assay; see Special Instructions.

### Highlights

This test uses next-generation sequencing to test for variants in the *ACTC1*, *ACTN2*, *ANKRD1*, *CAV3*, *CSRP3*, *DES*, *GLA*, *LAMP2*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *MYLK2*, *MYOZ2*, *NEXN*, *PLN*, *PRKAG2*, *RAF1*, *TCAP*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*, *TTN* (excluding the following genomic regions: Chr2(GRCh37):g. 179523879-179524002 and Chr2(GRCh37):g. 179523712-179523835), *TTR*, and *VCL* genes.

This test uses Sanger sequencing to test for variants in exon 27 of the *MYH7* gene.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Hypertrophic Cardiomyopathy Multi-Gene Panel Prior Authorization Ordering Instructions](#)
- [Hereditary Cardiomyopathies and Arrhythmias: Patient Information](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

### Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and supplemental Sanger Sequencing

### NY State Available

Yes

## Specimen

### Specimen Type

Whole Blood EDTA

### Advisory Information

[Targeted testing for familial variants \(also called site-specific or known mutation testing\) is available for the genes on](#)

[this panel. See:](#)

- KVAR1 / Known Variant Analysis-1 Variant, Varies
- KVAR2 / Known Variant Analysis-2 Variants, Varies
- KVAR3 / Known Variant Analysis-3+ Variants, Varies

Call 800-533-1710 to confirm the appropriate test for targeted testing.

**Necessary Information**

1. [Hereditary Cardiomyopathies and Arrhythmias: Patient Information \(T725\)](#) is required, see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.
2. Include physician name and phone number with specimen.

**Specimen Required**

**Container/Tube:** Lavender top (EDTA)

**Specimen Volume:** 3 mL

**Collection Instructions:** Send specimen in original tube.

**Additional Information:** Prior Authorization is available for this test. **Submit the required form with the specimen.**

**Forms**

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing-Spanish](#) (T826)

3. [Hypertrophic Cardiomyopathy Multi-Gene Panel Prior Authorization Ordering Instructions](#) in Special Instructions

4. If not ordering electronically, complete, print, and send a [Cardiovascular Test Request Form](#) (T724) with the specimen.

**Specimen Minimum Volume**

1 mL

**Reject Due To**

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Ambient (preferred)		
	Refrigerated		

## Clinical and Interpretive

### Clinical Information

The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC).

The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other cardiac or systemic causes that may cause hypertrophy of the heart muscle, such as longstanding, uncontrolled hypertension or aortic stenosis. The pathological hallmark of HCM is "myocyte disarray" where there is a loss of parallel alignment of myocytes in the heart wall. HCM is most often caused by genes encoding the cardiac sarcomere, the functional contractile unit of the heart muscle. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals, but can cause life-threatening arrhythmias, which increase the risk of sudden cardiac death. The incidence of HCM in the general population is approximately 1 in 500. Inheritance is autosomal dominant, but compound heterozygosity (biallelic variants in the same gene) and digenic inheritance (variants in 2 different HCM-associated genes) do occur.

The *MYBPC3*, *MYL2*, *MYL3*, *MYH7*, *ACTC*, *TPM1*, *TNNI3*, *TNNT2*, and *CAV3* genes are involved in formation and regulation of the cardiac sarcomere, and account for the majority of variants in HCM. Left ventricular hypertrophy can also be caused by metabolic or storage disorders such as Fabry disease (*GLA* gene), Danon disease (*LAMP2* gene), and Wolf-Parkinson-White syndrome associated with variants in the *PRKAG2* gene. The *TTR* gene causes familial transthyretin amyloidosis, which is characterized by buildup of amyloid protein that affects the peripheral and autonomic nervous system. Other nonneuropathic changes may also be involved, including cardiomyopathy. See table for details regarding the genes tested by this panel and associated diseases.

### Genes included in the Hypertrophic Cardiomyopathy Multi-Gene Panel

Gene	Protein	Inheritance	Disease Association
<i>ACTC1</i>	Actin, alpha, cardiac muscle	AD	CHD, DCM, HCM, LVNC
<i>ACTN2</i>	Actinin, alpha-2	AD	DCM, HCM
<i>ANKRD1</i>	Ankyrin repeat domain-containing protein 1	AD	HCM, DCM
<i>CAV3</i>	Caveolin 3	AD, AR	HCM, LQTS, LGMD, Tateyama-type distal myopathy, rippling muscle disease
<i>CSRP3</i>	Cysteine-and glycine-rich protein 3	AD	HCM, DCM

<i>DES</i>	Desmin	AD, AR	DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD
<i>GLA</i>	Galactosidase, alpha	X-linked	Fabry disease
<i>LAMP2</i>	Lysosome-associated membrane protein 2	X-linked	Danon disease
<i>MYBPC3</i>	Myosin-binding protein-C, cardiac	AD	HCM, DCM
<i>MYH7</i>	Myosin, heavy chain 7, cardiac muscle, beta	AD	HCM, DCM, LVNC, myopathy
<i>MYL2</i>	Myosin, light chain 2, regulatory, cardiac, slow	AD	HCM
<i>MYL3</i>	Myosin, light chain 3, alkali, ventricular, skeletal, slow	AD, AR	HCM
<i>MYLK2</i>	Myosin light chain kinase 2	AD	HCM
<i>MYOZ2</i>	Myozenin 2	AD	HCM
<i>NEXN</i>	Nexilin	AD	HCM, DCM
<i>PLN</i>	Phospholamban	AD	HCM, DCM
<i>PRKAG2</i>	Protein kinase, amp-activated, noncatalytic, gamma2	AD	HCM, Wolff-Parkinson-White syndrome
<i>RAF1</i>	V-RAF-1 murine leukemia viral oncogene homolog 1	AD	Noonan/multiple lentigines syndrome
<i>TCAP</i>	Titin-cap (telethonin)	AD, AR	HCM, DCM, LGMD
<i>TNNC1</i>	Troponin C, slow	AD	HCM, DCM
<i>TNNI3</i>	Troponin I, cardiac	AD, AR	DCM, HCM, RCM
<i>TNNT2</i>	Troponin T2, cardiac	AD	HCM, DCM, RCM, LVNC
<i>TPM1</i>	Tropomyosin 1	AD	HCM, DCM, LVNC
<i>TTN</i>	Titin	AD, AR	HCM, DCM, myopathy
<i>TTR</i>	Transthyretin	AD	Transthyretin-related amyloidosis
<i>VCL</i>	Vinculin	AD	HCM, DCM

Abbreviations: Congenital heart defects (CHD), long QT syndrome (LQTS), limb-girdle muscular dystrophy (LGMD), autosomal dominant (AD), autosomal recessive (AR)

### Reference Values

An interpretive report will be provided.

### Interpretation

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Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

## Cautions

### Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of a hereditary hypertrophic cardiomyopathy or a related disorder.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a family history of hereditary hypertrophic cardiomyopathy or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual allows for more informative testing of at-risk individuals.

### Technical Limitations:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false-negative or false-positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, less than 6 weeks from time of sample collection) heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA.

### Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with a genetics professional should be considered for interpretation of this result.

A list of benign and likely benign variants detected for this patient is available from the laboratory upon request.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient's results.

## Clinical Reference

1. Cirino AL, Ho C: Hypertrophic Cardiomyopathy Overview. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle. 1993-2018. Updated 2014 Jan 16. Accessed June 2018. Available at [www.ncbi.nlm.nih.gov/books/NBK1768/](http://www.ncbi.nlm.nih.gov/books/NBK1768/)
2. Callis TE, Jensen BC, Weck KE, Willis MS: Evolving molecular diagnostics for familial cardiomyopathies: at the heart of it all. *Expert Rev Mol Diagn* 2010 April;10:3:329-351

3. Marian AJ, Roberts R: Molecular genetics of hypertrophic cardiomyopathy. *Ann Rev Med* 1995;46:213-222
4. van Rijsingen IA, Hermans-van Ast JF, Arens YH, et al: Hypertrophic cardiomyopathy family with double-heterozygous mutations; does disease severity suggest double heterozygosity? *Neth Heart J* 2009;17:458-463
5. Woo A, Rakowski H, Liew JC, et al: Mutations of the beta myosin heavy chain gene in hypertrophic cardiomyopathy: critical functional sites determine prognosis. *Heart* 2003;89:1179-1185
6. 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(9):1687-1713
7. Ackerman MJ, Priori SG, Willems S, et al: HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm* 2011;8:1308-1339

## Performance

### Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline. Supplemental and confirmatory Sanger sequencing are performed when necessary. (Unpublished Mayo method)

The following genes are evaluated in this multigene panel: *ACTC1, ACTN2, ANKRD1, CAV3, CSRP3, DES, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, MYLK2, MYOZ2, NEXN, PLN, PRKAG2, RAF1, TCAP, TNNC1, TNNT1, TNNT2, TPM1, TTN* (excluding the following genomic regions: Chr2(GRCh37):g. 179523879-179524002 and Chr2(GRCh37):g. 179523712-179523835), *TTR*, and *VCL*.

### PDF Report

No

### Day(s) and Time(s) Test Performed

Monday; Varies

### Analytic Time

4 weeks after prior authorization approved

### Maximum Laboratory Time

6 weeks

### Specimen Retention Time

Extracted DNA: 2 months

### Performing Laboratory Location

Rochester

## Fees and Codes

### Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

### Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

### CPT Code Information

81439

### LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HCMGP	Hypertrophic Cardiomyopathy Panel,B	In Process

Result ID	Test Result Name	Result LOINC Value
36806	Gene(s) Evaluated	48018-6
36807	Result Summary	50397-9
36808	Result Details	82939-0
36809	Interpretation	69047-9
36944	Additional Information	48767-8
36945	Method	49549-9
36946	Disclaimer	62364-5
36810	Reviewed by	18771-6

### Prior Authorization

Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.