MAYO CLINIC LABORATORIES

Test Definition: CCMGG

Comprehensive Cardiomyopathy Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of cardiomyopathy

Establishing a diagnosis of a hereditary form of cardiomyopathy

Genetics Test Information

This test utilizes next next-generation sequencing to detect single nucleotide and copy number variants in 83 genes associated with hereditary forms of cardiomyopathy: *ABCC9*, *ACAD9*, *ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, BAG3, BRAF, CDH2, CPT2, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, ELAC2, EMD, FHL1, FKRP, FKTN, FLNC, GAA, GLA, HCN4, HRAS, JPH2, JUP, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYLK3, MYPN, NEXN, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SGCD, SHOC2, SLC22A5, SOS1, SOS2, TAZ (TAFAZZIN), TBX20, TCAP, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRIM63, TTN, TTR*, and *VCL*. See Targeted Genes and Methodology Details for Comprehensive Cardiomyopathy Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for hereditary forms of cardiomyopathy.

Prior Authorization is available for this assay.

Special Instructions

- Informed Consent for Genetic Testing
- Hereditary Cardiomyopathies and Arrhythmias: Patient Information
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Comprehensive Cardiomyopathy Gene Panel
- Comprehensive Cardiomyopathy Panel (CCMGG) Prior Authorization Ordering Instructions

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH/ Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

Prior Authorization is available, **but not required**, for this test. If proceeding with the prior authorization process, submit the required form with the specimen.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated

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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Hereditary Cardiomyopathies and Arrhythmias Patient Information
3. Comprehensive Cardiomyopathy Panel (CCMGG) Prior Authorization Ordering 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 at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by either inherited, genetic factors or 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, 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 or AC), and left ventricular noncompaction (LVNC).(1)

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 incidence of HCM in the general population is approximately 1:200 to 1:500, and it is estimated that 30% to 60% of cases can be attributed to a genetic etiology.(2) Hereditary forms of HCM are most often caused by genes encoding proteins of the cardiac sarcomere, the functional contractile unit of the heart muscle.

Hereditary forms of DCM are characterized by ventricular dilation with reduced cardiac performance in the absence of other cardiac or systemic causes that may cause dilation of the heart muscle, such as hypertension and ischemic heart disease. The incidence of DCM in the general population is approximately 1 in 2500, and it is estimated that approximately 50% of cases can be attributed to a genetic etiology.(3) Hereditary forms of DCM are most often caused by genes encoding proteins of the cardiac cytoskeleton and sarcomere.

LVNC is characterized by prominent trabeculations of the left ventricle with trabecular recesses extending into the ventricular cavity. The incidence of LVNC in the general population is estimated to be 1 in 5000.(3) It is currently unclear if LVNC represents a genetically distinct form of cardiomyopathy, as many familial cases of LVNC have been linked to the same genes associated with other forms of hereditary cardiomyopathies and many affected individuals also meet diagnostic criteria for DCM or HCM.(3,4)

Arrhythmogenic cardiomyopathy (ACM) is characterized by the presence of arrhythmogenic cardiac muscle in the absence of ischemic, hypertensive, or valvular cardiac disease. ARVC, the most well-defined form of ACM, is characterized by the breakdown of the myocardium and replacement of right ventricular muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. In some cases, there may also be left ventricular involvement. The prevalence of ARVC (genetic and acquired) is estimated to be 1 in 2000 to 1 in 5000 in the general population.(5)

Hereditary forms of cardiomyopathy may be an isolated finding or may be a feature of an underlying systemic condition.

Hereditary forms of cardiomyopathy can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Mitochondrial inheritance is also possible, however, genes associated with mitochondrial inheritance of cardiomyopathy are not assessed on this panel.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the 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 clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If

there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the Targeted Genes and Methodology Details for Comprehensive Cardiomyopathy Gene Panel for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(6) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

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 periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Hershberger RE, Givertz MM, Ho CY, et al: Genetic evaluation of cardiomyopathy-a heart failure society of America practice guideline. J Card Fail. 2018;24(5):281-302. doi: 10.1016/j.cardfail.2018.03.004
2. Ommen SR, Mital S, Burke MA, et al: 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: Executive Summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation. 2020;142(25):e533-e557. doi: 10.1161/CIR.0000000000000938
3. Bozkurt B, Colvin M, Cook J, et al: Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association [published correction appears in Circulation. 2016 Dec 6;134(23):e652]. Circulation. 2016;134(23):e579-e646. doi: 10.1161/CIR.0000000000000455
4. Aung N, Doimo S, Ricci F, et al: Prognostic significance of left ventricular noncompaction: Systematic review and

meta-analysis of observational studies. Circ Cardiovasc Imaging. 2020 Jan;13(1):e009712. doi: 10.1161/CIRCIMAGING.119.009712
5. Corrado D, Link MS, Calkins H: Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2017 Jan;376(1):61-72. doi: 10.1056/NEJMra1509267
6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions, and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletion-insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Comprehensive Cardiomyopathy Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ABCC9, ACAD9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, BAG3, BRAF, CDH2, CPT2, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, ELAC2, EMD, FHL1, FKRP, FKTN, FLNC, GAA, GLA, HCN4, HRAS, JPH2, JUP, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYLK3, MYPN, NEXN, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SGCD, SHOC2, SLC22A5, SOS1, SOS2, TAZ (TAFAZZIN), TBX20, TCAP, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRIM63, TTN, TTR,* and *VCL*

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81439

Prior Auhtorization
Insurance preauthorization is available for this testing; forms are available.

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.

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CCMGG	Comprehensive Cardiomyopathy Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
617184	Test Description	62364-5
617185	Specimen	31208-2
617186	Source	31208-2
617187	Result Summary	50397-9
617188	Result	82939-0
617189	Interpretation	69047-9
617190	Additional Results	82939-0
617191	Resources	99622-3
617192	Additional Information	48767-8

617193	Method	85069-3
617194	Genes Analyzed	48018-6
617195	Disclaimer	62364-5
617196	Released By	18771-6