# Test Definition: PMCMG

Postmortem Cardiomyopathy Gene Panel, Tissue

## Overview

### Useful For

Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to cardiomyopathy or with a personal or family history suggestive of a hereditary form of cardiomyopathy

Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide variants and deletions-insertions (delins) 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 Method Description for additional details.

Identification of a disease-causing variant may assist with familial risk assessment, screening, and genetic counseling for hereditary cardiomyopathies.

### Special Instructions

- Informed Consent for Genetic Testing
- Hereditary Cardiomyopathies and Arrhythmias: Patient Information
- Informed Consent for Genetic Testing for Deceased Individuals
- Informed Consent for Genetic Testing (Spanish)

### Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS)

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Ordering Guidance

This test is intended for use when whole blood is not available and formalin-fixed, paraffin-embedded tissue is the only available specimen. If whole blood is available, consider CCMGG / Comprehensive Cardiomyopathy Gene Panel, Varies.

## Specimen Required

**Specimen Type:** Tissue (FFPE)
**Container/Tube:** Tissue block
**Collection Instructions**: Submit a formalin-fixed, paraffin-embedded tissue block
**Additional Information:** Testing will be attempted on blocks of any age but may be canceled if adequate DNA concentration cannot be obtained.

## 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)
-Informed Consent for Genetic Testing for Deceased Individuals (T782)
2. Hereditary Cardiomyopathies and Arrhythmias Patient Information (T725)
3. If not ordering electronically, complete, print, and send a Cardiovascular Test Request (T724) with the specimen.

## Specimen Minimum Volume

See Specimen Required

## 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 | Ambient (preferred) | | |
| | Refrigerated | | |

# Clinical & Interpretive

## Clinical Information

Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (15-35 years of age), the incidence of SCD is between 1 to 2 per 100,000. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of sudden cardiac death, autopsy may identify a structural abnormality, such as a form of cardiomyopathy. Postmortem diagnosis of a hereditary cardiomyopathy may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members.

Cardiomyopathies are a group of disorders characterized by heart muscle disease. 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.

Left ventricular noncompaction 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 a 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 Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing (NGS) 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 as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test.

Deletions-insertions (delins) of 40 or more base pairs, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/duplication analysis is not performed due to technical limitations of the formalin-fixed paraffin-embedded specimen type.

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. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

Reclassification of Variants**:**
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

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;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;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;17(5):405-424. doi:10.1038/gim.2015.30
7. Fishman GI, Chugh SS, Dimarco JP, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-2348
8. Stattin EL, Westin IM, Cederquist K, et al. Genetic screening in sudden cardiac death in the young can save future lives. Int J Legal Med. 2016;130(1):59-66

## Performance

### Method Description

Next-generation sequencing (NGS) 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 20X. Sensitivity is estimated at above 99% for single nucleotide variants and above 94% for deletions-insertions (delins) less than 40 base pairs.

There may be regions of genes that cannot be effectively evaluated by sequencing as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test.(Unpublished Mayo method)

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
No

### Day(s) Performed
Varies

### Report Available
28 to 42 days

### Specimen Retention Time
FFPE tissue block: Client provided paraffin blocks (FFPE) will be returned to client after testing is complete; Extracted DNA: 3 months.

### Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

## 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

# Test Definition: PMCMG

Postmortem Cardiomyopathy Gene Panel, Tissue

## LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| PMCMG | Postmortem Cardiomyopathy Panel | In Process |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 620611 | Test Description | 62364-5 |
| 620612 | Specimen | 31208-2 |
| 620613 | Source | 31208-2 |
| 620614 | Result Summary | 50397-9 |
| 620615 | Result | 82939-0 |
| 620616 | Interpretation | 69047-9 |
| 620617 | Additional Results | 82939-0 |
| 620618 | Resources | 99622-3 |
| 620619 | Additional Information | 48767-8 |
| 620620 | Method | 85069-3 |
| 620621 | Genes Analyzed | 82939-0 |
| 620622 | Disclaimer | 62364-5 |
| 620623 | Released By | 18771-6 |