MAYO CLINIC LABORATORIES

Test Definition: PMCMP

Postmortem Cardiomyopathy Panel, Varies

Overview

Useful For

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

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

Genetics Test Information

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

Testing Algorithm

The following genomic regions are excluded due to lack of coverage by next-generation sequencing:
TTN gene: Chr2(GRCh37):g.179523879-179524002 and Chr2(GRCh37):g.179523712-179523835
MYH6 gene: Chr14(GRCh37):g.23859675-23859246
MYH7 gene: Chr14(GRCh37):g.23889034-23889463

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)

Highlights

This test is intended for use on postmortem samples (eg; formalin-fixed, paraffin-embedded [FFPE] tissue block) when whole blood is not available.

This test uses next-generation sequencing to test for variants in the *ABCC9, ACTC1, ACTN2, ANKRD1, BRAF, CAV3, CBL, CRYAB, CSRP3, DES, DSC2, DSG2, DSP, DTNA, GLA, HRAS, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAP2K1, MAP2K2, MYBPC3, MYH6* (excluding Chr14[GRCh37]:g.23859675-23859246), *MYH7* (Chr14[GRCh37]:g.23889034-23889463), *MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEXN, NRAS, PKP2, PLN, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN5A, SGCD, SHOC2, SOS1, TAZ, TCAP, TMEM43, 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 may aid in the postmortem diagnosis of hereditary cardiomyopathy. Identification of a pathogenic variant may assist with familial risk assessment, screening, and genetic counseling.

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing

NY State Available

Yes

Specimen

Specimen Type
Varies

Ordering Guidance
This test is intended for use when EDTA whole blood is not available and formalin-fixed paraffin-embedded (FFPE) tissue or blood spots are the only available samples. If EDTA whole blood is available, order CCMGP / Comprehensive Cardiomyopathy Multi-Gene Panel, Blood.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

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. Pathology report **must** accompany specimen in order for testing to be performed. Include physician name and phone number with the specimen.

Specimen Required
Preferred:
Specimen Type: Tissue
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.
Specimen Stability Information: Ambient (preferred)

Acceptable:
Specimen Type: Blood spot
Container/Tube: Whatman FTA Classic Card or Whatman Protein Saver 903 Card
Specimen Volume: 3-5 blood spots
Collection Instructions:
1. Completely fill at least 3 circles on the filter paper card.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.
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 in Special Instructions:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
-Informed Consent for Genetic Testing for Deceased Individuals (T782)
2. If not ordering electronically, complete, print, and send a Cardiovascular Test Request (T724) with the specimen.

Specimen Minimum Volume
Tissue: See Specimen Required
Blood Spots: 3

Reject Due To
No specimen should be rejected.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	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 (ages 15-35), the incidence of SCD is between 1 to 2 per 100,000 young individuals. 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.

The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathies are often caused by inherited, genetic, factors. When the identified structural or functional abnormality observed in a patient cannot be explained by acquired causes, genetic testing is commonly employed to identify a genetic underpinning. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC).

HCM is characterized by left ventricular hypertrophy in the absence of other causes, such as structural abnormalities, systemic hypertension, or physiologic hypertrophy due to rigorous athletic training (so-called "athlete's heart"). The incidence of HCM in the general population is approximately 1 in 500, and is most often caused by variants in genes encoding the components of the cardiac sarcomere. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals who harbor pathogenic HCM-associated variants, but can cause life-threatening arrhythmias that increase the risk of sudden cardiac death in other individuals.

DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias or conduction system disease, or thromboembolic disease (stroke). The incidence of DCM is likely higher than originally reported due to subclinical phenotypes and underdiagnosis, with recent estimates suggesting that DCM affects approximately 1 in every 250 people. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as "idiopathic" dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy.

Arrhythmogenic cardiomyopathy (also referred to as arrhythmogenic right ventricular cardiomyopathy/dyplasia) (ARVD or AC) is characterized by replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. Age of onset and severity are variable, but symptoms typically develop in adulthood. The incidence of AC is approximately 1 in 1,000 to 1 in 2,500.

LVNC is characterized by left ventricular hypertrophy and prominent trabeculations of the ventricular wall, giving a spongy appearance to the muscle wall. It is thought to be caused by the arrest of normal myocardial morphogenesis. Clinical presentation is highly variable, ranging from no symptoms to congestive heart failure and life-threatening arrhythmias. An increased risk of thromboembolic events is also present with LVNC. Approximately 67% of LVNC is considered familial.

Restrictive cardiomyopathy (RCM) is the rarest form of cardiomyopathy and is associated with abnormally rigid ventricular walls. Systolic function can be normal or near normal, but diastolic dysfunction is present. There are several nongenetic causes of RCM, but this condition can be familial as well, with the *TNNI3* gene accounting for the majority of inherited cases. The age at presentation for familial RCM ranges from childhood to adulthood, and there is an increased risk of sudden death associated with this condition.

Noonan syndrome is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, and characteristic facial dysmorphology. HCM is present in approximately 20% to 30% of individuals affected with Noonan syndrome. There are a number of disorders with significant phenotypic overlap with Noonan syndrome, including Costello syndrome, cardiofaciocutaneous (CFC) syndrome, and multiple lentigines syndrome (formerly called LEOPARD syndrome). Noonan syndrome and related disorders (also called the RASopathies) are caused by variants in genes involved in the RAS-MAPK signaling pathway. In some cases, variants in these genes may cause cardiomyopathy in the absence of other syndromic features.

Cardiomyopathy may also be caused by an underlying disease such as a mitochondrial disorder, a muscular dystrophy, or a metabolic storage disorder. In these cases, heart disease may be the first feature to come to attention clinically. The hereditary forms of cardiomyopathy are most frequently associated with an autosomal dominant form of inheritance, however X-linked and autosomal recessive forms of disease are also present. In some cases, compound heterozygous or homozygous variants may be present in genes typically associated with autosomal dominant inheritance, often leading to a more severe phenotype. Digenic variants (2 different heterozygous variants at separate genetic loci) in autosomal dominant genes have also been reported to occur in patients with severe disease (particularly HCM and ARVC).

The inherited cardiomyopathies display both allelic and locus heterogeneity, whereby a single gene may cause different forms of cardiomyopathy (allelic heterogeneity) and variants in different genes can cause the same form of cardiomyopathy (locus heterogeneity). This comprehensive cardiomyopathy panel includes sequence analysis of 55 genes and may be considered for individuals with HCM, DCM, AC, or LVNC, whom have had uninformative test results

from a more targeted, disease-specific test. This test may also be helpful when the clinical diagnosis is not clear, or when there is more than 1 form of cardiomyopathy in the family history. It is important to note that the number of variants of uncertain significance detected by this panel may be higher than for the disease-specific panels, making clinical correlation more difficult.

Genes included in the Postmortem Cardiomyopathy Panel

Gene	Protein	Inheritance	Disease Association
ABCC9	ATP-binding cassette, subfamily C, member 9	AD	DCM, Cantu syndrome
ACTC1	Actin, alpha, cardiac muscle	AD	CHD, DCM, HCM, LVNC
ACTN2	Actinin, alpha-2	AD	DCM, HCM
ANKRD1	Ankyrin repeat domain-containing protein 1	AD	HCM, DCM
BRAF	V-RAF murine sarcoma viral oncogene homolog B1	AD	Noonan/CFC/Costello syndrome
CAV3	Caveolin 3	AD, AR	HCM, LQTS, LGMD, Tateyama-type distal myopathy, rippling muscle disease
CBL	CAS-BR-M murine ecotropic retroviral transforming sequence homolog	AD	Noonan-like syndrome disorder
CRYAB	Crystallin, alpha-B	AD, AR	DCM, myofibrillar myopathy
CSRP3	Cysteine-and glycine-rich protein 3	AD	HCM, DCM
DES	Desmin	AD, AR	DCM, AC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD
DSC2	Desmocollin	AD, AR	AC, ARVC + skin and hair findings
DSG2	Desmoglein	AD	AC
DSP	Desmoplakin	AD, AR	AC, DCM, Carvajal syndrome
DTNA	Dystrobrevin, alpha	AD	LVNC, CHD
GLA	Galactosidase, alpha	X-linked	Fabry disease
HRAS	V-HA-RAS Harvey rat sarcoma viral oncogene homolog	AD	Costello syndrome
JUP	Junction plakoglobin	AD, AR	AC, Naxos disease
KRAS	V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog	AD	Noonan/CFC/Costello syndrome
LAMA4	Laminin, alpha-4	AD	DCM
LAMP2	Lysosome-associated member protein 2	X-linked	Danon disease
LDB3	LIM domain-binding 3	AD	DCM, LVNC, myofibrillar myopathy
LMNA	Lamin A/C	AD, AR	DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing)
MAP2K1	Mitogen-activated protein kinase	AD	Noonan/CFC

	kinase 1		
MAP2K2	Mitogen-activated protein kinase kinase 2	AD	Noonan/CFC
MYBPC3	Myosin-binding protein-C, cardiac	AD	HCM, DCM
MYH6	Myosin, heavy chain 6, cardiac muscle, alpha		HCM, DCM
MYH7	Myosin, heavy chain 7, cardiac muscle, beta	AD	HCM, DCM, LVNC, myopathy
MYL2	Myosin, light chain 2, regulatory, cardiac, slow	AD	HCM
MYL3	Myosin, light chain 3, alkali, ventricular, skeletal, slow	AD, AR	HCM
MYLK2	Myosin light chain kinase 2	AD	HCM
MYOZ2	Myozenin 2	AD	HCM
MYPN	Myopalladin	AD	HCM, DCM
NEXN	Nexilin	AD	HCM, DCM
NRAS	Neuroblastoma RAS viral oncogene homolog	AD	Noonan syndrome
PKP2	Plakophilin 2	AD	AC
PLN	Phospholamban	AD	HCM, DCM
PRKAG2	Protein kinase, AMP-activated, noncatalytic, gamma2	AD	HCM, Wolff-Parkinson-White syndrome
PTPN11	Protein-tyrosine phosphatase, nonreceptor-type, 11	AD	Noonan/CFC/LEOPARD syndrome
RAF1	V-RAF-1 murine leukemia viral oncogene homolog 1	AD	Noonan/LEOPARD syndrome
RBM20	RNA-binding motif protein 20	AD	DCM
RYR2	Ryanodine receptor 2	AD	AC, CPVT, LQTS
SCN5A	Sodium channel, voltage gated, type V, alpha subunit	AD	Brugada syndrome, DCM, heart block, LQTS, SSS, SIDS
SGCD	Sarcoglycan, delta	AD, AR	DCM, LGMD
SHOC2	Suppressor of clear, C. elegans, homolog of	AD	Noonan- like syndrome with loose anagen hair
SOS1	Son of sevenless, dropsophil, homolog 1	AD	Noonan syndrome
TAZ	Tafazzin	X-linked	Barth syndrome, LVNC, DCM
TCAP	Titin-cap (telethonin)	AD, AR	HCM, DCM, LGMD
TMEM43	Transmembrane protein 43	AD	AC, EMD
TNNC1	Troponin C, slow	AD	HCM, DCM
TNNI3	Troponin I, cardiac	AD, AR	DCM, HCM, RCM
TNNT2	Troponin T2, cardiac	AD	HCM, DCM, RCM, LVNC
TPM1	Tropomyosin 1	AD	HCM, DCM, LVNC
TTN	Titin	AD, AR	HCM, DCM, ARVC, myopathy
TTR	Transthyretin	AD	Transthyretin-related

			amyloidosis
VCL	Vinculin	AD	HCM, DCM

Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (AC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), congenital heart defect (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive (AR)

Reference Values

An interpretive report will be provided.

Interpretation

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

Sample Quality:
This test is intended for use when EDTA whole blood is not available and formalin-fixed, paraffin-embedded (FFPE) tissue or blood spots are the only available samples. DNA extracted from FFPE tissue can be degraded, which results in a higher failure rate (approximately 5%) for next-generation sequencing when compared to DNA extracted from whole blood. Due to the quality of DNA extracted from FFPE, the acceptable coverage threshold is lower than that of the equivalent blood assays. Coverage of at least 40X is expected for all regions assessed but may be adjusted on a case-by-case basis at the discretion of the laboratory director. Sanger sequencing may be used in regions that do not achieve this rate of coverage at the discretion of laboratory director. Genomic regions that are not sufficiently covered for analysis and interpretation will be indicated on the laboratory report. Sanger sequencing on DNA extracted from FFPE may also result in quality limitations when compared to testing on DNA extracted from blood.

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 used (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of a hereditary 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 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 variants 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.

For blood spot sample type: If the patient has had an allogeneic blood or marrow transplant or a recent (ie, <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.

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

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2. Semsarian C, Ingles J: Molecular autopsy in victims of inherited arrhythmias. J Arrhythm. 2016;32(5):359-365
3. 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
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6. McNally E, MacLeod H, Dellefave-Castillo L: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews. University of Washington, Seattle. 1993-2017. Updated 2014 Jan 9. Accessed 8/29/2017. Available at www.ncbi.nlm.nih.gov/books/NBK1131/
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8. Ichida F: Left ventricular noncompaction. Circ J. 2009;73(1):19-26
9. 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
10. 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
11. Hoedemaekers YM, Caliskan K, Michels M, et al: The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. Circ Cardiovasc Genet. 2010;3:232-239

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 or confirmatory Sanger sequencing is performed when necessary.(Unpublished Mayo method)

The following genes are evaluated in this multigene panel: *ABCC9, ACTC1, ACTN2, ANKRD1, BRAF, CAV3, CBL, CRYAB, CSRP3, DES, DSC2, DSG2, DSP, DTNA, GLA, HRAS, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAP2K1, MAP2K2, MYBPC3, MYH6* (Chr14[GRCh37]:g.23859675-23859246)*, MYH7* (Chr14[GRCh37]:g.23889034-23889463)*, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEXN, NRAS, PKP2, PLN, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN5A, SGCD, SHOC2, SOS1, TAZ, TCAP, TMEM43, TNNC1, TNNI3, 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) Performed

Monday

Report Available

6 to 8 weeks

Specimen Retention Time

Extracted DNA: 2 months; Client provided paraffin blocks (FFPE) will be returned to client after testing is complete.

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 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 US Food and Drug Administration.

CPT Code Information

81439

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value

PMCMP	Postmortem Cardiomyopathy Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
BA1407	Gene(s) Evaluated	48018-6
BA1409	Result Details	82939-0
BA1410	Interpretation	69047-9
BA1411	Additional Information	48767-8
BA1412	Method	85069-3
BA1413	Disclaimer	62364-5
BA1414	Reviewed by	18771-6
BA1408	Result Summary	50397-9