Test Definition: DCMGP

Dilated Cardiomyopathy Panel, B

Overview

Useful For

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

Establishing a diagnosis of a hereditary DCM, 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 features that allows for predictive testing of at-risk family members

Genetics Test Information

This test uses next generation sequencing to test for variants in the *ABCC9, ACTC1, ACTN2, ANKRD1, CRYAB, CSRP3, DES, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYPN, NEXN, PLN, RAF1, RBM20, SCN5A, SGCD, TAZ, 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 certain exons of the following genes:

MYH6 exon 26

MYH7 exon 27

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

Prior Authorization is available for this assay; see Special Instructions.

Special Instructions

- Informed Consent for Genetic Testing
- Dilated 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)

2. Dilated Cardiomyopathy Multi-Gene Panel Prior Authorization Ordering Instructions in Special Instruction

3. 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).

DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias, and conduction system disease, or thromboembolic disease (stroke). The most recent estimates of the incidence of DCM suggest that the condition affects approximately 1 in every 250 people. These estimates are higher than originally reported due to subclinical phenotypes and underdiagnosis. 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.

The majority of familial dilated cardiomyopathy is inherited in an autosomal dominant manner; however, autosomal recessive and X-linked forms have also been reported. At least 28 genes have been reported in association with DCM, including genes encoding the cardiac sarcomere and other proteins involved in proteins responsible for cardiac muscle contraction. Some genes associated with DCM also cause other forms of hereditary cardiomyopathy, cardiac channelopathies, skeletal myopathies, or metabolic defects. See table for details regarding the genes tested by this panel and associated diseases.

Genes included in the Dilated Cardiomyopathy Multi-Gene 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
CRYAB	Crystallin, alpha-B	AD, AR	DCM, myofibrillar myopathy
CSRP3	Cysteine-and glycine-rich protein 3	AD	HCM, DCM

DES	Desmin	AD, AR	DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD
LAMA4	Laminin, alpha-4	AD	DCM
LAMP2	Lysosome-associated membrane 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)
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
MYPN	Myopalladin	AD	HCM, DCM
NEXN	Nexilin	AD	HCM, DCM
PLN	Phospholamban	AD	HCM, DCM
RAF1	V-raf-1 murine leukemia viral oncogene homolog 1	AD	Noonan/multiple lentigines syndrome, DCM
RBM20	RNA-binding motif protein 20	AD	DCM
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
TAZ	Tafazzin	X-linked	Barth syndrome, LVNC, DCM
TCAP	Titin-CAP (Telethonin)	AD, AR	HCM, DCM, LGMD
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 right ventricular cardiomyopathy (ARVC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), congenital heart defects (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

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 dilated cardiomyopathy (DMC) 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 DMC 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. Hershberger RE, Kushner JD, Parks SB: Dilated Cardiomyopathy Overview. In GeneReviews. 2007. Available at www.genetests.org

2. Hunt SA, Abraham WT, Chin MH, et al: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. Circulation 2005;112:e154-e235

3. 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

4. Herman DS, Lam L, Taylor MR, et al: Truncations of titin causing dilated cardiomyopathy. N Engl J Med 2012;366(7):619-628

5. Dhandapany PS, Razzaque MA, Muthusami U, et al: *RAF1* mutations in childhood-onset dilated cardiomyopathy. Nat Genet 2014;46(6):635-639

6. Hershberger RE, Morales A: Dilated Cardiomyopathy Overview. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle. 1993-2018. Updated 2015 Sep 24. Accessed June 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1309/

7. Ackerman M, 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/or confirmatory Sanger sequencing is performed when necessary.(Unpublished Mayo method)

The following genes are evaluated in this multigene panel: *ABCC9, ACTC1, ACTN2, ANKRD1, CRYAB, CSRP3, DES, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYPN, NEXN, PLN, RAF1, RBM20, SCN5A, SGCD, TAZ, 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*.

PDF Report

No

Day(s) and Time(s) Test Performed

Wednesday; 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
DCMGP	Dilated Cardiomyopathy Panel, B	In Process

Result ID	Test Result Name	Result LOINC Value
36811	Gene(s) Evaluated	36908-2
36812	Result Summary	50397-9
36813	Result Details	82939-0
36814	Interpretation	69047-9
36947	Additional Information	48767-8
36948	Method	49549-9
36949	Disclaimer	62364-5
36815	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.