Overview

Useful For

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

Establishing a diagnosis of a hereditary cardiomyopathy 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 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 *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, MYH7, 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 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.

Special Instructions

- Informed Consent for Genetic Testing
- Comprehensive 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 assay; see Special Instructions. **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. Comprehensive Cardiomyopathy Multi-Gene Panel Prior Authorization Ordering Instructions in Special Instructions

3. If not ordering electronically, complete, print, and send a Cardiovascular Test Request (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
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 or AC), and left ventricular noncompaction (LVNC).

The hereditary form of 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 (athlete's heart). The incidence of HCM in the general population is approximately 1 in 500, and the hereditary form 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, but can also cause life-threatening arrhythmias that increase the risk of sudden cardiac death.

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 right ventricular dysplasia (ARVD or AC) is characterized by breakdown of the myocardium and 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 ARVC 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 (NS) 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 NS. There are a number of disorders with significant phenotypic overlap with NS, including Costello syndrome, cardiofaciocutaneous (CFC) syndrome, and multiple lentigines syndrome (formerly called LEOPARD syndrome). NS 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 systemic disease such as a mitochondrial disorder, a muscular dystrophy, or a metabolic storage disorder. In these cases, cardiomyopathy 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, ARVC, 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 Comprehensive 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
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 syndrome-like 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, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD
DSC2	Desmocollin	AD, AR	ARVC, ARVC + skin and hair findings
DSG2	Desmoglein	AD	ARVC
DSP	Desmoplakin	AD, AR	ARVC, 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	ARVC, 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 kinase 1	AD	Noonan/CFC
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 cahin 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	ARVC
PLN	Phospholamban	AD	HCM, DCM
PRKAG2	Protein kinase, AMP-activated, noncatalytic, gamma2	AD	HCM, Wolff-Parkinson-White syndrome
PTPN11	Proetin-tyrosine phosphatase, nonreceptor-type, 11	AD	Noonan/CFC/multiple lentigines syndrome
RAF1	V-RAF-1 murine leukemia viral oncogene homolog 1	AD	Noonan/multiple lentigines syndrome
RBM20	RNA-binding motif protein 20	AD	DCM
RYR2	Ryanodine receptor 2	AD	ARVC, 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 syndrome-like 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	ARVC, 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 right ventricular cardiomyopathy (ARVC), 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

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

2. 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/

3. McNally E, MacLeod H, Dellefave-Castillo L: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle. 1993-2018. Updated 2017 May 25. Accessed June 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1131/

4. Allanson JE, Roberts AE: Noonan Syndrome. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle1993--2018. Updated 2016 Feb 25. Accessed June 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1124/

5. Ichida F: Left ventricular noncompaction. Circ J 2009;73(1):19-26

6. 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

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

8. 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 and confirmatory Sanger sequencing are 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, MYH7, 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) 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
CCMGP	Cardiomyopathy Genetic Panel, B	In Process

Result ID	Test Result Name	Result LOINC Value
36801	Gene(s) Evaluated	36908-2
36802	Result Summary	50397-9
36803	Result Details	82939-0
36804	Interpretation	69047-9
36941	Additional Information	48767-8
36942	Method	49549-9
36943	Disclaimer	62364-5

Result ID	Test Result Name	Result LOINC Value
36805	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.