Test Definition: PMARG

Postmortem Arrhythmia Gene Panel, Tissue

Overview

Useful For

Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death suspicious for cardiac arrhythmia or with a personal or family history suggestive of a hereditary form of cardiac arrhythmia

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 44 genes associated with hereditary forms of cardiac arrhythmias: *ABCC9, ANK2, CACNA1C, CACNA1D, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CDH2, DES, DSC2, DSG2, DSP, EMD, FLNC, GNB5, HCN4, JUP, KCND2, KCND3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ8, KCNQ1, LMNA, NKX2-5, PKP2, PLN, PPA2, PRKAG2, RBM20, RYR2, SCN5A, SLC4A3, TECRL, TMEM43, TNNI3K*, *TRDN,* and *TTN*. See Method Description for additional details.

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

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 (FFPE) tissue is the only available specimen. If whole blood is available, consider CARGG / Comprehensive Arrhythmia Gene Panel, Varies

Targeted testing for familial variants (also called site-specific or known variants 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.

Specimen Required

Specimen Type: 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 young individuals. The reported incidence of SCD is likely an underestimate since more overt causes of death, such as car accidents and drownings, may result from arrhythmogenic events. In cases of sudden unexplained death where autopsy does not detect a structural basis for sudden death, a hereditary arrhythmia may be suspected.

Cardiac arrhythmias are a group of conditions characterized by abnormal heart rhythms. Arrhythmias can be caused by either genetic (inherited) factors or nongenetic (acquired) causes, such as medications and infection. Hereditary forms of cardiac arrhythmias for which this panel assesses include, but are not limited to, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and familial atrial fibrillation.(1) This gene panel also assesses genes associated with rarer, syndromic conditions in which cardiac arrhythmia is a major feature, such as Andersen-Tawil syndrome, Carvajal syndrome, Jervell and Lange-Nielsen syndrome, Naxos disease, Timothy syndrome, and Emery-Dreifuss muscular dystrophy.(1-3)

Inherited cardiac arrhythmias can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Genes associated with mitochondrial inheritance of cardiac arrhythmias are not assessed on this panel.

Postmortem diagnosis of a hereditary arrhythmia may assist in confirmation of the cause and manner of death as well as risk assessment in living family members.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) 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 providers 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.(4) 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. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al. Inherited cardiac arrhythmias. Nat Rev Dis Primers. 2020;6(1):58. doi:10.1038/s41572-020-0188-7
2. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8(8):1308-1339. doi:10.1016/j.hrthm.2011.05.020
3. Bonne G, Leturcq F, Ben Yaou R. Emery-Dreifuss muscular dystrophy. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated August 15, 2019. Accessed August 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1436/
4. 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.
5. Fishman GI, Chugh SS, DiMarco JP, et al. Sudden cardiac death prediction and prevention: report from the National

Heart, Lung and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-2348
6. Semsarian C, Ingles J. Molecular autopsy in victims of inherited arrhythmias. J Arrhythm. 2016;32(5):359-365
7. 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 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 NGS results by Sanger sequencing is typically not performed for this test.(Unpublished Mayo method)

Genes analyzed: *ABCC9, ANK2, CACNA1C, CACNA1D, CACNA2D1, CACNB2, CALM1, CALM2 , CALM3, CASQ2, CAV3, CDH2, DES, DSC2, DSG2, DSP, EMD, FLNC, GNB5, HCN4, JUP, KCND2, KCND3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ8, KCNQ1, LMNA, NKX2-5, PKP2, PLN, PPA2, PRKAG2, RBM20, RYR2, SCN5A, SLC4A3, TECRL, TMEM43, TNNI3K, TRDN,* and *TTN*

PDF Report

Supplemental

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

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PMARG	Postmortem Arrhythmia Gene Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
620583	Test Description	62364-5
620584	Specimen	31208-2
620585	Source	31208-2
620586	Result Summary	50397-9
620587	Result	82939-0
620588	Interpretation	69047-9
620589	Additional Results	82939-0
620590	Resources	99622-3
620591	Additional Information	48767-8
620592	Method	85069-3
620593	Genes Analyzed	82939-0
620594	Disclaimer	62364-5
620595	Released By	18771-6