MAYO CLINIC LABORATORIES

Test Definition: PMARP

Postmortem Arrhythmia Panel, Varies

Overview

Useful For

Providing a postmortem genetic evaluation in the setting of sudden unexplained death and suspicion for long QT or Brugada syndrome

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 *AKAP9, ANK2,CACNA1C, CACNA2D1, CACNB2, CAV3, GPD1L, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, SCN1B, SCN3B, SCN4B, SCN5A*, and *SNTA1* genes.

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 *AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CAV3, GPD1L, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, SCN1B, SCN3B, SCN4B, SCN5A,* and *SNTA1* genes.

This test may aid in the postmortem diagnosis of long QT or Brugada syndrome.

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 followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger 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 1 of the following: BRGGP / Brugada Syndrome Multi-Gene Panel, Blood or LQTGP / Long QT Syndrome 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

Acceptable:
Specimen Type: Blood spot
Container/Tube: Whatman FTA Classic Card or Whatman Protein Saver 903 Card
Specimen Volume: 4-5 blood spots
Collection Instructions:
1. Completely fill at least 3 circles on the filter paper card (approximately 80 microliters of blood per circle)
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)	0 hours	
	Frozen	0 hours	
	Refrigerated	0 hours	

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. 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. Brugada syndrome (BrS) and long QT syndrome (LQTS) are inherited forms of cardiac arrhythmia that may cause sudden cardiac death. 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.

BrS is a genetic cardiac disorder characterized by ST segment elevation in leads V1-V3 on electrocardiography (EKG) with a high-risk for ventricular arrhythmias that can lead to sudden cardiac death. BrS is inherited in an autosomal dominant manner and is caused by pathogenic variants in genes that encode cardiac ion channels. The diagnosis of BrS is established based on the characteristic EKG abnormality along with personal and family health history, and also requires exclusion of other causes including cardiac structural abnormalities, medications, and electrolyte imbalances. Genes associated with BrS include *CACNA1C, CACNA2D1, GPD1L, KCNE3, KCNJ8, SCN3B, CACNB2, SCN1B*, and *SCN5A.* Additional clinical information about BrS can be found in MCL's BRGGP / Brugada Syndrome Multi-Gene Panel, Blood test.

LQTS is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on EKG, and may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS. LQTS may also be associated with congenital profound bilateral sensorineural hearing loss, a condition

known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either the *KCNQ1* or *KCNE1* genes. Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the *CACNA1C* gene. Genes associated with LQTS include *AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A,* and *SNTA1*. Additional clinical information about LQTS can be found in MCL's ID LQTGP / Long QT Syndrome Multi-Gene Panel, Blood test.

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 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 mutations, deep intronic mutations). The absence of a variant, therefore, does not eliminate the possibility of long QT syndrome, Brugada syndrome, 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 long QT syndrome, Brugada syndrome 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 samples: 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

1. 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
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):59-664
4. 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

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: *AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CAV3, GPD1L, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, SCN1B, SCN3B, SCN4B, SCN5A,* and *SNTA1.*

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

81443

LOINC® Information

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

Result ID	Test Result Name	Result LOINC® Value
BA1399	Gene(s) Evaluated	48018-6
BA1400	Result Summary	50397-9
BA1401	Result Details	82939-0
BA1402	Interpretation	69047-9
BA1403	Additional Information	48767-8
BA1404	Method	85069-3
BA1405	Disclaimer	62364-5
BA1406	Reviewed by	18771-6