Test Definition: MITON

Mitochondrial Nuclear Gene Panel

Overview

Useful For

Diagnosis of the subset of mitochondrial disease that results from mutations in the nuclear-encoded genes

A second-tier test for patients in whom previous targeted gene mutation analyses for specific mitochondrial disease-related genes were negative

Identifying mutations within genes of the nuclear genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

Genetics Test Information

This test includes next-generation sequencing and Sanger sequencing to evaluate for the genes listed on the panel. See Targeted Genes Interrogated by Mitochondrial Nuclear Gene Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Testing Algorithm

If skin biopsy is received, fibroblast culture will be added and charged separately.

See Neuromuscular Myopathy Testing Algorithm in Special Instructions.

Special Instructions

- Muscle Biopsy Specimen Preparation
- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Targeted Genes Interrogated by Mitochondrial Nuclear Gene Panel
- Neuromuscular Myopathy Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing when appropriate

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

3. To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Cultured fibroblasts

Container/Tube: T-75 or T-25 flask

Specimen Volume: 1 full T-75 or 2 full T-25 flasks

Specimen Stability Information: Ambient (preferred)/Refrigerated <24 hours

Specimen Type: Skin biopsy

Supplies: Fibroblast Biopsy Transport Media (T115)

Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin. Tubes can be supplied upon request (Eagle's minimum essential medium with 1% penicillin and streptomycin [T115]).

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

Specimen Type: Tissue biopsy

Supplies: Muscle Biopsy Kit (T541)

Collection Instructions: Prepare and transport specimen per instructions in Muscle Biopsy Specimen Preparation in Special Instructions.

Additional Information: Muscle Biopsy Shipping Kits (T541) are available.

Specimen Volume: 10-80 mg

Specimen Stability Information: Frozen (preferred)/Ambient/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)

2. Molecular Genetics: Biochemical Disorders Patient Information (T527) in Special Instructions.

3. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

-Neurology Specialty Testing Client Test Request (T732)

-Inborn Errors of Metabolism Test Request (T798)

Specimen Minimum Volume

Blood: 1 mL
Tissue Biopsy: 200 mg

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical and Interpretive

Clinical Information

The mitochondrion occupies a unique position in eukaryotic biology. It is the site of energy metabolism, and it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to mutations in either the mitochondrial genome or nuclear mitochondrial genes has been

well characterized.

The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and be associated with widely varying severities. Due to the considerable overlap in the clinical phenotypes of various mitochondrial disorders, it is often difficult to distinguish these specific inherited disorders without genetic testing. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to analyze 176 nuclear-encoded genes implicated in mitochondrial disease. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from mutations in the nuclear encoded genes. This includes disorders of mitochondrial protein synthesis, disorders of coenzyme Q10 biosynthesis, disorders of the respiratory chain complexes and disorders of mtDNA maintenance (ie, mitochondrial DNA depletion disorders).

See Targeted Genes Interrogated by Mitochondrial Nuclear Gene Panel in Special Instructions for details regarding the targeted genes identified by this test.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:

A small percentage of individuals who have involvement of 1 of more of the genes on the panel may have a mutation that is not identified by the methods performed (eg, large deletions/duplications, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of a mitochondrial disease. Mutations responsible for mitochondrial disorders encoded by the mitochondrial genome will not be detected with this assay. For predictive testing of asymptomatic individuals, it is important to first document the presence of a gene mutation in an affected family member.

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.

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently unvalidated.

Unless reported or predicted to cause disease, alterations in protein coding genes that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon

request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review likely deleterious alterations or variants of uncertain significance that have been previously 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.

Clinical Reference

1. Richards CS, Nazneen A, 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 May;17(5):405-424

2. Munnich A, Rotig A, Cormier-Daire V, Rustin P: Chapter 99: Clinical presentation of respiratory chain deficiency. In The Metabolic and Molecular Bases of Inherited Disease. Available at: Scriver's The Online Metabolic and Molecular Basis of Inherited Disease (OMBBID). Edited by D Valle, AL Beaudet, B Vogelstein, et al. McGraw-Hill Medical. Retrieved 2013

3. Wong LJ: Molecular genetics of mitochondrial disorders. Dev Disabil Res Rev 2010 Jun;16(2):154-162

Performance

Method Description

Next-generation sequencing and/or Sanger sequencing is performed to test for the presence of a mutation in the following genes: *AARS2, AASS, ABAT, ABCB7, ACACA, ACAD9, ACO2, AFG3L2, AGK, AIFM1, ALDH3A2, AMPD1, APOPT1, APTX, ATP5A1, ATP5E, ATP5G3, ATPAF2, AUH, BCS1L, BOLA3, C12orf65, CA5A, CHAT, CLPP, COA5, COA6, COQ2, COQ4, COQ6, COQ8A (ADCK3), COQ8B (ADCK4), COQ9, COX10, COX14, COX15, COX20, COX4I2, COX6B1, COX7B, CYC1, D2HGDH, DARS2, DGUOK, DLAT, DLD, DNA2, DNAJC19, DNM1L, EARS2, ELAC2, ETFA, ETFB, ETFDH, ETHE1, FARS2, FASTKD2, FBXL4, FH, FOXRED1, FXN, GAMT, GARS, GCDH, GFER, GFM1, HARS2, HIBCH, IARS2, IBA57, IDH2, ISCU, L2HGDH, LARS2, LIAS, LRPPRC, LYRM4, LYRM7, MARS2, MGME1, MICU1, MPC1, MPV17, MRPL3, MRPL44, MRPS16, MRPS22, MTFMT, MTO1, MTPAP, NDUFA1, NDUFA2, NDUFA9, NDUFA10, NDUFA11, NDUFA12, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFU1, NUBPL, OGDH, OPA1, OPA3, OXCT1, PANK2, PC, PCK2, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PNKD, PNPT1, POLG, POLG2, PUS1, RARS2, RMND1, RRM2B, SACS, SARS2, SCO1, SCO2, SDHAF1, SERAC1, SFXN4, SLC19A3, SLC25A1, SLC25A3, SLC25A4, SLC25A12, SLC25A19, SLC52A2, SUCLA2, SUCLG1, SUGCT, SURF1, TACO1, TARS2, TAZ, TIMM8A, TIMM44, TK2, TMEM126A, TMEM70, TPK1, TRAP1, TRMU, TSFM, TTC19, TUFM, TWNK (C10orf2), TYMP, UQCRB, UQCRC2, UQCRQ, VARS2, XPNPEP3,* and *YARS2*.

There are regions of the genes *COX10, COX20, NDUFV2*, and *TSFM* that cannot be effectively sequenced as a result of technical limitations of the assay. Regions of homology, high GC-rich content, and repetitive sequences may not provide accurate sequence. Therefore, all reported alterations detected by next-generation sequencing are confirmed by an independent reference method. However, this does not rule out the possibility of a false-negative result in these regions. Sanger sequencing is used to confirm alterations detected by next-generation sequencing when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly, varies

Analytic Time

8 weeks

Maximum Laboratory Time

10 weeks

Specimen Retention Time

Whole Blood: 2 weeks (if available); Extracted DNA: Indefinitely

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

81440

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
MITON	Mitochondrial Nuclear Gene Panel	In Process

Result ID	Test Result Name	Result LOINC Value
40220	Result Summary	50397-9
40221	Result	82939-0
40222	Interpretation	69047-9
40223	Additional Information	48767-8
40224	Specimen	31208-2
40225	Source	31208-2
40226	Released By	18771-6