MAYO CLINIC LABORATORIES

Test Definition: NMITO

Nuclear Mitochondrial Gene Panel, Next-Generation Sequencing, Varies

Overview

Useful For

Diagnosing the subset of mitochondrial disease that results from variants in the nuclear-encoded genes

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

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

Reflex Tests

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

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 221 genes associated with nuclear mitochondrial disease: *AARS2, ABAT, ABCB7, ACACA, ACAD9, ACO2, AFG3L2, AGK, AIFM1, ALDH3A2, APOPT1* (*COA8*), *APTX, ATP5F1A, ATP5F1E, ATPAF2, AUH, BCS1L, BOLA3, C12orf65 (MTRFR*), *CA5A, CARS2, CHAT, CHCHD10, CLPP, COA5, COA6, COA8* (*APOPT1*), *COASY, COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, COX10, COX14, COX15, COX20, COX4I1, COX4I2, COX6A1, COX6A2, COX6B1, COX7B, COX8A, CPT1C, CYC1, D2HGDH, DARS2, DGUOK, DLAT, DLD, DNA2, DNAJC19, DNM1L, EARS2, ELAC2, ETFA, ETFB, ETFDH, ETHE1, FARS2, FASTKD2, FBXL4, FDX2, FDXR, FH, FOXRED1, FXN, GAMT, GARS1, GCDH, GDAP1, GFER, GFM1, GFM2, GLYCTK, GPT2, GTPBP3, HARS2, HIBCH, HK1, HSPD1, IARS2, IBA57, IDH2, INF2, ISCU, L2HGDH, LARS2, LIAS, LRPPRC, LYRM4, LYRM7, MARS2, MFF, MGME1, MICU1, MPC1, MPV17, MRPL3, MRPL44, MRPS16, MRPS2, MRPS22, MRPS7, MSTO1, MTFMT, MTO1, MTPAP, MTRFR* (*C12orf65*), *NARS2, NBAS, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA13, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFU1, NR2F1, NUBPL, OGDH, OPA1, OPA3, OXCT1, PANK2, PARS2, PC, PCK2, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PET100, PNKD, PNPT1, POLG, POLG2, PTRH2, PUS1, QARS1, RARS1, RARS2, RMND1, RNASEH1, RRM2B, RTN4IP1, SACS, SARS2, SCO1, SCO2, SDHAF1, SERAC1, SFXN4, SLC19A3, SLC25A1, SLC25A12, SLC25A19, SLC25A22, SLC25A26, SLC25A3, SLC25A4, SLC25A42, SLC25A46, SLC52A2, SLC9A6, SOD1, SPG7, SUCLA2, SUCLG1, SUGCT, SURF1, TACO1, TAFAZZIN* (*TAZ*), *TARS2, TAZ* (*TAFAZZIN*), *TFAM, TIMM8A, TK2, TMEM126A, TMEM126B, TMEM70, TOP3A, TPK1, TRIT1, TRMT10C, TRMU, TRNT1, TSFM, TTC19, TUFM, TWNK, TYMP, UQCC2, UQCRB, UQCRC2, UQCRQ, VARS2, WDR45, XPNPEP3,* and *YARS2*.

See Targeted Genes and Methodology Details for Nuclear Mitochondrial Gene Panel, Next-Generation Sequencing, Varies in Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for nuclear mitochondrial disease.

Testing Algorithm

If skin biopsy is received, fibroblast culture will be added at an additional charge. If viable cells are not obtained, the client will be notified.

For more information see Neuromuscular Myopathy Testing Algorithm

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Neuromuscular Myopathy Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions
- Targeted Genes and Methodology Details for Nuclear Mitochondrial Gene Panel, Next-Generation, Varies

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

The diagnostic workup for a mitochondrial disorder may include testing to demonstrate elevations of the lactate-to-pyruvate ratio and an elevated growth differentiation factor 15 concentration. Consider LAPYP / Lactate Pyruvate Panel, Plasma and GDF15 / Growth Differentiation Factor 15, Plasma.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, 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.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with whole blood or dried blood spot testing. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA) or yellow top (ACD)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days

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.
Specimen Volume: 4-mm punch
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing, Chorionic Villi/Products of Conception/Tissue. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblast
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing, Chorionic Villi/Products of Conception/Tissue. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

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)
2. Molecular Genetics: Biochemical Disorders Patient Information (T527)
3. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-Neurology Specialty Testing Client Test Request (T732)

-Biochemical Genetics Test Request (T798)

Specimen Minimum Volume

Blood: 1 mL; Skin biopsy or cultured fibroblasts: 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	Varies		

Clinical & 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 variants 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, to analyze 221 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 variants in the nuclear genes encoding mitochondrial proteins. This includes disorders of mitochondrial protein synthesis, disorders of coenzyme Q10 biosynthesis, disorders of the respiratory chain complexes and disorders of mitochondrial DNA (mtDNA) maintenance (ie, mtDNA depletion disorders).

Reference Values

An interpretive report will be provided

Interpretation

All detected variants 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:
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 the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing 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 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 select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

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.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

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.(1) 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. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. 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
2. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of respiratory chain deficiency. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed March 8, 2024.
https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827
3. Wong LJ. Molecular genetics of mitochondrial disorders. Dev Disabil Res Rev. 2010;16(2):154-162
4. Barca E, Long Y, Cooley V, et al. Mitochondrial disease in North America: An analysis of the NAMDC Registry. Neurol Genet. 2020;6(2):e402

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are 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 30X. Sensitivity is estimated to be over 99% for single nucleotide variants, over 94% for deletions-insertions (delins) less than 40 base pairs (bp), and over 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

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. See Targeted Genes and Methodology Details for Nuclear Mitochondrial Gene Panel,

Next-Generation Sequencing, Varies for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *AARS2, ABAT, ABCB7, ACACA, ACAD9, ACO2, AFG3L2, AGK, AIFM1, ALDH3A2, APOPT1* (*COA8*), *APTX, ATP5F1A, ATP5F1E, ATPAF2, AUH, BCS1L, BOLA3, C12orf65* (*MTRFR*), *CA5A, CARS2, CHAT, CHCHD10, CLPP, COA5, COA6, COA8* (*APOPT1*), *COASY, COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, COX10, COX14, COX15, COX20, COX4I1, COX4I2, COX6A1, COX6A2, COX6B1, COX7B, COX8A, CPT1C, CYC1, D2HGDH, DARS2, DGUOK, DLAT, DLD, DNA2, DNAJC19, DNM1L, EARS2, ELAC2, ETFA, ETFB, ETFDH, ETHE1, FARS2, FASTKD2, FBXL4, FDX2, FDXR, FH, FOXRED1, FXN, GAMT, GARS1, GCDH, GDAP1, GFER, GFM1, GFM2, GLYCTK, GPT2, GTPBP3, HARS2, HIBCH, HK1, HSPD1, IARS2, IBA57, IDH2, INF2, ISCU, L2HGDH, LARS2, LIAS, LRPPRC, LYRM4, LYRM7, MARS2, MFF, MGME1, MICU1, MPC1, MPV17, MRPL3, MRPL44, MRPS16, MRPS2, MRPS22, MRPS7, MSTO1, MTFMT, MTO1, MTPAP, MTRFR* (*C12orf65*), *NARS2, NBAS, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA13, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFU1, NR2F1, NUBPL, OGDH, OPA1, OPA3, OXCT1, PANK2, PARS2, PC, PCK2, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PET100, PNKD, PNPT1, POLG, POLG2, PTRH2, PUS1, QARS1, RARS1, RARS2, RMND1, RNASEH1, RRM2B, RTN4IP1, SACS, SARS2, SCO1, SCO2, SDHAF1, SERAC1, SFXN4, SLC19A3, SLC25A1, SLC25A12, SLC25A19, SLC25A22, SLC25A26, SLC25A3, SLC25A4, SLC25A42, SLC25A46, SLC52A2, SLC9A6, SOD1, SPG7, SUCLA2, SUCLG1, SUGCT, SURF1, TACO1, TAFAZZIN* (*TAZ*), *TARS2, TAZ* (*TAFAZZIN*), *TFAM, TIMM8A, TK2, TMEM126A, TMEM126B, TMEM70, TOP3A, TPK1, TRIT1, TRMT10C, TRMU, TRNT1, TSFM, TTC19, TUFM, TWNK, TYMP, UQCC2, UQCRB, UQCRC2, UQCRQ, VARS2, WDR45, XPNPEP3,* and *YARS2*

PDF Report
No

Day(s) Performed
Varies

Report Available
21 to 35 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts: 1 month

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 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

81440

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NMITO	Nuclear Mitochondrial Gene Panel	101152-7

Result ID	Test Result Name	Result LOINC® Value
617091	Test Description	62364-5
617092	Specimen	31208-2
617093	Source	31208-2
617094	Result Summary	50397-9
617095	Result	82939-0
617096	Interpretation	69047-9
618172	Additional Results	82939-0
617097	Resources	99622-3
617098	Additional Information	48767-8
617099	Method	85069-3
617100	Genes Analyzed	48018-6
617101	Disclaimer	62364-5
617102	Released By	18771-6