

CONCERT GENETIC TESTING: METABOLIC, ENDOCRINE, AND MITOCHONDRIAL DISORDERS

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[Coding implications](#)

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See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

OVERVIEW

Hereditary metabolic disorders, also known as inborn errors of metabolism, are genetic disorders that interfere with the body's metabolism. There are hundreds of inherited metabolic disorders, and many are screened for at birth through newborn screening programs, while others are identified after a child or adult shows symptoms of the disorder. Genetic testing for metabolic disorders aids in quickly identifying the specific disorder so that proper treatment can be initiated and at-risk family members can be identified.

Hereditary endocrine disorders are a group of conditions involving the endocrine system, a network of glands that produce and release hormones in order to regulate body functions. This document aims to address hereditary endocrine disorders that are non-cancerous in nature.

Mitochondrial disorders are a clinically heterogeneous group of disorders caused by dysfunction of the mitochondrial respiratory chain. The diagnosis of a primary mitochondrial disease can be difficult, as the individual symptoms are nonspecific and symptom patterns often overlap significantly. Mitochondrial disorders can be caused by mutations in the genes encoded by the mitochondrial DNA (mtDNA), which are transmitted by maternal inheritance, or by genes encoded by the nuclear DNA, which can be transmitted in an autosomal recessive or autosomal dominant manner. There are over 1000 nuclear genes coding for proteins that support mitochondrial function. These disorders can present at any age and many involve multiple organ systems, often with neurologic and myopathic features.

Genetic testing for metabolic, endocrine, and mitochondrial disorders aids in identifying the specific disorder that is present, so that proper treatment (if any) can be initiated, and at-risk family members can be identified.

Of note, a family history in which affected ~~women~~parents with female reproductive systems transmit the disease to ~~male and female~~-children with male or female reproductive systems and

affected menparents with male reproductive systems do not transmit the disease to their children suggests the familial variant(s) is in the mtDNA, rather than in a nuclear gene.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted ~~2022~~2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert Genetics Platform](#) for a comprehensive list of registered tests.

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
<u>Known Familial Variant Analysis for Metabolic, Endocrine, and Mitochondrial Disorders</u>				
<u>Known Familial Variant Analysis for Metabolic, Endocrine, and Mitochondrial Disorders</u>	Targeted Mutation Analysis for a Known Familial Variant	81403*		12
<u>MTHFR Variant Analysis</u>				

MTHFR Variant Analysis	Methylenetetrahydrofolate Reductase (MTHFR) Thermolabile Variant, DNA Analysis (Labcorp)	81291*	E03.9, E55.9, E72.12, E78.2, E78.5, E88.9, O03, N96, R53.83, Z00.00	1, 2
	Methylenetetrahydrofolate Reductase (MTHFR), DNA Mutation Analysis (Quest Diagnostics)			
<u>Monogenic Diabetes (Including Maturity Onset Diabetes of the Young (MODY))</u>				
Maturity Onset Diabetes of the Young (MODY) Panel Monogenic Diabetes (Including Maturity Onset Diabetes of the Young (MODY)) Panels	Maturity Onset Diabetes of the Young (MODY) Panel (PreventionGenetics, part of Exact Sciences)	81403*, 81405*, 81406*, 81407*, 81479	E10, E11, E16.1, E16.2	5, 6 <u>11</u> , <u>12</u>
	Maturity-onset diabetes of the young (MODY) (Ambry Genetics)			
	Monogenic Diabetes (MODY) Five Gene Evaluation (GCK,HNF1A,HNF1B,HNF4A,IPF1) (Athena Diagnostics Inc)			
<u>Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Genes</u>				
Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel	Mito Genome Sequencing & Deletion Testing (GeneDx)	81460, 81465*	E88.40, E88.41, E88.42, E88.49, G31.82, H49.811-H49.819	3, 4
	Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)			
	Nuclear Mitochondrial Nuclear Gene Panel by , Next-Generation Sequencing (NGS) , Varies (Mayo Clinic Laboratories)	81440*		
	MitoXpanded Panel (GeneDx)			
	Genomic Unity Comprehensive Mitochondrial Disorders Analysis (Variantyx)	<u>0417U*</u>		
<u>Other Covered Metabolic, Endocrine, and Mitochondrial Disorders</u>				
Other Covered Metabolic, Endocrine,	See list below	81400*-81408*, 81205*, 81250*		<u>6</u> , 7, 8, 9, 10, 11

and Mitochondrial Disorders				
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OTHER RELATED POLICIES

This policy document provides criteria for metabolic, endocrine, and mitochondrial disorders. Please refer to:

- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for criteria related to prenatal or preconception **carrier** screening.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss **diagnostic** genetic testing.
- ***Genetic Testing: Preimplantation Genetic Testing*** for criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to genetic disorders that affect multiple organ systems.
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing for hereditary endocrine cancer predisposition syndromes.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to metabolic, endocrine, and mitochondrial disorders not specifically discussed in this or another non-general policy.

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CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

~~KNOWN FAMILIAL VARIANT ANALYSIS FOR METABOLIC, ENDOCRINE, AND MITOCHONDRIAL DISORDERS~~

- ~~I. Targeted mutation analysis for a known familial variant (81403*, 81404*, 81405*, 81406*, 81407*, 81479) for a metabolic, endocrine, or mitochondrial disorder is considered **medically necessary** when:~~
 - ~~A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant causing the condition.~~
- ~~II. Targeted mutation analysis for a known familial variant (81403-81404*, 81405*, 81406*, 81407*, 81479) for a metabolic, endocrine, or mitochondrial disorder is considered **investigational** for all other indications.~~

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MTHFR VARIANT ANALYSIS

- I. **MTHFR** targeted variant analysis (~~examples: e.g., 677T*, 1298C*~~) (81291*) is considered **investigational** for all indications, including but not limited to:
 - A. Evaluation for thrombophilia or recurrent pregnancy loss
 - B. Evaluation of at-risk relatives
 - C. Drug metabolism, such as in pharmacogenetic testing

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MONOGENIC DIABETES (INCLUDING MATURITY-ONSET DIABETES OF THE YOUNG (MODY)-) PANELS

Maturity-Onset Diabetes of the Young (MODY) Panel

- ~~II.I. Multigene panel analysis to establish or confirm a diagnosis of monogenic diabetes (including maturity-onset diabetes of the young (MODY)-) (81403*, 81405*, 81406*, 81407*, 81479) is considered **medically necessary** when:~~

~~A. The member/enrollee meets one of the following:~~

~~2.A. The member/enrollee has a diagnosis of diabetes within the first 612 months of life, **OR**~~

~~3.B.~~ The member/enrollee has a diagnosis of diabetes before ~~35~~30 years of age,
AND

~~A. The member/enrollee meets one of the following:~~

~~5.1.~~ The member/enrollee has ~~features atypical for type 1 diabetes mellitus, including~~ at least one of the following:

~~a) Absence of pancreatic islet autoantibodies, **OR**~~

~~b) Evidence of endogenous insulin production beyond the honeymoon period (i.e., 3-5 years after the onset of diabetes), **OR**~~

~~a) Measurable Autoantibody negative, **OR**~~

~~a) Retained C-peptide in the presence of hyperglycemia (C-peptide 0.60 ng/mL or greater, or 0.2 nmol/L), **OR**~~

~~b) Low insulin requirement for treatment (i.e., less than 0.5 U/kg/d), **OR**~~

~~c)b) Lack of ketoacidosis when insulin is omitted from treatment levels, **OR**~~

~~5.~~ The member/enrollee has ~~features atypical for a diagnosis of diabetes not characteristic of type 1 or type 2 diabetes mellitus, including at least one the following:~~

~~e) Onset of diabetes before age 45 years, **OR**~~

~~f) Lack of significant obesity, **OR**~~

~~g) Lack of acanthosis nigricans, **OR**~~

~~h)C.~~ Normal triglyceride levels and/or normal or elevated high-density lipoprotein cholesterol (HDL-C), **AND**

~~B.1.~~ The member/enrollee has a family history of diabetes consistent with an autosomal dominant pattern of inheritance, **AND**

~~The panel includes, at a minimum, the following genes: GCK, HNF1A, and HNF4A.~~

~~IV. II.~~ Multigene panel analysis to establish or confirm a diagnosis of monogenic diabetes (maturity-onset diabetes of the young (MODY)) (81403^{*,1}, 81404^{*,1}, 81405^{*,1}, 81406^{*,1}, 81407^{*,1}, 81479) is considered **investigational** for all other indications.

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MITOCHONDRIAL GENOME SEQUENCING, DELETION/DUPLICATION, AND/OR NUCLEAR GENES

- I. Mitochondrial genome sequencing (81460*), deletion/duplication (81465*), and/or nuclear genes analysis (0417U, 81440*) to establish or confirm a diagnosis of a primary mitochondrial disorder is considered **medically necessary** when:
 - A. The member/enrollee has a classic phenotype of one of the maternally inherited syndromes (e.g., [Leber hereditary optic neuropathy](#), [mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes \[MELAS\]](#), [myoclonic epilepsy with ragged red fibers \[MERRF\]](#), maternally inherited deafness and diabetes [MIDD], neuropathy, ataxia, retinitis pigmentosa [NARP], Kearns-Sayre syndrome/CPEO); or of a nuclear DNA mitochondrial disorder (e.g., [mitochondrial neurogastrointestinal encephalopathy \[MNGIE\]](#)); **OR**
 - B. The member/enrollee has non-specific clinical features suggestive of a primary mitochondrial disorder and meets **ALL** of the following:
 1. Clinical findings of at least two of the following:
 - a) Ptosis, **OR**
 - b) External ophthalmoplegia, **OR**
 - c) Proximal myopathy, **OR**
 - d) Exercise intolerance, **OR**
 - e) Cardiomyopathy, **OR**
 - f) Sensorineural deafness, **OR**
 - g) Optic atrophy, **OR**
 - h) Pigmentary retinopathy, **OR**
 - i) Diabetes mellitus, **OR**
 - j) Fluctuating encephalopathy, **OR**
 - k) Seizures, **OR**
 - l) Dementia, **OR**
 - m) Migraine, **OR**
 - n) Stroke-like episodes, **OR**
 - o) Ataxia, **OR**
 - p) Spasticity, **OR**
 - q) Chorea, **OR**
 - r) Multiple late term pregnancy loss, **AND**

2. Conventional biochemical laboratory studies have been completed and are non-diagnostic, including at least: -plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids, **AND**
 3. Additional diagnostic testing indicated by the member/enrollee's clinical presentation (e.g., fasting blood glucose, electrocardiography, neuroimaging, electromyography, echocardiography, audiology, thyroid testing, electroencephalography, exercise testing) have been completed and are non-diagnostic.
- II. Mitochondrial genome sequencing (81460*), deletion/duplication (81465*), and/or nuclear genes analysis (81440*) to establish or confirm a diagnosis of a primary mitochondrial disorder is considered **investigational** for all other indications.

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OTHER COVERED METABOLIC, ENDOCRINE, AND MITOCHONDRIAL DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

- I. Genetic testing to establish or confirm one of the following metabolic, endocrine, and mitochondrial conditions to guide management is considered **medically necessary** when the member/enrollee demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):
 - A. Congenital adrenal hyperplasia, including:
 1. [21-Hydroxylase deficiency](#)
 - B. Congenital disorders of glycosylation
 - C. [Congenital hyperinsulinism](#)
 - D. Disorders of amino acid and peptide metabolism, including:
 1. [Glutaric acidemia type I \(GA-1\)](#)
 2. [Homocystinuria caused by cystathionine beta-synthase \(CBS\) deficiency](#)
 3. [Methylmalonic acidemia](#)
 4. [Propionic acidemia](#)
 5. [Maple Syrup Urine Disease \(MSUD\)](#)
 - E. Disorders of biotin metabolism, including:
 1. [Biotinidase deficiency](#)
 - F. Disorders of carnitine transport and the carnitine cycle, including:
 1. [Carnitine palmitoyltransferase II deficiency](#)
 2. [Primary carnitine deficiency](#)

- G. Disorders of copper metabolism, including:
 - 1. [ATP7A-Related copper transport disorders](#) (e.g., Menkes disease, occipital horn syndrome (OHS), ATP7A-related distal motor neuropathies)
 - 2. [Wilson disease](#)
 - H. Disorders of fatty acid oxidation, including:
 - 1. [Medium-chain acyl-coenzyme A dehydrogenase deficiency \(MCAD deficiency\)](#)
 - I. Disorders of galactose metabolism, including:
 - 1. [Galactosemia](#)
 - J. Disorders of glucose transport, including:
 - 1. [Glucose transporter type I deficiency syndrome \(Glut1 DS\)](#)
 - K. Disorders of phenylalanine or tyrosine metabolism, including:
 - 1. [Alkaptonuria](#)
 - 2. [Phenylalanine hydroxylase deficiency](#)
 - L. Disorders of porphyrin and heme metabolism, including:
 - 1. [Acute intermittent porphyria](#)
 - M. [Fibrous Dysplasia/McCune-Albright Syndrome](#)
 - N. Glycogen storage disorders, including:
 - 1. [Glycogen Storage Disease Type I \(GSDI\)](#)
 - 2. [Pompe disease \(GSDII\)](#)
 - O. [Hypophosphatasia](#)
 - P. [Kallmann syndrome \(GnRH deficiency\)](#)
 - Q. Lysosomal storage disorders, including:
 - 1. [Gaucher disease](#)
 - 2. [Krabbe disease](#)
 - 3. [MPS-Type I \(Hurler syndrome\)](#)
 - 4. [MPS-Type II \(Hunter syndrome\)](#)
 - 5. [Mucopolipidosis IV](#)
 - R. Urea cycle disorders, including:
 - 1. [Ornithine Transcarbamylase \(OTC\) deficiency](#)
 - S. [Malignant hyperthermia](#)
 - T. [SHOX deficiency disorders](#)
- II. Genetic testing to establish or confirm the diagnosis of all other metabolic, endocrine, and [mitochondrial disorders](#) not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy for criteria).

*Clinical features for a specific disorder may be outlined in resources such as [GeneReviews](#), [OMIM](#), [National Library of Medicine, Genetics Home Reference](#), or other scholarly source.

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NOTES AND DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
 - a. **First-degree relatives** are parents, siblings, and children
 - b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
 - c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Mitochondrial disease** refers to a heterogenous group of disorders caused by dysfunctional mitochondria, the organelles responsible for oxidative phosphorylation within the cell.
3. **Autosomal dominant inheritance** refers to a type of transmission of a genetic condition in which only one mutated copy of a gene (rather than two) is necessary for an individual to manifest the disease. The mutation can be inherited from either parent, and the disease can typically be seen in any sex. A pedigree (family history) that has an autosomal dominant disorder will typically have affected family members in each generation, though some family members may be more severely affected than others.

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BACKGROUND AND RATIONALE

~~Known Familial Variant Analysis for Metabolic, Endocrine, and Mitochondrial Disorders~~

~~Genetic Support Foundation~~

~~The Genetic Support Foundation's Genetics 101 information on genetic testing says the following about testing for familial pathogenic variants:~~

~~Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial~~

~~pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.~~

MTHFR Variant Analysis

American College of Medical Genetics and Genomics (ACMG)

ACMG published a practice guideline for *MTHFR* polymorphism testing (2013, confirmed 2020) with the following recommendations:

- *MTHFR* polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss
- *MTHFR* polymorphism genotyping should not be ordered for at-risk family members
- A clinical geneticist who serves as a consultant for a patient in whom an *MTHFR* polymorphism(s) is found should ensure that the patient has received a thorough and appropriate evaluation for his or her symptoms
- If the patient is homozygous for the “thermolabile” variant c.665C to T, the geneticist may order a fasting total plasma homocysteine, if not previously ordered, to provide more accurate counseling
- *MTHFR* status does not change the recommendation that women of childbearing age should take the standard dose of folic acid supplementation to reduce the risk of neural tube defects as per the general population guidelines (p. 154)

Monogenic Diabetes (Including Maturity-Onset Diabetes of the Young (MODY) Panels)

American Diabetes Association

In 2021, the American Diabetes Association made the following recommendations:

- All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. (Category A)
- Children and those diagnosed in early adulthood who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. (Category A)
- In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling. (Category E) (p. 525)

GeneReviews: Maturity-Onset~~Murphy, et al.~~

Murphy, et al (2023) performed a systematic review and issued an expert opinion on how to use precision diagnostics to identify individuals with monogenic diabetes. The article states that the following individuals should be offered testing for monogenic diabetes:

1. All patients diagnosed with diabetes before the age of 6 months should be tested for monogenic forms of neonatal diabetes using the large-gene panel.
2. All patients diagnosed between 6 and 12 months should be tested for monogenic forms of neonatal diabetes using the large-gene panel. No demonstrable yield of monogenic etiology to support reflexive genetic testing patients diagnosed with diabetes between 12-24 months.
3. Women with gestational diabetes and fasting glucose above 5.5 mmol/L without obesity* should be tested for GCK etiology.
4. Those with persisting, mild hyperglycemia (HbA1c 38–62 mmol/mol, or fasting glucose 5.5–7.8 mmol/L) at any age, in the absence of obesity* should be tested for GCK etiology.
5. People without obesity under the age of 30 years who are either autoantibody negative and/or have retained C-peptide levels should be tested for monogenic diabetes using a large-gene panel. (p.10)

International Society for Pediatric and Adolescent Diabetes of the Young Overview(ISPAD)

~~GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Their recommendations are as follows:~~

~~A clinical diagnosis of MODY can be suspected in individuals with:~~

- ~~— Early onset diabetes in adolescence or young adulthood (typically age less than 35 years)~~
- ~~— Features atypical for type 1 diabetes mellitus including the following:~~
 - ~~● — Absence of pancreatic islet autoantibodies~~

~~Evidence of endogenous insulin production beyond the honeymoon period (i.e., 3–5 years after the~~
In 2022, the International Society for Pediatric and Adolescent Diabetes (ISPAD) released a clinical practice consensus guideline for the diagnosis and management of monogenic diabetes in children and adolescents. The statement includes the following recommendations for genetic testing in the setting of neonatal diabetes and maturity onset diabetes of the young:

“All infants diagnosed with diabetes in the first 6 months of life are recommended to have immediate molecular genetic testing. Genetic testing may be considered in infants diagnosed between 6 and 12 months, especially in those without islet autoantibodies or who have other features suggestive of a monogenic cause.” (p. 1190)

- ~~● — “The diagnosis of maturity onset of diabetes)~~
- ~~● — Measurable C-peptide in of the presence of hyperglycemia (C-peptide of at least 0.60 ng/mL or 0.2 nmol/L)~~

- ~~Low insulin requirement for treatment (i.e., less than 0.5 U/kg/d)~~
- ~~Lack of ketoacidosis when insulin young (MODY) is omitted from treatment~~
- ~~Features atypical for type 2 diabetes mellitus including recommended in the following:~~
 - ~~Onset of diabetes before age 45 years~~
 - ~~Lack of significant obesity~~
 - ~~Lack of acanthosis nigricans~~
 - ~~Normal triglyceride levels and/or normal or elevated high-density lipoprotein cholesterol (HDL-C)~~
 - ~~Mild, stable fasting hyperglycemia that does not progress or respond appreciably to pharmacologic therapy~~
 - ~~Extreme sensitivity to sulfonylureas~~
 - ~~Extrapaneatic features (e.g., renal, hepatic, gastrointestinal)~~
 - ~~A personal history or family history of neonatal diabetes or neonatal hypoglycemia~~
 - ~~A scenarios: family history of diabetes consistent with autosomal dominant inheritance in a parent and first-degree relatives of that contrasts with type 1 diabetes and type 2 diabetes in the following ways:~~
 - ~~Type 1 diabetes can run in families but is often sporadic: only 2%–6% of individuals with type 1 diabetes have an affected parent.~~
 - ~~Type 2 diabetes often runs in families: shared risk alleles and shared environment can lead to occurrence of type 2 diabetes in multiple family members. Family history that helps distinguish between type 2 diabetes and MODY are onset of in persons with diabetes after age 45 years in association with obesity (type 2 diabetes) versus onset of diabetes before age 35 years and who lack of obesity (MODY the characteristics of T1D and T2D.” (p. 1191)~~

Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Genes

Mitochondrial Medicine Society

The Mitochondrial Medicine Society (2015) published the following consensus recommendations for DNA testing for mitochondrial disorders:

1. Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.
2. Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.

3. Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m. 3243A>G mutation.
4. mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.
 - a. If a single small deletion is identified using polymerase chain reaction–based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.
 - b. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.
5. When a tissue specimen is obtained for mitochondrial studies, mtDNA content (copy number) testing via real-time quantitative polymerase chain reaction should strongly be considered for mtDNA depletion analysis because mtDNA depletion may not be detected in blood.
 - a. mtDNA proliferation is a nonspecific compensatory finding that can be seen in primary mitochondrial disease, secondary mitochondrial dysfunction, myopathy, hypotonia, and as a by-product of regular, intense exercise.
6. When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered. (p. 692-693)

GeneReviews: Primary Mitochondrial Disorders Overview

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Their recommendations are as follows:

Common clinical features of mitochondrial disorders include:

- ptosis
- external ophthalmoplegia
- proximal myopathy
- exercise intolerance
- cardiomyopathy
- sensorineural deafness
- optic atrophy

- pigmentary retinopathy
- diabetes mellitus
- fluctuating encephalopathy
- seizures
- dementia
- migraine
- stroke-like episodes
- ataxia
- spasticity
- chorea
- high incidence of mid- and late-pregnancy loss

When a patient's clinical picture is nonspecific but highly suggestive of a mitochondrial disorder, the clinician should start with measurement of plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids.

Traditionally, the diagnosis of mitochondrial disorders has been based on demonstrating mitochondrial dysfunction in a relevant tissue biopsy (e.g., a skeletal muscle or liver biopsy, or skin fibroblasts), with the particular pattern of biochemical abnormality being used to direct targeted molecular genetic testing of mtDNA, specific nuclear genes, or both.

However, the more widespread availability of molecular diagnostic techniques and the advent of exome and genome sequencing has changed the diagnostic approach.

One important caveat arises from the fact that many mtDNA pathogenic variants are heteroplasmic, and the proportion of mutated mtDNA in blood may be undetectable. This can be circumvented by analyzing mtDNA from another tissue – typically skeletal muscle or urinary epithelium – in which the level of heteroplasmy tends to be higher. Some common mtDNA pathogenic variants (e.g., large-scale deletions causing CPEO) may only be detected in skeletal muscle.

In individuals with a specific clinical phenotype (e.g., MELAS, LHON, POLG-related disorders) it may be possible to reach a diagnosis with targeted analysis of specific mtDNA pathogenic variants or single-gene testing of a nuclear gene.

A mitochondrial disorders multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Such testing includes exome sequencing, genome sequencing, and mitochondrial sequencing which can simultaneously analyze nuclear DNA and mtDNA.

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Converted corporate to local policy.	09/23	11/27/23
Semi-annual review. Overview, coding, reference-table, background and references updated. Throughout policy: replaced “coverage criteria” with “criteria. For MTHFR Variant Analysis: under I. added “but not limited to:”. For Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Genes Panel: under I.B.1.i. removed “and deafness”. For Other Covered Metabolic, Endocrine, and Mitochondrial Disorders Panel: under II. Added “and Molecular”; added II.3. “Autosomal dominant inheritance...”. For Background and Rationale; Known Familial Variant Analysis for Metabolic, Endocrine, and Mitochondrial Disorders panel: replaced “inheritance patterns” with “genetic testing”; under MTHFR Variant Analysis: added “. Confirmed 2020”.	2/24	4/26/24
<u>Semi-annual review. In Known Familial Variant Analysis for Metabolic, Endocrine, and Mitochondrial Disorders, moved criteria to policy “Genetic Testing: General Approach to Genetic and Molecular Testing” to consolidate criteria for known familial variant tests. In Monogenic Diabetes (Including Maturity-Onset Diabetes of the Young (MODY)) Panels, criteria set name changed (formerly “Maturity-Onset Diabetes of the Young (MODY)”). Minor rewording for clarity throughout. Coding, reference-table, background and references updated.</u>	<u>06/24</u>	

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