GENETIC TESTING: METABOLIC, ENDOCRINE, AND MITOCHONDRIAL DISORDERS

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, 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 disorders 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.

POLICY REFERENCE TABLE

Below are a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Known Familial Variant Analysis for Metabolic, Endocrine, and Mitochondrial Disorders				
Known Familial Variant Analysis	Targeted Mutation Analysis for a Known Familial Variant	81403		
MTHFR Variant Analysis				
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, 3
	Methylenetetrahydrofolate Reductase (MTHFR), DNA Mutation Analysis (Quest Diagnostics)			
Maturity Onset Diabetes of the Young (MODY)				
Maturity Onset Diabetes of the Young (MODY) Panel	Maturity Onset Diabetes of the Young (MODY) Panel (PreventionGenetics)	81403, 81404, 81405, 81406, 81407, 81479	E10, E11, E16.1, E16.2	7, 8
	Maturity-onset diabetes of the young (MODY) (Ambry Genetics)	81405, 81406, 81479		
Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Genes				
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,	4, 5, 6
	Mitochondrial Full Genome Analysis, Next-Generation	81460, 81465		

	Sequencing (NGS), Varies (Mayo Clinic Laboratories)		H49.811-H49.819	
	Mitochondrial Nuclear Gene Panel by Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)	81440		
	MitoXpanded Panel (GeneDx)			
Other Covered Metabolic, Endocrine, and Mitochondrial Disorders				
Other Covered Metabolic, Endocrine, and Mitochondrial Disorders	See list below	81400-81408		9, 10, 11, 12, 13

OTHER RELATED POLICIES

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

- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage 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 coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to genetic disorders that affect multiple organ systems.
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for coverage criteria related to genetic testing for hereditary endocrine cancer predisposition syndromes.

- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to metabolic, endocrine, and mitochondrial disorders not specifically discussed in this or another non-general policy.

COVERAGE CRITERIA

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

I. Targeted mutation analysis for a known familial variant (81403) for a metabolic, endocrine, or mitochondrial disorder is considered **medically necessary** when:

   A. The member 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) 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: 677T, 1298C) (81291) is considered **investigational** for all indications, including:

   A. Evaluation for thrombophilia or recurrent pregnancy loss
   B. Evaluation of at-risk relatives
   C. Drug metabolism (e.g., pharmacogenetic testing)

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MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

Maturity-onset Diabetes of the Young (MODY) Panel

I. Multigene panel analysis to establish or confirm a diagnosis of maturity-onset diabetes of the young (MODY) (81403, 81404, 81405, 81406, 81407, 81479) is considered **medically necessary** when:

   A. The member has a diagnosis of diabetes before 35 years of age, **AND**

   B. Mild, stable fasting hyperglycemia that does not progress or respond appreciably to pharmacologic therapy, **AND**

   C. The member does **not** have clinical features of syndromic diabetes mellitus (e.g., cystic fibrosis, hereditary hemochromatosis, myotonic dystrophy), **AND**

   D. The member does **not** have any of the following:

      1. Pancreatic islet autoantibodies suggestive of diabetes type 1, **OR**

      2. Body mass index (BMI) greater than or equal to 35 kg/m^2, **OR**

      3. Acanthosis nigricans,

      4. Drug or chemical induced diabetes, **AND**

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

II. Multigene panel analysis to establish or confirm a diagnosis of maturity-onset diabetes of the young (MODY) (81403, 81404, 81405, 81406, 81407, 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 (81440) to establish or confirm a diagnosis of a primary mitochondrial disorder is considered **medically necessary** when:

A. The member 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 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
b) External ophthalmoplegia
c) Proximal myopathy
d) Exercise intolerance
e) Cardiomyopathy
f) Sensorineural deafness
g) Optic atrophy
h) Pigmentary retinopathy
i) Diabetes mellitus
j) Deafness
k) Fluctuating encephalopathy
l) Seizures
m) Dementia
n) Migraine
o) Stroke-like episodes
p) Ataxia
q) Spasticity

r) Chorea

s) Dementia, **AND**

2. Conventional biochemical laboratory studies, including at least: complete blood count, creatine kinase, uric acid, complete metabolic panel, lactate, blood amino acids, and urine organic acids, have been completed and are non-diagnostic, **AND**

3. Additional diagnostic testing indicated by the member'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 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

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. Pompe disease
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)
R. Malignant hyperthermia

S. 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 Testing* (see policy for coverage 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.

CLINICAL CONSIDERATIONS

Mitochondrial Disorders

A family history in which affected women transmit the disease to male and female children and affected men do not transmit the disease to their children suggests the familial variant(s) is in the mtDNA, rather than in a nuclear gene.

BACKGROUND AND RATIONALE

MTHFR Variant Analysis

American College of Medical Genetics and Genomics (ACMG)

ACMG published a practice guideline for *MTHFR* polymorphism testing (2013) 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→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

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 197 (2018), which stated that, "There is insufficient evidence to support assessment of methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms or measurement of fasting homocysteine levels in the evaluation of a thrombophilic etiology for VTE."

Society for Maternal Fetal Medicine (SMFM)

SMFM (2019) published a list of "Fifteen Things Physicians and Patients Should Question" which included, "Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption".

Maturity-Onset Diabetes of the Young (MODY)

American Diabetes Association

In 2020, 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)

GeneReviews

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 onset of diabetes)
- Measurable C-peptide in 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 is omitted from treatment

• Features atypical for type 2 diabetes mellitus including 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

• Extrapancreatic features (e.g., renal, hepatic, gastrointestinal)

• A personal history or family history of neonatal diabetes or neonatal hypoglycemia

• A family history of diabetes consistent with autosomal dominant inheritance 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 [Harjutsalo et al 2010].
- 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 diabetes after age 45 years in association with obesity (type 2 diabetes) versus onset of diabetes before age 35 years and lack of obesity (MODY)

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.

The Mitochondrial Medicine Society (2017) released consensus guidelines for patient care standards. Within this set of guidelines, they state, “Pregnancy in mitochondrial disease also elicits the concern of transmission of a genetic disorder. Appropriate preconception genetic counseling and discussion of options of prenatal testing are needed. A fetus affected by mitochondrial disease may also be at higher risk for prenatal morbidity. Finally, premature ovarian failure is a feature of several mitochondrial disorders and affected women should be referred for assisted reproductive technologies if they wish to have children.

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