Medica Coverage Policy

Policy Name:	**Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders**
Medica Effective Date:	**July 01, 2024**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between policy requirements and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

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 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.

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage 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.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
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
	Methylenetetrahydrofolate Reductase (MTHFR), DNA Mutation Analysis (Quest Diagnostics)			
Monogenic Diabetes (Including Maturity Onset Diabetes of the Young (MODY))				
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, 11, 12
	Maturity-onset diabetes of the young (MODY) (Ambry Genetics)			
	Monogenic Diabetes (MODY) Five Gene Evaluation (GCK,HNF1A,HNF1B,HNF4A,IPF1) (Athena Diagnostics Inc)			
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, H49.811-H49.819	3, 4
	Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)			
	Nuclear Mitochondrial Gene Panel, Next-Generation Sequencing, Varies (Mayo Clinic Laboratories)	81440		
	MitoXpanded Panel (GeneDx)			
	Genomic Unity Comprehensive Mitochondrial Disorders Analysis	0417U		

	(Variantyx)			
Other Covered Metabolic, Endocrine, and Mitochondrial Disorders				
Other Covered Metabolic, Endocrine, and Mitochondrial Disorders	See list below	81400-81408, 81205, 81250		6, 7, 8, 9, 10

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

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COVERAGE CRITERIA

MTHFR VARIANT ANALYSIS

I. *MTHFR* targeted variant analysis (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

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 has a diagnosis of diabetes within the first 12 months of life, **OR**

B. The member has a diagnosis of diabetes before 30 years of age, **AND**

1. The member has at least one of the following:

a) Autoantibody negative, **OR**

b) Retained C-peptide levels, **OR**

C. The member has a diagnosis of diabetes not characteristic of type 1 or type 2 diabetes, **AND**

1. The member has a family history of diabetes consistent with an autosomal dominant pattern of inheritance.

II. Multigene panel analysis to establish or confirm a diagnosis of monogenic diabetes (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 (0417U, 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, **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'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
   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. Mucolipidosis 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 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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PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

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

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)

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 (ISPAD)

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 diabetes of the young (MODY) is recommended in the following scenarios: family history of diabetes in a parent and first-degree relatives of that affected parent in persons with diabetes who lack 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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Note: Medica uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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