Genetic testing: metabolic, endocrine, and mitochondrial disorders

These services may or may not be covered by your HealthPartners plan. Please see your plan documents for your specific coverage information. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage.

Administrative Process

Prior authorization is required for the following services:

- Testing for Monogenic Diabetes (Including Maturity Onset Diabetes of the Young (MODY))
- Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel
- Testing that is associated with a procedure code listed in “Box A”, below.

Prior authorization is not required for:

- Other Covered Metabolic, Endocrine, and Mitochondrial Disorders

The following genetic tests are considered investigational/experimental and, therefore, not covered:

- MTHFR Variant Analysis

Tests that require prior authorization will be reviewed for medical necessity of the testing as a whole. That is, a single coverage decision will apply to all of the tests, services, and/or procedure codes associated with the genetic test, whether they are requested/billed together or separately.

Box A: Genetic testing procedure codes that require prior authorization
Molecular pathology procedures, Tier 2 or unlisted (CPT 81400-81408, 81479)
Unlisted multianalyte assays (CPT 81599)
Any other listed or unlisted laboratory/pathology CPT code when it is used in association with a genetic test.

Policy Reference Table

If available, codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes
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
	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)) Panel	Maturity Onset Diabetes of the Young (MODY) Panel (PreventionGenetics, part of Exact Sciences)	81403, 81405, 81406, 81407, 81479	E10, E11, E16.1, E16.2
	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,	Mito Genome Sequencing & Deletion Testing (GeneDx)	81460, 81465	E88.40, E88.41, E88.42, E88.49,

Deletion/Duplication, and/or Nuclear Gene Panel	Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)		G31.82, H49.811-H49.819
	Nuclear Mitochondrial Gene Panel, Next-Generation Sequencing, Varies (Mayo Clinic Laboratories)	81440	
	MitoXpanded Panel (GeneDx)		
	Genomic Unity Comprehensive Mitochondrial Disorders Analysis (Variantyx)	0417U	
Other Covered Metabolic, Endocrine, and Mitochondrial Disorders			
Other Covered Metabolic, Endocrine, and Mitochondrial Disorders	See list below	81205, 81250, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	

Coverage

MTHFR Variant Analysis

1. MTHFR targeted variant analysis (e.g., 677T, 1298C) 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

1. Multigene panel analysis to establish or confirm a diagnosis of monogenic diabetes (including maturity-onset diabetes of the young (MODY)) 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**
     - i. The member meets 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**
     - i. The member has a family history of diabetes consistent with an autosomal dominant pattern of inheritance**.**
2. Multigene panel analysis to establish or confirm a diagnosis of monogenic diabetes (including maturity-onset diabetes of the young (MODY)) is considered **investigational** for all other indications.

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

1. Mitochondrial genome sequencing, deletion/duplication, and/or nuclear genes analysis 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.

2. Mitochondrial genome sequencing, deletion/duplication, and/or nuclear genes analysis 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

1. Genetic testing to establish or confirm one of the following metabolic, endocrine, and mitochondrial disorders 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 2 below):

A. Congenital adrenal hyperplasia, including:
   i. 21-Hydroxylase deficiency
B. Congenital disorders of glycosylation
C. Congenital hyperinsulinism
D. Disorders of amino acid and peptide metabolism, including:
   i. Glutaric acidemia type I (GA-1)
   ii. Homocystinuria caused by cystathionine beta-synthase (CBS) deficiency
   iii. Methylmalonic acidemia
   iv. Propionic acidemia
   v. Maple Syrup Urine Disease (MSUD)
E. Disorders of biotin metabolism, including:
   i. Biotinidase deficiency
F. Disorders of carnitine transport and the carnitine cycle, including:
   i. Carnitine palmitoyltransferase II deficiency
   ii. Primary carnitine deficiency
G. Disorders of copper metabolism, including:
   i. ATP7A-Related copper transport disorders (e.g., Menkes disease, occipital horn syndrome (OHS), ATP7A-related distal motor neuropathies)
   ii. Wilson disease
H. Disorders of fatty acid oxidation, including:
   i. Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD deficiency)
I. Disorders of galactose metabolism, including:
   i. Galactosemia
J. Disorders of glucose transport, including:
   i. Glucose transporter type I deficiency syndrome (Glut1 DS)
K. Disorders of phenylalanine or tyrosine metabolism, including:
   i. Alkaptonuria
   ii. Phenylalanine hydroxylase deficiency
L. Disorders of porphyrin and heme metabolism, including:
   i. Acute intermittent porphyria
M. Fibrous Dysplasia/McCune-Albright Syndrome
N. Glycogen storage disorders, including:
   i. Glycogen Storage Disease Type I (GSDI)
   ii. Pompe disease (GSDII)
O. Hypophosphatasia

P. Kallmann syndrome (GnRH deficiency)
Q. Lysosomal storage disorders, including:
i. Gaucher disease
ii. Krabbe disease
iii. MPS-Type I (Hurler syndrome)
iv. MPS-Type II (Hunter syndrome)
v. Mucolippidosis IV
R. Urea cycle disorders, including
i. Ornithine Transcarbamylase (OTC) deficiency
S. Malignant hyperthermia
T. SHOX deficiency disorders

2. 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 sources.

Definitions

1. **Mitochondrial disease** refers to a heterogenous group of disorders caused by dysfunctional mitochondria, the organelles responsible for oxidative phosphorylation within the cell.
2. **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.

Products

This information is for most, but not all, HealthPartners plans. Please read your plan documents to see if your plan has limits or will not cover some items. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage. These coverage criteria do not apply to Medicare Products. For more information regarding Medicare coverage criteria or for a copy of a Medicare coverage policy, contact Member Services at 952-883-7272 or 1-877-778-8384.

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