Clinical Policy: Genetic Testing Metabolic, Endocrine, and Mitochondrial Disorders

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Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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 member/enrollees 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 member/enrollee can be identified.

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

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81403	Targeted Mutation Analysis for a Known Familial Variant	Known Familial Variant Analysis	N/A
81291	MTHFR C677T & A1298C Variant Analysis	MTHFR Variant Analysis	E03.9, E55.9, E72.12, E78.2, E78.5, E88.9, O03, N96, R53.83, Z00.00

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81404,81405, 81406, 81479	Maturity Onset Diabetes of the Young (MODY) Panel (PreventionGenetics) Monogenic Diabetes (MODY) Evaluation (Cleveland Clinic Laboratories) Maturity-onset diabetes of the young (MODY) (Ambry Genetics)	Maturity Onset Diabetes of the Young (MODY) Panel	E10, E11, E16.1, E16.2
81460, 81465	CHOP MitoGenome Sequencing + Deletion Analysis (Children's Hospital of Philadelphia - Division of Genomic Diagnostics) Mito Genome Sequencing & Deletion Testing (GeneDx)	Mitochondrial Genome Sequencing, Deletion/Duplication and/or Nuclear Gene Panel	E88.40, E88.41, E88.42, E88.49, G31.82, H49.811-H49.819
81460	Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)	Mitochondrial Genome Sequencing, Deletion/Duplication and/or Nuclear Gene Panel	E88.40, E88.41, E88.42, E88.49, G31.82, H49.811-H49.819
81440	Mitochondrial Nuclear Gene Panel by Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)	Mitochondrial Genome Sequencing, Deletion/Duplication and/or Nuclear Gene Panel	E88.40, E88.41, E88.42, E88.49, G31.82, H49.811-H49.819
81440, 81460, 81465	Combined Mito Genome Plus Mito Focused Nuclear Gene Panel (GeneDx)	Mitochondrial Genome Sequencing, Deletion/Duplication and/or Nuclear Gene Panel	E88.40, E88.41, E88.42, E88.49, G31.82, H49.811-H49.819
81400-81408	See list below	Other Covered Metabolic, Endocrine, and Mitochondrial Disorders	N/A

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

- ***CP.MP.234 Genetic Testing: Prenatal and Preconception Carrier Screening*** for criteria related to prenatal or preconception **carrier** screening.
- ***CP.MP.235 Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for criteria related to prenatal and pregnancy loss **diagnostic** genetic testing.
- ***CP.MP.233 Genetic Testing: Preimplantation Genetic Testing*** for criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to genetic disorders that affect multiple organ systems.
- ***CP.MP.225 Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing for hereditary endocrine cancer predisposition syndromes.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to metabolic, endocrine, and mitochondrial disorders not specifically discussed in this or another non-general policy.

Policy/Criteria

Known Familial Variant Analysis For Metabolic, Endocrine, And Mitochondrial Disorders

I. It is the policy of health plans affiliated with Centene Corporation® that targeted mutation analysis for a known familial variant (81403) for a metabolic, endocrine, or mitochondrial disorder is considered **medically necessary** when:

   A. The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant causing the condition.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support targeted mutation analysis for a known familial variant (81403) for a metabolic, endocrine, or mitochondrial disorder for all other indications.

Mthfr Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *MTHFR* targeted variant analysis (e.g., 677T, 1298C) (81291) 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)

Maturity-Onset Diabetes Of The Young (Mody)

I. It is the policy of health plans affiliated with Centene Corporation® multigene panel analysis to establish or confirm a diagnosis of maturity-onset diabetes of the young (MODY) (81405, 81406, 81479) is considered **medically necessary** when meeting all of the following:

   A. The member/enrollee has a diagnosis of diabetes before 35 years of age;

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

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

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

      1. Pancreatic islet autoantibodies suggestive of diabetes type 1;

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

      3. Acanthosis nigricans;

      4. Drug or chemical induced diabetes;

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support multigene panel analysis to establish or confirm a diagnosis of maturity-onset diabetes of the young (MODY) (81405, 81406, 81479) for all other indications.

Mitochondrial Genome Sequencing, Deletion/Duplication, And/Or Nuclear Genes

I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting either of the following:

   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]);

   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

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

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,

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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support mitochondrial genome sequencing (81460), deletion/duplication (81465), and/or nuclear genes analysis (81440) to establish or confirm a diagnosis of a primary mitochondrial disorder for all other indications.

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, these genetic tests may be appropriate to establish or confirm a diagnosis.

I. It is the policy of health plans affiliated with Centene Corporation® that 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

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. It is the policy of health plans affiliated with Centene Corporation® that 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 CP.MP.222 *General Approach to Genetic 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.

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.

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

MTHFR Gene Testing

American College of Medical Genetics and Genomics:
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 member/enrollees
- 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 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 (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".

Neonatal Diabetes and Maturity-Onset Diabetes of the Young (MODY)

American Diabetes Association (2020) 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)

Mitochondrial Disorders

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 member/enrollees 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.

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 2021, 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. 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.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of member/enrollee. This clinical policy is not intended to recommend treatment for member/enrollee. Member/enrollee should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.