MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR MITOCHONDRIAL DISORDERS
POLICY NUMBER	MP 2.273

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**4/1/2026**

POLICY

Genetic testing to establish a genetic diagnosis of a mitochondrial disorder may be considered **medically necessary** when signs and symptoms of a mitochondrial disorder are present, and genetic testing may eliminate the need for muscle biopsy.

Targeted genetic testing for a known familial variant of at-risk relatives may be considered **medically necessary** as preconceptional carrier testing under the following conditions:

- There is a defined mitochondrial disorder in the family of sufficient severity to cause impairment of quality of life or functional status; **and**
- A variant that is known to be pathogenic for that specific mitochondrial disorder has been identified in the index case.

Genetic testing for mitochondrial disorders is considered **investigational** in all other situations when the criteria for medical necessity are not met. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Mitochondrial disorders can be caused by variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). A three (3)-generation family history may suggest a mode of inheritance. 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. A family history consistent with Mendelian autosomal dominant or autosomal recessive inheritance or with X-linked inheritance suggests the familial variant(s) is in the nDNA. De novo pathogenic variants are also possible.

Testing Strategy

Individuals with a Suspected Mitochondrial Disorder

If the phenotype is highly suggestive of a specific disorder that is supported by the inheritance pattern noted in the family history, it would be reasonable to begin genetic testing with single genes or targeted multigene panels that test for pathogenic variants specific for that disorder.

If a mitochondrial disorder is suspected, but the phenotype is nonspecific, broader genetic testing is appropriate under the guidance of a clinical geneticist and genetics counselor. For

patients in whom the family history is suggestive of a disorder due to pathogenic variant(s) in mtDNA, multigene panels or sequencing of the mitochondrial genome may be appropriate. If multiple mtDNA deletions are noted, or the family history is suggestive of a disorder due to variants in nDNA, then multigene panels covering known nuclear genes associated with mitochondrial disease may be appropriate. Testing using whole exome sequencing is reviewed in **MP 2.324 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders**.

Individuals with a Family Member with a Mitochondrial Disorder and Known Familial Variant

Targeted testing for a known familial variant in at-risk relatives as part of preconceptional carrier testing is appropriate. At-risk relatives include only female relatives if the familial pathogenic variant is in the mtDNA but includes both male and female relatives if the familial pathogenic variant is in the nDNA.

Mitochondrial Medicine Society

The Mitochondrial Medicine Society (MMS, 2015) developed consensus recommendations using the Delphi method.

- Recommendations for DNA Testing
  - "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."
  - "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 guides genetic counseling."
  - "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 mutation is identified via known NGS panels, then whole exome sequencing should be considered."

- Recommendations for pathology testing
  - "Muscle (and/or liver) biopsies should be performed in the routine analysis for mitochondrial disease when the diagnosis cannot be confirmed with DNA testing

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table

PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology— "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing.

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Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-References:

MP 2.326 General Approach to Genetic Testing
MP 2.323 General Approach to Evaluating the Utility of Genetic Panels
MP 2.324 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO – Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

DESCRIPTION/BACKGROUND

Mitochondrial DNA

Mitochondria are organelles within each cell that contain their own set of DNA, distinct from the nuclear DNA that makes up most of the human genome. Human mitochondrial DNA (mtDNA) consists of 37 genes. Thirteen genes code for protein subunits of the mitochondrial oxidative phosphorylation complex and the remaining 24 genes are responsible for proteins involved in the translation and/or assembly of the mitochondrial complex. Additionally, there are over 1000 nuclear genes coding for proteins that support mitochondrial function. The protein products from these genes are produced in the nucleus and later migrate to the mitochondria.

Mitochondrial DNA differs from nuclear DNA (nDNA) in several important ways. Inheritance of mtDNA does not follow traditional Mendelian patterns. Rather, mtDNA is inherited only from maternal DNA so that disorders that result from variants in mtDNA can only be passed on by the mother. Also, there are thousands of copies of each mtDNA gene in each cell, as opposed to nDNA, which contains only 1 copy per cell. Because there are many copies of each gene, variants may be present in some copies of the gene but not others. This phenomenon is called heteroplasmy. Heteroplasmy can be expressed as a percentage of genes that have the variant ranging from 0% to 100%. Clinical expression of the variant will generally depend on a threshold effect (i.e., clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).

Mitochondrial Disorders

Mitochondrial disorders have emerged as a common cause of inherited metabolic disease, affecting approximately 1 in 5000 people. The prevalence of these disorders has risen over the last 2 decades as the pathophysiology and clinical manifestations have been better characterized. They are caused by mutations in genes that primarily affect oxidative

phosphorylation and ATP synthesis. Mutations can occur in either mitochondrial or nuclear DNA. Primary mitochondrial disorders arise from dysfunction of the mitochondrial respiratory chain. The mitochondrial respiratory chain is responsible for aerobic metabolism, and dysfunction, therefore, affects a wide variety of physiologic pathways dependent on aerobic metabolism. Organs with a high-energy requirement, such as the central nervous system, cardiovascular system, and skeletal muscle, are preferentially affected by mitochondrial dysfunction.

Mitochondrial disorders are a clinically diverse group of diseases that may present at any age and affect a single organ or present as a multi-system condition in which neurologic and myopathic features predominate. Extensive clinical variability and phenotypic overlap exists among the many discrete mitochondrial disorders.

Some specific mitochondrial disorders are listed next:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome;
- Myoclonic epilepsy with ragged red fibers syndrome;
- Kearns-Sayre syndrome;
- Leigh syndrome;
- Chronic progressive external ophthalmoplegia;
- Leber hereditary optic neuropathy;
- Neurogenic weakness with ataxia and retinitis pigmentosa.

Most of these disorders are characterized by multisystem dysfunction, which generally includes myopathies and neurologic dysfunction and may involve multiple other organs. Each defined mitochondrial disorder has a characteristic set of signs or symptoms. The severity of illness is heterogeneous and can vary markedly. Some patients will have only mild symptoms for which they never require medical care, while other patients have severe symptoms, a large burden of morbidity, and a shortened life expectancy.

Diagnosis

The diagnosis of mitochondrial diseases can be difficult. The individual symptoms are nonspecific, and symptom patterns can overlap considerably. As a result, a patient often cannot be easily classified into one particular syndrome. Biochemical testing is indicated for patients who do not have a clear clinical picture of one specific disorder. Measurement of serum lactic acid is often used as a screening test but the test is neither sensitive nor specific for mitochondrial diseases.

A tissue biopsy, typically muscle, has often been thought of as the gold standard for mitochondrial diagnosis, although the test is affected by concerns of limited sensitivity and specificity. With newer molecular testing, there is less of a need to rely primarily on biochemical testing of tissue for diagnosis, although selectively testing tissue remains a very informative procedure, especially for a clinically heterogeneous condition such as mitochondrial disease. New data and guidelines suggest that a muscle (and/or liver) biopsy should only be performed in routine analysis for mitochondrial disease when the diagnosis cannot be confirmed with DNA testing. Biopsy is an invasive test and is not definitive in all cases. The presence of “ragged red fibers” on histologic analysis is consistent with a mitochondrial disorder. Ragged red

fibers represent a proliferation of defective mitochondrial. This characteristic finding may not be present in all types of mitochondrial disorders and also may be absent early in the course of disease.

Overall, the advent of newer technologies that rely on massive parallel or next-generation sequencing (NGS) methodologies have emerged as the new gold standard methodology for mtDNA genome sequencing because they allow significantly improved reliability and sensitivity of mtDNA genome analyses for point mutations, low-level heteroplasmy, and deletions, thereby providing a single test to accurately diagnose mtDNA disorders. This new approach may be considered as first-line testing for comprehensive analysis of the mitochondrial genome in blood, urine, or tissue, depending on symptom presentation and sample availability.

Treatment

Treatment of mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder. Identification of complications such as diabetes and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (e.g., coenzyme Q, riboflavin) have been used, but empirical evidence of benefit is lacking. Exercise therapy for myopathy is often prescribed, but the effect on clinical outcomes is uncertain. The possibility of gene transfer therapy is under consideration, but is at an early stage of development and untested in clinical trials.

Genetic Testing

Mitochondrial disorders can be caused by pathogenic variants in the maternally inherited mtDNA or one of many nDNA genes. Genetic testing for mitochondrial disorders may involve testing for point mutations, deletion/duplication analysis, and/or whole exome sequencing of nuclear or mtDNA. The type of testing done depends on the specific disorder being considered. For some primary mitochondrial disorders such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes and myoclonic epilepsy with ragged red fibers, most variants are point mutations, and there are a finite number of variants associated with the disorder. When testing for one of these disorders, known pathogenic variants can be tested for with polymerase chain reaction, or sequence analysis can be performed on the particular gene. For other mitochondrial disorders, such as chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome, the most common variants are deletions, and therefore duplication/deletion analysis would be the first test when these disorders are suspected. Table 1 provides examples of clinical symptoms and particular genetic variants in mtDNA or nDNA associated with particular mitochondrial syndromes. A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database. Lists of mtDNA and nDNA genes that may lead to mitochondrial disorders and testing laboratories in the United States are provided at the GeneTests website (funded by BioReference Laboratories) and Genetic Testing Registry of the National Center for Biotechnology Information website.

Table 1. Examples of Mitochondrial Diseases, Clinical Manifestations, and Associated Pathogenic Genes

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	• Stroke-like episodes at age <40 • Seizures and/or dementia • Pigmentary retinopathy • Lactic acidosis	• *MT-TL1*, *MT-ND5* (>95%) • *MT-TF*, *MT-TH*, *MT-TK*, *MT-TQ*, *MT-TS1*, *MT-TS2*, *MT-ND1*, *MT-ND6* (rare)
MERFF	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• *MT-TK* (>80%) • *MT-TF*, *MT-TP* (rare)
CPEO	• External ophthalmoplegia • Bilateral ptosis	• Various deletions of mitochondrial DNA
Kearns-Sayre syndrome	• External ophthalmoplegia at age <20 • Pigmentary retinopathy • Cerebellar ataxia • Heart block	• Various deletions of mitochondrial DNA
Leigh syndrome	• Subacute relapsing encephalopathy • Infantile-onset • Cerebellar/brainstem dysfunction	• *MT-ATP6*, *MT-TL1*, *MT-TK*, *MT-TW*, *MT-TV*, *MT-ND1*, *MT-ND2*, *MT-ND3*, *MT-ND4*, *MT-ND5*, *MT-ND6*, *MT-CO3* • Mitochondrial DNA deletions (rare) • *SUCLA2*, *NDUSFx*, *NDFVx*, *SDHA*, *BCS1L*, *SURF1*, *SCO2*, *COX15*
LHON	• Painless bilateral visual failure • Male predominance • Dystonia • Cardiac pre-excitation syndromes	• *MT-ND1*, *MT-ND4*, *MT-ND6*
NARP	• Peripheral neuropathy • Ataxia • Pigmentary retinopathy	• *MT-ATP6*
MNGIE	• Intestinal malabsorption • Cachexia • External ophthalmoplegia • Neuropathy	• *TP*
IOSCA	• Ataxia • Hypotonia • Athetosis • Ophthalmoplegia • Seizures	• *TWINKLE*
SANDO	• Ataxic neuropathy • Dysarthria	• *POLG*

Syndrome	Main Clinical Manifestations	Major Genes Involved
	• Ophthalmoparesis	
Alpers syndrome	• Intractable epilepsy • Psychomotor regression • Liver disease	• *POLG*, *DGUOK*, *MPV17*
GRACILE	• Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis	• *NDUSFx*
Coenzyme Q_{10} deficiency	• Encephalopathy • Steroid-resistant nephrotic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss	• *COQ2* • *COQ9* • *CABC1* • *ETFDH*
MELAS	• Stroke-like episodes at age <40 • Seizures and/or dementia • Pigmentary retinopathy • Lactic acidosis	• *MT-TL1*, *MT-ND5* (>95%) • *MT-TF*, *MT-TH*, *MT-TK*, *MT-TQ*, *MT-TS1*, *MT-TS2*, *MT-ND1*, *MT-ND6* (rare)
MERFF	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• *MT-TK* (>80%) • *MT-TF*, *MT-TP* (rare)
CPEO	• External ophthalmoplegia • Bilateral ptosis	• Various deletions of mitochondrial DNA
Kearns-Sayre syndrome	• External ophthalmoplegia at age <20 • Pigmentary retinopathy • Cerebellar ataxia • Heart block	• Various deletions of mitochondrial DNA

Adapted from Chinnery et al (2014), and Angelini et al (2009). CPEO: chronic progressive external ophthalmoplegia; GRACILE: growth retardation, aminoaciduria, cholestasis, iron overload, early death; IOSCA: infantile onset spinal cerebellar atrophy; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF: myoclonic epilepsy with ragged-red fibers; MNGIE: mitochondrial neurogastrointestinal encephalopathy; NARP: neuropathy, ataxia, and retinitis pigmentosa; SANDO: sensory ataxia, neuropathy, dysarthria and ophthalmoplegia.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for mitochondrial

disorders is under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary Of Evidence

For individuals who have signs and/or symptoms of a mitochondrial disorder who receive genetic testing, the evidence includes case series and cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, functional outcomes, health status measures, and quality of life. There is some evidence on clinical validity that varies by the patient population and testing strategy. Studies reporting diagnostic yield for known pathogenic variants using next-generation sequencing panels tend to report rates ranging from 15% to 25%. Clinical specificity is unknown, but population-based studies have reported that the prevalence of certain variants exceeds the prevalence of clinical disease, suggesting that the variant will be found in some people without clinical disease (false positives). Clinical utility is relatively high for confirming the diagnosis of mitochondrial disorders in people who have signs and symptoms of disease. In these patients, a positive result on genetic testing can avoid a muscle biopsy and eliminate the need for further clinical workup. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are symptomatic with a close relative with a mitochondrial disorder and a known pathogenic variant and who receive targeted familial variant testing, the evidence includes case series and cohort studies. Relevant outcomes are test validity, other test performance measures, changes in reproductive decision making, symptoms, functional outcomes, health status measures, and quality of life. Clinical validity is expected to be high for targeted testing of a known familial variant, assuming sufficient analytic validity. Clinical utility can be demonstrated by testing of at-risk family members who have a close relative with a pathogenic variant. When a specific mitochondrial disease is present in the family that is severe enough to cause impairment and/or disability, genetic testing may impact reproductive decision making. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

DEFINITIONS

N/A

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and

eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
0417U	0614U	81401	81403	81405	81406	81440	81460	81465
81479								

ICD-10-CM Diagnosis Code	Description
E88.40	Mitochondrial metabolism disorder, unspecified
E88.41	MELAS syndrome
E88.42	MERRF syndrome
E88.43	Disorders of mitochondrial tRNA synthetases
E88.49	Other mitochondrial metabolism disorders
E88.82	Obesity due to disruption of MC4R pathway
G31.82	Leigh's disease
H49.811	Kearns-Sayre syndrome, right eye
H49.812	Kearns-Sayre syndrome, left eye
H49.813	Kearns-Sayre syndrome, bilateral
H49.819	Kearns-Sayre syndrome, unspecified eye
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.438	Encounter for other genetic testing of female for procreative management
Z84.81	Family history of carrier of genetic disease

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POLICY HISTORY

MP 2.273	**04/27/2020 Consensus Review**. The word preconceptual was changed to preconceptional, no change in policy intent. Policy Guideline, Background, References and Coding updated.
	09/22/2021 Consensus Review. No change to policy statement. References and FEP updated.
	10/19/2022 Minor Review. Removed “and genetic testing may eliminate the need for muscle biopsy” from criteria. Adjusted language for carrier testing. Updated policy guidelines, background, and references. No coding changes.
	10/01/2023 Administrative Update. New diagnosis code E88.43 added to policy from new code review. New code 0417U added as MN.
	11/17/2023 Consensus Review. No change to policy stance, new references.
	08/30/2024 Administrative Update. New ICD code added E88.82, effective 10/01/2024.
	12/16/2024 Minor Review. Statement now includes “and genetic testing may eliminate the need for muscle biopsy”. No coding changes.
	07/22/2025 Consensus Review. No change to policy stance,
	09/24/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/12/2026 Administrative Update. Added code 0614U as part of new code process, effective 04/01/2026.

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Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.