

POLICY TITLE	GENETIC TESTING FOR MITOCHONDRIAL DISORDERS
POLICY NUMBER	MP-2.273

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I. 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 preconceptual 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.

Note: Genetic counseling must be performed by an individual with experience and expertise in genetic medicine and genetic testing methods prior to the above genetic testing.

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 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 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.

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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.

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) 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 policy updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO).

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.

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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 for 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. 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

II. PRODUCT VARIATIONS

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This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO- Refer to FEP Medical Policy Manual MP-2.04.117, Genetic Testing for Mitochondrial Disorders. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

III. DESCRIPTION/BACKGROUND

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MITOCHONDRIAL DNA

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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.¹ Additionally, there are over 1000 nuclear genes coding for proteins that support mitochondrial function.² 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 (ie, clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).³

MITOCHONDRIAL DISORDERS

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. The prevalence of these disorders has risen over the last 2 decades as the pathophysiology and clinical manifestations have been better characterized. It is currently estimated that the minimum prevalence of primary mitochondrial disorders is at least 1 in 5000.^{1,4}

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

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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 disorders 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 1 particular syndrome.⁵ Biochemical testing is indicated for patients who do not have a clear clinical picture of 1 specific disorder. Measurement of serum lactic acid is often used as a screening test, but the test is neither sensitive nor specific for mitochondrial disorders.²

A muscle biopsy can be performed if the diagnosis is uncertain after biochemical workup. However, this 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.¹ This characteristic finding may not be present in all types of mitochondrial disorders and also may be absent early in the course of disease.²

Treatment

Treatment of mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder.⁵ Identification of complications such as diabetes and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (eg, coenzyme Q, riboflavin) have been used, but empirical evidence of benefit is lacking.⁶ Exercise therapy for myopathy is often prescribed, but the effect on clinical outcomes is uncertain.⁵ 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.^{5,7} A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database.⁸ Lists of mtDNA and nDNA genes that

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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.^{9,10}

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

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	<ul style="list-style-type: none"> Stroke-like episodes at age <40 y Seizures and/or dementia Pigmentary retinopathy Lactic acidosis 	<ul style="list-style-type: none"> MT-TL1, MT-ND5 (>95%) MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS₁, MT-TS₂, MT-ND1, MT-ND6 (rare)
MERFF	<ul style="list-style-type: none"> Myoclonus Seizures Cerebellar ataxia Myopathy 	<ul style="list-style-type: none"> MT-TK (>80%) MT-TF, MT-TP (rare)
CPEO	<ul style="list-style-type: none"> External ophthalmoplegia Bilateral ptosis 	<ul style="list-style-type: none"> Various deletions of mtDNA
Kearns-Sayre syndrome	<ul style="list-style-type: none"> External ophthalmoplegia at age <20 y Pigmentary retinopathy Cerebellar ataxia Heart block 	<ul style="list-style-type: none"> Various deletions of mtDNA
Leigh syndrome	<ul style="list-style-type: none"> Subacute relapsing encephalopathy Infantile-onset Cerebellar/brain stem dysfunction 	<ul style="list-style-type: none"> MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3 mtDNA deletions (rare) SUCLA2, NDUSF_x, NDFV_x, SDHA, BCS1L, SURF1, SCO2, COX15
LHON	<ul style="list-style-type: none"> Painless bilateral visual failure Male predominance Dystonia Cardiac pre-excitation syndromes 	<ul style="list-style-type: none"> MT-ND1, MT-ND4, MT-ND6
NARP	<ul style="list-style-type: none"> Peripheral neuropathy Ataxia Pigmentary retinopathy 	<ul style="list-style-type: none"> MT-ATP6
MNGIE	<ul style="list-style-type: none"> Intestinal malabsorption Cachexia External ophthalmoplegia Neuropathy 	<ul style="list-style-type: none"> TP
IOSCA	<ul style="list-style-type: none"> Ataxia Hypotonia Athetosis Ophthalmoplegia Seizures 	<ul style="list-style-type: none"> TWINKLE
SANDO	<ul style="list-style-type: none"> Ataxic neuropathy Dysarthria 	<ul style="list-style-type: none"> POLG

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Syndrome	Main Clinical Manifestations	Major Genes Involved
Alpers syndrome	<ul style="list-style-type: none"> • Ophthalmoparesis • Intractable epilepsy • Psychomotor regression • Liver disease 	<ul style="list-style-type: none"> • <i>POLG, DGUOK, MPV17</i>
GRACILE	<ul style="list-style-type: none"> • Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis 	<ul style="list-style-type: none"> • <i>NDUSF_x</i>
Coenzyme Q ₁₀ deficiency	<ul style="list-style-type: none"> • Encephalopathy • Steroid-resistant nephrotic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss 	<ul style="list-style-type: none"> • <i>COQ2</i> • <i>COQ9</i> • <i>CABC1</i> • <i>ETFDH</i>

Adapted from Chinnery et al (2014)⁵ and Angelini et al (2009).⁷
 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.

IV. RATIONALE

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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.

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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.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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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

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terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes®							
81440	81460	81465					

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ICD-10-CM Diagnosis Code	Description
E88.40	Mitochondrial metabolism disorder, unspecified
E88.41	MELAS syndrome
E88.42	MERRF syndrome
E88.49	Other mitochondrial metabolism disorders
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

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.273	CAC 7/22/14 New policy adopting BCBSA. Information related to genetic testing related to mitochondrial disorders was extracted from retired MP 2.232 Genetic Testing for Inheritable Disease and this separate policy created. Policy criteria changed. Medicare variation added referencing L33640 Biomarkers Overview for information related to testing of other family member such as possible/probable carriers which is not statutorily covered by Medicare.
	01/2015 -New 2015 CPT code added to the policy.
	CAC 7/21/15. Consensus. Wording of policy statements revised to be consistent with standardized genetic language. No change to intent. Rationale and references updated. No coding changes.
	11/2/15 Administrative change. LCD number changed from L33640 to L35062 due to Novitas update to ICD-10.
	CAC 7/26/16 Consensus. No change to policy statements. Background, rationale and references updated. Coding updated.
	1/1/17 Administrative update. Product variations reformatted.
	CAC 9/26/17 Minor revision. Policy statements revised so that genetic testing is no longer restricted to a set of specific mutations documented for a particular mitochondrial disorder. Genetic counseling also added as a requirement. Description/Background, Rationale and Reference sections updated. Coding Updated.
	6/13/18 Consensus review. No changes to the policy statements. Background and references updated. Rationale revised.

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