Medical Policy
Genetic Testing of Mitochondrial Disorders

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Policy Number: 685
BCBSA Reference Number: 2.04.117
NCD/LCD: N/A

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing to establish a genetic diagnosis of a mitochondrial disorder may be MEDICALLY NECESSARY when signs and symptoms of a mitochondrial disorder or in asymptomatic relatives of an individual with a mitochondrial disorder.

Targeted genetic testing for a known familial variant of at-risk relatives may be 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.

Genetic testing for mitochondrial disorders is considered INVESTIGATIONAL in all other situations when the criteria for medical necessity are not met.

Prior Authorization Information
Inpatient
• For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
• For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.
<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Prior authorization is not required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is not required.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>Prior authorization is not required.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>Prior authorization is not required.</td>
</tr>
</tbody>
</table>

### CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

#### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81440</td>
<td>Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP</td>
</tr>
<tr>
<td>81460</td>
<td>Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection</td>
</tr>
<tr>
<td>81465</td>
<td>Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed</td>
</tr>
</tbody>
</table>

### Description

**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**

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. Some specific mitochondrial disorders are listed next:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome;
- Myoclonic epilepsy with ragged red fibers syndrome;
- Kearn-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 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. 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.

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

**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 FOR MITOCHONDRIAL DISORDERS**

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 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**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Clinical Manifestations</th>
<th>Major Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELAS</td>
<td>Stroke-like episodes at age &lt;40 y</td>
<td>MT-TL1, MT-ND5 (&gt;95%)</td>
</tr>
<tr>
<td></td>
<td>Seizures and/or dementia</td>
<td>MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS1, MT-TS2, MTND1, MT-ND6 (rare)</td>
</tr>
<tr>
<td></td>
<td>Pigmentary retinopathy</td>
<td></td>
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<tr>
<td></td>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>MERFF</td>
<td>Myoclonus</td>
<td>MT-TK (&gt;80%)</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>MT-TF, MT-TP (rare)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
<td></td>
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<tr>
<td></td>
<td>Myopathy</td>
<td></td>
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<tr>
<td>CPEO</td>
<td>External ophthalmoplegia</td>
<td>Various deletions of mtDNA</td>
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<tr>
<td></td>
<td>Bilateral ptosis</td>
<td></td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>External ophthalmoplegia at age &lt;20 y</td>
<td>Various deletions of mtDNA</td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart block</td>
<td></td>
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<tr>
<td>Leigh syndrome</td>
<td>Subacute relapsing encephalopathy</td>
<td>MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</td>
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<tr>
<td></td>
<td>Infantile-onset</td>
<td>mtDNA deletions (rare)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar/brain stem dysfunction</td>
<td>SUCLA2, NDUSFx, NDFVx, SDHA, BCS1L, SURF1, SCO2, COX15</td>
</tr>
<tr>
<td>LHON</td>
<td>Painless bilateral visual failure</td>
<td>MT-ND1, MT-ND4, MT-ND6</td>
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<td></td>
<td>Male predominance</td>
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<tr>
<td></td>
<td>Dystonia</td>
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<tr>
<td></td>
<td>Cardiac pre-excitation syndromes</td>
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<tr>
<td>NARP</td>
<td>Peripheral neuropathy</td>
<td>MT-ATP6</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pigmentary retinopathy</td>
<td></td>
</tr>
<tr>
<td>MNGIE</td>
<td>Intestinal malabsorption</td>
<td>TP</td>
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<tr>
<td></td>
<td>Cachexia</td>
<td></td>
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<tr>
<td></td>
<td>External ophthalmoplegia</td>
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<tr>
<td></td>
<td>Neuropathy</td>
<td></td>
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<tr>
<td>OSCA</td>
<td>Ataxia</td>
<td>TWINKLE</td>
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<tr>
<td></td>
<td>Hypotonia</td>
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<td></td>
<td>Athetosis</td>
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<tr>
<td></td>
<td>Ophthalmoplegia</td>
<td></td>
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<tr>
<td></td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>SANDO</td>
<td>Ataxic neuropathy</td>
<td>POLG</td>
</tr>
</tbody>
</table>
• Dysarthria
• Ophthalmoparesis

Alpers syndrome
• Intractable epilepsy
• Psychomotor regression
• Liver disease
• POLG, DGUOK, MPV17

GRACILE
• Growth retardation
• Aminoaciduria
• Cholestasis
• Iron overload
• Lactic acidosis
• NDUSFx

Coenzyme Q10 deficiency
• Encephalopathy
• Steroid-resistant nephrotic syndrome
• Hypertrophic cardiomyopathy
• Retinopathy
• Hearing loss
• COQ2
• COQ9
• CABC1
• ETFDH

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.

Summary
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 accuracy and validity, other test performance measures, symptoms, functional outcomes, health status measures, and quality of life. There is a lack of published data on analytic validity. Commercial testing sites claim that analytic validity approaches 100% and describe testing methods expected to have high analytic validity. 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 accuracy and validity, other test performance measures, changes in reproductive decision making, symptoms, functional outcomes, health status measures, and quality of life. There is a lack of published data on analytic validity. Commercial testing sites claim analytic validity approaching 100% and describe testing methods expected to have high analytic validity. 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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>11/2017</td>
<td>BCBSA National medical policy review.</td>
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</table>
Policy statements revised so that genetic testing is no longer restricted to a set of specific mutations documented for a particular mitochondrial disorder. Effective 11/1/2017.

7/2016  New references added from BCBSA National medical policy.
1/2015  Clarified coding information.
10/2014  New policy describing medically necessary and not medically necessary indications. Effective October 1, 2014.

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


