Medical Policy
Genetic Testing of Mitochondrial Disorders

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- Policy: Medicare
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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 confirm the diagnosis of a mitochondrial disorder may be MEDICALLY NECESSARY when signs and symptoms of a specific mitochondrial disorder are present (see table 1) but a definitive diagnosis cannot be made without genetic testing, and both of the following criteria are present:
- Genetic testing avoids the need for a muscle biopsy; AND
- Genetic testing is restricted to the specific mutations that have been documented to be pathogenic for the particular mitochondrial disorder being considered. (See table 1).

Genetic testing of at-risk female 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 mutation that is known to be pathogenic for that specific mitochondrial disorder has been identified in the index case.

Genetic testing for mitochondrial disorders using expanded panel testing is INVESTIGATIONAL.

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

To maximize the positive and the negative predictive value of testing, testing should be restricted to patients with a clinical picture consistent with a specific disorder and to a small number of mutations that are known to be pathogenic for that disorder. Table 1 is a guide to clinical symptoms and particular genetic mutations that are associated with particular mitochondrial syndromes.
Table 1. Mitochondrial Disorders, Clinical Manifestations, and Associated Pathogenic Genes (Adapted from Chinnery et al)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Clinical Manifestations</th>
<th>Major Genes Involved</th>
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</thead>
<tbody>
<tr>
<td>MELAS</td>
<td>• Stroke-like episodes at age &lt;40 y&lt;br&gt;• Seizures and/or dementia&lt;br&gt;• Pigmentary retinopathy&lt;br&gt;• Lactic acidosis</td>
<td>• MT-TL1, MT-ND5 (&gt;95%)&lt;br&gt;• MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS1, MT-TS2, MTND1, MT-ND6 (rare)</td>
</tr>
<tr>
<td>MERFF</td>
<td>• Myoclonus&lt;br&gt;• Seizures&lt;br&gt;• Cerebellar ataxia&lt;br&gt;• Myopathy</td>
<td>• MT-TK (&gt;80%)&lt;br&gt;• MT-TF, MT-TP (rare)</td>
</tr>
<tr>
<td>CPEO</td>
<td>• External ophthalmoplegia&lt;br&gt;• Bilateral ptosis</td>
<td>• Various deletions of MT-DNA</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>• External ophthalmoplegia &lt;20 y&lt;br&gt;• Pigmentary retinopathy&lt;br&gt;• Cerebellar ataxia&lt;br&gt;• Heart block</td>
<td>• Various deletions of MT-DNA</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>• Subacute relapsing encephalopathy&lt;br&gt;• Infantile onset&lt;br&gt;• Cerebellar/brain stem dysfunction</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&lt;br&gt;• MT-DNA deletions (rare)</td>
</tr>
<tr>
<td>LHON</td>
<td>• Painless bilateral visual failure&lt;br&gt;• Male predominance&lt;br&gt;• Dystonia&lt;br&gt;• Cardiac pre-excitation syndromes</td>
<td>• MT-ND1, MT-ND4, MT-ND6</td>
</tr>
<tr>
<td>NARP</td>
<td>• Peripheral neuropathy&lt;br&gt;• Ataxia&lt;br&gt;• Pigmentary retinopathy</td>
<td>• MT-ATP6</td>
</tr>
</tbody>
</table>

CPEO: chronic progressive external ophthalmoplegia; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF: myoclonic epilepsy with ragged red fibers; NARP: neuropathy, ataxia, and retinitis pigmentosa.

Panels of mutations that are disease-specific (ie, contain only mutations associated with a specific type of mitochondrial disorder) may meet the criteria for medical necessity under certain circumstances (see Policy No. 734 General Approach to Evaluating the Utility of Genetic Panels). When criteria for medical necessity are met, these panels may be used in place of testing individual genes in sequence.

Disease-specific panels should include a list of mutations that approximates (but may not be identical to) those listed in Table 1 for each specific disorder.

**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

- Yes indicates that prior authorization is required.
- No indicates that prior authorization is not required.
- N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Commercial PPO and Indemnity</th>
<th>Medicare HMO Blue℠</th>
<th>Medicare PPO Blue℠</th>
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<td>No</td>
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</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 following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<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, DGUK, 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>
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</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 that are involved in the translation and/or assembly of the mitochondrial complex. In addition, there are over 1000 nuclear genes that code 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 in several important ways. Inheritance of mitochondrial DNA does not follow traditional Mendelian patterns. Rather, mtDNA is inherited only from maternal DNA so that disorders that result from mutations 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 nuclear DNA, which only has 1 copy per cell. Because there are many copies of each gene, mutations 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 mutation, ranging from 0% to 100%. Clinical expression of the mutation will generally depend on a threshold effect (ie, clinical symptoms will begin to appear when the percent 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 that are 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 been rising 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 5000.2,5

Some of the specific mitochondrial disorders are listed next:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome;
- Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome;
- Kearns-Sayre syndrome (KSS);
- Leigh syndrome (LS);
- Chronic progressive external ophthalmoplegia (CPEO);
- Leber hereditary optic neuropathy (LHON);
- Neurogenic weakness with ataxia and retinitis pigmentosa (NARP).

Most of these disorders are characterized by multisystem dysfunction, which generally includes myopathies and neurologic dysfunction and may involve multiple other organs. Each of the defined mitochondrial disorders has a characteristic set of signs of 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.

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 one particular syndrome.1 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 disorders.3

**Genetic Testing of 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.2 This characteristic finding may not be present in all types of mitochondrial disorders, and also may be absent early in the course of disease.3

Treatment of mitochondrial disease is largely supportive, as there are no specific therapies than impact the natural history of the disorder.1 Identification of complications such as diabetes mellitus 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.1 The possibility of gene transfer therapy is under consideration, but is at an early stage of development and has not yet been tested in clinical trials.

**Genetic Testing for Mitochondrial Disorders**

Genetic testing for mitochondrial disorders may involve testing for point mutations, deletion/duplication analysis, and/or whole mitochondrial exome sequencing. The type of testing done depends on the specific disorder being considered. For some primary mitochondrial disorders such as MELAS and MERRF, most mutations are point mutations, and there are a finite number of mutations associated with the disorder. When testing for one of these disorders, known pathogenic mutations can be tested for with polymerase chain reaction, or sequence analysis can be performed on the particular gene. For other mitochondrial disorders such as CPEO and KSS, the most common mutations are deletions, and therefore duplication/deletion analysis would be the first test when these disorders are suspected. Testing for the individual mutations associated with mitochondrial disorders is offered by numerous labs. Genetic panel testing is also available, with numerous different panels available. Some of these are
disease-specific panels that include only a small number of genes associated with a particular mitochondrial disorder. For example, Transgenomic™ offers a MELAS panel consisting of 10 mutations that have specific associations with MELAS syndrome.7

There are at least 7 labs that currently offer “expanded” panel testing for mitochondrial disorders by next-generation sequencing.8 The number of genes included in these panels varies widely, ranging from 37 to 1192. These types of panels include a larger number of genes that are associated with numerous different mitochondrial disorders. These expanded panels are often intended to be comprehensive panels that test for all known mitochondrial and nuclear genes associated with any mitochondrial disorder. All of the expanded panels, with the exception of MEDomics® include analysis of both mitochondrial genes and nuclear genes that are thought to be involved with mitochondrial function. The specific labs and number of genes tested, taken from websites and/or published literature. The composition of these expanded panels vary widely in terms of the number of genes, the percent of genes that are “classic” mutations for mitochondrial disorders, and the inclusion of genes that are not associated with any disease phenotype.8

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Number of Genes Included on Panel</th>
</tr>
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<tbody>
<tr>
<td>Gene Dx® (Gaithersburg, MD)</td>
<td>101</td>
</tr>
<tr>
<td>Transgenomic® (New Haven, CT)</td>
<td>447</td>
</tr>
<tr>
<td>Courtagen® (Woburn, MA)</td>
<td>1192</td>
</tr>
<tr>
<td>ARUP® (Salt Lake City, UT)</td>
<td>108</td>
</tr>
<tr>
<td>Baylor® (Houston, TX)</td>
<td>162</td>
</tr>
<tr>
<td>Medical Neurogenetics® (Atlanta, GA)</td>
<td>393</td>
</tr>
<tr>
<td>MEDomics® (Azusa, CA)</td>
<td>37</td>
</tr>
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</table>

**Summary**

Mitochondrial disorders are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes that are involved in oxidative metabolism. These disorders can be due to pathogenic mutations in the mitochondrial DNA that code for the protein complexes, or mutations in nuclear DNA that code for proteins involved in translation and assembly of mitochondrial complexes. Genetic sequencing of mitochondrial DNA and nuclear genes associated with mitochondrial processes is commercially available. This policy addresses the following categories of genetic testing for mitochondrial disorders: Diagnostic testing of an individual's germline to benefit the individual; testing an asymptomatic individual to determine future risk of disease; and preconceptual carrier testing.

Mitochondrial disorders can be difficult to diagnose. There are many different related but distinct syndromes, and some patients have overlapping syndromes. The “classic” forms of these disorders arise from mutations in mitochondrial DNA. Numerous other types of mitochondrial disorders arise from mutations in nuclear DNA that have a role in assembly or function of the mitochondria.

There is a lack of published data on analytic validity, but commercial testing uses methods that are expected to have high analytic validity. There is some evidence on clinical validity that varies by the specific disorder. For example, for the most well understood disorders such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, small series of patients with a clinically diagnosed disorder have reported that a high proportion of patients have a pathogenic mutation. Clinical specificity is unknown, but population-based studies have reported that the prevalence of certain mutations exceeds the prevalence of clinical disease, suggesting that the mutation will be found in some people without clinical disease (false positives). The use of expanded next-generation sequencing panels or whole exome sequencing will increase the detection rate for pathogenic mutations, but will also increase the false-positive rate and the number of variants of unknown significance.
Clinical utility is relatively high for confirming the diagnosis of mitochondrial disorders in people who have signs and symptoms indicating a moderate to high pretest likelihood of disease. In these patients, a positive result on genetic testing can avoid a muscle biopsy and can eliminate the need for further clinical workup. For testing of at-risk family members, clinical utility can also be demonstrated. When disease is present that is severe enough to cause impairment and/or disability, genetic testing for reproductive decision making is a reasonable choice that may prevent transmission of disease to offspring.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>7/2016</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>1/2015</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>10/2014</td>
<td>New policy describing medically necessary and not medically necessary indications. Effective October 1, 2014.</td>
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</table>

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