MEDICAL POLICY – 12.04.117
Genetic Testing for Mitochondrial Disorders

Introduction

Mitochondria are found in all cells of the body except red blood cells. The mitochondria have many functions within a cell, including creating most of the energy the cells need. When mitochondria are damaged, the cell has less energy. And less energy leads to problems within the cell and even cell death. Because mitochondria come from only the mother, a child can inherit mitochondrial DNA problems only from the mother. Mitochondrial disease is a chronic illness that may be present when a child is born or may develop later. It usually causes severe physical problems and developmental issues. Physical examination is usually enough to diagnose mitochondrial disease. Other specialized tests may also be needed for an accurate diagnosis. Genetic testing can be used when the other usual tests for mitochondrial disease are not able to make a clear diagnosis. This policy describes when genetic testing for mitochondrial disease is considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Testing | Medical Necessity
--- | ---
Genetic testing to establish a genetic diagnosis of a mitochondrial disorder | 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. Patients usually have complex multisystem clinical findings (see Table 3 below).

Targeted genetic testing | 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

Panel Testing | Investigational
--- | ---
Genetic testing for mitochondrial disorders | Genetic testing for mitochondrial disorders is considered investigational in all other situations when the criteria for medical necessity are not met.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
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<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
</tbody>
</table>
| 81440 | Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L,
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP</td>
<td></td>
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<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>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

There are CPT codes for genomic sequencing procedures (or next-generation sequencing panels) for mitochondrial diseases. If the panel complies with the requirements in the code descriptor, these codes may be used:

81440 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.

81460 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

81465 Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed.

If the panel does not meet the requirements in the codes above or the test is not a panel, there are several mitochondrial tests listed in the CPT tier 2 molecular pathology codes.

Code 81401 includes:

- MT-ATP6 (mitochondrially encoded ATP synthase 6) (eg, neuropathy with ataxia and retinitis pigmentosa [NARP], Leigh syndrome), common variants (eg, m.8993T>G, m.8993T>C)
• MT-ND4, MT-ND6 (mitochondrially encoded NADH dehydrogenase 4, mitochondrially encoded NADH dehydrogenase 6) (eg, Leber hereditary optic neuropathy [LHON]), common variants (eg, m.11778G>A, m.3460G>A, m.14484T>C)

• MT-TK (mitochondrially encoded tRNA lysine) (eg, myoclonic epilepsy with ragged-red fibers [MERRF]), common variants (eg, m.8344A>G, m.8356T>C)

• MT-ND5 (mitochondrially encoded tRNA leucine 1 [UUA/G], mitochondrially encoded NADH dehydrogenase 5) (eg, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes [MELAS]), common variants (eg, m.3243A>G, m.3271T>C, m.3252A>G, m.13513G>A)

• MT-TL1 (mitochondrially encoded tRNA leucine 1 [UUA/G]) (eg, diabetes and hearing loss), common variants (eg, m.3243A>G, m.14709 T>C)

• MT-TS1, MT-RNR1 (mitochondrially encoded tRNA serine 1 [UCN], mitochondrially encoded 12S RNA) (eg, nonsyndromic sensorineural deafness [including aminoglycoside-induced nonsyndromic deafness]), common variants (eg, m.7445A>G, m.1555A>G)

Code 81403 includes:

• MT-RNR1 (mitochondrially encoded 12S RNA) (eg, nonsyndromic hearing loss), full gene sequence

• MT-TS1 (mitochondrially encoded tRNA serine 1) (eg, nonsyndromic hearing loss), full gene sequence

Code 81404 includes:

• C10orf2 (chromosome 10 open reading frame 2) (eg, mitochondrial DNA depletion syndrome), full gene sequence,

• MPV17 (MpV17 mitochondrial inner membrane protein)(eg, mitochondrial DNA depletion syndrome), duplication/deletion analysis,

• NDUFA1 (NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 1, 7.5kDa) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence,

• NDUFAF2 (NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, assembly factor 2) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence,

• NDUFS4 (NADH dehydrogenase [ubiquinone] Fe-S protein 4, 18kDa [NADH-coenzyme Q reductase]) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence,
• SCO2 (SCO cytochrome oxidase deficient homolog 2 [SCO1L]) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence,

• SLC25A4 (solute carrier family 25 [mitochondrial carrier; adenine nucleotide translocator], member 4) (eg, progressive external ophthalmoplegia), full gene sequence,

• TACO1 (translational activator of mitochondrial encoded cytochrome c oxidase I) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence.

Code 81405 includes:

• BCS1L (BCS1-like [S. cerevisiae]) (eg, Leigh syndrome, mitochondrial complex III deficiency, GRACILE syndrome), full gene sequence,

• COX10 (COX10 homolog, cytochrome c oxidase assembly protein) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence,

• COX15 (COX15 homolog, cytochrome c oxidase assembly protein) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence,

• DGUOK (deoxyguanosine kinase) (eg, hepatocerebral mitochondrial DNA depletion syndrome), full gene sequence,

• MPV17 (MpV17 mitochondrial inner membrane protein)(eg, mitochondrial DNA depletion syndrome), full gene sequence,

• NDUFV1 (NADH dehydrogenase [ubiquinone] flavoprotein 1, 51kDa) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence,

• RRM2B (ribonucleotide reductase M2 B [TP53 inducible]) (eg, mitochondrial DNA depletion), full gene sequence,

• SCO1 (SCO cytochrome oxidase deficient homolog 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence,

• SURF1 (surfeit 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence,

• TK2 (thymidine kinase 2, mitochondrial) (eg, mitochondrial DNA depletion syndrome), full gene sequence,

• TYMP (thymidine phosphorylase) (eg, mitochondrial DNA depletion syndrome), full gene sequence.
Code 81406 includes:

- FASTKD2 (FAST kinase domains 2) (e.g., mitochondrial respiratory chain complex IV deficiency), full gene sequence,

- NDUFS1 (NADH dehydrogenase [ubiquinone] Fe-S protein 1, 75kDa [NADH-coenzyme Q reductase]) (e.g., Leigh syndrome, mitochondrial complex I deficiency), full gene sequence,

- SDHA (succinate dehydrogenase complex, subunit A, flavoprotein [Fp]) (e.g., Leigh syndrome, mitochondrial complex II deficiency), full gene sequence.

If there is no specific listing in the CPT molecular pathology code list for the mitochondrial DNA test that is performed, the unlisted molecular pathology code 81479 may be reported. If multiple unlisted mitochondrial DNA tests are performed, the unlisted code is only reported once for all of the unlisted tests.

**Related Information**

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.

**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.

**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 preconceptual 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**

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 (see Table 1). 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 and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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 2** shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table 1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</table>
Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Benefit Application

Some Plans may have contract or benefit exclusions for genetic testing.

Specific contract language must be reviewed and considered when determining coverage for genetic testing. In some cases, coverage for testing the index case may be available through the contract that covers the unaffected, at-risk individual who will benefit from knowing the results of the genetic test.
Description

Mitochondrial disorders are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes involved in oxidative metabolism. There are many related but distinct syndromes, and some patients have overlapping syndromes. As a result, these disorders can be difficult to diagnose. Genetic testing has the potential to improve the accuracy of the diagnosis of mitochondrial disorders. Genetic testing also has the potential to determine future risk of disease in individuals who have a close relative with a pathogenic mutation.

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 nuclear DNA, 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 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 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.\(^1,4\)

Some of the specific mitochondrial disorders are:

- 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 of the defined mitochondrial disorders 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 one 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 diseases.\(^2\)

A muscle biopsy can be performed if the diagnosis is uncertain after biochemical workup. However, this invasive test is not definitive in all cases. The presence of “ragged red fibers” on histologic analysis is consistent with a mitochondrial disease. Ragged red fibers represent a
proliferation of defective mitochondrial.\textsuperscript{1} This characteristic finding may not be present in all types of mitochondrial diseases, and also may be absent early in the course of disease.\textsuperscript{2}

**Treatment**

Treatment of mitochondrial disease is largely supportive, because there are no specific therapies that impact the natural history of the disorder.\textsuperscript{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.\textsuperscript{6} Exercise therapy for myopathy is often prescribed, but the effect on clinical outcomes is uncertain.\textsuperscript{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 mitochondrial 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 is 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 3* provides examples of clinical symptoms and particular genetic variants in mtDNA or nDNA associated with particular mitochondrial syndromes.\textsuperscript{5,7} A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database.\textsuperscript{8} Lists of mtDNA and nDNA genes that may lead to mitochondrial diseases and testing laboratories in the United States are provided at the Genetic Testing Registry of the National Center for Biotechnology Information website.\textsuperscript{9}
### Table 3. 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&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, MT-ND1, 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 mtDNA</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>External ophthalmoplegia at age &lt;20 y&lt;br&gt;Pigmentary retinopathy&lt;br&gt;Cerebellar ataxia&lt;br&gt;Heart block</td>
<td>Various deletions of mtDNA</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;mtDNA deletions (rare)&lt;br&gt;SUCLA2, NDUSFx, NDFVx, SDHA, BCS1L, SURF1, SCO2, COX15</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>
<tr>
<td>MNGIE</td>
<td>Intestinal malabsorption&lt;br&gt;Cachexia</td>
<td>TP</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Main Clinical Manifestations</td>
<td>Major Genes Involved</td>
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<tr>
<td>IOSCA</td>
<td>External ophthalmoplegia</td>
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<td></td>
<td>Neuropathy</td>
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<td></td>
<td>Ataxia</td>
<td>TWINKLE</td>
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<td></td>
<td>Hypotonia</td>
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<td>Athetosis</td>
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<td></td>
<td>Ophthalmoplegia</td>
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<td></td>
<td>Seizures</td>
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<tr>
<td>SANDO</td>
<td>Ataxic neuropathy</td>
<td>POLG</td>
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<td></td>
<td>Dysarthria</td>
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<tr>
<td></td>
<td>Ophthalmoparesis</td>
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<tr>
<td>Alpers syndrome</td>
<td>Intractable epilepsy</td>
<td>POLG, DGUOK, MPV17</td>
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<tr>
<td></td>
<td>Psychomotor regression</td>
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<tr>
<td></td>
<td>Liver disease</td>
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<tr>
<td>GRACILE</td>
<td>Growth retardation</td>
<td>NDUSFx</td>
</tr>
<tr>
<td></td>
<td>Aminoaciduria</td>
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<td></td>
<td>Cholestasis</td>
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<td></td>
<td>Iron overload</td>
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<tr>
<td></td>
<td>Lactic acidosis</td>
<td></td>
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<tr>
<td>Coenzympe Q10 deficiency</td>
<td>Encephalopathy</td>
<td>COQ2</td>
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<tr>
<td></td>
<td>Steroid-resistant nephrotic syndrome</td>
<td>COQ9</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic cardiomyopathy</td>
<td>CABC1</td>
</tr>
<tr>
<td></td>
<td>Retinopathy</td>
<td>ETFDH</td>
</tr>
<tr>
<td></td>
<td>Hearing loss</td>
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</tbody>
</table>

Adapted from Chinnery et al (2014)\textsuperscript{5} and Angelini et al (2009).\textsuperscript{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.
Summary of Evidence

For individuals who have signs and/or symptoms of a mitochondrial disease 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 NGS panels tend to report rates ranging from 15% to 25%. Clinical specificity is unknown, but population-based studies have indicated that the prevalence of certain variants exceeds the prevalence of clinical disease, suggesting that the variant will be found in some people without the clinical disease (false positives). Clinical utility is relatively high for confirming the diagnosis of mitochondrial diseases in people who have signs and symptoms of the 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 disease 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 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.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in May 2018 did not identify any ongoing or unpublished trials that would likely influence this review.
Practice Guidelines and Position Statements

*Foundation for Mitochondrial Medicine*

The Foundation for Mitochondrial Medicine (2013) published an overview of mitochondrial disease; genetic testing was specifically addressed. The overview included the following statements:

- Mitochondrial disease can look like a number of different diseases such as autism, Parkinson disease, Alzheimer disease, Lou Gehrig disease, muscular dystrophy, and chronic fatigue.
- There are 3 categories of diagnostic criteria:
  - Clinical
  - Biochemical
  - Genetic
- A diagnosis of mitochondrial disease requires an integrated approach; there is “no single test to diagnose mitochondrial disease in most patients.”
- Genetic testing, alone, is “rarely ... sufficient to diagnose mitochondrial disease.”

*Mitochondrial Medicine Society*

The Mitochondrial Medicine Society (2015) published a consensus statement on the diagnosis and management of mitochondrial disease. Most evidence was grade III or less (case-control, low-quality cohort studies, or expert opinion without explicit critical appraisal) using the Oxford Centre for Evidence-Based Medicine criteria. Consensus recommendations were reported using the Delphi method. A subset of the consensus recommendations for DNA testing are as follows:

1. Massively parallel sequencing/NGS [next-generation sequencing] 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. 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.

3. 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.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for mitochondrial diseases is under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**References**


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>08/11/14</td>
<td>New Policy. Policy developed with literature review through April 20, 2014. Genetic testing for specific mitochondrial mutations may be considered medically necessary for patients with signs and symptoms of mitochondrial disorders, and for at-risk family members if there is disease of at least moderate severity and a pathogenic mutation has been identified. The use of expanded genetic panels for mitochondrial disorders is considered investigational.</td>
</tr>
<tr>
<td>01/14/15</td>
<td>Coding update. New CPT code 81440, effective 1/1/15, added to the policy.</td>
</tr>
<tr>
<td>07/14/15</td>
<td>Annual Review. Policy updated with literature review through 05/01/15, references 8 and 22-24 added. Wording of policy statements revised to be consistent with standardized genetic language. ICD-9 and ICD-10 diagnosis codes removed; these were listed for informational purposes only.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Update Related Policies. Removed 12.04.520 as it was archived.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Annual Review, approved July 18, 2017. Policy moved into the new format. Policy updated with literature review through April 25, 2017; references 7-10, 13-14, 16-18, 20-22, and 30 added. Policy revised with updated genetics nomenclature. Policy statements revised so that genetic testing is no longer restricted to a set of specific mutations documented for a particular mitochondrial disorder.</td>
</tr>
<tr>
<td>09/01/18</td>
<td>Annual Review, approved August 10, 2018. Policy updated with literature review through April 2018; reference 10 was added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>
**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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Email: AppealsDepartmentInquinies@Premera.com

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You may also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

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This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

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يحمي هذا الإشعار معلومات حاسمة. قد يحمي هذا الإشعار لمعلومات معينة طلب أو
العملية التي تزيد الدعم عليها من خلال
Premera Blue Cross معلومات
قد تكون هناك تأثيرات مهمة
Premera Blue Cross
لمعلومات
800-722-1471 (TTY: 800-842-5357).

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Avi sina a gen Enfòmasyon Enpòtan ladan. Avi sina a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan osawa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sina a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka kente kouvèti asirans sante w la osawa pou yo ka ede w akav desans yo. Se dwa w pou reswewa enfòmasyon sa a ak asisants nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):


Italiano (Italian):


Oromoo (Cushite):


Français (French):


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Este aviso contiene información importante. Este aviso puede contener información importante sobre su solicitud o cobertura a través de Premera Blue Cross. Puede haber fechas clave en este aviso. Puede ser necesario que tome medidas antes de ciertas fechas para preservar su cobertura de salud o ayudas. Usted tiene el derecho a obtener esta información y asistencia en su idioma gratuitamente. Llame al 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):


Italiano (Italian):


037338 (07-2016)