**Policy Statement**

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 both of the following conditions (see Benefit Application section):

- 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.

**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.

Table PG1 is a guide to clinical symptoms and particular genetic mutations associated with particular mitochondrial syndromes.

**Table PG1. Mitochondrial Disorders, Clinical Manifestations, and Associated Pathogenic Genes (Adapted from Chinnery et al, 2014)**

<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 less than 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 (greater than 95%)&lt;br&gt;MT-TF, MT-TH, MT-TK, MT-TQ, MT-TSs, MT-TSs, 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 (greater than 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 at age less than 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;MTDNA deletions (rare)</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Main Clinical Manifestations</td>
<td>Major Genes Involved</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------</td>
<td>----------------------</td>
</tr>
</tbody>
</table>
| LHON     | • Painless bilateral visual failure  
         | • Male predominance  
         | • Dystonia  
         | • Cardiac pre-excitation syndromes | • MT-ND1, MT-ND4, MT-ND6 |
| NARP     | • Peripheral neuropathy  
         | • Ataxia  
         | • Pigmentary retinopathy | • MT-ATP6 |


**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 2.04.102 (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 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**

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 evidence review updates starting in 2017 (see Table PG2). 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 PG3 shows the recommended standard terminology - “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” - to describe variants identified that cause Mendelian disorders.

**Table PG2. 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>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td>Change in the DNA sequence</td>
</tr>
</tbody>
</table>

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Table PG3. 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
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.

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

- **81440**: Nuclear encoded mitochondrial genes (e.g., 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, SC01, SC02, SLC25A4, SUCLG1, TAZ, TK2, and TYMP
- **81460**: Whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERRF], neuroathy, 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 (e.g., 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) (e.g., neuropathy with ataxia and retinitis pigmentosa [NARP], Leigh syndrome), common variants (e.g., m.8993T>G, m.8993T>C)
MT-ND4, MT-ND6 (mitochondrially encoded NADH dehydrogenase 4, mitochondrial encoded NADH dehydrogenase 6) (e.g., Leber hereditary optic neuropathy [LHON]), common variants (e.g., m.11778G>A, m.3460G>T, m.1448T>C)
MT-TK (mitochondrially encoded tRNA lysine) (e.g., myoclonic epilepsy with ragged-red fibers [MERRF]), common variants (e.g., m.8344A>G, m.8356T>C)
MT-ND5 (mitochondrially encoded tRNA leucine 1 [UUA/G], mitochondrially encoded NADH dehydrogenase 5) (e.g., mitochondrial encephalopathy with lactic acidosis and stroke-like episodes [MELAS]), common variants (e.g., m.3243A>G, m.3271T>C, m.3252A>G, m.13513G>A)
MT-TL1 (mitochondrially encoded tRNA leucine 1 [UUA/G]) (e.g., diabetes and hearing loss), common variants (e.g., m.3243A>G, m.14709T>C)
MT-TS1, MT-RNR1 (mitochondrially encoded tRNA serine 1 [UCN], mitochondrially encoded 12S RNA) (e.g., nonsyndromic sensorineural deafness [including aminoglycoside-induced nonsyndromic deafness]), common variants (e.g., m.7445A>G, m.1555A>G).
Code 81403 includes:
- MT-RNR1 (mitochondrially encoded 12S RNA) (e.g., nonsyndromic hearing loss), full gene sequence
- MT-TS1 (mitochondrially encoded tRNA serine 1) (e.g., nonsyndromic hearing loss), full gene sequence.

Code 81404 includes:
- C10orf2 (chromosome 10 open reading frame 2) (e.g., mitochondrial DNA depletion syndrome), full gene sequence,
- MPV17 (MpV17 mitochondrial inner membrane protein) (e.g., mitochondrial DNA depletion syndrome), duplication/deletion analysis,
- NDUFA1 (NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 1, 7.5kDa) (e.g., Leigh syndrome, mitochondrial complex I deficiency), full gene sequence,
- MT-TS1 (mitochondrially encoded tRNA serine 1) (e.g., nonsyndromic hearing loss), full gene sequence.

Code 81405 includes:
- BCS1L (BCS1-like [S. cerevisiae]) (e.g., Leigh syndrome, mitochondrial complex III deficiency, GRACILE syndrome), full gene sequence,
- COX10 (COX10 homolog, cytochrome c oxidase assembly protein) (e.g., mitochondrial respiratory chain complex IV deficiency), full gene sequence,
- COX15 (COX15 homolog, cytochrome c oxidase assembly protein) (e.g., mitochondrial respiratory chain complex IV deficiency), full gene sequence,
- DGUOK (deoxyguanosine kinase) (e.g., hepatocerebral mitochondrial DNA depletion syndrome), full gene sequence,
- MPV17 (MpV17 mitochondrial inner membrane protein) (e.g., mitochondrial DNA depletion syndrome), full gene sequence,
- NDUFV1 (NADH dehydrogenase [ubiquinone] flavoprotein 1, 51kDa) (e.g., Leigh syndrome, mitochondrial complex I deficiency), full gene sequence,
- RRM2B (ribonucleotide reductase M2 B [TP53 inducible]) (e.g., mitochondrial DNA depletion), full gene sequence,
- SCO1 (SCO cytochrome oxidase deficient homolog 1) (e.g., mitochondrial respiratory chain complex IV deficiency), full gene sequence,
- SURF1 (surfeit 1) (e.g., mitochondrial respiratory chain complex IV deficiency), full gene sequence,
- TK2 (thymidine kinase 2, mitochondrial) (e.g., mitochondrial DNA depletion syndrome), full gene sequence,
- TYMP (thymidine phosphorylase) (e.g., 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,
- NDUF51 (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.

**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 diagnosis for mitochondrial disorders. Genetic testing also has the potential to determine future risk of disease in individuals who have a close relative with a pathogenic variant.

**Related Policies**

- N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of the FDA-approved technologies on the basis of medical necessity alone.

**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 disorders 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.

**Rationale**

**Background**

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).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 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 (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. A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database. Lists of mtDNA and nDNA genes that may lead to mitochondrial disorders and testing laboratories in the United States are provided at the GeneTests website (funded by BioReference Laboratories) and Genetic Testing Registry of the National Center for Biotechnology Information website.

**Table 1. Examples of Mitochondrial 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, MT-ND1,</td>
</tr>
<tr>
<td></td>
<td>• Pigmentary retinopathy</td>
<td>• MT-ND6 (rare)</td>
</tr>
<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>
</tr>
<tr>
<td></td>
<td>• Myopathy</td>
<td></td>
</tr>
<tr>
<td>CPEO</td>
<td>• External ophthalmoplegia</td>
<td>• Various deletions of mtDNA</td>
</tr>
<tr>
<td></td>
<td>• Bilateral ptosis</td>
<td></td>
</tr>
<tr>
<td>Keams-Sayre syndrome</td>
<td>• External ophthalmoplegia at age &lt;20 y</td>
<td>• Various deletions of mtDNA</td>
</tr>
<tr>
<td></td>
<td>• Pigmentary retinopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cerebellar ataxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Heart block</td>
<td></td>
</tr>
<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,</td>
</tr>
<tr>
<td></td>
<td>• Infantile-onset</td>
<td>• MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</td>
</tr>
<tr>
<td></td>
<td>• Cerebellar/brain stem dysfunction</td>
<td>• mtDNA deletions (rare)</td>
</tr>
<tr>
<td></td>
<td>• Various deletions of mtDNA</td>
<td>• SUCLA2, NDUSFx, NDFVx, SDHA, BC51L, SURF1, SCO2, COX15</td>
</tr>
<tr>
<td>LHON</td>
<td>• Painless bilateral visual failure</td>
<td>• MT-ND1, MT-ND4, MT-ND6</td>
</tr>
<tr>
<td></td>
<td>• Male predominance</td>
<td></td>
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<tr>
<td></td>
<td>• Dystonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cardiac pre-excitation syndromes</td>
<td></td>
</tr>
<tr>
<td>NARP</td>
<td>• Peripheral neuropathy</td>
<td>• MT-ATP6</td>
</tr>
<tr>
<td></td>
<td>• Ataxia</td>
<td></td>
</tr>
<tr>
<td>MNGIE</td>
<td>• Intestinal malabsorption</td>
<td>• TP</td>
</tr>
<tr>
<td></td>
<td>• Cachexia</td>
<td></td>
</tr>
<tr>
<td>IOSCA</td>
<td>• External ophthalmoplegia</td>
<td>• TWINKLE</td>
</tr>
<tr>
<td></td>
<td>• Neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ataxia</td>
<td></td>
</tr>
</tbody>
</table>
### Syndrome | Main Clinical Manifestations | Major Genes Involved
--- | --- | ---
SANDO | Ataxic neuropathy, Dysarthria, Ophthalmoparesis | POLG
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

Adapted From Chinnery Et Al (2014)\(^5\) And Angelini Et Al (2009).\(^7\)


### Literature Review
This review of the evidence focuses on the following BCBSA categories of genetic testing: diagnostic testing of an individual’s germline to benefit the individual (1a) and testing an asymptomatic individual to determine future risk of disease (3) (see Appendix Table 1 for all BCBSA genetic testing categories).

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

### Mitochondrial Disorders
We discuss the analytic and clinical validity of testing for mitochondrial disorders for both indications together, focusing on discretely on each indication when evaluating clinical utility.

### Clinical Context and Test Purpose
The purpose of genetic testing in patients who have signs and symptoms of mitochondrial disorders is to confirm diagnosis. Diagnosis of a specific mitochondrial disorder is complex due to the phenotypic heterogeneity and general lack of genotype-phenotype associations, particularly in infants and children. Identifying a disease-causing variant can end the diagnostic odyssey for families, help to avoid muscle biopsy for patients, and provide information needed for testing in asymptomatic family members. While the current treatment for most patients with mitochondrial disease is primarily supportive, potential treatments exist for patients with coenzyme Q\textsubscript{10} deficiency and mitochondrial neurogastrointestinal encephalopathy, although evidence for their effectiveness is not conclusive.

The 2 questions addressed in this evidence review are: (1) Does genetic testing for mitochondrial disorders improve the net health outcome in individuals with signs and symptoms of a
mitochondrial disorder and (2) Does genetic testing for mitochondrial disorders improve the net health outcome in asymptomatic relatives of an individual with a mitochondrial disorder? The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant populations of interest for both indications are individuals with signs and symptoms of mitochondrial disorders and individuals who are asymptomatic with a close relative with a mitochondrial disorder and a known pathogenic variant.

**Interventions**

Testing for the individual variants associated with mitochondrial disorders is offered by numerous labs. Genetic panel testing is also available, with numerous panels available. Some are disease-specific panels that include only a small number of genes associated with a particular mitochondrial disorder. For example, Transgenomic offers a mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) panel consisting of 10 pathogenic variants with specific associations with MELAS syndrome.

Several labs currently offer panel testing for mitochondrial and nuclear genes associated with multiple mitochondrial disorders by next-generation sequencing (NGS). The number of genes included in these panels varies widely. Examples of panels and the number of genes tested, accessed from websites, are listed in Table 2 although the number of genes on a given panel can change over time. This list is not exhaustive.

**Table 2. Examples of Commercially Available Panels Simultaneously Testing for Multiple Mitochondrial Disorders**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Test Name</th>
<th>No. of Genes on Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Dx® (Gaithersburg, MD)</td>
<td>Comprehensive Mitochondrial Nuclear Gene Panel</td>
<td>319</td>
</tr>
<tr>
<td>Transgenomic® (New Haven, CT)</td>
<td>Complete Mitochondrial Evaluation</td>
<td>485</td>
</tr>
<tr>
<td>Courtagen® (Woburn, MA)</td>
<td>nucSEEK® Comprehensive</td>
<td>1189</td>
</tr>
<tr>
<td></td>
<td>nucSEEK® Focus</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>mtSEEK®</td>
<td>40</td>
</tr>
<tr>
<td>ARUP® (Salt Lake City, UT)</td>
<td>Mitochondrial Disorders Panel</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial Disorders (mtDNA) Sequencing</td>
<td>33</td>
</tr>
<tr>
<td>Baylor Genetics Laboratory (Houston, TX)</td>
<td>BCM-MitomeNG SSM</td>
<td>201</td>
</tr>
<tr>
<td>MEDomics® (Azusa, CA)</td>
<td>MitoMED1204™</td>
<td>&gt;1200</td>
</tr>
<tr>
<td>Emory Genetics Laboratory (Tucker, GA)</td>
<td>Mitochondrial Diseases: Sequencing Panel</td>
<td>44</td>
</tr>
<tr>
<td>Knight Diagnostics Laboratories (Portland, OR)</td>
<td>Comprehensive Mitochondrial Metabolic Panel</td>
<td>196</td>
</tr>
</tbody>
</table>

**Comparators**

Standard clinical workup for diagnosis without genetic testing might include measurements of lactate and pyruvate in plasma and cerebrospinal fluid; plasma, urine, and cerebrospinal fluid amino acids; plasma acylcarnitines; and urine organic acids. Additionally, a muscle biopsy has been traditionally considered the criterion standard for diagnosis of mitochondrial disorders.

**Outcomes**

The beneficial outcomes resulting from a true test result are establishing a diagnosis and avoiding muscle biopsy. The harmful outcomes resulting from a false test result are a delay in diagnosis and additional testing.

**Time**

The timeframe of interest is the time to establish a diagnosis or perform preconceptual carrier testing.
Setting
Genetic testing for variants associated with mitochondrial disease is complex. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
The analytic validity of testing for mitochondrial DNA (mtDNA) may vary by the type of testing performed, the type of variant present, and the particular gene being evaluated. The 2 main types of genetic testing are polymerase chain reaction analysis and NGS. In general, both are associated with high analytic validity (>95%).

The Courtagen webpage cites sensitivity and specificity both greater than 99%.12 No further information is provided, but this presumably refers to the analytic validity of the Courtagen panel to detect variants present and exclude variants not present.

In addition to determining the presence of the variant, another important component of analytic validity is whether the degree of heteroplasmy has been accurately measured. The proportion of DNA mutated is an important component of whether clinical symptoms will develop and is generally reported along with the presence or absence of the variant. No information was available to judge the accuracy of heteroplasmy determination for variants in mtDNA.

Section Summary: Analytic Validity
There is a lack of published data on the analytic validity of genetic testing for mitochondrial disorders. There are manufacturer claims that the analytic validity approaches 100%, but no empirical data are available. The analytic validity of testing mtDNA has the added complexity of heteroplasmy, and we could not identify any evidence evaluating the accuracy of methods for determining heteroplasmy.

Clinical Validity
The evidence on the clinical sensitivity and specificity of genetic testing for mitochondrial disorders is limited. There are some small case series of patients with a well-defined syndrome such as MELAS syndrome, and some studies include larger numbers of patients with less specific clinical diagnose. There are wide variations reported in testing yield, probably reflecting the selection process used to evaluate patients for testing. Some representative information pertinent to clinical validity is reviewed here.

Clinical Sensitivity
Several series of patients with mixed diagnoses or suspected mitochondrial disorders have been published. In these studies, the variant detection rate (or yield) may or may not be an accurate estimate of clinical sensitivity, because the proportion of patients with a mitochondrial disorder is uncertain (see Table 3).

Table 3. Studies Reporting Diagnostic Yield in Patient with Suspected Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Population</th>
<th>N</th>
<th>Genetic Test Design</th>
<th>Yield, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legati et al (2016)13</td>
<td>Patients clinically diagnosed with mitochondrial disease</td>
<td>Custom NGS panel of 132 genes followed by WES for those negative after NGS</td>
<td>NGS: • 19 (15%) with “causative” variants • 27 (22%) with possible pathogenic variant WES:</td>
<td></td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Population</td>
<td>N</td>
<td>Genetic Test</td>
<td>Design</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------------</td>
<td>----------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pronicka et al (2016)14</td>
<td>Patients referred for possible or probable mitochondrial disorder</td>
<td>113 (including 47 neonates)</td>
<td>WES followed by Sanger sequencing</td>
<td>Prospective/retrospective samples included; consecutive patients included in prospective sample; selection method for retrospective samples not reported</td>
</tr>
<tr>
<td>Kohda et al (2016)15</td>
<td>Children with early-onset respiratory chain disease</td>
<td>142</td>
<td>NGS of the entire mtDNA plus WES of the nDNA</td>
<td>Prospective enrollment; selection method not reported</td>
</tr>
<tr>
<td>Wortmann et al (2015)16</td>
<td>Children and young adults suspected of having mitochondrial disorder</td>
<td>109</td>
<td>Panel of 238 genes associated with mitochondrial disease followed by WES</td>
<td>Prospective enrollment; selection method not reported</td>
</tr>
<tr>
<td>Ohtake et al (2014)17</td>
<td>Patients with mitochondrial respiratory chain disorders</td>
<td>104</td>
<td>NGS of exome of nDNA</td>
<td>Prospective/retrospective not reported; selection method not reported</td>
</tr>
<tr>
<td>Taylor et al (2014)18</td>
<td>Patients with suspected mitochondrial disease and multiple respiratory chain complex defects</td>
<td>53</td>
<td>WES validated with Sanger sequencing</td>
<td>Prospective/retrospective not reported; selection method not reported but only included patients with multiple respiratory chain complex defects</td>
</tr>
<tr>
<td>Lieber et al (2013)19</td>
<td>Patients with suspected mitochondrial disorders and heterogeneous clinical symptoms</td>
<td>102</td>
<td>NGS of entire mitochondrial genome and 1598 nuclear genes</td>
<td>Prospective/retrospective not reported; patients in a repository having highest clinical suspicion of disease selected</td>
</tr>
<tr>
<td>DaRe et al (2013)20</td>
<td>Patients with diagnosed or suspected mitochondrial disorders</td>
<td>148</td>
<td>NGS panel of 447 genes (Transgenomic)</td>
<td>Prospective/retrospective not reported; consecutive patients</td>
</tr>
</tbody>
</table>


Clinical Specificity

The clinical specificity of genetic testing for mitochondrial disorders is largely unknown, but false-positive results have been reported. Some epidemiologic evidence is available on the population prevalence of pathogenic variants, which provides some indirect evidence on the potential for false-positive results.

A study of population-based testing reported that the prevalence of pathogenic variants is higher than the prevalence of clinical disease. In this 2008 study, 3168 consecutive newborns were tested for the presence of 1 or more of the 10 most common mtDNA variants thought to be associated with clinical disease. At least 1 pathogenic variant was identified in 15 (0.54%) of 3168 people (95% confidence interval, 0.30% to 0.89%). This finding implies that there are many more people with a variant who are asymptomatic than there are people with clinical disease, and this raises the possibility of false-positive results on genetic testing.

An earlier population-based study (1998) evaluated the prevalence of the nucleotide 3243 variant associated with MELAS syndrome. This study included 245,201 subjects from Finland. Participants were screened for common symptoms associated with MELAS, and screen-positive patients were tested for the variant. The population prevalence was estimated at 16.3 (0.16%) in 100,000. This study may have underestimated the prevalence because patients who screened negative were not tested for the variant.

In addition to false-positive results, there are variants of uncertain significance detected in substantial numbers of patients. The number of variants increases when NGS methods are used.
to examine a larger portion of the genome. In 1 study (2013) using targeted exome sequencing, variants of uncertain significance were far more common than definite pathogenic variants.\(^{20}\) In that study, 148 patients with suspected or confirmed mitochondrial disorders were tested using a genetic panel that included 447 genes. Thirteen patients were found to have pathogenic variants. In contrast, variants of uncertain significance were very common, occurring at a rate of 6.5 per patient.

A further consideration is the clinical heterogeneity of variants known to be pathogenic. Some variants associated with mitochondrial disorders can result in heterogeneous clinical phenotypes, and this may cause uncertainty about the pathogenicity of the variant detected. For example, the nucleotide 3243 variant in the \(MT-TL1\) gene is found in most patients with clinically defined MELAS syndrome.\(^{27}\) This same variant has also been associated with chronic progressive external ophthalmoplegia and Leigh syndrome.\(^{28}\) Therefore, the more closely the clinical syndrome matches MELAS, the more likely a positive genetic test will represent a pathogenic variant.

**Section Summary: Clinical Validity**

Case series and cohort studies has provided information on the diagnostic yield of testing. For patients with signs and symptoms of mitochondrial disorders, but without a well-defined clinical syndrome, the variant detection rate differs by the population included, testing strategy, and outcome reported. Studies reporting a yield of known pathogenic variants for NGS panels tend to report rates, in the 15% to 25% range. There is very little evidence on clinical specificity, but there have been false-positive tests reported.

**Clinical Utility**

No direct evidence on clinical utility was identified. There are 2 ways that clinical utility might be demonstrated from a chain of evidence. First, confirmation of the diagnosis may have benefits in ending the need for further clinical workup and eliminating the need for a muscle biopsy. Second, knowledge of pathogenic variant status may have benefits for family members in determining their risk of developing disease.

**Confirmation of Diagnosis in Individuals with Signs and/or Symptoms of a Mitochondrial Disorder**

For patients with signs and symptoms consistent with a defined mitochondrial syndrome, testing can be targeted to those pathogenic variants associated with that particular syndrome. In the presence of a clinical picture consistent with the syndrome, the presence of a known pathogenic variant will confirm the diagnosis with a high degree of certainty. Confirmation of the diagnosis by genetic testing can result in reduced need for further testing, especially a muscle biopsy. However, a negative genetic test in blood does not rule out a mitochondrial disorder and should be reflexed to testing in the affected tissue to avoid the possibility of missing tissue-specific variants or low levels of heteroplasmy in blood.

There is no specific therapy for mitochondrial disorders. Treatment is largely supportive management for complications of the disease. It is possible that confirmation of the diagnosis by genetic testing would lead to management changes, such as increased surveillance for complications of disease and/or the prescription of exercise therapy or antioxidants. However, the impact of these management changes on health outcomes is not known.

**Testing of Asymptomatic individuals with a Close Relative with a Mitochondrial Disorder and a Known Pathogenic Variant**

Confirmation of a pathogenic variant has implications for family members of the affected person. Knowledge of variant status will clarify the inheritance pattern of the variant, thus clarifying risk to family members. For example, for a male patient with MELAS syndrome, confirmation of a pathogenic variant in the mtDNA would indicate that his offspring are not at risk for inheriting the variant, because the inheritance of the mitochondrial variant could only occur through the mother. In contrast, identification of a pathogenic variant in nuclear DNA would indicate that his offspring are at risk for inheriting the variant.
Reproductive Testing
When there is a disease of moderate severity or higher, it is reasonable to assume that many patients will consider results of testing in reproductive decision making. For purposes of informing family planning, when a pathogenic variant is detected in the nDNA of prospective parent or in the mtDNA of a prospective mother, the prospective parent can choose to refrain from having children. If the variant is in the nuclear DNA, the prospective parent could also choose medically assisted reproduction during which preimplantation testing would permit a choice to avoid an affecting offspring. The use of preimplantation testing when a pathogenic variant is identified in the mtDNA of an affected mother are complicated by issues of heteroplasmy of the mtDNA variant, threshold levels, phenotypic expression leading.

Section Summary: Clinical Utility
For diagnostic testing, clinical utility is relatively high when a definite diagnosis cannot be made without genetic testing. In this situation, a positive test for a pathogenic variant will confirm the diagnosis and may avoid further testing, including invasive tests (e.g., muscle biopsy). It is likely that confirmation of the diagnosis will lead to management changes, including referral to a specialist in mitochondrial disease. However, it is not known whether these management changes improve outcomes because of the lack of research on treatment interventions for mitochondrial disorders.

For testing at-risk relatives, clinical utility can also be demonstrated. When a disease phenotype displays moderate-to-severe disease, it is likely that knowledge of variant status will affect reproductive decision making. When a pathogenic variant is detected in a prospective parent, the prospective parent can choose to refrain from having children or may be able to choose medically assisted reproduction.

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 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.

Supplemental Information
Practice Guidelines and Position Statements

Foundation for Mitochondrial Medicine
The Foundation for Mitochondrial Medicine published an overview of mitochondrial disease in 2013; 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, and 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 published a consensus statement on the diagnosis and management of mitochondrial disease in 2015. 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.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in May 2017 did not identify any ongoing or unpublished trials that would likely influence this review.
References

2.04.117 Genetic Testing for Mitochondrial Disorders


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**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)

- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

**Post Service**

- Results/reports of tests performed
- Procedure report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms
of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>CPT®</td>
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<td>Nuclear encoded mitochondrial genes (e.g., 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, SUCL2, SUCLG1, TAZ, TK2, and TYMP</td>
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<td>MOLECULAR PATHOLOGY PROCEDURE LEVEL 2</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>08/01/2016</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
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</table>

Definitions of Decision Determinations

**Medically Necessary**: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.
Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.