DISCLAIMER/INSTRUCTIONS FOR USE

Medical Policy provides general guidance for applying Blue Cross of Idaho benefit plans (for purposes of Medical Policy, the terms “benefit plan” and “member contract” are used interchangeably). Coverage decisions must reference the member specific benefit plan document. The terms of the member specific benefit plan document may be different than the standard benefit plan upon which this Medical Policy is based. If there is a conflict between a member specific benefit plan and the Blue Cross of Idaho’s standard benefit plan, the member specific benefit plan supersedes this Medical Policy. Any person applying this Medical Policy must identify member eligibility, the member specific benefit plan, and any related policies or guidelines prior to applying this Medical Policy. Blue Cross of Idaho Medical Policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the member specific benefit plan coverage. Blue Cross of Idaho reserves the sole discretionary right to modify all its Policies and Guidelines at any time. This Medical Policy does not constitute medical advice.

POLICY

Genetic testing to establish a genetic diagnosis of a mitochondrial disorder may be considered medically necessary when signs and symptoms of a mitochondrial disorder are present and genetic testing may eliminate the need for muscle biopsy.

Targeted genetic testing for a known familial variant in at-risk relatives may be considered medically necessary as preconceptional carrier testing under 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.
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 preconceptional carrier testing is appropriate. At-risk relatives include only female relatives if the familial pathogenic variant is in the mtDNA but includes both male and female relatives if the familial pathogenic variant is in the nDNA.

Genetics Nomenclature Update

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. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). 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 PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. 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></td>
<td>Variant</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG2. 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>
</tbody>
</table>
Genetic Testing of Mitochondrial Disorders

Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease
Likely benign | Likely benign change in the DNA sequence
Benign | Benign change in the DNA sequence

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

Genetic Counseling

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.

Coding

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 BC51L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SC O2, 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,
TYMP (thymidine phosphorylase) (eg, mitochondrial DNA depletion syndrome), full gene sequence.

Code 81406 includes:
FASTKD2 (FAST kinase domains 2) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence,
Genetic Testing of Mitochondrial Disorders

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.

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**

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.

**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 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 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 one copy per cell. Because there are many copies of each gene, variants may be present in some copies of the gene but not others. This phenomenon is called heteroplasmy. Heteroplasmy can be expressed as a percentage of genes that have the variant ranging from 0% to 100%. Clinical expression of the variant will generally depend on a threshold effect (i.e., clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).

Mitochondrial diseases

Primary mitochondrial diseases 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 two decades as the pathophysiology and clinical manifestations have been better characterized. It is currently estimated that the minimum prevalence of primary mitochondrial diseases is at least 1 in 5000.14
Some specific mitochondrial diseases 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 disease 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 diseases 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. Biochemical testing is indicated for patients who do not have a clear clinical picture of one specific disorder. Measurement of serum lactic acid is often used as a screening test but the test is neither sensitive nor specific for mitochondrial diseases.

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

**Treatment**

Treatment of mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder. Identification of complications such as diabetes and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (eg, 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**

Mitochondrial diseases can be caused by pathogenic variants in the maternally inherited mtDNA or one of many nDNA genes. Genetic testing for mitochondrial diseases may involve testing for point mutations, deletion and 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 diseases 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 diseases, such as chronic progressive...
external ophthalmoplegia and Kearns-Sayre syndrome, the most common variants are deletions, and therefore duplication and 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 diseases and testing laboratories in the U. S. are provided at Genetic Testing Registry of the National Center for Biotechnology Information website.

Table 1. Examples of Mitochondrial Diseases, 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 mitochondrial DNA</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 mitochondrial DNA</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>• Subacute relapsing encephalopathy&lt;br&gt;• Infantile-onset&lt;br&gt;• Cerebellar/brainstem 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;• Mitochondrial DNA deletions (rare)&lt;br&gt;• SUCL₂, 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</td>
<td>• MT-ATP₆</td>
</tr>
</tbody>
</table>
### Syndromes, Main Clinical Manifestations, and Major Genes Involved

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Clinical Manifestations</th>
<th>Major Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pigmentary retinopathy</td>
<td></td>
</tr>
<tr>
<td>MNGIE</td>
<td>Intestinal malabsorption, Cachexia, External ophthalmoplegia, Neuropathy</td>
<td>TP</td>
</tr>
<tr>
<td>IOSCA</td>
<td>Ataxia, Hypotonia, Athetosis, Ophthalmoplegia, Seizures</td>
<td>TWINKLE</td>
</tr>
<tr>
<td>SANDO</td>
<td>Ataxic neuropathy, Dysarthria, Ophthalmoparesis</td>
<td>POLG</td>
</tr>
<tr>
<td>Alpers syndrome</td>
<td>Intractable epilepsy, Psychomotor regression, Liver disease</td>
<td>POLG, DGUOK, MPV17</td>
</tr>
<tr>
<td>GRACILE</td>
<td>Growth retardation, Aminoaciduria, Cholestasis, Iron overload, Lactic acidosis</td>
<td>NDUSFx</td>
</tr>
<tr>
<td>Coenzyme Q_{10} deficiency</td>
<td>Encephalopathy, Steroid-resistant nephrotic syndrome, Hypertrophic cardiomyopathy, Retinopathy, Hearing loss</td>
<td>COQ2, COQ9, CABC1, ETFDH</td>
</tr>
</tbody>
</table>

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

CPEO: chronic progressive external ophthalmoplegia; GRACILE: growth retardation, aminoaciduria, cholestasis, iron overload, early death; IOSCA: infantile onset spinal cerebellar atrophy; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF: myoclonic epilepsy with ragged-red fibers; MNGIE: mitochondrial neuro-gastrointestinal encephalopathy; NARP: neuropathy, ataxia, and retinitis pigmentosa; SANDO: sensory ataxia, neuropathy, dysarthria and ophthalmoplegia.

### Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests 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.

RATIONALE

This evidence review was created in May 2014 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 1, 2019.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Mitochondrial diseases

The clinical validity and utility of testing for mitochondrial diseases for both indications are presented together, focusing discretely on each indication when evaluating clinical usefulness.

Clinical Context and Test Purpose

The purpose of genetic testing in patients who have signs and symptoms of mitochondrial diseases is to confirm the diagnosis. Diagnosis of a specific mitochondrial disease 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 the information needed for testing asymptomatic family members. While the current treatment for most patients with mitochondrial disease is primarily supportive, potential treatments exist for patients with coenzyme Q₁₀ deficiency and mitochondrial neuro-gastrointestinal encephalopathy, although evidence for their effectiveness is not conclusive.

The two questions addressed in this evidence review are: (1) Does genetic testing for mitochondrial diseases improve the net health outcome in individuals with signs and symptoms of a mitochondrial disease and (2) Does genetic testing for mitochondrial diseases improve the net health outcome in asymptomatic relatives of an individual with a mitochondrial disease?

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 diseases and individuals who are asymptomatic with a close relative who has a mitochondrial disease and a known pathogenic variant.

Interventions

Testing for the individual variants associated with mitochondrial diseases 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 disease.
Several labs currently offer panel testing for mitochondrial and nuclear genes associated with multiple mitochondrial diseases by next-generation sequencing (NGS). The number of genes included in these panels varies widely.

Comparators
The following practice is currently being used: standard clinical workup for diagnosis without genetic testing, which might include measurements of lactate and pyruvate in plasma and cerebrospinal fluid; plasma, urine, and cerebrospinal fluid amino acids; plasma acylcarnitine’s; and urine organic acids. Additionally, a muscle biopsy has been traditionally considered the criterion standard for the diagnosis of mitochondrial diseases.

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.

Timing
The time frame of interest is the time to establish a diagnosis for those who are asymptomatic or to perform preconceptional carrier testing for those with a close relative who has a mitochondrial disease and a known pathogenic variant.

Setting
Genetic testing for variants associated with mitochondrial disease is complex. Referral for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for mitochondrial disorders, methodologically credible studies were selected using the following principles:

For the evaluation of clinical validity of the tests, studies that meet the following eligibility criteria were considered

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
The evidence on the clinical sensitivity and specificity of genetic testing for mitochondrial diseases 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 diagnoses. There are wide variations in reported testing yields, 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 diseases 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 disease is uncertain (see Table 2).

**Table 2. Studies Reporting Diagnostic Yield in Patient With Suspected Mitochondrial Diseases**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Genetic Test</th>
<th>Design</th>
<th>Yield, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fang et al (2017)</td>
<td>Children and young adults suspected of having mitochondrial disease</td>
<td>141</td>
<td>Targeted NGS</td>
<td>• Prospective enrollment; • Selection method not reported</td>
<td>40 (28%)</td>
</tr>
<tr>
<td>Legati et al (2016)</td>
<td>Patients clinically diagnosed with mitochondrial disease</td>
<td>21</td>
<td>Custom NGS panel of 132 genes followed by WES for those negative after NGS</td>
<td>NGS: 19 (15%) with &quot;causative&quot; variants; WES: 27 (22%) with possible pathogenic variants</td>
<td>NGS: 19 (15%) with &quot;causative&quot; variants; WES: 27 (22%) with possible pathogenic variants</td>
</tr>
<tr>
<td>Pronicka et al (2016)</td>
<td>Patients referred for possible or probable mitochondrial disease</td>
<td>113</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>
<td>67 (59%) with likely pathogenic variants; 30 (64%) of neonates with likely pathogenic variants</td>
</tr>
<tr>
<td>Kohda et al (2016)</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>
<td>29 (20%)</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>N</td>
<td>Genetic Test</td>
<td>Design</td>
<td>Yield, n (%)</td>
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<tr>
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<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
  • Selection method not reported  
  • 42 (39%) with pathogenic variants                                                      | inconclusive but possibly pathogenic variants                                           |
| Ohtake et al (2014)   | Patients with mitochondrial respiratory chain diseases                      | 104 | NGS of exome of nDNA                                                          | • Prospective/retrospective  
  • Selection method not reported  
  • 18 (17%) with known pathogenic variants  
  • 27 (26%) with likely pathogenic variants                                              | 10% with inconclusive but possibly pathogenic variants                                  |
| Taylor et al (2014)   | Patients with suspected mitochondrial disease and multiple respiratory chain complex defects | 53  | WES validated with Sanger sequencing                                           | • Prospective/retrospective  
  • Selection method not reported; selection method not reported but only included patients with multiple respiratory chain complex defects  
  • 28 (53%) with known pathogenic variants  
  • 4 (8%) with likely pathogenic variants                                                | 53% with known pathogenic variants                                                    |
| Lieber et al (2013)   | Patients with suspected mitochondrial diseases and heterogeneous clinical symptoms | 102 | NGS of entire mitochondrial genome and 1598 nuclear genes                    | • Prospective/retrospective  
  • Patients in a repository having highest clinical suspicion of disease selected  
  • 22 (22%) with likely pathogenic variants  
  • 26 (25%) VUS                                                                         | 22% with likely pathogenic variants                                                   |
| DaRe et al (2013)     | Patients with diagnosed or suspected mitochondrial diseases                 | 148 | NGS panel of 447 genes (Transgenomic)                                        | • Prospective/retrospective  
  • Selection method not reported; consecutive patients  
  • 13 (9%) possible pathogenic variants  
  • 67 (45%) with VUS                                                                   | 9% possible pathogenic variants                                                       |
| McCormick et al (2013) | Patients with suspected mitochondrial disease                             | 152 | mtDNA genome sequencing, genome-wide SNV microarray, and step-wise individual sequencing of select nuclear genes | • Retrospective chart review; consecutive patients included  
  • 25 (16%) with "definite" mitochondrial disease  
  • 46 (30%) with "probable"                                                              | 16% with "definite" mitochondrial disease                                                 |
## Genetic Testing of Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Genetic Test</th>
<th>Design</th>
<th>Yield, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvo et al (2012)</td>
<td>Infants with clinical and biochemical evidence of oxidative phosphorylation disease</td>
<td>42</td>
<td>NGS of entire mitochondrial genome and 1034 nuclear genes</td>
<td>• Prospective/retrospective not reported • Selection method not reported</td>
<td>10 (24%) with known pathogenic variants • 13 (31%) possible pathogenic variants</td>
</tr>
<tr>
<td>Qi et al (2007)</td>
<td>Patients with mitochondrial encephalopathies (MELAS, MERRF, Leigh syndrome, LHON, or an overlap syndrome)</td>
<td>552</td>
<td>PCR-RFLP analysis, site-specific PCR, and PCR-sequencing methods of common mitochondrial pathogenic variants</td>
<td>• Prospective/retrospective not reported • Selection method not reported</td>
<td>64 (12%) with pathogenic variants</td>
</tr>
</tbody>
</table>

LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF: myoclonic epilepsy with ragged red fibers; mtDNA: mitochondrial DNA; nDNA: nuclear DNA; NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SNV: single nucleotide variant; VUS: variant of uncertain significance; WES: whole-exome sequencing.

### Clinical Specificity

The clinical specificity of genetic testing for mitochondrial diseases 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 study by Elliott et al (2008), 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 by Majamaa et al (1998) evaluated the prevalence of the nucleotide 3243 variant associated with MELAS syndrome. This study included 245201 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 100000. This study might 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 the study by DaRe et al (2013), which used targeted exome sequencing, variants of uncertain significance were far more common than definite pathogenic variants. In that
study, 148 patients with suspected or confirmed mitochondrial diseases 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 diseases 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. This same variant has also been associated with chronic progressive external ophthalmoplegia and Leigh syndrome. Therefore, the more closely the clinical syndrome matches MELAS, the more likely a positive genetic test will represent a pathogenic variant.

Section Summary: Clinically Valid

Case series and cohort studies have provided information on the diagnostic testing yield. For patients with signs and symptoms of mitochondrial diseases, but without a well-defined clinical syndrome, the variant detection rates differ 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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence on clinical utility was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

There are two 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 the disease.

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

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 a reduced need for further testing, especially a muscle biopsy. However, a negative genetic test in the blood does not rule out a mitochondrial disease 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 diseases. 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 the 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 Who Has a Mitochondrial Disease 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 the results of testing in reproductive decision making. For purposes of informing family planning, when a pathogenic variant is detected in the nDNA of a 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 nDNA, the prospective parent could also choose medically assisted reproduction during which pre-implantation testing would permit a choice to avoid an affecting offspring. The use of pre-implantation testing when a pathogenic variant is identified in the mtDNA of an affected mother is complicated by issues of heteroplasmia of the mtDNA variant, threshold levels, phenotypic expression leading.

Section Summary: Clinically Useful

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 (eg, 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 diseases.

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 disease who receive genetic testing, the evidence includes case series and cohort studies. The 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 in 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. The 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.

SUPPLEMENTAL INFORMATION

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 three 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 (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 an 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 [mitochondrial DNA] 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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in May 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

ESSENTIAL HEALTH BENEFITS

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntarily offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

REFERENCES


CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
<td>See Policy Guidelines</td>
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<tr>
<td>ICD-10-CM</td>
<td>E88.40</td>
<td>Mitochondrial metabolism disorder, unspecified</td>
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<tr>
<td></td>
<td>E88.41</td>
<td>MELAS syndrome</td>
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<td></td>
<td>E88.42</td>
<td>MERRF syndrome</td>
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<tr>
<td></td>
<td>E88.49</td>
<td>Other mitochondrial metabolism disorders</td>
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<td></td>
<td>G31.82</td>
<td>Leigh’s disease</td>
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<td></td>
<td>H49.811-</td>
<td>Kears-Sayre syndrome, code range</td>
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<td>H49.819</td>
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</table>

ICD-10-PCS

Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.

Type of Service: Pathology
Place of Service: Laboratory/Physician’s Office

POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>05/22/14</td>
<td>New Policy – Add to Medicine-Pathology/ Laboratory section</td>
<td>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>08/14/14</td>
<td>Replace policy – correction only</td>
<td>Regulatory status corrected to say mitochondrial disorders</td>
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<tr>
<td>11/13/14</td>
<td>Replace policy – coding update only</td>
<td>New CPT codes added to policy</td>
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<tr>
<td>05/22/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 1, 2015, references 8 and 22-24 added. Wording of policy statements revised to be consistent with standardized genetic language.</td>
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### MP 2.04.117
Genetic Testing of Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Date</th>
<th>Type of Update</th>
<th>Details</th>
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<tbody>
<tr>
<td>07/09/15</td>
<td>Replace policy – coding update only</td>
<td>CPT code 81440 added to policy</td>
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<tr>
<td>06/16/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 29, 2016; references 10 and 13 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>06/22/17</td>
<td>Replace policy</td>
<td>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>
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<tr>
<td>06/27/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through April 4, 2018; reference 10 was added. Policy statements unchanged.</td>
</tr>
<tr>
<td>08/20/18</td>
<td>Replace policy – correction only</td>
<td>The Ongoing and Unpublished Clinical Trials section corrected</td>
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<tr>
<td>06/20/19</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 06/20/2019. Policy updated with literature review through April 1, 2019; no references added. Correct insertion of term “preconceptional” made to policy statement and elsewhere in policy as appropriate. Policy statements otherwise unchanged.</td>
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