



Louisiana

Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 09/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing to confirm the diagnosis of a mitochondrial disorder when signs and symptoms of a mitochondrial disorder are present (see Policy Guidelines section) but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for genetic testing to confirm the diagnosis of a mitochondrial disorder will be considered when either one of the following criteria is met:

- Genetic testing avoids the need for a muscle biopsy AND Genetic testing is restricted to the specific mutations that have been documented to be pathogenic for the specific mitochondrial disorder being considered (see Policy Guidelines); OR
- 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.

Based on review of available data, the Company may consider targeted genetic testing for a known familial variant of at-risk relatives as part of a preconceptual evaluation*** to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for targeted genetic testing of at-risk relatives as part of a preconceptual evaluation will be considered when all of the following criteria are met:

- 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.

*****Note:** *Coverage for genetic testing maybe provided only if benefits are available in the member's contract/certificate.*

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of genetic testing for mitochondrial disorders in all other situations to be **investigational**.*

The use of genetic testing for mitochondrial disorders when patient selection criteria are not met is considered to be **investigational**.*

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 Medical Policy 00389 (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.

To maximize the positive and the negative predictive value of testing, testing should be restricted to patients with a clinical picture consistent with a specific disorder and to a small number of mutations known to be pathogenic for that disorder. Table PG1 is a guide to clinical symptoms and particular genetic mutations associated with particular mitochondrial syndromes.

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

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	<ul style="list-style-type: none"> Stroke-like episodes at age <40 y Seizures and/or dementia Pigmentary retinopathy Lactic acidosis 	<ul style="list-style-type: none"> <i>MT-TL1, MT-ND5</i> (>95%) <i>MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS₁, MT-TS₂, MT-ND1, MT-ND6</i> (rare)
MERRF	<ul style="list-style-type: none"> Myoclonus Seizures Cerebellar ataxia Myopathy 	<ul style="list-style-type: none"> <i>MT-TK</i> (>80%) <i>MT-TF, MT-TP</i> (rare)
CPEO	<ul style="list-style-type: none"> External ophthalmoplegia Bilateral ptosis 	<ul style="list-style-type: none"> Various deletions of MT-DNA
Kearns-Sayre syndrome	<ul style="list-style-type: none"> External ophthalmoplegia at age <20y Pigmentary retinopathy Cerebellar ataxia Heart block 	<ul style="list-style-type: none"> Various deletions of MT-DNA
Leigh syndrome	<ul style="list-style-type: none"> Subacute relapsing encephalopathy Infantile onset Cerebellar/brain stem dysfunction 	<ul style="list-style-type: none"> <i>MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</i> MT-DNA deletions (rare)
LHON	<ul style="list-style-type: none"> Painless bilateral visual failure Male predominance Dystonia Cardiac pre-excitation syndromes 	<ul style="list-style-type: none"> <i>MT-ND1, MT-ND4, MT-ND6</i>
NARP	<ul style="list-style-type: none"> Peripheral neuropathy Ataxia Pigmentary retinopathy 	<ul style="list-style-type: none"> <i>MT-ATP6</i>

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

Panels of mutations that are disease-specific (i.e., contain only mutations associated with a specific type of mitochondrial disorder) may meet the criteria for medical necessity under certain circumstances. When criteria for medical necessity are met, these panels may be used in place of testing individual genes in sequence. Disease-specific panels should include a list of mutations that approximates (but may not be identical to) those listed in Table PG1 for each specific disorder.

Background/Overview

MITOCHONDRIAL DNA

Mitochondria are organelles within each cell that contain their own set of DNA, distinct from the nDNA 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.

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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.

mtDNA differs from nDNA in several important ways. Inheritance of mtDNA does not follow traditional Mendelian patterns. Rather, mtDNA is inherited only from maternal DNA so that disorders that result from variants in mtDNA can only be passed on by the mother. Also, there are thousands of copies of each mtDNA gene in each cell, as opposed to nDNA, which contains only 1 copy per cell. Because there are many copies of each gene, variants may be present in some copies of the gene but not others. This phenomenon is called heteroplasmy. Heteroplasmy can be expressed as a percentage of genes that have the variant ranging from 0% to 100%. Clinical expression of the variant will generally depend on a threshold effect (i.e., clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).

MITOCHONDRIAL DISORDERS

Primary mitochondrial disorders arise from dysfunction of the mitochondrial respiratory chain. The mitochondrial respiratory chain is responsible for aerobic metabolism, and dysfunction, therefore, affects a wide variety of physiologic pathways dependent on aerobic metabolism. Organs with a high-energy requirement, such as the central nervous system, cardiovascular system, and skeletal muscle, are preferentially affected by mitochondrial dysfunction.

The prevalence of these disorders has risen over the last 2 decades as the pathophysiology and clinical manifestations have been better characterized. It is currently estimated that the minimum prevalence of primary mitochondrial disorders is at least 1 in 5000.

Some specific mitochondrial disorders are listed next:

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

Most of these disorders are characterized by multisystem dysfunction, which generally includes myopathies and neurologic dysfunction and may involve multiple other organs. Each 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.

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Diagnosis

The diagnosis of mitochondrial disorders can be difficult. The individual symptoms are nonspecific, and symptom patterns can overlap considerably. As a result, a patient often cannot be easily classified into 1 particular syndrome. Biochemical testing is indicated for patients who do not have a clear clinical picture of 1 specific disorder. Measurement of serum lactic acid is often used as a screening test, but the test is neither sensitive nor specific for mitochondrial disorders.

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

Treatment

Treatment of mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder. Identification of complications such as diabetes and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (e.g., coenzyme Q, riboflavin) have been used, but empirical evidence of benefit is lacking. Exercise therapy for myopathy is often prescribed, but the effect on clinical outcomes is uncertain. The possibility of gene transfer therapy is under consideration, but is at an early stage of development and untested in clinical trials.

GENETIC TESTING FOR MITOCHONDRIAL DISORDERS

Mitochondrial disorders can be caused by pathogenic variants in the maternally inherited mtDNA or one of many nDNA genes. Genetic testing for mitochondrial disorders may involve testing for point mutations, deletion/duplication analysis, and/or whole exome sequencing of nuclear or mtDNA. The type of testing done depends on the specific disorder being considered. For some primary mitochondrial disorders such as MELAS 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.

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Table 1. Examples of Mitochondrial Disorders, Clinical Manifestations, and Associated Pathogenic Genes

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	<ul style="list-style-type: none"> Stroke-like episodes at age <40 y Seizures and/or dementia Pigmentary retinopathy Lactic acidosis 	<ul style="list-style-type: none"> <i>MT-TL1, MT-ND5</i> (>95%) <i>MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS₁, MT-TS₂, MT-ND1, MT-ND6</i> (rare)
MERRF	<ul style="list-style-type: none"> Myoclonus Seizures Cerebellar ataxia Myopathy 	<ul style="list-style-type: none"> <i>MT-TK</i> (>80%) <i>MT-TF, MT-TP</i> (rare)
CPEO	<ul style="list-style-type: none"> External ophthalmoplegia Bilateral ptosis 	<ul style="list-style-type: none"> Various deletions of mtDNA
Kearns-Sayre syndrome	<ul style="list-style-type: none"> External ophthalmoplegia at age <20 y Pigmentary retinopathy Cerebellar ataxia Heart block 	<ul style="list-style-type: none"> Various deletions of mtDNA
Leigh syndrome	<ul style="list-style-type: none"> Subacute relapsing encephalopathy Infantile-onset Cerebellar/brain stem dysfunction 	<ul style="list-style-type: none"> <i>MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</i> mtDNA deletions (rare) <i>SUCLA2, NDUSF_x, NDFV_x, SDHA, BCS1L, SURF1, SCO2, COX15</i>
LHON	<ul style="list-style-type: none"> Painless bilateral visual failure Male predominance Dystonia Cardiac pre-excitation syndromes 	<ul style="list-style-type: none"> <i>MT-ND1, MT-ND4, MT-ND6</i>
NARP	<ul style="list-style-type: none"> Peripheral neuropathy Ataxia Pigmentary retinopathy 	<ul style="list-style-type: none"> <i>MT-ATP6</i>
MNGIE	<ul style="list-style-type: none"> Intestinal malabsorption Cachexia External ophthalmoplegia Neuropathy 	<ul style="list-style-type: none"> <i>TP</i>
IOSCA	<ul style="list-style-type: none"> Ataxia Hypotonia Athetosis Ophthalmoplegia Seizures 	<ul style="list-style-type: none"> <i>TWINKLE</i>
SANDO	<ul style="list-style-type: none"> Ataxic neuropathy Dysarthria Ophthalmoparesis 	<ul style="list-style-type: none"> <i>POLG</i>
Alpers syndrome	<ul style="list-style-type: none"> Intractable epilepsy Psychomotor regression 	<ul style="list-style-type: none"> <i>POLG, DGUOK, MPV17</i>

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Syndrome	Main Clinical Manifestations	Major Genes Involved
GRACILE	<ul style="list-style-type: none"> • Liver disease • Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis 	<ul style="list-style-type: none"> • <i>NDUSF_x</i>
Coenzyme deficiency	<ul style="list-style-type: none"> • Encephalopathy • Steroid-resistant nephrotic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss 	<ul style="list-style-type: none"> • <i>COQ2</i> • <i>COQ9</i> • <i>CABC1</i> • <i>ETFDH</i>

Adapted from Chinnery et al (2014) and Angelini et al (2009).

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; MERRF: myoclonic epilepsy with ragged-red fibers; MNGIE: mitochondrial neurogastrointestinal encephalopathy; NARP: neuropathy, ataxia, and retinitis pigmentosa; SANDO: sensory ataxia, neuropathy, dysarthria and ophthalmoplegia.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

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.

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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 Q₁₀ deficiency and mitochondrial neurogastrointestinal encephalopathy (MNGIE), 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 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

Laboratory	Test Name	No. of Genes on Panel
Gene Dx ^{®†} (Gaithersburg, MD)	Comprehensive Mitochondrial Nuclear Gene Panel	319
Transgenomic (New Haven, CT)	Complete Mitochondrial Evaluation	485
Courtagen ^{®†} (Woburn, MA)	nucSEEK ^{®†} Comprehensive	1189

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	nucSEEK [®] Focus	181
	mtSEEK [®]	40
ARUP[®] (Salt Lake City, UT)	Mitochondrial Disorders Panel	121
	Mitochondrial Disorders (mtDNA) Sequencing	33
Baylor Genetics Laboratory (Houston, TX)	BCM-MitomeNGSSM	201
MEDomics[®] (Azusa, CA)	MitoMED1204 [™]	>1200
Emory Genetics Laboratory (Tucker, GA)	Mitochondrial Diseases: Sequencing Panel	44
Knight Diagnostics Laboratories (Portland, OR)	Comprehensive Mitochondrial Metabolic Panel	196

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 preconceptional 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 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%. 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

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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

Study (Year)	Population	N	Genetic Test	Design	Yield, n (%)
Legati et al (2016)	Patients clinically diagnosed with mitochondrial disease	<ul style="list-style-type: none"> • NGS=125 • WES=10 	Custom NGS panel of 132 genes followed by WES for those negative after NGS	Prospective/retrospective not reported; selection method not reported	NGS: <ul style="list-style-type: none"> • 19 (15%) with "causative" variants • 27 (22%) with possible pathogenic variant WES: <ul style="list-style-type: none"> • 6 (60%) with "causative" variant
Pronicka et al (2016)	Patients referred for possible or probable mitochondrial disorder	113 (including 47 neonates)	WES followed by Sanger sequencing	Prospective/retrospective samples included; consecutive patients included in prospective sample; selection method for retrospective samples not reported	<ul style="list-style-type: none"> • 67 (59%) with likely pathogenic variant • 30 (64%) of neonates with likely pathogenic variant
Kohda et al (2016)	Children with early-onset respiratory chain disease	142	NGS of the entire mtDNA plus WES of the nDNA	Prospective enrollment; selection method not reported	<ul style="list-style-type: none"> • 29 (20%) with known pathogenic variants • 53 (37%) inconclusive but possibly pathogenic variants

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Study (Year)	Population	N	Genetic Test	Design	Yield, n (%)
Wortmann et al (2015)	Children and young adults suspected of having mitochondrial disorder	109	Panel of 238 genes associated with mitochondrial disease followed by WES	Prospective enrollment; selection method not reported	<ul style="list-style-type: none"> • 42 (39%) with pathogenic variant
Ohtake et al (2014)	Patients with mitochondrial respiratory chain disorders	104	NGS of exome of nDNA	Prospective/retrospective not reported; selection method not reported	<ul style="list-style-type: none"> • 18 (17%) with known pathogenic variants • 27 (26%) with likely 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 not reported; selection method not reported but only included patients with multiple respiratory chain complex defects	<ul style="list-style-type: none"> • 28 (53%) with known pathogenic variant • 4 (8%) with likely pathogenic variant
Lieber et al (2013)	Patients with suspected mitochondrial disorders and heterogeneous clinical symptoms	102	NGS of entire mitochondrial genome and 1598 nuclear genes	Prospective/retrospective not reported; patients in a repository having highest clinical suspicion of disease selected	<ul style="list-style-type: none"> • 22 (22%) with likely pathogenic variants • 26 (25%) VUS
DaRe et al (2013)	Patients with diagnosed or suspected mitochondrial disorders	148	NGS panel of 447 genes (Transgenomic)	Prospective/retrospective not reported; consecutive patients	<ul style="list-style-type: none"> • 13 (9%) possible pathogenic variants • 67 (45%) with VUS
McCormick et al (2013)	Patients referred for outpatient-based evaluation of 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	<ul style="list-style-type: none"> • 25 (16%) with "definite" mitochondrial disease • 46 (30%) with "probable" or "possible" mitochondrial disease
Calvo et al (2012)	Infants with clinical and biochemical evidence of oxidative phosphorylation disease	42	NGS of entire mitochondrial genome and 1034 nuclear genes	Prospective/retrospective not reported; selection method not reported	<ul style="list-style-type: none"> • 10 (24%) with known pathogenic variant • 13 (31%) possible pathogenic variants
Qi et al (2007)	Patients with mitochondrial encephalopathies (MELAS, MERRF, Leigh syndrome, LHON, or an overlap syndrome)	552	PCR-RFLP analysis, site-specific PCR, and PCR-sequencing methods of common mitochondrial	Prospective/retrospective not reported; selection method not reported	<ul style="list-style-type: none"> • 64 (12%) with pathogenic variant

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Study (Year)	Population	N	Genetic Test	Design	Yield, n (%)
			pathogenic variants		

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 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. 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. 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.

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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 nDNA 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

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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 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 NGS 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

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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.

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07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. New policy.
06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. Updated coverage statements for clarification. Combined investigational statements for clarification.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. 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. Removed the investigational statement for the use of genetic testing for mitochondrial disorders using expanded panel testing.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date:	09/2019

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ICD-10 Diagnosis	E88.40-E88.49 F84.2 G31.81-G31.82 H49.811-H49.819 H50.89

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