2.04.117	Genetic Testing for Mitochondrial Disorders		
Original Policy Date:	August 1, 2016	**Effective Date:**	October 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 20

Policy Statement

I. 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.

II. Targeted genetic testing for a known familial variant in at-risk relatives may be considered **medically necessary** as preconceptional carrier testing under **both** of the following conditions (see Benefit Application section):
   A. There is a defined mitochondrial disorder in the family of sufficient severity to cause impairment of quality of life or functional status
   B. A variant that is known to be pathogenic for that specific mitochondrial disorder has been identified in the index case

III. Genetic testing for mitochondrial disorders is considered **investigational** in **all** other situations when the criteria for medical necessity are not met.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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.

Carrier screening for mitochondrial disorders associated with autosomal recessive inheritance of nDNA variants is addressed in Blue Shield of California Medical Policy: Carrier Screening for Genetic Diseases.

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 individuals 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 Blue Shield of California Medical Policy: 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 of the parents of a proband with a mitochondrial disorder and a confirmed pathogenic/likely pathogenic gene variant is done to identify mode of transmission [germline (autosomal recessive, autosomal dominant, X-linked, mitochondrial) vs. *de novo*] thereby indicating risk for future offspring and other family members. Targeted testing for a known familial variant in parents and other 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. American College of Medical Genetics and Genomics-Association for Molecular Pathology Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
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

Genetic Counseling
Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding
See the Codes table for details.

Description

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

Diagnostic genetic testing for mitochondrial disorders and carrier testing of known familial variants associated with mitochondrial disorders is addressed in this review. Carrier screening for mitochondrial disorders associated with autosomal recessive inheritance of nuclear DNA variants is addressed in Blue Shield of California Medical Policy: Carrier Screening for Genetic Diseases.

Summary of Evidence
For individuals with signs and/or symptoms of a mitochondrial disease who receive genetic testing, the evidence includes case series and cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, functional outcomes, health status measures, and quality of life. There is some evidence on clinical validity that varies by the patient population and testing strategy. Studies reporting diagnostic yield for known pathogenic variants using next-generation sequencing (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 an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative with a mitochondrial disease and a known pathogenic variant and who receive targeted familial variant testing, the evidence includes case series and cohort studies. Relevant outcomes are test validity, other test performance measures, changes in reproductive decision making, symptoms, functional outcomes, health status measures, and quality of life. Clinical validity is expected to be high for targeted testing of a known familial variant, assuming sufficient analytic validity. Clinical utility can be demonstrated by testing at-risk family members who have a close relative with a pathogenic variant. When a specific mitochondrial disease is present in the family that is severe enough to cause impairment and/or disability, genetic testing may impact reproductive decision making. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Not applicable.

Related Policies

- Carrier Screening for Genetic Diseases **(to be published)**
- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Benefit Application

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

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 496
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview
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

Background
Mitochondrial DNA
Mitochondria are organelles within each cell that contain their own set of DNA, distinct from the nuclear DNA (nDNA) that makes up most of the human genome. Human mitochondrial DNA (mtDNA) consists of 37 genes. Thirteen genes code for protein subunits of the mitochondrial oxidative phosphorylation complex and the remaining 24 genes are responsible for proteins involved in the translation and/or assembly of the mitochondrial complex.[1,] Additionally, there are over 1000 nuclear genes coding for proteins that support mitochondrial function.[2,] The protein products from these genes are produced in the nucleus and later migrate to the mitochondria.

Mitochondrial DNA 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 disorders that result from variants in mtDNA can only be passed on by the mother. Also, there are thousands of copies of each mtDNA gene in each cell, as opposed to nDNA, which contains only 1 copy per cell. Because there are many copies of each gene, variants may be present in some copies of the gene but not others. This phenomenon is called heteroplasmy. Heteroplasmy can be expressed as a percentage of genes that have the variant ranging from 0% to 100%. Clinical expression of the

variant will generally depend on a threshold effect (i.e., clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).[3,]

Diagnostic genetic testing for mitochondrial disorders and carrier testing of known familial variants associated with mitochondrial disorders is addressed in this review. Carrier screening for mitochondrial disorders associated with autosomal recessive inheritance of nDNA variants is addressed in Blue Shield of California Medical Policy: Carrier Screening for Genetic Diseases..

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 2 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.[1,4,]

Some specific mitochondrial diseases are listed next:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like symptoms (MELAS) syndrome;
- Myoclonus epilepsy with ragged red fibers syndrome (MERFF);
- Kearns-Sayre syndrome;
- Leigh syndrome;
- Chronic progressive external ophthalmoplegia (CPEO);
- Leber hereditary optic neuropathy (LHON);
- Neuropathy, 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 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 a particular syndrome.[5,] Biochemical testing is indicated for patients who do not have a clear clinical picture of a specific disorder. Measurement of serum lactic acid is often used as a screening test but the test is neither sensitive nor specific for mitochondrial diseases.[2,]
A muscle biopsy can be performed if the diagnosis is uncertain after biochemical workup. However, this invasive test is not definitive in all cases. The presence of "ragged red fibers" on histologic analysis is consistent with a mitochondrial disease. Ragged red fibers represent a proliferation of defective mitochondria.[1,] This characteristic finding may not be present in all types of mitochondrial diseases and also may be absent early in the course of disease.[2,]

Treatment

Treatment of mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder.[5,] Identification of complications such as diabetes and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (e.g., coenzyme Q, riboflavin) have been used but empirical evidence of benefit is

lacking.[6,] Exercise therapy for myopathy is often prescribed but the effect on clinical outcomes is uncertain.[5,] The possibility of gene transfer therapy is under consideration but is at an early stage of development and untested in clinical trials.

Genetic Testing

Mitochondrial 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 MELAS and MERFF, 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 CPEO 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.[5,7,] A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database.[8,] 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.[9,]

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

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	• Stroke-like episodes at age <40 y • Seizures and/or dementia • Pigmentary retinopathy • Lactic acidosis	• *MT-TL1*, *MT-ND5* (>95%) • *MT-TF*, *MT-TH*, *MT-TK*, *MT-TQ*, *MT-TS*$_1$, *MT-TS*$_2$, *MT-ND1*, *MT-ND6* (rare)
MERFF	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• *MT-TK* (>80%) • *MT-TF*, *MT-TP* (rare)
CPEO	• External ophthalmoplegia • Bilateral ptosis	• Various deletions of mitochondrial DNA
Kearns-Sayre syndrome	• External ophthalmoplegia at age <20 y • Pigmentary retinopathy • Cerebellar ataxia • Heart block	• Various deletions of mitochondrial DNA
Leigh syndrome	• Subacute relapsing encephalopathy • Infantile onset • Cerebellar/brainstem dysfunction	• *MT-ATP6*, *MT-TL1*, *MT-TK*, *MT-TW*, *MT-TV*, *MT-ND1*, *MT-ND2*, *MT-ND3*, *MT-ND4*, *MT-ND5*, *MT-ND6*, *MT-CO3* • Mitochondrial DNA deletions (rare) • *SUCLA2*, *NDUSFx*, *NDFVx*, *SDHA*, *BCS1L*, *SURF1*, *SCO2*, *COX15*
LHON	• Painless bilateral visual failure • Male predominance	• *MT-ND1*, *MT-ND4*, *MT-ND6*

Syndrome	Main Clinical Manifestations	Major Genes Involved
	• Dystonia • Cardiac pre-excitation syndromes	
NARP	• Peripheral neuropathy • Ataxia • Pigmentary retinopathy	• *MT-ATP6*
MNGIE	• Intestinal malabsorption • Cachexia • External ophthalmoplegia • Neuropathy	• *TP*
IOSCA	• Ataxia • Hypotonia • Athetosis • Ophthalmoplegia • Seizures	• *TWINKLE*
SANDO	• Ataxic neuropathy • Dysarthria • Ophthalmoparesis	• *POLG*
Alpers syndrome	• Intractable epilepsy • Psychomotor regression • Liver disease	• *POLG*, *DGUOK*, *MPV17*
GRACILE	• Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis	• *NDUSFx*
Coenzyme Q_{10} deficiency	• Encephalopathy • Steroid-resistant nephrotic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss	• *COQ2* • *COQ9* • *CABC1* • *ETFDH*

Adapted from Chinnery et al (2014)[5] and Angelini et al (2009).[7]
CPEO: chronic progressive external ophthalmoplegia; GRACILE: growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, early death; IOSCA: infantile onset spinocerebellar ataxia; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms; MERFF: myoclon us epilepsy with ragged red fibers; MNGIE: mitochondrial neurogastrointestinal encephalopathy; NARP: neuropathy, ataxia, and retinitis pigmentosa; SANDO: sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.

Literature Review

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 neurogastrointestinal encephalopathy (MNGIE), although evidence for their effectiveness is not conclusive.

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

The tests being considered are genetic testing and targeted familial variant testing. 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 for patients with signs and/or symptoms of a mitochondrial disorder: 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 acylcarnitines; and urine organic acids. Additionally, a muscle biopsy has been traditionally considered the criterion standard for the diagnosis of mitochondrial diseases. For individuals who are asymptomatic with a close relative who has a mitochondrial disease and a known pathogenic variant, the following practice is currently being used: standard risk assessment without genetic testing.

Outcomes

The general outcomes of interest include test validity, other test performance measures, symptoms, functional outcomes, changes in reproductive decision making, health status measures, and quality of life.

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.

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.

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.

Study Selection Criteria

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

- 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.

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).

Review of Evidence

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 mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms (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

Study	Population	N	Genetic Test	Design	Yield, n (%)
Riley et al (2020)[10,]	Australian cohort of children with suspected mitochondrial disease	40	Trio GS	• Prospective enrollment • Selection method not reported	• 22 (67.5%) with "causal" variants • 22 (50%) with a "definitive molecular diagnosis" per modified Nijmegen mitochondrial disease severity scale

Study	Population	N	Genetic Test	Design	Yield, n (%)
Nogueira et al (2019)[11,]	Children and adults suspected of having mitochondrial disease	146 (including 110 children)	Custom NGS panel of 209 genes followed by Sanger sequencing	• Prospective/retrospective not reported • Selection method not reported	• 16 (11%) with "causative" variants • 20 (14%) with VUS • 54/107 (50%) with defects identified on muscle biopsy
Fang et al (2017)[12,]	Children and young adults suspected of having mitochondrial disease	141	Targeted NGS	• Prospective enrollment • Selection method not reported	• 40 (28%) with "causative" variants
Legati et al (2016)[13,]	Patients clinically diagnosed with mitochondrial disease	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:* • 19 (15%) with "causative" variants • 27 (22%) with possible pathogenic variants *WES:* • 6 (60%) with "causative" variants
Pronicka et al (2016)[14,]	Patients referred for possible or probable mitochondrial disease	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	• 67 (59%) with likely pathogenic variants • 30 (64%) of neonates with likely pathogenic variants
Kohda et al (2016)[15,]	Children with early-onset respiratory chain disease	142	NGS of the entire mtDNA plus WES of the nDNA	• Prospective enrollment • Selection method not reported	• 29 (20%) with known pathogenic variants • 53 (37%) inconclusive but possibly pathogenic variants
Wortmann et al (2015)[16,]	Children and young adults with a suspected mitochondrial disease	109	Panel of 238 genes associated with mitochondrial disease followed by WES	• Prospective enrollment • Selection method not reported	• 42 (39%) with pathogenic variants
Ohtake et al (2014)[17,]	Patients with mitochondrial respiratory chain diseases	104	NGS of exome of nDNA	• Prospective/retrospective not reported	• 18 (17%) with known pathogenic variants

Study	Population	N	Genetic Test	Design	Yield, n (%)
				• Selection method not reported	• 27 (26%) with likely pathogenic variants
Taylor et al (2014)[18],	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	• 28 (53%) with known pathogenic variants • 4 (8%) with likely pathogenic variants
Lieber et al (2013)[19],	Patients with suspected mitochondrial diseases 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	• 22 (22%) with likely pathogenic variants • 26 (25%) VUS
DaRe et al (2013)[20],	Patients with diagnosed or suspected mitochondrial diseases	148	NGS panel of 447 genes (Transgenomic)	• Prospective/retrospective not reported; consecutive patients	• 13 (9%) possible pathogenic variants • 67 (45%) with VUS
McCormick et al (2013)[21],	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" or "possible" mitochondrial disease
Calvo et al (2012)[22],	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	• 10 (24%) with known pathogenic variants • 13 (31%) possible pathogenic variants
Qi et al (2007)[23],	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	• 64 (12%) with pathogenic variants

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

GS: genome sequencing; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms; MERRF: myoclon us 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.[24,] 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 mitochondrial DNA (mtDNA) variants thought to be associated with clinical disease.[25,] At least 1 pathogenic variant was identified in 15 (0.54%) of 3168 people (95% confidence interval [CI], 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.[26,] This study included 24,5201 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 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 (VUS) 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, VUS were far more common than definite pathogenic variants.[20,] 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, VUS 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.[27,] This same variant has also been associated with chronic progressive external ophthalmoplegia (CPEO) and Leigh syndrome.[28,] Therefore, the more closely the clinical syndrome matches MELAS, the more likely a positive genetic test will represent a pathogenic variant.

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 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 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. A Cochrane review updated in 2012 by Pfeffer and coworkers did not find any clear evidence supporting the use of any intervention for the treatment of mitochondrial disorders.[29,]

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 (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 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 affected 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 heteroplasmy of the mtDNA variant, threshold levels, and phenotypic expression leading.

Section Summary: Mitochondrial Diseases

Case series and cohort studies have provided information on 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. 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 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Mitochondrial Medicine Society

The Mitochondrial Medicine Society (2015) published a consensus statement on the diagnosis and management of mitochondrial disease.[30,] 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 August 2024 did not reveal any ongoing trials that might influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history
  - Reason for test
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results as applicable
- Consultation(s), when applicable
- Laboratory results

Post Service (in addition to the above, please include the following):

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

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81440	Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
	81460	Whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [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 (e.g., Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
	0417U	Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear-encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification and categorization of mitochondrial disorder-associated genetic variants
HCPCS	None	

Policy History

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

Effective Date	Action
08/01/2016	BCBSA Medical Policy adoption
08/01/2017	Policy revision with position change
08/01/2018	Policy revision without position change
08/01/2019	Policy revision without position change
08/01/2020	Annual review. No change to policy statement.
12/01/2020	No change to policy statement. Policy guidelines and literature review updated.
01/01/2021	Coding Update
11/01/2021	Annual review. No change to policy statement. Policy guidelines and literature review updated.
11/01/2022	Annual review. No change to policy statement. Policy guidelines and literature review updated.
12/01/2022	Administrative update.
11/01/2023	Annual review. No change to policy statement. Literature review updated. Coding update
10/01/2025	Policy reactivated. Previously archived from 04/01/2024 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

- The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
- The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

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

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Mitochondrial Disorders 2.04.117** **Policy Statement:** I. 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. II. Targeted genetic testing for a known familial variant in at-risk relatives may be considered **medically necessary** as preconceptional carrier testing under **both** of the following conditions (see Benefit Application section): A. There is a defined mitochondrial disorder in the family of sufficient severity to cause impairment of quality of life or functional status B. A variant that is known to be pathogenic for that specific mitochondrial disorder has been identified in the index case. III. Genetic testing for mitochondrial disorders is considered **investigational** in **all** other situations when the criteria for medical necessity are not met.