PHP_2.04.117	Genetic Testing for Mitochondrial Disorders		
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Section:	2.0 Medicine	**Page:**	Page 1 of 21

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 0001M thru 0999U (tar and non cd0)
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- Pathology: Molecular Pathology (path molec)

Below is an excerpt of the Molecular Pathology guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing
Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test. As such, the particular biomarker or pharmacogenomic test code may be covered with an approved Treatment Authorization Request (TAR) if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.

Biomarker Testing
Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

Requirements for CPT code 81401:
Tier 2, Molecular Pathology Procedure, Level 2
Coverage for CPT code 81401 (molecular pathology procedure, Level 2) is limited to the listed services. Reimbursement for code 81401 requires an approved TAR and requires providers to document one of the following on the TAR:

- MT-ATP6 (neuropathy with ataxia and retinitis pigmentosa [NARP], Leigh syndrome) –The member has clinical features suspicious for, or requires the service as a confirmatory test for NARP or Leigh syndrome.

Requirements for CPT code 81403:
Tier 2, Molecular Pathology Procedure, Level 4
Coverage for CPT code 81403 (molecular pathology procedure, Level 4) is limited to the listed services. Reimbursement for code 81403 requires an approved TAR and requires providers to document one of the following on the TAR:

- Known family variant not otherwise specified, for gene listed in Tier 1 or Tier 2, or identified during a genomic sequencing procedure (GSP), DNA sequence analysis, each variant exon:
  - Documentation of the specific gene listed in Tier 1, Tier 2 or GSP for which further analysis is being requested

Requirements for CPT code 81406:
Tier 2, Molecular Pathology Procedure, Level 7
Coverage for CPT code 81406 (molecular pathology procedure, Level 7) is limited to the listed services. Reimbursement for code 81406 requires an approved Treatment Authorization Request (TAR) and requires providers to document one of the following on the TAR:

- POLG (polymerase [DNA directed], gamma [e.g., Alpers-Huttenlocher syndrome, autosomal dominant progressive external ophthalmoplegia], full gene sequence). TAR may be approved based on one of the following numbered criteria:
  - The member is undergoing consideration for treatment using valproic acid, or
  - The member is undergoing evaluation for potentially having any one of the following conditions:
    - Alpers-Huttenlocher syndrome
    - Ataxia neuropathy spectrum (ANS), previously known as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy, dysarthria and ophthalmoplegia (SANDO)
    - Autosomal dominant progressive external ophthalmoplegia
    - Autosomal recessive progressive external ophthalmoplegia
    - Childhood myocerebrohepatopathy spectrum
    - Myoclonic epilepsy myopathy sensory ataxia

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:

- N/A

Policy Statement

Any criteria that are not specifically addressed in the above Provider Manual, please refer to the criteria below.

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:
   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.

Policy Guidelines

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

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 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 Promise 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.

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

- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09
California laws that require 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.

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.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

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.

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.[1,4,5]

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.[6,7] 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.[2,7]

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.[6,7] 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.[8] Exercise therapy for myopathy is often prescribed but the effect on clinical outcomes is uncertain.[6] 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.[6,9] A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database.[10] 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.[11]

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 • Dystonia • Cardiac pre-excitation syndromes	• *MT-ND1*, *MT-ND4*, *MT-ND6*
NARP	• Peripheral neuropathy • Ataxia • Pigmentary retinopathy	• *MT-ATP6*
MNGIE	• Intestinal malabsorption • Cachexia	• *TP*

Syndrome	Main Clinical Manifestations	Major Genes Involved
	• External ophthalmoplegia • Neuropathy	
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)[6] and Angelini et al (2009).[9]
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: myoclonus 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)[12]	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
Nogueira et al (2019)[13]	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)[14]	Children and young adults suspected of having	141	Targeted NGS	• Prospective enrollment	• 40 (28%) with "causative" variants

Study	Population	N	Genetic Test	Design	Yield, n (%)
	mitochondrial disease			• Selection method not reported	
Legati et al (2016)[15]	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)[16]	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)[17]	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)[18]	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)[19]	Patients with mitochondrial respiratory chain diseases	104	NGS of exome of nDNA	• Prospective / retrospective not reported • Selection method not reported	• 18 (17%) with known pathogenic variants • 27 (26%) with likely pathogenic variants
Taylor et al (2014)[20]	Patients with suspected mitochondrial disease and multiple	53	WES validated with Sanger sequencing	• Prospective / retrospective not reported; selection method not	• 28 (53%) with known pathogenic variants

Study	Population	N	Genetic Test	Design	Yield, n (%)
	respiratory chain complex defects			reported but only included patients with multiple respiratory chain complex defects	• 4 (8%) with likely pathogenic variants
Lieber et al (2013)[21]	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)[22]	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)[23]	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)[24]	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)[25]	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 pathogenic variants	• Prospective / retrospective not reported • Selection method not reported	• 64 (12%) with pathogenic variants

GS: genome sequencing; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms; MERRF: myoclonus 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.[26] 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.[27] 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.[28] 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.[22] 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.[29] This same variant has also been associated with chronic progressive external ophthalmoplegia (CPEO) and Leigh syndrome.[30] 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.[31]

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.

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.

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 U.S. professional society, an international society with U.S. 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.[32] 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 2025 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
  - Treatment plan
  - 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®	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 ***(Includes Genomic Unity® Comprehensive Mitochondrial Disorders Analysis, Variantyx Inc)***
	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)

Type	Code	Description
	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
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
03/01/2026	New policy.

Definitions of Decision Determinations

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

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42

USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan 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 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/en/bsp/providers.

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

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan 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 of California Promise Health Plan reserves the right to review and update policies as appropriate.