



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA

Subject Genetic Testing for Mitochondrial Disorders

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Genetic Counseling
 Genetic Testing of Heritable Disorders
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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

Coverage of genetic testing is dependent upon benefit plan language and may be governed by federal and/or state mandates. Under some benefit plans, genetic testing may be entirely excluded from coverage or only covered when certain conditions apply. Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage.

CIGNA covers genetic molecular testing for mitochondrial disorders as medically necessary for ANY of the following indications:

- Confirmatory testing when clinical examination and conventional studies are suggestive of a mitochondrial disorder but a definitive diagnosis remains uncertain.
- Carrier testing when there is a positive family history of mitochondrial disorders in a first degree* or second degree* relative and the couple has the capacity and intention to reproduce.
- Prenatal testing of a fetus or preimplantation genetic diagnosis (PGD) of the embryo for autosomal recessive nuclear gene mutations suggestive of mitochondrial disorders when the fetus or embryo has been identified to be at risk for inheriting a mitochondrial disorder (i.e., either parent has the diagnosis, is a known carrier of the disorder or has a family history of the disorder).

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half siblings.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or licensed or certified genetic counselor.

CIGNA does not cover molecular genetic testing for mitochondrial disorders in the general population, because such screening is considered not medically necessary or of unproven benefit.

General Background

Mitochondrial diseases are a group of disorders that result from dysfunctions of the mitochondrial respiratory chain. A conservative estimate for the prevalence of all mitochondrial diseases is 11.5/100,000. The disorders can be caused by mutations of nuclear deoxyribonucleic acid (DNA) or mitochondrial deoxyribonucleic acid (mtDNA). The mitochondrial respiratory chain is the essential final common pathway for aerobic metabolism. Tissues and organs that depend heavily on aerobic metabolism are preferentially involved in mitochondrial disorders. DNA replication and protein synthesis, which are essential for cellular functioning, are costly metabolic reactions that require the provision of adenosine triphosphate (ATP). ATP is produced by the mitochondria. Mitochondria depend on several metabolic pathways within a cell to guarantee the supply of ATP under varying cellular conditions. Glycolysis, fatty acid oxidation, and oxidative phosphorylation are three metabolic pathways. Efficient cellular functioning requires ATP production and is contingent on the ability of the cell to utilize these different metabolic pathways (Chinnery, 2006).

Individuals with mitochondrial disorders may display a cluster of clinical features that fall into a separate clinical syndrome. Some of the mitochondrial disorders include (Chinnery, 2006):

- Kearns-Sayre syndrome (KSS)
- Pearsons syndrome
- progressive external ophthalmoplegia (PEO)
- neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP)
- Leigh syndrome (LS)
- Leber hereditary optic neuropathy (LHON)
- mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- myoclonic epilepsy with ragged red fibers (MERRF)

Each human cell contains thousands of copies of mtDNA. At birth, these copies are usually identical (i.e., homoplasmic). By contrast, individuals with mitochondrial disorders resulting from mtDNA mutations may harbor a mixture of mutant and wild-type mtDNA within each cell (i.e., heteroplasmy). Cell studies have shown that the proportion of mutant mtDNA must exceed a critical threshold level before a cell expresses a biochemical abnormality of the mitochondrial respiratory chain (the threshold effect). The percentage level of mutant mtDNA may vary among individuals within the same family, as well as among organs and tissues within the same individual. This varying percentage level of mutant mtDNA is one explanation for the varied clinical presentation (Chinnery, 2006).

Nuclear DNA (nDNA) is inherited in a Mendelian pattern: one copy of each gene is inherited from the mother and one from the father. If nuclear DNA encodes the mutated protein, the disease may be inherited in an autosomal-dominant or autosomal-recessive fashion. Because mtDNA is inherited almost exclusively from the mother, mitochondrial disease also may be inherited maternally. MtDNA is governed by population genetics, because each cell contains many mitochondria, and each mitochondrion contains multiple copies of mtDNA. As a result, the genetic make-up of each cell is not necessarily the same from one cell to another. Mutations may be present in all of the mtDNA or only in a subpopulation. All cells have multiple copies of mtDNA. Since mitochondria are randomly sorted during meiosis, different cells have varying concentrations of mutated mtDNA. As a result, siblings from the same mother may have marked variations in the expression of mitochondrial disease (Chinnery, 2006).

Mitochondrial genetic defects can be inherited in several ways (Chinnery, 2006):

- mtDNA inheritance carries up to 100% risk for future siblings, since all mitochondria come from the mother
- nuclear DNA inheritance involves dominant inheritance in which a single copy of a mutated gene is inherited from either parent, and recessive inheritance where two mutated copies of the same gene are inherited, one from each parent:
 - recessive inheritance carries a 25% risk of recurrence if no other family members appear to be affected
 - dominant inheritance often carries a 50% risk for future siblings if mitochondrial disease often occurs in other family members or ancestors
- combination of mtDNA and nDNA defects

Some mitochondrial disorders affect only a single organ, such as the eye in LHON, but many involve multiple organ systems and often present with prominent neurological and myopathic features. Mitochondrial disorders may present at any age. Generally, nuclear DNA mutations present in childhood, while mtDNA mutations (primary or secondary to nuclear DNA abnormalities) present in late childhood or in adulthood. Mitochondrial disease is difficult to classify. Many individuals do not fall into one specific disease category (Chinnery, 2006).

The diagnosis of mitochondrial disease is difficult when only one symptom is present. The diagnosis is easier to consider when two or more seemingly unrelated symptoms involving more than one organ system are present. The investigation can be relatively straightforward if the individual has a recognizable phenotype and if it is possible to identify a known pathogenic mtDNA mutation. Difficulty arises when no mtDNA defect can be found or when the clinical abnormalities are complex and not easily matched to those of more common mitochondrial disorders (Chinnery, 2006).

Family history is important in making a diagnosis and directing molecular genetic testing. Many of the childhood onset encephalomyopathies occur only once in a family and may stem from recessive nuclear gene defects or mtDNA defects. The range of clinical features is broad, and there may be members with only one feature or mild features of a related disease (Chinnery, 2006).

Clinical tests are used to support a diagnosis of mitochondrial disease. Neuroimaging and neuropsychological studies are indicated in individuals with suspected central nervous system (CNS) disease. Electroencephalography (EEG) is indicated in individuals with suspected encephalopathy or seizures. Peripheral neuropsychological studies are indicated in individuals with limb weakness, sensory symptoms, or areflexia. Magnetic resonance spectroscopy and exercise testing (with measurement of blood lactate concentration) may be used to detect evidence of abnormal mitochondrial function noninvasively. An elevated concentration of fasting blood glucose may indicate diabetes mellitus. Cardiac electrocardiography (EKG) and echocardiography (ECHO) may indicate cardiac involvement. Lactate/pyruvate measurement of blood lactate concentration is indicated in individuals with features of a myopathy or CNS disease. A fasting blood lactate concentration > 3 mm/l supports a diagnosis of mitochondrial disease. Measurement of cerebrospinal fluid (CSF) lactate concentration is indicated in individuals with suspected CNS disease. A fasting CSF lactate concentration > 1.5 mm/l supports a diagnosis of mitochondrial disease. More specific tests for mitochondrial disease include analyzing muscle biopsies for histological or histochemical evidence of mitochondrial disease. Respiratory chain complex studies are then usually carried out on skeletal muscle or skin fibroblasts (Chinnery, 2006).

Molecular genetic testing can be carried out on genomic DNA extracted from blood (suspected nuclear DNA mutations and some mtDNA mutations), or on genomic DNA extracted from skeletal muscle (suspected mtDNA mutations). Southern blot is a molecular genetic testing technique used to detect a pathogenic mtDNA rearrangement. The deletion or duplication breakpoint may be mapped by mtDNA sequencing. Targeted mutation analysis of a panel of genes may be performed. If a recognized point mutation is not identified, the entire mitochondrial genome may be sequenced. Mitochondrial disorders caused by defects of mitochondrial ribosomal (mrDNA) are transmitted by maternal inheritance. Offspring of males with mtDNA mutation are not at risk. All offspring of females with an mtDNA mutation are at risk of inheriting the mutation (Chinnery, 2006).

Prenatal genetic testing and interpretation for mtDNA disorders is difficult because of mtDNA heteroplasmy. The interpretation of a chorionic villus biopsy is difficult, and for most mtDNA mutations prenatal diagnosis is not

recommended. Prenatal testing for autosomal dominant nuclear gene mutations has not yet been accomplished. Prenatal diagnosis for pregnancies at increased risk for autosomal recessive nuclear gene mutations is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis, usually performed at approximately 15–18 weeks' gestation or chorionic villus sampling (CVS) at about 10–12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified or linkage established in the family before prenatal testing can be performed. Prenatal biochemical testing for established respiratory chain complex defects (i.e., autosomal recessive nuclear gene mutations) are possible once the disease-causing mutation is found in the affected family member. Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) has/have been identified in an affected family member in a clinical or research laboratory (Chinnery, 2006).

Currently there are no cures for mitochondrial diseases. The treatments and medications address only the symptoms of the mitochondrial disorder. Treatment is individualized for each person by their physician and can include supplements and special diets (Chinnery, et al., 2006).

Kearns-Sayre Syndrome (KSS), Pearson Syndrome and Progressive External Ophthalmoplegia (PEO)

KSS, Pearson syndrome and PEO are mtDNA deletion syndromes that comprise three overlapping phenotypes. These phenotypes may be observed in different members of the same family or may evolve in a given individual over time. KSS is defined by the triad of onset before age 20, and at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration > 100 mg/dl, or cerebellar ataxia. Pearson syndrome is a usually fatal disorder of infancy characterized by sideroblastic anemia and exocrine pancreatic dysfunction. PEO is a mitochondrial myopathy with drooping of the eyelids (ptosis), paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness. A few individuals with PEO have other manifestations of KSS but do not fulfill all the clinical criteria for KSS diagnosis. This situation is called KSS minus or PEO plus (DiMauro and Hirano, 2007).

Molecular Genetic Testing for KSS, Pearson Syndrome and PEO: Molecular genetic testing may be used for diagnostic testing and prenatal diagnosis. Southern blot analysis for mtDNA deletion syndromes is the preferred clinical method for molecular genetic testing. Approximately 90% of individuals with KSS have a large-scale (i.e., 2–10 kb) mtDNA deletion. Deletions can vary in size and abundance among individuals, but deleted mtDNA of any given length is present in each individual. Large-scale duplications of mtDNA coexist with deletions in some individuals with KSS. Deletions are usually present in all tissues of individuals with KSS and can be looked for in blood leukocytes. The occurrence of heteroplasmy in disorders of mtDNA can result in varying tissue distribution of deleted mtDNA. Since mutant mtDNA may be undetectable in blood cells, muscle biopsy may be necessary. Mitochondrial DNA deletions are usually more abundant in blood than in other tissues. The diagnosis of Pearson syndrome can be made reliably by southern blot analysis of leukocytes. The molecular diagnosis of PEO requires Southern blot analysis of a muscle biopsy (DiMauro and Hirano, 2007).

Leigh Syndrome (LS) and Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP)

LS and NARP are part of a continuum of progressive neurodegenerative disorders caused by abnormalities of mitochondrial energy generation. NARP is characterized by proximal neurogenic muscle weakness with sensory neuropathy, ataxia, and pigmentary retinopathy. Onset of symptoms, particularly ataxia and learning difficulties, often occurs in early childhood. Individuals with NARP can remain relatively stable for many years but may suffer episodic deterioration, often in association with viral illnesses. LS, also known as subacute necrotizing encephalomyelopathy, is characterized by onset of symptoms typically at age 3–12 months, often following a viral infection. Decompensation (often with lactic acidosis) during an illness is typically associated with psychomotor retardation or regression. Neurological features include hypotonia, spasticity, movement disorders (including chorea), cerebellar ataxia, and peripheral neuropathy. Extraneurological manifestations may include hypertrophic cardiomyopathy. About 75% of affected individuals die by age 2–3, most often from respiratory or cardiac failure (Thorburn and Rahman, 2006).

Molecular Genetic Testing for LS and NARP: Clinical methods used in molecular genetic testing of LS and NARP include targeted mutation analysis or sequence analysis. Molecular genetic testing may be used for diagnostic testing and prenatal diagnosis. The proportion of individuals with NARP who have detectable mutations at MTATP6 nucleotide 8993 is not known, but is likely to be greater than 50%, at least in individuals with lactic acidosis. ATG transversion (T8993G) is most common; a T to C transition (T8993C) has also been described. Approximately 10–20% of individuals with LS have either the T8993G or the T8993C MTATP6 mutation. Approximately 10–20% have mutations in other mitochondrial genes. Mutation analysis for the

MTATP6 mutations T8993G and T8993C is available on a clinical basis. It is likely that approximately 30–40% of individuals with LS, and more than 50% of individuals with NARP, have pathogenic mtDNA mutations that could be identified by full sequence analysis. Mutation analysis for other mtDNA mutations identified in individuals with LS, such as the mutations in genes MTATP6, MTTL1, MTTK, MTND1, MTND3, MTND4, MTND5, MTND6, MTCO3, MTTW and MTTV, is offered on a clinical basis by some laboratories (Thorburn and Rahman, 2006).

Leber Hereditary Optic Neuropathy (LHON)

LHON typically presents in young adults as painless, subacute bilateral visual failure affecting males more commonly than females. The acute phase begins with blurring of central vision and color desaturation that affect both eyes simultaneously in up to 25% of cases. After the initial symptoms, both eyes are usually affected within an average of eight weeks later. The central visual acuity deteriorates to the level of counting fingers in most cases. Individuals then proceed into the atrophic phase and significant improvements in visual acuity are rare; in most individuals, vision remains severely impaired and within the legal requirement for blind registration. Minor neurological abnormalities (e.g., such as a postural tremor or peripheral neuropathy) are said to be common in individuals with LHON. Some individuals with LHON, usually women, also have a multiple sclerosis-like illness (Chinnery, 2008).

Molecular Genetic Testing for LHON: Molecular genetic testing for these mutations is clinically available by targeted mutation analysis or sequence analysis/mutation scanning and is used for diagnostic testing and prenatal diagnosis. The prevalence of each mutation varies considerably; worldwide, the G11778A mutation is the most common, accounting for 70% of cases. Only about 5% of individuals with LHON do not harbor one of the three common mtDNA point mutations. Further investigation of these families is difficult because mtDNA is highly polymorphic. Clinical testing for some secondary mutations is available. The clinical interpretation of secondary LHON mtDNA mutations is complex; therefore, testing for these alleles is not routine. Approximately 15% of individuals with LHON are found to have a mixture of mutant and wild-type mtDNA in blood leukocytes. It is possible that heteroplasmy influences the expression and inheritance pattern of LHON, but no rigorous prospective studies have been performed to clarify this possibility. Heteroplasmy does not influence the sensitivity of molecular genetic testing for LHON, because affected individuals generally have > 75% mutant mtDNA in leukocytes, a concentration that is easily detected by standard techniques. The level of heteroplasmy may have a bearing on the risk of developing LHON in asymptomatic individuals and on the risk of transmission (Chinnery, 2008).

Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-Like Episodes (MELAS)

MELAS is a multisystem disorder with onset typically occurring in childhood. Early psychomotor development is usually normal, and short stature is common. First onset of symptoms frequently ranges from ages 2–10 (DiMauro and Hirano, 2005).

Molecular Genetic Testing for MELAS:

- Targeted mutation analysis: Testing for recurrent MTTL1 mutations is available on a clinical basis. The specific mutations included in testing panels vary across laboratories and may include the MTTL1 mutations A3243G, T3271C and A3252G, as well as additional rare mutations. Targeted mutation analysis for the most common MT-ND5 mutation, G13513A, is clinically available.
- Sequence analysis/mutation scanning: Sequence analysis of the MTTL1 gene is available on a clinical basis and may be an option for individuals in whom no mutation is detected through mutation analysis. Sequence analysis of the MT-ND5 gene is clinically available (DiMauro and Hirano, 2005).

Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

MERRF is a multisystem disorder characterized by myoclonus, which is often the first symptom, followed by generalized epilepsy, ataxia, weakness and dementia. Onset usually occurs in childhood after normal early development. Common findings are hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White syndrome. Occasionally pigmentary retinopathy and lipomatosis are observed (DiMauro and Hirano, 2009).

Molecular Genetic Testing for MERRF:

- Targeted mutation analysis: Testing for the three common MERRF mutations (A8344G, T8356C and G8363A) is available on a clinical basis as a panel. Mutations are usually present in all tissues and are conveniently detected in blood leukocytes. The occurrence of heteroplasmy in disorders of mtDNA can result in varying tissue distribution of mutated mtDNA. Therefore, in individuals having only few symptoms consistent with MERRF or in asymptomatic maternal relatives, the pathogenic mutation may be undetectable in leukocytes and may be detected only in other tissues, such as cultured skin fibroblasts, urinary sediment, oral mucosa (from mouthwash), hair follicles or, most reliably, skeletal muscle.
- Mutation scanning/sequence analysis: Mutation scanning/sequence analysis is used to detect mutations throughout mtDNA and is not specific for MERRF (DiMauro and Hirano, 2009).

Summary

Mitochondrial disorders may associate with either nuclear or mitochondrial deoxyribonucleic acid (DNA). Nuclear DNA is inherited in a Mendelian pattern: one copy of each gene is inherited from the mother and one from the father. If nuclear DNA encodes the mutated protein, the disease may be inherited in an autosomal-dominant or autosomal-recessive fashion. Because mitochondrial DNA (mtDNA) is inherited almost exclusively from the mother, mitochondrial disease may also be inherited maternally. Mitochondrial disorders caused by defects of mitochondrial ribosomal (mrDNA) are transmitted by maternal inheritance. Offspring of males with mtDNA mutation are not at risk. All offspring of females with an mtDNA mutation are at risk of inheriting the mutation.

In some individuals, the clinical picture is characteristic of a specific mitochondrial disorder (e.g., LHON, NARP or maternally inherited LS), and the diagnosis can be confirmed by molecular genetic testing of DNA extracted from a blood sample. In many individuals, this is not the case, and a more structured approach is needed, including family history, blood and/or CSF lactate concentration, neuroimaging, cardiac evaluation, and muscle biopsy for histological or histochemical evidence of mitochondrial disease, and molecular genetic testing for an mtDNA mutation. Prenatal testing and preimplantation genetic diagnosis (PGD) may be used to identify disorders in embryos at risk of inheriting the disorder.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered as medically necessary when used to report genetic testing for mitochondrial disorders as outlined as covered in this policy:

CPT [®] * Codes	Description
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892	Molecular diagnostics; enzymatic digestion
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide)
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern)
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83903	Molecular diagnostics; mutation scanning, by physical properties (eg, single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'ase A), single segment, each
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83909	Molecular diagnostics; separation and identification by high resolution technique

	(eg, capillary electrophoresis)
83912	Molecular diagnostics; interpretation and report
83914	Mutation identification by enzymatic ligation or primer extension, single segment, each segment [eg, oligonucleotide ligation assay (OLA), single base chain extension (SBCE), or allele-specific primer extension (ASPE)]

ICD-9-CM Diagnosis Codes	Description
250	Diabetes mellitus
276.2	Acidosis: lactic
277.87	Disorders of mitochondrial metabolism
330.8	Leigh's disease
389.10	Sensorineural hearing loss, unspecified
425.1	Hypertrophic obstructive cardiomyopathy

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	10/15/2008	0201	Genetic Testing for Mitochondrial Disorders

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