Whole Mitochondrial Genome Sequencing and Multigene Panels for Mitochondrial Disorders

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Medical Coverage Policy

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Description

Mitochondria are organelles found in eukaryotic cells (cell or organism that has a clearly defined nucleus) and are responsible for breaking down carbohydrates and fatty acids to power biochemical reactions and metabolism within the cell. Mitochondrial disorders are chronic, genetic conditions that are often inherited and occur when the mitochondria fail to produce sufficient energy for the body to function.

Mitochondrial disorders can affect almost any part of the body, including but not limited to, cells of the brain, ears, eyes, heart, kidneys, liver, muscles, nerves or pancreas. Some individuals display features that

fall into distinct syndromes while others present with overlapping features making a definitive diagnosis difficult.

Mitochondrial disorders include, but are not limited to:

- Barth syndrome
- Chronic progressive external ophthalmoplegia (CPEO)
- Encephalopathy of infancy and childhood
- Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis and early death (GRACILE)
- Kearns-Sayre syndrome (KSS)
- Leber hereditary optic neuropathy (LHON)
- Leigh syndrome (LS)
- Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- Mitochondrial recessive ataxia syndrome (MIRAS)
- Multisystem disease with myopathy
- Myoclonic epilepsy with ragged-red fibers (MERRF)
- Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)
- Pearson syndrome
- *POLG*-related disorders including, but may not be limited to:

    - Alpers syndrome
    - Autosomal dominant progressive external ophthalmoplegia
    - Autosomal recessive progressive external ophthalmoplegia
    - Childhood myocerebrohepatopathy syndrome
    - Myoclonic epilepsy myopathy sensory ataxia

Mitochondrial disorders are caused by pathogenic variants in deoxyribonucleic acid (DNA) (nuclear DNA [nDNA]) or in DNA contained within the mitochondria (mitochondrial DNA [mtDNA]).

Multigene panels, whole genome/exome sequencing (of nDNA) and whole mitochondrial genome sequencing are laboratory techniques that use next-generation sequencing (NGS) to detect gene variations associated with mitochondrial disorders and have been suggested to aid in the diagnosis of these conditions.

Multigene (or expanded) panels analyze a broad set of genes simultaneously (as opposed to single gene testing that searches for variants in one specific gene) and have been proposed to evaluate the DNA of an individual with a personal and/or family history of more than one hereditary condition or syndrome. Panels often include medically actionable genes but may also include those with unclear medical management. Targeted (or focused) multigene panels analyze a limited number of genes targeted to a specific condition.

Whole genome sequencing of mtDNA detects pathogenic point mutations and single large-scale deletions with heteroplasmy (the presence of more than one type of mtDNA in an individual) that contribute to mitochondrial dysfunction. However, nuclear gene variants that may cause mitochondrial dysfunction are not detected by this analysis.

Coverage Determination

Any state mandates for whole mitochondrial genome sequencing and multigene panels for mitochondrial disorders take precedence over this medical coverage policy.

Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.

Humana members may **NOT** be eligible under the Plan for **whole mitochondrial genome sequencing or multigene panels for mitochondrial disorders**. Examples include, but may not be limited to:

- 65 mtDNA Point Mutations Plus Large Deletions Panel
- Combined Mito Genome Plus Mito Nuclear Gene Panel
- Comprehensive Mitochondrial Nuclear Gene Panel
- Dual Genome Leigh Disease Panel by Massively Parallel Sequencing
- Genomic Unity Comprehensive Mitochondrial Disorders Analysis (0417U)
- Mitochondrial Disorders Panel
- Mitochondrial Encephalopathy/Leigh Syndrome Nuclear Gene Panel
- Mitochondrial Genome: Sequencing
- Mitochondrial Respiratory Chain Complex V Deficiency Panel by Massively Parallel Sequencing
- MitoMet Plus aCGH Analysis
- MitoSwab
- Nuclear encoded mitochondrial genomic sequencing panel of at least 100 genes for mitochondrial disorders including, but may not be limited to, neurologic or myopathic phenotypes (81440)
- Whole mitochondrial genome large deletion analysis panel for mitochondrial disorders including, but may not be limited to, KSS or CPEO (81465)
- Whole mitochondrial genome sequencing for mitochondrial disorders including, but may not be limited to, Leigh syndrome, MELAS, MERFF, NARP or LHON (81460)

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2	**Not Covered if used to report any test outlined in Coverage Limitations section**
81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4	**Not Covered if used to report any test outlined in Coverage Limitations section**
81404	MOLECULAR PATHOLOGY PROCEDURE LEVEL 5	**Not Covered if used to report any test outlined in Coverage Limitations section**
81405	MOLECULAR PATHOLOGY PROCEDURE LEVEL 6	**Not Covered if used to report any test outlined in Coverage Limitations section**
81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7	**Not Covered if used to report any test outlined in Coverage Limitations section**

81440	Nuclear encoded mitochondrial genes (eg, 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	**Not Covered**
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection	**Not Covered**
81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed	**Not Covered**
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
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	**Not Covered** **New Code Effective 10/01/2023**
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

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Change Summary

- 01/25/2024 Annual Review, No Coverage Change.