

# Whole Mitochondrial Genome Sequencing, Whole Mitochondrial Genome Deletion/Duplication, and Nuclear Encoded Mitochondrial Gene Sequencing Panel Genetic Testing Policy

Procedure(s) addressed by this policy:	Procedure Code(s)
Whole Mitochondrial Genome Sequencing	81460
Whole Mitochondrial Genome Large Deletion/Duplication Analysis Panel	81465
Nuclear Encoded Mitochondrial Genes Sequencing Panel (Nuclear Mitome Sequencing)	81440

## What are mitochondrial conditions?

- Mitochondrial disorders are conditions resulting from the nuclear or mtDNA genes that are involved in the production, function, maintenance, or transmission of mitochondria. They comprise a clinically diverse group of diseases that may present at any age and affect a single organ or present as a multi-system condition in which neurologic and myopathic features predominate. Extensive clinical variability and phenotypic overlap exists among the many discrete mitochondrial disorders.
- Mitochondrial disease is suspected in patients with a combination of clinical features in:
  - muscle: proximal myopathy or cardiomyopathy
  - nervous system: encephalopathy, seizures, dementia, stroke-like episodes, ataxia, spasticity, peripheral neuropathy, and migraine
  - eye: ptosis, ophthalmoparesis, ophthalmoplegia, optic atrophy, pigmentary retinopathy
  - hepatopathy
  - gastrointestinal: recurrent vomiting, anorexia
  - sensorineural hearing loss
  - diabetes mellitus
  - growth: failure to thrive, short stature
  - mid- or late pregnancy loss
- While mitochondrial disease is currently not curable, examples where application of specific treatments as well as withholding of contraindicated treatments for certain mitochondrial conditions are known and include:
  - **Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE)**
    - MNGIE is a multisystem mitochondrial disease<sup>1</sup> that typically is characterized by progressive gastrointestinal dysmotility, which may present with nausea, dysphagia, reflux, early satiety, vomiting after a meal, episodic abdominal pain,



- bloating, and/or diarrhea. Additionally individuals may present with cachexia (a wasting syndrome), ocular muscle weakness: ptosis (drooping eyelids), ophthalmoparesis/ophthalmoplegia (weak/paralyzed eye muscles), leukoencephalopathy on brain MRI, or peripheral neuropathy (tingling, numbness, and/or pain in the extremities). Onset is usually between the first and fifth decade of life. MNGIE is caused by biallelic mutations in TYMP and is inherited in an autosomal recessive pattern.<sup>1</sup>
- Treatments: In individuals with advanced illness, liver transplant or allogenic hematopoietic stem cell transplant, have been suggested as possible curative treatment options, although risks and benefits of these procedures must be properly weighed.<sup>2,3</sup> Peritoneal dialysis has also been suggested as a method of reduction of the thymidine concentration and should be considered as an additional or alternative form of treatment.<sup>4</sup>
- **Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike Episodes (MELAS)**
    - MELAS is a progressive, multisystem genetic disease.<sup>5</sup> Typical initial clinical presentation includes stroke-like episodes or cortical blindness often occurring with generalized tonic-clonic seizures, and these episodes may be recurrent and associated with altered consciousness. Almost all individuals with MELAS (94%) have lactic acidemia. Individuals may also have recurrent headaches, anorexia, recurrent vomiting, possibly exercise intolerance or proximal limb weakness, Wolff-Parkinson-White syndrome, and diabetes mellitus. Short stature in children and sensorineural hearing loss in both children and adults is also common. MELAS symptoms can present at any age. Individuals with MELAS typically experience disease progression that results in death.<sup>5</sup> MELAS is caused by mutations in the mitochondrial DNA.<sup>5</sup>
    - Screening: At-risk individuals may benefit from assessment to initiate baseline evaluations (neurology, cardiology, ophthalmology, and audiology) and potential intervention prior to exhibiting clinical manifestations.<sup>6</sup> Screening for diabetes mellitus by fasting serum glucose concentration and glucose tolerance test is recommended.<sup>5</sup>
    - Treatments: Use of oral and intravenous (IV) L-arginine and citrulline has shown reduction of frequency and/or severity of stroke-like episodes.<sup>6,7,8,9,10</sup> Both endurance and resistance exercise have been studied and shown to increase mitochondrial metabolism.<sup>8</sup> Vitamin and cofactor supplementation including CoQ<sub>10</sub>, alpha lipoic acid, and riboflavin should be offered, and addition of folic acid and L-carnitine should be considered, especially if there is documented deficiency.<sup>7</sup>
    - Designer endonucleases (TALENs and CRISPR-CAS9) are under active investigation as tools for reducing mutation heteroplasmy below the phenotypic threshold.<sup>11</sup>
  - **Leber Hereditary Optic Neuropathy (LHON)**
    - LHON is a mitochondrial disorder that mainly affects the eye and is characterized by bilateral painless subacute vision loss that begins in the second and third

decades of life. Vision loss may begin as unilateral, and then rapidly progress. Visual acuity usually deteriorates to 20/200 or worse, but vision may sometimes return.<sup>12,13,14</sup> Other neurologic features may include: tremor, peripheral neuropathy, myopathy and/or movement disorders.<sup>12</sup> Additionally, women may develop a multiple sclerosis-like progressive disease.<sup>12</sup> LHON is caused by point mutations (usually homoplasmic) in the mitochondrial genome.<sup>12</sup>

- Screening: Ophthalmological exam for bitemporal involvement.
- Treatments: Some clinicians treat children presymptomatically with antioxidants when their genetic status is known. People who have a pathogenic variant consistent with LHON should strictly avoid smoking and secondary smoke. Restriction of alcohol consumption and exposure to mitotoxic agents is also advisable.<sup>12</sup> Idebenone has been approved in Europe for stabilizing the visual loss of the remaining better eye in LHON.<sup>15</sup>
- *POLG*-related disorders
  - Encompass a wide spectrum of disorders involving multiple organ systems, with variable severity and age of onset.<sup>16,17</sup> Onset of the *POLG*-related disorders ranges from infancy to late adulthood. Pediatric patients typically present with seizures, lactic acidosis, and often hepatopathy; while myopathy, chronic progressive external ophthalmoplegia (CPEO), sensory ataxia, and sensory neuropathy are the major presenting features later in life.<sup>18,19</sup> *POLG*-related disorders are categorized into 6 recognizable phenotypes. Most affected individuals have some, but not all, of the features of a given phenotype.<sup>18</sup> All 6 *POLG*-related disorders are caused by mutations in the *POLG* gene; some are autosomal recessive and some are autosomal dominant.<sup>18</sup>
  - Treatments: Valproic acid (Depakene®) and sodium divalproate (divalproex) (Depakote®) should be avoided because of the risk of precipitating and/or accelerating liver disease.<sup>16</sup>
- At-risk individuals may also benefit from clinical assessment to initiate baseline evaluations (neurology, cardiology, ophthalmology, and audiology) and potential intervention prior to exhibiting clinical manifestations.<sup>20,21</sup>
- Underlying nuclear and mtDNA causes are frequently indistinguishable based on this symptomology. Diagnosis of the majority of mitochondrial conditions is based on a combination of clinical findings and genetic testing.<sup>20,22</sup>
- Mitochondrial conditions caused by nuclear DNA variants can be maternally or paternally inherited and may follow autosomal dominant, autosomal recessive, or X-linked modes of inheritance.
- Mitochondrial DNA is maternally transmitted. Pathogenic variants in the mtDNA may be de novo or maternally inherited. This means that a female who carries a mtDNA mutation at high mutation load will typically pass it on to all of her children. However, due to the meiotic bottleneck, the heteroplasmy level may vary significantly between generations. A male who carries a mtDNA mutation cannot pass it on to his children.<sup>20,23</sup> mtDNA deletions are rarely transmitted (<1% empiric risk).<sup>24</sup> If the mother is symptomatic, then the recurrence risk is ~4%.<sup>25</sup>

- For all mtDNA mutations, clinical expressivity depends on the three following factors:<sup>20</sup>
  - The ratio of mutant mtDNA (mutational load or heteroplasmy),
  - The organs and tissues in which the mutant mtDNA is found (tissue distribution), and
  - The vulnerability of each tissue to impaired oxidative metabolism (threshold effect).
- Analysis of an individual’s family history may provide information regarding the most likely inheritance patterns for a suspected mitochondrial condition. This may guide decisions regarding the pursuit of mtDNA sequencing, mtDNA deletion/duplication testing, nuclear encoded DNA sequencing, and/or nuclear encoded DNA deletion/duplication testing.
- While genetic test results alone cannot predict the exact course or phenotype of the disease, severity does correlate with mutation load for mitochondrial DNA mutations.<sup>5,23</sup>
- Identification of a pathogenic variant in a proband can allow for informative testing of relatives at risk for conditions in the corresponding phenotypic range.
- Prenatal testing may be available for mitochondrial conditions if the familial mutation(s) are known.
- Mitochondrial replacement therapy by spindle transfer has been performed to prevent transmission of mitochondrial disease from mother to child in the United Kingdom.<sup>26,27,28</sup>

## Test Information

- The investigation and diagnosis of patients with mitochondrial disease often necessitates a combination of techniques including muscle histochemistry, biochemical assessment and molecular genetic studies along with clinical assessment. Any molecular genetic test for a mtDNA mutation should ideally be directed by the clinical phenotype and results of these other investigations<sup>23</sup>
- While biochemical analyses of an affected tissue may be informative, they are not sensitive or specific enough to definitively diagnose most mitochondrial conditions. In addition, alternative tissue testing should only be considered when the diagnosis cannot be confirmed with DNA testing of other more accessible tissues, such as blood.
- “Approaches to molecular genetic testing of a proband to consider are serial testing of single genes, multi-gene panel testing (simultaneous testing of multiple genes), and/or genomic testing (e.g., sequencing of the entire mitochondrial genome, genome sequencing, or exome sequencing to identify a pathogenic variant in a nuclear gene). In many individuals in whom molecular genetic testing does not yield or confirm a diagnosis, further investigation of suspected mitochondrial disease can involve a range of different clinical tests, including muscle biopsy for respiratory chain function.”<sup>29</sup>
- The efficiency of next generation sequencing (NGS) has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. As a result, several laboratories have begun to combine genes involved in certain conditions which often have both of those characteristics.
- Due to overlap of clinical findings of mitochondrial conditions and non-mitochondrial conditions, many of these patients are at risk to have multiple tests performed before a

molecular genetic cause is identified. If an individual's clinical findings clearly correlate with a specific mitochondrial condition, then testing can be focused on the most appropriate approach for that condition. However, if the clinical picture strongly suggests a mitochondrial condition but there is uncertainty about which subset of conditions, then it can be most efficient in some cases to start with mtDNA genome sequencing, mitochondrial genome deletion/duplication, nuclear encoded mitochondrial genes sequencing panel, or whole exome sequencing to reduce time and resources lost during progressive sequential testing.

- If clinical findings overlap with mitochondrial and non-mitochondrial conditions, then whole exome sequencing may be the most efficient approach to testing to reduce the diagnostic odyssey and reduce resources otherwise expended by a sequential testing approach. These individuals should be evaluated by a Board-Certified or Board-Eligible Medical Geneticist, an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), or a provider with expertise in mitochondrial disorders to determine if whole exome sequencing is the most appropriate testing strategy.
- **Mitochondrial Genome Sequencing Panels and Mitochondrial Genome Deletion/Duplication Analysis Panels:**
  - **Sequencing Panels:** Full sequencing of the entire mitochondrial genome. NGS testing is capable of simultaneously detecting point mutations, deletions, and point mutation heteroplasmies. Typically, Sanger sequence analysis will miss heteroplasmy below 20%. With suitable depth of coverage, NGS can detect heteroplasmy down to ~1%.<sup>30,31)</sup>
  - **Deletion/Duplication Analysis Panels:** Testing for deletions and duplications of any portion of the entire mitochondrial genome.
  - Testing of mtDNA in leukocytes will often detect a mutation if present. However, chance variance in tissue heteroplasmy or negative selection may produce a normal or attenuated result in some tissues. Thus, it is sometimes necessary to test additional tissues: muscle (often reliable), buccal mucosa, cultured skin fibroblasts, hair bulbs, or urine sediment. Typically this is done when the phenotype is highly suggestive of presence of a mutation associated with a specific gene or set of genes, or when there is a need to assess reproductive risk.
  - If cultured fibroblasts are used, measures such as limited passaging and uridine or pyruvate supplementation should be taken to reduce selection against mutant genotypes that may reduce mutant load.
  - The potential for informativeness versus the invasiveness and procedural costs are factors to consider. For instance, muscle biopsy also allows enzymatic analysis of the electron transport chain, light and ultrastructural microscopy, and mtDNA copy number analysis—all of which may provide highly useful information for some conditions, such as MERFF, and can provide differentiation of mtDNA versus nuclear DNA etiology. Muscle (and/or liver) biopsies are often not necessary and should be avoided when possible due to their invasive nature. Biopsies should only be considered when the

diagnosis cannot be confirmed with mtDNA testing of other more accessible tissues, for example, when presence of ragged red fibers in muscle is required for diagnosis.

- **Nuclear Encoded Mitochondrial Genes Sequencing Panels (Nuclear Mitome Sequencing):** A number of large panels are available that sequence numerous nuclear-encoded mitochondrial genes for a broad approach to testing. Multi-gene panel tests, even for similar clinical scenarios, vary considerably laboratory by laboratory in the genes that are included and in technical specifications (e.g. depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).
- **Whole Exome Sequencing:** Large panels sequence protein-coding nuclear-encoded genes throughout the human genome for a broad approach to testing. Testing varies by laboratory in the technical specifications (e.g. depth of coverage, extent of intron/exon boundary analysis, methodology). Given the extensive overlap between mitochondrial disorders and other neurologic or muscle diseases, consideration should be given to whether a nuclear encoded mitochondrial genes sequencing panel (that contains a subset of possible causative genes) is appropriate for patients with complex disease presentation. In cases that cannot be clearly classified as a mitochondrial disorder, whole exome sequencing should be considered.
- **Prenatal Testing for At-Risk Pregnancies:**
  - Prenatal testing for a known mitochondrial DNA mutation has limited clinical utility. For example, the mother of a child affected with MERFF usually exhibits relatively high heteroplasmy for the causative mutation. Consequently, each subsequent pregnancy is at a high risk to inherit the mutation. Heteroplasmy detected in a fetus is of limited value because for many mtDNA conditions the level of heteroplasmy may change over time and between tissues, therefore, it may not be possible to ensure an acceptably low level of postnatal morbidity after detection of a heteroplasmic mutation in the prenatal setting.<sup>32</sup>
  - Published guidelines from the 74<sup>th</sup> European Neuromuscular Centre International Consensus stated that prenatal testing via CVS in asymptomatic women with family history of NARP (<50% mutant mtDNA) is appropriate, while women with >50% mutant load should consider oocyte donation and pre-implantation genetic screening. Alternatively, prenatal testing via CVS in asymptomatic women with family history of MERFF (>40% mutant mtDNA in blood) is appropriate, while women with high mutant load should consider oocyte donation and pre-implantation genetic screening. For women with a load of <40% MERFF mutant mtDNA in blood, severe disease is estimated to be rare in offspring,<sup>33</sup>
  - A retrospective chart review of prenatal samples processed in Europe concluded that prenatal testing for mitochondrial diseases was informative for the select mutations studied. Results of mtDNA heteroplasmy analyses from other family members are helpful in interpreting the prenatal mtDNA result.<sup>34</sup>
  - As a result of the issues described above, the availability of prenatal testing for mtDNA mutations is presently limited.



## Guidelines and Evidence

- No specific evidence-based U.S. testing guidelines were identified.
- There are few prospective studies. The Mitochondrial Medicine Society developed consensus recommendations using the Delphi method and published them in 2015.<sup>7</sup>
  - Recommendations for testing blood, urine, and spinal fluid
    - The initial evaluation in blood for mitochondrial disease should include complete blood count, creatine phosphokinase, transaminases, albumin, lactate and pyruvate, amino acids, and acylcarnitines, along with quantitative or qualitative urinary organic acids. Caution must be taken to ensure that specimens are collected appropriately, especially for lactate and pyruvate measurements.
    - Postprandial lactate levels are more sensitive than fasting specimens and are preferred when possible. *Caution must be taken to not overinterpret small elevations in postprandial lactate.*
    - The lactate/pyruvate ratio in blood or CSF is of value only when the lactate level is elevated.
    - Quantitative 3-methylglutaconic acid (3MG) measurements in plasma and urine should be obtained when possible in addition to urine organic acids in patients being evaluated for mitochondrial disease.
    - Creatine phosphokinase and uric acid should be assessed in patients with muscle symptoms who are suspected of having mitochondrial diseases.
    - Urine amino acid analysis should be obtained in the evaluation of mitochondrial tubulopathy.
    - When CSF is obtained, it should be sent for lactate, pyruvate, amino acid, and 5-methyltetrahydrofolate measurements.
    - Further research is needed for biomarkers such as FGF21, GDF15, glutathione, and CSF neopterin.
  - Recommendations for DNA testing
    - “Massively parallel sequencing/NGS of the mtDNA 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.”
    - “Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and guides genetic counseling.”
    - “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 mutation is identified via known NGS panels, then whole exome sequencing should be considered.”

- Recommendations for pathology testing
  - Biopsy should only be considered when the diagnosis cannot be confirmed with DNA testing of other more accessible tissues. Muscle (and/or liver) biopsies are often not necessary and should be avoided when possible due to their invasive nature, unless other types of analyses such as pathology, enzymology, or mtDNA copy number analyses in these tissues are required for diagnosis.
- Quantitative 3-methylglutaconic (3MG) may be useful, if elevations are observed in organic acids.
- Growth differentiation factor 15 (GDF15) has been shown to be a sensitive and specific biomarker for mitochondrial dysfunction.<sup>35</sup>
- A workshop of the **National Institute of Neurological Disorders and Stroke (2008)**<sup>36</sup> summarizes:
  - "The diagnosis of mitochondrial diseases is complicated by their heterogeneous presentations and by the lack of screening procedures or diagnostic biomarkers that are both sensitive and specific. The workshop panelists explained that diagnosis is often a lengthy process beginning with a general clinical evaluation followed by metabolic screening and imaging and finally by genetic tests and more invasive biochemical and histological analyses. The identification of known mitochondrial mutations in tissue has greatly aided diagnosis. However, even when clinical features and family history strongly suggest mitochondrial disease, the underlying genetic mutation can elude detection, and there is no current screening procedure that would be practical for all cases of suspected mitochondrial disease."
- The **Clinical Molecular Genetics Society (CMGS) of the United Kingdom (2008)**<sup>37</sup> practice-based guidelines for the molecular diagnosis of mitochondrial disease state that: "In cases with strong clinical evidence [of MERFF], testing should begin with checking for the common mutation, m.8344A>G. Subsequent testing for other mutations, such as m.8356T>C, may be indicated in cases with a strong clinical indication of MERRF."<sup>23</sup> "For routine referrals for NARP, presence of m.8993T>G and m.8993T>C mutations should be investigated."
- The **European Federation of Neurological Sciences (2009)**<sup>22</sup> provided molecular diagnostic consensus-based guidelines based on literature reviews: "If the phenotype suggests syndromic mitochondrial disease due to mtDNA point mutations (MELAS, MERRF, NARP, LHON) DNA-microarrays using allele-specific oligonucleotide hybridisation, real-time-PCR or single-gene sequencing are indicated."



## Criteria

### Whole mtDNA Sequencing

- Whole mtDNA sequencing is considered medically necessary when the following criteria are met:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
  - Member has not had previous whole mtDNA sequencing performed\*, AND
  - Biochemical testing appropriate for the suspected disorder has been performed and is not confirmatory of a diagnosis of a mitochondrial condition, AND
  - Member has multiple organ system involvement suggestive of a mitochondrial disorder, AND
  - Member has one or more of the following: proximal myopathy, cardiomyopathy, encephalopathy, seizures, dementia, stroke-like episodes, ataxia, spasticity, ptosis, ophthalmoparesis, ophthalmoplegia, optic atrophy, pigmentary retinopathy, sensorineural hearing loss, diabetes mellitus, mid- or late pregnancy loss, MRI and/or MRS imaging results consistent with a mitochondrial process, pathology results consistent with a mitochondrial process, AND
  - Member's clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available (e.g. LHON), AND
  - Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), AND
  - Family history strongly suggests mitochondrial inheritance (e.g., no evidence of paternal transmission).

### Whole mtDNA Deletion/Duplication Analysis

- Whole mtDNA deletion/duplication is considered medically necessary when the following criteria are met:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
  - Member has not had previous whole mtDNA deletion/duplication analysis performed\*, AND
  - Biochemical testing appropriate for the suspected disorder has been performed and is not confirmatory of a diagnosis of a mitochondrial condition, AND
  - Member has multiple organ system involvement suggestive of a mitochondrial disorder, AND
  - Member has one or more of the following: proximal myopathy, cardiomyopathy, encephalopathy, seizures, dementia, stroke-like episodes, ataxia, spasticity, ptosis, ophthalmoparesis, ophthalmoplegia, optic atrophy, pigmentary retinopathy, sensorineural hearing loss, diabetes mellitus, mid- or late pregnancy loss, MRI and/or MRS imaging results consistent with a mitochondrial process, pathology results consistent with a mitochondrial process, AND

- Member’s clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available (e.g. LHON), AND
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), AND
- Family history strongly suggests mitochondrial inheritance (e.g., no evidence of paternal transmission).

### **Nuclear Encoded Mitochondrial Gene Sequencing Panel**

- A nuclear encoded mitochondrial gene sequencing panel is considered medically necessary when the following criteria are met:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
  - Member has not had previous nuclear encoded mitochondrial gene sequencing panel testing\* performed, AND
  - Biochemical testing appropriate for the suspected disorder has been performed and is not confirmatory of a diagnosis of a mitochondrial condition, AND
  - Member has multiple organ system involvement suggestive of a mitochondrial disorder, AND
  - Member has one or more of the following: proximal myopathy, cardiomyopathy, encephalopathy, seizures, dementia, stroke-like episodes, ataxia, spasticity, ptosis, ophthalmoparesis, ophthalmoplegia, optic atrophy, pigmentary retinopathy, sensorineural hearing loss, diabetes mellitus, mid- or late pregnancy loss, MRI and/or MRS imaging results consistent with a mitochondrial process, pathology results consistent with a mitochondrial process, AND
  - Member’s clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available (e.g. LHON), AND
  - Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), AND
  - Family history *does not* strongly suggest mitochondrial inheritance (e.g., paternal transmission observed, autosomal inheritance likely).

\*Genetic testing has rapidly advanced over the last 20 years. Exceptions may be considered if an individual has previously had negative genetic testing, but technical advances in testing demonstrate significant advantages that would support a medical need to re-test or reanalyze data from previous testing.

## Exclusions and Other Considerations

- Testing addressed in this guideline applies to patients in whom a mitochondrial disorder is suspected based on a constellation of findings commonly seen in these conditions, while not fitting clearly into one of the discrete mitochondrial syndromes. This policy is not applicable in the following cases:
  - The patient’s findings fit into a discrete mitochondrial syndrome for which more specific testing is appropriate. Please see one of the following guidelines for information on specific mitochondrial conditions (MELAS, LHON, MNGIE, MERRF, NARP, etcetera); or
  - The patient’s findings could be explained nonspecifically by a mitochondrial disorder or other neurological or myopathic condition not related to mitochondrion for which a different genetic test may be considered; or
  - Individuals who have no increased risk above the general population risk to have inherited a mitochondrial disease and have just one of the following findings in isolation: fatigue; muscle weakness; developmental delay; migraines; abnormal biochemical test results (e.g., elevated lactate); autism<sup>38</sup>; psychiatric symptoms.

## Billing and Reimbursement Considerations

- Whole mtDNA Sequencing will only be considered for coverage when billed under the appropriate panel CPT code: 81460
- Whole mtDNA Deletion/Duplication will only be considered for coverage when billed under the appropriate panel CPT code: 81465
- Nuclear Encoded Mitochondrial Gene Sequencing Panel will only be considered for coverage when billed under the appropriate panel CPT code: 81440
- If the panel will be billed with separate procedure codes for each gene analyzed, the medical necessity of each billed procedure will be assessed independently.
- If more than one code is requested at one time, the member meets criteria for all tests requested, and each test is equally likely based on personal history, clinical findings, and family history, the testing will be tiered in the following order: 81460; 81465; 81440.

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