Cigna Medical Coverage Policy

Subject: Genetic Testing for Mitochondrial Disorders

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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 confirmatory (diagnostic) genetic testing for a mitochondrial disorder when ALL of the following criteria are met:

- conventional testing cannot establish the diagnosis
- genetic testing results will impact management
- EITHER of the following:
  - clinical features are consistent with ONE of the following syndromes and the associated described genetic testing is being requested:
    - Kearns Sayre syndrome - duplication/deletion analysis of mitochondrial deoxyribonucleic acid (mtDNA) in blood or by muscle biopsy
    - Pearson syndrome - duplication/deletion analysis of mtDNA in blood
    - Progressive external ophthalmoplegia (PEO) - duplication/deletion analysis of mtDNA in skeletal muscle
    - Leigh syndrome
      - targeted mutation analysis of mtDNA in blood for the MT-ATP genome
      - sequence analysis of the mtDNA genome, when Leigh syndrome is suspected and BOTH of the following criteria are met:
        - targeted mutation analysis is negative but clinical suspicion remains high
• no evidence of paternal transmission  
  o Neurogenic muscle weakness with ataxia and retinitis pigmentosa (NARP) - targeted mutation analysis of mtDNA in blood for the MT-ATP6 gene  
  o Leber hereditary optic neuropathy (LHON)  
    ▪ targeted mutation analysis of mtDNA in blood for the MT-ND1, MT-ND4, MT-ND4L, and MT-ND6 genes  
    ▪ sequence analysis of the mtDNA genome, when LHON is suspected and BOTH of the following criteria are met:  
      • targeted mutation analysis is negative but clinical suspicion for this disorder remains high  
      • there is no evidence of paternal transmission  
  o Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) - targeted mutation analysis of mtDNA in blood for the MT-L1 and MT-ND5 genes  
  o Myoclonic epilepsy with ragged red fibers (MERRF)  
    ▪ targeted mutation analysis of mtDNA in blood, cultured skin fibroblasts, urinary sediment, oral mucosa, hair follicles, and skeletal muscle for the MT-TK, MT-TL1, MT-TH, and MT-TS1 genes  
    ▪ sequence analysis of the mtDNA genome, when MERRF is suspected and ALL of the following criteria are met  
      • presence of ALL of the following:  
        ➢ myoclonus  
        ➢ generalized epilepsy  
        ➢ ataxia  
        ➢ ragged red fibers in the muscle biopsy  
      • targeted mutation analysis is negative but clinical suspicion remains high  
      • no evidence of paternal transmission  
    ➢ clinical features are not consistent with one of the mitochondrial disorders described above but clinical examination and results of conventional testing are suggestive of mitochondrial disease but a definitive diagnosis remains uncertain and requested testing is directed toward a specific mitochondrial disorder (s) or subset of mitochondrial disease (i.e., specific respiratory chain complex deficiency)

Cigna does not cover next generation sequence analysis that is not specific to a targeted mitochondrial disorder because such testing is considered experimental, investigational and unproven.

Cigna covers prenatal or preconception (carrier) testing for the known familial mutation when there is a positive family history of a mitochondrial disorder in a blood relative and the couple has the capacity and intention to reproduce.

Cigna covers prenatal testing of a fetus or preimplantation genetic diagnosis (PGD) for nuclear gene mutations suggestive of a mitochondrial disorder when the fetus or embryo has been identified to be at risk for inheriting a mitochondrial disorder (i.e., either parent has the known familial mutation).

Any individual undergoing genetic testing for a mitochondrial disorder should have both pre-and post-test genetic counseling completed by ONE of the following:

• an independent Board-Certified or Board-Eligible Medical Geneticist  
• an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).  
• a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
Cigna does not cover molecular genetic testing for a mitochondrial disorder in the general population, because such screening is considered not medically necessary.

General Background

Mitochondrial diseases are a group of disorders resulting from dysfunction of the mitochondrial respiratory chain (i.e., electron transport). This term refers to any illness resulting from deficiency of any mitochondria-located protein which is involved in energy metabolism. Over 100 pathological mutations within the mitochondrial deoxyribonucleic acid (mtDNA) genome have been described. Among the over 1000 proteins located in the mitochondria, 13 are encoded by the mtDNA, while the remainder are nuclear-encoded (i.e., on the chromosomes, nuclear DNA) and imported into mitochondria (United Mitochondrial Disease Foundation, 2010). Disorders caused by mutations of nuclear deoxyribonucleic acid follow a Mendelian inheritance pattern (e.g., autosomal recessive, autosomal dominant, X-linked) while mutations of the mtDNA are those of a maternal transmission pattern. Mutations may also develop de novo. Although genetically dissimilar, all of these disorders share clinical similarities in that they result in an energy deficient state (United Mitochondrial Disease Foundation, 2010).

Mitochondrial Maternal Inheritance: Maternal inheritance, also known as mitochondrial or cytoplasmic inheritance, involves mtDNA genes/mitochondrial-encoded proteins. All maternally inherited diseases are mitochondrial disorders.

In normal tissues, all mtDNA molecules are identical (homoplasmy). Deleterious mutations of mtDNA usually affect some, but not all mtDNAs within a cell, tissue, or an individual (heteroplasmy). The clinical expression of a mtDNA mutation is largely determined by the relative proportion of normal and mutant mtDNA genomes in different tissues (Mitochondrial Medicine Society, 2000-2013). As a result the symptoms, severity, and age of onset can vary tremendously within a family. Although a female with a mtDNA mutation will pass that mutation to all of her offspring not all of the children will become symptomatic (United Mitochondrial Disease Foundation, 2010). When transmitted through the mtDNA paternal transmission does not occur, that is, the mutation cannot be inherited from the male (United Mitochondrial Disease Foundation, 2010). Generally, nuclear DNA mutations present in childhood, while mtDNA mutations present in late childhood or in adulthood, primary or secondary to nuclear DNA abnormalities (Chinnery, 2010).

Nuclear Inheritance: An estimated 75%-90% of pediatric primary mitochondrial disease results from nuclear DNA mutations (Mitochondrial Medicine Society, 2000-2013). Nuclear DNA inheritance patterns may be autosomal recessive, autosomal dominant, and X-linked, and symptoms and severity of disease are very consistent within families. Most commonly, the inheritance pattern is autosomal recessive. Leigh syndrome caused by defects in complexes I and IV is one of the most common forms of mitochondrial encephalomyopathy inherited in this fashion (United Mitochondrial Disease Foundation, 2010).

Other Inheritance Patterns: In some syndromes, mtDNA mutations tend to occur spontaneously, that is, the mutation is not present in the mother or the father but occurs early in the development of the embryo. Generally, spontaneously acquired mutations are not passed to the next generation (United Mitochondrial Disease Foundation, 2010).

Individuals with mitochondrial disorders may display a cluster of clinical features that fall into a specific clinical syndrome; however, considerable clinical variability exists and many individuals do not fit into one particular category. Mitochondrial disease is difficult to classify; some mitochondrial disorders affect only a single organ, but many involve multiple organ systems and often present with prominent neurological and myopathic features.

Some of the more common mitochondrial disorders include the following:

- Kearns-Sayre syndrome (KSS)
- Pearson syndrome
- Progressive external ophthalmoplegia (PEO)
- Neurogenic muscle weakness with 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) (Chinnery, 2010)

**Clinical Utility of Genetic Testing:** Although there is no curative treatment at this time for any mitochondrial disorder establishing a genetic diagnosis permits accurate etiologic and prognostic assessment, as well as estimation of recurrence risk, and management counseling. In the future, it is hoped that this will also permit for accurate sub-grouping among the heterogeneous category of mitochondrial disease patients in an effort to develop disease-focused interventions (Mitochondrial Medicine Society, 2000-2013).

**Genetic Testing Strategy:** The ability to identify a causative genetic mutation in a given patient has increased the ability to definitively diagnose primary mitochondrial disease. Diagnosis of a mitochondrial disorder should follow a step-wise approach, based on results of conventional testing and the type of mitochondrial disorder suggested by phenotype. In some individuals, the clinical picture is characteristic of a specific mitochondrial disorder (e.g., KSS, Pearson syndrome, PEO, NARP, LHON, LS, MELAS, MERRF), and the diagnosis can be confirmed by a specific type of genetic test. Duplication/deletion analysis is useful for the diagnosis of Kearns Sayre syndrome, Pearson syndrome, and CPEO/PEO. Gene deletions and duplications involve the loss or addition of DNA sequences; phenotypic expression is affected by the size and location of deleted sequences. In the case of mitochondrial disorders, deletion/duplication genetic testing involves the analysis of the mitochondrial DNA (mtDNA).

Targeted mutation analysis is a type of test for specific genes that have been identified as causative or implicated in the specific disorder in question. Targeted mutation analysis is appropriate to confirm the diagnosis of several disorders including Leigh syndrome, NARP, LHON, MELAS, and MERRF. Specific to the disorder, testing is performed on mtDNA extracted from blood, or other tissue (e.g., muscle, cultured skin fibroblasts, urinary sediment, oral mucosa, hair follicles) (GeneReviews, 2011; Chinnery, 2010; United Mitochondrial Disease Foundation, 2010).

For some disorders (i.e., MERRF, Leigh syndrome, Leber syndrome) sequence analysis of the mtDNA genome may be appropriate if targeted mutation analysis is negative but clinical suspicion remains high and there is no evidence of paternal transmission. Prenatal or preconception carrier testing for the known familial mutation is appropriate when there is a positive family history of a mitochondrial disorder in a blood relative. Accurate interpretation of prenatal testing (i.e., of a fetus or embryo) or preimplantation genetic diagnosis (PGD) results is difficult because of the varying degrees to which the mutation may be transmitted to the mtDNA (i.e., heteroplasmy). However, testing for nuclear gene mutations suggestive of a mitochondrial disorder is appropriate when the fetus or embryo has been identified to be at risk for inheriting a mitochondrial disorder (i.e., either parent has the known familial mutation). When clinical examination and results of conventional testing are suggestive of a specific mitochondrial disorder or subset of mitochondrial disease (i.e., specific respiratory chain complex deficiency) but a definitive diagnosis remains uncertain, genetic testing is appropriate using deletion/duplication testing, targeted mutation analysis or sequence analysis of the mitochondrial or nuclear genome.

**Genetic Testing for Kearns Sayre Syndrome, Pearson Syndrome and PEO:** More than 150 different mtDNA deletions have been associated with KSS. Large-scale duplications of mtDNA coexist with deletions in some individuals with KSS. These same deletions and numerous other types of deletions have been identified in Pearson Syndrome and PEO. Southern blot analysis for mtDNA deletion syndromes is the preferred clinical method for molecular genetic testing. Deletion/duplication analysis of mitochondrial DNA is appropriately sampled in blood or biopsy of muscle for diagnosis of KSS. The diagnosis of Pearson syndrome can also be made reliably by deletion/duplication analysis of blood (leukocytes) while molecular diagnosis of PEO requires Southern blot analysis of skeletal muscle (DiMauro and Hirano, 2011).

**Genetic Testing for Leigh Syndrome (LS):** Leigh syndrome can be caused by mutations in one of over 30 different genes. Mutations can take place in nuclear DNA or mtDNA and impair mitochondrial energy production. While most people with Leigh syndrome have a mutation in nuclear DNA, about 20 to 25 percent have a mutation in mtDNA. Many of the gene mutations associated with Leigh syndrome affect proteins in complexes I, II, IV, or V, or disrupt the assembly of these complexes. Disruption of complex IV, also called cytochrome c
oxidase or COX, is the most common cause of Leigh syndrome. The most frequently mutated gene in COX-deficient Leigh syndrome, found in nuclear DNA, is SURF1. The most common mitochondrial DNA mutation in Leigh syndrome affects the MT-ATP6 gene. The mutation, which is found in 10-20 percent of individuals with Leigh syndrome, blocks the generation of ATP (Gene Reviews, 2014). Other genes implicated in Leigh syndrome include BCS1L, COX15, FOXRED1, NDUF10, NDUF12, NDUF12, NDUF19, NDUF12F2, NDUF16F6, NDUF33, NDUF4S4, NDUF57, NDUF68, and SDHA.

Clinical methods used in confirmatory genetic testing of LS include targeted mutation analysis and sequence analysis of the mitochondrial or nuclear genome, including next generation sequence analysis methods. Prenatal or preconception (carrier) testing for the known familial mutation is appropriate when there is a positive family history of a mitochondrial disorder in a blood relative and a reproductive couple has the capacity and intention to reproduce. Prenatal testing of a fetus or preimplantation genetic diagnosis (PGD) for autosomal recessive nuclear gene mutations suggestive of a mitochondrial disorder is appropriate when the fetus or embryo has been identified to be at risk for inheriting a mitochondrial disorder (i.e., either parent has the known familial mutation).

**Genetic Testing for NARP:** Mutations in the MT-ATP6 gene, which is found in the mitochondrial DNA, cause NARP. Genetic testing using targeted analysis for the MT-ATP6 gene in blood is appropriate for molecular diagnosis of this disorder (Genetic Home Reference, 2006). Prenatal or preconception testing for the known familial mutation may be appropriate when there is a positive family history of a NARP in a blood relative and the reproductive couple has the capacity and intention to reproduce.

**Genetic Testing for LHON:** Mutations in the MT-ND1, MT-ND4, MT-ND4L, and MT-ND6 gene can cause LHON. These genes are found in the mitochondrial DNA, therefore LHON has a mitochondrial pattern of inheritance (Genetics Home Reference, 2013, Chinnery, 2012). Targeted mutation analysis for one of the genes that have been identified as causative of LHON is appropriate to confirm the diagnosis of LHON. Sequence analysis of the mtDNA genome, including next generation sequence analysis methods, is also appropriate when results of targeted mutation analysis is negative but clinical suspicion for this disorder remains high and there is no evidence of paternal transmission. Mutations in three additional mitochondrial genes, MT-4B, MT-6C3, and MTATP6 are also thought to cause LHON but require further confirmation as they have only been found in single affected individuals or a single family (Chinnery, 2012).

**Genetic Testing for MELAS:** MELAS can result from mutations in one of several genes, most frequently the MT-TL1 and MT-ND5 genes. These genes are found in mtDNA and impair the ability of mitochondria to make proteins, use oxygen, and produce energy. Mutations in MT-TL1 are present in more than 80 percent of all cases of MELAS (Genetics Home Reference, 2013). Targeted mutation analysis for the targeted mutation analysis of mtDNA in blood for the MT-L1 and MT-ND5 genes is appropriate to confirm the diagnosis of MELAS (GeneReviews, 2013).

**Genetic Testing for MERRF:** This disorder can result from mutations in the MT-TK, MT-TL1, MT-TH, and MTS1 genes, which are found in the mitochondrial DNA. Targeted mutation analysis for these genes is appropriate to confirm the diagnosis of MERRF. In addition to blood samples, other tissues (i.e., cultured skin fibroblasts, urinary sediment, oral mucosa, hair follicles, and skeletal muscle) may be used for analysis. Sequence analysis of the mtDNA genome, including next generation sequence methods, is appropriate when MERRF is suspected and myoclonus, generalized epilepsy, ataxia, and ragged red fibers are all present, targeted mutation analysis is negative but clinical suspicion remains high, and there is no evidence of paternal transmission. Prenatal or preconception (carrier) testing for the known familial mutation when there is a positive family history of a mitochondrial disorder in a blood relative and the reproductive couple has the capacity and intention to reproduce is also appropriate.

**Genetic Testing for Other Suspected Mitochondrial Disorders:** When clinical features are not consistent with Kearns Sayre syndrome, Pearson syndrome, PEO, LS, NARP, LHON, MELAS, or MERRF, but clinical examination and results of conventional testing are suggestive of a specific mitochondrial disorder or subset of mitochondrial disease (i.e., specific respiratory chain complex deficiency), genetic testing may be appropriate. Testing methods may include deletion/duplication analysis, targeted mutation analysis, and sequence analysis of the mtDNA or nuclear DNA genome, including next-generation sequencing methods. Additional genes which have been implicated include, but are not limited to MT-RNR1, C10orf2, COX6B1, SCO2, SLC25A4, TACO1, BCS1L, COX10, COX15, DGUOK, RRM2B, SCO1, TK2, TYMP, and FASTKD1.
Genetic Counseling

Genetic testing should be undertaken only after independent genetic counseling has been provided to an individual in order to assist in complex clinical decision-making. Post-genetic testing counseling should be planned. The genetic counseling should be provided by a specialty-trained genetics professional who is an independent Board-Certified or Board-Eligible Medical Geneticist, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor (CGC) or a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC). These individuals should not be employed by a commercial genetic testing laboratory. CGCs and credentialed genetic nurses are not excluded from providing genetic counseling services if they are employed by or contracted with a laboratory that is part of an integrated health system which routinely delivers health care services beyond just the laboratory test itself.

Professional Societies/Organizations

United Mitochondrial Disease Foundation (UMDF): Regarding evaluation of the patient for the presence of mitochondrial disease, UMDF notes that secondary laboratory evaluation may include testing for specific, known mitochondrial DNA point mutations or mitochondrial DNA by Southern Blot if a patient fits into a specific, well-described mitochondrial phenotype. These tests are also mentioned as tertiary lab testing.

Use Outside of the US

European Federation of Neurological Sciences (EFNS): On behalf of the EFNS, Finsterer et al. (2009) notes diagnostic work-up for suspected mitochondrial disease is a stepwise procedure, including a comprehensive individual and family history, and clinical investigations by various specialists as a first step. In a second step a determination should be made whether an individual phenotype conforms to any of the syndromic or nonsyndromic mitochondrial disorder, including the type of inheritance pattern. Genetic testing is the third step and is specific to the type of disorder suggested by the phenotype.

Summary

When conventional testing methods fail to confirm the diagnosis of a mitochondrial disorder and results of testing will impact patient management, genetic testing may be of benefit. The type of genetic test which is appropriate depends on the type of genetic disorder that is suspected. Genetic tests may include deletion/duplication analysis of mitochondrial DNA (mtDNA) extracted from a blood sample or from other tissues, targeted analysis, or sequence analysis of the mitochondrial genome. Clinical utility has not been established for next generation sequencing panels that are not specific to targeted disorders or general population screening.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
       2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

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

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, level 2 (eg, 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)</td>
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<tr>
<td></td>
<td>- MT-RNR1 (mitochondrially encoded 12S RNA) (eg, nonsyndromic hearing loss), common variants (eg, m.1555A&gt;G, m.1494C&gt;T)</td>
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<tr>
<td></td>
<td>- MT-ATP6 (mitochondrially encoded ATP synthase 6) (eg, neuropathy with ataxia and retinitis pigmentosa [NARP], Leigh syndrome), common variants (eg, m.8993T&gt;G, m.8993T&gt;C)</td>
</tr>
</tbody>
</table>
- **MT-ND4**, **MT-ND6** (mitochondrially encoded NADH dehydrogenase 4, mitotically encoded NADH dehydrogenase 6) (eg, Leber hereditary optic neuropathy [LHON]), common variants (eg, m.11778G>A, m.3460G>A, m.14484T>C)
- **MT-TK** (mitochondrially encoded tRNA lysine) (eg, myoclonic epilepsy with ragged red fibers [MERRF]), common variants (eg, m.8344A>G, m.8356T>C)
- **MT-TL1** (mitochondrially encoded tRNA leucine 1 [UUA/G]) (eg, diabetes and hearing loss), common variants (eg, m.3243A>G, m.14709 T>C)
- **MT-ND5** (mitochondrially encoded tRNA leucine 1 [UUA/G], mitochondially encoded NADH dehydrogenase 5) (eg, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes [MELAS]), common variants (eg, m.3243A>G, m.3271T>C, m.3252A>G, m.13513G>A)
- **MT-TS1**, **MT-RNR1** (mitochondrially encoded tRNA serine 1 [UCN], mitochondrially encoded 12S RNA) (eg, nonsyndromic sensorineural deafness [including aminoglycoside-induced nonsyndromic deafness]), common variants (eg, m.7445A>G, m.1555A>G)

### Molecular pathology procedure, Level 4 (eg, 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)
- **MT-RNR1** (mitochondrially encoded 12S RNA) (eg, nonsyndromic hearing loss), full gene sequence
- **MT-TS1** (mitochondrially encoded tRNA serine 1) (eg, nonsyndromic hearing loss), full gene sequence

### Molecular pathology procedure, Level 5 (eg, 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)
- **C10orf2** (chromosome 10 open reading frame 2) (eg, mitochondrial DNA depletion syndrome), full gene sequence
- **COX6B1** (cytochrome c oxidase subunit VIb polypeptide 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
- **NDUFA1** (NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 1, 7.5kDa) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
- **NDUFAF2** (NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, assembly factor 2) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
- **NDUFS4** (NADH dehydrogenase [ubiquinone] Fe-S protein 4, 18kDa [NADH-coenzyme Q reductase]) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
- **SCO2** (SCO cytochrome oxidase deficient homolog 2 [SCO1L]) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
- **SLC25A4** (solute carrier family 25 [mitochondrial carrier; adenine nucleotide translocator], member 4) (eg, progressive external ophthalmoplegia), full gene sequence
- **TACO1** (translational activator of mitochondrial encoded cytochrome c oxidase 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence

### Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons, by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
- **NDUF10** (mitochondrially encoded NADH dehydrogenase Fe-S protein) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
- **NDUFV2** (mitochondrially encoded NADH dehydrogenase [ubiquinone] Fe-S protein 2) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
- **SCPD1** (SCD1 cytochrome c oxidase deficient homolog 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
• BCS1L (BCS1-like [S cerevisiae]) (eg, Leigh syndrome, mitochondrial complex III deficiency, GRACILE syndrome), full gene sequence
• COX10 (COX 10 homolog, cytochrome c oxidase assembly protein) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
• COX15 (COX15 homolog, cytochrome c oxidase assembly protein) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
• DGUOX (deoxyguanosine kinase) (eg, hepatocerebral mitochondrial DNA depletion syndrome), full gene sequence
• MPV17 (MpV17 mitochondrial inner membrane protein) (eg, mitochondrial DNA depletion syndrome), full gene sequence
• NDUFS7 (NADH dehydrogenase [ubiquinone] Fe-S protein 7, 20kDa (NADH-co-enzyme Q reductase)) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
• NDUFS8 (NADH dehydrogenase [ubiquinone] Fe-D protein 8, 23kDa (NADH-coenzyme Q reductase)) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
• NDUFV1 (NADH dehydrogenase [ubiquinone] flavoprotein 1, 51kDa) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence
• RRM2B (ribonucleic reductase M2 B [TP53 inducible] (eg, mitochondrial DNA deletion), full gene sequence
• SCO1 (SCO cytochrome oxidase deficient homolog 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
• SURF1 (surfeit 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
• TK2 (thymidine kinase 2, mitochondrial) (eg, mitochondrial DNA deletion syndrome), full gene sequence
• TYMP (thymidine phosphoylase) (eg, mitochondrial DNA depletion syndrome), full gene sequence

81406 Molecular pathology procedure , level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cyogenomic array analysis for neplasia)
• FASTKD2 (FAST kinase domains 2) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence
• SDHA (succinate dehydrogenase complex, subunit A, flavoprotein [Fp]) (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence

81479 Unlisted molecular pathology procedure
• When used to report testing for other mitochondrial disorders not mentioned in this policy.


References


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