



FEP Medical Policy Manual

FEP 2.04.117 Genetic Testing for Mitochondrial Disorders

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Related Policies:

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

2.04.107 - Carrier Screening for Genetic Diseases

Genetic Testing for Mitochondrial Disorders

Description

Description

Mitochondrial diseases are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes involved in oxidative metabolism. There are many related but distinct syndromes and some patients have overlapping syndromes. As a result, these disorders can be difficult to diagnose. Genetic testing has the potential to improve the accuracy of diagnosis for mitochondrial diseases. Genetic testing also has the potential to determine the future risk of disease in individuals who have a close relative with a pathogenic variant.

Primary mitochondrial diseases arise from dysfunction of the mitochondrial respiratory chain. The mitochondrial respiratory chain is responsible for aerobic metabolism, and dysfunction, therefore, affects a wide variety of physiologic pathways dependent on aerobic metabolism. Organs with a high-energy requirement, such as the central nervous system, cardiovascular system, and skeletal muscle, are preferentially affected by mitochondrial dysfunction.

The prevalence of these disorders has risen over the last 2 decades as the pathophysiology and clinical manifestations have been better characterized. It is currently estimated that the minimum prevalence of primary mitochondrial diseases is at least 1 in 5000.^{1,4}

Some specific mitochondrial diseases are listed next:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like symptoms (MELAS) syndrome;
- Myoclonus epilepsy with ragged red fibers syndrome (MERFF);
- Kearns-Sayre syndrome;
- Leigh syndrome;
- Chronic progressive external ophthalmoplegia (CPEO);
- Leber hereditary optic neuropathy (LHON);
- Neuropathy, ataxia, and retinitis pigmentosa (NARP).

Most of these disorders are characterized by multisystem dysfunction, which generally includes myopathies and neurologic dysfunction and may involve multiple other organs. Each defined mitochondrial disease has a characteristic set of signs or symptoms. The severity of illness is heterogeneous and can vary markedly. Some patients will have only mild symptoms for which they never require medical care, while other patients have severe symptoms, a large burden of morbidity, and a shortened life expectancy.

Diagnosis

The diagnosis of mitochondrial diseases can be difficult. The individual symptoms are nonspecific, and symptom patterns can overlap considerably. As a result, a patient often cannot be easily classified into a particular syndrome.⁵ Biochemical testing is indicated for patients who do not have a clear clinical picture of a specific disorder. Measurement of serum lactic acid is often used as a screening test but the test is neither sensitive nor specific for mitochondrial diseases.²

A muscle biopsy can be performed if the diagnosis is uncertain after biochemical workup. However, this invasive test is not definitive in all cases. The presence of "ragged red fibers" on histologic analysis is consistent with a mitochondrial disease. Ragged red fibers represent a proliferation of defective mitochondria.¹ This characteristic finding may not be present in all types of mitochondrial diseases and also may be absent early in the course of disease.²

Treatment

Treatment of mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder.⁵ Identification of complications such as diabetes and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (eg, coenzyme Q, riboflavin) have been used but empirical evidence of benefit is lacking.⁶ Exercise therapy for myopathy is often prescribed but the effect on clinical outcomes is uncertain.⁵ The possibility of gene transfer therapy is under consideration but is at an early stage of development and untested in clinical trials.

Genetic Testing

Mitochondrial diseases can be caused by pathogenic variants in the maternally inherited mtDNA or one of many nDNA genes. Genetic testing for mitochondrial diseases may involve testing for point mutations, deletion and duplication analysis, and/or whole exome sequencing of nuclear or mtDNA. The type of testing done depends on the specific disorder being considered. For some primary mitochondrial diseases such as MELAS and MERFF, most variants are point mutations, and there is a finite number of variants associated with the disorder. When testing for one of these disorders, known pathogenic variants can be tested for with polymerase chain reaction, or sequence analysis can be performed on the particular gene. For other mitochondrial diseases, such as CPEO and Kearns-Sayre syndrome, the most common variants are deletions, and therefore duplication and deletion analysis would be the first test when these disorders are suspected. Table 1 provides examples of clinical symptoms and particular genetic variants in mtDNA or nDNA associated with particular mitochondrial syndromes.^{5,7} A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database.⁸ Lists of mtDNA and nDNA genes that may lead to mitochondrial diseases and testing laboratories in the U.S. are provided at Genetic Testing Registry of the National Center for Biotechnology Information website.⁹

Table 1. Examples of Mitochondrial Diseases, Clinical Manifestations, and Associated Pathogenic Genes

| Syndrome | Main Clinical Manifestations | Major Genes Involved |
|-----------------------|---|--|
| MELAS | <ul style="list-style-type: none"> Stroke-like episodes at age <40 y Seizures and/or dementia Pigmentary retinopathy Lactic acidosis | <ul style="list-style-type: none"> <i>MT-TL1, MT-ND5</i> (>95%) <i>MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS₁, MT-TS₂, MT-ND1, MT-ND6</i> (rare) |
| MERFF | <ul style="list-style-type: none"> Myoclonus Seizures Cerebellar ataxia Myopathy | <ul style="list-style-type: none"> <i>MT-TK</i> (>80%) <i>MT-TF, MT-TP</i> (rare) |
| CPEO | <ul style="list-style-type: none"> External ophthalmoplegia Bilateral ptosis | <ul style="list-style-type: none"> Various deletions of mitochondrial DNA |
| Kearns-Sayre syndrome | <ul style="list-style-type: none"> External ophthalmoplegia at age <20 y Pigmentary retinopathy Cerebellar ataxia Heart block | <ul style="list-style-type: none"> Various deletions of mitochondrial DNA |
| Leigh syndrome | <ul style="list-style-type: none"> Subacute relapsing encephalopathy Infantile onset Cerebellar/brainstem dysfunction | <ul style="list-style-type: none"> <i>MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</i> Mitochondrial DNA deletions (rare) <i>SUCLA2, NDUSF_x, NDFV_x, SDHA, BCS1L, SURF1, SCO2, COX15</i> |
| LHON | <ul style="list-style-type: none"> Painless bilateral visual failure Male predominance Dystonia Cardiac pre-excitation syndromes | <ul style="list-style-type: none"> <i>MT-ND1, MT-ND4, MT-ND6</i> |
| NARP | <ul style="list-style-type: none"> Peripheral neuropathy Ataxia Pigmentary retinopathy | <ul style="list-style-type: none"> <i>MT-ATP6</i> |
| MNGIE | <ul style="list-style-type: none"> Intestinal malabsorption Cachexia External ophthalmoplegia | <ul style="list-style-type: none"> <i>TP</i> |

| Syndrome | Main Clinical Manifestations | Major Genes Involved |
|-------------------------------------|--|--|
| | <ul style="list-style-type: none"> • Neuropathy | |
| IOSCA | <ul style="list-style-type: none"> • Ataxia • Hypotonia • Athetosis • Ophthalmoplegia • Seizures | <ul style="list-style-type: none"> • <i>TWINKLE</i> |
| SANDO | <ul style="list-style-type: none"> • Ataxic neuropathy • Dysarthria • Ophthalmoparesis | <ul style="list-style-type: none"> • <i>POLG</i> |
| Alpers syndrome | <ul style="list-style-type: none"> • Intractable epilepsy • Psychomotor regression • Liver disease | <ul style="list-style-type: none"> • <i>POLG, DGUOK, MPV17</i> |
| GRACILE | <ul style="list-style-type: none"> • Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis | <ul style="list-style-type: none"> • <i>NDUSF_x</i> |
| Coenzyme Q ₁₀ deficiency | <ul style="list-style-type: none"> • Encephalopathy • Steroid-resistant nephrotic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss | <ul style="list-style-type: none"> • <i>COQ2</i> • <i>COQ9</i> • <i>CABC1</i> • <i>ETFDH</i> |

Adapted from Chinnery et al (2014)⁵, and Angelini et al (2009).⁷ CPEO: chronic progressive external ophthalmoplegia; GRACILE: growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, early death; IOSCA: infantile onset spinocerebellar ataxia; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms; MERFF: myoclonus epilepsy with ragged red fibers; MNGIE: mitochondrial neurogastrointestinal encephalopathy; NARP: neuropathy, ataxia, and retinitis pigmentosa; SANDO: sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for mitochondrial diseases improves the net health outcome in individuals with signs and symptoms of a mitochondrial disease or in asymptomatic relatives of an individual with a mitochondrial disease.

POLICY STATEMENT

Genetic testing to establish a genetic diagnosis of a mitochondrial disorder may be considered **medically necessary** when signs and symptoms of a mitochondrial disorder are present and genetic testing may eliminate the need for muscle biopsy.

Targeted genetic testing for a known familial variant in at-risk relatives may be considered **medically necessary** as preconceptional carrier testing under the following conditions (see Benefit Application section):

- There is a defined mitochondrial disorder in the family of sufficient severity to cause impairment of quality of life or functional status; AND
- A variant that is known to be pathogenic for that specific mitochondrial disorder has been identified in the index case.

Genetic testing for mitochondrial disorders is considered **investigational** in all other situations when the criteria for medical necessity are not met.

POLICY GUIDELINES

Mitochondrial disorders can be caused by variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). A 3-generation family history may suggest a mode of inheritance. A family history in which affected women transmit the disease to male and female children and affected men do not transmit the disease to their children suggests the familial variant(s) is in the mtDNA. A family history consistent with Mendelian autosomal dominant or autosomal recessive inheritance or with X-linked inheritance suggests the familial variant(s) is in the nDNA. *De novo* pathogenic variants are also possible.

Carrier screening for mitochondrial disorders associated with autosomal recessive inheritance of nDNA variants is addressed in evidence review 2.04.107.

Testing Strategy

Individuals With a Suspected Mitochondrial Disorder

If the phenotype is highly suggestive of a specific disorder that is supported by the inheritance pattern noted in the family history, it would be reasonable to begin genetic testing with single genes or targeted multigene panels that test for pathogenic variants specific for that disorder.

If a mitochondrial disorder is suspected, but the phenotype is nonspecific, broader genetic testing is appropriate under the guidance of a clinical geneticist and genetics counselor. For individuals in whom the family history is suggestive of a disorder due to pathogenic variant(s) in mtDNA, multigene panels or sequencing of the mitochondrial genome may be appropriate. If multiple mtDNA deletions are noted, or the family history is suggestive of a disorder due to variants in nDNA, then multigene panels covering known nuclear genes associated with mitochondrial disease may be appropriate. Testing using whole exome sequencing is reviewed in 2.04.102 (whole exome and whole genome sequencing for diagnosis of genetic disorders).

Individuals With a Family Member With a Mitochondrial Disorder and Known Familial Variant

Targeted testing of the parents of a proband with a mitochondrial disorder and a confirmed pathogenic/likely pathogenic gene variant is done to identify mode of transmission [germline (autosomal recessive, autosomal dominant, X-linked, mitochondrial) vs. *de novo*] thereby indicating risk for future offspring and other family members. Targeted testing for a known familial variant in parents and other at-risk relatives as part of preconceptional carrier testing is appropriate. At-risk relatives include only female relatives if the familial pathogenic variant is in the mtDNA but includes both male and female relatives if the familial pathogenic variant is in the nDNA.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the

recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

| Previous | Updated | Definition |
|----------|----------------------------|---|
| Mutation | Disease-associated variant | Disease-associated change in the DNA sequence |
| | Variant | Change in the DNA sequence |
| | Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

Table PG2. American College of Medical Genetics and Genomics-Association for Molecular Pathology Standards and Guidelines for Variant Classification

| Variant Classification | Definition |
|-----------------------------------|--|
| Pathogenic | Disease-causing change in the DNA sequence |
| Likely pathogenic | Likely disease-causing change in the DNA sequence |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign | Likely benign change in the DNA sequence |
| Benign | Benign change in the DNA sequence |

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Specific contract language must be reviewed and considered when determining coverage for genetic testing. In some cases, coverage for testing the index case may be available through the contract that covers the unaffected, at-risk individual who will benefit from knowing the results of the genetic test.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for mitochondrial diseases is under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals with signs and/or symptoms of a mitochondrial disease who receive genetic testing, the evidence includes case series and cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, functional outcomes, health status measures, and quality of life. There is some evidence on clinical validity that varies by the patient population and testing strategy. Studies reporting diagnostic yield for known pathogenic variants using next-generation sequencing (NGS) panels tend to report rates ranging from 15% to 25%. Clinical specificity is unknown, but population-based studies have indicated that the prevalence of certain variants exceeds the prevalence of clinical disease, suggesting that the variant will be found in some people without the clinical disease (false-positives). Clinical utility is relatively high for confirming the diagnosis of mitochondrial diseases in people who have signs and symptoms of the disease. In these patients, a positive result in genetic testing can avoid a muscle biopsy and eliminate the need for further clinical workup. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a close relative with a mitochondrial disease and a known pathogenic variant and who receive targeted familial variant testing, the evidence includes case series and cohort studies. Relevant outcomes are test validity, other test performance measures, changes in reproductive decision making, symptoms, functional outcomes, health status measures, and quality of life. Clinical validity is expected to be high for targeted testing of a known familial variant, assuming sufficient analytic validity. Clinical utility can be demonstrated by testing at-risk family members who have a close relative with a pathogenic variant. When a specific mitochondrial disease is present in the family that is severe enough to cause impairment and/or disability, genetic testing may impact reproductive decision making. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Mitochondrial Medicine Society

The Mitochondrial Medicine Society (2015) published a consensus statement on the diagnosis and management of mitochondrial disease.³⁰ Most evidence was grade III or less (case-control, low-quality cohort studies, or expert opinion without an explicit critical appraisal) using the Oxford Centre for Evidence-Based Medicine criteria. Consensus recommendations were reported using the Delphi method. A subset of the consensus recommendations for DNA testing are as follows:

1. "Massively parallel sequencing/NGS [next-generation sequencing] of the mtDNA [mitochondrial DNA] genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.

2. mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.
 1. If a single small deletion is identified using polymerase chain reaction-based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.
 2. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.
3. When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|----------------|----------------|---|
| September 2014 | New policy | |
| September 2015 | Replace policy | Policy updated with literature review through May 1, 2015, references 8 and 22-24 added. Wording of policy statements revised to be consistent with standardized genetic language |
| December 2016 | Replace policy | Policy updated with literature review through April 29, 2016; references 10 and 13 added. Policy statements unchanged |
| September 2018 | Replace policy | Policy updated with literature review through April 4, 2018; reference 10 was added. Policy statement revised so that genetic testing is no longer restricted to a set of specific mutations documented for a particular mitochondrial disorder and "at-risk, relative statement removed due to benefit considerations. |
| September 2019 | Replace policy | Policy updated with literature review through April 1, 2019; no references added. Policy statements unchanged. |
| December 2020 | Replace policy | Policy updated with literature review through June 19, 2020; references added. Policy statements unchanged. |
| December 2021 | Replace policy | Policy updated with literature review through August 9, 2021; no references added. Policy statements unchanged. |
| December 2022 | Replace policy | Policy updated with literature review through August 5, 2022; no references added. No changes to policy statements; intent unchanged. |
| December 2023 | Replace policy | Policy updated with literature review through July 18, 2023; no references added. Policy statements unchanged. |

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