Genetic Testing for Mitochondrial Disorders

Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With signs and/or symptoms of a mitochondrial disorder</td>
<td>• Genetic testing for the diagnosis of disease</td>
<td>• Standard clinical workup without genetic testing</td>
<td>• Test accuracy</td>
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<td>• Test validity</td>
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<td>• Other test performance measures</td>
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<td>• Symptoms</td>
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<td>• Functional outcomes</td>
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<td>• Health status measures</td>
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<td>• Quality of life</td>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<tr>
<td>• Who are asymptomatic with a close relative with a mitochondrial disorder and a known pathogenic mutation</td>
<td>• Genetic testing to determine future risk of disease</td>
<td>• Standard risk assessment without genetic testing</td>
<td>• Test accuracy</td>
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<td>• Test validity</td>
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<td>• Other test performance measures</td>
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<td>• Changes in reproductive decision making</td>
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<td>• Symptoms</td>
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<td>• Quality of life</td>
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</table>

Description

Mitochondrial disorders are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes that are 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 disorders. Genetic testing also has the potential to determine future risk of disease in individuals who have a close relative with a pathogenic mutation.

Summary of Evidence

For individuals who have signs and/or symptoms of a mitochondrial disorder who receive genetic testing for
diagnosis of disease, the evidence includes case series and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, functional outcomes, health status measures, and quality of life. There is a lack of published data on analytic validity. Commercial testing sites claim analytic validity approaches 100% and describe testing methods expected to have high analytic validity. There is some evidence on clinical validity that varies by the specific disorder. For example, for the most well understood disorders such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, small series of patients with a clinically diagnosed disorder have reported that a high proportion of patients have a pathogenic mutation. Clinical specificity is unknown, but population-based studies have reported that the prevalence of certain mutations exceeds the prevalence of clinical disease, suggesting that the mutation will be found in some people without clinical disease (false positives). Clinical utility is relatively high for confirming the diagnosis of mitochondrial disorders in people who have signs and symptoms indicating a moderate-to-high pretest likelihood of disease. In these patients, a positive result on genetic testing can avoid a muscle biopsy and eliminate the need for further clinical workup. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are symptomatic with a close relative with a mitochondrial disorder and a known pathogenic mutation and who receive genetic testing to determine future risk of disease, the evidence includes case series and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, symptoms, functional outcomes, health status measures, and quality of life. There is a lack of published data on analytic validity. Commercial testing sites claim analytic validity approaching 100% and describe testing methods expected to have high analytic validity. There is some evidence on clinical validity that varies by the specific disorder. For example, for the most well understood disorders such as MELAS syndrome, small series of patients with a clinically diagnosed disorder have reported that a high proportion of patients have a pathogenic mutation. Clinical specificity is unknown, but population-based studies have reported that the prevalence of certain mutations exceeds the prevalence of clinical disease, suggesting that the mutation will be found in some people without clinical disease (false positives). Clinical utility can be demonstrated for testing of at-risk family members who have a close relative with a pathogenic mutation. 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. If genetic testing is used in this situation, there will be a decreased risk of a mitochondrial disorder in live offspring. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Policy

Genetic testing to confirm the diagnosis of a mitochondrial disorder may be considered medically necessary when signs and symptoms of a specific mitochondrial disorder are present (see Policy Guidelines), but a definitive diagnosis cannot be made without genetic testing, and both of the following criteria are present:

- Genetic testing avoids the need for a muscle biopsy; AND
- Genetic testing is restricted to the specific mutations that have been documented to be pathogenic for the particular mitochondrial disorder being considered (see Policy Guidelines).

Genetic testing of at-risk female relatives may be considered medically necessary as preconceptual carrier testing under the following conditions:

- There is a defined mitochondrial disorder in the family of sufficient severity to cause impairment of quality of life or functional status; AND
- A mutation that is known to be pathogenic for that specific mitochondrial disorder has been identified in the index case.
Genetic testing for mitochondrial disorders using expanded panel testing is considered investigational (see Policy Guidelines).

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

Policy Guidelines

To maximize the positive and the negative predictive value of testing, testing should be restricted to patients with a clinical picture consistent with a specific disorder and to a small number of mutations that are known to be pathogenic for that disorder. Table 1 is a guide to clinical symptoms and particular genetic mutations associated with particular mitochondrial syndromes.

Table 1. Mitochondrial Disorders, Clinical Manifestations, and Associated Pathogenic Genes (Adapted from Chinnery et al, 2014)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Clinical Manifestations</th>
<th>Major Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELAS</td>
<td>Stroke-like episodes at age &lt; 40 y</td>
<td>MT-TL1, MT-ND5 (&gt; 95%)</td>
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<tr>
<td></td>
<td>Seizures and/or dementia</td>
<td>MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS&lt;sub&gt;1&lt;/sub&gt;, MT-TS&lt;sub&gt;2&lt;/sub&gt;, MT-ND1, MT-ND6 (rare)</td>
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<td></td>
<td>Pigmentary retinopathy</td>
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<td></td>
<td>Lactic acidosis</td>
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</tr>
<tr>
<td>MERFF</td>
<td>Myoclonus</td>
<td>MT-TK (&gt; 80%)</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>MT-TF, MT-TP (rare)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
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<tr>
<td></td>
<td>Myopathy</td>
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<tr>
<td>CPEO</td>
<td>External ophthalmoplegia</td>
<td>Various deletions of MT-DNA</td>
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<tr>
<td></td>
<td>Bilateral ptosis</td>
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<tr>
<td>Kearns-Sayre syndrome</td>
<td>External ophthalmoplegia &lt; 20 y</td>
<td>Various deletions of MT-DNA</td>
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<td></td>
<td>Painless bilateral visual failure</td>
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<tr>
<td></td>
<td>Male predominance</td>
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<td></td>
<td>Dystonia</td>
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<tr>
<td></td>
<td>Infantile onset</td>
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<td></td>
<td>Cerebellar/brain stem dysfunction</td>
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<td></td>
<td>Heart block</td>
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<tr>
<td>Leigh syndrome</td>
<td>Subacute relapsing encephalopathy</td>
<td>MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</td>
</tr>
<tr>
<td></td>
<td>Infantile onset</td>
<td>MT-DNA deletions (rare)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar/brain stem dysfunction</td>
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<tr>
<td>LHON</td>
<td>Painless bilateral visual failure</td>
<td>MT-ND1, MT-ND4, MT-ND6</td>
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<tr>
<td></td>
<td>Dystonia</td>
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<tr>
<td></td>
<td>Cardiac pre-excitation syndromes</td>
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<tr>
<td></td>
<td>Heart block</td>
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<tr>
<td>NARP</td>
<td>Peripheral neuropathy</td>
<td>MT-ATP6</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td></td>
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<td></td>
<td>Pigmentary retinopathy</td>
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</tbody>
</table>

CPEO: chronic progressive external ophthalmoplegia; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF: myoclonic epilepsy with ragged-red fibers; NARP: neuropathy, ataxia, and retinitis pigmentosa.

Panels of mutations that are disease-specific (i.e., contain only mutations associated with a specific type of mitochondrial disorder) may meet the criteria for medical necessity under certain circumstances (see the General Approach to Evaluating the Utility of Genetic Panels Protocol). When criteria for medical necessity are met, these panels may be used in place of testing individual genes in sequence. Disease-specific panels should include a list of mutations that approximates (but may not be identical to) those listed in Table 1 for each specific disorder.
“Expanded” panels refer to panels of many genes that are associated with numerous different types of mitochondrial disorders, typically including both mitochondrial and nuclear genes. These expanded panels include much higher numbers of genes than are associated with any particular disorder.

Examples of commercially available expanded panel testing are provided in Table 2.

**Genetic Counseling**

Genetic counseling is primarily aimed at patients 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.

**Background**

**Mitochondrial DNA**

Mitochondria are organelles within each cell that contain their own set of DNA, distinct from the nuclear DNA that makes up most of the human genome. Human mitochondrial DNA (mtDNA) consists of 37 genes. Thirteen genes code for protein subunits of the mitochondrial oxidative phosphorylation complex, and the remaining 24 genes are responsible for proteins that are involved in the translation and/or assembly of the mitochondrial complex. In addition, there are over 1000 nuclear genes that code for proteins that support mitochondrial function. The protein products from these genes are produced in the nucleus and later migrate to the mitochondria.

Mitochondrial DNA differs from nuclear DNA in several important ways. Inheritance of mitochondrial DNA does not follow traditional Mendelian patterns. Rather, mtDNA is inherited only from maternal DNA so that disorders that result from mutations in mtDNA can only be passed on by the mother. Also, there are thousands of copies of each mtDNA gene in each cell, as opposed to nuclear DNA, which only has one copy per cell. Because there are many copies of each gene, mutations may be present in some copies of the gene but not others. This phenomenon is called heteroplasmy. Heteroplasmy can be expressed as a percentage of genes that have the mutation, ranging from 0% to 100%. Clinical expression of the mutation will generally depend on a threshold effect (i.e., clinical symptoms will begin to appear when the percent of mutated genes exceeds a threshold amount).

**Mitochondrial Disorders**

Primary mitochondrial disorders 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 that are 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 been rising over the last two decades as the pathophysiology and clinical manifestations have been better characterized. It is currently estimated that the minimum prevalence of primary mitochondrial disorders is at least one in 5000.

Some of the specific mitochondrial disorders are listed next:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome;
- Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome;
• Kearns-Sayre syndrome (KSS);
• Leigh syndrome (LS);
• Chronic progressive external ophthalmoplegia (CPEO);
• Leber hereditary optic neuropathy (LHON);
• Neurogenic weakness with 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 of the defined mitochondrial disorders has a characteristic set of signs and 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.

The diagnosis of mitochondrial disorders 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 one particular syndrome. Biochemical testing is indicated for patients who do not have a clear clinical picture of one specific disorder. Measurement of serum lactic acid is often used as a screening test, but the test is neither sensitive nor specific for mitochondrial disorders.

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

Treatment of mitochondrial disease is largely supportive, as there are no specific therapies than impact the natural history of the disorder. Identification of complications such as diabetes mellitus and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (e.g., coenzyme Q, riboflavin) have been used, but empiric evidence of benefit is lacking. Exercise therapy for myopathy is often prescribed, but the effect on clinical outcomes is uncertain. The possibility of gene transfer therapy is under consideration, but is at an early stage of development and has not yet been tested in clinical trials.

Genetic Testing for Mitochondrial Disorders

Genetic testing for mitochondrial disorders may involve testing for point mutations, deletion/duplication analysis, and/or whole mitochondrial exome sequencing. The type of testing done depends on the specific disorder being considered. For some primary mitochondrial disorders such as MELAS and MERFF, most mutations are point mutations, and there are a finite number of mutations associated with the disorder. When testing for one of these disorders, known pathogenic mutations can be tested for with polymerase chain reaction, or sequence analysis can be performed on the particular gene. For other mitochondrial disorders such as CPEO and KSS, the most common mutations are deletions, and therefore duplication/deletion analysis would be the first test when these disorders are suspected.

Testing for the individual mutations associated with mitochondrial disorders is offered by numerous labs. Genetic panel testing is also available, with numerous different panels available. Some of these are disease-specific panels that include only a small number of genes associated with a particular mitochondrial disorder. For example, Transgenomic™ offers a MELAS panel consisting of 10 mutations that have specific associations with MELAS syndrome.

At least seven labs currently offer “expanded” panel testing for mitochondrial disorders by nextgeneration sequencing. The number of genes included in these panels varies widely, ranging from 37 to 1192. These types of panels include a larger number of genes that are associated with numerous different mitochondrial disorders.
These expanded panels are often intended to be comprehensive panels that test for all known mitochondrial and nuclear genes associated with any mitochondrial disorder. All of the expanded panels, with the exception of MEDomics®, include analysis of both mitochondrial genes and nuclear genes that are thought to be involved with mitochondrial function. The specific labs and number of genes tested, taken from websites and/or published literature, are listed in Table 2. The composition of these expanded panels vary widely in terms of the number of genes, the percent of genes that are “classic” mutations for mitochondrial disorders, and the inclusion of genes that are not associated with any disease phenotype.

Table 2. Commercially Available Expanded Genetic Panels for Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Number of Genes Included on Panel</th>
<th>Percent of Total That Are “Classic” Mutations</th>
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</thead>
<tbody>
<tr>
<td>Gene Dx® (Gaithersburg, MD)</td>
<td>101</td>
<td>94%</td>
</tr>
<tr>
<td>Transgenomic® (New Haven, CT)</td>
<td>447</td>
<td>49%</td>
</tr>
<tr>
<td>Courtagen® (Woburn, MA)</td>
<td>1192</td>
<td>18%</td>
</tr>
<tr>
<td>ARUP® (Salt Lake City, UT)</td>
<td>108</td>
<td>68%</td>
</tr>
<tr>
<td>Baylor® (Houston, TX)</td>
<td>162</td>
<td>63%</td>
</tr>
<tr>
<td>Medical Neurogenetics® (Atlanta, GA)</td>
<td>393</td>
<td>28%</td>
</tr>
<tr>
<td>MEDomics® (Azusa, CA)</td>
<td>&gt; 1200</td>
<td>No information</td>
</tr>
</tbody>
</table>

Regulatory Status

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

Related Protocols

General Approach to Evaluating the Utility of Genetic Panels

General Approach to Genetic Testing

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


