2.04.117 Genetic Testing of Mitochondrial Disorders

Summary

Mitochondrial disorders 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 disorders. Genetic testing also has the potential to determine future risk of disease in individuals who have a close relative with a pathogenic mutation.

FDA 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.

POLICY STATEMENT

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 section) 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 section).

Genetic testing of at-risk female relatives may be considered medically necessary as preconceptual 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 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 section).

Genetic testing for mitochondrial disorders is considered **investigational** in all other situations when the criteria for medical 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 known to be pathogenic for that disorder. Table PG1 is a guide to clinical symptoms and particular genetic mutations associated with particular mitochondrial syndromes.

**Table PG1. 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%) MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS1, MT-TS2, MT-ND1, MT-ND6 (rare)</td>
</tr>
<tr>
<td></td>
<td>Seizures and/or dementia</td>
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<tr>
<td></td>
<td>Pigmentary retinopathy</td>
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<tr>
<td></td>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>MERFF</td>
<td>Myoclonus</td>
<td>MT-TK (&gt;80%)</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>MT-TP (rare)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myopathy</td>
<td></td>
</tr>
<tr>
<td>CPEO</td>
<td>External ophthalmoplegia</td>
<td>Various deletions of MT DNA</td>
</tr>
<tr>
<td></td>
<td>Bilateral ptosis</td>
<td></td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>External ophthalmoplegia at age &lt;20 y</td>
<td>Various deletions of MT DNA</td>
</tr>
<tr>
<td></td>
<td>Pigmentary retinopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart block</td>
<td></td>
</tr>
<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>
<td></td>
</tr>
<tr>
<td>LHON</td>
<td>Painless bilateral visual failure</td>
<td>MT-ND1, MT-ND4, MT-ND6</td>
</tr>
<tr>
<td></td>
<td>Male predominance</td>
<td></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>NARP</td>
<td>Peripheral neuropathy</td>
<td>MT-ATP6</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td></td>
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<tr>
<td></td>
<td>Pigmentary retinopathy</td>
<td></td>
</tr>
</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.
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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.

BENEFIT APPLICATION

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.

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

RATIONALE

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
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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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
The Foundation for Mitochondrial Medicine published an overview of mitochondrial disease in 2013; genetic testing was specifically addressed. The overview includes the following statements:

- Mitochondrial disease can look like a number of different diseases such as autism, Parkinson disease, Alzheimer disease, Lou Gehrig disease, muscular dystrophy, and chronic fatigue.
- There are 3 categories of diagnostic criteria: clinical, biochemical, and genetic.
- A diagnosis of mitochondrial disease requires an integrated approach; there is “no single test to diagnose mitochondrial disease in most patients.”
- Genetic testing, alone, is “rarely … sufficient to diagnose mitochondrial disease.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2014</td>
<td>New Policy</td>
<td>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.</td>
</tr>
<tr>
<td>September 2015</td>
<td>Policy Update</td>
<td>Policy updated with literature review through April 29, 2016; references 10 and 13 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2016</td>
<td>Policy Update</td>
<td>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.</td>
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</table>

Signature on File

Deborah M. Smith, MD, MPH