Corporate Medical Policy

Genetic Testing of Mitochondrial Disorders AHS – M2085

File Name: genetic_testing_of_mitochondrial_disorders
Origination: 01/2019
Last CAP Review: 03/2020
Next CAP Review: 03/2021
Last Review: 03/2020

Description of Procedure or Service

Definitions
Mitochondrial disease refers to a heterogeneous group of disorders caused by dysfunctional mitochondria, the organelles responsible for oxidative phosphorylation within the cell. The mitochondrial diseases can be classified according to the primary genetic defect, including those affecting respiratory chain proteins or ancillary proteins, mitochondrial RNA translation defects, inner membrane lipid defects, mutations causing depletion of mitochondrial DNA, or mutations to mitochondrial dynamics. Tissues with high energy demands, such as brain, heart, and skeletal muscle, are those most affected by mitochondrial diseases (O’Ferrall, 2017).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing of mitochondrial disorders when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing of Mitochondrial Disorders is covered

1. Genetic testing to confirm the diagnosis of a mitochondrial disorder (Eg. MELAS, MERRF, CPEO, Kearns-Sayre syndrome, Leigh’s syndrome) is considered medically necessary as an alternative to muscle biopsy when clinical signs and symptoms are consistent with a specific mitochondrial disorder, but the diagnosis cannot be made with certainty without genetic testing.

2. In patients strongly suspected of having a mitochondrial disorder without symptomology associated with a specific mitochondrial condition, genomic sequencing and large deletion detection of the entire mitochondrial genome with heteroplasmcy detection is considered medically necessary.
3. Genetic counseling for mitochondrial disorder genetic testing is considered medically necessary.

When Genetic Testing of Mitochondrial Disorders is not covered

Genetic testing for mitochondrial disorders is considered investigational in all other situations.

Policy Guidelines

Background

Previously, the prevalence of mitochondrial diseases was considered low; however, numerous studies now have shown that the incidence of mitochondrial diseases is more common. A meta-analysis of the prevalence of the three primary mitochondrial DNA (mtDNA) mutations that cause Leber hereditary optic neuropathy (LHON) in Europe shows that LHON has a prevalence of approximately 1:45,000 (Mascialino, Leinonen, & Meier, 2012). A longitudinal study in Sweden reports an incidence of mitochondrial encephalomyopathies, in general, at 1:11,000 and an incidence of infantile mitochondrial myopathy with cytochrome C oxidase deficiency of 1:51,000. The authors conclude that “mitochondrial encephalomyopathies are relatively common neurometabolic disorders in childhood (Darin, Oldfors, Moslemi, Holme, & Tulinius, 2001).” A 2015 study in the United Kingdom reports that their “data confirm that the total prevalence of adult mitochondrial disease, including pathogenic mutations of both the mitochondrial and nuclear genomes (≈1 in 4,300), is among the commonest adult forms of inherited neurological disorders (Gorman et al., 2015).” An Australian study estimates a “minimum birth prevalence of 13.1/100,000 or 1/7634 for respiratory chain disorders with onset at any age (Skladal, Halliday, Thorburn, 2003).

The figure below (taken from (O’Brien, Cryan, Brett, Howley, & Farrell, 2014)) gives examples of classical phenotype mitochondrial diseases along with the clinical features and molecular genetics associated with each disorder.
Mitochondrial defects can be caused by mutation in either the nuclear or mitochondrial genome. These dual genomic origins, along with the phenotypic variability and severity, can create challenges to diagnosing affected patients (O’Ferrall, 2017). 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 (Chinnery, 2014). The evaluation and diagnostic approach varies according to age, clinical phenotype, and presumed inheritance pattern. 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 (Schon, DiMauro, & Hirano, 2012). “Identifying causative mutations underlying mitochondrial dysfunction is the ultimate gold standard for the diagnosis. Two mitochondrial diseases (MNGIE and coenzyme Q10 deficiency) are particularly important to identify because of potential treatments (O’Ferrall, 2017).”
**Clinical Validity and Utility**

Clinical utility is relatively high for confirming the diagnosis of mitochondrial disorders in people who have clinical features consistent with a specific mitochondrial disease. In these patients, a positive result on genetic testing can avoid a muscle biopsy and eliminate the need for further clinical workup. Additionally, genetic testing may impact reproductive decision making when a defined mitochondrial disease is present in the family that is severe enough to cause impairment and/or disability. If genetic testing is used in this situation, there will be a decreased risk of a mitochondrial disorder in the offspring.

Expanded panels are defined as panels that include many more genes than are associated with any specific disorder. They are sometimes promoted for individuals with signs and/or symptoms that are not consistent with any specific disorder. When these panels are used in individuals with nonspecific signs and symptoms that are not consistent with a “classic” presentation of a mitochondrial disorder, the probability of finding a pathogenic mutation is considerably less. Conversely, the likelihood of a false-positive result and the number of VUS (a variant of uncertain significance) may be substantially increased (O'Brien et al., 2014). Table 1, below, lists examples of commercially available expanded genetic panels for mitochondrial disorders.

**Table 1. Examples of Commercially Available Expanded Genetic Panels for Mitochondrial Disorders**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Lab Test or Panel</th>
<th>Number of Genes Included on Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Dx® (Gaithersburg, MD)</td>
<td>MitoXpanded Panel (GeneDX, 2018b)</td>
<td>~1800</td>
</tr>
<tr>
<td></td>
<td>Combined Mito Genome Plus Mito Focused Nuclear Gene Panel (GeneDX, 2018a)</td>
<td>202</td>
</tr>
<tr>
<td>Transgenic® (New Haven, CT)</td>
<td>Nuclear Mitome Test (Transgenomic, 2011)</td>
<td>&gt;400</td>
</tr>
<tr>
<td>ARUP® (Salt Lake City, UT)</td>
<td>Mitochondrial Disorders Panel (ARUP, 2018)</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Baylor® Miraca Genetics Laboratories (Houston, TX)</td>
<td>Mitome Nuclear Genes (BMGL, 2015)</td>
<td>164</td>
</tr>
<tr>
<td>Medical Neurogenetics® (Atlanta, GA)</td>
<td>Mitochondrial Genome Sequencing &amp; Deletion Analysis (Medical Neurogenetics, 2018)</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

The potential role of genomic testing is where single-gene testing (and/or use of a multi-gene panel) has not confirmed a diagnosis in an individual with features of a mitochondrial disorder. Such testing includes whole-exome sequencing, whole-genome sequencing, and whole mitochondrial sequencing. Whole exome sequencing has also been examined to detect mutations associated with mitochondrial disorders (Ohtake et al., 2014; Taylor et al., 2014). This technique is likely to increase the detection rate but will also increase the rate of VUS. In one study from the U.K. of 53 patients who had biochemical evidence of a mitochondrial disorder but were negative on genetic testing of the primary mitochondrial disorder, mutations underwent whole exome sequencing. Probable pathogenic mutations causative of a mitochondrial disorder were identified in 28 patients (53%), and there were an additional four patients who had variants that were possibly pathogenic (Taylor et al., 2014). “False negative rates vary by genomic region;
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therefore, genomic testing may not be as accurate as targeted single gene testing or multigene molecular genetic testing panels. Most laboratories confirm positive results using a second, well-established method (Chinnery, 2014).”

A study by Fang and colleagues of 141 children with suspected mitochondrial disorders used NGS to identify genetic characteristics. Forty children were gene confirmed with a known mitochondrial disease, and 62.5% of those cases were due to an mtDNA mutation. This study found the most prevalent disorder to be MELAS (Fang et al., 2017). Another study clearly demonstrates the heterogeneity of genetic mutations causing mitochondrial disorders. Of the 142 patients with childhood-onset mitochondrial disorders, the researchers “identified 37 novel mutations in known mitochondrial disease genes and 3 mitochondria-related genes (MRPS23, QRL1, and PNPLA4) as novel causative genes (Kohda et al., 2016).” Another study suggests that whole-exome sequencing (WES) is a better diagnostic tool than NGS since 50.5% of all detected genetic changes in their cohort of 113 patients with suspected mitochondrial disorders were novel variants (Pronicka et al., 2016). The research of Legati and colleagues suggests a two-tiered approach to genetic testing where targeted NGS is used first in cases of suspected mitochondrial disorders followed by WES of those patients who have unresolved cases. “Importantly, WES on selected cases has unraveled the presence of pathogenic mutations in genes encoding non-mitochondrial proteins (e.g. the transcription factor E4F1), an observation that further expands the intricate genetics of mitochondrial disease and suggests a new area of investigation in mitochondrial medicine (Legati et al., 2016).”

Applicable Federal Regulations

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Foundation for Mitochondrial Medicine (FMM, 2018)

The Foundation for Mitochondrial states, “There is no single test to diagnose mitochondrial disease in most patients. Today, OXPHOS (oxidative phosphorylation) enzymology by itself is no longer sufficient for a diagnosis… Diagnosis of mitochondrial disease can be made through a combination of clinical observations, laboratory evaluation, brain imaging, and muscle biopsies. And an experienced integrated approach is necessary – not just one test. Referral to a specialist in mitochondrial medicine is often needed for diagnosis. Rarely is genetic testing sufficient for the diagnosis of mitochondrial disease. Even with the advent of new gene sequencing techniques like Next Generation sequencing, many of the identified changes in genes require the information obtained from a muscle biopsy for interpretation (FMM, 2018).”

Mitochondrial Medicine Society (Parikh et al., 2017; Parikh et al., 2015)

The Mitochondrial Medicine Society published the following consensus recommendations on genetic testing for mitochondrial disorders (Parikh et al., 2015):

1. “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.

2. 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;
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tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.

3. Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m. 3243A>G mutation.

4. 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.

   a. 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.
   b. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.

5. When a tissue specimen is obtained for mitochondrial studies, mtDNA content (copy number) testing via real-time quantitative polymerase chain reaction should strongly be considered for mtDNA depletion analysis because mtDNA depletion may not be detected in blood.

   a. mtDNA proliferation is a nonspecific compensatory finding that can be seen in primary mitochondrial disease, secondary mitochondrial dysfunction, myopathy, hypotonia, and as a by-product of regular, intense exercise.

6. 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.”

7. The Mitochondrial Medicine Society in 2017 released their guidelines regarding patient care standards. Within this set of guidelines, they state, “Pregnancy in mitochondrial disease also elicits the concern of transmission of a genetic disorder. Appropriate preconception genetic counseling and discussion of options of prenatal testing are needed. A fetus affected by mitochondrial disease may also be at higher risk for prenatal morbidity. Finally, premature ovarian failure is a feature of several mitochondrial disorders and affected women should be referred for assisted reproductive technologies if they wish to have children (Parikh et al., 2017).”

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81401, 81403, 81440, 81460, 81465, 96040, S0265

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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


BMGL. (2015, 08/03/2015). MITOCHONDRIAL DNA (mtDNA) TEST REQUISITION. Retrieved from https://www.bcm.edu/research/medical-genetics-labs/index.cfm?pmid=26409


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Policy Implementation/Update Information

1/1/2019  New policy developed. BCBSNC will provide coverage for genetic testing of mitochondrial disorders when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)
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4/16/2019  Description section and policy guidelines updated. When Covered section revised for clarity and removed criteria concerning prenatal testing as this is addressed in a separate policy. Policy intent unchanged. Added 96040 and S0265 for genetic counseling which was added as item #3 under the When Covered section. Medical Director review 4/2019 (jd)

2/11/20   Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change to policy intent. Medical Director review 12/2019. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.