Genetic Testing for Mitochondrial Disorders

Policy # 00435
Original Effective Date: 07/16/2014
Current Effective Date: 09/21/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing to confirm the diagnosis of a mitochondrial disorder 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 to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for genetic testing to confirm the diagnosis of a mitochondrial disorder will be considered when all of the following criteria are met:

- 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).

Based on review of available data, the Company may consider genetic testing of at-risk female relatives as part of a preconceptual evaluation to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for genetic testing of at-risk female relatives as part of a preconceptual evaluation will be considered when all of the following criteria are met:

- 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.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of genetic testing for mitochondrial disorders using expanded panel testing to be investigational.*
Based on review of available data, the Company considers the use of genetic testing for mitochondrial disorders in all other situations or when the patient selection criteria outlined above are not met to be investigational.*

**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>
<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>
</tr>
<tr>
<td></td>
<td>• Seizures and/or dementia</td>
<td>• MT-TF, MT-TK, MT-TQ, MT-TS1, MT-TS2, MT-ND1, MT-ND6 (rare)</td>
</tr>
<tr>
<td></td>
<td>• Pigmentary retinopathy</td>
<td></td>
</tr>
<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-TF, 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>Kearn-Sayre</td>
<td>• External ophthalmoplegia at age &lt;20y</td>
<td>• Various deletions of MT-DNA</td>
</tr>
<tr>
<td>Syndrome</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>
</tr>
<tr>
<td></td>
<td>• Dystonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cardiac pre-excitation syndromes</td>
<td></td>
</tr>
<tr>
<td>NARP</td>
<td>• Peripheral neuropathy</td>
<td>• MT-ATP6</td>
</tr>
<tr>
<td></td>
<td>• Ataxia</td>
<td></td>
</tr>
<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.

Panels of mutations that are disease-specific (ie, contain only mutations associated with a specific type of mitochondrial disorder) may meet the criteria for medical necessity under certain circumstances. When criteria for medical necessity are met, these panels may be used in place of testing individual genes in
Genetic Testing for Mitochondrial Disorders

Policy # 00435
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sequence. Disease-specific panels should include a list of mutations that approximates (but may not be identical to) those listed in Table PG1 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 1.

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/Overview
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.

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 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 mtDNA 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 1 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
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 1 in 5000.

Some of the specific mitochondrial disorders are listed below:
- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome;
- Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome;
- Kearns-Sayre (KSS) syndrome;
- Leigh syndrome (LS);
- Chronic progressive external ophthalmoplegia (CPEO);
- Lieber 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 of 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 mitochondria. This characteristic finding may not be present in all types of mitochondrial disorders, and also may be absent early in the course of disease.
Genetic Testing for Mitochondrial Disorders

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 (eg, 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 (PCR), 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, Transgenomics™ offers a MELAS panel consisting of 10 mutations that have specific associations with MELAS syndrome.

At least 7 labs currently offer “expanded” panel testing for mitochondrial disorders by next-generation 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 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 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. Specific labs and number of genes tested, accessed from websites and/or published literature, are listed in Table 1. The composition of these expanded panels vary widely in terms of the number of genes, the percentage of genes that are “classic” mutations for mitochondrial disorders, and the inclusion of genes that are not associated with any disease phenotype.

Table 1. Commercially Available Expanded Genetic Panels for Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>No. of Genes Included on Panel</th>
<th>Percentage of Total That Are “Classic” Mutations</th>
</tr>
</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>
</tbody>
</table>
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**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
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 FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Rationale/Source**

This policy was created in 2014, and updated periodically with literature review of the MEDLINE database. The most recent update with literature review covers the period through April 29, 2016.

Review of evidence will be focused on the following categories of genetic testing: diagnostic testing of an individual's germline to benefit the individual; testing an asymptomatic individual to determine future risk of disease; and preconceptual carrier testing.

The evaluation of a genetic test focuses on 3 main principles: 1) analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); 2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and 3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

**Analytic Validity**

The analytic validity of testing for mtDNA may vary by the type of testing performed, the type of mutation present, and the particular gene being evaluated. The 2 main types of genetic testing are PCR analysis and next generation sequencing (NGS). Both of these are, in general, associated with high analytic validity of greater than 95%.

The Courtagen webpage cites a sensitivity and specificity both greater than 99%. No further information is provided, but this presumably refers to the analytic validity of the Courtagen panel to detect mutations that are present and exclude mutations that are not present.

In addition to determining the presence of the mutation, another important component of analytic validity is whether the degree of heteroplasmy has been accurately measured. The proportion of DNA that is mutated is an important component of whether clinical symptoms will develop and is generally reported along with
the presence or absence of the mutation. No information was available to judge the accuracy of heteroplasmy determination for mutations in mtDNA.

Section Summary: Analytic Validity
There is a lack of published information on the analytic validity of genetic testing for mitochondrial disorders. There are manufacturer claims that the analytic validity approaches 100%, but no empirical data is available. The analytic validity of testing mtDNA has the added complexity of heteroplasmy, and no evidence was identified that evaluated the accuracy of methods for determining heteroplasmy.

Clinical Validity
The evidence on the clinical sensitivity and specificity of genetic testing for mitochondrial disorders is limited. There are some small case series of patients with well-defined syndrome such as MELAS syndrome, and there are some studies that include larger numbers of patients with less specific clinical diagnosis. There are wide variations reported in the yield of testing, probably reflecting the selection process used to select patients for testing. Some of the representative information that is pertinent to clinical validity is reviewed here.

Clinical Sensitivity
Several series of patients with mixed diagnoses, or suspected mitochondrial disorders, have been published. In these studies, the mutation detection rate may or may not be an accurate estimate of clinical sensitivity, because the proportion of patients with a mitochondrial disorder is uncertain.

Kohda et al evaluated a cohort of 142 children with early-onset respiratory chain disease using NGS of the entire mtDNA together with whole exome sequencing of the nuclear DNA. There were 37 (26.1%) patients who had a likely pathogenic mutation identified. Most (37/42 [88.1%]) were novel mutations discovered in the mtDNA. Two 2 (1.4%) patients were found to have a known pathogenic mutation in a mitochondrial gene.

Qi et al studied 552 patients with mitochondrial encephalopathies and tested them for the presence of 4 of the most common mitochondrial mutations.11 Patients had a diagnosis of MELAS, myoclonic epilepsy with ragged-red fibers (MERRF) syndrome, Leigh syndrome (LS), Leber hereditary optic neuropathy, or an overlap syndrome. A total of 64 (11.6%) patients had a pathogenic mutation, most of which (57/64) were the n3243 variant.

Lieber et al studied 102 patients with heterogeneous clinical symptoms suspected to be due to mitochondrial disorders. Using NGS, the authors sequenced the entire mitochondrial genome and the exons of 1598 nuclear genes. Twenty-two (22.4%) patients had mutations thought to be pathogenic. An additional 26 variants identified were of uncertain clinical significance. A similar population of patients with heterogeneous symptoms and suspected mitochondrial disease was evaluated by Remenyi et al. In this study, 1328 patients from China were tested for the 5 most common mitochondrial mutations. A pathogenic mutation was found in 22.5% of patients. The most common mutations were those associated with Leber hereditary optic neuropathy, occurring in 17.9% of patients.
Genetic Testing for Mitochondrial Disorders

Policy # 00435
Original Effective Date: 07/16/2014
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For patients with a well-defined syndrome, smaller case series have been published. For MELAS syndrome, a high proportion of patients were diagnosed clinically with the disorder test positive for a pathogenic mutation. The most common mutation is an A→G base pair substitution at nucleotide pair 3,243. Goto et al tested 31 nonrelated patients with MELAS for the presence of this point mutation and reported that 83.9% (26/31) were positive.

For MERRF, it is commonly cited that more than 80% of patients with the clinically defined syndrome will have a mutation in the MT-TK gene, with an A→G substitution at (nt)8344, and that an additional 10% of patients with MERRF will have 1 of 3 other mutations in the MT-TK gene. However, there is a lack of published evidence that supports this claim.

Leigh syndrome has criteria for diagnosis that include 1) Nneurodegenerative disease with symptoms of mitochondrial dysfunction, 2) hereditary pattern of disease, and 3) bilateral central nervous system (CNS) lesions on imaging. There are at least 12 genes that have been associated with LS, with each gene accounting for only a small minority of cases. The most common gene involved is the MT-ATP6 gene, which is implicated in approximately 10% of cases.

**Clinical Specificity**
The clinical specificity of genetic testing for mitochondrial disorders is largely unknown, but false positive results have been reported. Some epidemiologic evidence is available on the population prevalence of pathogenic mutations, which provides some indirect evidence on the potential for false positive results.

A study of population-based testing reported that the prevalence of pathogenic mutations is higher than the prevalence of clinical disease. In this study, 3168 consecutive newborns were tested for the presence of 1 or more of the 10 most common mtDNA mutations thought to be associated with clinical disease. At least 1 pathogenic mutation was identified in 15/3168 people (0.54%, 95% CI, 0.30% to 0.89%). This finding implies that there are many more people with a mutation who are asymptomatic than there are people with clinical disease and raises the possibility of false positive results on genetic testing.

An earlier population-based study evaluated the prevalence of the n3243 mutation that is associated with MELAS syndrome. This study included 245,201 subjects from Finland. Participants were screened for common symptoms associated with MELAS and screen-positive patients were tested for the mutation. The population prevalence was estimated at 16.3/100,000 (0.16%). This study may have underestimated the prevalence because patients who screened negative were not tested for the mutation.

In addition to false positive results, there are variants of uncertain significance that are detected in substantial numbers of patients. The number of variants increases when next generation sequencing methods are used to examine a larger portion of the genome. In 1 study using targeted exome sequencing, variants of uncertain significance were far more common than definite pathogenic mutations. In that study, 148 patients with suspected or confirmed mitochondrial disorders were tested by a genetic panel including 447 genes. A total of 13 patients were found to have pathogenic mutations. In contrast, variants of unknown significance were very common, occurring at a rate of 6.5 per patient.
A further consideration is the clinical heterogeneity of mutations known to be pathogenic. Some mutations associated with mitochondrial disorders can result in heterogeneous clinical phenotypes, and this may cause uncertainty about the pathogenicity of the mutation detected. For example, the (nt)3243 mutation in the \( MT-TL1 \) gene is found in most patients with clinically defined MELAS syndrome. However, this same mutation has also been associated with CPEO and LS. Therefore, the more closely the clinical syndrome matches MELAS, the more likely a positive genetic test will represent a pathogenic mutation.

**Section Summary: Clinical Validity**

Case series and cohort studies provide information on the clinical sensitivity of testing. For patients with signs and symptoms of mitochondrial disorders, but without a well-defined clinical syndrome, the mutations detection rate is low, ranging from 11.6% to 26.1%. This rate is an underestimation of clinical sensitivity because at least some patients do not have a mitochondrial disorder, but the degree to which it approximates clinical sensitivity is uncertain. For patients with a defined clinical syndrome, the clinical sensitivity is higher (range, >80%). However, clinical sensitivity has not been reported for all mitochondrial disorders. There is very little evidence on clinical specificity, but there have been false-positive tests reported.

**Clinical Utility**

No direct evidence on clinical utility was identified. There are 2 ways that clinical utility might be demonstrated from an indirect chain of evidence. First, confirmation of the diagnosis may have benefits in ending the need for further clinical workup and eliminating the need for a muscle biopsy. Second, knowledge of mutation status may have benefits for family members in determining their risk of developing disease.

**Confirmation of Diagnosis**

For patients with signs and symptoms that are consistent with a defined mitochondrial syndrome, testing can be targeted to those mutations associated with that particular syndrome. In the presence of a clinical picture consistent with the syndrome, the presence of a known pathogenic mutation will confirm the diagnosis with a high degree of certainty. Confirmation of the diagnosis by genetic testing can result in reduced need for further testing, especially a muscle biopsy. The clinical utility of testing will be maximized if patients are selected who have at least a moderate to high pretest probability of disease. If confirmation of the diagnosis depends on both on the presence of signs of and symptoms of a specific disorder in conjunction with the presence of a known pathogenic mutation, then the problem of potential false positive results will be minimized.

There is no specific therapy for mitochondrial disorders. Treatment is largely supportive management for complications of the disease. It is possible that confirmation of the diagnosis by genetic testing leads to management changes, such as increased surveillance for complications of disease and/or the prescription of exercise therapy or antioxidants. However, the impact of these management changes on health outcomes is not known.
Genetic Testing for Mitochondrial Disorders

Policy # 00435
Original Effective Date: 07/16/2014
Current Effective Date: 09/21/2016

Testing of At-Risk Relatives
Confirmation of a genetic mutation has implications for family members of the affected person. Knowledge of mutation status will clarify the inheritance pattern of the mutation, thus clarifying risk to family members. For example, for a male patient with MELAS syndrome, confirmation of a pathogenic mutation in the mtDNA would indicate that his offspring are not at risk for inheriting the mutation, because inheritance of the mitochondrial mutation could only occur through the mother. In contrast, identification of a pathogenic mutation in nuclear DNA would indicate that his offspring are at risk for inheriting the mutation.

Reproductive Testing
When there is disease of moderate severity or higher, it is reasonable to assume that many patients will consider results of testing in reproductive decision making. Prevention of disease through genetic testing is one way in which the burden of illness can be reduced. Preconceptual carrier testing can lead to informed reproductive decision making, which may alter decisions on pursuing pregnancy or lead to preimplantation genetic testing. Nesbitt et al published a retrospective review of 62 patients who underwent prenatal genetic testing for mitochondrial disorders at a European center. Based on test results and their review of records, the authors estimated that at least 11 cases of mitochondrial disorder had been prevented.

Expanded Panel Testing and Whole Exome Sequencing
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 may be substantially increased.

Whole exome sequencing has also been examined to detect mutations associated with mitochondrial disorders. This technique is likely to increase the detection rate but will also increase the rate of VUS. In 1 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 4 patients who had variants that were possibly pathogenic. Further research is needed into the benefits and harms of expanded panel testing and whole exome sequencing for the diagnosis of mitochondrial disorders. At present, due the uncertainty about the balance of benefits and harms, it is not possible to determine whether there is a net health outcome benefit.

Section Summary: Clinical Utility
For diagnostic testing, clinical utility is relatively high when a definite diagnosis cannot be made without genetic testing. In this situation a positive test for a pathogenic mutation will confirm the diagnosis and may avoid further testing, including invasive tests (e.g., muscle biopsy). It is likely that confirmation of the diagnosis will lead to management changes, including referral to a specialist in mitochondrial disease. However, it is not known whether these management changes improve outcomes, because of the lack of research on treatment interventions for mitochondrial disorders. For testing at-risk relatives, clinical utility can also be demonstrated. When a disease phenotype displays moderate-to-severe disease, it is likely that
Genetic Testing for Mitochondrial Disorders

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knowledge of mutation status will affect reproductive decision making. Genetic testing prior to pregnancy, with or without preimplantation genetic testing, is likely to reduce the likelihood of live offspring with mitochondrial disorders.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in June 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

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 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 with 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.
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07/10/2014  Medical Policy Committee review
07/16/2014  Medical Policy Implementation Committee approval. New policy.
06/25/2015  Medical Policy Committee review
07/15/2015  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/08/2016  Medical Policy Committee review
09/21/2016  Medical Policy Implementation Committee approval. Updated coverage statements for clarification.
Combined investigational statements for clarification.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date:  9/2017

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®‡, copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81401, 81403, 81440, 81460, 81465</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>E88.40-E88.49 F84.2 G31.81-G31.82 H49.811-H49.819 H50.89</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means
Genetic Testing for Mitochondrial Disorders

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of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.