BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-083-0031
EFFECTIVE DATE August 1, 2014	**SUBJECT:** Genetic Testing of Mitochondrial Disorders

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

DESCRIPTION:

Mitochondrial disorders are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes that are involved in oxidative metabolism. These disorders can be due to pathogenic mutations in the mitochondrial DNA that code for the protein complexes, or mutations in nuclear DNA that code for proteins involved in translation and assembly of mitochondrial complexes. Genetic sequencing of mitochondrial DNA and nuclear genes associated with mitochondrial processes is commercially available.

BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

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. (1) In addition, there are over 1000 nuclear genes that code for proteins that support mitochondrial function. (2) 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 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 depend on a threshold effect, ie clinical symptoms will begin to appear when the percent of mutated genes exceeds a threshold amount. (3)

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. (4)

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. (1, 5)

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. (6) 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. (2)

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. (1) This characteristic finding may not be present in all types of mitochondrial disorders, and also may be absent early in the course of disease. (2)

Treatment of mitochondrial disease is largely supportive, as there are no specific therapies than impact the natural history of the disorder. (6) 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. (7) Exercise therapy for myopathy is often prescribed, but the effect on clinical outcomes is uncertain. (6) 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. (8)

There are at least 7 labs that currently offer "expanded" panel testing for mitochondrial disorders by next generation sequencing. (4) 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 are listed below:

Table 1. Commercially Available Expanded Genetic Panels for Mitochondrial Disorders

Laboratory	Number of genes included on panel
Gene Dx® (Gaithersburg, MD)	101
Transgenomic® (New Haven, CT)	447
Courtagen® (Woburn, MA)	1192
ARUP® (Salt Lake City, UT)	108
Baylor® (Houston, TX)	162
Medical Neurogenetics® (Atlanta, GA)	393
MEDomics® (Azusa, CA)	37

MEDICAL POLICY STATEMENT:

BCNEPA will provide coverage for genetic testing to confirm the diagnosis of a mitochondrial disorder when medically necessary.

Genetic testing to confirm the diagnosis of a mitochondrial disorder may be considered medically necessary as an alternative to muscle biopsy under the following conditions:

- Clinical signs and symptoms are consistent with a specific mitochondrial disorder (see Guidelines), but the diagnosis cannot be made with certainty by clinical and/or biochemical evaluation; AND
- Genetic testing is restricted to the specific mutations that have been documented to be pathogenic for the particular mitochondrial disorder being considered (see Guidelines)

Genetic testing of at-risk female relatives may be considered medically necessary as part of a preconceptual evaluation 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 Guidelines).

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

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 2 is a guide to clinical symptoms and particular genetic mutations that are associated with particular mitochondrial syndromes.

Table 2. Mitochondrial Disorders, Clinical Manifestations, and Associated Pathogenic Genes (Adapted from Chinnery et al (6)).

Syndrome	Main clinical manifestations	Major genes involved
MELAS	• Stroke-like episodes at age <40 • Seizures and/or dementia • Pigmentary retinopathy • Lactic acidosis	• *MT-TL1, MT-ND5* (>95%) • *MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS1, MT-TS2, MT-ND1, MT-ND6* (rare)
MERFF	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• MT-TK (>80%) • *MT-TF, MT-TP* (rare)
CPEO	• External ophthalmoplegia • Bilateral ptosis	• Various deletions of MT-DNA

Syndrome	Main clinical manifestations	Major genes involved
KSS	• External ophthalmoplegia <20yo • Pigmentary retinopathy • Cerebellar ataxia • Heart block	• Various deletions of MT-DNA
LS	• Subacute relapsing encephalopathy • Infantile onset • Cerebellar/brain stem dysfunction	• *MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3* • MT-DNA deletions (rare)
LHON	• Painless bilateral visual failure • Male predominance • Dystonia • Cardiac pre-excitation syndromes	• *MT-ND1, MT-ND4, MT-ND6*
NARP	• Peripheral neuropathy • Ataxia • Pigmentary retinopathy	• MT-ATP6

Panels of mutations that are disease-specific, ie contain only mutations associated with a specific type of mitochondrial disorder, can 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 2 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 are contrasted with the smaller number of genes associated with any particular disorder (Table 2). Examples of commercially available expanded panel testing are provided in Table 1.

RATIONALE:

Mitochondrial disorders are multisystem diseases that can present with a variety of symptoms and which can be difficult to diagnose. There are many different related but distinct syndromes, and some patients have overlapping syndromes. The "classic" forms of these disorders arise from mutations in mitochondrial DNA. Numerous other types of mitochondrial disorders arise from mutations in nuclear DNA that have a role in assembly or function of the mitochondria.

There is a lack of published data on analytic validity, but commercial testing uses methods that are 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). Variants of unknown significance occur commonly, especially with the use of next generation sequencing.

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 can eliminate the need for further clinical workup. For testing of at-risk family members, clinical utility can also be demonstrated. When disease is present that is severe enough to cause impairment and/or disability, genetic testing for reproductive decision making is a reasonable choice that may prevent transmission of disease to offspring.

Medicare National Coverage
None

DEFINITIONS:

N/A

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

81401 81403 81479

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APPROVALS:

Approved by Vice President, Clinical Operations & Chief Medical Officer:

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