Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Genetic Testing for Mitochondrial Disorders

Description/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 variants in mtDNA can only be passed on by the mother. In addition, 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, variants 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.[3]

MITOCHONDRIAL DISEASES

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 2 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.[1,4]

Some of the specific mitochondrial disorders include:

- 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.

Diagnosis

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.[5] 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 may be absent early in the course of disease.[2]

Treatment

Treatment of mitochondrial disease is largely supportive, as there are no specific therapies than impact the natural history of the disorder.[5] 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.[6] Exercise therapy for myopathy is often prescribed, but the effect on clinical outcomes is uncertain.[5] 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

Mitochondrial disorders can be caused by pathogenic variants in the maternally inherited mtDNA or one of many nDNA genes. Genetic testing for mitochondrial disorders may involve testing for point variants, 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 variants are point variants, and there are a finite number of variants associated with the disorder. When testing for one of these disorders, known pathogenic variants 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 variants are deletions, and therefore duplication/deletion analysis would be the first test when these disorders are suspected. Table 1 provides examples of clinical symptoms and particular genetic variants in mtDNA or nDNA associated with particular mitochondrial syndromes.[5,7] A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database.[8] Lists of mtDNA and nDNA genes that may lead to mitochondrial disorders and testing laboratories in the United States are provided at the GeneTests website (funded by BioReference Laboratories) and Genetic Testing Registry of the National Center for Biotechnology Information website.[9]

Table 1. Examples of Mitochondrial Disorders, Clinical Manifestations, and Associated Pathogenic Genes

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	• Stroke-like episodes at age <40 y • Seizures and/or dementia • Pigmentary retinopathy • Lactic acidosis	• MT-TL1, MT-ND5 (>95%) • MT-TF, MT-TH, MT-TK, MT-QM, NT-TS_1, MT-TS_2, 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 mtDNA
Kearns-Sayre syndrome	• External ophthalmoplegia at age <20 y • Pigmentary retinopathy • Cerebellar ataxia • Heart block	Various deletions of mtDNA
Leigh syndrome	• 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 • mtDNA deletions (rare) • SUCLA2, NDUSFx, NDFVx, SDHA, BCS1L, SURF1, SCO2, COX15
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
MNGIE	• Intestinal malabsorption	• TP

	• Cachexia • External ophthalmoplegia • Neuropathy	
IOSCA	• Ataxia • Hypotonia • Athetosis • Ophthalmoplegia • Seizures	• TWINKLE
SANDO	• Ataxic neuropathy • Dysarthria • Opthalmoparesis	• POLG
Alpers syndrome	• Intractable epilepsy • Psychomotor regression • Liver disease	• POLG, DGUOK, MPV17
GRACILE	• Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis	• NDUSFx
Coenyzme Q_{10} deficiency	• Encephalopathy • Steroid-resistant nephritic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss	• COQ2 • COQ9 • CABC1 • ETFDH

Adapted from Chinnery et al (2014)[5] and Angelini et al (2009).[7]
CPEO: chronic progressive external ophthalmoplegia; GRACILE: growth retardation, aminoaciduria, cholestasis, iron overload, early death; IOSCA: infantile onset spinal cerebellar atrophy; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF: myoclonic epilepsy with ragged-red fibers; MNGIE: mitochondrial neurogastrointestinal encephalopathy; NARP: neuropathy, ataxia, and retinitis pigmentosa; SANDO: sensory ataxia, neuropathy, dysarthria and ophthalmoplegia.

Regulatory Status

No U.S. Food and Drug Administration–cleared genotyping tests were identified. The available commercial genetic tests for epilepsy are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

Medical Policy Statement

The safety and effectiveness of genetic testing to confirm the diagnosis of a specific mitochondrial disorder, or for at-risk female relatives to determine carrier status prior to conception, have been established. It is an effective diagnostic option for patients meeting patient selection criteria.

Genetic testing for mitochondrial disorders using expanded panel testing is considered experimental/investigational.

Inclusionary and Exclusionary Guidelines

(Please refer to policy guidelines below)

Inclusions:
For confirming a diagnosis of a mitochondrial disorder
Both conditions must be met:

- The patient has clinical signs and symptoms consistent with a *specific* mitochondrial disorder, but the diagnosis cannot be made with certainty by clinical and/or biochemical evaluation; AND
- Genetic testing is restricted to the specific variants that have been documented to be pathogenic for the particular mitochondrial disorder being considered.

Genetic testing of at-risk female relatives may be considered established 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 experimental/investigational.

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

Informational 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 variants that are known to be pathogenic for that disorder. Table 1 is a guide to clinical symptoms and particular genetic variants that are associated with particular mitochondrial syndromes.

Panels of variants that are disease-specific, i.e. contain only variants 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 variants 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 are contrasted with the smaller number of genes associated with any particular disorder.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81401 81403 81479

Other codes (investigational, not medically necessary, etc.):

81440 81460 81465

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

MITOCHONDRIAL DISEASES
The clinical validity and utility of testing for mitochondrial diseases for both indications are presented together, focusing discretely on each indication when evaluating clinical usefulness.

Clinical Context and Test Purpose
The purpose of genetic testing in patients who have signs and symptoms of mitochondrial disorders is to confirm diagnosis. Diagnosis of a specific mitochondrial disorder is complex due to the phenotypic heterogeneity and general lack of genotype-phenotype associations, particularly in infants and children. Identifying a disease-causing variant can end the diagnostic odyssey for families, help to avoid muscle biopsy for patients, and provide information needed for testing in asymptomatic family members. While the current treatment for most patients with mitochondrial disease is primarily supportive, potential treatments exist for patients with coenzyme Q_{10} deficiency and mitochondrial neurogastrointestinal encephalopathy, although evidence for their effectiveness is not conclusive.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant populations of interest for both indications are individuals with signs and symptoms of mitochondrial disorders and individuals who are asymptomatic with a close relative with a mitochondrial disorder and a known pathogenic variant.

Interventions
Testing for the individual variants associated with mitochondrial disorders is offered by numerous labs. Genetic panel testing is also available, with numerous panels available. Some are disease-specific panels that include only a small number of genes associated with a particular mitochondrial disorder.

Several labs currently offer panel testing for mitochondrial and nuclear genes associated with multiple mitochondrial disorders by next-generation sequencing (NGS). The number of genes included in these panels varies widely. Examples of panels and the number of genes tested, accessed from websites, are listed in Table 2 although the number of genes on a given panel can change over time. This list is not exhaustive.

Comparators
Standard clinical workup for diagnosis without genetic testing might include measurements of lactate and pyruvate in plasma and cerebrospinal fluid; plasma, urine, and cerebrospinal fluid amino acids; plasma acylcarnitines; and urine organic acids. Additionally, a muscle biopsy has been traditionally considered the criterion standard for diagnosis of mitochondrial disorders.

Outcomes
The general outcomes of interest include test validity, other test performance measures, symptoms, functional outcomes, changes in reproductive decision making, health status measures, and quality of life.

The beneficial outcomes resulting from a true test result are establishing a diagnosis and avoiding muscle biopsy. The harmful outcomes resulting from a false test result are a delay in diagnosis and additional testing.

The timeframe of interest is the time to establish a diagnosis for those who are asymptomatic or to perform preconceptual carrier testing for those with a close relative who has a mitochondrial disease and a known pathogenic variant.

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for mitochondrial disorders, methodologically credible studies were selected using the following principles:

For the evaluation of clinical validity of the tests, studies that meet the following eligibility criteria were considered

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

Clinical Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

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 mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, and there are some studies that include larger numbers of patients with less specific clinical diagnose. 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 (see Table 2).

Table 2. Studies Reporting Diagnostic Yield in Patient With Suspected Mitochondrial Disorders

Study (Year)	Population	N	Genetic Test	Design	Yield, n (%)
Riley et al (2020)[10]	Australian cohort of children with suspected mitochondrial disease	40	Trio GS	• Prospective enrollment • Selection method not reported	• 22 (67.5%) with "causal" variants • 22 (50%) with a "definitive molecular diagnosis" per modified Nijmegen mitochondrial disease severity scale
Nogueira et al (2019)[11]	Children and adults suspected of having mitochondrial disease	146 (including 110 children)	Custom NGS panel of 209 genes followed by Sanger sequencing	• Prospective /retrospective not reported • Selection method not reported	• 16 (11%) with "causative" variants • 20 (14%) with VUS • 54/107 (50%) with defects identified on muscle biopsy
Fang et al (2017)[12]	Children and young adults suspected of having mitrochondrial disease	141	Targeted NGS	Prospective enrollment, selection method not reported	40 (28%) with “causative” variants
Legati et al (2016)[13]	Pts clinically diagnosed with mitochondrial disease	NGS = 125 WES = 10	Custom NGS panel of 132 genes followed by WES for those negative after NGS	Prospective, retrospective not reported; selection method not reported	NGS: • 19 (15%) with “causative” variant • 27 (22%) with possible pathogenic variant WES: • 6 (60%) with “causative” variant •
Pronicka et al (2016)[14]	Pts referred for possible or probable	113 (including 47	WES followed by Sanger sequencing	Prospective, retrospective samples included;	• 67 (59%) with likely pathogenic variant • 30 (64%) of

	mitochondrial disorder	neonates)		consecutive patients included in prospective sample; selection method for retrospective samples not reported	neonates with likely pathogenic variant
Kohda et al (2016)[15]	Children with early onset respiratory chain disease	142	NGS of the entire mtDNA plus WES of the nDNA	Prospective enrollment; selection method not reported	• 29 (20%) with known pathogenic variants • 53 (37%) inconclusive but possibly pathogenic variants
Wortmann et al (2015)[16]	Children and young adults suspected of having mitochondrial disorder	109	Panel of 238 genes associated with mitochondrial disease followed by WES	Prospective enrollment; selection method not reported	• 42 (39%) with pathogenic variant
Ohtake et al (2014)[17]	Pts with mitochondrial respiratory chain disorder	104	NGS of exome of nDNA	Prospective retrospective not reported; selection method not reported	• 18 (17%) with known pathogenic variants • 27 (26%) with likely pathogenic variants
Taylor et al (2014)[18]	Pts with suspected mitochondrial disease and multiple respiratory chain complex defects	53	WES validated with Sanger sequencing	Prospective / retrospective not reported; selection method not reported but only included pts with multiple respiratory chain complex defects	• 28 (53%) with known pathogenic variant • 4 (8%) with likely pathogenic variant
Lieber et al (2013)[19]	Pts with suspected mitochondrial disorders and heterogeneous clinical symptoms	102	NGS of entire mitochondrial genome and 1598 nuclear genes	Prospective / retrospective not reported; pts in a repository having highest clinical suspicion of disease selected	• 22 (22%) with likely pathogenic variants • 26 (25%) VUS
DaRe et al (2013)[20]	Pts with diagnosed or suspected mitochondrial disorders	148	NGS panel of 447 genes (Transgenomic)	Prospective / retrospective not reported; consecutive pts	• 13 (9%) possible pathogenic variant • 67 (45%) with VUS
McCormick et al (2013)[21]	Pts referred for outpt based evaluation of suspected mitochondrial disease	152	mtDNA genome sequencing genome-wide SNV microarray, and step-wise individual sequencing of select nuclear genes	Retrospective chart review; consecutive pts included	• 25 (16%) with “definite” mitochondrial disease • 46 (30%) with “probable” or “possible” mitochondrial disease

Calvo et al (2012)[22]	Infants with clinical and biochemical evidence of oxidative phosphorylation disease	42	NGS of entire mitochondrial genome and 1034 nuclear genes	Prospective / retrospective not reported; selection method not reported	• 10 (24%) with known pathogenic variant • 13 (31%) possible pathogenic variants
Qi et al (2007)[23]	Pts with mitochondrial encephalopathies (MELAS, MERRF, LHON, Leigh syndrome, or an overlap syndrome	552	PCR-PFLP analysis, site specific PCR, and PCR-sequencing methods of common mitochondrial pathogenic variants	Prospective / retrospective not reported; selection method not reported	• 64 (12%) with pathogenic variant

LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF: myoclonic epilepsy with ragged red fibers; mtDNA: mitochondrial DNA; nDNA: nuclear DNA: NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SNV: single-nucleotide variant; VUS: variant of uncertain significance; WES: whole-exome sequencing.

Clinical Specificity

The clinical specificity of genetic testing for mitochondrial disorders is largely unknown, but false positive results have been reported.[24] Some epidemiologic evidence is available on the population prevalence of pathogenic variants, which provides some indirect evidence on the potential for false positive results.

A study of population-based testing reported that the prevalence of pathogenic variants 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 mitochondrial DNA variants thought to be associated with clinical disease.[25] At least one pathogenic mutation was identified in 15 of 3168 people (0.54%; 95% confidence interval, 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.[26] 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 in 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 (VOUS) 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 one study using targeted exome sequencing, variants of uncertain significance were far more common than definite pathogenic variantsvariants.[20] 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 variants. 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 variants known to be pathogenic. Some variants associated with mitochondrial disorders can result in heterogenous 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.[27] However, this same mutation has also been associated with chronic progressive external ophthalmoplegia (CPEO) and LS.[28] Therefore, the more closely the clinical syndrome matches MELAS, the more likely a positive genetic test will represent a pathogenic mutation.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence on clinical utility was identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

There are 2 ways that clinical utility might be demonstrated from a 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 pathogenic variant status may have benefits for family members in determining their risk of developing the disease.

Confirmation of Diagnosis in Individuals With Signs and/or Symptoms of Mitochondrial Disease
For patients with signs and symptoms that are consistent with a defined mitochondrial syndrome, testing can be targeted to those variants 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. Confirmation of the diagnosis by genetic testing can result in reduced need for further testing, especially a muscle biopsy. However, a negative genetic test in blood does not rule out a mitochondrial disorder and should be referred to testing in the affected tissue to avoid the possibility of missing tissue-specific variants or low levels of heteroplasmy in blood.

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. A Cochrane

review updated in 2012 by Pfeffer and coworkers did not find any clear evidence supporting the use of any intervention for the treatment of mitochondrial disorders.[29]

Testing of Asymptomatic Individuals With a Close Relative With a Mitochondrial Disease and a Known Pathogenic Variant

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 mitochondrial DNA 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. For purposes of informing family planning, when a pathogenic variant is detected in the nDNA of prospective parent or in the mtDNA of a prospective mother, the prospective parent could also choose medically assisted reproduction during which preimplantation testing would permit a choice to avoid an affecting offspring. The use of preimplantation testing when a pathogenic variant is identified in the mtDNA of an affected mother are complicated by issues of heteroplasmy of the mtDNA variant, threshold levels, phenotypic expression leading.

Section Summary: Mitochondrial Diseases

Case series and cohort studies have provided information on the diagnostic testing yield. For patients with signs and symptoms of mitochondrial diseases, but without a well-defined clinical syndrome, the variant detection rates differ by the population included testing strategy, and outcome reported. Studies reporting a yield of known pathogenic variants for NGS panels tend to report rates, in the 15% to 25% range. There is very little evidence on clinical specificity, but there have been false-positive tests reported. 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.

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. Studies reporting diagnostic yield for known pathogenic variants using next-generation sequencing panels tend to report rates ranging from 15% to 25%. Clinical specificity is unknown, but population-based studies have reported that the prevalence of certain variants 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 variants 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 influence 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

Mitochondrial Medicine Society

The Mitochondrial Medicine Society published a consensus statement on the diagnosis and management of mitochondrial disease in 2015.[31] Most evidence was grade III or less (case-control, low-quality cohort studies, or expert opinion without explicit critical appraisal) using the Oxford Centre for Evidence-Based Medicine criteria. Consensus recommendations were reported using the Delphi method. A subset of the consensus recommendations for DNA testing are as follows:

1. "Massively parallel sequencing/NGS [next-generation sequencing] 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 variants.
2. 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.

3. 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 variants 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."

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

Ongoing and Unpublished Clinical Trials
A search of clinicaltrials.gov did not reveal any ongoing trials that might influence this review.

Government Regulations

National:
There is no national coverage determination (NCD) for genetic testing for mitochondrial disorders. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers

Local:

A55190, MolDX: Mitochondrial Nuclear Gene Tests, Effective date 10/28/2021
MITOCHONDRIAL disorders are a group of conditions caused by dysfunction in the MITOCHONDRIAL respiratory chain. Current genetic testing methods are unable to detect mutations in all individuals with suspected MITOCHONDRIAL disease, and there is no proven effective treatment for persons with a known MITOCHONDRIAL disease. Therefore, the MolDX Team has determined MITOCHONDRIAL nuclear gene tests do not support the required clinical utility for the established Medicare benefit category and are statutorily excluded tests.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing for Maple Syrup Urine Disease (BCKD Deficiency)
- Genetic Testing for Prader-Willi and Angelman Syndromes (Chromosome 15 Abnormalities)
- Genetic Testing, Including Chromosomal Microarray (CMA) Analysis and Next-Generation Sequencing Panels, for Prenatal Evaluation and the Evaluation of Children with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder
- Genetic Testing-Whole Exome Sequencing

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/15	10/21/14	11/3/14	Joint policy established
3/1/16	12/10/15	12/10/15	Routine maintenance
3/1/17	12/13/16	12/13/16	Routine policy maintenance, updated rationale and references.
3/1/18	12/12/17	12/12/17	Routine policy maintenance. Updated rationale section, added references 7-10, 13-14, 16-18, 20-22 and 30.
3/1/19	12/11/18		Routine policy maintenance, added reference # 10. No change in policy status.
3/1/20	12/17/19		Routine policy maintenance. No change in medical policy.
3/1/21	12/15/20		Updated CMS and clinical trials sections. References 10 and 11 added. No change in policy status.
3/1/22	12/14/21		Routine policy maintenance. No change in medical policy.
3/1/23	12/20/22		Routine policy maintenance, no change in policy status.
3/1/24	12/19/23		Routine policy maintenance, no changes in policy status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR MITOCHONDRIAL DISORDERS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.