



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

*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 establish a genetic diagnosis of a mitochondrial disorder when signs and symptoms of a mitochondrial disorder are present (see Policy Guidelines section) and genetic testing may eliminate the need for muscle biopsy to be **eligible for coverage.\*\***

#### Patient Selection Criteria

Coverage eligibility for genetic testing to establish the diagnosis of a mitochondrial disorder will be considered when EITHER ONE of the following criteria is 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 specific mitochondrial disorder being considered (see Policy Guidelines); OR
- If a mitochondrial disorder is suspected, but the phenotype is nonspecific, broader genetic testing is appropriate under the guidance of a clinical geneticist and genetics counselor.

Based on review of available data, the Company may consider targeted genetic testing for a known familial variant of at-risk relatives as preconceptional carrier testing\*\*\* to be **eligible for coverage.\*\***

#### Patient Selection Criteria

Coverage eligibility for targeted genetic testing of at-risk relatives as part of a preconceptional evaluation will be considered when ALL of the following criteria are met:

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

- There is a defined mitochondrial disorder in the family of sufficient severity to cause impairment of quality of life or functional status; AND
- A variant that is known to be pathogenic for that specific mitochondrial disorder has been identified in the index case.

**\*\*\*Note:** *Coverage for genetic testing maybe provided only if benefits are available in the member's contract/certificate.*

## 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 in all other situations to be **investigational**.\*

The use of genetic testing for mitochondrial disorders when patient selection criteria are not met is considered to be **investigational**.\*

## Policy Guidelines

Mitochondrial disorders can be caused by variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). A 3-generation family history may suggest a mode of inheritance. A family history in which affected women transmit the disease to male and female children and affected men do not transmit the disease to their children suggests the familial variant(s) is in the mtDNA. A family history consistent with Mendelian autosomal dominant or autosomal recessive inheritance or with X-linked inheritance suggests the familial variant(s) is in the nDNA. De novo pathogenic variants are also possible.

## Testing Strategy

### Individuals With a Suspected Mitochondrial Disorder

If the phenotype is highly suggestive of a specific disorder that is supported by the inheritance pattern noted in the family history, it would be reasonable to begin genetic testing with single genes or targeted multigene panels that test for pathogenic variants specific for that disorder.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

If a mitochondrial disorder is suspected, but the phenotype is nonspecific, broader genetic testing is appropriate under the guidance of a clinical geneticist and genetics counselor. For patients in whom the family history is suggestive of a disorder due to pathogenic variant(s) in mtDNA, multigene panels or sequencing of the mitochondrial genome may be appropriate. If multiple mtDNA deletions are noted, or the family history is suggestive of a disorder due to variants in nDNA, then multigene panels covering known nuclear genes associated with mitochondrial disease may be appropriate. Testing using whole exome sequencing is reviewed in medical policy 00389 (Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders).

### **Individuals With a Family Member With a Mitochondrial Disorder and Known Familial Variant**

Targeted testing for a known familial variant in at-risk relatives as part of preconceptional carrier testing is appropriate. At-risk relatives include only female relatives if the familial pathogenic variant is in the mtDNA but includes both male and female relatives if the familial pathogenic variant is in the nDNA.

### **Genetics Nomenclature Update**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

### Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

## Background/Overview

### 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.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

Thirteen genes code for protein subunits of the mitochondrial oxidative phosphorylation complex and the remaining 24 genes are responsible for proteins involved in the translation and/or assembly of the mitochondrial complex. Additionally, there are over 1000 nuclear genes coding 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 (nDNA) in several important ways. Inheritance of mtDNA does not follow traditional Mendelian patterns. Rather, mtDNA is inherited only from maternal DNA so disorders that result from variants 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 nDNA, which contains only one 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 variant ranging from 0% to 100%. Clinical expression of the variant will generally depend on a threshold effect (ie, clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).

### **Mitochondrial diseases**

Primary mitochondrial diseases 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 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 risen 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 diseases is at least 1 in 5000.

Some specific mitochondrial diseases are listed next:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome;
- Myoclonic epilepsy with ragged red fibers syndrome;
- Kearns-Sayre syndrome;
- Leigh syndrome;
- Chronic progressive external ophthalmoplegia;

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

- Leber hereditary optic neuropathy;
- Neurogenic weakness with ataxia and retinitis pigmentosa.

Most of these disorders are characterized by multisystem dysfunction, which generally includes myopathies and neurologic dysfunction and may involve multiple other organs. Each defined mitochondrial disease has a characteristic set of signs or 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 diseases 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 diseases.

A muscle biopsy can be performed if the diagnosis is uncertain after biochemical workup. However, this invasive test is not definitive in all cases. The presence of "ragged red fibers" on histologic analysis is consistent with a mitochondrial disease. Ragged red fibers represent a proliferation of defective mitochondrial. This characteristic finding may not be present in all types of mitochondrial diseases and also may be absent early in the course of disease.

### **Treatment**

Treatment of mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder. Identification of complications such as diabetes 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 empirical 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 untested in clinical trials.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

### Genetic Testing

Mitochondrial diseases can be caused by pathogenic variants in the maternally inherited mtDNA or one of many nDNA genes. Genetic testing for mitochondrial diseases may involve testing for point mutations, deletion and duplication analysis, and/or whole exome sequencing of nuclear or mtDNA. The type of testing done depends on the specific disorder being considered. For some primary mitochondrial diseases such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes and myoclonic epilepsy with ragged red fibers, most variants are point mutations, and there is 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 diseases, such as chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome, the most common variants are deletions, and therefore duplication and 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. A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database. Lists of mtDNA and nDNA genes that may lead to mitochondrial diseases and testing laboratories in the U. S. are provided at Genetic Testing Registry of the National Center for Biotechnology Information website.

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

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	<ul style="list-style-type: none"> <li>Stroke-like episodes at age &lt;40 y</li> <li>Seizures and/or dementia</li> <li>Pigmentary retinopathy</li> <li>Lactic acidosis</li> </ul>	<ul style="list-style-type: none"> <li><i>MT-TL1</i>, <i>MT-ND5</i> (&gt;95%)</li> <li><i>MT-TF</i>, <i>MT-TH</i>, <i>MT-TK</i>, <i>MT-TQ</i>, <i>MT-TS<sub>1</sub></i>, <i>MT-TS<sub>2</sub></i>, <i>MT-ND1</i>, <i>MT-ND6</i> (rare)</li> </ul>
MERFF	<ul style="list-style-type: none"> <li>Myoclonus</li> <li>Seizures</li> </ul>	<ul style="list-style-type: none"> <li><i>MT-TK</i> (&gt;80%)</li> <li><i>MT-TF</i>, <i>MT-TP</i> (rare)</li> </ul>

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

Syndrome	Main Clinical Manifestations	Major Genes Involved
	<ul style="list-style-type: none"> <li>• Cerebellar ataxia</li> <li>• Myopathy</li> </ul>	
CPEO	<ul style="list-style-type: none"> <li>• External ophthalmoplegia</li> <li>• Bilateral ptosis</li> </ul>	<ul style="list-style-type: none"> <li>• Various deletions of mitochondrial DNA</li> </ul>
Kearns-Sayre syndrome	<ul style="list-style-type: none"> <li>• External ophthalmoplegia at age &lt;20 y</li> <li>• Pigmentary retinopathy</li> <li>• Cerebellar ataxia</li> <li>• Heart block</li> </ul>	<ul style="list-style-type: none"> <li>• Various deletions of mitochondrial DNA</li> </ul>
Leigh syndrome	<ul style="list-style-type: none"> <li>• Subacute relapsing encephalo-pathy</li> <li>• Infantile-onset</li> <li>• Cerebellar/brainstem dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>• <i>MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</i></li> <li>• Mitochondrial DNA deletions (rare)</li> <li>• <i>SUCLA2, NDUSFx, NDFVx, SDHA, BCSIL, SURF1, SCO2, COX15</i></li> </ul>
LHON	<ul style="list-style-type: none"> <li>• Painless bilateral visual failure</li> <li>• Male pre-dominance</li> <li>• Dystonia</li> <li>• Cardiac pre-excitation syndromes</li> </ul>	<ul style="list-style-type: none"> <li>• <i>MT-ND1, MT-ND4, MT-ND6</i></li> </ul>
NARP	<ul style="list-style-type: none"> <li>• Peripheral neuropathy</li> <li>• Ataxia</li> </ul>	<ul style="list-style-type: none"> <li>• <i>MT-ATP6</i></li> </ul>

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

Syndrome	Main Clinical Manifestations	Major Genes Involved
	<ul style="list-style-type: none"> <li>• Pigmentary retinopathy</li> </ul>	
MNGIE	<ul style="list-style-type: none"> <li>• Intestinal mal-absorption</li> <li>• Cachexia</li> <li>• External ophthalmoplegia</li> <li>• Neuropathy</li> </ul>	<ul style="list-style-type: none"> <li>• <i>TP</i></li> </ul>
IOSCA	<ul style="list-style-type: none"> <li>• Ataxia</li> <li>• Hypotonia</li> <li>• Athetosis</li> <li>• Ophthalmoplegia</li> <li>• Seizures</li> </ul>	<ul style="list-style-type: none"> <li>• <i>TWINKLE</i></li> </ul>
SANDO	<ul style="list-style-type: none"> <li>• Ataxic neuropathy</li> <li>• Dysarthria</li> <li>• Ophthalmoparesis</li> </ul>	<ul style="list-style-type: none"> <li>• <i>POLG</i></li> </ul>
Alpers syndrome	<ul style="list-style-type: none"> <li>• Intractable epilepsy</li> <li>• Psychomotor regression</li> <li>• Liver disease</li> </ul>	<ul style="list-style-type: none"> <li>• <i>POLG, DGUOK, MPV17</i></li> </ul>
GRACILE	<ul style="list-style-type: none"> <li>• Growth retardation</li> <li>• Aminoaciduria</li> <li>• Cholestasis</li> <li>• Iron overload</li> <li>• Lactic acidosis</li> </ul>	<ul style="list-style-type: none"> <li>• <i>NDUSF<sub>x</sub></i></li> </ul>
Coenzyme Q <sub>10</sub> deficiency	<ul style="list-style-type: none"> <li>• Encephalopathy</li> </ul>	<ul style="list-style-type: none"> <li>• <i>COQ2</i></li> <li>• <i>COQ9</i></li> </ul>

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

Syndrome	Main Clinical Manifestations	Major Genes Involved
	<ul style="list-style-type: none"> <li>• Steroid-resistant nephrotic syndrome</li> <li>• Hypertrophic cardiomyopathy</li> <li>• Retinopathy</li> <li>• Hearing loss</li> </ul>	<ul style="list-style-type: none"> <li>• <i>CACCI</i></li> <li>• <i>ETFDH</i></li> </ul>

Adapted from Chinnery et al (2014) and Angelini et al (2009).

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.

## **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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for mitochondrial diseases is under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

## **Rationale/Source**

Mitochondrial diseases are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes involved in oxidative metabolism. There are many related but distinct syndromes and some patients have overlapping syndromes. As a result, these disorders can be difficult to diagnose. Genetic testing has the potential to improve the accuracy of diagnosis for mitochondrial

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

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

For individuals who have signs and/or symptoms of a mitochondrial disease who receive genetic testing, the evidence includes case series and cohort studies. The relevant outcomes are test validity, other test performance measures, symptoms, functional outcomes, health status measures, and quality of life. There is some evidence on clinical validity that varies by the patient population and testing strategy. 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 indicated that the prevalence of certain variants exceeds the prevalence of clinical disease, suggesting that the variant will be found in some people without the clinical disease (false-positives). Clinical utility is relatively high for confirming the diagnosis of mitochondrial diseases in people who have signs and symptoms of the disease. In these patients, a positive result in genetic testing can avoid a muscle biopsy and eliminate the need for further clinical workup. The evidence is sufficient to determine 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 disease and a known pathogenic variant and who receive targeted familial variant testing, the evidence includes case series and cohort studies. The relevant outcomes are test validity, other test performance measures, changes in reproductive decision making, symptoms, functional outcomes, health status measures, and quality of life. Clinical validity is expected to be high for targeted testing of a known familial variant, assuming sufficient analytic validity. Clinical utility can be demonstrated by testing at-risk family members who have a close relative with a pathogenic variant. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

## **Supplemental Information**

### **Practice Guidelines and Position Statements**

#### **Foundation for Mitochondrial Medicine**

The Foundation for Mitochondrial Medicine (2013) published an overview of mitochondrial disease; genetic testing was specifically addressed. The overview included the following statements:

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

#### **Mitochondrial Medicine Society**

The Mitochondrial Medicine Society (2015) published a consensus statement on the diagnosis and management of mitochondrial disease. Most evidence was grade III or less (case-control, low-quality cohort studies, or expert opinion without an 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 [mitochondrial DNA] genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.
2. 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

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered."

### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

### **Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### **Ongoing and Unpublished Clinical Trials**

A search of [ClinicalTrials.gov](http://ClinicalTrials.gov) in May 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

## **References**

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for Mitochondrial Disorders", 2.04.117, July 2019.
2. Schon EA, DiMauro S, Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. *Nat Rev Genet.* Dec 2012;13(12):878-890. PMID 23154810.
3. Wong LJ. Diagnostic challenges of mitochondrial DNA disorders. *Mitochondrion.* Feb-Apr 2007;7(1-2):45-52. PMID 17276740.
4. DiMauro S, Schon EA. Mitochondrial DNA mutations in human disease. *Am J Med Genet.* Spring 2001;106(1):18-26. PMID 11579421.
5. Falk MJ, Sondheimer N. Mitochondrial genetic diseases. *Curr Opin Pediatr.* Dec 2010;22(6):711-716. PMID 21045694.
6. Chinnery PF. Mitochondrial Disorders Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2014.
7. Chinnery P, Majamaa K, Turnbull D, et al. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev.* Jan 25 2006(1):CD004426. PMID 16437486.
8. Angelini C, Bello L, Spinazzi M, et al. Mitochondrial disorders of the nuclear genome. *Acta Myol.* Jul 2009;28(1):16-23. PMID 19772191.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

9. FOSWIKI. MITOMAP: a human mitochondrial genome database. 2018; <https://www.mitomap.org//MITOMAP>.
10. National Center for Biotechnology Information. GTR: Genetic Testing Registry. n.d.; <https://www.ncbi.nlm.nih.gov/gtr/>.
11. Fang F, Liu Z, Fang H, et al. The clinical and genetic characteristics in children with mitochondrial disease in China. *Sci China Life Sci.* Jul 2017;60(7):746-757. PMID 28639102.
12. Legati A, Reyes A, Nasca A, et al. New genes and pathomechanisms in mitochondrial disorders unraveled by NGS technologies. *Biochim Biophys Acta.* Aug 2016;1857(8):1326-1335. PMID 26968897.
13. Pronicka E, Piekutowska-Abramczuk D, Ciara E, et al. New perspective in diagnostics of mitochondrial disorders: two years' experience with whole-exome sequencing at a national paediatric centre. *J Transl Med.* Jun 12 2016;14(1):174. PMID 27290639.
14. Kohda M, Tokuzawa Y, Kishita Y, et al. A comprehensive genomic analysis reveals the genetic landscape of mitochondrial respiratory chain complex deficiencies. *PLoS Genet.* Jan 2016;12(1):e1005679. PMID 26741492.
15. Wortmann SB, Koolen DA, Smeitink JA, et al. Whole exome sequencing of suspected mitochondrial patients in clinical practice. *J Inherit Metab Dis.* May 2015;38(3):437-443. PMID 25735936.
16. Ohtake A, Murayama K, Mori M, et al. Diagnosis and molecular basis of mitochondrial respiratory chain disorders: exome sequencing for disease gene identification. *Biochim Biophys Acta.* Apr 2014;1840(4):1355-1359. PMID 24462578.
17. Taylor RW, Pyle A, Griffin H, et al. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. *JAMA.* Jul 2 2014;312(1):68-77. PMID 25058219.
18. Lieber DS, Calvo SE, Shanahan K, et al. Targeted exome sequencing of suspected mitochondrial disorders. *Neurology.* May 7 2013;80(19):1762-1770. PMID 23596069.
19. DaRe JT, Vasta V, Penn J, et al. Targeted exome sequencing for mitochondrial disorders reveals high genetic heterogeneity. *BMC Med Genet.* Nov 11 2013;14:118. PMID 24215330.
20. McCormick E, Place E, Falk MJ. Molecular genetic testing for mitochondrial disease: from one generation to the next. *Neurotherapeutics.* Apr 2013;10(2):251-261. PMID 23269497.
21. Calvo SE, Compton AG, Hershman SG, et al. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. *Sci Transl Med.* Jan 25 2012;4(118):118ra110. PMID 22277967.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

22. Qi Y, Zhang Y, Wang Z, et al. Screening of common mitochondrial mutations in Chinese patients with mitochondrial encephalomyopathies. *Mitochondrion*. Feb-Apr 2007;7(1-2):147-150. PMID 17276742.
23. Deschauer M, Krasnianski A, Zierz S, et al. False-positive diagnosis of a single, large-scale mitochondrial DNA deletion by Southern blot analysis: the role of neutral polymorphisms. *Genet Test*. Winter 2004;8(4):395-399. PMID 15684869.
24. Elliott HR, Samuels DC, Eden JA, et al. Pathogenic mitochondrial DNA mutations are common in the general population. *Am J Hum Genet*. Aug 2008;83(2):254-260. PMID 18674747.
25. Majamaa K, Moilanen JS, Uimonen S, et al. Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes: prevalence of the mutation in an adult population. *Am J Hum Genet*. Aug 1998;63(2):447-454. PMID 9683591.
26. DiMauro S, Hirano M. Melas. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2013.
27. Jean-Francois MJ, Lertrit P, Berkovic SF, et al. Heterogeneity in the phenotypic expression of the mutation in the mitochondrial tRNA(Leu) (UUR) gene generally associated with the MELAS subset of mitochondrial encephalomyopathies. *Aust N Z J Med*. Apr 1994;24(2):188-193. PMID 8042948.
28. Foundation for Mitochondrial Medicine. *Mitochondrial Disease: Overview of Mitochondrial Disease*. n.d.;  
<http://mitochondrialdiseases.org/mitochondrial-disease/>  
 and <http://mitochondrialdiseases.org/mitochondrial-disease/diagnosis-and-treatments/>.
29. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med*. Sep 2015;17(9):689-701. PMID 25503498.

## **Policy History**

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

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.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

- 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
- 09/07/2017 Medical Policy Committee review
- 09/20/2017 Medical Policy Implementation Committee approval. Policy revised with updated genetics nomenclature. Policy statements revised so that genetic testing is no longer restricted to a set of specific mutations documented for a particular mitochondrial disorder. Removed the investigational statement for the use of genetic testing for mitochondrial disorders using expanded panel testing.
- 09/06/2018 Medical Policy Committee review
- 09/19/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 09/05/2019 Medical Policy Committee review
- 09/11/2019 Medical Policy Implementation Committee approval. Revisions made to the eligible for coverage statements to track BCBSA. First statement revised to read: “genetic testing to establish a genetic diagnosis of a mitochondrial disorder when signs and symptoms of a mitochondrial disorder are present and genetic testing may eliminate the need for muscle biopsy may be eligible for coverage.” Correct insertion of term “preconceptional carrier testing” made to the second eligible for coverage statement. Added a “Note” that coverage for genetic testing maybe provided only if benefits are available in the member’s contract/certificate.
- 09/03/2020 Medical Policy Committee review
- 09/09/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 09/22/2020 Coding update
- Next Scheduled Review Date: 09/2021

## 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 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of*

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

*descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

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:

Code Type	Code
CPT	81401, 81403, 81405, 81406, 81440, 81460, 81465, 81479 Add codes eff 10/1/2020: 0214U, 0215U
HCPCS	No codes
ICD-10 Diagnosis	E88.40-E88.49, F84.2, G31.81-G31.82, H49.811-H49.819, H50.89

\*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. Food and Drug Administration (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

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

- 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 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:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Genetic Testing for Mitochondrial Disorders

Policy # 00435

Original Effective Date: 07/16/2014

Current Effective Date: 10/12/2020

**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.

©2020 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.