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Medical Policy Manual Genetic Testing, Policy No. 54

Genetic Testing for Primary Mitochondrial Disorders

Effective: March 1, 2022

Next Review: January 2023
Last Review: January 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Primary mitochondrial disorders are caused by variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) that directly affect the function of the oxidative phosphorylation complex in mitochondria. They often manifest as progressive, multisystem disorders. There are currently no effective treatments for mitochondrial disorders, but genetic testing may allow patients to avoid more invasive laboratory testing and provide information for reproductive decision-making.

MEDICAL POLICY CRITERIA

Notes: This policy applies only to diagnostic testing for primary mitochondrial disorders (see Policy Guidelines). It does not apply to reproductive carrier screening of asymptomatic individuals or testing for other disorders that affect mitochondria, such as fatty acid oxidation disorders (see Cross References).

I. Genetic testing for the diagnosis of primary mitochondrial disorders (see Policy Guidelines), including single-gene testing, panel testing and/or whole mitochondrial genome sequencing, may be considered **medically necessary** when all of the following Criteria are met:

A. Signs and symptoms of a primary mitochondrial disorder are present (see Policy Guidelines); and

B. One of the following is met:

1. A clinical diagnosis cannot be made without additional testing, and a muscle or liver biopsy has not been performed; or

2. A genetic diagnosis may be informative for reproductive planning purposes.

II. Genetic testing for diagnosis of primary mitochondrial disorders is considered **investigational** when Criterion I. is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

EXAMPLES OF PRIMARY MITOCHONDRIAL DISORDERS

(Not all-inclusive)

- Alpers (aka Alpers-Huttenlocher) syndrome
- Barth syndrome
- Chronic progressive external ophthalmoplegia (CPEO)
- Coenzyme Q_{10} deficiency
- Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE) syndrome
- Infantile-onset spinocerebellar ataxia (IOSCA)
- Kearns-Sayre syndrome
- Leber hereditary optic neuropathy (LHON)
- Leigh syndrome
- Maternally inherited deafness and diabetes (MIDD)
- Mitochondrial DNA depletion syndrome; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
- Mitochondrial recessive ataxia syndrome (MIRAS)
- Myoclonus epilepsy with ragged red fibers (MERFF)
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- Pearson syndrome
- Sensory ataxia neuropathy, dysarthria, ophthalmoplegia (SANDO)

SIGNS AND SYMPTOMS

Primary mitochondrial disorders can have a variety of presentations, depending on the molecular cause. They are often multisystem disorders, and may include (not all-inclusive):

- skeletal muscle myopathy
- cardiomyopathy
- encephalopathy
- ophthalmoplegia
- neuropathy

- hypotonia/muscle weakness
- seizures
- developmental delay
- ataxia
- deafness
- short stature

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any specific signs and symptoms and/or relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

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 involved in the translation and/or assembly of the mitochondrial complex.[1] Additionally, there are over 1000 nuclear genes coding 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 (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 (i.e., clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).[3]

PRIMARY MITOCHONDRIAL DISORDERS

Primary mitochondrial disorders arise from dysfunction of the mitochondrial electron transport chain (ETC). The ETC 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.

Table 1 (below) lists some of the more common primary mitochondrial disorders. 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.

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.[1 4]

Diagnosis

The diagnosis of primary 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 any particular syndrome.[5] Biochemical testing is indicated for patients who do not have a clear clinical diagnosis of a 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.[2]

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 mitochondria.[1] This characteristic finding may not be present in all types of mitochondrial diseases and also may be absent early in the course of disease.[2]

Treatment

Treatment of primary mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder.[5] Identification of complications such as diabetes 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 empirical 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 untested in clinical trials.

Genetic Testing

Primary 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 single nucleotide variants, 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 (MELAS) and myoclonic epilepsy with ragged red fibers (MERFF), most variants are single nucleotide variants, 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.[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 diseases and testing laboratories in the U.S. are provided at Genetic Testing Registry of the National Center for Biotechnology Information website.[9]

Table 1. Examples of Mitochondrial Diseases, Clinical Manifestations, and Associated Pathogenic Genes (not all inclusive)

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-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 mitochondrial DNA
Kearns-Sayre syndrome	• External ophthalmoplegia at age <20 y • Pigmentary retinopathy • Cerebellar ataxia • Heart block	• Various deletions of mitochondrial DNA
Leigh syndrome	• Subacute relapsing encephalopathy • Infantile-onset • Cerebellar/brainstem 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* • *Mitochondrial DNA 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*

Syndrome	Main Clinical Manifestations	Major Genes Involved
NARP	• Peripheral neuropathy • Ataxia • Pigmentary retinopathy	• *MT-ATP6*
MNGIE	• Intestinal malabsorption • Cachexia • External ophthalmoplegia • Neuropathy	• *TP*
IOSCA	• Ataxia • Hypotonia • Athetosis • Ophthalmoplegia • Seizures	• *TWINKLE*
SANDO	• Ataxic neuropathy • Dysarthria • Ophthalmoparesis	• *POLG*
Alpers syndrome	• Intractable epilepsy • Psychomotor regression • Liver disease	• *POLG, DGUOK, MPV17*
GRACILE	• Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis	• *NDUSFx*
Coenzyme Q_{10} deficiency	• Encephalopathy • Steroid-resistant nephrotic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss	• *COQ2* • *COQ9* • *CABC1* • *ETFDH*

Adapted from Chinnery (2014)5, and Angelini (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 with 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.

EVIDENCE SUMMARY

The purpose of genetic testing in patients who have signs and symptoms of mitochondrial diseases is to confirm the diagnosis. Diagnosis of a specific mitochondrial disease 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 and help to avoid muscle (or in some cases, liver) biopsy for patients. 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.

CLINICAL VALIDITY

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).

The evidence on the clinical sensitivity and specificity of genetic testing for mitochondrial diseases is limited. There are some small case series of patients with a well-defined syndrome such as MELAS syndrome, and some studies include larger numbers of patients with less specific clinical diagnoses. There are wide variations in reported testing yields, probably reflecting the selection process used to evaluate patients for testing.

Several series of patients with mixed diagnoses or suspected mitochondrial diseases have been published. In these studies, the variant detection rate (or yield) may or may not be an accurate estimate of clinical sensitivity, because the proportion of patients with a mitochondrial disease is uncertain (see Table 2).

Table 2. Studies Reporting Diagnostic Yield for Suspected Mitochondrial Diseases

Study	Population	N	Genetic Test	Design	Yield, n (5)
Riley (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 (2019)[11]	Children and adults suspected of having mitochondrial disease	146	Panel of 209 genes	• 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 (2017)[12]	Children and young adults suspected of having mitochondrial disease	141	Targeted panel	• Prospective enrollment • Selection method not reported	• 40 (28%) with "causative" variants
Legati (2016)[13]	Patients clinically diagnosed with mitochondrial disease	NGS: 125 WES: 10	Custom panel of 132 genes, WES for those negative	• Prospective/ retrospective not reported • Selection method not reported	*NGS:* • 19 (15%) with "causative" variants • 27 (22%) with possible pathogenic variants *WES:* • 6 (60%) with "causative" variants
Pronicka (2016)[14]	Patients referred for possible or probable	113	WES followed by SS	• Prospective /retrospective samples included;	• 67 (59%) with likely pathogenic variants

Study	Population	N	Genetic Test	Design	Yield, n (5)
	mitochondrial disease			consecutive patients included in prospective sample • Selection method for retrospective samples not reported	• 30 (64%) of neonates with likely pathogenic variants
Kohda (2016)[15]	Children with early-onset respiratory chain disease	142	mtWGS 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 (2015)[16]	Children and young adults with a suspected mitochondrial disease	109	Panel of 238 genes followed by WES	• Prospective enrollment • Selection method not reported	• 42 (39%) with pathogenic variants
Ohtake (2014)[17]	Patients with mitochondrial respiratory chain diseases	104	WES of the nDNA	• Prospective/ retrospective not reported • Selection method not reported	• 18 (17%) with known pathogenic variants • 27 (26%) with likely pathogenic variants
Taylor (2014)[18]	Patients with suspected mitochondrial disease and multiple respiratory chain complex defects	53	WES validated with SS	• Prospective/ retrospective not reported; selection method not reported but only included patients with multiple respiratory chain complex defects	• 28 (53%) with known pathogenic variants • 4 (8%) with likely pathogenic variants
Lieber (2013)[19]	Patients with suspected mitochondrial diseases and heterogeneous clinical symptoms	102	mtWGS and 1,598 nuclear genes	• Prospective/ retrospective not reported • Patients in a repository having highest clinical suspicion of disease selected	• 22 (22%) with likely pathogenic variants • 26 (25%) VUS
DaRe (2013)[20]	Patients with diagnosed or	148	Panel of 447 genes	• Prospective /retrospective	• 13 (9%) possible pathogenic variants

Study	Population	N	Genetic Test	Design	Yield, n (5)
	suspected mitochondrial diseases			not reported; consecutive patients	• 67 (45%) with VUS
McCormick (2013)[21]	Patients with suspected mitochondrial disease	152	mtWGS, array, SS	• Retrospective chart review; consecutive patients included	• 25 (16%) with "definite" mitochondrial disease • 46 (30%) with "probable" or "possible" mitochondrial disease
Calvo (2012)[22]	Infants with clinical and biochemical evidence of oxidative phosphorylation disease	42	mtWGS and 1034 nuclear genes	• Prospective/ retrospective not reported • Selection method not reported	• 10 (24%) with known pathogenic variants • 13 (31%) possible pathogenic variants
Qi (2007)[23]	Patients with mitochondrial encephalopathies (MELAS, MERRF, Leigh syndrome, LHON, or an overlap syndrome)	552	PCR-RFLP analysis, PCR	• Prospective/ retrospective not reported • Selection method not reported	• 64 (12%) with pathogenic variants

GS: genome sequencing; 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; VUS: variant of uncertain significance; WES: whole-exome sequencing; mtWGS: whole mitochondrial genome sequencing; SS: Sanger sequencing.

The clinical specificity of genetic testing for mitochondrial diseases 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.

Elliott (2008) published a study of population-based testing reported that the prevalence of pathogenic variants is higher than the prevalence of clinical disease.[25] In this study, 3,168 consecutive newborns were tested for the presence of one or more of the 10 most common mtDNA variants thought to be associated with clinical disease. At least one pathogenic variant was identified in 15 (0.54%) of 3,168 people (95% confidence interval 0.30% to 0.89%). This finding implies that there are many more people with a variant who are asymptomatic than there are people with clinical disease, and this raises the possibility of false-positive results on genetic testing.

An earlier population-based study by Majamaa (1998) evaluated the prevalence of the nucleotide 3,243 variant 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 variant. The population prevalence was estimated at 16.3 (0.16%) in 100,000. This study might have underestimated the prevalence because patients who screened negative were not tested for the variant.

In addition to false-positive results, there are variants of uncertain significance detected in substantial numbers of patients. The number of variants increases when NGS methods are used to examine a larger portion of the genome. In a study by DaRe (2013), which used targeted exome sequencing, variants of uncertain significance (VUS) were far more common than definite pathogenic variants.[20] In that study, 148 patients with suspected or confirmed mitochondrial diseases were tested using a genetic panel that included 447 genes. Thirteen patients were found to have pathogenic variants. In contrast, VUS 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 diseases can result in heterogeneous clinical phenotypes, and this may cause uncertainty about the pathogenicity of the variant detected. For example, the nucleotide 3,243 variant in the *MT-TL1* gene is found in most patients with clinically defined MELAS syndrome.[27] This same variant has also been associated with chronic progressive external ophthalmoplegia and Leigh syndrome.[28] Therefore, the more closely the clinical syndrome matches MELAS, the more likely a positive genetic test will represent a pathogenic variant.

CLINICAL UTILITY

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 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.

There are two 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 individuals in determining their risk of passing on the disorder to offspring.

Confirmation of Diagnosis in Individuals with Signs and/or Symptoms of a Mitochondrial Disease

For patients with signs and symptoms consistent with a defined mitochondrial syndrome, testing can be targeted to those pathogenic variants associated with that particular syndrome. In the presence of a clinical picture consistent with the syndrome, the presence of a known pathogenic variant will confirm the diagnosis with a high degree of certainty. Confirmation of the diagnosis by genetic testing can result in a reduced need for further testing, especially a muscle biopsy. However, a negative genetic test in the blood does not rule out a mitochondrial disease and should be reflexed 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 diseases. Treatment is largely supportive management for complications of the disease. It is possible that confirmation of the diagnosis by genetic testing would lead to management changes, such as increased surveillance for

complications of the 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 by Pfeffer (2012) did not find any clear evidence supporting the use of any intervention for the treatment of mitochondrial disorders.[29]

Reproductive Testing

When there is a disease of moderate severity or higher, it is reasonable to assume that many patients will consider the results of testing in reproductive decision-making. For purposes of informing family planning, when a pathogenic variant is detected in the nDNA of a prospective parent or in the mtDNA of a prospective mother, the prospective parent can choose to refrain from having children. If the variant is in the nDNA, the prospective parent could also choose medically-assisted reproduction during which pre-implantation testing would permit a choice to avoid an affected offspring. The use of pre-implantation testing when a pathogenic variant is identified in the mtDNA of an affected mother is complicated by issues of heteroplasmy of the mtDNA variant, threshold levels, and phenotypic expression leading.

PRACTICE GUIDELINE SUMMARY

MITOCHONDRIAL MEDICINE SOCIETY

The Mitochondrial Medicine Society (2015) published a consensus statement on the diagnosis and management of mitochondrial disease.[30] 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 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."

SUMMARY

There is enough research to show that diagnostic genetic testing for primary mitochondrial diseases can improve health outcomes for certain patients. Primary mitochondrial diseases are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes involved in oxidative metabolism. Although there are no specific treatments for these disorders, they can be difficult to diagnose, and genetic testing may allow patients to avoid more invasive muscle or liver biopsies. Genetic testing also has the potential to inform reproductive testing and decision-making. Therefore, diagnostic genetic testing may be considered medically necessary when policy criteria are met.

There is not enough research to show that genetic testing to diagnose primary mitochondrial disorders can improve health outcomes for patients that do not meet the policy criteria. There is no specific therapy for mitochondrial diseases. Treatment is largely supportive management for complications of the disease. It is possible that confirmation of the diagnosis by genetic testing would lead to management changes, such as increased surveillance for complications of the disease and/or the prescription of exercise therapy or antioxidants. However, the impact of these management changes on health outcomes is not known. Therefore, this testing is considered investigational when policy criteria are not met.

REFERENCES

1. Schon EA, DiMauro S,Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. *Nat Rev Genet.* 2012;13:878-90. PMID: 23154810
2. Wong LJ. Diagnostic challenges of mitochondrial DNA disorders. *Mitochondrion.* 2007;7:45-52. PMID: 17276740
3. DiMauro S,Schon EA. Mitochondrial DNA mutations in human disease. *Am J Med Genet.* 2001;106:18-26. PMID: 11579421
4. Falk MJ,Sondheimer N. Mitochondrial genetic diseases. *Current opinion in pediatrics.* 2010;22(6):711-6. PMID: 21045694
5. Chinnery PF. Mitochondrial Disorders Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2014.
6. Chinnery P, Majamaa K, Turnbull D, et al. Treatment for mitochondrial disorders. *The Cochrane database of systematic reviews.* 2006(1):CD004426. PMID: 16437486
7. Angelini C, Bello L, Spinazzi M, et al. Mitochondrial disorders of the nuclear genome. *Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology.* 2009;28(1):16-23. PMID: 19772191
8. FOSWIKI. MITOMAP: a human mitochondrial genome database. 2018. Secondary FOSWIKI. MITOMAP: a human mitochondrial genome database. 2018 [cited 1/19/2022]. 'Available from:' https://www.mitomap.org//MITOMAP.
9. National Center for Biotechnology Information. GTR: Genetic Testing Registry. n.d. Secondary National Center for Biotechnology Information. GTR: Genetic Testing Registry. n.d. [cited 1/19/2022]. 'Available from:' https://www.ncbi.nlm.nih.gov/gtr/.
10. Riley LG, Cowley MJ, Gayevskiy V, et al. The diagnostic utility of genome sequencing in a pediatric cohort with suspected mitochondrial disease. *Genet Med.* 2020;22:1254-61. PMID: 32313153

11. Nogueira C, Silva L, Pereira C, et al. Targeted next generation sequencing identifies novel pathogenic variants and provides molecular diagnoses in a cohort of pediatric and adult patients with unexplained mitochondrial dysfunction. *Mitochondrion.* 2019;47:309-17. PMID: 30831263
12. Fang F, Liu Z, Fang H, et al. The clinical and genetic characteristics in children with mitochondrial disease in China. *Sci China Life Sci.* 2017;60:746-57. PMID: 28639102
13. Legati A, Reyes A, Nasca A, et al. New genes and pathomechanisms in mitochondrial disorders unraveled by NGS technologies. *Biochimica et biophysica acta.* 2016;1857(8):1326-35. PMID: 26968897
14. 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.* 2016;14:174. PMID: 27290639
15. Kohda M, Tokuzawa Y, Kishita Y, et al. A Comprehensive Genomic Analysis Reveals the Genetic Landscape of Mitochondrial Respiratory Chain Complex Deficiencies. *PLoS Genet.* 2016;12:e1005679. PMID: 26741492
16. Wortmann SB, Koolen DA, Smeitink JA, et al. Whole exome sequencing of suspected mitochondrial patients in clinical practice. *Journal of inherited metabolic disease.* 2015;38(3):437-43. PMID: 25735936
17. Ohtake A, Murayama K, Mori M, et al. Diagnosis and molecular basis of mitochondrial respiratory chain disorders: exome sequencing for disease gene identification. *Biochimica et biophysica acta.* 2014;1840(4):1355-9. PMID: 24462578
18. 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.* 2014;312:68-77. PMID: 25058219
19. Lieber DS, Calvo SE, Shanahan K, et al. Targeted exome sequencing of suspected mitochondrial disorders. *Neurology.* 2013;80:1762-70. PMID: 23596069
20. DaRe JT, Vasta V, Penn J, et al. Targeted exome sequencing for mitochondrial disorders reveals high genetic heterogeneity. *BMC Med Genet.* 2013;14:118. PMID: 24215330
21. McCormick E, Place E,Falk MJ. Molecular genetic testing for mitochondrial disease: from one generation to the next. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics.* 2013;10(2):251-61. PMID: 23269497
22. Calvo SE, Compton AG, Hershman SG, et al. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. *Sci Transl Med.* 2012;4:118ra10. PMID: 22277967
23. Qi Y, Zhang Y, Wang Z, et al. Screening of common mitochondrial mutations in Chinese patients with mitochondrial encephalomyopathies. *Mitochondrion.* 2007;7:147-50. PMID: 17276742
24. 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. *Genetic testing.* 2004;8(4):395-9. PMID: 15684869
25. Elliott HR, Samuels DC, Eden JA, et al. Pathogenic mitochondrial DNA mutations are common in the general population. *Am J Hum Genet.* 2008;83:254-60. PMID: 18674747
26. 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.* 1998;63:447-54. PMID: 9683591
27. DiMauro S, Hirano M. Melas. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2013.

28. 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. *Australian and New Zealand journal of medicine.* 1994;24(2):188-93. PMID: 8042948
29. Pfeffer G, Majamaa K, Turnbull DM, et al. Treatment for mitochondrial disorders. *The Cochrane database of systematic reviews.* 2012(4):CD004426. PMID: 22513923
30. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med.* 2015;17:689-701. PMID: 25503498

CODES

Codes	Number	Description
CPT	81401	Molecular Path Level 2: includes the following genes: MT-TS1, MT-RNR1, MT-ATP6, MT-ND4, MT-ND6, MT-ND5, MT-TL1, MT-TS1, MT-RNR1
	81403	Molecular Path Level 4: includes the following genes: MT-RNR1, MT-TS1
	81404	Molecular Path Level 5: includes the following genes: C10orf2, MPV17, NDUFA1, NDUFAF2, NDUFS4, SCO2, SLC25A4 , TACO1
	81405	Molecular Path Level 6: includes the following genes: BCS1L, COX10, COX15, DGUOK, MPV17, NDUFV1, RRM2B, SCO1, SURF1, TK2 , TYMP
	81406	Molecular Path Level 7: includes the following genes: FASTKD2, NDUFS1, SDHA
	81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
	81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
	81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
HCPCS	None	

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