

Policy: MP356

Section: Medical Policy

Subject: Genetic Testing for Mitochondrial Disorders

Applicable Lines of Business

Commercial	X	CHIP	X
Medicare	X	ACA	X
Medicaid	X		

I. Policy: Genetic Testing for Mitochondrial Disorders

II. Purpose/Objective:

To provide a policy of coverage regarding Genetic Testing for Mitochondrial Disorders

III. Responsibility:

- A. Medical Directors
- B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.

- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

DESCRIPTION:

Mitochondrial disorders may be caused by mutation of a mitochondrial DNA (mtDNA) gene or mutation of a nuclear gene (nDNA).

Mitochondrial dysfunction should be considered in the differential diagnosis of any progressive multisystem disorder. A full evaluation for a mitochondrial disorder is often warranted in individuals with a complex neurologic picture or a single neurologic manifestation and other system involvement. Mitochondrial disorders can affect most organ systems, but a particular emphasis on the neuromuscular system and cardiovascular system is important.

Determining the molecular etiology of primary mitochondrial disease in an affected individual can be particularly challenging given the extensive heterogeneity of clinical symptoms, poorly understood genotype-phenotype correlations, and non-specific nature of many symptoms with significant clinical overlap for other conditions.

Inconsistencies exist among clinical diagnostic laboratories in the pathogenicity interpretation and reporting of mtDNA variants, as a potentially disease-causing mtDNA variant may be reported as pathogenic by one laboratory but benign by another due to differing variant classification algorithms or practices, therefore the rationale for testing once per lifetime does not apply to mitochondrial DNA. Benign variants may not be reported at one laboratory generating a negative report, so prior negative testing is not an exclusionary criterion for this testing.

Mitochondria diseases can present across the lifespan, as such, there are no age restrictions on this testing given the potential impact on symptom management, prognosis, and heritability.

CRITERIA FOR COVERAGE: REQUIRES PRIOR AUTHORIZATION BY A PLAN MEDICAL DIRECTOR OR DESIGNEE

Genetic testing (whole mtDNA sequencing and deletion/duplication analysis) for mitochondrial disorders (e.g, Alpers' syndrome; Leigh syndrome; Leber's hereditary optic neuropathy (LHON); mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS); Myoclonic Epilepsy and Ragged-Red Fibers (MERRF); Chronic Progressive External Ophthalmoplegia (CPEO); Kearns-Sayre syndrome) will be considered medically necessary when the following criteria are met:

- Genetic counseling by a qualified professional has been completed; **and**
- Whole mtDNA testing has either not been performed **OR** mtDNA results from a different laboratory indicate a negative or uninformative result.
- Member's clinical presentation does not fit a well-described mendelian disorder or genetic syndrome for which single-gene or targeted nDNA panel testing is available; **or**

AND

Any one of the following criteria are met:

- Member is being concurrently tested through whole exome sequencing; **or**
- Member has one or more of the following clinical features: progressive wasting, milestone regression, ataxia, encephalopathy, seizures, developmental regression, lactic acidosis, and stroke-like episodes (MELAS), pigmentary retinopathy (NARP), mitochondrial myopathy, diabetes mellitus, sensorineural hearing loss or bilateral deafness, early-onset peripheral neuropathy, optic neuropathy, optic atrophy, ophthalmoplegia, ptosis, cardiomyopathy, heart block; **or**
- Family history is strongly suggestive mitochondrial inheritance (e.g. paternal transmission has been ruled out); or
- A mtDNA variant has been reported in a maternal blood relative.

EXCLUSIONS:

Requests for mitochondrial DNA sequencing and deletion/duplication analysis not meeting the criteria outlined above will be considered **unproven** and therefore **NOT COVERED**.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

CODING ASSOCIATED WITH:

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.

- 81440 Nuclear encoded mitochondrial genes (e.g., 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 Sequencing
- 81465 Whole Mitochondrial Genome Deletion/Duplication Analysis
- 0417U Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear-encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification and categorization of mitochondrial disorder-associated genetic variants

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LINE OF BUSINESS:

Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

REFERENCES:

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Calvo SE, Compton AG, Hershman SG, et al. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. *Sci Transl Med*. 2012; 4(118):118ra10

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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.

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This policy will be revised as necessary and reviewed no less than annually.

Devised: 3/22

Revised: 3/23 (Revise criteria); 4/24 (Revise criteria)

Reviewed:

CMS UM Oversight Committee Approval: 12/23, 7/24

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.