Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP)

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is NARP

Definition

Neurogenic muscle weakness, Ataxia, and Retinitis Pigmentosa is a multisystem mitochondrial disease.¹ NARP is characterized by proximal neurogenic muscle weakness with sensory neuropathy, ataxia, learning difficulties, and pigmentary retinopathy.¹ Most cases present in childhood with ataxia and learning difficulties. Seizures may also be present.¹ Additional clinical features include short stature, sensorineural hearing loss, progressive external ophthalmoplegia, and cardiac conduction defects (heart block).¹

- NARP is caused by mutations in the mitochondrial DNA (mtDNA) and follows maternal inheritance. This means that a female who carries the mtDNA mutation at high mutation load will typically pass it on to all of her children. A male who carries the mtDNA mutation cannot pass it on to his children.¹,²
- For all mtDNA mutations, clinical expressivity depends on the three following factors:¹
  - The relative abundance of mutant mtDNA, mutational load (heteroplasy)
  - The organs and tissues in which the mutant mtDNA is found (tissue distribution), and
  - The vulnerability of each tissue to impaired oxidative metabolism (threshold effect).
- The mutation load in given tissues can change over time, and mtDNA deletions are not usually detectable in white blood cells from adults.¹
• The exact prevalence of NARP is unknown.¹

• Management of NARP is generally supportive. Regular neurologic, ophthalmologic, and cardiologic screenings are recommended for affected individuals. Anti-epileptic drugs that affect the mitochondrial respiratory chain should be avoided, as they may cause secondary carnitine deficiency or can be used with L-carnitine supplementation.¹

Test information

• The investigation and diagnosis of patients with mitochondrial disease often necessitates a combination of techniques including muscle histocytochemistry, biochemical assessment, and molecular genetic studies along with clinical assessment. Any molecular genetic test for a mtDNA mutation should ideally be directed by the clinical phenotype and results of these other investigations.²

• NARP Targeted Mutation Analysis
  o m.8993T>G (T8993G) and m.8993T>C (T8993C) in MT-ATP6 cause ~50% of cases of NARP.¹
  o If negative, whole genome sequencing of mitochondrial DNA can detect more rare mutations associated with NARP, but does not significantly increase the detection rate over testing for the common two mutations.¹

• The clinical course for mitochondrial diseases is subject to the concepts of heteroplasmy, tissue distribution, and threshhold effect.¹,³ While genetic test results alone cannot predict the exact course or phenotype of the disease, severity does correlate with mutation load.¹,⁴

• Due to its ability to simultaneously sequence the entire mtDNA and measure heteroplasmy at each position, next generation sequencing (NGS) is an attractive option for assessing NARP and overlapping syndromes. However, certain targeted mutation analyses can estimate heteroplasmy. Typically, Sanger sequence analysis will miss heteroplasmy below 20%.

• Genetic testing can also be done on skin fibroblasts, urinary sediment, or buccal mucosa.¹ If cultured fibroblasts are used, measures such as limited passaging and uridine supplementation should be taken to reduce selection against mutant genotypes that may lead to skewed heteroplasmy.

• If genetic testing is negative in a blood sample in a person with symptoms of NARP, testing can be done on other specimens. Typically this is done when the phenotype is highly suggestive of presence of a NARP mutation or when there is a need to assess reproductive risk for offspring with higher mutant load and risk for developing Leigh disease.
  o Muscle may be considered as a secondary tissue. Muscle biopsy allows enzymatic analysis of the electron transport chain, light and ultrastructural
microscopy, and mtDNA copy number analysis—all of which may provide highly useful information.

- However, muscle (and/or liver) biopsies are often not necessary and should be avoided when possible due to their invasive nature. Biopsies should only be considered when the diagnosis cannot be confirmed with DNA testing of other more accessible tissues.

Guidelines and evidence

- No specific evidence-based U.S. testing guidelines were identified.
- Case reports and a limited number of case series are the primary evidence base available for the diagnosis of mitochondrial disease.\(^4-6\)
- The Mitochondrial Medicine Society developed consensus recommendations using the Delphi method and published them in 2015.\(^7\)
  - Recommendations for DNA testing
    - “Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.”
    - “Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.”
    - “Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m.3243 A>G mutation.”
    - “When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease gene is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no mutation is identified via known NGS panels, then whole exome sequencing should be considered.”
- A workshop of the National Institute of Neurological Disorders and Stroke (2008)\(^3\) summarizes:
  - “The diagnosis of mitochondrial diseases is complicated by their heterogeneous presentations and by the lack of screening procedures or diagnostic biomarkers that are both sensitive and specific. The workshop panelists explained that diagnosis is often a lengthy process beginning with a general clinical evaluation
followed by metabolic screening and imaging and finally by genetic tests and more invasive biochemical and histological analyses. The identification of known mitochondrial mutations in tissue has greatly aided diagnosis. However, even when clinical features and family history strongly suggest mitochondrial disease, the underlying genetic mutation can elude detection, and there is no current screening procedure that would be practical for all cases of suspected mitochondrial disease."

- The Clinical Molecular Genetics Society (CMGS) of the United Kingdom (2008)\(^2\) practice-based guidelines for the molecular diagnosis of mitochondrial disease state: “For routine referrals for NARP, presence of T8993G and T8993C mutations should be investigated.”

- The European Federation of Neurological Sciences (2009)\(^8\) evidence-based molecular diagnostic guidelines state: “If the phenotype suggests syndromic mitochondrial disease due to mtDNA point mutations (MELAS, MERRF, NARP, LHON) DNA-microarrays using allele-specific oligonucleotide hybridization, real-time-PCR or single-gene sequencing are indicated.”

### Criteria

#### Known NARP Familial Mutation Testing

- **Genetic Counseling**
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- **Previous Genetic Testing**
  - No previous genetic testing in the individual for NARP*, and
  - NARP pathogenic variant identified in matrilineal relative, AND

- **Predictive Testing for Asymptomatic Individual:**
  - 18 years of age or older, or
  - Under the age of 18 years, and
    - Screening for learning disabilities, retinitis pigmentosa, and/or ataxia is being considered, OR

- **Diagnostic Testing for Symptomatic Individual:**
  - Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of NARP, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy
NARP Targeted Mutation Analysis

- Genetic Counseling
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing for NARP*, and
  - No known NARP pathogenic variants in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of NARP, and
  - Genetic testing is needed to confirm the diagnosis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Whole mtDNA Sequencing

- Genetic Counseling
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for NARP targeted mutation analysis is met, AND
- No pathogenic variants identified in the NARP targeted mutation analysis, AND
- Paternal transmission has been ruled out

* Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

References


