Mitochondrial DNA Deletion Syndromes

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.

<table>
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<th>Procedure addressed by this guideline</th>
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What are mtDNA deletion syndromes

Definition

Mitochondrial DNA deletion syndromes include three overlapping phenotypes: Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO).\(^1\)\(^2\)

- The three phenotypes may be observed in different members of the same family or may evolve in a given individual over time.\(^1\)
  - **KSS** is a multisystem disorder defined by three key signs and symptoms: onset before age 20 years (typically in childhood), pigmentary retinopathy, and PEO. Affected individuals must also have at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration >100 mg/dL, or cerebellar ataxia. Other findings may include short stature, hearing loss, dementia, limb weakness, diabetes mellitus, hypoparathyroidism, and growth hormone deficiency.\(^1\)\(^2\)
  - **Pearson syndrome** includes the findings of sideroblastic anemia and exocrine pancreas dysfunction. It is usually fatal in infancy. Those surviving into childhood develop features of KSS.\(^1\)\(^3\)
  - Symptoms may first occur between the first and fifth decade of life and may not appear in any particular order.\(^1\)
  - **PEO** is a mitochondrial myopathy characterized by findings including drooping of the eyelids (ptosis), paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness.\(^1\)
  - Rarely Leigh syndrome can manifest due to a mtDNA deletion which is characterized by basal ganglia and brain stem lesions.\(^1\)

- These conditions are caused by pathogenic variants in mitochondrial DNA (mtDNA). Pathogenic variants can be sporadic (not inherited) or maternally
inherited. 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.\textsuperscript{1-3}

- The wide variability in clinical presentation depends on how much mutant mtDNA is present in a tissue (heteroplasmy), which organs and tissues have mutant mtDNA, and how vulnerable those tissues are to impaired mitochondrial function (threshold effect).\textsuperscript{1}

- Management is usually symptomatic and supportive.\textsuperscript{1} Consensus based recommendations have been published by the Mitochondrial Medicine Society for the routine care and management of individuals with mitochondrial disease, including those with mtDNA deletions.\textsuperscript{4}

- An epidemiologic study of an adult population in the North East of England estimated the prevalence of large-scale mtDNA deletions at 1.2:100,000.\textsuperscript{5}

Test information

- Diagnosis of mtDNA deletion syndromes is based on a combination of clinical findings and genetic testing.\textsuperscript{1,2}

- Findings in KSS and PEO may include elevated lactate and pyruvate levels in blood and cerebrospinal fluid while at rest, with excessive increases in blood after moderate activity. MRI can demonstrate leukencephalopathy, often associated with cerebral or cerebellar atrophy or basal ganglia lesions.\textsuperscript{1} Biochemical studies may also be performed, though: “It is important to note that biochemical abnormalities may not be present during periods when the mitochondrial disease is quiescent/dormant.” \textsuperscript{6}

- Detection rate for cases of KSS and PEO by deletion/duplication analysis is 90% and 50% respectively.\textsuperscript{1}
  - In cases of KSS and PEO, the disease-causing rearrangements can be detected on a muscle specimen but typically are undetectable in blood (especially in PEO), therefore mutational analysis is best obtained through skeletal muscle biopsy by NGS.\textsuperscript{1} The same would apply to the rare cases of Leigh syndrome.\textsuperscript{1}
  - For Pearson syndrome, the rearrangements can best be detected in blood by whole mitochondrial genome amplification followed by massively parallel sequencing detecting about 90% of those affected.\textsuperscript{1,2}

- Any molecular genetic test for a mtDNA mutation should ideally be directed by the clinical phenotype and results of other clinical, laboratory, and radiological investigations.\textsuperscript{2}

- Genetic test results alone cannot predict the exact course or phenotype of the disease. Therefore, testing is not appropriate for asymptomatic at-risk individuals.\textsuperscript{1,2}
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. There are few prospective studies. 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) summarizes:6
    - “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 European Federation of Neurological Sciences (2009)\textsuperscript{8} provided molecular diagnostic evidence-based guidelines for these conditions:
  o “If the phenotype suggests syndromic MID [mitochondrial disorders] due to mtDNA deletion (mtPEO, KSS, Pearson's syndrome), mtDNA analysis starts with RFLP or Southern-blot from appropriate tissues. mtDNA deletions with low heteroplasmy rate may be detected only by long-range PCR. If neither a single deletion nor multiple deletions are found, mtDNA sequencing is recommended.”

Criteria

Known Familial Mutation Testing

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

• Previous Genetic Testing
  o No previous genetic testing in the individual for mtDNA deletion syndromes, and
  o A maternal deletion identified in the mother, AND

• Diagnostic Testing for Symptomatic Individual:
  o Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of a mtDNA deletion syndrome, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy

mtDNA Deletion Testing

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

• Previous Testing:
  o No previous genetic testing for mtDNA deletions,\textsuperscript{**} and
  o No known mitochondrial pathogenic variants or deletions in the family, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of a mtDNA deletion syndrome, and
  o Genetic testing is needed to confirm the diagnosis, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

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

References


