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>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>mtDNA Deletion Analysis</td>
<td>81465</td>
</tr>
</tbody>
</table>

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).

- The three phenotypes may be observed in different members of the same family or may evolve in a given individual over time.
  - **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 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, sensorineural hearing loss, impaired intellect (intellectual disability and/or dementia), ptosis, oropharyngeal and esophageal dysfunction, exercise intolerance, muscle weakness, endocrinopathy (diabetes mellitus, hypoparathyroidism, and/or growth hormone deficiency), and renal impairment.
  - **Pearson syndrome** includes the findings of sideroblastic anemia and exocrine pancreas dysfunction. It may be fatal in infancy. Most affected individuals surviving into childhood are thought to develop features of KSS.
  - **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 with exercise intolerance.
  - Rarely Leigh syndrome can manifest due to a mtDNA deletion which is characterized by basal ganglia and brain stem lesions.
These conditions are caused by pathogenic variants in mitochondrial DNA (mtDNA). Pathogenic variants can be sporadic (not inherited) or maternally inherited. Deletions of mitochondrial DNA (mtDNA), ranging in size from 1.1 to 10 kb, are associated with Kearns-Sayre syndrome, Pearson syndrome, progressive external ophthalmoplegia, and rarely Leigh syndrome. Deletions of mtDNA are rarely transmitted. 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{1,4}

The same mtDNA deletion can be responsible for different syndromes. 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{5}

The estimated the prevalence of large-scale mtDNA deletions is 1.2:100,000, based on an epidemiologic study of an adult population in the North East of England.\textsuperscript{6}

Test information

In an individual with characteristic clinical features of a mtDNA deletion syndrome, the diagnosis is confirmed through molecular genetic testing identifying a mtDNA single large-scale deletion ranging in size from 1.1 to 10 kb.

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 leukoencephalopathy, often associated with cerebral or cerebellar atrophy or basal ganglia lesions.\textsuperscript{1} Biochemical studies may also be performed, although “biochemical abnormalities may not be present during periods when the mitochondrial disease is quiescent/dormant.”\textsuperscript{6}

- 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 typically best obtained through skeletal muscle biopsy by NGS. The same would apply to the rare cases of Leigh syndrome. Note that while a 2019 expert review states, “with improved molecular methodologies, a single, large-scale mtDNA deletion can be found in blood and/or urine in all reported affected children, making muscle biopsy unnecessary to confirm the diagnosis in this age group”, there is disagreement among clinical experts regarding this matter.\textsuperscript{1}

- For Pearson syndrome, the rearrangements can best be detected in blood by whole mitochondrial genome amplification followed by massively parallel sequencing.\textsuperscript{1,3}
The most commonly used methods for detection of mtDNA deletions previously included Southern blot and long range (deletion-specific) PCR analysis. However, Southern blot analysis lacks sufficient sensitivity to detect low levels of heteroplasmic deletions. In contrast, array comparative genome hybridization detects deletions and also estimates the deletion breakpoints and deletion heteroplasmy. All of these methodologies are being replaced by NGS of the entire mitochondrial genome which provides sufficiently deep coverage uniformly across the mtDNA genome to sensitively detect and characterize either single or multiple deletions.

Genetic test results alone cannot predict the exact course or phenotype of the disease. Therefore, testing is not appropriate for asymptomatic at-risk individuals.¹²

Guidelines and evidence

No specific evidence-based U.S. testing guidelines were identified.

An expert-authored review (2019) states:¹

- "The diagnosis of a mitochondrial DNA (mtDNA) deletion syndrome is confirmed in a proband with the above Suggestive Findings by identification on molecular genetic testing of a mtDNA single large-scale deletion ranging in size from 1.1 to 10 kb (see Table 1). Establishing a molecular diagnosis for primary mitochondrial disease is important for prognosis and genetic counseling [Lieber et al 2013, Nesbitt et al 2013]."
- "Molecular genetic testing approaches can include deletion/duplication analysis of the mtDNA genome, use of a multigene panel, and comprehensive genomic testing."
- "The occurrence of mtDNA heteroplasmy may result in variable tissue distribution of deleted mtDNA molecules. Since mtDNA deletions may be undetectable in blood, skeletal muscle biopsy may be necessary to identify a mtDNA deletion. However, with improved molecular methodologies, a single, large-scale mtDNA deletion can be found in blood and/or urine in all reported affected children, making muscle biopsy unnecessary to confirm the diagnosis in this age group [Broomfield et al 2015]."
  - "Sequencing of long-range PCR products or quantitative PCR analysis may reveal a pathogenic mtDNA deletion/duplication. The deletion/duplication breakpoint may then be mapped by mtDNA sequencing."
  - "Next-generation sequencing can quantify the presence of one or more mtDNA deletions or duplications together with their exact breakpoints."
  - "Quantitative PCR methods, such as digital droplet PCR analysis, can quantify the mtDNA deletion heteroplasmy level."
- "Southern analysis was historically used for mtDNA deletion detection, but is not as sensitive as next-generation sequencing in detecting low heteroplasmy levels"
of mtDNA deletions, and may fail to distinguish single from multiple mtDNA deletions in the same genomic region.”

- 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

  o 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.”

- The European Federation of Neurological Sciences (2009)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
- 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 mtDNA deletion syndromes, and
  - A mtDNA deletion identified in the mother, AND

- Diagnostic Testing for Symptomatic Individual:
  - 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
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Testing:
  - No previous genetic testing for mtDNA deletions,** and
  - No known mitochondrial pathogenic variants or deletions in the family, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of a mtDNA deletion syndrome, and
  - No evidence of paternal transmission, and
  - 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


