

Mitochondrial DNA Deletion Syndromes

Genetic Testing Policy

Procedure(s) addressed by this policy:	Procedure Code(s)
mtDNA Deletion Analysis	81465

What are mtDNA Deletion Syndromes?

- Mitochondrial DNA deletion syndromes include three overlapping phenotypes: Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO).^{1,2} These 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}
 - **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. 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. mtDNA deletions are rarely transmitted. A male who carries the mtDNA mutation cannot pass it on to his children.^{1,2,4}
- 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).¹
- Management is usually symptomatic and supportive.¹
- An epidemiologic study of an adult population in the North East of England estimated the prevalence of large-scale mtDNA deletions at 1.2:100,000.⁵



Test Information

- Diagnosis of mtDNA deletion syndromes is based on a combination of clinical findings and genetic testing.^{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 leukoencephalopathy, often associated with cerebral or cerebellar atrophy or basal ganglia lesions.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."⁶
- Detection rate for cases of KSS and PEO by deletion/duplication analysis is 90% and 50%, respectively.¹
 - In cases of KSS and PEO, the disease-causing rearrangements can be detected on a muscle specimen but typically are undetectable in blood, therefore mutational analysis is best obtained through muscle biopsy by NGS.¹ The same would apply to the rare cases of Leigh syndrome.¹
 - For Pearson syndrome, the disease-causing rearrangements can be detected in blood by whole mitochondrial genome amplification followed by massively parallel sequencing, detecting about 90% of those affected.^{1,2,3}
- 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.^{2(CMGS)}
- Genetic test results alone cannot predict the exact course or phenotype of the disease. Therefore, testing is not appropriate for asymptomatic at-risk individuals.^{1,2}
- Prenatal Testing for At-Risk Pregnancies:
 - Prenatal testing for a known mitochondrial mutation has limited clinical utility. Even in circumstances where a mother is carrier of a mtDNA deletion, it is rare to transmit it.⁷ And when transmitted, it is typically transmitted as a duplication, which does not produce symptoms.^{8,9,10}
 - As a result of the issues described above, the availability of prenatal testing for mtDNA deletions is presently limited.
 - Published guidelines from the 74th European Neuromuscular Centre International Consensus stated regarding prenatal testing via CVS: "Recurrence risks for Kearns Sayre syndrome (KSS) are complex. For women with KSS due to mtDNA rearrangements, particularly those in whom rearrangements are detectable in blood (>5%), we recommend CVS. The analysis should be done by Southern blotting (PCR analysis may be misleading both because of contamination with maternal mtDNA and of problems with interpretation). For women with chronic progressive external ophthalmoplegia (CPEO) in whom only mtDNA deletions are detectable in muscle, we believe that the risk of transmitting the disease is very low and that no special precautions are essential. For healthy women with a single affected child with KSS or Pearson's syndrome and no detectable deletion in blood, the risk of another affected child is probably very low. CVS analysis may be an option."¹⁰

- A retrospective chart review of prenatal samples processed in Europe concluded that prenatal testing for mitochondrial diseases was informative for the select mutations studied.¹¹

Guidelines and Evidence

- No specific evidence-based U.S. testing guidelines were identified.
- The Mitochondrial Medicine Society developed consensus recommendations using the Delphi method and published them in 2015.¹²
 - Recommendations for testing blood, urine, and spinal fluid
 - The initial evaluation in blood for mitochondrial disease should include complete blood count, creatine phosphokinase, transaminases, albumin, lactate and pyruvate, amino acids, and acylcarnitines, along with quantitative or qualitative urinary organic acids. Caution must be taken to ensure that specimens are collected appropriately, especially for lactate and pyruvate measurements.
 - Postprandial lactate levels are more sensitive than fasting specimens and are preferred when possible. *Caution must be taken to not overinterpret small elevations in postprandial lactate.*
 - The lactate/pyruvate ratio in blood or CSF is of value only when the lactate level is elevated.
 - Quantitative 3-methylglutaconic acid (3MG) measurements in plasma and urine should be obtained when possible in addition to urine organic acids in patients being evaluated for mitochondrial disease. Creatine phosphokinase and uric acid should be assessed in patients with muscle symptoms who are suspected of having mitochondrial diseases.
 - Urine amino acid analysis should be obtained in the evaluation of mitochondrial tubulopathy.
 - When CSF is obtained, it should be sent for lactate, pyruvate, amino acid, and 5-methyltetrahydrofolate measurements.
 - Further research is needed regarding other biomarkers such as FGF21, glutathione, and CSF neopterin.
 - 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 additional tissues can selectively be more informative and accurate than testing in blood alone.

may be detected only by long-range PCR. If neither a single deletion nor multiple deletions are found, mtDNA sequencing is recommended."

Criteria

mtDNA Deletion Known Familial Mutation

- 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, OR
- Prenatal Testing for At-Risk Pregnancies:
 - mtDNA deletion syndrome-causing mutation identified in a previous child or in the mother.

mtDNA Deletion 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 in the individual for mtDNA deletions*, and
 - No known mitochondrial pathogenic variants or deletions in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Clinical examination and/or biochemical testing suggestive, but not confirmatory, of one of the mtDNA deletion syndromes described above, and
 - Genetic testing is needed for one of the following purposes:
 - To confirm the diagnosis, or
 - To offer testing to family members, or
 - For prenatal diagnostic purposes, AND
- No evidence of paternal transmission.

*Genetic testing has rapidly advanced over the last 20 years. Exceptions may be considered if an individual has previously had negative genetic testing, but technical advances in testing demonstrate significant advantages that would support a medical need to re-test.

Exclusions and Other Considerations:

- Testing addressed in this guideline is not applicable in the following cases:
 - Mitochondrial DNA depletion syndromes, and
 - Conditions in which secondary mtDNA deletions are due to variants in nuclear genes.

References

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