Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) Genetic Testing

**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 MELAS**

**Definition**

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) is a progressive, multisystem genetic disease.¹

- The estimated prevalence of the A3243G pathogenic mutation associated with MELAS is about 16-18/100,000 individuals in Finland.²³ This prevalence was 236/100,000 in an Australian study.⁴
- MELAS symptoms can present at any age. Most cases present in childhood, with 65%-76% developing symptoms before age 20. Few cases present before age 2 (5%-8%) and after age 40 (1%-6%).¹
- Individuals with MELAS typically experience disease progression that results in death. Median survival time from point of diagnosis is about 16.9 years, with a subgroup of 20.8% who are more severely affected and die within 7.3 years of diagnosis.¹ Overall, children and young adults diagnosed with MELAS who have classical symptoms have a shorter lifespan than older adults with milder symptoms.
- Common clinical findings of MELAS include stroke-like episodes, encephalopathy with seizures, and/or dementia, muscle weakness and exercise intolerance, normal early psychomotor development, recurrent headaches, recurrent vomiting, hearing impairment, peripheral neuropathy, learning disability, and short stature. Other
findings including hemiparesis, peripheral neuropathy, and Wolff-Parkinson-White syndrome.¹

- Initial clinical presentation typically includes stroke-like episodes or cortical blindness often occurring with seizures, recurrent headaches, muscle weakness, recurrent vomiting, and short stature. Initial manifestations may also include altered consciousness, impaired mentation, hearing impairment, diabetes mellitus (type 1 or 2), developmental delay, and fever.¹

- Almost all individuals with MELAS have lactic acidemia. If performed, muscle biopsy commonly shows ragged red fibers.¹

- The natural history of MELAS involves gradual impairment of motor abilities, vision, and cognitive ability by adolescence or young adulthood due to recurring stroke-like episodes.¹

- There is no cure for MELAS. Several types of treatment, however, have demonstrated benefit in affected individuals. The use of oral and intravenous (IV) L-arginine and citrulline has shown reduction of frequency and/or severity of stroke-like episodes.⁵⁻⁹ Arginine therapy is recommended for management of stroke-like episodes.¹,¹⁰,¹¹ Both endurance and resistance exercise have been studied and shown to increase mitochondrial metabolism.⁷ Vitamin and cofactor supplementation including CoQ10, alpha lipoic acid, and riboflavin should be offered, and addition of folinic acid and L-carnitine should be considered, especially if there is documented deficiency.⁵ Creatine supplementation should also be considered.¹

- At-risk individuals may benefit from assessment to initiate baseline evaluations (neurology, cardiology, ophthalmology, and audiology) and potential intervention prior to exhibiting clinical manifestations.¹⁰ Screening for diabetes mellitus by fasting serum glucose concentration and glucose tolerance test is recommended.¹

- Diagnosis of MELAS is based on a combination of clinical and laboratory findings and genetic testing.¹

- MELAS is caused by mutations in the mitochondrial DNA (mtDNA) that are always maternally inherited. This means that a female who carries the mtDNA mutation at high mutation load will typically pass it on to all of her children. However, due to the meiotic bottleneck, the heteroplasmy level may vary significantly between generations. A male who carries the mtDNA mutation will not pass it on to his children.¹

- Mutations in the mtDNA gene, MT-TL1, cause MELAS. A majority of affected individuals with classic symptoms, about 80%, have a specific mutation, A3243G.¹,¹² Other rare mtDNA mutations in the MT-TL1 gene, T3271C and A3252G, and in 9 other mtDNA genes are also associated with MELAS.¹

- Genetic test results alone cannot predict the exact course or phenotype of the disease.¹ For all mtDNA mutations, clinical expressivity depends on the three following factors:¹
  - The relative abundance of mutant mtDNA, mutational load (heteroplasmy)
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).

- Clinical utility of genetic testing for MELAS may include changes to stroke treatment, treatment during illness, the use of anesthesia, the use of exercise as treatment, and the use of vitamin and xenobiotics.\(^7\)

**Test information**

- The investigation and diagnosis of patients with mitochondrial disease often necessitate a combination of techniques including clinical assessment along with biochemical assessment, molecular genetic studies, and sometimes muscle biopsy. Molecular genetic testing for a mtDNA mutation should ideally be directed by the clinical phenotype and results of these other investigations.\(^13\)

- Targeted mutation testing for MELAS is available at many laboratories. The specific mutations included in these targeted tests can vary by laboratory; however, they typically include the most common pathogenic variant found in MELAS, A3243G.

- The common MELAS mutations are also included on a number of more general mitochondrial targeted mutation panels (in conjunction with genes for LHON, MERRF and Leigh syndrome).

- Full sequencing of the entire mitochondrial genome can be done to identify the remaining rare mtDNA mutations in individuals affected with MELAS. Since the mitochondrial genome is highly polymorphic, this is not routinely offered unless clinical suspicion is very high and there is no evidence of paternal transmission.\(^1\) 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 MELAS and overlapping syndromes. However, certain targeted mutation analyses can estimate heteroplasmy. Typically, Sanger sequence analysis will miss heteroplasmy below 20%. With suitable depth of coverage, NGS can detect heteroplasmy down to \(\sim 1\%\).\(^{14,15}\)

- A number of large panels sequence the mitochondrial genome in conjunction with nuclear-encoded mitochondrial genes for a broad approach to testing.

- DNA testing can be performed on a blood specimen. Muscle biopsy is generally not necessary, but some labs accept blood, saliva and muscle samples.

- A muscle biopsy or heteroplasmy analysis in urine may be recommended for testing of A3243G variant in cases with a clinical presentation of classic MELAS and where the variant is not detected on blood or urine specimens.\(^{1,5}\) If the status of heteroplasmy is of concern, next generation testing with high read depth may be preferable, however certain targeted mutation analysis can detect low level heteroplasmy.
Guidelines and evidence

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

• The Mitochondrial Medicine Society (2015) developed consensus recommendations for the diagnosis and management of mitochondrial disease. Testing strategies, including strategies for genetic testing, were discussed.

  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.3243A>G mutation.”

  o Recommendations for pathology testing
    ▪ “Muscle (and/or liver) biopsies should be performed in the routine analysis for mitochondrial disease when the diagnosis cannot be confirmed with DNA testing.”

• The European Federation of Neurological Sciences (EFNS, 2009) provided molecular diagnostic consensus-based guidelines based on literature reviews:

  o “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

MELAS 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 MELAS, and
- MELAS pathogenic variant identified in 1st degree biological maternal relative, AND

- Predictive Testing for Asymptomatic Individual:
  - 18 years of age or older, or
  - Under the age of 18 years, and
    - Presymptomatic screening for diabetes mellitus is being considered, OR

- Diagnostic Testing for Symptomatic Individual:
  - Clinical exam and biochemical testing suggestive, but not confirmatory, of a diagnosis of MELAS, OR

- Prenatal Testing for At-Risk Pregnancies:
  - MELAS causing pathogenic variant in a previous child or in the mother, AND

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

**MELAS Targeted Mutation Analysis (A3243G)**

- 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 MELAS, and
  - No known MELAS pathogenic variants in the family, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Clinical exam and biochemical testing suggestive, but not confirmatory, of a diagnosis of MELAS by one or more of the following:
    - Lactic acidosis both in blood and in the CSF,¹ and/or
    - Muscle biopsy showing ragged red fibers,¹ and/or
    - Respiratory chain enzyme studies that are consistent with a diagnosis of MELAS,¹ and/or
    - Stroke-like episodes before the age of 40 years,¹ and/or
    - Encephalopathy with seizures and/or dementia,¹ 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
MELAS Targeted Mutation Analysis (G13513A, T3271C, and A3252G)

- Genetic Counseling
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for MELAS targeted mutation analysis (A3243G) is met, AND
- No pathogenic variants identified in the targeted mutation analysis (A3243G)

Whole mtDNA Sequencing

- Genetic Counseling
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for MELAS targeted mutation analysis is met, AND
- No pathogenic variants identified in the targeted mutation analysis (A3243G, G13513A, T3271C, and A3252G), AND
- No evidence of paternal transmission

References


