

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

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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.

Procedures addressed by this guideline	Procedure codes
MELAS Known Familial Mutation Analysis	81403
MT-TL1 Targeted Mutation Analysis	81401
MT-ND5 Targeted Mutation Analysis	81401
Whole Mitochondrial Genome	81460

What is MELAS

Definition

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

- The estimated prevalence of MELAS is about 16-18/100,000 individuals.^{2,3}
- 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.
- Typical initial clinical presentation includes stroke-like episodes or cortical blindness often occurring with generalized tonic-clonic seizures, and these episodes may be recurrent and associated with altered consciousness. Almost all individuals with MELAS (94%) have lactic acidemia. Individuals may also have recurrent headaches, anorexia, recurrent vomiting, possibly exercise intolerance or proximal limb weakness, Wolff-Parkinson-White syndrome, and diabetes mellitus. Short

stature in children and sensorineural hearing loss in both children and adults are also common.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.⁴⁻⁹ Both endurance and resistance exercise have been studied and shown to increase mitochondrial metabolism.⁶ 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.⁴
- At-risk individuals may benefit from assessment to initiate baseline evaluations (neurology, cardiology, ophthalmology, and audiology) and potential intervention prior to exhibiting clinical manifestations.⁵ 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.^{1,11}
- 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 will pass it on to all of her children. A male who carries the mtDNA mutation will not pass it on to his children.^{1,11}
- Mutations in the mtDNA gene, MT-TL1, cause MELAS. A majority of affected individuals with classic symptoms, about 80%, have a specific mutation, A3243G.^{1,10,11} Other rare mtDNA mutations in the MT-TL1 gene, T3271C and A3252G, and in 9 other mtDNA genes are also associated with MELAS.^{1,11}
- Genetic test results alone cannot predict the exact course or phenotype of the disease.^{1,11} 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).
- There is suggested clinical utility with the use of genetic testing for MELAS at the present time. Each patient and family is unique; therefore, it is necessary to consider the specific case to determine the clinical utility in regards to impactful management.¹¹ This 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.⁶

Test information

- The investigation and diagnosis of patients with mitochondrial respiratory chain disease often necessitates a combination of techniques including muscle histochemistry, 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.¹¹
- 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, m.3243 A>G.
- 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 mutation in individuals affected with MELAS. Since the mitochondrial genome is highly polymorphic, this is not routinely offered unless clinical suspicion is very high and paternal transmission has been ruled out.¹ If the status of heteroplasmy is of concern, next generation testing with high read depth may be preferable.
- 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 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)⁴ developed consensus recommendations for the diagnosis and management of mitochondrial disease. Testing strategies, including strategies for genetic testing, were discussed.
 - 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.”²
 - 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:^{1,2}
 - “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.”⁵
 - The clinical utility of genetic testing for MELAS was described by a workshop of the National Institute of Neurological Disorders and Stroke (2008):^{1,3}
 - “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.”
 - Initial screening includes testing for blood lactate, urine amino acids, acyl-carnitine profile, and MRI. “It is important to note that biochemical abnormalities may not be present during periods when the mitochondrial disease is quiescent/dormant.”
 - The Clinical Molecular Genetics Society (CMGS) of UK (2008) provided practice-based guidelines for the molecular diagnosis of mitochondrial disease:¹¹

- In cases with strong clinical evidence, testing should begin with checking for the common A3243G mutation. Testing for the rare mutations including T3271C and A3252G is not routinely indicated unless there is strong clinical diagnosis of MELAS testing.

Criteria

Known Familial Mutation Analysis

- 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 MELAS, and
 - MELAS pathogenic variant identified in 1st degree biological maternal relative, AND
- 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
- 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
- Paternal transmission has been ruled out

Benefit exclusion

Exclusions and other considerations

Testing unaffected individuals (e.g. carrier testing, predictive testing, presymptomatic testing, etc) is a BCBSAZ benefit exclusion and, therefore, not eligible for reimbursement.

MELAS

References

1. El-Hattab AW, Almannai M, Scaglia F. MELAS. 2001 Feb 27 [Updated 2018 Nov 29]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1233/>.
2. K. Majamaa, J.S. Moilanen, S. Uimonen, A.M. Remes, P.I. Salmela, M. Kärppä, K.A. Majamaa-Voltti, H. Rusanen, M. Sorri, K.J. Peuhkurinen, I.E. Hassinen, Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes: prevalence of the mutation in an adult population. *Am. J. Hum. Genet.* 1998;63:447–454.
3. J. Uusimaa, J.S. Moilanen, L. Vainionpää, P. Tapanainen, P. Lindholm, M. Nuutinen, T. Löppönen, E. Mäki-Torkko, H. Rantala, K. Majamaa, Prevalence, segregation, and phenotype of the mitochondrial DNA 3243ANG mutation in children. *Ann. Neurol.* 2007;62:278–287.
4. Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns G, Saneto R, Anselm I, Cohen B, Falk M, Greene C, Gropman A, Haas R, Hirano M, Morgan P, Sims K, Tanopolsky M, Van Hove JLK, Wolfe L, DiMauro S. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Gen in Med.* 2015;17:689-701.
5. Y. Koga, Y. Akita, J. Nishioka, S. Yatsuga, N. Povalko, Y. Tanabe, S. Fujimoto, T. Matsuishi, L-Arginine improves the symptoms of stroke-like episodes in MELAS. *Neurology.* 2005;64:710–712.
6. Y. Koga, Y. Akita, J. Nishioka, S. Yatsuga, N. Povalko, K. Katayama, T. Matsuishi, MELAS and L-arginine therapy. *Mitochondrion* 2007;7:133–139
7. A.W. El-Hattab, J.W. Hsu, L.T. Emrick, L.J. Wong, W.J. Craigen, F. Jahoor, F. Scaglia, Restoration of impaired nitric oxide production in MELAS syndrome with citrulline and arginine supplementation. *Mol. Genet. Metab.* 2012;105:607–614.
8. A.W. El-Hattab, L.T. Emrick, W.J. Craigen, F. Scaglia, Citrulline and arginine utility in treating nitric oxide deficiency in mitochondrial disorders. *Mol. Genet. Metab.* 2012;107:247–252.
9. K. Majamaa, J.S. Moilanen, S. Uimonen, A.M. Remes, P.I. Salmela, M. Kärppä, K.A. Majamaa-Voltti, H. Rusanen, M. Sorri, K.J. Peuhkurinen, I.E. Hassinen, Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes: prevalence of the mutation in an adult population. *Am. J. Hum. Genet.* 1998;63:447–454.
10. Mao C, Holt I. Clinical and Molecular Aspects of Diseases of Mitochondrial DNA Instability. *Chang Gung Med J.* 2009;32:354-69.
11. Clinical Molecular Genetics Society Guidelines (CMGS), UK. Practice guidelines for the molecular diagnosis of mitochondrial diseases. July 2008. Available at: http://www.acgs.uk.com/media/774654/mito_2008.pdf.

12. Finsterer J, Harbo HF, Baets J, et al.; European Federation of Neurological Sciences. EFNS guidelines on the molecular diagnosis of mitochondrial disorders. *Eur J Neurol.* 2009;16(12):1255-64.
13. National Institute of Neurological Disorders and Stroke (NINDS, NIH). Available at: http://wayback.archive-it.org/1170/20161005013715/https://www.ninds.nih.gov/news_and_events/proceedings/20090629_mitochondrial.htm.