Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE), *TYMP*-Related Genetic Testing Policy

Procedure(s) addressed by this policy:	Procedure Code(s)
TYMP sequencing	81405
TYMP del/dup	81479
Known familial mutation	81403

What Is MNGIE?

- **M**itochondrial **N**eurog**g**astro**i**ntestinal **E**ncephalopathy (MNGIE) is a multisystem mitochondrial disease.[1]
    - It typically is characterized by progressive gastrointestinal dysmotility, which may present with nausea, dysphagia, reflux, early satiety, vomiting after a meal, episodic abdominal pain, bloating, and/or diarrhea. Additionally, individuals may present with cachexia (a wasting syndrome), ptosis/ophthalmoplegia (drooping/weakness of the eyelid), leukoencephalopathy on brain MRI, and/or peripheral neuropathy (tingling, numbness, and/or pain in the extremities) [1]
- Symptoms may occur independently of other symptoms and in no particular order.[1]
- Onset usually between first and fifth decade.[1]
- MNGIE is caused by biallelic mutations in *TYMP* and is inherited in an autosomal recessive pattern, meaning parents of an affected individual must be obligate carriers. The chance of having another child with MNGIE to the same parents is 25%.
- *TYMP* encodes thymidine phosphorylase, which is an enzyme that catalyzes the phosphorylation of thymidine or deoxyuridine to thymine or uracil; it is essential for the nucleotide salvage pathway.[2]
- Mutations that disrupt the function of *TYMP* will therefore disrupt the enzyme activity causing it to decrease and levels of thymidine or deoxyuridine to increase.
- Prevalence is largely unknown, but MNGIE is rare.[1]
- Management can be supportive, and may include assistance with swallowing difficulties, medication for nausea and vomiting, gastrostomy and parenteral nutrition for nutritional support, pain medications for neuropathy, and physical therapy and occupational therapy.[1]
    - In individuals with advanced illness, liver transplant or allogenic hematopoietic stem cell transplant, have been suggested as possible curative treatment options, although risks and benefits of these procedures must be properly weighed.[3,4]
    - Peritoneal dialysis has also been suggested as a method of reduction of the thymidine concentration and should be considered as an additional or alternative form of

treatment or to improve the health of a patient waiting for liver or hematopoietic stem cell transplant.[5]

Testing Information

- Reduced thymidine phosphorylase enzyme activity or elevated thymidine and deoxyuridine levels are consistent with a diagnosis of MNGIE.[1] Plasma is the preferred specimen for thymidine and deoxyuridine levels, but testing may be performed on urine.
- The majority of *TYMP* mutations are detected by gene sequencing. *TYMP* deletions and duplications are less common.[1]
    - Complete sequencing of *TYMP* for pathogenic mutations.
    - If only one *TYMP* mutation identified or variant of uncertain significance results are returned, pursue *TYMP* deletion/duplication analysis.[1]

Guidelines and Evidence

- No specific evidence-based U.S. testing guidelines were identified.
- The **European Federation of Neurological Sciences (2009)** provided molecular diagnostic consensus-based guidelines based on literature reviews: "Sequencing of *TYMP* should be performed only if serum thymidine is elevated."[6]
- Evidence from three different peer reviewed journals provide symptoms, clinical findings, imaging, and family history suggestive of MNGIE[7,8,9]
    - Severe gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoparesis/ophthalmoplegia, and sensorimotor neuropathy
    - Brain MRI that demonstrates abnormal brain white matter (increased FLAIR or T_2-weighted signal) consistent with asymptomatic leukoencophalopathy
    - Family history consistent with autosomal recessive inheritance.

Criteria

TYMP 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 for MNGIE for the individual*, and
    - *TYMP* pathogenic variants previously identified in parents and/or sibling(s), AND
- Predictive Testing for Asymptomatic Individual:
    - 18 years of age or older, OR
- Diagnostic Testing for Symptomatic Individual:
    - Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of MNGIE, OR
- Prenatal Testing for At-Risk Pregnancies:
    - *TYMP* pathogenic variants previously identified in parents.

***TYMP* Sequencing 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 for the individual for MNGIE* , and
  - No known *TYMP* familial mutations, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of MNGIE, 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.

***TYMP* Deletion/Duplication Analysis**

- Genetic Counseling:
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for *TYMP* Sequencing is met, AND
- No pathogenic variants or only one pathogenic variant identified in *TYMP* Sequencing.

*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.

References

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