MTHFR Variant Analysis for Hyperhomocysteinemia

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>
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<th>Procedure addressed by this guideline</th>
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What is hyperhomocysteinemia

Definition

Hyperhomocysteinemia generally refers to mild to moderate elevations of plasma homocysteine levels, which may be defined as 15 to 40 µmol/L.¹

- Hyperhomocysteinemia may be caused by nutritional deficiencies, various medical conditions, certain drugs, smoking, and inherited factors — such as MTHFR gene variants.¹
- The MTHFR gene encodes the 5, 10-methylenetetrahydrofolate reductase (MTHFR) enzyme. MTHFR is involved in folate metabolism. The major circulating form of folate is key to converting homocysteine into methionine. Therefore, MTHFR gene variants that reduce MTHFR enzyme function may predispose one to impaired folate metabolism and ultimately mild to moderate hyperhomocysteinemia. However, homocysteine levels are usually normal if folate intake is sufficient.¹
- Both hyperhomocysteinemia in general, and MTHFR variants specifically, have been reported in association with cardiovascular disease, venous thromboembolism, pregnancy complications, and certain birth defects, such as neural tube defects.¹² However, data is inconsistent and associated risks generally small.

Test information

- MTHFR genetic testing looks for two very common gene variants: C677T and A1298C.²
- Individuals who have two variants, including at least one C677T, may have an increased risk for hyperhomocysteinemia. However, the connection between these
MTHFR variants, hyperhomocysteinemia itself, and ultimate disease risk remains unclear.³,⁴

- Many experts suggest that measuring homocysteine levels directly is more informative than MTHFR variant testing.⁵
- Note that pathogenic variants in the MTHFR gene (not the common benign variants discussed here) are rarely associated with a genetic disorder called homocystinuria.² MTHFR variant testing will not find the pathogenic variants that cause homocystinuria.
- MTHFR gene testing may be a component of panels for thrombophilia, cardiovascular disease risk, psychiatric conditions, or preeclampsia. There is insufficient evidence in the peer-reviewed literature to establish clinical utility for any of these indications for testing.

Guidelines and evidence

- As part of the Choosing Wisely campaign, the American College of Medical Genetics and Genomics (2015) released “Five Things Physicians and Patients Should Question,” which states:⁶
  - “Don’t order MTHFR genetic testing for the risk assessment of hereditary thrombophilia. The common MTHFR gene variants, 677C>T and 1298A>G, are prevalent in the general population. Recent meta-analyses have disproven an association between the presence of these variants and venous thromboembolism.”

- Also as part of the Choosing Wisely campaign, the Society for Maternal Fetal Medicine (2014) released “Five Things Physicians and Patients Should Question,” which states:⁷
  - “Don’t do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption. Scientific data supporting a causal association between either methylenetetrahydrofolate reductase (MTHFR) polymorphisms or other common inherited thrombophilias and adverse pregnancy outcomes, such as recurrent pregnancy loss, severe preeclampsia and IUGR, are lacking.”

- The American College of Medical Genetics and Genomics (ACMG, 2013) states:⁸
  - “It was previously hypothesized that reduced enzyme activity of MTHFR led to mild hyperhomocysteinemia which led to an increased risk for venous thromboembolism, coronary heart disease, and recurrent pregnancy loss. Recent meta-analyses have disproven an association between hyperhomocysteinemia and risk for coronary heart disease and between MTHFR polymorphism status and risk for venous thromboembolism. There is growing evidence that MTHFR polymorphism testing has minimal clinical utility and, therefore should not be ordered as a part of a routine evaluation for thrombophilia.”
• The American College of Obstetricians and Gynecologists (ACOG, 2013) states: 
  “Because of the lack of association between either heterozygosity or homozygosity for the 
  methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and any negative 
  pregnancy outcomes, including any increased risk for venous thromboembolism, 
  screening with either MTHFR mutation analyses or fasting homocysteine levels is not 
  recommended.”

• The National Society of Genetic Counselors (NSGC, 2005) state that MTHFR 
  variant testing is specifically not justified in the case of recurrent pregnancy loss 
  based on available studies.

Criteria
This test is considered investigational and/or experimental.

• Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer 
  to assays involving chromosomes, DNA, RNA, or gene products that have insufficient 
  data to determine the net health impact, which typically means there is insufficient 
  data to support that a test accurately assesses the outcome of interest (analytical 
  and clinical validity), significantly improves health outcomes (clinical utility), 
  and/or performs better than an existing standard of care medical management 
  option. Such tests are also not generally accepted as standard of care in the 
  evaluation or management of a particular condition.

• In the case of MolGen testing, FDA clearance is not a reliable standard given the 
  number of laboratory developed tests that currently fall outside of FDA oversight 
  and FDA clearance often does not assess clinical utility.

References
3. Ray JG, Shmorgun D, Chan WS. Common C677T Polymorphism of the 
   Methylenetetrahydrofolate Reductase Gene and the Risk of Venous 
   Homocysteine and Coronary Heart Disease: Meta-analysis of MTHFR Case-
   doi:10.1371/journal.pmed.1001177


