HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Methylenetetrahydrofolate Reductase (MTHFR) Mutation Testing

Policy MP-020

Origination Date: 10/31/2018

Review/Revised Date: 10/25/2023

Next Review Date: 10/25/2024

Current Effective Date: 10/25/2023

Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, CHIP and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

Methylenetetrahydrofolate Reductase (MTHFR) is a gene that provides instructions for making an enzyme used in processing amino acids, the building blocks of proteins. MTHFR is important for a chemical reaction involving forms of the vitamin folate (aka vitamin B9). Specifically, this enzyme converts a molecule called 5, 10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate. This reaction is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

There are two variants of the MTHFR gene: C677T and A1298C. Because each person has two copies of the MTHFR gene (one from each parent), people can inherit zero, one, or two copies of a MTHFR gene variant. People who inherit two copies of C677T have a higher risk for having a child with a neural tube defect. Having two C677T variants and elevated homocysteine levels may cause a slightly higher risk for blood clots.

Polymorphisms of methylenetetrahydrofolate reductase (MTHFR) have been associated with various conditions including diastolic blood pressure, hypertension, and other cardiovascular diseases, hereditary thrombophilia, clotting disorders, neural tube defects and various pharmacologic responses to medications, however, results of many of these studies have failed to demonstrate a definitive association and clinical utility to this testing.

Policy Statement and Criteria

1. Commercial Plans/CHIP

U of U Health Plans DOES NOT COVER methylenetetrahydrofolate reductase (MTHFR) mutation testing. It is considered investigational and not medically necessary for all indications.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: https://medicaid.utah.gov/utah-medicaid-official-publications/ or the Utah Medicaid code Look-Up tool

CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

A significant volume of research has occurred attempting to identify a correlation of MTHFR gene mutations with clinical conditions. Studies have looked at using this testing to identify patients at increased risk for vascular disease, thrombotic conditions, behavioral health disorders and drug metabolism. None have identified clinical utility for this testing.

A 2015 meta-analysis (Yang et al) studied three groups of individuals with neural tube defects to investigate the association between the MTHFR C677T polymorphism and neural tube defect risks. A total of 40 articles were analyzed including tests for heterogeneity, sensitivity analysis, and assessment of publication bias. Thirteen studies compared 1329 persons with neural tube defects to 2965 healthy controls; 34 studies compared 3018 mothers with neural tube defect progeny to 8746 healthy controls; and, 3 studies compared 157 fathers with neural tube defect progeny to 705 healthy controls. The analysis results identified allele contrast in individuals with neural tube defects (odds ratio, 1.445; 95% CI, 1.186, 1.760); allele contrast in mothers (odds ratio, 1.342; 95% CI, 1.166, 1.544); and allele contrast in fathers (odds ratio, 1.062; 95% CI, 0.821, 1.374). The authors concluded there was no association between any of the father's genotypes and neural tube defects, whereas a significant correlation between MTHFR C677T polymorphism and neural tube defect risk was found in persons with neural tube defects and in their mothers. However, there were several limitations of this meta-analysis, including the potential for selection bias as only studies in English or Chinese were selected and the number of studies and sample size in some subgroups was relatively small.

A 2015 case-control study (Perez-Razo et al) examined if two functional variants (rs1801133 and rs13306560) within the MTHFR are associated with hypertension in Mexican-Mestizos. The study included 1,214 subjects, both adults (764 participants [372 patients and 391 controls]) and children (418 participants [209 patients and 209 controls]). The authors concluded that these findings suggested that the rs13306560 polymorphism of the MTHFR may be part of the observed hypertension process in Mexican-Mestizo populations, but further studies are needed.

In a 2016 cross-sectional study to assess the role of 5, 10- MTHFR C677T gene polymorphism in essential hypertension (Amrani-Midoun et al) noting many studies have investigated this with conflicting results.

The authors observed no significant differences between allelic and genotypic frequencies between cases and controls for C677T polymorphism (OR = 1.51, 95 % CI: 0.89 to 2.56, p = 0.13). Analyses adjusted for age, sex and body mass index improved the association level, though the association was still not significant (30% versus 22%, OR = 1.75, 95% CI: 0.95 to 3.24, p = 0.07). The authors concluded that the findings of this study demonstrated that genetic polymorphism related to the MTHFR gene (C677T) is not associated with the risk of hypertension in this sample of Algerian population.

An analysis in 2016 (Silver et al) attained data collected through the Stillbirth Collaborative Researcher Network and evaluated the clinical utility of MTHFR C677T testing for prothrombin-related thrombophilia. In addition to testing for MTHFR C677T and A1298C mutations, testing for factor V Leiden (FVL), prothrombin G20210A, and plasminogen activating inhibitor-1 4G/5G variants was performed on maternal and fetal (or placental) DNA from single pregnancies. There was an increased odds of stillbirth for maternal homozygous FVL variant. However, there were no significant differences in the odds of stillbirth for any other maternal thrombophilia, even after stratified analyses. The data did not support routine testing of MTHFR C677T and A1298C mutations for heritable thrombophilias as part of an evaluation for possible causes of stillbirth.

In a 2017 study (Zhao et el) performed an analysis of data collected from the China Stroke Primary Prevention Trial. Data from 20,424 hypertensive adults was collected as part of the study. Participants were grouped by MTHFR C677T genotypes, then randomized to receive enalapril and folic acid or enalapril alone. Treatment assignments were double-blinded. Median follow-up was 4.5 years. Participants' homocysteine (Hcy) levels were measured and incidence of stroke was collected. Among controls, Hcy levels were associated with risk of first stroke only among participants with CC and CT genotypes (hazard ratio, 3.1; 1.1-9.2). Among patients receiving folic acid, Hcy levels were not associated with stroke. In conclusion, folic acid intervention significantly reduced stroke risk in participants with CC/CT genotypes and high homocysteine levels (hazard ratio, 0.73; 0.55-0.97).

Another study completed in 2017 (Xu et al) collected data from the same trial (the China Stroke Primary Prevention Trial) to determine the relationship between MTHFR C677T polymorphisms and all-cause mortality in hypertensive adults. The study found that the MTHFR genotype alone did not significantly associate with mortality, but the Hcy-mortality association was significantly stronger in the CC/CT genotype than in the TT genotype (P for interaction <0.05).

A 2017 multivariate logistic regression analysis (Hendrix et al), reported results from exploring if there was an association between cystathionine β-synthase (CBS) polymorphisms and aneurysmal subarachnoid hemorrhage and its consequences. The analysis used genotype results from 149 patients enrolled in the Cerebral Aneurysm Renin Angiotensin System study and 50 controls. No association was found with clinical vasospasm or delayed cerebral ischemia.

Another 2017 study (Horita et al) reported the relationship between MTRR rs326119 polymorphism and biochemical parameters of vitamin B12 metabolism, coronary lesions, and congenital heart disease (CHD) in Brazilian subjects. Patients enrolled underwent coronary angiography (n = 1432) plus blood donors (n = 156) were used as both a control group for CHD (n = 722), and as samples for testing the association between MTRR polymorphism and coronary atherosclerosis and homocysteine levels. Overall, those with the AC and CC genotypes had significantly higher homocysteine (9.7 ± 0.4 µmol/L and 10.1 ± 0.6 µmol/L) and lower cobalamin concentrations (260.5 ± 13.3 pmol/L and 275.6 ± 19.9 pmol/L) compared to subjects with the AA genotype (8.7 ± 0.5 µmol/L and 304.8 ± 14.7 pmol/L). A significant association was identified between the number of C variant alleles and the concentrations of homocysteine and cobalamin. No association was found between variants and coronary heart disease or coronary atherosclerosis.

The findings from the various studies have been validated in a couple of systematic reviews completed by Hayes in 2021. In one review MTHFR testing in common clinical conditions for improved outcomes using various supplements was reviewed. Seven studies were chosen to evaluate the clinical utility of MTHFR genotyping (6 RTC's and 1 case control study) for supplemental treatment in the following indications: Riboflavin for hypertension may reduce blood pressure, however, determining the dose/ treatment duration, long term effectiveness, and improved outcomes warrant further studies; Folic acid may prevent first stroke in patients with hypertension, although optimal folic acid doses and baseline folate levels remain to be established; Increased folate and the time duration of supplementation reduced pregnancy complications for most age groups in China, yet further testing would need to be done before utilizing in the U.S.; folate supplementation, compared with placebo, did not show any reduction of symptoms in schizophrenia patients; Commercial vitamin and nutrient preparation for major depressive disorder did significantly decreased an average depression rating scale score and significantly improved the rate of achieving remission compared with placebo, regardless no usual treatment comparison arm was included in the trial, therefor further testing is necessary. The review concluded, some applications of *MTHFR* genotyping for common variants present evidence of possible clinical utility, however, further follow-up studies are needed before immediate use.

A second 2021 Hayes review looked at MTHFR pharmacogenomic genotyping for altering drug treatments in pediatric or adult patients with multiple conditions. Assessment of the clinical utility to alter drug choice, drug dose, or otherwise mitigate drug treatment according to patient genotype in order to avoid adverse events, maintain adherence, and improve disease outcomes was included. The researchers identified 1109 titles/abstracts and 48 studies to include in this report. Only one study met criteria for full review of 141 patients (all Spanish medical centers), who were newly diagnosed with childhood non-B acute lymphoblastic leukemia, to assess clinical utility. The study found unfavorable genotype were 4.3 times more likely to suffer an adverse event compared with those with a favorable genotype (95% CI, 1.3-14.0). The results suggest that increasing the methotrexate dose in a genetically favorable group does not increase toxicity. Nonetheless, this study alone was felt to be insufficient to represent the range of evidence required to address this topic. Also no comparative trials were found for MTHFR pharmacogenomic applications to other treatment types, such as 5-FU treatment in cancer patients. MTHFR may only be one of several genes affecting drug treatment efficacy and mitigating toxicity or be insubstantial of treatment. Further large, well-characterized cohort studies are needed. In assessing the clinical utility of this testing in this circumstance, Hayes noted a very-low-quality body of evidence for studies looking directly at clinical utility was available. They determined there is insufficient evidence to determine the clinical utility of *MTHFR* genotyping to alter drug choice, drug dose, or otherwise mitigate drug treatment and improve outcomes.

Hayes completed a new clinical utility evaluation on MTHFR genetic testing for severe MTHFR enzyme deficiency in 2023. The essential findings were that only case reports and family studies were identified. Genetic testing for rare MTHFR gene variants in neonatal subjects allowed for early treatment for 4 patients in 3 studies. Neonates who received early treatment went on to have normal development. Family testing for rare MTHFR gene variants in parents of subjects with genetically confirmed severe MTHFR enzyme deficiency allowed for prenatal diagnosis in subsequent pregnancies (4 families in 2 studies). Prenatal diagnosis led to pregnancy-related decision-making (1 family) and early treatment initiation for an impacted neonate (1 family). In conclusion, MTHFR genotyping has clear implied clinical utility among populations with a family history of severe MTHFR enzyme deficiency so that family-planning and effective treatment-related decisions can be made. Some evidence of clinical utility was found for MTHFR genotyping to aid in diagnosis among patients identified as high risk in newborn metabolic screening in order to institute immediate and effective treatment and prevent developmental abnormalities. No studies directly compared genotyping with other diagnostic tests, such as biochemical

tests for MTHFR enzyme activity. Given the rarity of the disease, such studies are not likely to be forthcoming. Thus, it is reasonable to expect that any future studies of severe MTHFR enzyme deficiency would continue to demonstrate the benefits of early identification and treatment, particularly in high-risk families.

Several medical societies have also come out with recommendations against performing MTHFR testing. In 2013 the American College of Medical Genetics and Genomics (ACMG, 2013) recommended MTHFR should not be ordered for clinical evaluation of thrombophilia, at risk family members or recurrent pregnancy loss. The American College of Obstetricians and Gynecologists (ACOG, 2018) clinical management guidelines for inherited thrombophilias in pregnancy state that a definitive causal link cannot be made between inherited thrombophilias and adverse pregnancy outcomes. Screening is not recommended for women with a history of fetal loss, adverse pregnancy outcomes (including abruption and preeclampsia) or fetal growth restriction. There is insufficient evidence that antepartum prophylaxis with unfractionated heparin or low dose molecular-weight heparin prevents recurrence in these patients. Also screening with either heterozygosity or homozygosity for the MTHFR C677T polymorphism and any negative pregnancy outcomes, including any risk for VTE, has not shown an association. Therefore either MTHFR mutation analyses or fasting homocysteine levels are not recommended.

Applicable Coding

CPT Codes

81291 MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

HCPCS Codes

No applicable codes found

References:

1. American College of Obstetricians and Gynecologists (ACOG). Inherited thrombophilias in pregnancy. Practice Bulletin No. 197. Obstet Gynecol. 2018; 132(1):e18-e34.
2. Amrani-Midoun A, Kiando SR, Treard C, et al. The relationship between MTHFR C677T gene polymorphism and essential hypertension in a sample of an Algerian population of Oran city. Int J Cardiol. 2016;225:408-411.
3. Hayes, Inc. (Aug, 17, 2017); GTE indication: "*MTHFR* Genetic Testing in Common Clinical Conditions." Winifred Hayes, Inc. May 12, 2020. Annual Review: May 23, 2021 Accessed: October 24, 2023. Available at: https://evidence.hayesinc.com/report/gti.mthfrdeficiency4179
4. Hayes, Inc. (Mar 23, 2017); GTE indication: "*MTHFR* Pharmacogenomic Genotyping for Altering Drug Treatments." Winifred Hayes, Inc. May 2, 2020. Annual Review: May 23, 2021 Accessed: October 24, 2023. Available at: https://evidence.hayesinc.com/report/gti.mthfrgenetic3947
5. Hayes Inc. (Sep 29, 2023). Clinical Utility Evaluation. "MTHFR Genetic Testing for Severe MTHFR Enzyme Deficiency". Accessed: October 24, 2023. Available at: https://evidence.hayesinc.com/report/gti.clinicalmthfr3695
6. Hayes, Inc. (2019) "Genetic Testing for Common Forms of Hereditary Thrombophilia in Adults with Unprovoked Venous Thromboembolism". May 21, 2019. Annual Review: June 21, 2022. Accessed: October 19, 2022. Archived: May 21, 2023. Available at: https://evidence.hayesinc.com
7. Hendrix, P, Foreman, PM, Harrigan, MR, et al. Association of cystathionine beta-synthase polymorphisms and aneurysmal subarachnoid hemorrhage. Journal of neurosurgery. 2017 Aug 4:1-7. PMID: 28777022
8. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013; 15(2):153-156.
9. Horita, M, Bueno, CT, Horimoto, AR, et al. MTRR rs326119 polymorphism is associated with plasma concentrations of homocysteine and cobalamin, but not with congenital heart disease or coronary atherosclerosis in Brazilian patients. Int J Cardiol Heart Vasc. 2017;14:1-5. PMID: 28616555
10. Millar, H. MTHFR Hope or Hype? National Society of Genetic Counselors (NSGC). Genome Web. April 17, 2017 Blog: 906: 40-42. Available at: https://www.nsgc.org/p/bl/et/blogaid=906

11. Perez-Razo JC, Cano-Martínez LJ, Vargas Alarcon G, et al. Functional polymorphism rs13306560 of the MTHFR gene Is associated with essential hypertension in a Mexican-Mestizo population. Circ Cardiovasc Genet. 2015;8(4):603-609.
12. Silver RM, Saade GR, Thorsten V, et al. Factor V Leiden, prothrombin G20210A, and methylene tetrahydrofolate reductase mutations and stillbirth: the Stillbirth Collaborative Research Network. Am J Obstet Gynecol. 2016; 215(4):468.
13. UpToDate® "Screening for inherited thrombophilia in asymptomatic adults" Literature review current through September 2022. Topic last updated: August 16, 2021. Accessed: October 19, 2022. Available at: https://www.uptodate.com
14. U.S. Department of Health and Human Services (HHS). National Institutes of Health (NIH).Genetic and Rare Diseases (GARD) Information Center. MTHFR GENE VARIANT. Assessed October 2018. Available at: https://rarediseases.info.nih.gov/diseases/10953/mthfr-gene-mutation
15. U.S. National Library of Medicine (NLM). Genetics Home Reference (GHR): MTHFR. Reviewed April 2016. Available at: https://ghr.nlm.nih.gov/gene/MTHFR#.
16. Xu, B, Kong, X, Xu, R, et al. Homocysteine and all-cause mortality in hypertensive adults without pre-existing cardiovascular conditions: Effect modification by MTHFR C677T polymorphism. Medicine. 2017;96(8):e5862. PMID: 28225483
17. Yang Y, Chen J, Wang B, et al. Association between MTHFR C677T polymorphism and neural tube defect risks: a comprehensive evaluation in three groups of NTD patients, mothers, and fathers. Birth Defects Res A Clin Mol Teratol. 2015; 103(6):488-500.
18. Zhao, M, Wang, X, He, M, et al. Homocysteine and Stroke Risk: Modifying Effect of Methylenetetrahydrofolate Reductase C677T Polymorphism and Folic Acid Intervention. Stroke. 2017;48(5):1183-90. PMID: 28360116