Genetic Testing: *MTHFR*

MEDICAL POLICY NUMBER: 311

Effective Date: 10/1/2023

Last Review Date: 8/2023

Next Annual Review: 6/2024

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Note: Genetic testing for mutations in *MTHFR* may be considered medically necessary when billed as part of a multi-gene panel that meets criteria per the Medical Policy, Next Generation Sequencing for Cancer.

I. Genetic testing for mutations in methylenetetrahydrofolate reductase (*MTHFR*) is considered **not medically necessary** for the treatment of any indication, including but not limited testing performed as part of any of the following panels: (A.-C.)

   A. Neuro IDGenetix (AltheaDx, Inc.)
   B. Polypharmacy Comprehensive Panel (Genelex Corporation)
   C. RightMed Comprehensive Test (OneOme)

Link to Evidence Summary

POLICY CROSS REFERENCES

- Next Generation Sequencing for Cancer, MP352

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Methylenetetrahydrofolate reductase (*MTHFR*)

The *MTHFR* gene provides instructions to make the MTHR protein, which helps the body process folate. Variations in the *MTHFR* gene have been proposed as risk factors for numerous conditions, including cardiovascular disease, thrombophilia, stroke, hypertension, behavioral health conditions, pharmacological management and pregnancy-related complications.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

Four genotyping tests for variations in the *MTHFR* gene have been approved by the U.S. Food and Drug Administration (FDA):

- Verigene *MTHFR* Nucleic Acid Test (Nanosphere, Inc.),
- eSensor *MTHFR* Genotyping Test (Osmetech Molecular Diagnostics),
- Invader *MTHFR* 677 (Hologic, Inc.),
- Invader *MTHFR* 1298 (Hologic, Inc.).

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of genetic testing of the *MTHFR* gene for the treatment of various indications. Below is a summary of the available evidence identified through May 2023.

Systematic Reviews

- In 2017 (updated 2021), Hayes conducted an evidence review assessing the clinical utility of *MTHFR* genetic testing in common clinical conditions.[1] In total, 7 studies were evaluated to assess the evidence for the clinical utility of *MTHFR* genotyping. Three studies from 1 research group were judged as presenting low-quality but consistent evidence that riboflavin supplementation may be an effective method to reduce BP in a genotype-targeted hypertensive population that has difficulty achieving BP goals. However, optimal riboflavin dose and treatment duration, long-term effectiveness, and improved outcomes would still need to be demonstrated in larger trials. A good quality RCT suggested that folic acid therapy may prevent first

stroke based on *MTHFR* genotype and baseline folate level, . Relevance to the U.S. population—a diet-supplemented population nationwide—as well as optimal folic acid doses by genotype and baseline folate levels, however, remain to be established. Increased folate dose beyond usual recommendations according to *MTHFR* and *MTRR* risk variants and time course reduced pregnancy-associated complications for most age categories in 1 trial in China. Applicability to U.S. populations would require additional data.

Psychiatric disorders associated with disruptions in folate metabolism have been hypothesized to improve by administering related supplements according to *MTHFR* genotype. In 1 small RCT of folate treatment in schizophrenic outpatients, no evidence of improvement by genotype was found compared with placebo. In another larger trial of MDD patients selected by high-risk *MTHFR* genotype, a commercial vitamin and nutrient preparation significantly decreased an average depression rating scale score and significantly improved the rate of achieving remission compared with placebo, but no usual treatment comparison arm was included in the trial. In general, some applications of *MTHFR* genotyping for common variants present evidence of possible clinical utility and warrant follow-up study, but none appear to be ready for immediate use.

The following Hayes Ratings were based on the low-quality body of evidence for studies looking directly at the clinical utility of *MTHFR* genotyping in pediatric or adult patients to detect common variants and support genotype-directed treatment of common conditions:

- For use of *MTHFR* C677T genotyping in patients with premature cardiovascular disease or hypertension to support genotype-directed supplemental treatment of hypertension with riboflavin. (*low quality of evidence, "C" rating – potential but unproven benefit*)

- For use of *MTHFR* C677T genotyping in patients with hypertension but no prior stroke, myocardial infarction, or heart disease, to support genotype-directed prevention of stroke with folic acid. (*very low quality of evidence, "D2" rating – insufficient evidence*)

- For use of *MTHFR* C677T and A1298C genotyping in pregnant women to support genotype-directed folate supplementation for the prevention of pregnancy complications. (*very low quality of evidence, "D2" rating – insufficient evidence*)

- For use of *MTHFR* C677T genotyping in schizophrenia patients treated with antipsychotic medication to support genotype-directed folate supplementation for the reduction of negative symptoms. (*very low quality of evidence, "D2" rating – insufficient evidence*)

- For use of *MTHFR* C677T and A1298C genotyping in patients with major depressive disorder and no other psychiatric or behavioral features to support genotype-directed supplementation with a commercial vitamin/nutrient preparation to improve symptoms. (*very low quality of evidence, "D2" rating – insufficient evidence*)

- In 2017 (updated 2021), Hayes conducted an evidence review assessing the clinical utility of *MTHFR* pharmacogenetic genotyping for altering drug treatment.[2] In total, 1 study was included for review to assess the evidence for the clinical utility of *MTHFR* pharmacogenomic genotyping.

This study (n=141) enrolled patients with newly diagnosed childhood non-B acute lymphoblastic leukemia. All patients were treated with the same protocol, except that those with a favorable genotype (677CC or 677CT; n=106) were given an increased dose of methotrexate whereas those with an unfavorable genotype (677TT, 1298CC, 677CT/1298AC; n=35) were given the standard dose. Patients with an 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). These results suggested that increasing the methotrexate dose in a genetically favorable group does not increase toxicity. This study was limited by the following: complete controls were lacking, overall disease outcomes were not assessed, and the results of this trial cannot be generalized to patients with other clinical conditions who are also treated with methotrexate, nor to other antifolate medications. On the basis of the very-low quality of evidence, Hayes ultimately assigned a "D2" rating (insufficient evidence) for use of *MTHFR* pharmacogenomic genotyping to alter drug choice, drug dose, or otherwise mitigate drug treatment in order to avoid adverse events, maintain adherence, and improve disease-related outcomes.

- In 2017 (updated 2021), Hayes conducted an evidence review assessing the clinical utility of *MTHFR* genetic testing for severe *MTHFR* enzyme deficiency.[3] In total, 4 studies were included for review of *MTHFR* genotyping for severe enzyme deficiency. These studies were assessed as demonstrating clinical utility. One study employed a limited newborn screening program for known *MTHFR* variants in a relatively closed or isolated population at high risk (e.g., due to a founder variant) to identify new cases. All four studies addressed case identification by genotyping with subsequent direct benefit to the patient and/or prenatal screening so that family planning and effective treatment-related decisions in subsequent pregnancies can be made. No studies directly compared genotyping with other definitive diagnostic tests such as *MTHFR* enzyme activity. Therefore, no evidence was found that clarifies best methods for laboratory diagnosis. On the basis of several case studies, Hayes concluded that *MTHFR* genotyping for severe enzyme deficiency has clinical utility in screening for known, rare *MTHFR* variants in relatively closed or isolated populations at high risk (e.g., due to a founder variant), and where the condition has already been diagnosed in a family, in prenatal screening so that family planning and effective treatment-related decisions can be made. Some clinical utility was found for *MTHFR* genotyping for severe enzyme deficiency to aid in case diagnosis so that immediate and effective treatment may be instituted. However, no studies directly compared genotyping with other definitive diagnostic tests such as *MTHFR* enzyme activity. Therefore, no evidence was found that clarifies best methods for laboratory diagnosis. The following Hayes Ratings were given:

    - For use of *MTHFR* genotyping to screen for known, rare *MTHFR* variants in relatively closed or isolated populations at high risk (e.g., due to a founder variant). (*moderate quality of evidence, "B" rating; some proven benefit*)

    - For use of *MTHFR* genotyping to aid in the diagnosis of new, individual cases to improve treatment outcomes. (*low quality of evidence, "C" rating; potential but unproven benefit*)

    - For use of *MTHFR* genotyping to detect rare variants in prenatal screening where the condition has already been diagnosed in a family, in order to improve case identification

as well as treatment and/or family planning outcomes. (*moderate quality of evidence, "B" rating; some proven benefit*)

- In 2018, ECRI published a genetic test product brief assessing the clinical utility of the Neuro IDgenetix (AltheaDx, Inc.) for guiding medication selection for patients with psychiatric disorders or acute or chronic pain.[4] Two clinical utility RCTs were included for review. One RCT reported improved short-term remission and response rates in patients with moderate to severe anxiety, depression, or both at 12-week follow-up. The second RCT of patients with anxiety, depression, ADHD, or psychosis found no difference in patient symptoms after treatment guided and not guided by the test at 3 month follow-up. Due to the study's small sample sizes and lack of long-term follow-up, evidence supporting the test's clinical utility was determined to be "inconclusive."[4]

CLINICAL PRACTICE GUIDELINES

American College of Medical Genetics and Genomics (ACMG)

In 2013, the ACMG published a clinical practice guideline on *MTHFR* polymorphism testing with respect to the clinical evaluation for thrombophilia.[5] A summary of the recommendations is as follows:

- *MTHFR* genotyping should neither be ordered for the clinical evaluation of thrombophilia or recurrent pregnancy loss nor for at-risk family members.
- Patients found to carry *MTHFR* variants should receive an appropriate symptom-based evaluation by a clinical geneticist.
- Fasting total plasma homocysteine levels should be ordered for patients carrying the *MTHFR* 677TT homozygous variant.
- *MTHFR* genotype does not change general population folic acid supplementation recommendations for women of childbearing age.

In 2017, the ACMG updated their guidelines and did not include *MTHFR* in their list of genes for which pathologic variants for severe deficiency should be reported if detected as secondary findings in a sequencing assay.[6]

American College of Obstetricians and Gynecologists (ACOG)

In 2018, ACOG published a Practice Bulletin regarding inherited thrombophilias in pregnancy and recommended screening and management for these conditions.[7] The authors found insufficient evidence to support assessment of *MTHFR* variants or plasma homocysteine levels in the evaluation of a thrombophilic etiology for VTE. Therefore, screening with either *MTHFR* variant analysis or fasting homocysteine level was not recommended.

Society for Maternal-Fetal Medicine

In 2014, SMFM recommended avoiding an inherited thrombophilia evaluation for women with histories of "pregnancy loss, intrauterine growth restriction, preeclampsia, and abruption." SMFM notes that scientific data do not support a causal association between *MTHFR* variants or other inherited thrombophilias and adverse pregnancy outcomes.[8]

Academy of Nutrition and Dietetics (AND)

In 2014, the AND published a position paper on nutritional genomics.[9] Therefore, the use of nutrigenetic testing is considered not to be ready for routine dietetics practice. The authors report that although the *MTHFR* C677T variant has been associated with a moderately increased risk of cardiovascular disease (CVD) in some studies, the overall risk of 677TT carriers is unclear. Therefore, the authors conclude that there is insufficient evidence to modify current folate recommendations from those currently provided for the general population.

EVIDENCE SUMMARY

There is not enough research to show that testing for variants in the *MTHFR* gene improves health outcomes, no matter their medical issue. Published studies have not yet demonstrated that treating patients based on genetic testing for variants the MTHR gene can improve patients' medical condition. While some studies show that *MTHFR* genotyping for severe enzyme deficiency has clinical utility in screening for known, rare *MTHFR* variants in relatively closed or isolated populations at high risk, larger studies are needed to confirm these findings. In addition, clinical practice guidelines such as the American College of Medical Genetics and Genomics specifically recommend against *MTHFR* genetic testing. Therefore, genetic testing for *MTHFR* is considered not medically necessary.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
	0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
	0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
	0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
	0411U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
	81291	*MTHFR* (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

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9. Camp KM, Trujillo E. Position of the Academy of Nutrition and Dietetics: nutritional genomics. *Journal of the Academy of Nutrition and Dietetics.* 2014;114(2):299-312.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.

7/2023	Annual update. Changed denial to “not medically necessary.” Added note regarding cancer testing.
10/2023	Q4 2023 code set update.