Genetic Testing for *MTHFR*

MEDICAL POLICY NUMBER: 311

Effective Date: 7/1/2026

Last Review Date: 6/2026

Next Annual Review: 6/2027

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.

PHP follows Guideline Notes 172 and 173 of the OHP Prioritized List of Health Services for guidance on New and Emerging Technology. In the absence of OHP guidance, PHP will follow this policy.

**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 to 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 2026.

Systematic Reviews

- In 2024, Hayes conducted an evidence review assessing the clinical utility of *MTHFR* genetic testing for hypertension.[1] Four studies (3 fair quality and 1 good quality; 5 publications) were identified that met inclusion criteria and evaluated the clinical utility of *MTHFR* genetic testing in patients with hypertension. Three fair-quality studies suggest that *MTHFR* C677T testing may identify patients who would benefit from riboflavin or folic acid supplementation for reducing blood pressure. Studies generally reported that short-term (16-24 weeks) supplementation was

associated with improved blood pressure over placebo, particularly for patients with TT genotypes. Follow-up duration was limited, and it is unclear whether blood pressure improvements are durable or associated with any change in risk for cardiovascular events. One good-quality study reported that patients receiving longer-term (4.5 years) folic acid supplementation had fewer strokes than patients receiving placebo, regardless of *MTHFR* genotype. Hazard ratios for the occurrence of stroke were not statistically different among patients with CC, CT, or TT genotypes. This suggests that all patients, regardless of *MTHFR* genotype, may benefit from folic acid supplementation. The generalizability of these data to populations with different levels of dietary folate is unclear.

Hayes gave an "Insufficient" rating for use of methylenetetrahydrofolate reductase (*MTHFR*) genotyping to impact management and clinical outcomes for patients with hypertension. "The available evidence is insufficient to evaluate *MTHFR* testing to direct treatment for hypertension and reduce the risk of associated cardiovascular events. Data suggests that *MTHFR* C677T testing may identify patients who could have blood pressure improvements with short-term riboflavin or folic acid supplementation. However, there is no evidence to suggest that genotype-directed treatment has longer-term cardiovascular benefits beyond standard treatment that is not genotype informed."

- 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 2024, 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.

Hayes gave an "Uncertain" clinical utility score for the use of methylenetetrahydrofolate reductase (MTHFR) genotyping to detect rare variants in fetuses or neonates considered high risk for severe MTHFR enzyme deficiency due to previous familial diagnosis or metabolic findings for the purposes of initiating early treatment and informing family-planning decisions. They concluded, "his score reflects evidence deriving from case reports indicating that early identification of MTHFR enzyme deficiency allows for treatment that prevents severe adverse developmental consequences and facilitates family-planning decisions. Some uncertainty remains regarding the benefits of genetic versus biochemical assay-based diagnosis; however, due to the rarity of the disease, more robust comparative evidence is not likely to be forthcoming. Weighing the severity of the disease and potential devastating consequences of delaying identification and treatment, a higher clinical utility score is reasonable."

- In 2023 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. ECRI gave a "favorable" score to the test, stating, "Compared with empirical medication selections, IDgenetix-guided medication selection improves response and remission rates for patients with major depressive disorder and response rates for patients with anxiety at up to 12-week follow-up, based on evidence from 2 randomized controlled trials that enable low-confidence conclusions. No studies provide data to assess IDgenetix's utility for guiding treatment for other mental health disorders."[4]

CLINICAL PRACTICE GUIDELINES

American College of Medical Genetics and Genomics (ACMG)

In 2013, reaffirmed in 2020, 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, and updated in 2022, 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.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

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
	0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes
	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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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.
7/2024	Annual review. Q3 2024 code set update, code added.
7/2025	Annual review. No changes.
7/2026	Annual review. No changes.