

Clinical Policy: Homocysteine Testing

Reference Number: CP.MP.121

Last Review Date: 05/19

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Description

Homocysteine is a nonproteinogenic amino acid that is generated during the conversion of methionine to cysteine. Mutations of the enzymes within the biochemical pathways that regulate homeostatic homocysteine levels are associated with risk factors for various diseases, including venous thromboembolism. Supplementation of folic acid, vitamin B6, and vitamin B12 are known to modulate homocysteine levels, given the interplay between the folate cycle and metabolism. This policy describes the medical necessity requirements for testing levels of homocysteine.

Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation[®] that homocysteine testing is **medically necessary** for the following indications:
 - A. Borderline vitamin B12 deficiency;
 - B. Homocystinuria caused by cystathionine beta-synthase deficiency;
 - C. Idiopathic (unprovoked) venous thromboembolism, recurrent venous thromboembolism, thrombosis occurring at < 45 years of age, or thrombosis at an unusual site.

- II. It is the policy of health plans affiliated with Centene Corporation[®] that homocysteine testing is considered **investigational** for the following indications:
 - A. Cardiovascular risk testing;
 - B. For the testing of all other conditions.

Background

Homocysteine is a naturally occurring intermediary amino acid that is generated during the conversion of methionine to cysteine. While homeostatic plasma levels of homocysteine typically range at low micro molar concentrations, epistatic mutations and other aberrant modifications of the metabolic pathways modulate homocysteine levels.¹ The metabolic pathway of homocysteine consists of upstream remethylation pathways and a downstream transsulfuration pathway. Notably, mutations in cystathionine- β -synthase, a key enzyme of the transsulfuration pathway, are associated with excess levels of homocysteine and premature thrombotic events.¹ Furthermore, a common mutation at a single nucleotide (677C \rightarrow T) in the gene encoding 5,10-methylenetetrahydrofolate reductase, an enzyme in the folate cycle whose byproducts are necessary cofactors in the metabolism of homocysteine, affects homeostatic levels of homocysteine. This mutation predisposes the individual to low folate plasma levels, and consequently a status of hyperhomocysteine.²

Changes in the plasma homocysteine levels can result from alterations in folate or vitamin B6 or vitamin B12.⁷ A meta-analysis of 25 randomized clinical trials demonstrated that daily supplementation of ≥ 0.8 mg folic acid is sufficient to achieve the maximal reduction in plasma homocysteine levels.⁸ Moreover, basal levels of homocysteine range between 5-15 $\mu\text{mol/L}$,

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while moderate hyperhomocysteine concentrations are 15-30 $\mu\text{mol/L}$, intermediate levels are 30-100 $\mu\text{mol/L}$ and severe hyperhomocysteine concentrations are $>100 \mu\text{mol/L}$.⁷

Hyperhomocysteine was identified as an independent risk factor for ischemic heart disease and vascular disease.^{3,4} Initial reports hypothesized that heterozygosity of cystathionine- β -synthase contributed to the accumulation of homocysteine, and these reports were corroborated by later meta-analyses.^{3,4} However, this rationale has not been corroborated, as two randomized controlled trials, the Heart Outcomes Prevention Evaluation 2 (Hope-2) and the Norwegian Vitamin (NORVIT) trials simultaneously demonstrated no effect from lowering homocysteine levels, by way of folic acid or vitamin B6 supplementation, on cardiovascular outcomes.^{5,6}

A 2017 Cochrane review of homocysteine-lowering interventions for preventing cardiovascular events concluded that B-vitamin supplements lowered homocysteine but did not reduce risk of myocardial infarction or reduce death rates in patients at risk of, or living with cardiovascular disease.¹¹ Compared with placebo, lowered homocysteine resulting from B-vitamin supplementation combined with antihypertensive medications produced uncertain benefit in preventing stroke- approximately 143 people would need to be treated for 5.4 years to prevent 1 stroke.¹¹

Hyperhomocysteine is also a risk factor for venous thromboembolic disease. Ray et al. performed a meta-analysis of 9 case control studies measuring fasting plasma homocystine, as well as 5 studies measured after methionine loading. All 9 studies demonstrated a similar trend in the levels and the associated risk for venous thromboembolism; following methionine loading, the trend increased toward the risk of venous thromboembolism.^{9,10} Hyperhomocysteinemia has been associated with venous thromboembolic disease in some but not all studies. Additional research, however, has concluded that associations between “mild” hyperhomocysteinemia and the VTE may have been due to confounding.¹⁷ The measurement of homocysteinemia may be indicated in unexplained idiopathic venous thrombosis, or recurrent episodes or venous thrombosis that occurred at an early age or at an uncommon site.¹⁹

High levels of serum homocysteine have been proposed as a risk factor for dementia, and several studies have evaluated the role of B-vitamin supplementation in lowering homocysteine and thus improving cognitive function, or preventing cognitive decline. A meta-analysis by Clarke et al. determined that B-vitamin supplementation significantly reduced homocysteine levels, but did not have a clinically significant effect on global cognitive function or on cognitive aging.¹² In contrast, a 2018 International Consensus Statement argues for the presence of a causal relationship between homocysteine levels and cognitive decline, and for screening for hyperhomocysteine and treatment with B vitamins in patients presenting to memory clinics.¹³ However, the consensus body notes that 76% of the participants in the trials in the largest meta-analysis on the topic did not include baseline measures of cognitive function, and thus couldn't adequately compare the intervention group to the placebo group. Furthermore, they point to the lack of an established homocysteine threshold for intervention, which reduces the clinical relevance of the measure.

Coding Implications

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CPT® Codes	Description
83090	Homocysteine

HCPCS Codes	Description
N/A	

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
D51.0-D51.9	Vitamin B12 deficiency anemia
E53.8	Deficiency of other unspecified B group vitamins
E72.10	Disorders of sulfur-bearing amino-acid metabolism, unspecified
E72.11	Homocystinuria
E72.19	Other disorders of sulphur-bearing amino-acid metabolism
I26.01-I26.99	Pulmonary embolism
I81	Portal vein thrombosis
I82.0-I82.91	Other venous embolism and thrombosis
Z86.711	Personal history of pulmonary embolism
Z86.718	Personal history of other venous thrombosis or embolism

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed	07/16	08/16
References reviewed and updated	07/17	08/17
Background updated. References reviewed and updated.	05/18	05/18
Background updated. References reviewed and updated.	04/19	05/19

References

1. Wierzbicki, Anthony S. "Homocysteine and cardiovascular disease: a review of the evidence." *Diabetes and Vascular Disease Research* 4.2 (2007): 143-149.
2. Födingeer, Manuela, et al. "Recent insights into the molecular genetics of the homocysteine metabolism." *Kidney international* 59 (2001): S238-S242.
3. Clarke, Robert, et al. "Hyperhomocysteinemia: an independent risk factor for vascular disease." *N Engl J Med* 324.17 (1991): 1149-1155.

4. Homocysteine Studies Collaboration. "Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis." *JAMA* 288.16 (2002): 2015-2022.
5. Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. "Homocysteine lowering with folic acid and B vitamins in vascular disease." *N Engl J Med* 2006.354 (2006): 1567-1577.
6. Boona, K. H., I. Njolstad, and P. M. Ueland. "Homocysteine lowering and cardiovascular events after myocardial infarction." *N Engl J Med* 354 (2006): 1578-1588.
7. Rosenson RS, Smith CC, Bauer KA. "Overview of homocysteine." In: UpToDate, Freeman MW(Ed), UpToDate, Waltham, MA. Accessed on April 8, 2019.
8. Graham, I. M., E. DalyL, and H. M. Refsum. "Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials." *Am J Clin Nutr* 82.4 (2005): 806-812.
9. Ray, Joel G. "Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease." *Archives of internal medicine* 158.19 (1998): 2101-2106.
10. Den Heijer, Martin, et al. "Hyperhomocysteinemia and venous thrombosis: a meta-analysis." *Thrombosis and Haemostasis-Stuttgart-* 80 (1998): 874-877.
11. Martí-Carvajal AJ1, Solà I, Lathyris D, Dayer M. Homocysteine-lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev.* 2017 Aug 17;8:CD006612. doi: 10.1002/14651858.CD006612.pub5.
12. Clarke R, Bennett D, Parish S, et al. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. *Am J Clin Nutr.* 2014 Aug; 100(2): 657–666.
13. Smith AD, Refsum H, Bottiglieri T, et al. Homocysteine and dementia: an international consensus statement. *J Alzheimers Dis.* 2018;62(2):561-570. doi: 10.3233/JAD-171042.
14. Press D, Alexander M. Prevention of dementia. UpToDate. Dekosky ST, Schmader KE (Eds.) Accessed 4/8/2019.
15. Bauer KA, Lip G. Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors. UpToDate. Leung L, Mandel J (Eds). In: UpToDate. Accessed 4/10/19
16. Bauer KA, Lip G. Overview of the causes of venous thrombosis. Leung L, Mandel J (Eds). In: UpToDate. Accessed 4/10/19
17. Ospina-Romero M, Cannegieter SC, den Heijer M, et al. Hyperhomocysteinemia and Risk of First Venous Thrombosis: The Influence of (Unmeasured) Confounding Factors. *Am J Epidemiol* 2018; 187:1392.
18. den Heijer M, Willems HP, Blom HJ, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: A randomized, placebo-controlled, double-blind trial. *Blood.* 2007 Jan 1;109(1):139-44. Epub 2006 Sep 7.
19. Hoţoleanu C, Porojan-Iuga M, Rusu ML, Andercou A. Hyperhomocysteinemia: clinical and therapeutical involvement in venous thrombosis. *Rom J Intern Med.* 2007;45(2):159-64.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical

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The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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