

Clinical Policy: Homocysteine Testing

Reference Number: LA.CP.MP.121

Date of Last Revision: 5/23

Coding Implications
Revision Log

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Homocysteine is a nonproteinogenic amino acid generated during the conversion of methionine to cysteine.² Mutations of the enzymes within the biochemical pathways that regulate homeostatic homocysteine levels are associated with risk factors for various diseases, such as venous thromboembolic disease.^{18,19} Supplementation of folic acid, vitamin B6, and vitamin B12 are known to modulate homocysteine levels, due to 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 Louisiana Healthcare Connections that homocysteine testing is **medically necessary** for homocystinuria caused by cystathionine beta-synthase deficiency.
- II. It is the policy of Louisiana Healthcare Connections that homocysteine testing has not been proven to improve outcomes compared to other technologies for the following indications:
 - a. Cardiovascular risk testing;
 - b. Borderline vitamin B12 deficiency;
 - c. Idiopathic (unprovoked) venous thromboembolism, recurrent venous thromboembolism, thrombosis occurring at < 45 years of age, or thrombosis at an unusual site;
 - d. For the testing of all other conditions.

Background

Homocysteine is a naturally occurring intermediary amino acid generated during the conversion of methionine to cysteine.² Homocystinuria is a rare inherited condition where the body cannot produce methionine and is characterized by severe elevations in plasma and urine homocysteine concentrations.⁷ 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. Mutations in cystathionine- β -synthase, a key enzyme of the transsulfuration pathway, are associated with excess levels of homocysteine and premature thrombotic events.¹ Additionally, homeostatic levels of homocysteine are impacted by, a common mutation at nucleotide position 677 of the gene coding for 5,10-methylenetetrahydrofolate reductase, which is an enzyme in the folate cycle whose byproducts are necessary cofactors in the metabolism of homocysteine.² 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 or vitamin B6, vitamin B12, or folate.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 Basal levels of homocysteine range between 5 to 15 $\mu\text{mol/L}$, while

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

Observational studies have suggested that elevated homocysteine is an independent risk factor for ischemic heart disease and vascular disease.^{3-4,15} However, large randomized controlled studies have shown that reduction in homocysteine levels does not result in lower reports of stroke or myocardial infarction.²¹ A 2017 Cochrane review of homocysteine-lowering interventions for preventing cardiovascular events concluded that B-vitamin supplements lowered homocysteine but did not reduce the risk of myocardial infarction or reduce death rates in patients with or at risk of cardiovascular disease.¹¹ Additionally, two randomized controlled trials in 2006 simultaneously demonstrated no effect on cardiovascular outcomes from lowering homocysteine levels with folic acid or vitamin B6 supplementation.⁵⁻⁶ Compared with placebo, lowered homocysteine resulting from B-vitamin supplementation combined with antihypertensive medications produced uncertain benefits in preventing stroke.¹¹

Hyperhomocysteine has also been suggested as a risk factor for venous thromboembolic disease.^{15,16,18,19} Ray et al. performed a meta-analysis of 9 case control studies measuring fasting plasma homocysteine, as well as 5 studies measured after methionine loading. All 9 studies demonstrated a similar trend in the levels and the increased associated risk for venous thromboembolism (VTE); following methionine loading.^{9,10} However, hyperhomocysteinemia has been associated with venous thromboembolic disease in some but not all studies. Additional research has concluded that associations between mild hyperhomocysteinemia and VTE may have been due to failure to take into account additional confounding risk factors such as body mass index and cigarette smoking.¹⁷

Homocysteine testing has also been used to diagnose vitamin B12 deficiency in combination with methylmalonic acid (MMA). Homocysteine levels are a sensitive and specific measure of established vitamin B12 deficiency, but its role is unclear in the evaluation of borderline B12 deficiency, where it would be most useful.²⁰ Furthermore, MMA testing without concurrent homocysteine testing has been recommended in the assessment of low-normal vitamin B12 levels.²¹

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 could not 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.¹³ At this time there is a lack of conclusive evidence that vitamin supplementation prevents dementia.¹⁴

Coding Implications

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CPT® Codes	Description
83090	Homocysteine

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
E72.10	Disorders of sulfur-bearing amino-acid metabolism, unspecified
E72.11	Homocystinuria
E72.19	Other disorders of sulphur-bearing amino-acid metabolism

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Converted corporate to local policy.	08/15/2020	
In the policy statement in section II, replaced “investigational” with the statement that homocysteine testing has not been proven to improve outcomes compared to other technologies. References and coding reviewed and updated. Replaced all instances of “member” with “member/enrollee.”	1/2022	1/2022
Annual review. References reviewed and updated. Updated description and background with no impact on criteria. Reviewed by specialist. Added and may not support medical necessity to Coding Implications service	5/22	
Annual review. Updated description and background with no impact on criteria. References reviewed and updated.	5/23	7/24/23

References

1. Föding M, Wagner OF, Hörl WH, Sunder-Plassmann G. Recent insights into the molecular genetics of the homocysteine metabolism. *Kidney Int Suppl.* 2001;78:S238 to S242. doi:10.1046/j.1523-1755.2001.59780238.x
2. 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;109(1):139 to 144. doi:10.1182/blood-2006-04-014654

3. 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 to 164.
4. Rosenson RS, Smith CC, Bauer KA. Overview of homocysteine. UpToDate. www.uptodate.com. Published December 06, 2021. Accessed February 15, 2023.
5. Wierzbicki AS. Homocysteine and cardiovascular disease: a review of the evidence. *Diab Vasc Dis Res*. 2007;4(2):143 to 150. doi:10.3132/dvdr.2007.033
6. Homocysteine Lowering Trialists' Collaboration. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. *Am J Clin Nutr*. 2005;82(4):806 to 812. doi:10.1093/ajcn/82.4.806
7. Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med*. 1991;324(17):1149 to 1155. doi:10.1056/NEJM199104253241701
8. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA*. 2002;288(16):2015 to 2022. doi:10.1001/jama.288.16.2015
9. Bauer KA, Lip G. Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors. UpToDate. www.uptodate.com. Published October 25, 2022. Accessed February 15, 2023.
10. Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. *Am Fam Physician*. 2017;96(6):384 to 389.
11. Martí-Carvajal AJ, Solà I, Lathyris D, Dayer M. Homocysteine-lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev*. 2017;8(8):CD006612. Published 2017 Aug 17. doi:10.1002/14651858.CD006612.pub5
12. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease [published correction appears in *N Engl J Med*. 2006 Aug 17;355(7):746]. *N Engl J Med*. 2006;354(15):1567 to 1577. doi:10.1056/NEJMoa060900
13. Bønaa KH, Njølstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med*. 2006;354(15):1578 to 1588. doi:10.1056/NEJMoa055227
14. Bauer KA, Lip G. Overview of the causes of venous thrombosis. UpToDate. www.uptodate.com. Published February 8, 2023. Accessed February 15, 2023.
15. Ray JG. Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease. *Arch Intern Med*. 1998;158(19):2101 to 2106. doi:10.1001/archinte.158.19.2101
16. den Heijer M, Rosendaal FR, Blom HJ, Gerrits WB, Bos GM. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. *Thromb Haemost*. 1998;80(6):874 to 877.
17. Ospina-Romero M, Cannegieter SC, den Heijer M, Doggen CJM, Rosendaal FR, Lijfering WM. Hyperhomocysteinemia and Risk of First Venous Thrombosis: The Influence of (Unmeasured) Confounding Factors. *Am J Epidemiol*. 2018;187(7):1392 to 1400. doi:10.1093/aje/kwy004
18. Means RT, Farifield KM. Clinical manifestations and diagnosis of vitamin B12 and folate deficiency. UpToDate. www.uptodate.com. Published February 9, 2023. Accessed February 15, 2023..
19. 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;100(2):657 to 666. doi:10.3945/ajcn.113.076349
20. Smith AD, Refsum H, Bottiglieri T, et al. Homocysteine and Dementia: An International Consensus Statement. *J Alzheimers Dis*. 2018;62(2):561 to 570. doi:10.3233/JAD-171042

21. Press D, Alexander M. Prevention of dementia. UpToDate. www.uptodate.com. Published January 07, 2020. Accessed February 15, 2023.
22. Yuan S, Mason AM, Carter P, Burgess S, Larsson SC. Homocysteine, B vitamins, and cardiovascular disease: a Mendelian randomization study. *BMC Med*. 2021;19(1):97. Published 2021 Apr 23. doi:10.1186/s12916-021-01977-8
23. Wilson P WF. Overview of possible risk factors for cardiovascular disease. UpToDate. www.uptodate.com. Published September 20, 2022. Accessed February 16, 2023.
24. Son P, Lewis L. Hyperhomocysteinemia. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; May 8, 2022.

Important Reminder

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