

Clinical Policy: Homocysteine Testing

Reference Number: CP.MP.121

Date of Last Revision: 03/23

Effective Date: 05/01/23

[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.⁷ 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 homocystinuria caused by cystathionine beta-synthase deficiency.

- II. It is the policy of health plans affiliated with Centene Corporation 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

CLINICAL POLICY

Homocysteine Testing

Changes in the plasma homocysteine levels can result from alterations in 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

CLINICAL POLICY
Homocysteine Testing

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

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT®	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	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. Specialist review	04/19	05/19
References reviewed and updated. Revised I.A from “Borderline vitamin B12 deficiency” to “Borderline low or inconclusive Vitamin B12 deficiency, or discordant with the clinical picture.”	03/20	04/20
Changed borderline B12 deficiency and idiopathic VTE/thromboembolism indications from medically necessary to investigational. Added supporting background information and references. Removed from the list of ICD-10 codes supporting coverage criteria: D51.0 through D51.9, E53.8, I26.01 through I26.99, I81, I82.0 through I82.91, Z86.711, Z86.718.	05/20	05/20
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.”	04/21	05/21

Reviews, Revisions, and Approvals	Date	Approval Date
Annual review. References reviewed and updated. Updated description and background with no impact on criteria. Reviewed by specialist.	03/22	03/22
Annual review. References reviewed and updated.	03/23	03/23

References

- Födinger 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
- 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
- Hoțoleanu 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.
- Rosenson RS, Smith CC, Bauer KA. Overview of homocysteine. UpToDate. www.uptodate.com. Published December 06, 2021. Accessed February 15, 2023.
- 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
- 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
- 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
- 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
- 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.
- Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. *Am Fam Physician.* 2017;96(6):384 to 389.
- 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
- 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
- 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
- Bauer KA, Lip G. Overview of the causes of venous thrombosis. UpToDate. www.uptodate.com. Published February 8, 2023. Accessed February 15, 2023.
- 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

CLINICAL POLICY

Homocysteine Testing

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

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 policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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.

CLINICAL POLICY

Homocysteine Testing

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/enrollees, 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.

Note: For Medicare members/enrollees, 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.

©2016 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.