HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Homocysteine Level Testing

Policy MP-055

Origination Date: 06/24/2020

Reviewed/Revised Date: 07/19/2023

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Current Effective Date: 07/19/2023

Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

Homocysteine is a sulfur-containing amino acid that is rapidly oxidized in plasma into homocysteine and cysteine-homocysteine disulfide. Measurement of total plasma homocysteine is the sum of homocysteine and its oxidized forms.

Plasma levels of homocysteine have been actively researched as a risk factor for cardiovascular disease (CVD), initially based on the observation that patients with hereditary homocystinuria, an inborn error of metabolism associated with high plasma levels of homocysteine, had a markedly increased risk of CVD. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine was an independent risk factor for CVD and could be used to improve current risk prediction models. Several case-control studies have also suggested that elevated homocysteine is a risk factor for venous thromboembolism (VTE; pulmonary embolism, deep vein thrombosis).

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans covers homocysteine testing in individuals suspected of having homocystinuria or in first-degree relatives of patients with homocystinuria.

U of U Health Plans does NOT cover Homocysteine Level testing for cardiovascular disease as it is considered investigational.

U of U Health Plans does NOT cover homocysteine plasma levels in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism as it is considered INVESTIGATIONAL.

U of U Health Pans does NOT cover Homocysteine Level testing for any other indication as it is considered investigational.

2. **Medicaid Plans**
   Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: https://medicaid.utah.gov/utah-medicaid-official-publications/ or the Utah Medicaid code Look-Up tool

   CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

For individuals who are asymptomatic with the risk of CVD or individuals with CVD who receive homocysteine testing, the evidence includes observational studies and randomized controlled trials (RCTs) of homocysteine-lowering interventions. The relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and CVD risk, especially in patients with pre-existing vascular disease. However, evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves cardiovascular outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. One systematic review, with a subgroup analysis of patients from three RCTs who were not on antiplatelet therapy at baseline, found that homocysteine-lowering treatment reduced the risk of stroke in that group. However, replication of this effect in countries with folic acid enriched grain would be needed. Given the large amount of evidence from placebo-controlled randomized trials that homocysteine-lowering interventions do not improve health outcomes, it is unlikely that routine homocysteine testing has the potential to change management that improves health outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who are asymptomatic with the risk of venous thromboembolism (VTE) or individuals who have experienced VTE events who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. The relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and VTE risk, although the association was specific to men in the largest prospective study. Evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces the risk of VTE. Only a single RCT was designed to test for VTE as a primary outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

In its revised 2022 overview of homocysteine, UpToDate® concluded that patients with suspected homocystinuria should have their homocysteine levels tested along with first-degree relatives of patients diagnosed with homocystinuria. Furthermore, despite some limitations, clinical trials have generally found that reducing levels of homocysteine with B vitamin supplementation does not prevent cardiovascular disease or reduce the incidence of recurrent venous thromboembolism (VTE) or arterial thrombosis. Thus, they suggest not testing for or treating hyperhomocysteinemia, unless homocystinuria is suspected or confirmed.

Applicable Coding

CPT Codes

83090 Homocysteine

HCPCS Codes

No applicable codes

ICD-10 Codes

E72.11 Homocystinuria

References:

1. Bashore TM, Granger CB, Jackson KP, Patel MR. Coronary Heart Disease (Atherosclerotic CAD, Ischemic Heart Disease). In: Papadakis MA, McPhee SJ, Rabow MW. eds. Current Medical Diagnosis & Treatment 2021. McGraw-Hill; Accessed June 14, 2021. https://accessmedicine.mhmedical.com/content.aspx?bookid=2957&sectionid=249371789Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med. Apr 13 2006;354(15):1578-1588. PMID 16531614
2. Catena C, Colussi G, Nait F, et al. Elevated homocysteine levels are associated with the metabolic syndrome and cardiovascular events in hypertensive patients. Am J Hypertens. Jul 2015;28(7):943-950. PMID 25498997
3. Clarke R, Halsey J, Bennett D, et al. Homocysteine and vascular disease: review of published results of the homocysteine-lowering trials. J Inherit Metab Dis. Feb 2011;34(1):83-91. PMID 21069462
4. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a metaanalysis of published epidemiological studies. J Thromb Haemost. Feb 2005;3(2):292-299. PMID 15670035
5. den Heijer M, Rosendaal FR, Blom HJ, et al. Hyperhomocysteinemia and venous thrombosis: a metaanalysis. Thromb Haemost. Dec 1998;80(6):874-877. PMID 9869152
6. 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. Jan 1 2007;109(1):139-144. PMID 16960155
7. Evans RW, Shaten BJ, Hempel JD, et al. Homocyst(e)ine and risk of cardiovascular disease in the Multiple Risk Factor Intervention Trial. Arterioscler Thromb Vasc Biol. Oct 1997;17(10):1947-1953. PMID 9351358
8. Folsom AR, Nieto FJ, McGovern PG, et al. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. Jul 21 1998;98(3):204-210. PMID 9697819
9. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Jul 1 2014;63(25 Pt B):2935-2959. PMID 24239921
10. Han L, Wu Q, Wang C, et al. Homocysteine, ischemic stroke, and coronary heart disease in hypertensive patients: a population-based, prospective cohort study. Stroke. Jul 2015;46(7):1777-1786. PMID 26038522
11. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta- analysis. Jama. Oct 23-30 2002;288(16):2015-2022. PMID 12387654
12. Huang T, Chen Y, Yang B, et al. Meta-analysis of B vitamin supplementation on plasma homocysteine, cardiovascular and all-cause mortality. Clin Nutr. Aug 2012;31(4):448-454. PMID 22652362
13. Jacques PF, Selhub J, Bostom AG, et al. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. N Engl J Med. May 13 1999;340(19):1449-1454. PMID 10320382

14. Kang SS, Rosenson RS, Analytic Approaches for the Treatment of Hyperhomocysteinemia and Its Impact on Vascular Disease. Cardiovasc Drugs Ther. 2018;32(2):233.
15. Keijzer MB, Borm GF, Blom HJ, et al. No interaction between factor V Leiden and hyperhomocysteinemia or MTHFR 677TT genotype in venous thrombosis. Results of a meta-analysis of published studies and a large case-only study. Thromb Haemost. Jan 2007;97(1):32-37. PMID 172007686
16. Knekt P, Reunanen A, Alfthan G, et al. Hyperhomocystinemia: a risk factor or a consequence of coronary heart disease? Arch Intern Med. Jul 9 2001;161(13):1589-1594. PMID 11434790
17. Liu Y, Tian T, Zhang H, et al. The effect of homocysteine-lowering therapy with folic acid on flow mediated vasodilation in patients with coronary artery disease: a meta-analysis of randomized controlled trials. Atherosclerosis. Jul 2014;235(1):31-35. PMID 24814647
18. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. Apr 13 2006;354(15):1567-1577. PMID 16531613
19. Ma Y, Li L, Geng XB, et al. Correlation between hyperhomocysteinemia and outcomes of patients with acute myocardial infarction. Am J Ther. Nov/Dec 2016;23(6):e1464-e1468. PMID 25405897
20. Martí-Carvajal AJ, Solà I, Lathyris D, Dayer M. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev 2017; 8:CD006612. PMID: 28816346
21. Marti-Carvajal AJ, Sola I, Lathyris D, et al. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. Jan 31 2013;1(1):CD006612. PMID 23440809
22. Marti-Carvajal AJ, Sola I, Lathyris D. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. Jan 15 2015;1:CD006612. PMID 25590290
23. Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement. 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
24. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. Dec 2014;45(12):3754-3832. PMID 25355838
25. Myers GL, Christenson RH, Cushman M, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines: emerging biomarkers for primary prevention of cardiovascular disease. Clin Chem. Feb 2009;55(2):378-384. PMID 19106185 Venous Thromboembolic Disease
26. Naess IA, Christiansen SC, Romundstad PR, et al. Prospective study of homocysteine and MTHFR677TT genotype and risk for venous thrombosis in a general population--results from the HUNT 2 study. Br J Haematol. May 2008;141(4):529-535. PMID 18318759
27. National Institute for Health and Care Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification [CG181]. 2016; https://www.nice.org.uk/guidance/cg181/chapter/1- Recommendations#identifying-and-assessingcardiovascular-disease-cvd-risk-2. Accessed May 25, 2020.
28. National Institute for Health and Care Excellence (NICE). Venous thromboembolism in over 16s:reducing the risk of hospital acquired deep vein thrombosis or pulmonary embolism. [NG89]. 2018; https://www.nice.org.uk/guidance/ng89. Accessed June 1, 2020.
29. Nygard O, Nordrehaug JE, Refsum H, et al. Plasma homocysteine levels and mortality in patients with coronary artery disease. N Engl J Med. Jul 24 1997;337(4):230-236. PMID 9227928
30. Park CS, Ihm SH, Yoo KD, et al. Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levels and leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA. Am J Cardiol. May 1 2010;105(9):1284-1288. PMID 20403480
31. Park JH, Saposnik G, Ovbiagele B, et al. Effect of B-vitamins on stroke risk among individuals with vascular disease who are not on antiplatelets: A meta-analysis. Int J Stroke. Feb 2016;11(2):206-211. PMID 26783312
32. Peng HY, Man CF, Xu J, et al. Elevated homocysteine levels and risk of cardiovascular and all-cause mortality: a meta-analysis of prospective studies. J Zhejiang Univ Sci B. Jan 2015;16(1):78-86. PMID 25559959
33. Ray JG, Kearon C, Yi Q, et al. Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial. Ann Intern Med. Jun 5 2007;146(11):761-767. PMID 17470822
34. Ray JG. Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease. Arch Intern Med. Oct 26 1998;158(19):2101-2106. PMID 9801176
35. Sheng L, Wu C, Bai YY, et al. Plasma homocysteine levels are independently associated with alterations of large artery stiffness in men but not in women. J Geriatr Cardiol. May 2015;12(3):251-256. PMID 26089849
36. Shi Z, Guan Y, Huo YR, et al. Elevated total homocysteine levels in acute ischemic stroke are associated with long-term mortality. Stroke. Sep 2015;46(9):2419-2425. PMID 26199315
37. Shoamanesh A, Preis SR, Beiser AS, et al. Circulating biomarkers and incident ischemic stroke in the Framingham Offspring Study. Neurology. Sep 20 2016;87(12):1206-1211. PMID 27558379

38. Study of the Effectiveness of Additional Reductions in Cholesterol Homocysteine Collaborative Group, Armitage JM, Bowman L, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. Jama. Jun 23 2010;303(24):2486- 2494. PMID 20571015
39. UpToDate, Inc. (2022) "Overview of Homocysteine". Topic 6837 version 48.0. Last updated: December 6, 2021. Literature review current through: May 2022. Accessed June 23, 2022. Available at: https://www.uptodate.com
40. U.S. Preventive Services Task Force (USPSTF). Cardiovascular Disease: Risk Assessment Using Nontraditional Risk Factors. 2018; https://www.uspreventiveservicestaskforce.org. Accessed June 1, 2020.
41. U.S. Preventive Services Task Force (USPSTF). Coronary Heart Disease: Screening Using Non-Traditional Risk Factors. 2009; Accessed June 1, 2020. Available at: http://www.uspreventiveservicestaskforce.org
42. U.S. Preventive Services Task Force (USPSTF). Vitamin, Mineral, and Multivitamin Supplementation to Prevent Cardiovascular Disease and Cancer: Preventive Medication. Final Recommendation Statement. June 21, 2022. Accessed June 23, 2022. Available at: https://www.uspreventiveservicestaskforce.org
43. van Dijk SC, Enneman AW, Swart KM, et al. Effects of 2-year vitamin B12 and folic acid supplementation in hyperhomocysteinemic elderly on arterial stiffness and cardiovascular outcomes within the B-PROOF trial. J Hypertens. Sep 2015;33(9):1897-1906; discussion 1906. PMID 26147383
44. Veeranna V, Zalawadiya SK, Niraj A, et al. Homocysteine and reclassification of cardiovascular disease risk. J Am Coll Cardiol. Aug 30 2011;58(10):1025-1033. PMID 21867837
45. Wald NJ, Watt HC, Law MR, et al. Homocysteine and ischemic heart disease: results of a prospective study with implications regarding prevention. Arch Intern Med. Apr 27 1998;158(8):862-867. PMID 9570171
46. Wang C, Han L, Wu Q, et al. Association between homocysteine and incidence of ischemic stroke in subjects with essential hypertension: A matched case-control study. Clin Exp Hypertens. Nov 2015;37(7):557-562. PMID 25992490
47. Wang CY, Chen ZW, Zhang T, et al. Elevated plasma homocysteine level is associated with ischemic stroke in Chinese hypertensive patients. Eur J Intern Med. Jul 2014;25(6):538-544. PMID 248247585
48. Yi X, Zhou Y, Jiang D, et al. Efficacy of folic acid supplementation on endothelial function and plasma homocysteine concentration in coronary artery disease: A meta-analysis of randomized controlled trials. Exp Ther Med. May 2014;7(5):1100-1110. PMID 24940394
49. Zhou K, Zhao R, Geng Z, et al. Association between B-group vitamins and venous thrombosis: systematic review and meta-analysis of epidemiological studies. J Thromb Thrombolysis. Nov 2012;34(4):459-467. PMID 22743781
50. Zhou YH, Tang JY, Wu MJ, et al. Effect of folic acid supplementation on cardiovascular outcomes: a systematic review and meta-analysis. PLoS One. Oct 2011;6(9):e25142. PMID 21980387