Protocol

Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease

(20423)

(Formerly Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease)

Medical Benefit		**Effective Date**: 10/01/17	**Next Review Date**: 07/18
Preauthorization	No	**Review Dates**: 09/09, 09/10, 07/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17	

This protocol considers this test or procedure not medically necessary and investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic with risk of cardiovascular disease	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Change in disease status • Morbid events
Individuals: • With cardiovascular disease	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Change in disease status • Morbid events
Individuals: • Who are asymptomatic with risk of venous thromboembolism	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Change in disease status • Morbid events
Individuals: • Who have experienced venous thromboembolic events	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Change in disease status • Morbid events

Description

Homocysteine is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD) and increased risk of thrombosis in the general population and as a potential risk marker for people with CVD

and thrombotic disorders. The association between homocysteine-lowering interventions and risk of CVD or thrombotic events has also been examined.

Summary of Evidence

For individuals who are asymptomatic with risk of CVD or who have CVD who receive homocysteine testing, the evidence includes observational studies and randomized controlled trials (RCTs) of homocysteine-lowering interventions. Relevant outcomes are test accuracy and 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 preexisting 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 of a subgroup analysis from three RCTs of patients not on antiplatelets at baseline found that homocysteine-lowering treatment reduced the risk of stroke in that group. However, replication of this effect in countries with grain enriched with folic acid would be needed. Given the large amount of evidence from placebo-controlled RCTs 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 risk of venous thromboembolism (VTE) or who have experienced VTE events who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are test accuracy and 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 limited to men in the largest prospective study. However, evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces risk of VTE. Only one 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.

Policy

Measurement of plasma levels of homocysteine is considered **not medically necessary** in the screening, evaluation, and management of patients for cardiovascular disease.

Measurement of plasma levels of homocysteine is considered **investigational** in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism.

Background

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 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).

Interest in homocysteine as a potentially modifiable risk factor has been stimulated by the epidemiologic finding that levels of homocysteine inversely correlate with levels of folate. This finding has raised the possibility that treatment with folic acid might lower homocysteine levels and, in turn, reduce the risk of CVD and thrombotic events. Therefore, homocysteine has potential utility both as a risk predictor and as a target of treatment.

Determination of homocysteine concentration may be offered as a component of a comprehensive cardiovascular risk assessment that may include evaluation of small-density lipoproteins, subclassification of high-density lipoproteins, evaluation of lipoprotein (a), high-sensitivity C-reactive protein, and genotyping of apolipoprotein E. Determination of homocysteine concentration may also be offered as part of risk assessment for patients at high risk of VTE events or who have experienced idiopathic VTE, recurrent VTE, thrombosis occurring at a young age, or thrombosis at an unusual site.

Regulatory Status

Several homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA product code: LPS. Examples are listed in Table 1.

Table 1. Homocysteine Test Systems

Test	Manufacturer	Cleared
Homocysteine Enzymatic Assay	Roche Diagnostics	2012
Diazyme Enzymatic Homocysteine Assay	Diazyme Laboratories	2012
A/C Automatic Enzymatic Hcy [Homocysteine] Assay	AntiCancer Inc.	2008
Teco Enzymatic Homocysteine Assay	Teco Diagnostics	2007

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: C-reactive protein as a cardiac risk marker. TEC Assessments. 2002; 17: Tab 23.

2. 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
3. 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
4. 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
5. 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
6. 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
7. 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
8. 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 24824758
9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
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. 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
18. 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
19. 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
20. Marti-Carvajal AJ, Sola I, Lathyris D, et al. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2013; 1:CD006612. PMID 23440809
21. Marti-Carvajal AJ, Sola I, Lathyris D. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2015; 1:CD006612. PMID 25590290
22. Zhou YH, Tang JY, Wu MJ, et al. Effect of folic acid supplementation on cardiovascular outcomes: a systematic review and meta-analysis. PLoS ONE. 2011; 6(9):e25142. PMID 21980387

23. 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
24. 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
25. 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
26. 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
27. 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
28. Bonaa 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
29. 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
30. 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
31. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. J Thromb Haemost. Feb 2005; 3(2):292-299. PMID 15670035
32. den Heijer M, Rosendaal FR, Blom HJ, et al. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. Thromb Haemost. Dec 1998; 80(6):874-877. PMID 9869152
33. 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
34. 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 17200768
35. Naess IA, Christiansen SC, Romundstad PR, et al. Prospective study of homocysteine and MTHFR 677TT 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
36. 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
37. 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
38. 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
39. 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-assessing-cardiovascular-disease-cvd-risk-2. Accessed November 16, 2016.

40. 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
41. 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
42. 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
43. Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement. 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
44. National Institute for Health and Care Excellence (NICE). Venous thromboembolism: reducing the risk for patients in hospital [CG92]. 2015; https://www.nice.org.uk/guidance/CG92. Accessed November 16, 2016.
45. U.S. Preventive Services Task Force. Using Nontraditional Risk Factors In Coronary Heart Disease Risk Assessment. 2009; http://www.uspreventiveservicestaskforce.org/uspstf/uspscoronaryhd.htm. Accessed November 14, 2016.
46. U.S. Preventive Services Task Force. Topic Update in Process. Cardiovascular Disease: Risk Assessment Using Nontraditional Risk Factors. 2015; http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/coronary-heart-disease-screening-using-non-traditional-risk-assessment. Accessed November 14, 2016.