

Evidence Based Guideline

Homocysteine Testing in Cardiac Disease Risk Assessment

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Description of Procedure or Service

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. The laboratory test is referred to as either homocysteine or homocyst(e)ine.

Plasma levels of homocysteine have been actively researched as a risk factor for cardiovascular disease, 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 cardiovascular disease. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine was an independent risk factor for cardiovascular disease, and could be used to improve current risk prediction models.

Interest in homocysteine as a potentially modifiable risk factor has been stimulated by the epidemiologic finding that levels of homocysteine are inversely correlated 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 coronary artery disease (CAD). Therefore, homocysteine has potential utility both as a risk predictor and as a target of treatment.

Determination of homocysteine 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.

*****Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Evidence Based Guideline for Homocysteine Testing in Cardiac Disease Risk Assessment

Measurement of plasma levels of homocysteine may not be appropriate in the screening, evaluation, and management of patients for cardiovascular disease.

Medical Evidence Regarding Homocysteine Testing in Cardiac Disease Risk Assessment

Observational evidence generally supports the association of homocysteine levels with risk of cardiovascular disease, especially in patients with pre-existing vascular disease. However, evidence from randomized controlled trials does not support the hypothesis that lowering homocysteine levels by treatment with folate and/or B vitamins improves cardiovascular outcomes. Numerous large, randomized

Homocysteine Testing in Cardiac Disease Risk Assessment

controlled trials and meta-analyses of these trials are consistent in reporting that treatment with folic acid is ineffective in reducing major cardiovascular events including stroke, myocardial infarction and total mortality.

Due to the large amount of evidence from placebo-controlled RCTs that homocysteine-lowering interventions do not improve health outcomes, routine testing for homocysteine and intervention for patients with hyperhomocysteinemia is not recommended. In 2009, the U.S. Preventive Services Task Force (USPSTF) issued a recommendation statement that the evidence is insufficient (I statement) to assess the benefits and harms of using nontraditional risk factors to screen asymptomatic adults with no history of coronary heart disease (CHD) to prevent CHD events. Homocysteine was one of the nontraditional risk factors considered in the recommendation.

A 2010 statement issued by the American Heart Association (AHA) states that the organization does not consider high homocysteine levels in the blood to be a major risk factor for cardiovascular disease. (18) It further states that a causal link between homocysteine levels and atherosclerosis has not been established.

A 2010 guideline from the American College of Cardiology Foundation and the American Heart Association on assessment of cardiovascular risk in asymptomatic adults did not address measurement of homocysteine levels.

Benefits Application

Please refer to certificate for availability of benefit. This guideline relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore certificate language should be reviewed before applying the terms of the guideline.

Billing/Coding/Physician Documentation Information

This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 83090

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.23, 4/24/09.

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Homocysteine Testing in Cardiac Disease Risk Assessment

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Senior Medical Director review 9/2009

Specialty Matched Consultant Advisory Panel review 3/2010

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Abraham JM, Cho L. The homocysteine hypothesis: still relevant to the prevention and treatment of cardiovascular disease? *Cleve Clin J Med*. 2010 Dec;77(12):911-8. Retrieved on March 10, 2011 from <http://www.ccjm.org/content/77/12/911.long>

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Specialty Matched Consultant Advisory Panel review 4/2011

American Heart Association. AHA Recommendation: Homocysteine, Folic Acid and Cardiovascular Risk. Retrieved on march 21, 2012 from http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/Homocysteine-Folic-Acid-and-Cardiovascular-Disease_UCM_305997_Article.jsp.

Greenland P, Alpert JS, Beller GA et al. American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA guideline for assessment of cardiovascular risk on asymptomatic adults. *Circulation* 2010; 21: 122(25):e584-636. Retrieved on March 21, 2012 from <http://circ.ahajournals.org/content/122/25/2748.full.pdf>

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.23, 4/12/12

Policy Implementation/Update Information

- 10/26/09 New Evidence Based Guideline. Measurement of plasma levels of homocysteine may not be appropriate in the screening, evaluation, and management of patients for cardiovascular disease. (adn)
- 4/27/10 Specialty Matched Consultant Advisory Panel review 3/24/2010. Removed Policy Guideline number. No change to policy.(mco)
- 5/10/11 Specialty Matched Consultant Advisory Panel review 4/2011. References Updated. (mco)
- 5/1/12 Specialty Matched Consultant Advisory Panel review 4/2012. “When not Recommended” section updated. References updated. (mco)

Homocysteine Testing in Cardiac Disease Risk Assessment

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