

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 homocystine 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:

Research has evaluated the clinical utility of homocysteine as a risk predictor of coronary artery disease (CAD) in the general population and as a modifiable risk factor for patients with CAD. Several prospective studies have evaluated the relationship between homocysteine and cardiovascular disease in asymptomatic patients, but the data derived from these studies are inconclusive. For patients with known CAD, prospective data are more consistent in supporting the utility of homocysteine as a risk factor for future events. A meta-analysis of 30 observational studies concluded that homocysteine was, in general, a modest independent risk factor for the occurrence of cardiovascular events and strokes. The association between homocysteine levels and CAD was much stronger in retrospective studies involving subjects diagnosed with vascular disease than in prospective studies of healthy individuals.

Several limitations are involved in evaluating whether or not reducing homocysteine levels leads to reduced cardiovascular risk. First, improved prediction of risk does not by itself result in better health outcomes. Clinical trial evidence on the impact of intervening and modifying the risk factor is required. Also, to improve outcomes, clinicians must have the tools to translate this information into clinical practice. This process involves guidelines that incorporate emerging risk factors into existing risk prediction models that are demonstrated to more accurately classify patients into risk categories and that are accompanied by treatment guidelines that better target interventions toward patients who will benefit the most. Currently, no target levels exist for optimal homocysteine levels.

The American Heart Association does not recommend population-wide screening for homocysteine levels nor does it recommend routine supplementation with folate and/or B vitamins to reduce homocysteine levels. The Association's statement suggests that measurement of plasma homocysteine may have some role in patients with a personal or family history consistent with premature cardiovascular disease and that those with levels above 10.0 micromol/L would be advised to increase their intake of folic acid. However the outcomes of this treatment strategy have not been addressed in controlled trials.

Observational evidence generally supports the association of homocysteine levels with risk of cardiovascular disease, especially in patients with pre-existing vascular disease. In addition, some indirect evidence suggests that homocysteine lowering may have cardiovascular benefits. 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 controlled trials are consistent in reporting that treatment with folic acid is ineffective in reducing cardiac events. For the outcome of stroke, the evidence is less conclusive, with some randomized controlled trials reporting a benefit and others reporting no benefit. A meta-analysis of the effect of treatment on prevention of stroke suggests that there may be an overall benefit, but that this benefit is concentrated within populations in whom fortification of grain with folate is not present.

Therefore, the utility of routine testing for homocysteine and intervention for patients with hyperhomocysteinemia is questionable.

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 policy.

Billing/Coding/Physician Documentation Information

This policy 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

Policy: Homocysteine Testing in Cardiac Disease Risk Assessment

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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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* 1997; 17(10):1947-53.

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Senior Medical Director review 9/2009

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)

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