Name of Policy: Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease

Policy #: 341       Latest Review Date: April 2014
Category: Laboratory     Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**

Homocysteine is an amino acid found in the blood; levels are inversely correlated with folate levels. Homocysteine has been evaluated as a potential marker of cardiovascular disease (CVD) in the general population and as a potential risk marker among people with CVD. The association between homocysteine-lowering interventions and risk of CVD has also been examined.

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 (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 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 cardiovascular disease. 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.

**Policy:**

**Measurement of plasma levels of homocysteine** for the screening, evaluation, and management of patients for cardiovascular disease does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*
Key Points:

Rationale
This policy is updated regularly with searches of the MEDLINE database. Following is a summary of the key literature to date:

Homocysteine testing can be evaluated in a similar framework as other novel cardiac risk factors. There are several conditions that must be met in order for a cardiovascular risk factor to demonstrate clinical utility. A 2002 TEC Assessment summarized three steps necessary for clinical utility:

- Standardization of measurement of the risk factor.
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor contributes independently to risk assessment compared to established risk factors.
- Determination of how the novel risk factor will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcomes.

Is measurement of homocysteine standardized?
There are FDA-cleared commercially available kits for measuring homocysteine.

Is homocysteine an independent risk factor for cardiovascular disease?
In 2002, the Homocysteine Studies Collaboration published a meta-analysis of observational studies evaluating the association between homocysteine concentration and risk of ischemic heart disease or stroke. A total of 30 studies were identified that had individual patient data available; this included 18 retrospective studies and 13 prospective studies. In the prospective studies, blood for measuring homocysteine concentration was collected before the clinical onset of disease. The adjusted odds ratio (OR) of ischemic heart disease associated with a 25% lower homocysteine level were 0.83 (95% confidence interval [CI]: 0.77 to 0.89) in prospective studies, 0.67 (95% CI: 0.62-0.71) in retrospective studies using population controls, and 0.73 (95% CI: 0.64-0.83) in retrospectives studies with other controls. The adjusted OR of stroke associated with a 25% lower homocysteine level was 0.77 (95% CI: 0.66-0.90) in prospective studies, 0.86 (95% CI: 0.73-1.01) in retrospective studies with population controls, and 0.46 (95% CI: 0.30-0.70) in retrospective studies with other controls. The authors noted that the risk of ischemic heart disease and stroke was significantly weaker in the prospective studies than the retrospective studies, which may reflect biases in retrospective studies.

Among the prospective studies was one by Folsom et al that identified patients who developed coronary heart disease among an initial cohort of 15,792 patients participating in the Atherosclerosis Risk in Communities (ARIC) trial. The median follow-up time was 3.3 years. Plasma homocysteine was evaluated from the stored blood samples of the 232 patients plus a random sample of the rest of the cohort. While homocysteine was a significant univariate predictor of coronary artery disease (CAD), this association was not significant after adjusting for other cardiac risk factors in multivariate analysis. Another prospective study was published by Evans et al. The investigators identified 240 cases of nonfatal myocardial infarction (MI) or coronary death among a cohort of 12,866 men participating in the Multiple Risk Factor Intervention Trial (MRFIT). Homocysteine from stored blood samples from these patients plus
472 control patients were evaluated. With a follow-up ranging from 11 to 17 years, homocysteine levels did not appear to be an independent risk factor for coronary heart disease (CHD). In contrast, in a nested case-control study derived from a prospective cohort study of 21,520 men enrolled in the British United Provident Study, Wald et al reported that the initial stored plasma level of homocysteine was significantly higher among 229 men who ultimately died of IHD compared with a control group of 1126 men who did not die of IHD and did not have a history of IHD.

For patients with known CVD, prospective data more consistently support the utility of homocysteine as a risk factor for future events. In 1997, for example, Nygard et al reported on a prospective study of the plasma homocysteine levels in 587 patients with angiographically confirmed CAD. After a median follow-up of 4.6 years, the authors compared the initial homocysteine levels of the 64 patients (10.9%) who had died with those of the remaining 523 survivors. The authors reported a strong graded dose-response relationship between plasma homocysteine and mortality. In addition, Knekt et al reported the outcomes at 13 years’ follow-up of 3471 middle-aged Finnish men, 884 of whom had known cardiovascular disease at baseline. Using the homocysteine values from stored blood samples, a strong positive correlation was noted between homocysteine concentration and subsequent major coronary events in men with known CVD at baseline. However, they found no association between serum homocysteine concentration and the incidence of major coronary events (death from CHD or nonfatal MI) among men originally free of heart disease.

Since the publication of the Homocysteine Studies Collaboration meta-analysis, a number of studies have reported on the association between homocysteine and CVD. In 2010, Park et al published an analysis of data from a large nationally representative survey of U.S. residents. The analysis was restricted to the 6371 individuals aged 40 to 79 years who had no history of MI, stroke, peripheral artery disease, or stroke. The investigators stratified participants according to their estimated 10-year risk of CVD, using the Framingham risk score; low-risk, less than 10% (n=2527), intermediate-risk, 10% to 20% (n=3336), and high-risk, greater than 20% (n=508). Information on homocysteine level was available for 3860 (61%) patients. There was a statistically significant association between elevated homocysteine levels (defined as at least the 85% percentile) and being categorized as having a high 10-year risk of CVD (OR=2.11, 95% CI, 1.48 to 3.01). The association between elevated homocysteine levels and intermediate cardiovascular risk was not significant (OR=1.11, 95% CI, 0.89 to 1.38). The survey was cross-sectional rather than prospective, limiting possible/potential conclusions about the predictive value of homocysteine levels.

In 2011, Veeranna and colleagues published a post-hoc analysis of national survey databases to evaluate whether adding homocysteine to the Framingham risk score model improves risk classification. The data were taken from the nationally representative surveys Multi-Ethnic Study of Atherosclerosis (MESA), which included individuals between the ages of 45 and 84 years with no prior history of CVD and the National Health and Nutrition Survey III (NHANES III), a sample of non-institutionalized individuals. Homocysteine level was associated with CVD risk in both databases. In a receiver-operating curve (ROC) analysis, the area under the curve (AUC) for predicting CHD events in the MESA database was 0.74 using the Framingham risk score and 0.76 when homocysteine level was added to the Framingham score. The improvement in risk
prediction was statistically significant, p<0.001. The AUC for predicting CHD deaths in NHANES III was 0.84 using the Framingham risk score alone and 0.87 when homocysteine level was added to the Framingham score; this difference was statistically significant, p<0.001. Adding homocysteine to the Framingham model resulted in reclassification of 832 (12.9%) individuals in the MESA cohort and 1,243 (18%) in the NHANES III cohort. This study does not address whether testing for homocysteine would improve health outcomes. This would involve evaluating the impact of homocysteine-lowering interventions on risk of cardiovascular disease, which is discussed in the next section of the policy.

Section Summary
A meta-analysis of observational studies found a statistically significant moderate association between homocysteine levels and risk of cardiovascular disease. Studies have also found a significant correlation between homocysteine levels in individuals with known cardiovascular disease and subsequent coronary events. One recent study analyzing nationally representative survey data found that adding homocysteine level to the Framingham risk score significantly improved risk prediction.

Will identification of homocysteine level lead to changes in patient management, and will these changes in management lead to improved patient outcomes?
Vitamin B and folic acid supplementation are potential interventions that could be used for patients with homocysteine levels to improve health outcomes. However, public health measures are already in place that requires all enriched grain products be fortified with folic acid to reduce the risk of neural-tube defects in newborns. This fortification has been associated with a decrease in plasma homocysteine concentration in a population-representative adult sample. Trials evaluating the impact of homocysteine-lowering therapy on health outcomes should thus evaluate the utility of treatments that lower homocysteine levels beyond those achieved by these general public health measures. In addition, clear target levels for homocysteine concentration would need to be established for translating information on homocysteine lowering into clinical practice.

Numerous randomized, controlled trials (RCTs) have been published that provide evidence on the benefit of vitamin therapy to reduce homocysteine levels and prevent cardiovascular events. Moreover, several meta-analyses have synthesized the available RCT evidence on this question. Most recently, in 2013, a Cochrane systematic review on the effectiveness of homocysteine-lowering interventions for preventing cardiovascular events, including both MI and stroke, was updated. The review included trials that recruited adults with established CVD and had at least one year of follow-up and excluded trials with end-stage renal disease patients. Twelve trials with a total of 47,429 participants met eligibility criteria. Nine of the studies included more than 1,000 participants. Nine studies used placebo controls, two used usual care controls and one compared high and low doses of homocysteine-lowering therapy. In a pooled analysis of 11 trials, there was no statistically significant difference in non-fatal or fatal MI between intervention and control groups [relative risk (RR): 1.02, 95% CI: 0.95 to 1.10]. In a pooled analysis of nine studies, there was no significant difference between groups in the rate of non-fatal or fatal stroke (RR: 0.91; 95% CI: 0.82 to 1.00). There was also no significant mortality benefit in groups assigned to homocysteine-lowering therapy. For mortality of any cause, the relative risk was 1.01 (95% CI: 0.96 to 1.07) in a meta-analysis of data from 10 trials.
In 2011 Zhou et al conducted a systematic review of double-blind placebo-controlled RCTs evaluating the impact of folic acid supplementation on cardiovascular outcomes. Interventions were included whether or not they involved supplementation with vitamin B in addition to folic acid. The review was limited to trials that included at least 100 patients and had at least six months follow-up. Of 66 articles retrieved for detailed inspection, 16 trials with data on 44,841 patients met the review’s inclusion criteria. In a meta-analysis of findings from 12 trials, folic acid supplementation was not found to have a significant effect on major cardiovascular events compared to placebo (RR: 0.98, 95% CI: 0.93 to 1.04). In addition, folic acid supplementation did not have a significant effect on individual outcomes including stroke (12 trials, RR: 0.89, 95% CI: 0.78 to 1.01), myocardial infarction (11 trials, RR: 1.00, 95% CI: 0.93 to 1.07), or all-cause mortality (14 trials, RR: 1.00, 95% CI: 0.96 to 1.05).

Also in 2011, Clarke et al published a meta-analysis of placebo-controlled homocysteine-lowering RCTs. This meta-analysis was limited to studies that included at least 1,000 participants and have at least one year of follow-up. A total of eight trials with 37,485 individuals met the review’s inclusion criteria. In a pooled analysis of findings from the eight trials, vitamin B supplementation did not have a significant effect on risk of coronary heart disease (CHD) events compared to placebo; RR: 1.01 (95% CI: 0.96 to 1.07). In addition, in pooled analyses of data from the eight trials, vitamin B supplementation was not found to have a significant effect on stroke events (RR: 0.96, 95% CI: 0.87 to 1.07), cancer events (RR: 1.08, 95% CI: 0.99 to 1.17) or all-cause mortality (RR: 1.02, 95% CI: 0.97 to 1.07).

A fourth meta-analysis, published in 2012 by Huang et al, included RCTs evaluating B vitamin supplementation in patients with pre-existing vascular disease. This review had more lenient inclusion criteria, as there was no limitation on study size or intervention duration. A total of 19 trials with 47,921 patients were included in the meta-analysis. Unlike the other meta-analyses discussed above, in a pooled analysis of study data, the authors found a statistically significant benefit of vitamin B supplementation on stroke (RR: 0.88, 95% CI: 0.82 to 0.95). Similar to the other meta-analyses, vitamin B supplementation was not found to have a statistically significant impact on other outcomes, including CHD, myocardial infarction and all-cause mortality. Given the more relaxed entry criteria, the meta-analysis may have included some lower-quality studies; the authors did not present a formal analysis of trial quality.

Representative RCTs are described below:

The HOPE-2 trial included 5,522 patients with pre-existing vascular disease. Patients were randomized to treatment with a regimen of folate, vitamin B6, and vitamin B12 or placebo and followed up for an average of approximately five years. There were no significant differences in the composite outcome of cardiovascular death, MI, or stroke (relative risk [RR]: 0.95; 95% CI: 0.84–1.07). However, there was a significant decrease in the risk of stroke for patients in the treatment group (RR: 0.75; 95% CI: 0.59-0.97, p=0.03). For the secondary outcome of hospitalization for unstable angina, a significantly increased risk was reported for the treatment group (RR: 1.24; 95% CI: 1.04-1.49, p=0.02).

The NORVIT enrolled 3,749 patients with a recent MI and randomized patients to combinations of folate and/or B vitamins. Patients were followed up for a mean of 3.3 years for the primary
outcome, which was a composite of recurrent MI, stroke, and sudden cardiac death. For patients assigned to the active treatment groups, no significant reductions were noted in any of the primary or secondary outcomes. For patients assigned to the combined folate/vitamin B6/vitamin B12 group, an increased risk that was marginally significant (RR: 1.22; 95% CI: 1.00–1.50, p=0.05) was observed for the primary composite outcome group.

In 2010, findings from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) in the U.K. were reported. A total of 12,064 adult patients with a history of MI were randomized to receive folic acid and vitamin B12 or placebo. An additional eligibility criterion was blood cholesterol of at least 135 mg/dL if taking a statin or 174 mg/dL otherwise. Prior to randomization, patients participated in a run-in period to confirm that they were adherent to treatment. (Patients were also randomized to receive different doses of simvastatin; those findings are not reported here.) After three to four years of follow-up, due to the low number of major coronary events in the treatment group, the steering committee (blinded to interim between-group outcomes) decided to change the primary outcome from major coronary events to major vascular events. This composite variable included nonfatal MI, death from CHD, fatal or nonfatal stroke, or any arterial revascularization. After a mean follow-up of 6.7 years, vitamin treatment was not associated with a statistically significant reduction in the primary outcome. The number of major vascular events were 1,537 (25.5%) in the vitamin group and 1,493 (24.8%) in the placebo group (RR: 1.04; 95% CI: 0.97-1.12). There were no significant differences in risk for any of the components of the composite outcome. In addition, death from all causes did not differ significantly between groups; there were 983 (16.3%) deaths in the vitamin group and 951 (15.8%) in the placebo group (RR: 1.04; 95% CI: 0.96 to 1.13).

Section Summary
Numerous large placebo-controlled RCTs have been published that evaluate the impact of folic acid/ vitamin B supplementation on risk of cardiovascular events, including MI and stroke. With few exceptions, meta-analyses of these RCTs have found that homocysteine-lowering interventions do not have a statistically significant effect on the rate of major cardiovascular events.

Summary
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 controlled trials and meta-analyses of these trials are consistent in reporting that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. 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 considered investigational.

Practice Guidelines and Position Statements
In 2009, the U.S. Preventive Services Task Force (USPSTF) issued a recommendation statement that the evidence is insufficient (one 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 (updated March 2014) 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. 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.

Key Words:
Homocysteine, homocystine, hyperhomocysteinemia

Approved by Governing Bodies:
Several homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. These include the liquid-stable two-part homocysteine reagent test by Catch Incorporated (Maple Valley, WA) in 2006. Catch Inc. was purchased by Axis-Shield (Scotland) in 2010 and the Catch branded products were phased out in 2011. The test is indicated for the in vitro quantitative determination of total homocysteine in serum and plasma to assist in diagnosing and treating patients with suspicion of homocystinuria and hyperhomocysteinemia. Other homocysteine test systems cleared for marketing by FDA include the Diazyme Enzymatic Homocysteine Assay (General Atomics, Poway, CA) cleared in 2012, and the A/C Automatic Enzymatic Hcy [Homocysteine] Assay (AntiCancer, Inc., San Diego, CA) cleared in 2008.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan.

Current Coding:
CPT Codes:
83090 Homocysteine

References:
1. American Heart Association. AHA Recommendation: Homocysteine, Folic Acid and Cardiovascular Risk. Available online at:
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). C-reactive protein as a cardiac risk marker (Special Report). TEC Assessments 2002; Volume 17, Tab 23.
32. The Homocysteine Studies collaboration. Homocysteine and risk of ischemic heart disease and stroke; a meta-analysis. JAMA 2002; 288(16); 2015-22.


Policy History:
Medical Policy Group, January 2009 (2)
Medical Policy Administration Committee, February 2009
Available for comment January 22-March 8, 2009
Medical Policy Group, May 2009 (2)
Medical Policy Administration Committee, June 2009
Medical Policy Group, April 2011 (1): Update to Description, Key Points and References
Medical Policy Group, November 2012 (1): 2012 Updates to Key Points and References. Policy statement remains unchanged
Medical Policy Group, February 2014 (1): Update to Key Points and References; no change to policy statement
Medical Policy Panel, April 2014
Medical Policy Group, April 2014 (1): Policy updated with literature review through February 2014; no references added; no change to policy statement