Policy Replaced by LCDs L33418, L34419 & L36129
Effective February 26, 2018

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 341
Category: Laboratory

Latest Review Date: January 2016
Policy Grade: A

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

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Description of Procedure or Service:

Homocysteine is an amino acid found in the blood which 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:

Effective for dates of service on or after March 16, 2009 and prior to February 26, 2018:
Blue Advantage will treat **measurement of plasma levels of homocysteine** for the screening, evaluation, and management of patients for **cardiovascular disease** as a **non-covered** benefit and as **investigational**.

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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:

The most recent literature update was performed through November 9, 2015. The 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. The most recent literature update was performed through November 9, 2015. The 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.

Standardized Measurement of Homocysteine

There are FDA-cleared commercially available kits for measuring homocysteine.

Homocysteine As 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 retrospectives studies, which may reflect biases in retrospective studies.

Subsequent meta-analyses of observational studies have found significant associations between homocysteine and morbidity and mortality, including a 2015 meta-analysis of 12 studies, three which found increased coronary artery disease (CAD), cardiovascular, and all-cause mortality with higher homocysteine levels.

Among the prospective studies included in the Homocysteine Studies Collaboration meta-analysis 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.

Since the publication of the Homocysteine Studies Collaboration meta-analysis, a number of studies have reported on the association between homocysteine and various types of cardiovascular disease (CVD). Representative studies are described in Table 1.

Table 1: Individual Studies of Homocysteine and Cardiovascular Disease Risk

Study	Population	Outcome(s) Evaluated	Major Findings
Park et al (2010)	6371 individuals ages 40-79 y without history of MI, stroke, or PAD; 3860 (61%) with homocysteine level available	10-y CVD risk based on Framingham score: • Low risk (n=2527) • Intermediate risk (n=3336) • High risk (n=508)	• Homocysteine levels at ≥85th percentile associated with high Framingham risk score: OR=2.1 (95% CI, 1.48 to 3.01) • Homocysteine levels at ≥85th percentile not significantly associated with intermediate Framingham risk score: OR=1.11 (95% CI, 0.89 to 1.38)
Wang et al (2014)	5935 individuals with hypertension enrolled in a population-based prospective cohort study	• Incident ischemic stroke • CHD	• Homocysteine levels ≥30 µmol/L (vs <15 µmol/L) associated with higher ischemic stroke rates after adjusting for ischemic stroke risk factors: OR=2.86 (95% CI, 1.72 to 4.75) • Homocysteine levels ≥30 µmol/L (vs <15 µmol/L) not associated with CHD
Han et al (2015)	5488 individuals with follow-up available from population-based prospective cohort study of 5935 hypertensive individuals	Incident ischemic stroke	• Homocysteine levels ≥15 µmol/L associated with higher ischemic stroke rates: HR=2.18 (95% CI, 1.65 to 2.89) • Among 501 subjects who took folic acid supplementation, plasma homocysteine levels declined an average 6.7 µmol/L (clinical outcomes not reported

			separately)
Wang et al (2015)	200 cases with hypertension and ischemic stroke, vs 400 age-matched controls with hypertension and without ischemic stroke	Incident stroke	After adjusting for ischemic stroke risk factors, total homocysteine associated with ischemic stroke among women but not men: • Women: OR for stroke (comparing highest with lowest total homocysteine quartile), 4.51 (95% CI, 1.29 to 15.7) • Men: OR for stroke, 0.83 (95% CI, 0.36 to 1.90)
Catena et al (2015)	562 consecutive patients with hypertension evaluated at a single center	Prevalence of: • Metabolic syndrome • CHD • Cerebrovascular disease	After adjustment for confounding variables, homocysteine significantly associated with: • Presence of metabolic syndrome: OR=1.01 (95% CI, 1.00 to 1.02; p=0.02) • Presence of cerebro-/cardiovascular disease: OR=1.011 (95% CI, 1.00 to 1.02; p=0.01)
Sheng et al (2015)	1680 subjects with arterial stiffness measurements enrolled in a community-based cross-sectional study	Vascular function measurements: • CF-PWV • CA-PWV • Heart rate-corrected AI	Homocysteine levels positively correlated with: • CF-PWV: r=0.211 (p<0.001) • CA-PWV: r=0.148 (p<0.001) Levels negatively correlated with AI: r = -0.052 (p=0.016)
Shi et al (2015)	3799 adults with ischemic stroke enrolled a single hospital in China	Poststroke mortality	Among 223 patients who died during follow-up, those with highest 3rd and 4th quartiles of homocysteine had higher risk of stroke death, after adjusting for confounding variables: • 3th vs 1st quartile: adjusted HR=2.27 (95% CI, 1.06 to 4.86; p=0.029) • 4th vs 1st quartile: adjusted HR=2.15 (95% CI, 1.01 to 4.63; p=0.049)

AI: augmentation index; CA-PWV: carotid-ankle pulse wave velocity; CF-PWV: carotid-femoral pulse wave velocity; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; MI: myocardial infarction; OR: odds ratio; PAD: peripheral arterial disease .

For patients with known CVD, prospective data more consistently demonstrate that homocysteine is 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.

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, $p<0001$. 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.

Section Summary: Homocysteine as an Independent Risk Factor for Cardiovascular Disease
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. Overall, the available evidence suggests that homocysteine levels are associated with increased risk of a variety of cardiovascular disorders and outcomes among patients with existing CVD.

Impact on Identification of Homocysteine Level Leading to Changes in Patient Management and 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.

Systematic Reviews

In 2015, a Cochrane systematic review, originally published in 2009 and updated in 2013, on the effectiveness of homocysteine-lowering interventions for preventing cardiovascular events, including both MI and stroke, was updated. The review included RCTs assessing the effects of homocysteine-lowering interventions for preventing cardiovascular events with at least one year of follow-up and considered MI and stroke as the primary outcomes. No new trials published since the last update were identified. 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 ten 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.

A 2014 meta-analysis included RCTs that compared folic acid supplementation (at least 5 mg/d for at least four weeks), without vitamin B supplementation, with placebo and evaluated endothelial function and homocysteine level as outcomes in patients with CAD. A total of six trials with 377 subjects were included. In pooled analysis, folic acid supplementation was associated with increased flow-mediated dilation (FMD), a noninvasive, ultrasound-based method to assess vascular endothelial function (mean difference (MD), 57.72μm; 95% CI, 50.14 to 65.3; $p<0.05$). Folic acid supplementation was also associated with reduced plasma homocysteine concentration (MD = -3.66μmol/L; 95% CI, -5.44 to -7.87; $p<0.05$). For other measures of endothelial function, there was no significant change in the response to end diastolic diameter, glyceryl-trinitrate diameter, heart rate, baseline and peak hyperemic flow, and systolic and diastolic blood pressure between the folic acid and placebo groups.

Liu et al also reported results of a meta-analysis of placebo-controlled RCTs that evaluated the effect of homocysteine-lowering therapies on FMD in patients with CAD. A total of eight studies with 611 subjects were included; folic acid doses ranged from 400 to 10,000μg/d. In pooled analysis, folic acid supplementation was associated with improved FMD compared with placebo (standardized MD=1.65; 95% CI, 1.12 to 2.17; $p<0.001$), but there was significant heterogeneity across studies.

Randomized Controlled Trials

Representative RCTs evaluating homocysteine-lower interventions are described next.

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 was 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).

Since the publication of the systematic reviews and meta-analyses described above, van Dijk et al reported results of the B-PROOF trial, an RCT comparing B vitamins (vitamin B_{12} 500 mg and folic acid 400 mg) with placebo for improving cardiovascular outcomes among elderly patients with hyperhomocysteinemia. The study included 2929 subjects over age 65 with an elevated homocysteine level (12-50 µmol/L) who were randomized to two years of B vitamin therapy (n=1458) or placebo (n=1461). A random sample of participants (n=569) underwent baseline vascular measurements. Within the vascular subgroup, the aortic pulse pressure after two years of intervention was significantly higher in the B vitamin treatment group than in the placebo group (49.6 mm Hg vs 47.2 mm Hg, p=0.02). However, aortic-femoral pulse wave velocity and carotid intima-media thickness did not differ significantly between groups. In the vascular subgroup, serum homocysteine increased by 0.6 µmol/L in the placebo group but decreased by 3.6 µmol/L in the B vitamin therapy group. In the entire study population, the treatment groups did not differ significantly in terms of blood pressure or hypertension incidence, cerebrovascular event incidence, or MI incidence. In subgroup analyses, among women, treatment group subjects had lower incidence of cerebrovascular events than placebo group subjects (OR=0.33; 95% CI, 0.15 to 0.71).

Section Summary: Management Changes and Outcome Improvements Associated With Homocysteine Level Measurements

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. Two meta-analyses of RCTs reported that homocysteine-lowering interventions are associated with improvements in a measure of vascular endothelial function, but it is uncertain whether these changes are associated with improved clinical outcomes.

Summary

The evidence for the use of homocysteine testing in individuals who are asymptomatic with risk of cardiovascular disease (CVD) or patients with CVD includes of 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 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 evaluating homocysteine-lowering interventions 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. 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 lead to changes in management that improve health outcomes. The evidence is sufficient to determine qualitatively that the technology is unlikely to improve the net health outcome.

Practice Guidelines and Position Statements
In 2013, the American College of Cardiology Foundation and the American Heart Association Task Force on Practice Guidelines issued guidelines on the assessment of cardiovascular risk, which did not address measurement of homocysteine levels.

U.S. Preventive Services Task Force Recommendations
In 2009, the U.S. Preventive Services Task Force issued a recommendation statement that the evidence is insufficient (1 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. The recommendation statements are currently being updated.

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 Homocysteine Enzymatic Assay (Roche Diagnostics, Indianapolis, IN) in 2012, the Diazyme Enzymatic Homocysteine Assay (Diazyme Laboratories, Poway, CA) cleared in 2012, the A/C Automatic Enzymatic Hcy [Homocysteine] Assay (AntiCancer, Inc., San Diego, CA) cleared in 2008, and the Teco Enzymatic Homocysteine Assay (Teco Diagnostics, Anaheim, CA) in 2007.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

83090 Homocysteine

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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review in Blue Cross and Blue Shield's administration of plan contracts.