



Policy #: 016

**Original policy date: 3/2008
Revised date: 10/27/09**

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Title

Homocysteine Testing: Screening, Diagnosis, and Management of Cardiovascular Disease

When services are not covered for commercial products and for Medicare HMOB, Medicare PPO Blue and Blue Medicare PFFS PlusRx products

We do not cover **the measurement of plasma levels of homocysteine**, in the screening, evaluation, and management of patients for cardiovascular disease since it is considered investigational and does not meet the BCBSMA Medical Technology Assessment Guidelines, #350.^{1,2}

Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual’s unique circumstances may be considered in light of current scientific literature.

For consideration of an individual patient, physicians may send relevant clinical information to:

For services already billed

Blue Cross Blue Shield of Massachusetts
Provider Appeals
PO Box 986065
Boston, MA 02298

Prior to performance of service

Blue Cross Blue Shield of Massachusetts
Case Creation/Medical Policy
One Enterprise Drive
Quincy, MA 02171
Tel: 1-800-327-6716
Fax: 1-888-641-5330

Managed care guidelines

- Any specialist visit requires a referral for **Medicare HMO Blue**.
- For all other Managed Care plans, any specialist visit requires a referral, except for visits performed by OB/GYN specialists.
- Authorization is required for an inpatient admission.

Indemnity and PPO guidelines

All authorization requirements are determined by the individual’s subscriber certificate, however:

- Authorizations are required for all inpatient services.
- Authorizations are not required for most outpatient services as determined by the individual’s subscriber certificate.
- Referrals to a specialist are not required.

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and

American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

CPT code:

- **83090:** homocysteine

Policy update history

Non-coverage effective date: August 2006, BCBSMA document #400 published in May 2006 Provider Focus. Medical Policy #016 published 3/2008; medical policy benchmarks BCBSA National medical policy, *Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease*; footnote #1 developed and includes BCBSA national medical policy rationale and references and existing reference on BCBSMA document #400. 4/08 Completed comparison review of the BCBSA medical policy, *Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease*; coverage statement unchanged- investigational. BCBSMA benchmarks this investigational status; footnote #1 updated. Reviewed 4/08 MPG-Cardiology, no changes in coverage were made. Reviewed 4/09 MPG – Cardiology, no changes in coverage were made. Updated 6/09 based on the comparison review of the BCBSA national medical policy, *Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease*; BCBSA's investigational non-coverage language is unchanged; BCBSMA benchmarks the BCBSA medical policy; footnote 1 edited including condensing and reordering of references-added 12, 15, 17, and 20.

Scientific background, Rationale and References

¹ Based on the Blue Cross Blue Shield Association National medical policy; *Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease*, #2.04.23

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.

Homocysteine as a risk factor for 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 example, Folsom and colleagues identified all patients who developed coronary heart disease among an initial cohort of 15,792 patients who participated in the Atherosclerosis Risk in Communities (ARIC) trial. (1) 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 CAD, this association was not significant after adjusting for other cardiac risk factors in multivariate analysis. Similarly, Evans and colleagues 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). (2) Plasma 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. In contrast, in a prospective study using similar methodology as the previously cited studies, Wald and colleagues reported that the initial stored plasma level of homocysteine was significantly higher among 229 men who ultimately died of ischemic heart disease compared to a control group of 1,126 men who were drawn from the original study of 21,520 men. (3) Also, Arnesen and colleagues found homocysteine was a risk factor for coronary heart disease based on their study of 122 patients who developed coronary heart disease from a sample of 21,826 men and women. (4)

For patients with known CAD, prospective data are more consistent in supporting the utility of homocysteine as a risk factor for future events. For example, Nygard and colleagues prospectively studied the plasma homocysteine levels in 587 patients with angiographically confirmed coronary artery disease. (5) 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 to those of the remaining 523 survivors. The authors reported a strong graded dose-response relationship between plasma homocysteine and mortality. Stubbs and colleagues evaluated the relationship between plasma homocysteine levels and cardiac events in 440 patients with acute coronary syndromes admitted to the hospital. (6) Plasma homocysteine levels at admission were not related to short-term outcomes at 28 days; however, in long-term follow-up, patients with homocysteine levels in the 2 highest quintiles had a 2.6-fold increase in the subsequent risk of a cardiac event.

Knekt and colleagues reported the outcomes at 13 years' follow-up of 3,471 middle-aged Finnish men, 884 of whom had known cardiovascular disease at baseline. (7) Using the homocysteine values from stored blood samples, they found no association between serum homocysteine concentration and the incidence of major coronary events (death from coronary heart disease or nonfatal MI) among men originally free of heart disease. However, a strong positive correlation was noted between homocysteine concentration and subsequent major coronary events in men with known cardiovascular disease at baseline.

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. (8)

Homocysteine levels as a modifiable risk factor. 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.

In addition, adherence to a diet meeting the recommended daily allowance (RDA) for folate intake, regardless of homocysteine and/or folate levels, could result in decreased levels of homocysteine. In 1996, the U.S. Food and Drug Administration (FDA) required that 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 homocysteine concentration. (9) Trials of homocysteine-lowering therapy, therefore, should evaluate the utility of treatments that lower homocysteine levels beyond those achieved by these general public health measures.

Indirect evidence suggests that homocysteine lowering may have beneficial effects on cardiovascular disease. Homocysteine lowering has been associated with favorable alterations in some vascular disease surrogates, such as ultrasound-measured endothelial function and exercise electrocardiogram (ECG). (10, 11) Also, epidemiologic evidence suggests that folate fortification of grain may have had a beneficial effect on the incidence of cardiovascular disease. (12) Since fortification has been mandatory in the United States, an increase in serum folate levels and a corresponding decrease in serum homocysteine levels have been observed. During this same time period, an acceleration in the decline of stroke in the United States has been noted, a phenomenon that has not been seen in the United Kingdom, where fortification of grain with folate is not mandated. This indirect evidence, however, is not definitive in determining whether lowering homocysteine improves cardiovascular outcomes.

Numerous randomized, controlled trials have now been published that provide direct evidence on the benefit of vitamin therapy to reduce homocysteine and prevent cardiovascular events. These trials primarily included patients with pre-existing cardiovascular disease or patients at high risk for cardiovascular disease. Among the

largest of these trials to date are the Heart Outcomes Prevention Evaluation Trial 2 (HOPE-2) (13), the Norwegian Vitamin Trial (NORVIT) (14), the Western Norway B Vitamin Intervention Trial (WENBIT) (15), the Vitamin Intervention for Stroke Prevention (VISP) trial (16), and the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS). (17)

The HOPE-2 (13) 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 5 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, an increased risk was reported for the treatment group (RR 1.24; 95% CI: 1.04-1.49, $p=0.02$).

The NORVIT (14) 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.

A second randomized, controlled trial from Norway was published in 2008, the Western Norway B Vitamin Intervention Trial (WENBIT). (15) A total of 3,096 participants referred for coronary angiography were randomized to B vitamins alone, B vitamins plus folate, or placebo. Patients were followed up for a mean of 3.2 years with a primary composite outcome of all-cause mortality, MI, stroke, and hospitalization for unstable angina. There were no significant reductions in the incidence of the primary outcome for any of the treatment groups. For patients treated with a combination of folate/vitamin B6/vitamin B12, the hazard ratio for the primary outcome was 0.90 (95% CI: 0.74–1.09, $p=0.28$). Stroke was reduced for patients treated with folate versus those not treated with folate, but this difference did not reach statistical significance (HR 0.72; 95% CI: 0.44-1.17, $p=0.19$).

The VISP (16) enrolled 3,680 patients with a prior history of ischemic stroke and randomized them to either a high dose or a low dose of folate, vitamin B6 and vitamin B12. There was no significant difference reported for the primary outcome, risk of recurrent stroke, which was 9.2% in the high-dose group compared with 8.8% in the low-dose group. Similarly, there were no significant differences reported in the rate of cardiac outcomes between groups.

Another recently published large, randomized controlled trial was the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS). (17) This trial randomized 5,442 women with a history of cardiovascular disease or at least three cardiovascular disease risk factors to a combination of folate, vitamin B6, and vitamin B12, with a mean follow-up of 7.3 years. The primary outcome was a composite of cardiovascular mortality, MI, stroke, and myocardial revascularization. There was no significant reduction in the primary outcome for the treatment group (RR 1.03; 95% CI: 0.90–1.13, $p=0.65$). There were also no significant reductions in risk for the individual endpoints, including stroke.

Several meta-analyses have been published that synthesize the available randomized controlled trial evidence on this question. (18-20) Bazzano and colleagues (18) included nearly 17,000 subjects from 12 studies. Pooled results did not reveal a significant decrease in cardiovascular disease (RR 0.95; 95% CI: 0.88–1.03) or all-cause mortality (RR 0.96; 95% CI: 0.88–1.04). The authors concluded that folic acid supplementation does not reduce the risk of cardiovascular events and that clinicians should focus their energies on proven cardiovascular risk reduction strategies such as smoking cessation, control of hypertension, and lipid-lowering therapies. Wald and colleagues (19) synthesized data from 7 studies of over 15,000 subjects and reported a similar RR for the outcome of ischemic heart disease (RR 0.98; 95% CI: 0.78–1.05). However, these authors concluded that the weight of observational and genetic studies, combined with the possibility that the trials

were underpowered to detect small changes in RR and were of insufficient duration, prevented concluding a null effect with certainty.

A third meta-analysis evaluated the impact of folic acid supplementation for the prevention of stroke. (20) This analysis included 8 randomized controlled trials and approximately 17,000 patients. For all studies, a significant reduction was reported in the risk of stroke associated with folic acid supplementation (RR 0.82; 95% CI: 0.68–1.00, p=0.045). On sensitivity analysis, the beneficial effect appeared to be concentrated in study populations in whom grain fortification was not present (RR 0.75; 95% CI: 0.62–0.91, p=0.003). In contrast, no significant benefit was observed for study populations in whom grain fortification was provided (RR 0.89; 95% CI: 0.55–1.42, p=0.62).

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. (21) 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.

Summary and Conclusions. 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. There is currently insufficient evidence to prompt reconsideration of the current policy, which remains unchanged.

References:

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² Blue Cross Blue Shield of Massachusetts' *non-covered* clinical indications.

NOTE: This list of ICD-9-CM diagnosis codes that represent the non-covered clinical indications is subject to update.

V12.50-V12.59, V12.60-V12.69, V13.00-V13.09, V15.81-V15.89, V15.9, V17.1, V17.3-V17.4, V17.6, V18.0-V18.1, V18.61-V18.69, V19.5, V19.8,
V20.0-V20.2,
V43.21-V43.22, V43.3, V43.5, V43.60-V43.65, V43.7, V45.00-V45.01, V45.81-V45.82,
V58.41, V58.49,
V65.3, V65.40, V65.46, V65.49, V65.5, V67.09, V67.51-V67.59, V67.6- V67.9,
V70.0-V70.9, V71.7, V71.89, V71.9, V72.5-V72.6, V72.81-V72.86, V72.9, V77.0-V77.1, V77.91-V77.99
V81.0-V81.6, V82.9
250.00-250.93,
251.0-251.9,
272.0-272.9,
401.0-401.9, 402.00-402.01, 402.10-402.11, 402.90-402.91, 403.00-403.91, 404.00- 404.93, 405.01-405.09,
405.11-405.19, 405.91-405.99
410.00-410.92,
411.0-411.1, 411.81-411.89,
412,
413.0-413.9,
414.00-414.07, 414.10-414.19 414.8-414.9,
426.0, 426.11-426.13, 426.2-426.4, and 426.50-426.54, 426.6-426.7, 426.82-426.89, 426.9, 427.0-427.2,
427.31-427.32, 427.41-427.42, 427.60-427.69, 427.81-427.89, 427.9, 429.2, 429.71-429.79

440.0-440.1, 440.8-440.9, 440.20-440.32, 440.8-440.9,
443.0-443.1, 443.21-443.29, 443.81-443.89, 443.9
459.9
508.9, 511.0, 515, 517.3, 519.8, 530.0, 530.10-530.19, 530.20-530.21, 530.3-530.7, 530.81-530.89, 530.9,
592.0, 592.1-592.9, 593.2 593.9, 595.0-596.9, 597.0-593.78, 593.81-593.89, 594.0-594.9, 595.0-595.4, 595.81-
595.89, 595.9, 596.0-596.4, 596.51-596.59, 596.9, 597.80-597.89, 598, 598.00-598.01, 598.1-598.9, 599.0-
599.5599.60-599.69, 599.81-599.89, 599.9
717.0-717.3, 717.40-717.49, 717.5-717.7, 717.8-717.9, 718.00-718.99, 719.00-719.99,
753.4-753.5
780.94, 780.99, 784.0-784.3, 784.40-784.49, 784.5, 784.60-784.69, 784.9, 785.0-785.3, 785.9,
786.00-786.09, 786.1-786.4, 786.50-786.59, 786.6-786.9, 788.0-788.1, 788.20-788.29, 788.30-788.38, 788.41-
788.43, 788.5, 788.61-788.69, 788.7-788.9
790.21-790.22, 790.29, 790.95
793.1,
794.30-794.31, 794.39
796.2, 796.4, 796.9

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