Medical Policy

Title: Homocysteine Testing

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Current Effective Date: July 1, 2019

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DESCRIPTION
Homocysteine is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD) and as a potential risk marker among people with CVD. The association between homocysteine-lowering interventions and risk of CVD has also been examined.

Objective
The objective of this evidence review is to assess whether homocysteine testing in asymptomatic patients at risk of cardiovascular disease or venous thromboembolism, or in patients who have cardiovascular disease or previous venous thromboembolism, improves health outcomes.

Background
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.

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 CVD. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine was an independent risk factor for CVD and could be used to improve current risk prediction models. Several case-control studies have also suggested that elevated homocysteine is a risk factor for venous thromboembolism (VTE; pulmonary embolism, deep vein thrombosis).

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 CVD and thrombotic events.
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. Determination of homocysteine concentration may also be offered as part of risk assessment for patients at high risk of VTE events or who have experienced idiopathic VTE, recurrent VTE, thrombosis occurring at a young age, or thrombosis at an unusual site.

**Regulatory Status**
Several homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Food and Drug Administration product code: LPS. Examples are listed in Table 1.

**Table 1. Homocysteine Test Systems**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Laboratory</th>
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<tr>
<td>Homocysteine Enzymatic Assay</td>
<td>Roche Diagnostics</td>
<td>2012</td>
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<tr>
<td>Diazyme Enzymatic Homocysteine Assay</td>
<td>Diazyme Laboratories</td>
<td>2012</td>
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POLICY

I. Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease

A. Measurement of plasma levels of homocysteine is considered experimental / investigational in the screening, evaluation, and management of patients for cardiovascular disease.

B. Measurement of plasma levels of homocysteine is considered experimental / investigational in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism.

II. Other Homocysteine Testing

A. Homocysteine Testing may be considered medically necessary for non-cardiovascular diagnoses of:
   1. homocystinuria
   2. recurrent pregnancy loss
   3. borderline vitamin B 12 deficiency

B. Homocysteine Testing is considered experimental / investigational for any other diagnoses.

RATIONALE
This evidence review and has been updated with searches of the MEDLINE database. The most recent literature update was performed through October 1, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Cardiovascular Disease
Clinical Context and Test Purpose
The purpose of testing homocysteine levels in asymptomatic patients at risk of cardiovascular disease (CVD) or in patients who have CVD is to inform management decisions such as whether to lower homocysteine levels.
The question addressed in this evidence review is: Does homocysteine testing of asymptomatic patients at risk of CVD or of patients who have CVD improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant populations of interest are individuals who are asymptomatic with the risk of CVD and those who have CVD.

**Interventions**
The relevant intervention of interest is homocysteine testing.

**Comparators**
The following practice is currently being used to manage those at risk of CVD and those with CVD: routine care without homocysteine testing.

**Outcomes**
The general outcomes of interest are test validity, other test performance measures, and change in disease status. Morbid events attributable to CVD, including stroke and myocardial infarction, may also be assessed.

**Timing**
The time frame for an outcome varies from 1 to 2 years, for assessment of hypertension or vascular changes, to 3 or more years, for assessment of coronary artery disease or stroke events.

**Setting**
Patients with or at risk of CVD may be assessed in the outpatient setting by a primary care medical provider or a specialist managing CVD.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:
- To assess the clinical validity of homocysteine testing in the screening, diagnosis, and management of CVD, studies should report on the relation between homocysteine levels and CVD events such as myocardial infarction, angina, and stroke.
- To assess the clinical utility of homocysteine testing in the management of CVD, studies should demonstrate how test results impact treatment decisions and overall patient management and lead to improvement in the net health outcome.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
The Homocysteine Studies Collaboration (2002) published a meta-analysis of observational studies evaluating the association between homocysteine concentration and risk of ischemic heart disease (IHD) or stroke.¹ Thirty 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 of IHD associated with a 25% lower homocysteine level was 0.83 (95% confidence interval [CI], 0.77 to 0.89) in prospective studies, 0.67 (95% CI, 0.62 to 0.71) in retrospective studies using population controls, and 0.73 (95% CI, 0.64 to 0.83) in retrospective studies with other controls. The adjusted odds ratio of stroke associated with a 25% lower homocysteine level was 0.77 (95% CI, 0.66 to 0.90) in prospective studies, 0.86 (95% CI, 0.73 to 1.01) in retrospective studies with population controls, and 0.46 (95% CI, 0.30 to 0.70) in retrospective studies with other controls. The risk of IHD and stroke was significantly weaker in the prospective studies than in the retrospective 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, which reported increased coronary artery disease, CVD, and all-cause mortality with higher homocysteine levels.²

Among the prospective studies included in the Homocysteine Studies Collaboration meta-analysis was one by Folsom et al (1998) that identified patients who developed congenital heart disease (CHD) among an initial cohort of 15,792 patients participating in the Atherosclerosis Risk in Communities trial.³ 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, this association was not statistically significant after adjusting for other cardiac risk factors in multivariate analysis. Another prospective study was published by Evans et al (1997).⁴ They 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. Homocysteine from stored blood samples of 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 CHD. In contrast, in a nested case-control study derived from a prospective cohort of 21520 men enrolled in the British United Provident Study, Wald et al (1998) 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.⁵

Representative studies on the association between homocysteine and various types of CVD are described in Table 2.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcomes</th>
<th>Major Findings (95% CI)</th>
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<tr>
<td>Shoamanesh et al (2016)⁶</td>
<td>3224 adults from Framingham Offspring Cohort (community-dwelling sample)</td>
<td>Incident ischemic stroke</td>
<td>After adjusting for SBP, hypertension treatment, current smoking, diabetes, CVD, and atrial fibrillation, total homocysteine associated with incident ischemic stroke: · HR=1.20 (1.01 to 1.43)</td>
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<td>Outcomes</td>
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| Han et al (2015)      | 5488 individuals with follow-up from a 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 (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 (vs highest with lowest total homocysteine quartile), 4.51 (1.29 to 15.7)  
  • Men: OR for stroke, 0.83 (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 adjusting for confounding variables, homocysteine significantly associated with:  
  • Presence of metabolic syndrome: OR=1.01 (1.00 to 1.02; p=0.02)  
  • Presence of cerebrovascular disease or CVD: OR=1.01 (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 measures:  
  • CF-PWV  
  • CA-PWV  
  • Heart rate-corrected AI | • Homocysteine levels positively correlated with: CF-PWV (r=0.211, p<0.001) and 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 in a single hospital in China    | Post stroke 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:  
  • 3rd vs 1st quartile: adjusted HR=2.27 (1.06 to 4.86; p=0.029)  
  • 4th vs 1st quartile: adjusted HR=2.15 (1.01 to 4.63; p=0.049) |
| 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 (1.72 to 4.75)  
  • Homocysteine levels ≥30 µmol/L (vs <15 µmol/L) not associated with CHD |
| 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 FRS:  
  • Low risk (n=2527)  
  • Intermediate risk (n=3336)  
  • High risk (n=508) |  
  • Homocysteine levels at ≥85th percentile associated with high FRS: OR=2.1 (1.48 to 3.01)  
  • Homocysteine levels at ≥85th percentile not significantly associated with intermediate FRS: OR=1.11 (0.89 to 1.38) |

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; FRS: Framingham Risk Score; HR: hazard ratio; MI: myocardial infarction; OR: odds ratio; PAD: peripheral arterial disease; SBP: systolic blood pressure.
For patients with known CVD, prospective data have more consistently demonstrated that homocysteine is a risk factor for future events. A prospective study by Ma et al (2016) assessed 30-day outcomes in 805 patients who were admitted to a single center for the treatment of acute MI; 348 patients had low homocysteine levels (<15 mmol/L), and 457 patients had homocysteine levels greater than 15 mmol/L. The groups were compared for incidence of 5 adverse cardiac events (angina pectoris, reinfarction, heart failure [Killip class II-IV], cardiac rupture, death); of these end points, three were more prevalent in the high homocysteine group than in the low homocysteine group. Heart failure occurred in 44 (9.6%) of the high homocysteine group, but only 8 (2.3%) of the low homocysteine group (p<0.001); cardiac rupture occurred in 16 (3.5%) of the patients with high homocysteine levels, compared with 4 (1.1%) of those with low levels (p=0.03). Differences were also found between the low- and high-Hcy groups for the end points of death (2.3% vs 7.9%; p<0.001) and total adverse outcomes (22.8% vs 11.8%; p<0.001); however, no significant difference was found for either angina pectoris or reinfarction (p=0.45 and p=0.65, respectively). As independent predictors of adverse events following acute MI, age and homocysteine levels were determined to have significant odds ratios (OR; OR=2.114; 95% CI, 1.416 to 3.156; p<0.001; OR=2.055; 95% CI, 1.376 to 3.068; p<0.001, respectively). The authors acknowledged a lack of data on potential "pathogenic mechanisms" in the association between homocysteine levels and adverse cardiac events, recommending that future studies include a larger study sample and longer follow-up.

Veeranna et al (2011) published a post hoc analysis of national survey databases to evaluate whether adding homocysteine to the Framingham Risk Score (FRS) model improves risk classification. Data were taken from the nationally representative Multi-Ethnic Study of Atherosclerosis (MESA) survey, which included subjects between the ages of 45 and 84 years with no history of CVD, and the National Health and Nutrition Survey III (NHANES III), a sample of noninstitutionalized subjects. Homocysteine level was associated with CVD risk in both databases. In a receiver operating characteristic curve analysis, the area under the curve for predicting CHD events in the MESA database was 0.74 using the FRS and 0.76 when homocysteine level was added to the FRS. The improvement in risk prediction was statistically significant (p<0.001). The area under the curve for predicting CHD deaths in NHANES III was 0.84 using the FRS alone and 0.87 when homocysteine level was added to the FRS; this difference was also statistically significant (p<0.001). Adding homocysteine to the FRS model resulted in the reclassification of 832 (12.9%) subjects in the MESA cohort and 1243 (18%) in the NHANES III cohort. This study did not address whether testing for homocysteine would improve health outcomes.

For example, Nygard et al (1997) reported on a prospective study of the plasma homocysteine levels in 587 patients with angiographically confirmed coronary artery disease. After a median follow-up of 4.6 years, authors compared the initial homocysteine levels of the 64 (10.9%) patients who had died with those of the remaining 523 survivors. The authors reported a strong graded dose-response relation between plasma homocysteine and mortality. In addition, Knekt et al (2001) reported on outcomes at 13-year follow-up for 3471 middle-aged Finnish men, 884 of whom had known CVD at baseline. Using the homocysteine levels 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, investigators found no association between serum homocysteine concentration and the incidence of major coronary events (death from CHD, nonfatal MI) among men originally free of heart disease.
Section Summary: Clinically Valid
A meta-analysis of observational studies found a moderately statistically significant association between homocysteine levels and the risk of CVD. One study analyzing nationally representative survey data found that adding homocysteine level to the FRS significantly improved risk prediction.

Studies have also found a significant correlation between homocysteine levels in patients with known CVD and subsequent coronary events. One study analyzing nationally representative survey data found that adding homocysteine level to the FRS significantly improved risk prediction. Overall, the available evidence has suggested that homocysteine levels are associated with increased risk of a variety of cardiovascular disorders and outcomes among patients with existing CVD.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Vitamin B and folic acid supplementation are potential interventions that could lower homocysteine levels in be used for patients with high homocysteine levels and 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 general public health measures. In addition, clear homocysteine target levels need to be established to impact clinical practice.

Numerous RCTs and meta-analyses of these trials have provided evidence on the benefit of vitamin therapy to reduce homocysteine levels and prevent cardiovascular (CV) events.

Systematic Reviews
A 2016 meta-analysis by Park et al (2016) of RCTs evaluated homocysteine-lowering therapy with B vitamins for reducing the risk of subsequent stroke among high CVD risk individuals who were not taking antiplatelet medications. Reviewers included 3 trials from 1966 to April 2015 that had at least 1 year of follow-up with stroke as the primary outcome: The Vitamin Intervention for Stroke Prevention trial (n=1773), the VITArms TO Prevent Stroke trial (n=1463), and the Heart Outcomes Prevention Evaluation (HOPE) 2 trial (n=1407). There was no evidence of heterogeneity for the stroke outcome. Those taking vitamin B supplementation had a lower risk of recurrent stroke (hazard ratio [HR], 0.71; 95% CI, 0.58 to 0.88) compared with controls (low-dose supplementation or placebo). In the VITArms TO Prevent Stroke trial, participants not on antiplatelet therapy were more likely to be East Asian. In the HOPE-2 trial, the effect of supplementation on stroke was highest in those with hyperhomocysteinemia or residing in a country without food fortification. Therefore, it is not clear whether the effect of
homocysteine-lowering therapy on stroke risk in those not on antiplatelets would apply to a U.S. population.

A Cochrane systematic review (2015; originally published in 2009 and updated in 2013\(^{20}\)) on the effectiveness of homocysteine-lowering interventions for preventing CV events, including both MI and stroke, was again updated.\(^{21}\) Reviewers included RCTs assessing the effects of homocysteine-lowering interventions for preventing cardiovascular events with at least 1 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 (total N=47,429 subjects) met eligibility criteria. Nine included more than 1000 participants. Nine studies used placebo controls, two used usual care controls, and one compared high with low doses of homocysteine-lowering therapy. In a pooled analysis of 11 trials, there was no statistically significant difference in nonfatal 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 9 studies, there was no significant difference between groups in the rate of nonfatal 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 RR was 1.01 (95% CI, 0.96 to 1.07) in a meta-analysis of 10 trials.

A meta-analysis by Yi et al (2014) included RCTs that compared folic acid supplementation (at least 5 mg/d for at least 4 weeks), without vitamin B supplementation, with placebo and evaluated endothelial function and homocysteine levels as outcomes in patients with coronary artery disease.\(^{22}\) Six trials (total N=377 subjects) were included. In the pooled analysis, folic acid supplementation was associated with increased flow-mediated dilation, a noninvasive, ultrasound-based method to assess vascular endothelial function (mean difference, 57.72 μm; 95% CI, 50.14 to 65.3 μm; \(p<0.05\)). Folic acid supplementation was also associated with reduced plasma homocysteine concentration (mean difference, -3.66 μmol/L; 95% CI, -5.44 to -7.87 μmol/L; \(p<0.05\)). 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, or systolic and diastolic blood pressure between the folic acid and placebo groups.

Liu et al (2014) also reported the results of a meta-analysis of placebo-controlled randomized trials that evaluated the effect of homocysteine-lowering therapies on flow-mediated dilation in patients with coronary artery disease.\(^{23}\) Eight studies (total N=611 subjects) were included; folic acid doses ranged from 400 to 10,000 μg/d. In the pooled analysis, folic acid supplementation was associated with improved flow-mediated dilation compared with placebo (standardized mean difference, 1.65; 95% CI, 1.12 to 2.17; \(p<0.001\)), but there was significant heterogeneity across studies.

A meta-analysis by Huang et al (2012) assessed RCTs evaluating vitamin B supplementation in patients with preexisting vascular disease.\(^{24}\) This review had more lenient inclusion criteria because there was no limitation on study size or intervention duration. Nineteen trials (total N=47,921 patients) were selected for the meta-analysis. In a pooled analysis of study data, reviewers 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 did not have a statistically significant impact on other outcomes, including CHD, MI, and all-cause mortality. Given the more relaxed entry criteria, the meta-analysis might have included lower quality studies; reviewers did not present a formal analysis of trial quality.
Zhou et al (2011) conducted a systematic review of double-blind placebo-controlled randomized trials evaluating the impact of folic acid supplementation on CV outcomes. Interventions were included if they involved supplementation with vitamin B in addition to folic acid. Reviewers selected only trials that included at least 100 patients and had at least 6 months of follow-up. Of 66 articles retrieved, 16 trials with data on 44,841 patients met reviewers’ inclusion criteria. In a meta-analysis of findings from 12 trials, folic acid supplementation did not have a significant effect on major CV events compared with 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), MI (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).

Clarke et al (2011) published a meta-analysis of placebo-controlled homocysteine-lowering randomized trials. This meta-analysis selected studies that included at least 1000 participants and had at least 1 year of follow-up. Eight trials (total N=37,485 individuals) met reviewers’ inclusion criteria. In a pooled analysis of findings from the 8 trials, vitamin B supplementation did not have a significant effect on risk of CHD events compared with placebo (RR=1.01; 95% CI, 0.96 to 1.07). In addition, in pooled analyses of data from the 8 trials, vitamin B supplementation did not 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).

**Randomized Controlled Trials**

Representative RCTs evaluating homocysteine-lower interventions are described next. Van Dijk et al (2015) reported on the results of the B-Vitamins for the Prevention Of Osteoporotic Fractures trial, an RCT comparing B vitamins (vitamin B₁₂ 500 mg, folic acid 400 mg) with placebo for improving CV outcomes among elderly patients with hyperhomocysteinemia. The trial included 2929 subjects over age 65 with an elevated homocysteine levels (12-50 µmol/L) who were randomized to 2 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 2 years of intervention was significantly higher in the B-vitamin treatment group (49.6 mm Hg) than in the placebo group (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, CV event incidence, or MI incidence. In a subgroup analysis, women in the treatment group experienced fewer CV events compared with women in the placebo group (OR=0.33; 95% CI, 0.15 to 0.71).

In 2010, findings from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine in the U.K. were reported. A total of 12064 adults with a history of MI were randomized to folic acid plus 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. Before randomization, patients participated in a run-in period to confirm adherence to treatment. (Patients were also randomized to receive different doses of simvastatin; those findings were 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) changed 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 1537 (25.5%) in the vitamin group and 1493 (24.8%) in the placebo group (RR=1.04; 95% CI, 0.97 to 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).

The HOPE-2 trial, which was reported by Lonn et al (2006), included 5522 patients with preexisting vascular disease.29 Patients were randomized to a regimen of folate, vitamin B₆, plus vitamin B₁₂ or placebo and followed for an average of five years. There were no significant differences in the composite outcome of CV death, MI, or stroke (RR=0.95; 95% CI, 0.84 to 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 to 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 to 1.49; p=0.02).

The Norwegian Vitamin Trial (2006) enrolled 3749 patients with a recent MI who were randomized to combinations of folate and/or B vitamins.30 Patients were followed for a mean of 3.3 years for the primary outcome (a composite of recurrent MI, stroke, and sudden cardiac death). For patients assigned to the active treatment groups, no significant reductions were noted for any of the primary or secondary outcomes. For patients assigned to the combined folate/vitamin B₆/vitamin B₁₂ group, a marginally significant increased risk (RR=1.22; 95% CI, 1.00 to 1.50; p=0.05) was observed for the primary composite outcome group.

### Section Summary: Cardiovascular Disease

Numerous large placebo-controlled randomized trials evaluated the impact of folic acid plus vitamin B supplementation on risk of cardiovascular events, including MI and stroke. Most meta-analyses of these RCTs reported that homocysteine-lowering interventions did not have a statistically significant effect on the rate of major CV events. Two meta-analyses of RCTs reported that homocysteine-lowering interventions were associated with improvements in a measure of vascular endothelial function, but the effect of these changes on clinical outcomes is unknown.

### Venous Thromboembolic Disorders

#### Clinical Context and Test Purpose

The purpose of testing homocysteine levels in asymptomatic patients at risk of venous thromboembolism (VTE) or of patients who have VTE events is to inform management decisions such as whether to lower homocysteine levels.

The question addressed in this evidence review is: Does the use of homocysteine testing of asymptomatic patients at risk of VTE or of patients who have had previous VTE events improve net health outcomes?

The following PICOTS were used to select literature to inform this review.

#### Patients

The relevant populations of interest are individuals who are asymptomatic with the risk of VTE and those who have had VTE events.
**Interventions**
The relevant intervention of interest is homocysteine testing.

**Comparators**
The following practice is currently being used to manage those at risk of VTE and those who have had VTEs: routine care without homocysteine testing.

**Outcomes**
The general outcomes of interest are test validity, other test performance measures, and change in disease status. Morbid events associated with VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), may be studied.

**Timing**
The time frame from outcomes varies but it is expected to be 3 or more years for assessment of DVT or PE.

**Setting**
Patients with or at risk of VTE may be assessed in the outpatient setting by a primary care medical provider or a specialist managing VTE.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of homocysteine testing in the screening, diagnosis, and management of CVD, studies should report on the relation between homocysteine levels and VTE events such as DVT or PE.
- To assess the clinical utility of homocysteine testing in the management of CVD, studies should demonstrate how test results impact treatment decisions and overall patient management and lead to improvement in the net health outcome.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Systematic Reviews**
Den Heijer et al (2005) published a meta-analysis of observational studies on the relation between homocysteine and risk of venous thrombosis.\(^{31}\) Twenty-four retrospective studies (n=3289 patients) and 3 prospective studies (n=476 patients) published before July 2003 were included. A 5 µmol/L higher total plasma homocysteine level was associated with a 27% (95% CI, 1% to 59%) higher risk of venous thrombosis in prospective studies and a 60% (95% CI, 10% to 134%) higher risk in retrospective studies. Selected studies had varying cutoffs for high homocysteine and a mix of first-time and recurrent VTE. Two earlier systematic reviews reached similar conclusions on the association between homocysteine and risk of VTE.\(^{32,33}\)
Several studies have examined the risk of VTE in patients with both homocysteinemia and an inherited thrombophilia (eg, factor V Leiden), with mixed results. Keijzer et al (2007) performed a meta-analysis of the interaction between factor V Leiden and hyperhomocysteinemia. In 5 observational studies (825 patients with venous thrombosis, 2109 controls), there was no evidence for additive or multiplicative interaction between factor V Leiden and hyperhomocysteinemia. The relative excess risk due to additive interaction was -1.77 (95% CI, -8.61 to 5.08) and multiplicative interaction term was 0.86 (95% CI, 0.35 to 2.14).

Prospective Studies
Following the systematic reviews, a 2008 case-cohort from the large Norwegian Health Study of Nord-Trøndelag study prospectively investigated whether elevated plasma homocysteine levels before the event were associated with subsequent first VTE in a general population. VTE was identified in 505 patients, and 1458 age- and sex-matched controls were selected for the case-cohort study from the original cohort of 66,140 Norwegian Health Study of Nord-Trøndelag participants. Serum total homocysteine blood was collected between 1995 and 1997, a median of 33 months before the events. The odds for VTE for homocysteine levels above vs below the 95th percentile was 1.50 (95% CI, 0.97 to 2.30). Results were similar after control for age, predisposing risk factors, or time to event. The association was limited to men (OR=2.17; 95% CI, 1.20 to 3.91); no association was found in women (OR=1.00; 95% CI, 0.52 to 1.92). There was not a dose-response relation between VTE and homocysteine.

Section Summary: Clinically Valid
A meta-analysis of observational studies found a statistically significant moderate association between homocysteine levels and risk of VTE, though the association was imprecise, with a wide CI. Additionally, a subsequent large prospective study found an increased risk of VTE in men with high homocysteine levels. The available evidence has suggested that homocysteine levels may be associated with an increased risk of VTE in the general population.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

A systematic review of observational studies, along with 2 RCTs, have provided evidence relevant to the discussion of vitamin therapy to reduce homocysteine levels and prevent VTE.

Systematic Reviews
Zhou et al (2012) published a systematic review including 2 observational studies and 3 RCTs on the association between B-group vitamins and VTE. The studies included an uncontrolled interventional study in patients with homocystinuria, an observational study of pregnant women, a trial with measured homocysteine levels as the primary outcome, a secondary analysis of the HOPE-2 trial, and a secondary prevention trial. Reviewers did not perform a meta-analysis due to heterogeneity in study designs and baseline homocysteine levels. The uncontrolled study in patients with homocystinuria and the study in pregnant women both found an association.
between supplementation and decreased risk of VTE. The trial with homocysteine levels as an outcome showed that supplementation with a multivitamin (folic acid 5 mg, vitamin B₁₂ 0.4 mg, vitamin B₆ 50 mg) reduced homocysteine levels in patients with recurrent VTE and in healthy volunteers. The 2 trials with VTE outcomes are detailed in the following section.

Randomized Controlled Trials
The Vitamins and Thrombosis RCT (2007) evaluated the effect of homocysteine-lowering by daily supplementation with B vitamins on the risk reduction of DVT and PE.³⁷ Patients between 20 and 80 years of age with a first DVT or PE in the absence of major risk factors and a homocysteine concentration above the 75th percentile of a reference group were eligible (the hyperhomocysteinemic group). The second group of patients with homocysteine below the 75th percentile of the reference group (called the normohomocysteinemic [placebo] group) were also enrolled. Patients were randomized to daily multivitamin supplementation of folic acid 5 mg, pyridoxine 50 mg, plus cyanocobalamin 0.4 mg, or to a placebo. Follow-up continued for 2.5 years. The primary outcome was objectively diagnosed recurrent DVT or PE. A total of 701 patients were enrolled (360 in the hyperhomocysteinemic group, 341 in the normohomocysteinemic group). Of the 353 assigned to the vitamin group, 43 events were observed (54/1000 person-years). In the 348 assigned to the placebo group, 50 events were observed (64/1000 person-years). The HR was not statistically significant (HR=0.84; 95% CI, 0.56 to 1.26). There was no statistically significant reduction in recurrent VTE in the 360 patients with baseline homocysteine levels above the 75th percentile (HR=1.14; 95% CI, 0.65 to 1.98), or in the 341 patients with normal homocysteine levels (HR=0.58; 95% CI, 0.31 to 1.07).

The HOPE-2 trial (2007) evaluated whether long-term supplementation with folic acid, vitamin B₆, and vitamin B₁₂ aimed at lowering homocysteine levels would reduce the rates of major fatal and nonfatal CV events in patients with established CVD and/or diabetes.³⁸ HOPE-2 was conducted at 145 clinical centers in 13 countries and enrolled 5522 patients 55 years of age or older with known CVD or diabetes and at least 1 other risk factor for vascular disease. Baseline information on previous VTE was not available. A secondary analysis from the HOPE-2 trial evaluated whether supplementation could reduce the risk of symptomatic VTE. VTE occurred in 88 patients during a mean 5-year follow-up. There was no effect of vitamin supplementation on rates of VTE in the total population (HR=1.01; 95% CI, 0.66 to 1.53) or in the 821 patients with baseline homocysteine levels in the highest quartile (>13.8 µmol/L) in the study (HR=1.71; 95% CI, 0.48 to 6.06).

Section Summary: Venous Thromboembolic Disorders
Two placebo-controlled randomized trials have evaluated the impact of folic acid and vitamin B supplementation on the risk of VTE. Homocysteine-lowering interventions did not have a statistically significant effect on the rate of VTE in patients with previous VTE or in patients unselected for previous VTE but with CVD. Based on these trials, there is insufficient evidence to conclude that supplementation to reduce homocysteine will reduce the risk of VTE.

Summary of Evidence
For individuals who are asymptomatic with risk of CVD or individuals with CVD who receive homocysteine testing, the evidence includes observational studies and randomized controlled trials (RCTs) of homocysteine-lowering interventions. Relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and CVD risk, especially in patients with preexisting vascular disease. However, evidence from RCTs evaluating
homocysteine-lower interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves cardiovascular outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. One systematic review, with a subgroup analysis of patients from 3 RCTs who were not on antiplatelet therapy at baseline, found that homocysteine-lowering treatment reduced the risk of stroke in that group. However, replication of this effect in countries with grain enriched with folic acid would be needed. Given the large amount of evidence from placebo-controlled randomized trials that homocysteine-lowering interventions do not improve health outcomes, it is unlikely that routine homocysteine testing has the potential to change management that improves health outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who are asymptomatic with risk of venous thromboembolism (VTE) or individuals who have experienced VTE events who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and VTE risk, although the association was specific to men in the largest prospective study. However, evidence from RCTs evaluating homocysteine-lower interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces the risk of VTE. Only a single RCT was designed to test for VTE as a primary outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

**Cardiovascular Disease**

**National Institute for Health and Care Excellence**
The National Institute for Health and Care Excellence (2016) updated its guidance on risk assessment and reduction of cardiovascular disease (CVD), including lipid modification. The guidance asserted that full formal risk assessments should use a combination of risk assessment tools as well as informed clinical judgment. Homocysteine testing was not mentioned.

**American Heart Association and American Stroke Association**
The American Heart Association and the American Stroke Association (2014) issued joint guidelines on the primary prevention of stroke. These guidelines were endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Preventive Cardiovascular Nurses Association. The guidelines stated that patients with hyperhomocysteinemia may be treated with B-complex vitamins to prevent ischemic stroke, but that the effectiveness was not clearly established (class IIb; level of evidence B).

**American College of Cardiology and American Heart Association**
The American College of Cardiology and the American Heart Association (2013) issued joint guidelines on the assessment of arteriosclerotic cardiovascular risk. These guidelines were endorsed by 6 medical specialty associations. The guidelines developed multivariable equations to estimate age- and race-specific arteriosclerotic cardiovascular risk. The equations included age, total and high-density cholesterol levels, systolic blood pressure, antihypertensive treatment use, diabetes history, and current smoking status. The use of homocysteine screening for assessing the arteriosclerotic cardiovascular risk was not considered in these guidelines.
National Academy of Clinical Biochemistry
The National Academy of Clinical Biochemistry (2009) published guidelines on biomarkers for primary prevention of CVD. The Academy concluded that while homocysteine is a modest independent CVD risk factor, homocysteine screening for primary prevention and assessment in healthy individuals was unwarranted.

Venous Thromboembolism
Agency for Healthcare Research and Quality
The Agency for Healthcare Research and Quality (2016) issued guidelines for effective quality improvement on preventing hospital-associated venous thromboembolism. The venous thromboembolism prevention protocol recommended involves a venous thromboembolism risk assessment, a bleeding risk assessment, and a clinical decision support on prophylactic choices. Homocysteine testing was not mentioned in these guidelines.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2018) issued guidance on reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. Homocysteine testing was not mentioned in this guidance.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force (2009) issued a recommendation stating that the evidence was insufficient to assess the benefits and harms of using nontraditional risk factors to screen asymptomatic adults with no history of coronary heart disease to prevent coronary heart disease events. Homocysteine was one of the nontraditional risk factors considered in the recommendation. The Task Force (2018) issued an assessment of CVD risk with nontraditional risk factors. Homocysteine levels were not mentioned in this recommendation.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
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<td>NCT02207023</td>
<td>Healthy Lifestyles after Stroke (Stroke Coach)</td>
<td>124</td>
<td>Dec 2018</td>
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<td>NCT00671346</td>
<td>Combined Analyses and Long-term Follow-up in the Two Norwegian Homocysteine Lowering B-Vitamin Trials NORVIT and WENBIT</td>
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<td>NCT03122002</td>
<td>A Prospective Cohort Study of Predictors and Prognostic Factors on the Acute Ischemic Stroke</td>
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<td>NCT01956786*</td>
<td>Efficacy of Amlodipine–Folic Acid Tablets on Reduction of Blood Pressure and Plasma Homocysteine in Patients With Mild to Moderate Hypertension, Hyperhomocysteinemia and Angiotensin-Converting Enzyme Inhibitor Intolerance</td>
<td>540</td>
<td>Feb 2014 (unknown)</td>
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NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) 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 of these services as it applies to an individual member.

CPT/HCPCS

83090 Homocysteine

- There is a CPT code specific to this test: 83090.

ICD-10 Diagnoses

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

Experimental / investigational for all diagnoses related to this policy language.

Other Homocysteine Testing

D51.0 Vitamin B12 deficiency anemia due to intrinsic factor deficiency
D51.1 Vitamin B12 deficiency anemia due to selective vitamin B12 malabsorption with proteinuria
D51.2 Transcobalamin II deficiency
D51.3 Other dietary vitamin B12 deficiency anemia
D51.8 Other vitamin B12 deficiency anemias
D51.9 Vitamin B12 deficiency anemia, unspecified
D53.1 Other megaloblastic anemias, not elsewhere classified
D68.8 Other specified coagulation defects
D68.9 Coagulation defect, unspecified
D81.818 Other biotin-dependent carboxylase deficiency
D81.819 Biotin-dependent carboxylase deficiency, unspecified
E53.8 Deficiency of other specified B group vitamins
E72.10 Disorders of sulfur-bearing amino-acid metabolism, unspecified
E72.11 Homocystinuria
E72.12 Methylenetetrahydrofolate reductase deficiency
E72.19 Other disorders of sulfur-bearing amino-acid metabolism
G60.3 Idiopathic progressive neuropathy
G60.8 Other hereditary and idiopathic neuropathies
G60.9 Hereditary and idiopathic neuropathy, unspecified
N96 Recurrent pregnancy loss
O03.2 Embolism following incomplete spontaneous abortion
O03.35 Other venous complications following incomplete spontaneous abortion
O03.39 Incomplete spontaneous abortion with other complications
O03.4 Complete spontaneous abortion without complication
O03.7 Embolism following complete or unspecified spontaneous abortion
O03.85 Other venous complications following complete or unspecified spontaneous abortion
O03.88 Urinary tract infection following complete or unspecified spontaneous abortion
O03.89 Complete or unspecified spontaneous abortion with other complications
O03.9 Complete or unspecified spontaneous abortion without complication
O26.21 Pregnancy care for patient with recurrent pregnancy loss, first trimester
O26.22 Pregnancy care for patient with recurrent pregnancy loss, second trimester
O26.23 Pregnancy care for patient with recurrent pregnancy loss, third trimester
## REVISIONS

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<td>08-17-2010</td>
<td>- The Homocysteine Testing and Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease medical policies were merged and entitled Homocysteine Testing.</td>
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<td>- Added the following medically necessary non-cardiac indications for testing</td>
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<td>- recurrent pregnancy loss</td>
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<td>- venous thromboembolism</td>
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<td>- Clarified that homocysteine testing for any diagnosis other than homocystinuria, recurrent pregnancy loss, borderline vitamin B 12 deficiency, or venous thromboembolism is considered E/I by adding, &quot;Homocysteine Testing is considered experimental / investigational for any other diagnoses.&quot;</td>
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<td>- Added Diagnosis codes: 281.0, 281.1, 281.3, 286.9, 356.4, 356.8, 356.9, 362.30, 415.11, 415.19, 444.0-444.1, 444.9, 451.0-451.9-, 452, 453.0, 453.1, 453.2, 453.3, 453.40-453.9, 454.0-454.9, 557.0, 629.81, 634.00-634.92, 646.30, 646.31, 646.33, V12.51</td>
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<td>- Removed ICD-9 Diagnoses codes: 444.01-444.1, 444.9, 454.0-454.9</td>
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<td>- Revise ICD-10 Code Nomenclature: I82.811, I82.812</td>
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In Policy Section
- In Item I added "and Venous Thromboembolic Disease" to read "Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease"
- In Item I added "B. Measurement of plasma levels of homocysteine is considered experimental / investigational in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism."
- In Item II A removed "venous thromboembolism"

In Coding Section:
Removed ICD-10 Codes: H34.8110, H34.8111, H34.8112, H34.8120, H34.8121, H34.8122, H34.8130, H34.8131, H34.8132, H34.8310, H34.8311, H34.8312, H34.8320, H34.8321, H34.8322, H34.8330, H34.8331, H34.8332, I26.09, I26.90, I26.99, I80.01, I80.02, I80.03, I80.11, I80.12, I80.13, I80.201, I80.202, I80.203, I80.211, I80.212, I80.213, I80.221, I80.222, I80.223, I80.231, I80.232, I80.233, I80.291, I80.292, I80.293, I80.8, I81, I82.0, I82.1, I82.210, I82.211, I82.220, I82.221, I82.290, I82.291 I82.3, I82.401, I82.402, I82.403, I82.411, I82.412, I82.413, I82.421, I82.422, I82.423, I82.431, I82.432, I82.433, I82.441, I82.442, I82.443, I82.491, I82.492, I82.493, I82.4Y1, I82.4Y2, I82.4Y3, I82.4Z1, I82.4Z2, I82.4Z3, I82.511, I82.512, I82.513, I82.521, I82.522, I82.523, I82.531, I82.532, I82.533, I82.541, I82.542, I82.543, I82.591, I82.592, I82.593, I82.5Y1, I82.5Y2, I82.5Y3, I82.5Z1, I82.522, I82.523, I82.601, I82.602, I82.603, I82.611, I82.612, I82.613, I82.621, I82.622, I82.623, I82.701, I82.702, I82.703, I82.711, I82.712, I82.713, I82.721, I82.722, I82.723, I82.811, I82.812, I82.813, I82.91, I82.A11, I82.A12, I82.A13, I82.A21, I82.A22, I82.A23, I82.B11, I82.B12, I82.B13, I82.B21, I82.B22, I82.B23, I82.C11, I82.C12, I82.C13, I82.C21, I82.C22, I82.C23, K55.011, K55.012, K55.019, K55.021, K55.022, K55.029, K55.031, K55.032, K55.039, K55.041, K55.042, K55.049, T81.72xA, T81.72xD, T81.72xS, Z86.718

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