This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

### Populations

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who are asymptomatic with risk of cardiovascular disease</td>
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<td>Routine care without homocysteine testing</td>
<td>Relevant outcomes include: Test accuracy, Test validity, Other test performance measures, Change in disease status, Morbid events</td>
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### Description

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 for people with CVD. The association between homocysteine-lowering interventions and risk of CVD has also been examined.

### Summary of Evidence

The evidence for the use of homocysteine testing in individuals who are asymptomatic with risk of cardiovascular disease (CVD) or patients with CVD includes 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 CVD, especially in patients with preexisting vascular disease. However, evidence from RCTs evaluating homocysteine-lower interventions does not support the hypothesis that lowering homocysteine levels by treatment with folate and/or B vitamins improves cardiovascular outcomes. Numerous large RCTs 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.

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

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. 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 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.

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. 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.

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. These include the liquid-stable two-part homocysteine reagent test by Catch Inc. (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) in 2012, the A/C Automatic Enzymatic Hcy [Homocysteine] Assay (AntiCancer Inc., San Diego, CA) in 2008, and the Teco Enzymatic Homocysteine Assay (Teco Diagnostics, Anaheim, CA) in 2007. FDA product code: LPS.
Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). C-reactive protein as a cardiac risk marker (special report). TEC Assessments. 2002; Volume 17 Tab 23.


