

# Protocol

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

(20423)

<b>Medical Benefit</b>		<b>Effective Date:</b> 10/01/17	<b>Next Review Date:</b> 07/21
<b>Preauthorization</b>	No	<b>Review Dates:</b> 09/09, 09/10, 07/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18, 07/19, 07/20	

***This protocol considers this test or procedure not medically necessary and 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	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic with risk of cardiovascular disease	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test validity • Other test performance measures • Change in disease status • Morbid events
Individuals: • With cardiovascular disease	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test validity • Other test performance measures • Change in disease status • Morbid events
Individuals: • Who are asymptomatic with risk of venous thromboembolism	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test validity • Other test performance measures • Change in disease status • Morbid events
Individuals: • Who have experienced venous thromboembolic events	Interventions of interest are: • Homocysteine testing	Comparators of interest are: • Routine care without homocysteine testing	Relevant outcomes include: • Test validity • Other test performance measures • Change in disease status • Morbid events

### DESCRIPTION

Homocysteine is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD) and as a potential risk marker for people with CVD and thrombotic disorders; the presence of this amino acid raises one's risk of developing a blood clot. The association between homocysteine-lowering interventions and the risk of CVD or thrombotic events has been examined.

## SUMMARY OF EVIDENCE

For individuals who are asymptomatic with the 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. The 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-lowering 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 three 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 a 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 the 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. The 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-lowering 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.

## POLICY

Measurement of plasma levels of homocysteine is considered **not medically necessary** in the screening, evaluation, and management of patients for cardiovascular disease.

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

## 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 inversely correlate 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 of the homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process. Food and Drug Administration product code: LPS. Examples are listed in Table 1.

Table 1. Homocysteine Test Systems

Assay	Laboratory	Approval Date
Homocysteine Enzymatic Assay	Roche Diagnostics	2012
Diazyme Enzymatic Homocysteine Assay	Diazyme Laboratories	2012
A/C Automatic Enzymatic Hcy [Homocysteine] Assay	AntiCancer Inc.	2008
Teco Enzymatic Homocysteine Assay	Teco Diagnostics	2007

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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.

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