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FEP Medical Policy Manual

FEP 2.04.23 Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disorders

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Related Policies:

None

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

Description

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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.

OBJECTIVE

The objective of this evidence review is to assess whether homocysteine testing in asymptomatic patients at risk of cardiovascular disease (CVD) or venous thromboembolism, or in patients who have CVD or previous venous thromboembolism, improves the net health outcome.

POLICY STATEMENT

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

Measurement of plasma levels of homocysteine is considered **not medically necessary** in the screening, evaluation, and management of individuals with venous thromboembolism or risk of venous thromboembolism.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Determination of homocysteine may be included as a component of a comprehensive cardiovascular risk assessment offered by reference laboratories. Comprehensive risk assessment may include evaluation of small low-density lipoproteins, subclassification of high-density lipoproteins, evaluation of apolipoprotein E genotype or phenotype, total plasma homocysteine, apolipoprotein B, and lipoprotein (a).

FDA REGULATORY STATUS

Several of the homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA 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

RATIONALE

Summary of Evidence

For individuals who are asymptomatic with the risk of cardiovascular disease (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 changes in disease status and morbid events such as cardiovascular (CV) events, including myocardial infarction (MI), stroke, and CV death. Evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves CV outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major CV events. A Cochrane systematic review found that homocysteine-lowering treatment reduced the risk of stroke. However, the investigators considered the results weak, and the clinical significance of this reduction is still unknown. 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 insufficient to determine that the technology results in an improvement in 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. Relevant outcomes are change in disease status and morbid events such as VTE occurrence. 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Cardiovascular Disease

National Institute for Health and Care Excellence

In 2016 , NICE updated its guidance on risk assessment and reduction of cardiovascular disease (CVD), including lipid modification.[29,] 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

In 2014, the American Heart Association (AHA) and the American Stroke Association (ASA) issued joint guidelines on the primary prevention of stroke.[30,] 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). In 2021, the AHA/ASA released a joint guideline on the prevention of stroke in patients with stroke and transient ischemic attack (TIA).[31,] The guideline stated that "in patients with ischemic stroke or TIA with hyperhomocysteinemia, supplementation with folate, vitamin B6, and vitamin B12 is not effective for preventing subsequent stroke".

American College of Cardiology and American Heart Association

In 2019, the American College of Cardiology (ACC) and the AHA issued a joint guideline on the primary prevention of CVD.[32,] The use of homocysteine was not mentioned as a marker to guide prevention strategy.

In 2016, the ACC and AHA issued a joint guideline for the management of patients with lower extremity peripheral disease.[33,] The guideline recommended against the use of B-complex vitamin supplementation to lower homocysteine, since it did not show benefit in the HOPE-2 trial.

In 2013, the ACC and AHA issued joint guidelines on the assessment of atherosclerotic cardiovascular risk.[34,] 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 atherosclerotic cardiovascular risk was not considered in these guidelines.

National Academy of Clinical Biochemistry

In 2009, the National Academy of Clinical Biochemistry published guidelines on biomarkers for primary prevention of CVD.[35,] 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

In 2016, the Agency for Healthcare Research and Quality issued guidelines for effective quality improvement in preventing hospital-associated venous thromboembolism.[36,]Content for this guidance was last reviewed in October 2022. The venous thromboembolism prevention protocol recommended a venous thromboembolism risk assessment, a bleeding risk assessment, and clinical decision support on prophylactic choices. Homocysteine testing was not mentioned in these guidelines.

National Institute for Health and Care Excellence

The NICE (2018; updated in 2019) issued guidance on reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism.[37,] Homocysteine testing was not mentioned in this guidance.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2018) issued a recommendation on the assessment of CVD risk with nontraditional risk factors.[38,] 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy-FEP	Policy updated with literature review through November 1, 2022; references added. Not medically necessary policy statement language changed to Investigational and other minor editorial refinements to policy statements; intent unchanged. FEP Benefit Brochure changes, FEP New Policy.