Homocysteine is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD) and increased risk of thrombosis in the general population and as a potential risk marker for people with CVD and thrombotic disorders. The association between homocysteine-lowering interventions and risk of CVD or thrombotic events has also been examined.

For individuals who are asymptomatic with risk of CVD or who have CVD who receive homocysteine testing, the evidence 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 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 of a subgroup analysis from 3 RCTs of patients not on antiplatelets 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 RCTs 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 who have experienced VTE events who receive homocysteine testing, the evidence includes of observational studies and 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 has generally supported the association between homocysteine levels and VTE risk, although the association was limited 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 risk of VTE. Only 1 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.

The objective of this evidence review is to examine 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.

Policy

Coding Information
Click the links below for attachments, coding tables & instructions.
Attachment I- CPT-code table

When a service may be considered medically necessary
Measurement of plasma levels of homocysteine are considered medically necessary for the following indications:

- Assessment of borderline vitamin B-12 deficiency when the results of homocysteine testing will impact the members treatment plan; OR
- Assessment of homocystinuria caused by cystationine beta synthase deficiency (Note: for newborn screening, measurements of plasma homocysteine/total homocysteine are performed only when hypermethioninemia has been confirmed; OR
- Assessment of idiopathic venous thrombo-embolism, recurrent venous thrombo-embolism, thrombosis occurring prior to age 45, or thrombosis at an unusual site; OR
- Recurrent pregnancy loss once all other indications have been ruled out.

When a service is considered not medically necessary
Measurement of plasma levels of homocysteine are considered not medically necessary in the screening, evaluation, and management of patients with cardiovascular disease and all other indications not mentioned within this policy.
When a service is considered investigational

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 for all indications other than those listed above.

Reference Resources

8. Park CS, Ihm SH, Yoo KD, et al. Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levels and leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA. Am J Cardiol. May 1 2010;105(9):1284-1288. PMID 20403480


Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer’s benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member’s contract/employer benefit plan language takes precedence.

Audit Information

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

Administrative and Contractual Guidance

Benefit Determination Guidance

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member’s benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member’s benefit.
Coverage varies according to the member’s group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict. If the member receives benefits through an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member’s employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

**Policy Implementation/Update information**

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<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1/2011</td>
<td>New policy</td>
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<tr>
<td>6/2015</td>
<td>Adoption of BCBSA policy# 2.04.23. Approved by MPC on 4/13/15</td>
</tr>
<tr>
<td>06/2017</td>
<td>Medical policy name changed. Policy updated with literature review through October 10, 2016. Updated references based on BCBSA policy #2.04.23. Updated DX list. Title changed to “Homocysteine Testing”. Added medically necessary criteria/section. Changed CVD from investigational to not medically necessary. Added investigational for homocysteine measurement in the evaluation of venous thromboembolic disease.</td>
</tr>
<tr>
<td>01/2019</td>
<td>Policy reviewed and updated references. Policy statements remain unchanged.</td>
</tr>
<tr>
<td>10/01/2019</td>
<td>Removed Z13.6, Z82.42 &amp; Z82.49 from investigational to medically necessary effective in 10/01/2019 adaptive maintenance cycle.</td>
</tr>
<tr>
<td>10/2019</td>
<td>Effective 01/01/2020 Medical Policy to be archived. Remove diagnosis table and make code 83090 medically necessary.</td>
</tr>
</tbody>
</table>

**Eligible providers**

Qualified healthcare professionals practicing within the scope of their license(s).

**Approved by BCBSVT Medical Directors**

Joshua Plavin, MD, MPH, MBA  
Chief Medical Officer

Kate McIntosh, MD, MBA, FAAP  
Senior Medical Director

*Medical Policy Number: UM.DIAG.02*
CPT® Code Table

<table>
<thead>
<tr>
<th>Code Type</th>
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<tr>
<td></td>
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<td>Homocysteine</td>
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</table>

The following codes may be considered as medically necessary when applicable criteria have been met.