Clinical Policy: Homocysteine Testing

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Coding Implications
Revision Log

Description
Homocysteine is a nonproteinogenic amino acid that is generated during the conversion of methionine to cysteine. Mutations of the enzymes within the biochemical pathways that regulate homeostatic homocysteine levels are associated with risk factors for various diseases, including venous thromboembolism. Supplementation of folic acid, vitamin B6, and vitamin B12 are known to modulate homocysteine levels, given the interplay between the folate cycle and metabolism. This policy describes the medical necessity requirements for testing levels of homocysteine.

Policy/Criteria

I. It is the policy of PA Health & Wellness that homocysteine testing is **medically necessary** for the following indications:
   A. Borderline vitamin B12 deficiency;
   B. Homocystinuria caused by cystathionine beta-synthase deficiency;
   C. Idiopathic venous thromboembolism, recurrent venous thromboembolism, thrombosis occurring at < 45 years of age, or thrombosis at an unusual site.

II. It is the policy PA Health & Wellness that homocysteine testing is considered **investigational** for the following indications:
   A. Cardiovascular risk testing;
   B. For the testing of all other conditions.

Background
Homocysteine is a naturally occurring intermediary amino acid that is generated during the conversion of methionine to cysteine. While homoeostatic plasma levels of homocysteine typically range at low micro molar concentrations, epistatic mutations and other aberrant modifications of the metabolic pathways modulate homocysteine levels.[1] The metabolic pathway of homocysteine consists of upstream remethylation pathways and a downstream transsulfuration pathway. Notably, mutations in cystathionine-β-synthase, a key enzyme of the transsulfuration pathway, are associated with excess levels of homocysteine and premature thrombotic events.[1] Furthermore, a common mutation at a single nucleotide (677C→T) in the gene encoding 5,10-methenetetrahydrolate reductase, an enzyme in the folate cycle whose byproducts are necessary cofactors in the metabolism of homocysteine, affects homoeostatic levels of homocysteine. This mutation predisposes the individual to low folate plasma levels, and consequently a status of hyperhomocysteine.[2]

Changes in the plasma homocysteine levels can result from alterations in folate or vitamin B6 or vitamin B12.[7] A meta-analysis of 25 randomized clinical trials demonstrated that daily supplementation of ≥ 0.8 mg folic acid is sufficient to achieve the maximal reduction in plasma homocysteine levels. [8] Moreover, basal levels of homocysteine range between 5-15 μmol/L,

while moderate hyperhomocysteine concentrations are 15-30 µmol/L, intermediate levels are 30-100 µmol/L and severe hyperhomocysteine concentrations are >100 µmol/L.[7]

Hyperhomocysteine was identified as an independent risk factor for ischemic heart disease and vascular disease.[3,4] Initial reports hypothesized that heterozygosity of cystathionine-β-synthase contributed to the accumulation of homocysteine, and these reports were corroborated by later meta-analyses.[3,4] However, this rationale has not been corroborated, as two randomized controlled trials, the Heart Outcomes Prevention Evaluation 2 (Hope-2) and the Norwegian Vitamin (NORVIT) trials simultaneously demonstrated no effect from lowering homocysteine levels, by way of folic acid or vitamin B6 supplementation, on cardiovascular outcomes.[5,6]

Furthermore, hyperhomocysteine is a risk factor for venous thromboembolic disease. Ray et al performed a meta-analysis of 9 case control studies measuring fasting plasma homocystine, as well as 5 studies measured after methionine loading. All 9 studies demonstrated a similar trend in the levels and the associated risk for venous thromboembolism; following methionine loading, the trend increased toward the risk of venous thromboembolism.[9,10]

Coding Implications

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CPT® Codes	Description
83090	Homocysteine

HCPCS Codes	Description
N/A	

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
D51.0-D51.9	Vitamin B12 deficiency anemia
E53.8	Deficiency of other unspecified B group vitamins
E72.10	Disorders of sulfur-bearing amino-acid metabolism, unspecified
E72.11	Homocystinuria
E72.19	Other disorders of sulphur-bearing amino-acid metabolism
I26.01-I26.99	Pulmonary embolism
I81	Portal vein thrombosis

CLINICAL POLICY
Homocysteine Testing

ICD-10-CM Code	Description
I82.0-I82.91	Other venous embolism and thrombosis
Z86.711	Personal history of pulmonary embolism
Z86.718	Personal history of other venous thrombosis or embolism

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed	04/18	06/18

References

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4. Homocysteine Studies Collaboration. "Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis." *JAMA* 288.16 (2002): 2015-2022.
5. Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. "Homocysteine lowering with folic acid and B vitamins in vascular disease."*N Engl J Med* 2006.354 (2006): 1567-1577.
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8. Graham, I. M., E. DalyL, and H. M. Refsum. "Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials." *Am J Clin Nutr* 82.4 (2005): 806-812.
9. Ray, Joel G. "Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease." *Archives of internal medicine* 158.19 (1998): 2101-2106.
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