

## Clinical Policy: Homocysteine Testing

Reference Number: CP.MP.121

Last Review Date: 05/20

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### 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 health plans affiliated with Centene Corporation® that homocysteine testing is **medically necessary** for homocystinuria caused by cystathionine beta-synthase deficiency.
  
- II. It is the policy of health plans affiliated with Centene Corporation that homocysteine testing is considered **investigational** for the following indications:
  - a. Cardiovascular risk testing;
  - b. Borderline vitamin B12 deficiency;
  - c. Idiopathic (unprovoked) venous thromboembolism, recurrent venous thromboembolism, thrombosis occurring at < 45 years of age, or thrombosis at an unusual site;
  - d. 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 homeostatic plasma levels of homocysteine typically range at low micro molar concentrations, epistatic mutations and other aberrant modifications of the metabolic pathways modulate homocysteine levels.<sup>1</sup> 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.<sup>1</sup> Furthermore, a common mutation at a single nucleotide (677C→T) in the gene encoding 5,10-methylenetetrahydrofolate reductase, an enzyme in the folate cycle whose byproducts are necessary cofactors in the metabolism of homocysteine, affects homeostatic levels of homocysteine. This mutation predisposes the individual to low folate plasma levels, and consequently a status of hyperhomocysteine.<sup>2</sup>

Changes in the plasma homocysteine levels can result from alterations in folate or vitamin B6 or vitamin B12.<sup>7</sup> 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.<sup>8</sup> Moreover, basal levels of homocysteine range between 5-15 μmol/L,

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while moderate hyperhomocysteine concentrations are 15-30  $\mu\text{mol/L}$ , intermediate levels are 30-100  $\mu\text{mol/L}$  and severe hyperhomocysteine concentrations are  $>100 \mu\text{mol/L}$ .<sup>7</sup>

Hyperhomocysteine was identified as an independent risk factor for ischemic heart disease and vascular disease.<sup>3,4</sup> Initial reports hypothesized that heterozygosity of cystathionine- $\beta$ -synthase contributed to the accumulation of homocysteine, and these reports were corroborated by later meta-analyses.<sup>3,4</sup> 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.<sup>5,6</sup>

A 2017 Cochrane review of homocysteine-lowering interventions for preventing cardiovascular events concluded that B-vitamin supplements lowered homocysteine but did not reduce risk of myocardial infarction or reduce death rates in patients at risk of, or living with cardiovascular disease.<sup>11</sup> Compared with placebo, lowered homocysteine resulting from B-vitamin supplementation combined with antihypertensive medications produced uncertain benefit in preventing stroke- approximately 143 people would need to be treated for 5.4 years to prevent 1 stroke.<sup>11</sup>

Hyperhomocysteine has been suggested as a risk factor for venous thromboembolic disease. Ray et al. performed a meta-analysis of 9 case control studies measuring fasting plasma homocysteine, 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.<sup>9,10</sup> However, hyperhomocysteinemia has been associated with venous thromboembolic disease in some but not all studies. Additional research has concluded that associations between “mild” hyperhomocysteinemia and VTE may have been due to confounding by body mass index and cigarette smoking.<sup>17</sup>

Homocysteine testing has also been used to diagnose vitamin B12 deficiency, in combination with methylmalonic acid (MMA). Homocysteine levels are a sensitive and specific measure of established vitamin B12 deficiency, but its role is unclear in the evaluation of borderline B12 deficiency, where it would be most useful.<sup>20</sup> Furthermore, MMA testing without concurrent homocysteine testing has been recommended in the assessment of low-normal vitamin B12 levels.<sup>21</sup>

High levels of serum homocysteine have been proposed as a risk factor for dementia, and several studies have evaluated the role of B-vitamin supplementation in lowering homocysteine and thus improving cognitive function, or preventing cognitive decline. A meta-analysis by Clarke et al. determined that B-vitamin supplementation significantly reduced homocysteine levels, but did not have a clinically significant effect on global cognitive function or on cognitive aging.<sup>12</sup> In contrast, a 2018 International Consensus Statement argues for the presence of a causal relationship between homocysteine levels and cognitive decline, and for screening for hyperhomocysteine and treatment with B vitamins in patients presenting to memory clinics.<sup>13</sup> However, the consensus body notes that 76% of the participants in the trials in the largest meta-analysis on the topic did not include baseline measures of cognitive function, and thus couldn't

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adequately compare the intervention group to the placebo group. Furthermore, they point to the lack of an established homocysteine threshold for intervention, which reduces the clinical relevance of the measure.

#### 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
E72.10	Disorders of sulfur-bearing amino-acid metabolism, unspecified
E72.11	Homocystinuria
E72.19	Other disorders of sulphur-bearing amino-acid metabolism

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed	07/16	08/16
References reviewed and updated	07/17	08/17
Background updated. References reviewed and updated.	05/18	05/18
Background updated. References reviewed and updated. Specialist review	04/19	05/19
References reviewed and updated. Revised I.A from “Borderline vitamin B12 deficiency” to “Borderline low or inconclusive Vitamin B12 deficiency, or discordant with the clinical picture.”	03/20	04/20
Changed borderline B12 deficiency and idiopathic VTE/thromboembolism indications from medically necessary to investigational. Added supporting background information and references. Removed from the list of ICD-10 codes supporting coverage criteria: D51.0-D51.9, E53.8, I26.01-I26.99, I81, I82.0-I82.91, Z86.711, Z86.718.	05/20	05/20

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#### **Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

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**Note: For Medicaid members,** when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare members,** to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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