Clinical Policy: Homocysteine Testing

Reference Number: LA.CP.MP.121
Date of Last Revision: ~~5/23~~06/24

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Homocysteine is a nonproteinogenic amino acid generated during the conversion of methionine to cysteine.[2] Mutations of the enzymes within the biochemical pathways that regulate homeostatic homocysteine levels are associated with risk factors for various diseases, such as venous thromboembolic disease.[18,19] Supplementation of folic acid, vitamin B6, and vitamin B12 are known to modulate homocysteine levels due to the interplay between the folate cycle and metabolism.[7] This policy describes the medical necessity requirements for testing levels of homocysteine.

Policy/Criteria

I. It is the policy of Louisiana Healthcare Connections that homocysteine testing is **medically necessary** for members/enrollees with suspected homocystinuria caused by cystathionine beta-synthase deficiency including one of the following:

A. First-degree relative with homocystinuria;
B. Markedly elevated serum and urine homocysteine;
C. Characteristic physical findings including one of the following:
   1. Developmental delay;
   2. Marfanoid appearance;
   3. Osteoporosis;
   4. Ocular abnormalities (ectopia lentis);
   5. Thromboembolic disease;
   6. Severe premature atherosclerosis.

II. It is the policy of Louisiana Healthcare Connections that homocysteine testing has not been proven to improve outcomes compared to other technologies for the following indications:

~~a.~~A. Cardiovascular risk testing;
~~b.~~B. Borderline vitamin B12 deficiency;
C. Dementia;
~~c.~~D. Idiopathic (unprovoked) venous thromboembolism, recurrent venous thromboembolism, thrombosis occurring at < 45 years of age, or thrombosis at an unusual site;
~~d.~~E. For the testing of all other conditions.

Background

Homocysteine is a naturally occurring intermediary amino acid generated during the conversion of methionine to cysteine.[2] Homocystinuria is a rare inherited condition where the body cannot produce methionine and is characterized by severe elevations in plasma and urine homocysteine concentrations.[7] 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. Mutations in cystathionine-β-synthase, a key enzyme of the transsulfuration pathway, are associated with excess levels of homocysteine and premature thrombotic events.[1] Additionally, homeostatic levels of homocysteine are impacted by a common mutation at nucleotide position 677of677 of the gene coding for 5,10-methenetetrahydrolate reductase, which is an enzyme in the folate cycle whose byproducts are necessary cofactors in the metabolism of homocysteine.[2] This[2] 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 orin vitamin B6, vitamin B12, or folate.[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] Basal levels of homocysteine range between 5 to 15 µmol/L, while moderate hyperhomocysteine concentrations are 15 to 30 µmol/L, intermediate levels are 30 to 100 µmol/L, and hyperhomocysteine concentrations >100 µmol/L are considered severe.[7]

Observational studies have suggested that elevated homocysteine is an independent risk factor for ischemic heart disease and vascular disease.[3,4,15] However, large randomized controlled studies have shown that reduction in homocysteine levels does not result in lower reports of stroke or myocardial infarction.[21] A 2017 Cochrane review of homocysteine-lowering interventions for preventing cardiovascular events concluded that B-vitamin supplements lowered homocysteine but did not reduce the risk of myocardial infarction or reduce death rates in patients with or at risk of cardiovascular disease.[11] Additionally, two randomized controlled trials in 2006 simultaneously demonstrated no effect on cardiovascular outcomes from lowering homocysteine levels with folic acid or vitamin B6 supplementation.[5,6] Compared with placebo, lowered homocysteine resulting from B-vitamin supplementation combined with antihypertensive medications produced uncertain benefits in preventing stroke.[11]

Hyperhomocysteine has also been suggested as a risk factor for venous thromboembolic disease.[15,16,18,19] Ray et al. performed a meta-analysis of 9 case control studies measuring fasting plasma homocystinehomocysteine, as well as 5 studies measured after methionine loading. All 9 studies demonstrated a similar trend in the levels and the increased associated risk for venous thromboembolism (VTE);) following methionine loading.[9,10] 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 failure to take into accountconsider additional confounding risk factors such as body mass index and cigarette smoking.[17]

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.[20] Furthermore, MMA testing without concurrent homocysteine testing has been recommended in the assessment of low-normal vitamin B12 levels.[21]

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.[12] 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.[13] 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 could not 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.[13] At this time there is a lack of conclusive evidence that vitamin supplementation prevents dementia.[14]

Coding Implications

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NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis.

CPT® Codes	Description
83090	Homocysteine

***Not Medically Necessary* *ICD-10*~~-CM Diagnosis~~ *Codes*~~ that Support Coverage Criteria~~**

The following is a list of ICD-10 codes which are NOT medically necessary unless an exception is noted in this policy.

ICD-10-CM Code	Description
~~E72.10~~F01.511	~~Disorders of sulfur-bearing amino-acid metabolism~~Vascular dementia, unspecified severity, with agitation
~~E72.11~~F01.518	~~Homocystinuria~~Vascular dementia, unspecified severity, with other behavioral disturbance
F01.52	Vascular dementia, unspecified severity, with psychotic disturbance
F01.53	Vascular dementia, unspecified severity, with mood disturbance
F01.54	Vascular dementia, unspecified severity, with anxiety

ICD-10-CM Code	Description
F01.A4	Vascular dementia, mild, with anxiety
F01.B4	Vascular dementia, moderate, with anxiety
F01.C4	Vascular dementia, severe, with anxiety
F03.9	Unspecified dementia, unspecified severity
F03.A4	Vascular dementia, mild, with anxiety
F03.A11	Unspecified dementia, mild, with agitation
F03.B11	Unspecified dementia, moderate, with agitation
F03.B4	Vascular dementia, moderate, with anxiety
F03.C11	Unspecified dementia, severe, with agitation
F03.C4	Unspecified dementia, severe, with anxiety
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer's disease
G30.9	Alzheimer's disease, unspecified
G31.0	Frontotemporal dementia
R41.81	Age-related cognitive decline
Z00.00	Encounter for general adult medical examination without abnormal findings
Z00.01	Encounter for general adult medical examination with abnormal findings
Z00.8	Encounter for other general examination
Z01.8	Encounter for other specified special examinations
~~E72.19~~Z13.6	~~Other~~Encounter for screening for cardiovascular disorders~~ of sulphur-bearing amino-acid metabolism~~
Z13.21	Encounter for screening for nutritional disorder

Reviews, Revisions, and Approvals	~~Revision~~ Date	Approval Date
Converted corporate to local policy.	08/15/2020	
In the policy statement in section II, replaced "investigational" with the statement that homocysteine testing has not been proven to improve outcomes compared to other technologies. References and coding reviewed and updated. Replaced all instances of "member" with "member/enrollee."	1/2022	1/2022
Annual review. References reviewed and updated. Updated description and background with no impact on criteria. Reviewed by specialist. Added and may not support medical necessity to Coding Implications service	5/22	
Annual review. Updated description and background with no impact on criteria. References reviewed and updated.	5/23	7/21/23
Annual review. Expanded criteria to include I.a. First-degree relative with homocystinuria; I.b. Markedly elevated serum and urine homocysteine; I.c. Characteristic physical findings including one of the following: I.c.i. Developmental delay; I.c.ii. Marfanoid appearance; I.c.iii. Osteoporosis;	06/24	

Reviews, Revisions, and Approvals	~~Revision~~ Date	Approval Date
I.c.iv. Ocular abnormalities (ectopia lentis); I.c.v. Thromboembolic disease; I.c.vi. Severe premature atherosclerosis. Added dementia as a not medically necessary indication. Updated background with no impact to criteria. Removed table of Medically Necessary ICD10 codes and replaced with a table of Not Medically Necessary ICD-10 codes. References reviewed and updated. Reviewed by external specialist.		

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Important Reminder

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