WellCare®

Clinical Policy: Homocysteine Testing

Reference Number: WNC.CP.135 — Coding Implications
Last Review Date: — Revision Log

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

Note: 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.

Description

Homocysteine is a nonproteinogenic amino acid that is 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 WellCare of North Carolina® that homocysteine testing is **medically necessary** for members 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 WellCare of North Carolina® that homocysteine testing has not been proven to improve outcomes compared to other technologies for the following indications:
   A. Cardiovascular risk testing;
   B. Borderline vitamin B12 deficiency;
   C. Dementia;
   D. Idiopathic (unprovoked) venous thromboembolism, recurrent venous thromboembolism, thrombosis occurring at < 45 years of age, or thrombosis at an unusual site;
   E. 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.[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 677 of the gene encoding 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 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 vitamin B6 or 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 are >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 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 benefit in preventing stroke.[11]

Hyperhomocysteine has 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 homocysteine, 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 consider 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

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2025, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT®* Codes	Description
83090	Homocysteine

Not Medically Necessary ICD-10 Codes

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 - *Not Medically Necessary ICD-10 Codes*
F01.511	Vascular dementia, unspecified severity, with agitation
F01.518	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
F01.A4	Vascular dementia, mild, with anxiety
F01.B4	Vascular dementia, moderate, with anxiety

ICD-10-CM Code	Description - *Not Medically Necessary ICD-10 Codes*
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
Z00.810	Encounter for preprocedural cardiovascular examination
Z00.811	Encounter for preprocedural respiratory examination
Z01.812	Encounter for preprocedural laboratory examination
Z01.818	Encounter for other preprocedural examination
Z13.6	Encounter for screening for cardiovascular disorders
Z13.21	Encounter for screening for nutritional disorder

Reviews, Revisions, and Approvals	Reviewed Date	Approval Date
Original approval date	03/21	06/21
Reviewed CPT and ICD-10-CM codes. References reviewed and updated.	03/22	05/22
Annual review. References reviewed and updated. Updated description and background with no impact on criteria.	02/23	02/23
NCHC verbiage removed from NC Guidance Verbiage.	04/23	04/23
Annual Review. References reviewed and updated. Updated description and background with no impact on criteria. Removed HCPCS table.	02/24	02/24
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.1. Developmental delay; I.C.2. Marfanoid appearance; I.C.3. Osteoporosis; I.C.4. Ocular abnormalities (ectopia lentis); I.C.5. Thromboembolic disease; I.C.6. Severe premature atherosclerosis. Added Criteria II.C.dementia as a not medically necessary indication. Updated background with no impact to criteria.	02/25	02/25

Reviews, Revisions, and Approvals	Reviewed Date	Approval Date
Removed table of Medically Necessary ICD10 codes and replaced with a table of Not Medically Necessary ICD-10 codes. References reviewed and updated.		
Annual review. Under NC Guidance/Claims related information, updated state web address.		

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North Carolina Guidance

Eligibility Requirements

a. An eligible beneficiary shall be enrolled in the NC Medicaid Program (Medicaid is NC Medicaid program, unless context clearly indicates otherwise);
b. Provider(s) shall verify each Medicaid beneficiary's eligibility each time a service is rendered.
c. The Medicaid beneficiary may have service restrictions due to their eligibility category that would make them ineligible for this service.

EPSDT Special Provision: Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age

a. 42 U.S.C. § 1396d(r) [1905(r) of the Social Security Act]

Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) is a federal Medicaid requirement that requires the state Medicaid agency to cover services, products, or procedures for Medicaid beneficiary under 21 years of age if the service is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition [health problem] identified through a screening examination (includes any evaluation by a physician or other licensed practitioner).

This means EPSDT covers most of the medical or remedial care a child needs to improve or maintain his or her health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

Medically necessary services will be provided in the most economic mode, as long as the treatment made available is similarly efficacious to the service requested by the beneficiary's physician, therapist, or other licensed practitioner; the determination process does not delay the delivery of the needed service; and the determination does not limit the beneficiary's right to a free choice of providers.

EPSDT does not require the state Medicaid agency to provide any service, product, or procedure:

1. that is unsafe, ineffective, or experimental or investigational.
2. that is not medical in nature or not generally recognized as an accepted method of medical practice or treatment.

Service limitations on scope, amount, duration, frequency, location of service, and other specific criteria described in clinical coverage policies may be exceeded or may not apply as long as the provider's documentation shows that the requested service is medically necessary "to correct or ameliorate a defect, physical or mental illness, or a condition" [health problem]; that is, provider documentation shows how the service, product, or procedure meets all EPSDT criteria, including to correct or improve or maintain the beneficiary's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

EPSDT and Prior Approval Requirements

1. If the service, product, or procedure requires prior approval, the fact that the beneficiary is under 21 years of age does NOT eliminate the requirement for prior approval.
2. **IMPORTANT ADDITIONAL INFORMATION** about EPSDT and prior approval is found in the *NCTracks Provider Claims and Billing Assistance Guide*, and on the EPSDT provider page. The Web addresses are specified below:

NCTracks Provider Claims and Billing Assistance Guide:
https://www.nctracks.nc.gov/content/public/providers/provider-manuals.html
EPSDT provider page: https://medicaid.ncdhhs.gov/

Provider(s) Eligible to Bill for the Procedure, Product, or Service
To be eligible to bill for the procedure, product, or service related to this policy, the provider(s) shall:

a. meet Medicaid qualifications for participation;

b. have a current and signed Department of Health and Human Services (DHHS) Provider Administrative Participation Agreement; and
c. bill only for procedures, products, and services that are within the scope of their clinical practice, as defined by the appropriate licensing entity.

Compliance
Provider(s) shall comply with the following in effect at the time the service is rendered:
a. All applicable agreements, federal, state, and local laws and regulations including the Health Insurance Portability and Accountability Act (HIPAA) and record retention requirements; and
b. All NC Medicaid's clinical (medical) coverage policies, guidelines, policies, provider manuals, implementation updates, and bulletins published by the Centers for Medicare and Medicaid Services (CMS), DHHS, DHHS division(s) or fiscal contractor(s).

Claims-Related Information
Provider(s) shall comply with the NC Tracks Provider Claims and Billing Assistance Guide, Medicaid bulletins, fee schedules, NC Medicaid's clinical coverage policies and any other relevant documents for specific coverage and reimbursement for Medicaid:
a. Claim Type - as applicable to the service provided:
Professional (CMS-1500/837P transaction)
Institutional (UB-04/837I transaction)
Unless directed otherwise, Institutional Claims must be billed according to the National Uniform Billing Guidelines. All claims must comply with National Coding Guidelines.
b. International Classification of Diseases and Related Health Problems, Tenth Revisions, Clinical Modification (ICD-10-CM) and Procedural Coding System (PCS) - Provider(s) shall report the ICD-10-CM and Procedural Coding System (PCS) to the highest level of specificity that supports medical necessity. Provider(s) shall use the current ICD-10 edition and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for code description, as it is no longer documented in the policy.
c. Code(s) - Provider(s) shall report the most specific billing code that accurately and completely describes the procedure, product or service provided. Provider(s) shall use the Current Procedural Terminology (CPT), Health Care Procedure Coding System (HCPCS), and UB-04 Data Specifications Manual (for a complete listing of valid revenue codes) and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for the code description, as it is no longer documented in the policy. If no such specific CPT or HCPCS code exists, then the provider(s) shall report the procedure, product or service using the appropriate unlisted procedure or service code.
Unlisted Procedure or Service
CPT: The provider(s) shall refer to and comply with the Instructions for Use of the CPT Codebook, Unlisted Procedure or Service, and Special Report as documented in the current CPT in effect at the time of service.
HCPCS: The provider(s) shall refer to and comply with the Instructions For Use of HCPCS National Level II codes, Unlisted Procedure or Service and Special Report as documented in the current HCPCS edition in effect at the time of service.

d. Modifiers - Providers shall follow applicable modifier guidelines.
e. Billing Units - Provider(s) shall report the appropriate code(s) used which determines the billing unit(s).
f. Co-payments -
For Medicaid refer to Medicaid State Plan:
https://medicaid.ncdhhs.gov/meetingsnotices/medicaid-state-plan-public-notices

g. Reimbursement - Provider(s) shall bill their usual and customary charges. For a schedule of rates, refer to: https://medicaid.ncdhhs.gov/.

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.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.