

Reimbursement Policy

Testing of Homocysteine Metabolism – Related Conditions

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I. Policy Description

Homocystinuria is a metabolic condition in which the body is unable to properly process certain amino acids, resulting in an abnormal accumulation of homocysteine and its metabolites in the blood and urine (NIH, 2023). Homocystinuria is primarily due to genetic causes; however, homocystinuria can also be due to non-genetic causes, including severe deficiency of vitamin B12, also known as cobalamin (Mudd et al., 2000).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" of this policy document.

- 1) Newborn screening for homocysteine-related conditions **MEETS COVERAGE CRITERIA** in **any** of the following situations:
 - a) Screening for classic homocystinuria due to CBS deficiency by performing quantitative plasma amino acids analysis and/or plasma or urine total homocysteine analysis.
 - b) Screening for homocystinuria in dried blood spots.
 - c) Screening for hypermethioninemia in dried blood spots.
- 2) When the initial screening test result exceeds the cut-off level of methionine, a repeat dried blood specimen submitted to the newborn screening program, **or** a quantitative plasma amino acid analysis and analysis of plasma total homocysteine **MEETS COVERAGE CRITERIA**.
- 3) For the diagnosis of phenotype variants of classic homocystinuria due to CBS deficiency, the pyridoxine (B6) challenge test **MEETS COVERAGE CRITERIA**.
- 4) For individuals over 18 years of age with homocystinuria suspected to be caused by CBS deficiency **and** for monitoring therapy in those with confirmed CBS deficiency, total homocysteine testing in plasma **MEETS COVERAGE CRITERIA**.
- 5) Plasma free homocysteine testing **DOES NOT MEET COVERAGE CRITERIA**.

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III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

On May 13, 2011, the FDA approved the Invader *MTHFR* 677 created by Hologic, Inc. The Invader *MTHFR* 677 is an in-vitro diagnostic test intended for the detection and genotyping of a single point mutation (C to T at position 677) of the human 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene in isolated genomic DNA obtained from whole blood Potassium EDTA samples from patients with suspected thrombophilia (FDA, 2011a).

On April 25, 2011, the FDA approved the Invader *MTHFR* 1298 created by Hologic, Inc. The Invader *MTHFR* 1298 test is an in vitro diagnostic test intended for the detection and genotyping of a single point mutation (A to C at position 1298) of the human 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene in isolated genomic DNA obtained from whole blood potassium EDTA samples from patients with suspected thrombophilia (FDA, 2011b).

On April 22, 2010, the FDA approved the eSensor Thrombophilia Risk Test on XT-8 System created by Osmetech Molecular Diagnostics. The *MTHFR*-specific portion is as follows: The eSensor *MTHFR* Genotyping Test is an in-vitro diagnostic for the detection and genotyping of point mutations (C to T at position 677) and (A to C at position 1298) of the human 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene in isolated genomic DNA obtained from whole blood samples. The test is intended to be used on the eSensor XT-8 System (FDA, 2010).

On October 11, 2007, the FDA approved the Verigene System created by Nanosphere Inc. The *MTHFR*-specific portion is as follows: The Verigene *MTHFR* Nucleic Acid Test is an in vitro diagnostic for the detection and genotyping of a single point mutation (C to T at position 677) of the human 5,10-methylenetetrahydrofolate reductase gene (*MTHFR*) in patients with suspected thrombophilia, from isolated genomic DNA obtained from whole blood samples. The test is intended to be used on the Verigene System (FDA, 2007).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of

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1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82136	Amino acids, 2 to 5 amino acids, quantitative, each specimen
82139	Amino acids, 6 or more amino acids, quantitative, each specimen
82615	Cystine and homocysteine, urine, qualitative
83090	Homocysteine
83921	Organic acid, single, quantitative
84207	Pyridoxal phosphate (Vitamin B-6)

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

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