



If a conflict arises between a Clinical Payment and Coding Policy and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. "Plan documents" include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. Blue Cross and Blue Shield of Oklahoma may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSOK has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act HIPAA approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing Editor, American Medical Association, Current Procedural Terminology, CPT® Assistant, Healthcare Common Procedure Coding System, ICD-10 CM and PCS, National Drug Codes, Diagnosis Related Group guidelines, Centers for Medicare and Medicaid Services National Correct Coding Initiative Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

Testing of Homocysteine Metabolism-Related Conditions

Policy Number: CPCPLAB067

Version 1.0

Approval Date: January 23, 2025

Plan Effective Date: April 15, 2025

Description

The Plan has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

Reimbursement Information:

1. Newborn screening for homocysteine-related conditions **may be reimbursable** in any of the following situations:
 - a. Screening for classic homocystinuria due to cystathionine β -synthase (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 **may be reimbursable**.
3. For the diagnosis of phenotype variants of classic homocystinuria due to cystathionine β -synthase (CBS) deficiency, the pyridoxine (B6) challenge test **may be reimbursable**.
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, total homocysteine testing in plasma **may be reimbursable**.
5. Plasma free homocysteine testing **is not reimbursable**.

Procedure Codes

The following is not an all-encompassing code list. The inclusion of a code does not guarantee it is a covered service or eligible for reimbursement.

Codes
82136, 82139, 82615, 83090, 83921, 84207

References:

- Abbott, M. H., Folstein, S. E., Abbey, H., & Pyeritz, R. E. (1987). Psychiatric manifestations of homocystinuria due to cystathionine beta-synthase deficiency: prevalence, natural history, and relationship to neurologic impairment and vitamin B6-responsiveness. *Am J Med Genet*, 26(4), 959-969. <https://doi.org/10.1002/ajmg.1320260427>
- ACMG. (2021a, December). *Methionine Elevated or Decreased*. American College of Medical Genetics and Genomics. <http://www.acmg.net/PDFLibrary/Methionine-Algorithm.pdf>
- ACMG. (2021b). Newborn Screening ACT Sheet [Increased Methionine] Homocystinuria (CBS Deficiency) file:///C:/Users/AHCS8503/Downloads/Methionine.pdf
- Al-Sadeq, D. W., & Nasrallah, G. K. (2020). The Spectrum of Mutations of Homocystinuria in the MENA Region. *Genes (Basel)*, 11(3). <https://doi.org/10.3390/genes11030330>
- Belkhiria, M. N., Ducros, V., Harzallah, K., Jarraya, F., Cordonnier, D., Favier, A., & Achour, A. (2007). [Evaluation of plasmatic homocysteine determination by gas chromatography-mass spectrometry]. *Ann Biol Clin (Paris)*, 65(4), 393-398. <https://pubmed.ncbi.nlm.nih.gov/17627920/>

- (Evaluation d'un transfert de methode : dosage de l'homocysteine plasmatique par chromatographie en phase gazeuse couplee a la spectrometrie de masse.)
- Collison, F. T., Xie, Y. A., Gambin, T., Jhangiani, S., Muzny, D., Gibbs, R., Lupski, J. R., Fishman, G. A., & Allikmets, R. (2015). Whole Exome Sequencing Identifies an Adult-Onset Case of Methylmalonic Aciduria and Homocystinuria Type C (cb1C) with Non-Syndromic Bull's Eye Maculopathy. *Ophthalmic Genet*, 36(3), 270-275. <https://doi.org/10.3109/13816810.2015.1010736>
- Concepción-Alvarez, A., Camayd-Viera, I., & Nuevas-Paz, L. (2016). Validation of an HPLC method for total homocysteine quantification in plasma. *Revista del Laboratorio Clinico*, 9(2), 40-47. <https://doi.org/10.1016/j.labcli.2016.02.003>
- de Sain-van der Velden, M. G. M., van der Ham, M., Jans, J. J., Visser, G., van Hasselt, P. M., Prinsen, H., & Verhoeven-Duif, N. M. (2015). Suitability of methylmalonic acid and total homocysteine analysis in dried bloodspots. *Anal Chim Acta*, 853, 435-441. <https://doi.org/10.1016/j.aca.2014.10.043>
- FDA. (2007, October 11, 2007). *Nanosphere 510(k) Summary*. Retrieved October 21, 2021 from https://www.accessdata.fda.gov/cdrh_docs/pdf7/K070597.pdf
- FDA. (2010, March 24, 2010). *eSensor Thrombophilia Risk Test on XT-8 System*. Retrieved October 21, 2021 from https://www.accessdata.fda.gov/cdrh_docs/pdf9/K093974.pdf
- FDA. (2011a, May 13, 2011). *Invader MTHFR 677 510(k) Summary*. Retrieved October 21, 2021 from https://www.accessdata.fda.gov/cdrh_docs/pdf10/K100987.pdf
- FDA. (2011b, April 25, 2011). *Invader MTHFR 1298 510(k) Summary*. Retrieved October 21, 2021 from https://www.accessdata.fda.gov/cdrh_docs/pdf10/K100496.pdf
- Froese, D. S., Kopec, J., Fitzpatrick, F., Schuller, M., McCorvie, T. J., Chalk, R., Plessl, T., Fettelschoss, V., Fowler, B., Baumgartner, M. R., & Yue, W. W. (2015). Structural Insights into the MMACHC-MMADHC Protein Complex Involved in Vitamin B12 Trafficking. *J Biol Chem*, 290(49), 29167-29177. <https://doi.org/10.1074/jbc.M115.683268>
- Frosst, P., Blom, H. J., Milos, R., Goyette, P., Sheppard, C. A., Matthews, R. G., Boers, G. J., den Heijer, M., Kluijtmans, L. A., van den Heuvel, L. P., & et al. (1995). A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet*, 10(1), 111-113. <https://doi.org/10.1038/ng0595-111>
- Gales, A., Masingue, M., Millecamps, S., Giraudier, S., Grosliere, L., Adam, C., Salim, C., Navarro, V., & Nadjar, Y. (2018). Adolescence/adult onset MTHFR deficiency may manifest as isolated and treatable distinct neuro-psychiatric syndromes. *Orphanet J Rare Dis*, 13(1), 29. <https://doi.org/10.1186/s13023-018-0767-9>
- Gaughan, D. J., Kluijtmans, L. A., Barboux, S., McMaster, D., Young, I. S., Yarnell, J. W., Evans, A., & Whitehead, A. S. (2001). The methionine synthase reductase (MTRR) A66G polymorphism is a novel genetic determinant of plasma homocysteine concentrations. *Atherosclerosis*, 157(2), 451-456. [https://doi.org/10.1016/s0021-9150\(00\)00739-5](https://doi.org/10.1016/s0021-9150(00)00739-5)
- Gaustadnes, M., Ingerslev, J., & Rütiger, N. (1999). Prevalence of Congenital Homocystinuria in Denmark. *New England Journal of Medicine*, 340(19), 1513-1513. <https://doi.org/10.1056/NEJM199905133401915>
- Gonzales, M. C., Yu, P., & Shiao, S. P. K. (2017). MTHFR Gene Polymorphism-Mutations and Air Pollution as Risk Factors for Breast Cancer: A Metaprediction Study. *Nursing research*, 66(2), 152-163. <https://doi.org/10.1097/NNR.0000000000000206>
- Guo, Q.-n., Wang, L., Liu, Z.-y., Wang, H.-d., Wang, L., Long, J.-g., & Liao, S.-x. (2022). Different effects of maternal homocysteine concentration, MTHFR and MTRR genetic polymorphisms on the occurrence of fetal aneuploidy. *Reproductive BioMedicine Online*, 45(6), 1207-1215. <https://doi.org/10.1016/j.rbmo.2022.06.024>

- Harmon, D. L., Shields, D. C., Woodside, J. V., McMaster, D., Yarnell, J. W., Young, I. S., Peng, K., Shane, B., Evans, A. E., & Whitehead, A. S. (1999). Methionine synthase D919G polymorphism is a significant but modest determinant of circulating homocysteine concentrations. *Genet Epidemiol*, 17(4), 298-309. [https://doi.org/10.1002/\(SICI\)1098-2272\(199911\)17:4%3C298::AID-GEPI5%3E3.0.CO;2-V](https://doi.org/10.1002/(SICI)1098-2272(199911)17:4%3C298::AID-GEPI5%3E3.0.CO;2-V)
- HHS. (2024, July 2024). *Recommended Uniform Screening Panel*. <https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html>
- Huemer, M., Diodato, D., Schwahn, B., Schiff, M., Bandeira, A., Benoist, J. F., Burlina, A., Cerone, R., Couce, M. L., Garcia-Cazorla, A., la Marca, G., Pasquini, E., Vilarinho, L., Weisfeld-Adams, J. D., Kožich, V., Blom, H., Baumgartner, M. R., & Dionisi-Vici, C. (2017). Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. *J Inherit Metab Dis*, 40(1), 21-48. <https://doi.org/10.1007/s10545-016-9991-4>
- Huemer, M., Kožich, V., Rinaldo, P., Baumgartner, M. R., Merinero, B., Pasquini, E., Ribes, A., & Blom, H. J. (2015). Newborn screening for homocystinurias and methylation disorders: systematic review and proposed guidelines. *Journal of inherited metabolic disease*, 38(6), 1007-1019. <https://doi.org/10.1007/s10545-015-9830-z>
- Ismayilova, N., MacKinnon, A. D., Mundy, H., & Fallon, P. (2019). Reversible Cerebral White Matter Abnormalities in Homocystinuria. *JIMD Rep*, 44, 115-119. https://doi.org/10.1007/8904_2018_135
- Janosík, M., Sokolová, J., Janosíková, B., Krijt, J., Klatovská, V., & Kozich, V. (2009). Birth prevalence of homocystinuria in Central Europe: frequency and pathogenicity of mutation c.1105C>T (p.R369C) in the cystathionine beta-synthase gene. *The Journal of pediatrics*, 154(3), 431-437. <https://doi.org/10.1016/j.jpeds.2008.09.015>
- Kluijtmans, L. A., Young, I. S., Boreham, C. A., Murray, L., McMaster, D., McNulty, H., Strain, J. J., McPartlin, J., Scott, J. M., & Whitehead, A. S. (2003). Genetic and nutritional factors contributing to hyperhomocysteinemia in young adults. *Blood*, 101(7), 2483-2488. <https://doi.org/10.1182/blood.V101.7.2483>
- Li, Barshop, Feigenbaum, & Khanna. (2018). Brain Magnetic Resonance Imaging Findings in Poorly Controlled Homocystinuria. *J Radiol Case Rep*. <https://doi.org/10.3941/jrcr.v12i1.3207>
- Long, S., & Goldblatt, J. (2016). MTHFR genetic testing: Controversy and clinical implications. *Australian Family Physician*, 45, 237-240. <http://www.racgp.org.au/afp/2016/april/mthfr-genetic-testing-controversy-and-clinical-implications/>
- Mazaheri, Mostofizadeh, & Hashemipour. (2017). Homocystinuria with Stroke and Positive Familial History. *Adv Biomed Res*. <https://doi.org/10.4103/2277-9175.217215>
- Morris, A. A. M., Kožich, V., Santra, S., Andria, G., Ben-Omran, T. I. M., Chakrapani, A. B., Crushell, E., Henderson, M. J., Hochuli, M., Huemer, M., Janssen, M. C. H., Maillot, F., Mayne, P. D., McNulty, J., Morrison, T. M., Ogier, H., O'Sullivan, S., Pavlíková, M., de Almeida, I. T., . . . Chapman, K. A. J. J. o. I. M. D. (2017). Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency [journal article]. 40(1), 49-74. <https://doi.org/10.1007/s10545-016-9979-0>
- Mudd, S. H., Finkelstein, J. D., Refsum, H., Ueland, P. M., Malinow, M. R., Lentz, S. R., Jacobsen, D. W., Brattstrom, L., Wilcken, B., Wilcken, D. E., Blom, H. J., Stabler, S. P., Allen, R. H., Selhub, J., & Rosenberg, I. H. (2000). Homocysteine and its disulfide derivatives: a suggested consensus terminology. *Arterioscler Thromb Vasc Biol*, 20(7), 1704-1706. <https://doi.org/10.1161/01.atv.20.7.1704>
- Mudd, S. H., Skovby, F., Levy, H. L., Pettigrew, K. D., Wilcken, B., Pyeritz, R. E., Andria, G., Boers, G. H., Bromberg, I. L., Cerone, R., & et al. (1985). The natural history of homocystinuria due to

cystathionine beta-synthase deficiency. *Am J Hum Genet*, 37(1), 1-31.

<https://pubmed.ncbi.nlm.nih.gov/3872065/>

Nelson, B. C., Pfeiffer, C. M., Sniegowski, L. T., & Satterfield, M. B. (2003). Development and evaluation of an isotope dilution LC/MS method for the determination of total homocysteine in human plasma. *Anal Chem*, 75(4), 775-784. <https://doi.org/10.1021/ac0204799>

Nexo, E., Engbaek, F., Ueland, P. M., Westby, C., O’Gorman, P., Johnston, C., Kase, B. F., Guttormsen, A. B., Alfheim, I., McPartlin, J., Smith, D., Møller, J., Rasmussen, K., Clarke, R., Scott, J. M., & Refsum, H. (2000). Evaluation of Novel Assays in Clinical Chemistry: Quantification of Plasma Total Homocysteine. *Clinical Chemistry*, 46(8), 1150. <https://doi.org/10.1093/clinchem/46.8.1150>

NIH. (2023). *Homocystinuria due to CBS deficiency*.

<https://rarediseases.info.nih.gov/diseases/6667/homocystinuria-due-to-cbs-deficiency>

Okun, J. G., Gan-Schreier, H., Ben-Omran, T., Schmidt, K. V., Fang-Hoffmann, J., Gramer, G., Abdoh, G., Shahbeck, N., Al Rifai, H., Al Khal, A. L., Haege, G., Chiang, C. C., Kasper, D. C., Wilcken, B., Burgard, P., & Hoffmann, G. F. (2017). Newborn Screening for Vitamin B6 Non-responsive Classical Homocystinuria: Systematical Evaluation of a Two-Tier Strategy. *JIMD Rep*, 32, 87-94.

https://doi.org/10.1007/8904_2016_556

Rose, N. C., & Dolan, S. M. (2012). Newborn screening and the obstetrician. *Obstetrics and gynecology*, 120(4), 908-917. <https://doi.org/10.1097/AOG.0b013e31826b2f03>

Rosenson, R. S., Smith, C. C., & Bauer, K. A. (2024, August 29, 2024). *Overview of homocysteine*.

<https://www.uptodate.com/contents/overview-of-homocysteine>

Sacharow, S. J., Picker, J. D., & Levy, H. L. (2004). Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews*((R)). University of Washington, Seattle.

<https://www.ncbi.nlm.nih.gov/pubmed/20301697>

Wang, W., Jiao, X. H., Wang, X. P., Sun, X. Y., & Dong, C. (2016). MTR, MTRR, and MTHFR Gene Polymorphisms and Susceptibility to Nonsyndromic Cleft Lip With or Without Cleft Palate. *Genet Test Mol Biomarkers*, 20(6), 297-303. <https://doi.org/10.1089/gtmb.2015.0186>

Weisberg, I., Tran, P., Christensen, B., Sibani, S., & Rozen, R. (1998). A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. *Mol Genet Metab*, 64(3), 169-172. <https://doi.org/10.1006/mgme.1998.2714>

Zhu, H., Blake, S., Chan, K. T., Pearson, R. B., & Kang, J. (2018). Cystathionine beta-Synthase in Physiology and Cancer. *Biomed Res Int*, 2018, 3205125. <https://doi.org/10.1155/2018/3205125>

Policy Update History:

Approval Date	Effective Date; Summary of Revisions
01/23/2025	04/15/2025; Document updated with literature review. Reimbursement Information unchanged. References revised.
03/15/2024	Document updated with literature review. Reimbursement Information unchanged. References revised; one new reference added.
11/01/2023	Document updated with literature review. Reimbursement information revised for clarity. References revised.
05/01/2022	New policy