***Effective November 1, 2023, refer to CMS Manual 100-02, Chapter 16-General Exclusions from Coverage for services included in this policy.***

BlueCross BlueShield of Alabama

**Name of Blue Advantage Policy:**

# Serum Holotranscobalamin as a Marker of Vitamin B12 (Cobalamin) Status

Policy #: 448
Latest Review Date: August 2023
Category: Laboratory
**ARCHIVED EFFECTIVE 11/1/2023**

## BACKGROUND:

***Blue Advantage*** *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

**Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare*** *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

## POLICY:

**Blue Advantage** will treat **measurement of holotranscobalamin** as a **non-covered** benefit and as **investigational** in the diagnosis and management of Vitamin B12 deficiency.

*Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

## DESCRIPTION OF PROCEDURE:

Holotranscobalamin (holo-TC) is a transcobalamin-vitamin B12 complex which has been investigated as a diagnostic test for vitamin B12 deficiency in symptomatic and at-risk populations, as well as an assay for monitoring response to therapy.

Vitamin B12 is also called cobalamin. It is present in foods derived from animal products. It is an essential vitamin that is required for DNA synthesis affecting red blood cell formation, and methionine synthesis affecting neurological functioning. The endogenous forms of Vitamin B12 include cobalamin and holotranscobalamin, which represent the active fraction of plasma cobalamin. Cobalamin deficiency can result from nutritional deficiencies or malabsorption. Dietary insufficiency is most common among vegetarians and the elderly. Malabsorption of vitamin B12 may be associated with autoantibodies as in pernicious anemia or can occur after gastrectomy, or in other gastrointestinal conditions such as celiac disease, Whipple's disease and Zollinger-Ellison syndrome. Clinical signs and symptoms of cobalamin deficiency include megaloblastic anemia, paresthesias and neuropathy, and psychiatric symptoms such as irritability, dementia, depression, or psychosis. While the hematologic abnormalities disappear promptly after treatment, neurologic disorders may become permanent if treatment is delayed.

The diagnosis of cobalamin deficiency has traditionally been based on low levels of total serum cobalamin, in conjunction with clinical evidence of disease. However, this laboratory test has been found to be poorly sensitive and specific. Therefore, attention has turned to measuring metabolites of cobalamin as a surrogate marker. In humans only two enzymatic reactions are known to be dependent on cobalamin: the conversion of methylmalonic acid (MMA) to succinyl-CoA, and the conversion of homocysteine and folate to methionine. Therefore, in the setting of cobalamin deficiency, serum levels of MMA and homocysteine are elevated, and have been investigated as surrogate markers.

There also is interest in the direct measurement of the subset of biologically-active cobalamin. Cobalamin in serum is bound to two proteins, transcobalamin and haptocorrin. Transcobalamin-cobalamin complex (called holotranscobalamin, or holo-TC) functions to transport cobalamin from its site of absorption in the ileum to specific receptors throughout the body. Less than 25%

of the total serum cobalamin exists as holo-TC, but this is considered the clinically relevant biologically active form. Serum levels of holo-TC can be measured using a radioimmunoassay or enzyme immunoassay.

## KEY POINTS:

This policy is based on a review of current literature as of August 21, 2023.

**Summary of Evidence**

Holotranscobalamin (holo-TC) is a transcobalamin-vitamin B12 complex that has been investigated as a diagnostic test for vitamin B12 deficiency in symptomatic and at-risk populations, as well as an assay for monitoring response to therapy. Holo-TC seems more suitable than total vitamin B-12 for the diagnosis of vitamin B-12 deficiency. There is currently no gold standard or true reference method to diagnose subtle vitamin B-12 deficiency, which makes evaluation of the clinical usefulness of holoTC and the estimation of sensitivity and specificity problematic. There is a need for well-designed studies that can prove or disprove this technology's clinical utility. There is a lack of evidence to establish holotranscobalamin testing as an alternative to either total serum cobalamin, or levels of MMA or homocysteine in the diagnosis of vitamin B12 deficiency. Evidence of the clinical utility of the test is lacking and the effect on net health outcomes in unproven.

**Practice Guidelines and Position Statements**

**American Academy of Family Physicians (AAFP)**

The AAFP does not recommend screening persons at average risk of vitamin B12 deficiency. Screening should be considered in patients with risk factors, and diagnostic testing should be considered in those with suspected clinical manifestations.

**American College of Gastroenterology (ACG)**

According to the ACG, "people with newly diagnosed celiac disease should undergo testing and treatment for micronutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12 (conditional recommendation, low level of evidence)"

**American Academy of Neurology (AAN)**

The American Academy of Neurology recommends serum vitamin B12 testing "as part of the assessment of elderly patients with dementia".

**The British Society for Haematology**

"Serum cobalamin currently remains the first-line test, with additional second-line plasma methylmalonic acid to help clarify uncertainties of underlying biochemical/functional deficiencies. Serum holotranscobalamin has the potential as a first-line test, but an indeterminate 'grey area' may still exist. Plasma homocysteine may be helpful as a second-line test, but is less specific than methylmalonic acid. The availability of these second-line tests is currently limited."

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

## KEY WORDS:
Holo-TC, Vitamin B12 Deficiency, Holotranscobalamin, Transcobalamin, Axis-Shield, HoloTC RIA

## APPROVED BY GOVERNING BODIES:
In January 2004, the device "HoloTC RIA" (Axis-Shield plc, Dundee, UK) is an example of a radioimmunoassay for holo-TC that was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for use in:

"Quantitative measurement of the fraction of cobalamin (vitamin B12) bound to the carrier protein transcobalamin in the human serum or plasma. Measurements obtained by this device are used in the diagnosis and treatment of vitamin B12 deficiency."

In November 2006, the device "Axis-Shield HoloTC Assay" (Axis-Shield, Dundee, UK), an enzyme immunoassay for holo-TC, was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for use in:

"Quantitative determination of holotranscobalamin…in human serum and plasma on the AxSym® System. HoloTC is used as an aid in the diagnosis and treatment of vitamin B12 deficiency."

## BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

## CURRENT CODING:
**CPT Codes:**

| | |
|---|---|
| 84999 | Unlisted chemistry procedure |

## REFERENCES:
1. Bondu JD, Nellickal AJ, Jeyaseelan L, Geethanjali FS. Assessing Diagnostic Accuracy of Serum Holotranscobalamin (Active-B12) in Comparison with Other Markers of Vitamin B12 Deficiency. Indian J Clin Biochem. 2020 Jul; 35(3):367-372.

2. Carmel R, Agrawal YP. Failures of cobalamin assays in pernicious anemia. Engl J Med. 2012; 367(4):385.
3. Carmel R. Biomarkers of cobalamin (vitamin B-12) status in the epidemiologic setting: a critical overview of context, applications, and performance characteristics of cobalamin, methylmalonic acid, and holotranscobalamin II. Am J Clin Nutr 2011; 94(1):348S-58S.
4. Collin SM, Metcalfe C, Refsum H, et al. Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: A case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev 2010; 19(6):1632-42.
5. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014; 166(4):496–513.
6. Dullemeijer C, Souverein OW, Doets EL et al. Systematic review with dose-response meta-analyses between vitamin B-12 intake and European Micronutrient Recommendations Aligned's prioritized biomarkers of vitamin B-12 including randomized controlled trials and observational studies in adults and elderly persons. Am J Clin Nutr 2013; 97(2):390-402.
7. Elin RJ and Winter WE. Methylmalonic acid: A test whose time has come? Arch Pathol Lab Med 2001; 125(6):824-7.
8. England JD, Gronseth GS, Franklin G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology 2009; 72(2):185-92.
9. Eussen SJ, de Groot LC, Joosten LW, et al. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: A randomized, placebo-controlled trial. Am J Clin Nutr 2006; 84(2):361-70.
10. Eussen SJ, Ueland PM, Hiddink GJ, et al. Changes in markers of cobalamin status after cessation of oral B-vitamin supplements in elderly people with mild cobalamin deficiency. Eur J Clin Nutr 2008; 62(10):1248-51.
11. Fedosov SN. Metabolic signs of vitamin B (12) deficiency in humans: computational model and its implications for diagnostics. Metabolism 2010; 59:1124–38.
12. Fragasso A, Mannarella C, Ciancio A, et al. Holotranscobalamin is a useful marker of vitamin B12 deficiency in alcoholics. Scientific World Journal. 2012; 2012:128182.
13. Hardlei TF, Mørkbak AL, Bor MV, Bailey LB, Hvas AM, Nexo E. Assessment of vitamin B (12) absorption based on the accumulation of orally administered cyanocobalamin on transcobalamin. Clin Chem 2010;56:432–6
14. Hay G, Clausen T, Whitelaw A, et al. Maternal folate and cobalamin status predicts vitamin status in newborns and 6-month-old infants. J Nutr 2010; 140(3):557-64.
15. Heil SG, de Jonge R, de Rotte MC et al. Screening for metabolic vitamin B12 deficiency by holotranscobalamin in patients suspected of vitamin B12 deficiency: a multicentre study. Ann Clin Biochem 2012; 49(Pt 2):184-9.

16. Herrmann W, Obeid R, Schorr H, Geisel J. Functional vitamin B12 deficiency and determination of holotranscobalamin in populations at risk. Clin Chem Lab Med. 2003 Nov; 41(11):1478-88.
17. Hill MH, Flatley JE, Barker ME et al. A vitamin B-12 supplement of 500 mug/d for eight weeks does not normalize urinary methylmalonic acid or other biomarkers of vitamin B-12 status in elderly people with moderately poor vitamin B-12 status. J Nutr 2013; 143(2):142-7.
18. Hoey L, Strain JJ and McNulty H. Studies of biomarker responses to intervention with vitamin B-12: A systematic review of randomized controlled trials. Am J Clin Nutr 2009; 89(6):1981S-96S.
19. Hvas AM and Nexo E. Holotranscobalamin--a first choice assay for diagnosing early vitamin B deficiency? J Intern Med 2005; 257(3):289-98.
20. Hvas AM, Nexo E. Holotranscobalamin as a predictor of vitamin B12 status. Clin Chem Lab Med. 2003 Nov; 41(11):1489-92.
21. IOM (Institute of Medicine). 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press.
22. Jarquin Campos A, Risch L, Nydegger U, Wiesner J, Vazquez Van Dyck M, Renz H, Stanga Z, Risch M. Diagnostic Accuracy of Holotranscobalamin, Vitamin B12, Methylmalonic Acid, and Homocysteine in Detecting B12 Deficiency in a Large, Mixed Patient Population. Dis Markers. 2020 Feb 7; 2020:7468506.
23. Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. Am Fam Physician. 2017 Sep 15; 96(6):384-389. PMID: 28925645.
24. Loikas S, Löppönen M, Suominen P, Møller J, Irjala K, Isoaho R, Kivelä SL, Koskinen P, Pelliniemi TT. RIA for serum holo-transcobalamin: method evaluation in the clinical laboratory and reference interval. Clin Chem. 2003 Mar; 49(3):455-62.
25. Matchar DB, McCrory DC, Millington DS, Feussner JR. Performance of the serum cobalamin assay for diagnosis of cobalamin deficiency. Am J Med Sci. 1994 Nov; 308(5):276-83.
26. Nexo E, Hoffmann-Lucke E. Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility. Am J Clin Nutr 2011; 94(1):359S-65S.
27. Nexo E, Hvas AM, Bleie O, et al. Holo-transcobalamin is an early marker of changes in cobalamin homeostasis. A randomized placebo-controlled study. Clin Chem 2002; 48(10):1768-71.
28. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician 2003; 67(5):979-86.
29. Ok Bozkaya I, Yarali N, Kizilgün M, Ozkan S, Tunc B. Relationship Between the Levels of Holotranscobalamin and Vitamin B12 in Children. Indian J Hematol Blood Transfus. 2017 Dec; 33(4):537-540.
30. O'Leary F, Allman-Farinelli M, Samman S. Vitamin B (1) (2) status, cognitive decline and dementia: a systematic review of prospective cohort studies. Br J Nutr 2012; 108(11):1948-61.
31. Remacha AF, Sardà MP, Canals C, Queraltò JM, Zapico E, Remacha J, Carrascosa C. Role of serum holotranscobalamin (holoTC) in the diagnosis of patients with low serum

cobalamin. Comparison with methylmalonic acid and homocysteine. Ann Hematol. 2014 Apr; 93(4):565-9.

32. Robinson DJ, O'Luanaigh C, Tehee E, O'Connell H, Hamilton F, Chin AV, Coen R, Molloy AM, Scott J, Cunningham CJ, Lawlor BA. Associations between holotranscobalamin, vitamin B12, homocysteine and depressive symptoms in community-dwelling elders. Int J Geriatr Psychiatry. 2011 Mar; 26(3):307-13.
33. Sobczyńska-Malefora A, Gorska R, Pelisser M, Ruwona P, Witchlow B, Harrington DJ. An audit of holotranscobalamin ("Active" B12) and methylmalonic acid assays for the assessment of vitamin B12 status: application in a mixed patient population. Clin Biochem. 2014 Jan; 47(1-2):82-6.
34. Valente E, Scott JM, Ueland PM et al. Diagnostic accuracy of holotranscobalamin, methylmalonic acid, serum cobalamin, and other indicators of tissue vitamin B(1)(2) status in the elderly. Clin Chem 2011; 57(6):856-63.
35. van Wijngaarden JP, Dhonukshe-Rutten RAM, Brouwer-Brolsma EM, Enneman AW, Swart KMA, van Dijk SC, In 't Veld PH, van Schoor NM, van der Velde N, de Jonge R, Lips P, Uitterlinden AG, de Groot LCPGM. Vitamin B12 Intake and Related Biomarkers: Associations in a Dutch Elderly Population. J Nutr Health Aging. 2017; 21(10):1268-1276.
36. Verma, A., Aggarwal, S., Garg, S., Kaushik, S., & Chowdhury, D. (2023). Comparison of Serum Holotranscobalamin with Serum Vitamin B12 in Population Prone to Megaloblastic Anemia and their Correlation with Nerve Conduction Study. Indian journal of clinical biochemistry : IJCB, 38(1), 42–50.
37. Wahbeh F, Manyama M. The role of Vitamin B12 and genetic risk factors in the etiology of neural tube defects: A systematic review. Int J Dev Neurosci. 2021 Aug; 81(5):386-406.

## POLICY HISTORY:

Adopted for Blue Advantage, September 2010
Available for comment September 22-November 5, 2010
Medical Policy Group, October 2012
Medical Policy Group, August 2013
Effective August 29, 2013: Active Policy but no longer scheduled for regular literature reviews and updates.
Medical Policy Group, December 2015
Medical Policy Group, September 2019
Medical Policy Group, August 2021
Medical Policy Group, October 2021: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
Medical Policy Group, August 2022: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
Medical Policy Group, August 2023: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
Medical Policy Group, November 2023: Archived effective 11/1/2023.

*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*