Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/24**
(See policy history boxes for previous effective dates)

Title: Holotranscobalamin as a Marker of Vitamin B12 (Cobalamin) Status

Description/Background

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.

Background

Vitamin B12 (cobalamin) is an essential vitamin that is required for DNA synthesis affecting red blood cell formation and methionine synthesis affecting neurologic functioning. Cobalamin deficiency can result from nutritional deficiencies or malabsorption. Dietary insufficiency is most common among vegetarians and elderly people. Malabsorption of vitamin B12 may be associated with autoantibodies, as in pernicious anemia, or can occur after gastrectomy, or in other gastrointestinal tract 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 promptly disappear 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, typically less than 200 pg/mL, in conjunction with clinical evidence of disease. However, this laboratory test has highly variable sensitivity and specificity. Attention has turned to measuring metabolites of cobalamin. 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 is also 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.

The World Health Organization Committee on Biological Standardization (2016) endorsed a proposal to assign a holoTC value of 107 pmol/L to 03/178, corresponding to 0.107 pmol per ampoule, for use as the first international standard for vitamin B12, serum folate, and holoTC.[25]

Regulatory Status

HoloTC RIA (Axis-Shield plc, Dundee, UK) is an example of a radioimmunoassay for holo-TC that was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process in 2004. 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."

In February 2013, the FDA approved the Active-B12 (Axis-Shield) through the 510(k) process. The labeled indication for use is as follows: "The Axis-Shield Active-B12 (Holotranscobalamin) assay is an enzyme-immunoassay (EIA) for the quantitative determination of holotranscobalamin (HoloTC) in human serum. HoloTC (vitamin B12 bound to transcobalamin) is used as an aid in the diagnosis and treatment of vitamin B12 deficiency."

Specific names of devices or tests are mentioned to provide examples. They are not intended to be an endorsement or a comprehensive list of all approved items available.

Medical Policy Statement

While safe, the clinical utility of holotranscobalamin as a marker of vitamin B12 status has not been established. Therefore, it is considered experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

84999

Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Validation of the clinical use of any diagnostic test focuses on three main principles:
1) Analytic validity, the technical feasibility of the test;
2) Clinical validity, the diagnostic performance of the test, such as sensitivity, specificity, and positive and negative predictive value in different populations of patients and compared to the gold standard; and
3) Clinical utility, how the results of the diagnostic test will be used to improve management of the patient.

Analytic Validity
The serum measurements of holo-TC involve the use of standard laboratory immunoassay techniques. In the first step, holo-TC in the serum sample is separated by magnetic microspheres coated with monoclonal antibodies to human transcobalamin. The cobalamin bound to the holo-TC is then released and measured by a competitive binding radioimmunoassay or by fluorescence, depending on the device used. The technical feasibility of holo-TC have been established.

Clinical Validity
The diagnostic performance must be compared to the established gold standard for measuring cobalamin deficiency. This is particularly problematic since there is currently no established gold standard. As previously noted, serum levels of total cobalamin are considered poorly sensitive and specific, and holo-TC measurements are not independent of total cobalamin measures, leading to a potential bias in the estimate of the test's diagnostic power. There have been several reports proposing serum measures of methylmalonic acid (MMA) and homocysteine as an alternative gold standard[1-5]; however, their specificity has been questioned.[6,7]
According to the U.S. Food and Drug Administration (FDA) decision summary, the cut-off values for holo-TC were based on a normal population instead of a population of those with known cobalamin deficiency. For example, the low value of holo-TC, 37 pmol/L, was based on

a study of 303 normal Finnish individuals. This study has also been published by Loikas and colleagues in the peer-reviewed literature.[8] Participants included 226 normal elderly subjects and 80 normal non-elderly adult subjects. Patients were excluded from the trial if they had hyperhomocysteinemia, evidence of a possible cobalamin deficiency. In addition, patients in the lowest one-third of holo-TC results underwent additional testing with MMA; those with elevated MMA levels were also excluded. In the normal reference population, the holo-TC range was 25–254 pmol/L with a 95% central reference interval of 37–171 pmol/L. Therefore, the cut-off value for a low result was established at 37 pmol/L. This cut-off value was then applied to the results of 107 patients with presumed cobalamin deficiency, as evidenced by different combinations of an increased plasma homocysteine or MMA level, or a low total serum cobalamin level, defining patients with potential, possible, or probable cobalamin deficiency. A total of 48% of those with presumed deficiency had a holo-TC below 37 pmol/L. The frequencies of low holo-TC levels increased with increasing pretest probability of cobalamin deficiency. For example, among the 16 patients thought to have the highest pretest probability of cobalamin deficiency, based on elevated levels of homocysteine and MMA, 100% had low levels of holo-TC. This study used levels of homocysteine and MMA as the gold standard. Based on this standard, the sensitivity of the test was only 48% among those with cobalamin deficiency rated as either potential, possible, or probable. The authors conclude that further studies are needed to confirm the clinical utility and specificity of holo-TC in diagnosis of subclinical cobalamin deficiency. Also, these values for a homogeneous population of Finnish subjects with a diet high in fish might not be able to be extrapolated to the heterogeneous American population and diet. Furthermore, these cut-off points require confirmation in a larger population of patients whose cobalamin status is unknown.

In a 2021 systematic review, Wahbeh reported on the role of vitamin B12 and genetic risk factors in the etiology of neural tube defects (NTD).[9] The authors evaluated 40 eligible studies based on specific criterion and found that levels of holotranscobalamin were reported lower in mothers of NTD-affected infants. It was summarized that low maternal holotranscobalamin is associated with a strong risk of NTDs in the offspring. Several other maternal factors have also been linked with significant NTD risk in addition to vitamin B12 deficiency including BMI, maternal diet, air pollutants, and low maternal age. The majority of studies on NTDs have a focus on the role of folic acid, therefore a need exists for well-designed studies on the role of risk factors like vitamin B12 deficiency in the etiology of NTDs.

Dullemeijer et al (2013) reported on a systematic review and meta-analysis of studies on biomarker responses to B12 supplementation.[10] The authors found doubling the intake of B12 increased serum or plasma levels of B12 by 11% and decreased MMA levels by 7%. Only two small RCTs with 3 holo-TC estimates were identified which showed B12 supplementation significantly increased serum or plasma holo-TC levels. However, the small size of the RCTs precluded meta-analysis. The authors cautioned the heterogeneity of studies limited the interpretation of the results reported.

O'Leary et al (2012) reported on a systematic review of B12 status and its relationship to cognitive decline and dementia.[11] The authors evaluated 35 cohort studies and found serum B12 levels were not associated with cognitive decline or dementia. However, four studies found increased risks of cognitive decline or dementia were associated with MMA and/or holo-TC levels. The use of underpowered cohort studies of short duration limits interpretation of these results.

Hoey et al (2009) published a systematic review of the response of various biomarkers to treatment with vitamin B12.[12] Only one RCT (Eussen et al) utilizing holo-TC was identified for the review[13] the authors concluded that data were insufficient to determine the effectiveness of serum holo-TC as a biomarker for vitamin B12 status.

Randomized Controlled Trials

Naik et al (2018) reported on B12-related biomarkers (circulating holotranscobalamin, B12, folate and homocysteine) measured in 119 young, healthy Indian vegetarians.[14] None of the participants had clinical signs of B12 deficiency. Receiver operating characteristic curve analysis demonstrated similar area under the curve (AUC) at the B12 concentration of 100 and 150 pmol/l when holoTC (0.777 and 0.784) and total homocysteine (tHcy; 0.924 and 0.928) were used as variables. A cut-off value of 100 pmol/l resulted in the highest sensitivity (77.8%) and specificity (71.05%) for holoTC, with a predictive value of 19.6 pmol/l. This cutoff resulted in a sensitivity of 82.72% and specificity of 89.7% with a predictive value of 21.7 µmol/l for homocysteine. The researchers found that combining B12, holoTC and tHcy improved diagnostic accuracy at these cutoffs.

Hill et al (2013) reported on a double-blind, placebo-controlled, randomized study of 100 elderly patients with poor B12 status.[15] Patients were treated for 8 weeks with vitamin B12 supplements of 10 µg/d, 100 µg/d, or 500 µg/d. Compared to placebo, all B12 dosages had an effect on holo-TC levels ($p< 0.01$). However, even after receiving 500 µg/d B12 for 56 days, 12% of patients had below threshold (>200pmol/L) plasma B12 levels and 56% still had elevated plasma and urine MMA levels suggesting continued metabolic insufficiency despite supplementation.

In a double-blind trial to determine the effects of B12 supplementation on cognitive functioning in older adults, Eussen et al (2006) measured holo-TC at baseline, 12, and 24 weeks in 195 subjects randomized to 3 groups: cobalamin, cobalamin plus folate supplementation, or placebo. The primary outcome measure was cognitive improvement.[13] The results did not support a significant difference in cognitive functioning. The authors noted a significant time-treatment interaction after 12 weeks in both treatment arms of holo-TC for all biomarkers measured (vitamin B12, MMA, holo-TC, homocysteine, and red blood cell folate [$p<0.0002$]). Specifically, for holo-TC, in the vitamin B12 group, mean levels increased from 58 +/- 21 to 183 +/- 124 ($p<0.05$ for difference from baseline). In the folate and vitamin B12 supplementation group, holo-TC increased from 68 +/- 33 to 222 +/- 133 ($p<0.05$ for difference from baseline). Comparatively, the placebo group's levels did not significantly change, from 70 +/- 39 to 65 +/- 43 ($p<0.05$ for difference from treatment groups). Further changes did not occur between 12 and 24 weeks of supplementation.

Eussen et al published a smaller trial in 2008.[15] Once again, patients were randomly assigned to cobalamin, cobalamin plus folate, or placebo supplementation in subjects with known mild cobalamin deficiency. Along with serum cobalamin and MMA levels, holo-TC was utilized to assess deficiency status and did rise in response to therapy. Other recent studies have utilized holo-TC as one of a number of measures of cobalamin status.[17-21] However, these studies do not attempt to assess the independent predictive capacity of the test and therefore do not add to the evidence base for this policy.

Valente and colleagues reported on the diagnostic accuracy of holotranscobalamin, MMA, serum cobalamin, and other indicators of tissue vitamin B12 status in an elderly population.[22] Elderly subjects (n=700), age range 63-97 years, were recruited from an ongoing observational

cohort study to collect data on 2,000 individuals older than 60 years with mild to moderate cognitive impairment. A separate reference population of 120 healthy volunteers, age 18-62 years, was used to determine a reference interval for the red cell cobalamin assay. The cut-offs for deficiency were defined as 20 pmol/L for holo-TC, 123 pmol/L for serum cobalamin, and less than 33 pmol/L for red cell cobalamin. The red cell lower limit of 33 pmol/L packed red cells was used to dichotomize the concentrations into deficient and nondeficient vitamin B12 status for the construction of receiver operating characteristic (ROC) plots. The areas under the curve (AUC) showed that serum holo-TC was the best predictor with AUC 0.90 (95% confidence interval [CI]: 0.86-0.93), and this was significantly better ($p \leq 0.0002$) than the next best predictors of serum cobalamin 0.80 (95% CI: 0.75-0.85), and MMA 0.78 (95% CI: 0.72-0.83). For these 3 analytes, the authors constructed a 3-zone partition of positive and negative zones and a deliberate indeterminate zone between. The boundaries were values of each test that resulted in a post-test probability of deficiency of 60% and a post-test probability of no deficiency of 98%. The proportion of indeterminate observations for holo-TC, cobalamin, and MMA was 14%, 45%, and 50%, respectively.

Clinical Utility

Advocates of holo-TC testing suggest that this laboratory test can identify early subclinical stages of cobalamin deficiency or other conditions, permitting prompt initiation of treatment, specifically cobalamin dietary supplementation. Further, this reasoning suggests that early diagnosis will lead to an improvement in health outcome in patients. This hypothesis was not directly tested in any of the identified published literature. In the absence of a gold standard, the clinical significance of subclinical cobalamin deficiency must be further studied by understanding the natural history of this condition. Does subclinical deficiency inevitably progress to clinical deficiency? Does cobalamin supplementation normalize the values? How variable are cobalamin levels within patients? These clinical issues have not been well-addressed in the literature. Finally, for all patients at risk, ie, vegetarians, elderly people, and postgastrectomy patients, the recommended treatment of subclinical disease is dietary supplementation of cobalamin. This recommendation is appropriate, regardless of the level of measured cobalamin.

Heil et al (2012) aimed to validate the clinical usefulness of holo-TC as an initial screening assay for metabolic vitamin B12 deficiency in a mixed patient population.[23] Three hundred and sixty blood samples were collected by five Dutch hospitals, and vitamin B12 and holo-TC in serum were measured. Methylmalonic acid (MMA) in serum was measured by tandem mass spectrometry. Receiver-operating-curve analysis demonstrated a greater area under the curve for holo-TC than for vitamin B12 in detecting vitamin B12 deficiency characterized by three predefined cut-off levels of MMA. A cut-off value of 32 pmol/L of holo-TC resulted in the highest sensitivity (83%) with acceptable specificity (60%) in detecting MMA concentrations above 0.45 µmol/L. The combination of vitamin B12 and holo-TC did not improve diagnostic accuracy at this cut-off level. The authors concluded that holo-TC has a better diagnostic accuracy than vitamin B12 and can replace the existing vitamin B12 assay as a primary screening test in patients suspected of vitamin B12 deficiency. Further randomized controlled studies are necessary to validate the 32 pmol/L cut-off value established in this study across differing populations. In addition, questions concerning the value of holoTC testing to improve clinical management need to be answered.

Afyoncu et al (2016) reported on a study assessing the association between vitamin B12 levels and Helicobacter Pylori infection and the clinical utility of holotranscobalamin measurement in children.[24] Thirty patients between the ages of six and 15 years, diagnosed with H. pylori

infection by Carbon-14 urea breath test, and 26 controls were participated the study. Complete blood count, serum vitamin B12 and folate, plasma total homocysteine, and holoTC levels were obtained. Results showed mean plasma holoTC concentrations were significantly lower in children with H. pylori infection before treatment (median 23.7 pmol/L (12.9-37.1 pmol/L)) versus after treatment (median 38.2 pmol/L (21.2-61.4 pmol/L)) and controls (median 36.1 pmol/L (12.6-58.7 pmol/L)). Based upon these findings, the authors suggest that H. pylori infection has a reversible negative effect on vitamin B12 status as evidenced by decreased level of plasma holoTC that normalizes upon treatment of the infection, while no change is observed in total plasma vitamin B12.

Summary

There are inadequate data to establish holotranscobalamin testing as an alternative to either total serum cobalamin, or levels of methylmalonic acid or homocysteine in the diagnosis of vitamin B12 deficiency. While technically feasible, and likely to have diagnostic performance that approaches that of currently utilized tests, no evidence of clinical utility has been demonstrated, neither as a screening tool in the general or at-risk population, nor as a diagnostic tool in symptomatic individuals. Sufficient evidence of the clinical utility of the test is currently lacking.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

The American Family Physician guidelines (2017) Vitamin B12 Deficiency: Recognition and Management key recommendations for practice state:
“Although not clinically validated or available for widespread use, measurement of holotranscobalamin, the metabolically active form of vitamin B12, is an emerging method of detecting deficiency.”[25]

The British Society for Haematology published guidelines (1994, revised 2014) for the diagnosis and treatment of cobalamin and folate disorders. The guideline states “Holotranscobalamin (HoloTC) is suggested as a suitable assay for assessment of cobalamin status in a routine diagnostic laboratory in the future (Grade 1B). Further studies are needed to evaluate the clinical utility of HoloTC in assessing cobalamin deficiency in a routine high output laboratory testing.”[26]

National Institute for Health and Care Excellence (NICE) published a document in September 2015 evaluating the evidence for active B12 assay for diagnosing vitamin B12 deficiency.[27] The document noted that “No diagnostic intervention studies were found that might give information on the effect of the Active-B12 assay on clinical decision-making or outcomes.”

Ongoing Clinical Trials

Some ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Clinical Trials

NCT number	Trial Name	Planned Enrollment	Completion Date
Completed			
NCT04243707	Cobalamin deficiency – Diagnosis and Therapy	3000	Nov 30, 2019 (No results posted)

Government Regulations
National:
There is no national coverage determination specific to this procedure.

Local:
There is no local coverage determination specific to this procedure.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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https://www.nice.org.uk/guidance/mib40/resources/active-b12-assay-for-diagnosing-vitamin-b12-deficiency-63499159342789 assessed 9/28/23

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/28/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/07	8/17/07	8/29/07	Joint policy established
1/1/09	10/13/08	12/30/08	Routine maintenance
11/1/11	8/16/11	8/16/11	Routine maintenance, Title changed from Holo-transcobalamin to Holotranscobalamin as a Marker of Vitamin B12 (Cobalamin) Status
3/1/13	12/11/12	12/31/12	Routine maintenance
5/1/14	2/24/14	3/3/14	Routine maintenance
3/1/16	12/10/15	12/10/15	Routine maintenance Deleted code 0103T; 12/31/15 Added code 84999; 1/1/16
3/1/17	12/13/16	12/13/16	Routine maintenance
3/1/18	12/12/17	12/12/17	Routine maintenance
3/1/19	12/11/18		Routine maintenance
3/1/20	12/17/19		Routine maintenance
3/1/21	12/15/20		Routine maintenance Ref 13, 24 added
3/1/22	12/14/21		Routine maintenance
3/1/23	12/20/22		Routine maintenance (jf) Vendor Managed: Avalon Added Ref: 9
3/1/24	12/19/23		Routine maintenance (jf) Vendor Managed: Avalon

Next Review Date: 4th Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: HOLOTRANSCOBALAMIN AS A MARKER OF VITAMIN B12 (COBALAMIN) STATUS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See Government Regulations Section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.