Corporate Medical Policy

Serum Holo-Transcobalamin as a Marker of Vitamin B12 Status

File Name:	serum_holo_transcobalamin_as_a_marker_of_vitamin_b12_status
Origination:	10/2009
Last CAP Review:	2/2012
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Description of Procedure or Service

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 (i.e., 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 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 been found to be poorly sensitive and specific. Therefore, attention has turned to measuring metabolites of cobalamin as a surrogate marker. For example, in humans only 2 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 has also been interest in the direct measurement of the subset of biologically active cobalamin. Cobalamin in serum is bound to 2 proteins, transcobalamin and haptocorrin. Transcobalamin-cobalamin complex (called holo-transcobalamin, 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.

The Axis-Shield HoloTC RIA is an example of a radioimmunoassay for holo-TC that was cleared for marketing by the U.S. Food and Drug Administration (FDA) in 2004 with the following labeled indication for use: "The Axis-Shield HoloTC RIA is an in vitro diagnostic assay for 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."

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Serum Holo-Transcobalamin as a Marker of Vitamin B12 Status

Policy

Measurement of serum holo-transcobalamin as a marker of Vitamin B12 status is considered investigational for all applications. BCBS does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When measurement of serum holo-transcobalamin as a marker of Vitamin B12 status is covered

Not applicable.

When measurement of serum holo-transcobalamin as a marker of Vitamin B12 status is not covered

Measurement of holo-transcobalamin is considered **investigational** in the diagnosis and management of Vitamin B12 deficiency.

Policy Guidelines

There are inadequate data to establish holo-TC testing as an alternative to either total serum cobalamin or levels of MMA or homocysteine. 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. Evidence of the clinical utility of the test is currently lacking.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0103T

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Sumner AE, Chin MM, Abrahm JL et al. Elevated methylmalonic acid and total homocysteine levels show high prevalence of vitamin B12 deficiency after gastric surgery. Ann Intern Med 1996; 124(5):469-76.

Elin RJ, Winter WE. Methylmalonic acid: a test whose time has come? Arch Pathol Lab Med 2001;

125(6):824-7.

Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician 2003; 67(5):979-86.

Loikas S, Lopponen M, Suominen P et al. RIA for serum holo-transcobalamin: method evaluation in the clinical laboratory and reference interval. Clin Chem 2003; 49(3):455-62.

Hvas AM, Nexo E. Holotranscobalamin as a predictor of vitamin B12 status. Clin Chem Lab Med 2003; 41(11):1489-92.

Herrmann W, Obeid R, Schorr H et al. Functional vitamin B12 deficiency and determination of holotranscobalamin in populations at risk. Clin Chem Lab Med 2003; 41(11):1478-88.

BCBSA Medical Policy Reference Manual [Electronic Version}. 2.04.39, 3/13/08

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.39, 8/12/10

Specialty Matched Consultant Advisory Panel 3/31/2011.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.39, 8/11/11

Specialty Matched Consultant Advisory Panel-2/2012

Policy Implementation/Update Information

11/9/09	New policy issued. Measurement of holo-transcobalamin is considered investigational in the diagnosis and management of Vitamin B12 deficiency. (adn)
6/22/10	Policy Number(s) removed (amw)
4/12/11	Specialty Matched Consultant Advisory Panel review meeting 3/31/2011. No changes to policy statement. (lpr)
12/6/11	References updated. No change to criteria. (lpr)
3/20/12	Specialty Matched Consultant Advisory Panel review meeting 2/29/2012. No change to policy statement. (lpr)