

Subject: Laboratory Evaluation of Vitamin B12

Guideline #: CG-LAB-19

Status: Reviewed

Publish Date: 01/03/2024

Last Review Date: 11/09/2023

Description

This document addresses the use of vitamin B12 blood test, methylmalonic acid blood test, and holotranscobalamin blood test for individuals with suspected or known vitamin B12 deficiency.

Clinical Indications

Medically Necessary:

Vitamin B12 blood testing is considered **medically necessary** for **any** of the following indications:

1. Alcohol dependence; **or**
2. Anemia; **or**
3. Autoimmune condition such as intrinsic factor deficiency, thyroid disease, or pernicious anemia; **or**
4. Blood dyscrasia (for example cytopenia, leukopenia, or thrombocytopenia); **or**
5. Diabetes mellitus with neurologic symptoms; **or**
6. Disorders of sulphur amino acid metabolism; **or**
7. Disruption of gastrointestinal anatomy or function (for example achlorhydria, gastrectomy, gastric bypass, gastric cancer, ileal resection, inflammatory bowel disease); **or**
8. Failure to thrive (pediatric); **or**
9. Glossitis; **or**
10. Homocystinuria; **or**
11. Inadequate dietary intake of vitamin B12 such as strict vegan diet without vitamin B12 supplementation; **or**
12. Infection known to be associated with vitamin B12 deficiency such as bacterial overgrowth syndrome, fish tapeworm infection, Helicobacter pylori infection, or human immunodeficiency virus (HIV); **or**
13. Malabsorption; **or**
14. Malignancy affecting absorption of nutrients or affecting blood or hematopoiesis; **or**
15. Malnutrition; **or**
16. Methylene tetrahydrofolate Reductase (MTHFR) deficiency; **or**
17. Neurologic or motor symptom abnormality; **or**
18. Pancreatic insufficiency; **or**
19. Unexplained mental status or cognitive changes; **or**
20. Chronic use of H₂ blocking agent and proton pump inhibitor (PPI) minimum of 1 year or metformin minimum of 4 months

Methylmalonic acid (MMA) testing is considered **medically necessary** for **ANY** of the following indications:

1. Vitamin B12 levels are low or borderline-low; **or**
2. Newborn screening; **or**
3. Use of metformin for Type 2 diabetes mellitus with neurologic symptoms.

Not Medically Necessary:

Vitamin B₁₂ and MMA testing is considered **not medically necessary** when the criteria above are not met and for all other indications.

Holotranscobalamin testing as a marker for vitamin B12 deficiency is considered **not medically necessary** for all indications.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Vitamin B12 testing

When services are Medically Necessary:

CPT

82607	Cyanocobalamin (Vitamin B-12);
82608	Cyanocobalamin (Vitamin B-12); unsaturated binding capacity

ICD-10-Diagnosis

B20	Human immunodeficiency virus [HIV] disease
B96.81	Helicobacter pylori [H. pylori] as the cause of diseases classified elsewhere
D50.0-D53.9	Nutritional anemias
D55.0-D59.9	Hemolytic anemias
D60.0-D64.9	Aplastic and other anemias and other bone marrow failure syndromes
E00.0-E07.9	Disorders of thyroid gland
E08.40-E08.49	Diabetes mellitus due to underlying condition with neurological complications
E09.40-E09.49	Drug or chemical induced diabetes mellitus with neurological complications
E10.40-E10.49	Type 1 diabetes mellitus with neurological complications

E11.40-E11.49	Type 2 diabetes mellitus with neurological complications
E13.40-E13.49	Other specified diabetes mellitus with neurological complications
E40-E46	Malnutrition
E72.10-E72.19	Disorders of sulfur-bearing amino-acid metabolism
F10.20-F10.29	Alcohol dependence
K14.0-K14.4	Glossitis
K31.83	Achlorhydria
K50.00-K50.919	Crohn's disease
K51.00-K51.919	Ulcerative colitis
K85.00-K86.89	Acute pancreatitis, other diseases of pancreas
K90.0-K90.9	Intestinal malabsorption
K91.0-K91.2	Vomiting following gastrointestinal surgery, postgastric surgery syndromes, postsurgical malabsorption, not elsewhere classified
O90.81	Anemia of the puerperium
P05.00-P05.9	Disorders of newborn related to slow fetal growth and fetal malnutrition
P92.6	Failure to thrive in newborn
R62.51	Failure to thrive (child)
Z98.0	Intestinal bypass and anastomosis status
Z98.84	Bariatric surgery status

When services may be Medically Necessary when criteria are met:

For the procedure codes listed above for all other diagnoses.

When services are Not Medically Necessary:

For the procedure codes listed above when criteria are not met, and for the following:

CPT	
84999	Unlisted chemistry procedure [when specified as holotranscobalamin (holoTC)]

ICD-10-Diagnosis

All diagnoses

MMA testing

When services may be Medically Necessary when criteria are met:

CPT	
83921	For the following code when specified as methylmalonic acid test Organic acid, single, quantitative [when specified as methylmalonic acid test]

ICD-10-Diagnosis

E11.40-E11.49	Type 2 diabetes mellitus with neurological complications
E53.8	Deficiency of other specified B group vitamins
Z00.110	Health examination for newborn under 8 days old
Z00.111	Health examination for newborn 8 to 28 days old
Z05.42	Observation and evaluation of newborn for suspected metabolic condition ruled out
Z79.84	Long term (current) use of oral hypoglycemic drugs [specified as metformin]

When services are Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met, and for all other diagnoses not listed.

Discussion/General Information

Vitamin B12 and Methylmalonic acid (MMA) Blood Testing

Vitamin B12, also known as cyanocobalamin, is a water-soluble vitamin occurring naturally in food sources derived from animal products. Vitamin B12 is also available as a mineral/multivitamin supplement in various doses and may be prescribed by a medical professional. Vitamin B12 is necessary for the development, myelination, and proper function of the central nervous system, hematopoietic cell formation, DNA synthesis, and also serves as cofactor for 2 enzymes. Vitamin B12 testing is not recommended for adults with average risk of deficiency. Risk factors for vitamin B12 deficiency include dietary deficiency, decreased absorption, autoimmune conditions, genetic conditions, or prolonged use of certain medications such as metformin or proton pump inhibitors. Deficiency symptoms in adults may lead to nerve damage, neurologic changes, depression, difficulty maintaining balance, and anemia. Vitamin B12 deficiency in the pediatric population include failure to thrive, developmental delays, movement disorders, and megaloblastic anemia.

MMA testing is useful as a confirmation test in asymptomatic high-risk individuals with low-normal levels of Vitamin B12 and as part of newborn screening to detect inborn errors of metabolism. MMA reacts with Vitamin B12 to produce coenzyme A (CoA) which ensures proper cellular function and in the setting of vitamin B12 deficiency MMA levels will be elevated. Numerous articles and practice guidelines have been published addressing the various risk factors indicated for B12 and MMA testing for vitamin B12 deficiency (Lee, 2019; NCCN, 2021; Snow, 1999; Quigley, 2020; Vashi, 2016)

In 2017, Langan published key recommendations for the workup and management of vitamin B12 deficiency. The recommendations for practice include the following:

- Patients with risk factors for vitamin B12 deficiency should be screened with a complete blood count and serum vitamin B12 level. (Evidence rating: C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series.)
- A serum methylmalonic acid level may be used to confirm vitamin B12 deficiency when it is suspected but the serum vitamin B12 level is normal or low-normal. (Evidence rating: C)

Holotranscobalamin

Holotranscobalamin testing assesses the level of transcobalamin circulating in the blood that is directly available to cells. Transcobalamin is the only protein that transports vitamin B12 into all cells of the body. Holotranscobalamin does not test the circulating, also known as free, vitamin B12. This limits the utility of the holotranscobalamin test as a diagnostic workup for malabsorption deficiency.

Published literature includes case reports, review articles, and comparison studies. There is a lack of acceptance for use of holotranscobalamin testing because there are no published guidelines indicating that it should be used in addition to total vitamin B12 levels, or in place of total B12 testing.

In 2021, Rothen published the results of a secondary data analysis to determine the best laboratory testing strategy for vitamin B12 deficiency. The study evaluated testing including vitamin B12 alone, holotranscobalamin alone, both vitamin B12 and holotranscobalamin, and reflex testing of holotranscobalamin when vitamin B12 levels were in the defined grey zone of 138-299 pmol/L. At least one sample was obtained for 7925 individuals and simultaneous testing of vitamin B12 and holotranscobalamin was completed in 3044 samples. Low cobalamin was detected in 591 samples, with vitamin B12 low in 305 samples and holotranscobalamin low in 436 samples. Concordant low values were detected in 150 samples and contradicting results occurred in 441 samples. A total of 2403 sample results were in the grey zone and the reflex holotranscobalamin found a total of 583 samples with cobalamin deficiency. With a restrictive grey zone of 138-219 pmol/L, a total of 511 samples were identified with cobalamin deficiency resulting in 86% of the 591 samples having both measurements simultaneously. This study shows that vitamin B12 and holotranscobalamin show poor concordance. The authors conclude, "Laboratory results alone are insufficient to determine unequivocally which patients need substitution. In this field of uncertainty, laboratory diagnostics must be complemented by patient history and clinical symptoms."

References

Peer Reviewed Publications:

1. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA*. 2013; 310(22):2435-2442.
2. Langan RC, Goodbred AJ. Vitamin B12 deficiency: recognition and management. *American Family Physician* 2017; 96(6):384-389.
3. Lee SM, Oh J, Chun MR, Lee SY. Methylmalonic acid and homocysteine as indicators of vitamin B12 deficiency in patients with gastric cancer after gastrectomy. *Nutrients*. 2019; 11(2):450.
4. Moridani M, Ben-Poorat S. Laboratory investigation of vitamin B12 deficiency. *Laboratory Medicine*. 2006; 37(3):166-174.
5. Rothen JP, Walter PN, Tsakiris DA, et al. Identification of patients with cobalamin deficiency crucially depends on the diagnostic strategy. *Clin Lab*. 2021; 67(5). Available at: <https://pubmed.ncbi.nlm.nih.gov/33978377/>. Accessed on September 6, 2023.
6. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. *Arch Intern Med*. 1999; 159(12):1289-1298.
7. Vashi P, Edwin P, Popiel B, et al. Methylmalonic acid and homocysteine as indicators of vitamin B-12 deficiency in cancer. *PLoS One*. 2016; 11(1):e0147843.

Government Agency, Medical Society, and Other Authoritative Publications:

1. National Institutes of Health. Vitamin B12 fact sheet for healthcare professionals. Updated: December 22, 2022. Available at: <https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/#h3>. Accessed on September 6, 2023.
2. NCCN Clinical Practice Guidelines in Oncology™ (NCCN). © 2011 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website at: <http://www.nccn.org/index.asp>. Accessed on September 6, 2023.
 - Gastric Cancer (V2.2023). Revised August 29, 2023.
 - Myelodysplastic Syndromes (V1.2023). Revised September 12, 2022.
3. Quigley EMM, Murray JA, Pimentel M. AGA clinical practice update on small intestinal bacterial overgrowth: expert review. *Gastroenterology*. 2020; 159(4):1526-1532.

Index

Vitamin B12
Methylmalonic acid
Holotranscobalamin

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References section.
Reviewed	11/10/2022	MPTAC review. Updated References section.
New	11/11/2021	MPTAC review. Initial document development.

Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

