Vitamin B12 and Methylmalonic Acid Testing

Policy Number: AHS – G2014 – Vitamin B12 and Methylmalonic Acid Testing	Effective Date: 11/01/2026

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I. Policy Description

Vitamin B12, also known as cobalamin, is a water-soluble vitamin required for proper red blood cell formation, key metabolic processes, neurological function, and DNA regulation and synthesis. Hematologic and neuropsychiatric disorders caused by a deficiency in B12 can often be reversed by early diagnosis and prompt treatment.[1]

Methylmalonic acid (MMA) is produced from excess methylmalonyl-CoA that accumulates when Vitamin B12 is unavailable and is considered an indicator of functional B12 deficiency.[2]

Holotranscobalamin (holoTC) is the metabolically active fraction of B12 and is an emerging marker of impaired vitamin B12 status.[3]

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1) Total vitamin B12 (serum cobalamin) testing **MEETS COVERAGE CRITERIA** once every three months for **any** of the following situations:
   a) For individuals with the following signs and symptoms of vitamin B12 deficiency:
      i) Cutaneous
         (a) Hyperpigmentation
         (b) Jaundice
         (c) Vitiligo
      ii) Gastrointestinal
         (a) Glossitis
      iii) Hematologic
         (a) Anemia (macrocytic, megaloblastic)
         (b) Leukopenia
         (c) Pancytopenia
         (d) Thrombocytopenia

(e) Thrombocytosis

iv) Neuropsychiatric

(a) Areflexia

(b) Cognitive impairment (including dementia-like symptoms and acute psychosis)

(c) Gait abnormalities

(d) Irritability

(e) Loss of proprioception and vibratory sense

(f) Olfactory impairment

(g) Peripheral neuropathy

b) For individuals undergoing treatment for vitamin B12 deficiency.

c) For individuals with one or more of the following risk factors for vitamin B12 deficiency:

i) For individuals with decreased ileal absorption due to:

(a) Crohn's disease.

(b) Ileal resection.

(c) Tapeworm infection.

(d) Having undergone, or for those who have been scheduled for, bariatric procedures such as Roux-en-Y gastric bypass, sleeve gastrectomy, or biliopancreatic diversion/duodenal switch.

ii) For individuals with decreased intrinsic factor due to:

(a) Atrophic gastritis.

(b) Pernicious anemia.

(c) Postgastrectomy syndrome.

iii) For individuals with transcobalamin II deficiency.

iv) For individuals with inadequate B12 intake:

(a) Due to alcohol abuse.

(b) In individuals older than 75 years or elderly individuals being evaluated for dementia.

(c) In vegans or strict vegetarians (including exclusively breastfed infants of vegetarian/vegan mothers).

(d) Due to an eating disorder.

v) For individuals with prolonged medication use:

(a) Histamine H2 blocker use for more than 12 months.

(b) Metformin use for more than four months.

(c) Proton pump inhibitor use for more than 12 months.

2) In asymptomatic high-risk individuals with low-normal levels of vitamin B12 or when vitamin B12 deficiency is suspected but the serum vitamin B12 level is normal or low-normal, methylmalonic acid testing to confirm vitamin B12 deficiency **MEETS COVERAGE CRITERIA**.

3) For the evaluation of inborn errors of metabolism, methylmalonic acid testing **MEETS COVERAGE CRITERIA**.

4) In healthy, asymptomatic individuals, screening for vitamin B12 deficiency **DOES NOT MEET COVERAGE CRITERIA.**

5) For the confirmation of vitamin B12 deficiency, homocysteine testing **DOES NOT MEET COVERAGE CRITERIA**.

6) For the screening, testing, or confirmation of vitamin B12 deficiency, holotranscobalamin testing **DOES NOT MEET COVERAGE CRITERIA**.

7) For all other situations not described above, total vitamin B12 (serum cobalamin) testing **DOES NOT MEET COVERAGE CRITERIA.**

III. Table of Terminology

Term	Definition
AACE	American Association of Clinical Endocrinology
AAFP	American Academy of Family Physicians
ACE	American College of Endocrinology
ACG	American College of Gastroenterology
ADA	American Diabetes Association
APA	American Psychiatric Association
ASMBS	American Society for Metabolic and Bariatric Surgery
ATT	Anti-tuberculosis treatment
BCMA	British Columbia Medical Association
BMJ	British Medical Journal
BOMSS	British Obesity and Metabolic Surgery Society
BPD/DS	Biliopancreatic diversion/duodenal switch
CBL	Cobalamin
CD	Celiac disease
CDC	Centers for Disease Control and Prevention
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CoA	Coenzyme A
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
E-HOD	European network and registry for homocystinurias and methylation defects
EL	Evidence level
FDA	Food and Drug Administration
GPP	Good practice point

H2	Histamine receptor H2
HAART	Highly active antiretroviral therapy
HCY	Homocysteine
HIV	Human immunodeficiency virus
holoTC	Holotranscobalamin
HQO	Health Quality Ontario
HR	Hazard ratio
LDT	Laboratory-developed test
LSG	Laparoscopic sleeve gastrectomy
MBS	Metabolic and bariatric surgery
MMA	Methylmalonic Acid
MTHFR	Methylenetetrahydrofolate reductase
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
OMA	Obesity Medicine Association
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
TB	Tuberculosis
tHCy	Total homocysteine
TIBC	Total iron-binding capacity
TOS	The Obesity Society
USPSTF	United States Preventative Services Task Force
WLS	Weight loss surgical

IV. Scientific Background

Vitamin B12 cannot be synthesized by human cells;[4] rather, it is obtained from animal-derived dietary sources, such as meat, eggs, and dairy products,[5] as well as fortified cereals and supplements.[6] Vitamin B12 deficiency is classically caused by pernicious anemia; however, with modern fortification of western diets, this condition now accounts for only a minority of cases and currently occurs most often due to malabsorption.[4]

The prevalence of vitamin B12 deficiency in the United States and United Kingdom is approximately 6% in persons younger than 60 years, reaching 20% in those older than 60 years. On the contrary, the prevalence is approximately 40% in Latin America, 70% in Kenyan school children, 80% in East Indian preschool-aged children, and 70% in East Indian adults.[5] Risk factors for deficiency include: decreased ileal absorption (Crohn disease, ileal resection, tapeworm infection), decreased intrinsic factor (atrophic gastritis, pernicious anemia, post-gastrectomy syndrome), genetic defects (transcobalamin II deficiency), inadequate intake (alcohol abuse, patients older than 75 years, vegans, or strict vegetarians), prolonged medication use (histamine H2 blocker use for more than 12 months, metformin use for more than four months, proton pump inhibitor use for more than 12 months).[3]

Vitamin B12 plays an essential role in nucleic acid synthesis. Deficiency can result in cell cycle arrest in the S phase or cause apoptosis[7] and ultimately bone marrow failure and demyelinating nervous system disease.[8] Vitamin B12 is also critical in the remethylation of homocysteine (Hcy), and deficiency in

Vitamin B12 can lead to hyperhomocysteinemia, a condition that has been associated with various cancers, such as breast and ovarian cancers, as well as Parkinson disease.[9,10]

Clinical manifestations of vitamin B12 deficiency vary in their presence and severity from mild fatigue to severe neurologic impairment.[3] Mild deficiency can present as fatigue and anemia with an absence of neurological features. Moderate deficiency may include obvious macrocytic anemia with some mild or subtle neurological features. Severe deficiency shows evidence of bone marrow suppression, clear evidence of neurological features, and risk of cardiomyopathy. While recent literature suggests a relationship between vitamin B12 and depression,[11] there is still insufficient evidence or societal support for assessing vitamin B12 levels in individuals with common psychiatric disorders when there is an absence of major risk factors for or cardinal symptoms of vitamin B12 deficiency.[12]

Vitamin B12 deficiency can cause glossitis and other gastrointestinal symptoms that vary with underlying diseases, such as inflammatory bowel disease or celiac disease.[4] Early detection and correction of vitamin B12 deficiency with supplementation prevents progression to macrocytic anemia, elevated homocysteine (Hcy), potentially irreversible peripheral neuropathy, memory loss, and other cognitive deficits.[2]

Analytical Validity

Both the clinical recognition of vitamin B12 deficiency and confirmation of the diagnosis by means of testing can be difficult. Several laboratory measures reflecting physiological, static, and functional B12 status have been developed;[5] however, there is no universally agreed upon gold standard assay for determining cobalamin levels in humans. The current convention is to estimate the abundance of vitamin B12 using total serum vitamin B12, despite the low sensitivity of this test.[2] Two reportedly highly sensitive vitamin B12 deficiency markers are elevated levels of serum homocysteine and methylmalonic acid, but testing is expensive, and many other conditions may cause an elevation in these markers, including familial hyperhomocysteinemia, folate deficiency, levodopa therapy, and renal insufficiency.[13] Serum methylmalonic acid levels tend to be just as sensitive but more specific than serum homocysteine levels in regards to vitamin B12 deficiency testing, highlighting the former as the preferred testing method by many.[13]

An in-depth meta-analysis by Willis, et al. (2011) of serum cobalamin testing included data from 54 different studies. The variability for sensitivity and specificity across the different studies ranged from 13% to 75% for sensitivity and 45% to 100% for specificity, depending on the reference standard used. Researchers conclude that "from the available evidence, diagnosis of conditions amenable to cbl [vitamin B12] supplementation on the basis of cbl [vitamin B12] level alone cannot be considered a reliable approach to investigating suspected vitamin deficiency."[14] The test measures total serum cobalamin including both serum holohaptocorrin and serum holotranscobalamin, which may mask true deficiency or falsely imply a deficient state.[5]

Vitamin B12 deficiency is present in both infant and pregnant individuals, and monitoring vitamin B12 levels is important in determining maternal and fetal health and growth. Low vitamin B12 levels during pregnancy are associated with a greater risk of preterm birth.[15] It seems that current pregnancy-specific cutoffs for vitamin B12 biomarkers are inadequate in the medical field.[16] Recently, a new study has identified a novel cutoff value in the vitamin B12 serum of newborns; the B12-related metabolite known as homocysteine (Hcy) is now recommended to have a cutoff value at "4.77 µmol/L (68.4% sensitivity, 58.3% specificity, $p = .012$) for the detection of vit-B12 deficiency."[17] Other pregnancy specific B12 biomarkers have been published. According to another study, "The central 95% reference interval limits

indicated that serum total B-12 <89.9 and <84.0 pmol/L, holoTC <29.5 and <26.0 pmol/L and MMA >371 and >374 nmol/L, in the first and second trimesters, respectively, may indicate B-12 deficiency in pregnant [individuals]. The lower limits of total B-12 and holoTC and the upper limits of MMA significantly differed by ethnicity in both trimesters. According to the change point analysis, total B-12 <186 and <180 pmol/L and holoTC <62.2 and <67.5 pmol/L in the first and second trimesters, respectively, suggested an increased probability of impaired intracellular B-12 status, with no difference between ethnicities."[16]

Elevated levels of downstream metabolites, MMA and Hcy, are commonly used as adjuvant diagnostics to confirm a suspected diagnosis of cobalamin deficiency.[18] The sensitivity of elevated serum MMA measurements in detecting patients with overt cobalamin deficiency is reported to be >95%; however, the specificity of this test has not been determined.[5] In a study by Rozmarič, et al. (2020) the cutoff for MMA as an indicator of B12 deficiency was 0.423 µM with a specificity of 0.90 and sensitivity of 0.91 in newborns; "applying a screening algorithm including only tHCy [total homocysteine] as a second-tier test that may be feasible for many newborn screening labs, newborns with low VitB12, low HoloTC, or elevated MMA can be identified with a positive predictive value between 59% and 87%."

Serum holoTC may be a better indicator of B12-deficiency than serum cobalamin because it represents the biologically active fraction of cobalamin in humans and may be depleted first in subclinical cobalamin deficiency. HoloTC measurements appear to have slighter better sensitivity; however, the specificity of this assay remains to be determined.[20] It also is not yet clinically validated or available for widespread use.[3]

Mak, et al. (2023) completed developed a targeted metabolite panel aiming to improve second-tier newborn screening for four inherited metabolic disorders: glutaric acidemia type I, methylmalonic acidemia, ornithine transcarbamylase deficiency, and very long-chain acyl-CoA dehydrogenase deficiency. The panel was assembled from "known disease markers and new features discovered by untargeted metabolomics" and is used to test dried blood samples. The authors completed a validation study on 883 infants. As a second-tier analysis method, the test had 100% screening sensitivity and an 84.5% reduction rate of MMA false positives. The authors conclude that "these findings establish the effectiveness of this second-tier test to improve screening for these four conditions."[21]

Criteria	Sensitivity	Specificity	Pitfalls
Serum total cobalamin (<200 pg/mL)	95–97%	Uncertain, possibly <80%	*Elevated levels seen with*:
			Assay technical failure
			Occult malignancy
			Alcoholic liver disease
			Renal disease
			Decreased levels also seen with:
			Haptocorrin deficiency
			Folate deficiency
			Plasma cell myeloma
			HIV
			Pregnancy
Elevated serum methylmalonic acid	>95%	Uncertain	*Elevated levels seen with*:
			Renal insufficiency

Criteria	Sensitivity	Specificity	Pitfalls
			Hypovolemia
			Congenital metabolic defects
			Amyotrophic lateral sclerosis
Elevated serum homocysteine	>95%	Uncertain, less specific than methylmalonic acid	*Elevated levels seen with*:
			Folate or pyridoxine deficiency
			Renal insufficiency
			Hypovolemia
			Hypothyroidism
			Psoriasis
			Congenital metabolic defects
			Neurodegenerative disease
			Malignancy
			Medications
Decreased serum holotranscobalamin	Similar to total cobalamin	Uncertain	*Levels may be affected by*:
			Liver disease
			Macrophage activation
			Autoantibodies

Clinical Utility and Validity

Health Quality Ontario (HQO) performed an extensive meta-analysis of the clinical utility of B12 testing in patients with suspected dementia or cognitive decline because more than 2.9 million serum B12 tests were performed in Ontario alone in 2010.[22] HQO included data from eighteen different studies to address three questions:

1. "Is there an association between vitamin B12 deficiency and the onset of dementia or cognitive decline?
2. Does treatment with vitamin B12 supplementation improve cognitive function in patients with dementia or cognitive decline and vitamin B12 deficiency?
3. What is the effectiveness of oral versus parenteral vitamin B12 supplementation in those with confirmed vitamin B12 deficiency?"

They concluded that "This evidence-based analysis assessed the usefulness of serum vitamin B12 testing as it relates to brain function. This review found very low-quality evidence that suggests a connection between high plasma homocysteine levels (a by-product of B vitamin metabolism in the body) and the onset of dementia. Moderate quality of evidence indicates treatment with vitamin B12 does not improve brain function. Moderate quality of evidence also indicates treatment using oral vitamin B12 supplements is as effective as injections of vitamin B12."[22]

Another meta-analysis, completed in 2015, utilized data from 12 studies and a total of 34,481 patients to determine if vitamin B12, vitamin B6, and folic acid supplementation affected homocysteine levels and/or reduced the risk of cardiovascular disease.[23] A combination of vitamin B12, vitamin B6, and folic acid was found to significantly reduce plasma homocysteine levels, but it did not seem to impact cardiovascular disease risk.[23] Therefore, it was concluded that vitamin B12 should not be utilized as a

cardiovascular disease prevention method. Additional research has also concluded that the "Use of vitamin B12 in patients with elevated serum homocysteine levels and cardiovascular disease does not reduce the risk of myocardial infarction or stroke, or alter cognitive decline."[3]

In other indications, vitamin B12 has recently been utilized as a biomarker for patients undergoing therapeutic treatment for tuberculosis (TB); vitamin B12 serum concentrations were observed to have significant differences in TB patients between baseline and six months after anti-TB treatment (ATT), attributing the decrements in vitamin B12 to the body "reclaiming normal physiological function of the affected organs and immune function improv[ing] by cleaning or a rapid drop in bacterial load."[24] Gebremicael, et al. (2019) also found that HIV (Human Immunodeficiency Virus) and HAART (Highly active antiretroviral therapy) status of TB patients at baseline had "no effect on the concentration levels of vitamin B12 and vitamin A," and HAART treatment did not affect vitamin B12 serum concentration in ATT treated HIV+/TB+ patients.

Wolffenbuttel, et al. (2020) recently conducted a study obtaining data from the general population of National Health and Nutrition Examination Survey (NHANES). A total of 24462 patients were included. The authors found a positive association between low serum B12 concentration and all-cause mortality (hazard ratio [HR] = 1.39), as well as between low serum B12 concentration and cardiovascular mortality (HR = 1.64). The authors also found a positive association of high serum B12 concentration and cardiovascular mortality (HR = 1.45), although the authors noted that participants with diagnoses such as hyperlipidemia and CVD tended to use vitamin B12-containing supplements more often than those without such diagnoses. However, the authors did not find an association between vitamin B12 supplement intake and mortality. This demonstrates the importance of testing for B12 in the long run to adjust dietary intake and reduce mortality.[25]

Sasaki, et al. (2023) studied the usefulness of the one-hour 13 C-propionate breath test in detecting Vitamin B12. The 13 C-propionate breath test can use vitamin B12 as a coenzyme of methylmalonyl-CoA in propionate metabolism to measure vitamin B12 deficiency. The authors collected samples from 49 patients in Japan with clinically suspected vitamin B12 deficiency and compared results between patients with or without low serum vitamin B12 levels, macrocytosis, and vitamin B12 supplementation. The results have no significant difference between the patients with or without low serum VB12 levels. The results did have significant differences between patients with and without macrocytosis and between patients before and after vitamin B12 supplementation.[26]

V. Guidelines and Recommendations

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. These manifestations are listed below:

- "Cutaneous
  - Hyperpigmentation
  - Jaundice
  - Vitiligo
- Gastrointestinal
  - Glossitis
- Hematologic

  - Anemia (macrocytic, megaloblastic)
  - Leukopenia
  - Pancytopenia
  - Thrombocytopenia
  - Thrombocytosis
- Neuropsychiatric
  - Areflexia
  - Cognitive impairment (including dementia-like symptoms and acute psychosis)
  - Gait abnormalities
  - Irritability
  - Loss of proprioception and vibratory sense
  - Olfactory impairment
  - Peripheral neuropathy"

"The recommended laboratory evaluation for patients with suspected vitamin B12 deficiency includes a complete blood count and serum vitamin B12 level." Also, "in patients with a normal or low-normal serum vitamin B12 level, complete blood count results demonstrating macrocytosis, or suspected clinical manifestations, a serum methylmalonic acid level is an appropriate next step and is a more direct measure of vitamin B12's physiologic activity. 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."

The AAFP notes that different causes of vitamin B12 deficiency have corresponding "time to improvement" after initiation of treatment. For abnormalities related to "Homocysteine or methylmalonic acid level, or reticulocyte count," AAFP lists an "expected time until improvement" of one week; for neurologic symptoms, six weeks to three months; for anemia, leukopenia, mean corpuscular volume, or thrombocytopenia, eight weeks.

Finally, AAFP lists risk factors for vitamin B12 deficiency, which are included below:

- "Decreased ileal absorption
  - Crohn disease
  - Ileal resection
  - Tapeworm infection
- Decreased intrinsic factor
  - Atrophic gastritis
  - Pernicious anemia
  - Postgastrectomy syndrome (includes Roux-en-Y gastric bypass)
- Genetic
  - Transcobalamin II deficiency
- Inadequate intake
  - Alcohol abuse
  - Patients older than 75 years
  - Vegans or strict vegetarians (including exclusively breastfed infants of vegetarian/vegan mothers)
- Prolonged medication use
  - Histamine H2 blocker use for more than 12 months.
  - Metformin use for more than four months

- Proton pump inhibitor use for more than 12 months."[3]

The AAFP comments on pernicious anemia, stating that "Patients diagnosed with vitamin B_{12} deficiency whose history and physical examination do not suggest an obvious dietary or malabsorptive etiology should be tested for pernicious anemia with anti-intrinsic factor antibodies (positive predictive value = 95%), particularly if other autoimmune disorders are present." The AAFP also notes that "Patients with pernicious anemia may have hematologic findings consistent with normocytic anemia."[3]

In their "Update on Vitamin B12 Deficiency" published in the *American Family Physician*, Langan and Zawistoski (2011) remarked that "No major medical organizations, including the U.S. Preventive Services Task Force, have published guidelines on screening asymptomatic or low-risk adults for vitamin B12 deficiency, but high-risk patients, such as those with malabsorptive disorders, may warrant screening."[13]

American College of Gastroenterology (ACG)

The ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease state that "tissue transglutaminase and deamidated gliadin peptide can be used for monitoring CD [celiac disease]. Other tests may include complete blood count, alanine aminotransferase, vitamins (A, D, E, B12), copper, zinc, carotene, folic acid, ferritin, and iron. Blood tests at follow-up should be individualized to verify correction of laboratory tests that were abnormal at baseline."[27]

Centers for Disease Control and Prevention (CDC)

The CDC emphasizes the importance of vitamin B12 for infants' healthy development. Infants may acquire sufficient vitamin B12 through breastmilk; however, if a breastfeeding mother is deficient in vitamin B12, the mother's infant may not receive enough of the vitamin. The CDC states breastfeeding mothers who have had a malabsorptive bariatric procedure (such as gastric bypass surgery), who have pernicious anemia (low number of red blood cells caused by a deficiency of vitamin B12), or who have certain gastrointestinal disorders, may not be able to absorb various vitamins and minerals, such as vitamin B12, folic acid (vitamin B9), iron, and calcium. "Healthcare providers should monitor these mothers for nutrient deficiencies, including vitamin B12 deficiency."[28]

British Committee for Standards in Haematology

The British Committee for Standards in Haematology guidelines for the diagnosis and treatment of cobalamin and folate disorders state that: "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."[29]

The Doctors of BC (formerly the British Columbia Medical Association)

The Doctors of BC updated their guidelines on vitamin B12 in 2023. The guideline's key recommendations are:

- "Routine B12 screening and testing in asymptomatic patients is not supported by evidence.
- Consider B12 supplementation without testing in asymptomatic patients with risk factors for B12 deficiency.

- B12 deficiency can cause preventable permanent injury and should be considered with new onset neurological conditions and symptoms suggestive of B12 deficiency.
- Folate testing is rarely indicated but may be available via consultation with the laboratory medicine physician or scientist."[30]

The guidelines go on to state: "In a clinically symptomatic patient with specific features of B12 deficiency, order a B12 test." In terms of repeat testing, the guidelines state that "Repeat testing of B12 may be warranted after a trial of therapy or as an assessment of adherence. Repeat testing should wait at least two months after therapy has been started. If the B12 is normal (rare probability of B12 deficiency – see Table 3: B12 Medication Table), a repeat investigation is not required in the absence of new signs of disease. In absence of a reversible factor therapy, supplementation in most cases is lifelong." Lastly, the guidelines state that "Serum folate and red blood cell (RBC) folate testing is no longer offered in BC."[30]

American Association of Clinical Endocrinology (AACE), the American College of Endocrinology (ACE) and The Obesity Society (TOS)

"Vitamin B12 levels should be checked periodically in older adults and patients on metformin therapy (Grade A, BEL 1). With the exception of early treatment of patients with neurologic symptoms, pernicious anemia, or malabsorptive bariatric surgery requiring parenteral (intramuscular or subcutaneous) vitamin B12 replacement, patients with vitamin B12 deficiency can generally be treated with oral vitamin B12 (1,000 µg per day of oral crystalline cobalamin) and may benefit from increasing the intake of vitamin B12 in food (Grade A, BEL 1)."[31]

American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE)

In a consensus statement on the Comprehensive Type 2 Diabetes Management Algorithm, the AACE/ACE states that "in patients taking metformin who develop neuropathy, B12 should be monitored and supplements given to affected patients, if needed."[32]

American Society for Metabolic and Bariatric Surgery (ASMBS) Integrated Health Nutritional Guidelines (2016 Update)

Concerning vitamin B12 screening and weight loss surgical (WLS) practices, the ASMBS states that "routine pre-WLS screening of B12 is recommended for all patients (Grade B, BEL 2)." Further, serum MMA [methylmalonic acid] testing is recommended to evaluate a possible B12 deficiency for both asymptomatic and symptomatic patients as well as in "those with history of B12 deficiency or preexisting neuropathy (Grade B, BEL 2)"

The ASMBS also makes the following recommendations for post-WLS nutrient screening:

- "Routine post-WLS screening of vitamin B12 status is recommended for patients who have undergone RYGB [Roux-en-Y gastric bypass], SG [sleeve gastrectomy], or BPD/DS [biliopancreatic diversion/duodenal switch]."
- "More frequent screening (e.g., every 3 mo) is recommended in the first post-WLS year, and then at least annually or as clinically indicated for patients who chronically use medications that exacerbate risk of B12 deficiency: nitrous oxide, neomycin, metformin, colchicine, proton pump inhibitors, and seizure medications."

- "Serum B12 may not be adequate to identify B12 deficiency. It is recommended to include serum MMA with or without homocysteine to identify metabolic deficiency of B12 in symptomatic and asymptomatic patients and in patients with history of B12 deficiency or preexisting neuropathy."[33]

American Association of Clinical Endocrinology/American College of Endocrinology (AACE/ACE), The Obesity Society (TOS), American Society for Metabolic & Bariatric Surgery (ASMBS), Obesity Medicine Association (OMA), and American Society of Anesthesiologists (ASA) (2019 Update)

The AACE/ACE, TOS, ASMBS, OMA, and ASA published clinical practice guidelines for perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures in 2019. In the preprocedural checklist, the recommendation includes "nutrient screening with iron studies, B12 and folic acid (RBC folate, homocysteine, methylmalonic acid optional), and 25-vitamin D (vitamins A and E optional); consider more extensive testing in patients undergoing malabsorptive procedures based on symptoms and risks." In the post-procedure checklist, for early postoperative care, vitamin B12 should be assessed "as needed for normal range levels," and in follow-up "annually; MMA and HCy optional; then q 3-6 months if supplemented)."[34] In addition, the societies state:

- Vitamin B12 screening is "recommended for patients who have undergone RYGB [Roux-en-Y gastric bypass], SG [sleeve gastrectomy], or BPD/DS (biliopancreatic diversion/duodenal switch]"
- "Patients who become pregnant following bariatric procedure should have nutritional surveillance and laboratory screening for nutrient deficiencies every trimester, including iron, folate, vitamin B12, vitamin D, and calcium, and if after a malabsorptive procedure, fat-soluble vitamins, zinc, and copper (Grade D)
- Baseline and annual post-bariatric procedure evaluation for vitamin B12 deficiency should be performed in all patients (Grade B; BEL 2)
- More frequent aggressive case finding (e.g., every three months) should be performed in the first postoperative year, and then at least annually or as clinically indicated for patients who chronically use medications that exacerbate risk of B12 deficiency: nitrous oxide, neomycin, metformin, colchicine, proton-pump inhibitors, and seizure medications (Grade B, BEL 2)
- Since serum B12 may not be adequate to identify B12 deficiency, consider measuring serum methylmalonic, with or without homocysteine, to identify a metabolic deficiency of B12 in symptomatic and asymptomatic patients and in patients with a history of B12 deficiency or pre-existing neuropathy (Grade B, BEL 2)
- B12 status should be assessed in patients on higher-dose folic acid supplementation (>1000 µg/day) to detect a masked B12- deficiency state (Grade D)."[34]

American Society for Metabolic & Bariatric Surgery (ASMBS)

Pratt, et al. (2018) state that "Anemia is common after MBS [metabolic and bariatric surgery] and may relate to low levels of iron, folate, B6, or B12. Dieticians with expertise in MBS are best equipped to assess nutritional status, including screening for frank nutrient deficiencies." Further, "preparation for MBS educates patients and families to the importance of taking vitamins and supplements regularly before MBS to reduce the risk of deficiencies after MBS. Preoperative nutritional assessment includes serum iron, folate, ferritin, and total iron-binding capacity (TIBC); thiamin (B1); vitamin B12; vitamin A and B6; calcium, Parathyroid Hormone, alkaline phosphatase, vitamin D, phosphorus, magnesium, and zinc. All except serum magnesium and zinc should be checked two months post surgery and all should be checked at six months and then yearly thereafter." Finally, "standard supplementation recommended

for adolescents includes vitamin B1 preoperatively and for at least six months postoperatively, vitamin B12 sublingual, multivitamin with iron, and calcium citrate with vitamin D daily."[35]

British Obesity & Metabolic Surgery Society (BOMSS) (2020 Update)

The BOMSS released 2020 perioperative and postoperative guidelines on biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery. On measuring vitamin B12 concentrations, the BOMSS has included checking a "full blood count including haemoglobin, ferritin, folate and vitamin B12 levels" in their preoperative nutritional assessment with a grade B and evidence level (EL) of 2. For postoperative care and biochemical monitoring, the BOMSS stated,

- "Check vitamin B12 levels at regular intervals following SG, RYGB and malabsorptive procedures such as BPD/DS" (Grade B, EL2).
- Consider the following frequency of monitoring vitamin B12 levels: 3, 6 and 12 months in the first year and at least annually thereafter so that changes in status may be detected" (GPP – good practice point)."

With relation to folic acid deficiency, O'Kane, et al. (2020) mentions, "check and treat for vitamin B12 deficiency, before initiating folic acid treatment to avoid precipitation of subacute combined degeneration of the spinal cord" (Grade D, EL4). For any presence of neurological symptoms/Wernicke's encephalopathy, the guidelines recommend to "check for vitamin B12, copper and vitamin E deficiencies and treat" (GPP). In pregnant individuals after undergoing bariatric surgery, checking for vitamin B12 deficiency, among other nutritional deficiencies, has been recommended for each trimester and prior to additional folic acid supplementation in the preconception period.[36]

Guidelines for Diagnosis and Management of the Cobalamin-related Remethylation Disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR Deficiency

This international consortium of scientists from Europe and the U.S. issued guidelines "within the frame of the 'European network and registry for homocystinurias and methylation defects' (E-HOD) project." For Recommendation 5, they state (Quality of the evidence: moderate), "we strongly recommend that in the case of high total homocysteine, plasma and urine samples for determination of MMA, methionine, folate and vitamin B12 are to be obtained before treatment is started."[37]

The American Diabetes Association (ADA)

The ADA states that in patients with type 2 diabetes, the long-term use of metformin may be associated with a vitamin B12 deficiency; therefore, a Grade B recommendation has been made that recommends considering "periodic assessment of vitamin B12 level in those taking metformin chronically should be considered to check for possible deficiency."[38] In 2024, the ADA stated that "Measurement of vitamin B12 levels should be considered for patients with type 1 diabetes and peripheral neuropathy or unexplained anemia."[39]

American Psychiatric Association (APA)

The APA released guidelines that state that vitamin B12 deficiencies can develop due to anorexia nervosa, atypical anorexia nervosa, or avoidant restrictive food intake disorder.[40]

The Vitamin B12 Consensus Panelists Group

A consensus group of experts developed a series of recommendations on Vitamin B12 screening and diagnosis.[41] The following recommendations pertain to biomarkers and their utility in clinical practice:

"Considering the cost–benefit and the added value of advanced laboratory tests beyond plasma B12 concentrations and blood cell count:

- Measurement of a metabolic marker such as plasma methylmalonic acid (or total homocysteine if methylmalonic acid is not available) is useful in guiding the diagnosis of B12 deficiency.
- If available, plasma methylmalonic acid concentration is a useful marker for monitoring the effectiveness of B12 treatment in general.
- If available, plasma methylmalonic acid concentration is useful in monitoring the success of oral B12 treatment in particular when it is questionable whether the B12 dose is appropriate or people can absorb B12.
- Plasma methylmalonic acid concentration (or at least total homocysteine) should be made available for all people suspected of having B12 deficiency.
- Although the metabolic markers (plasma methylmalonic acid and total homocysteine) have some limitations, they can be very helpful when the clinical picture is uncertain.
- Because chronic use of metformin in patients with diabetes is associated with lower plasma concentrations of B12 and linked to the frequency and severity of neuropathy, measurement of B12 status once per year in this group of patients can help detect a deficiency prior to clinical manifestation.
- If plasma B12 concentrations far above the reference range are encountered in a person without specific medical conditions:
    - Inquire if the person is using any supplemental B12 source (food supplements or OTC).
    - If the person is not using a B12-supplement, repeat plasma B12 test after few months.
    - Rule out disturbed blood count, liver and renal function markers that may explain high plasma B12 levels due to liver or kidney diseases or undiagnosed malignancies
- In context of the B12 diagnostic work-up, folate and iron status should also be assessed."[41]

National Institute for Health and Care Excellence (NICE)

NICE provides guidelines on the diagnosis and management of vitamin B12 deficiency, emphasizing targeted testing based on specific symptoms and risk factors to improve diagnostic accuracy. Testing is advised when patients display both a common symptom and a common risk factor for B12 deficiency. Clinical judgment is advised in cases where a patient presents only symptoms and no risk factors.[42] Common symptoms and common risk factors are outlined below:

"Common symptoms and signs of vitamin B12 deficiency

- abnormal findings on a blood count such as anaemia or macrocytosis
- cognitive difficulties such as difficulty concentrating or short-term memory loss (sometimes described as 'brain fog'), which can also be symptoms of delirium or dementia
- eyesight problems related to optic nerve dysfunction:
    - blurred vision
    - optic atrophy
    - visual field loss (scotoma)
- glossitis
- neurological or mobility problems related to peripheral neuropathy, or to central nervous system disease including myelopathy (spinal cord disease):

  - balance issues and falls caused by impaired proprioception (the ability to sense movement, action and location) and linked to sensory ataxia (which may have been caused by spinal cord damage)
  - impaired gait
  - pins and needles or numbness (paraesthesia)
- symptoms or signs of anaemia that suggest iron treatment is not working properly during pregnancy or breastfeeding
- unexplained fatigue.

Common risk factors for vitamin B12 deficiency

- diet low in vitamin B12 (without the regular use of over-the-counter preparations), for example, in people who:
  - follow a diet that excludes, or is low in, animal-source foods (such as a vegan diet, or diets excluding meat for religious beliefs)
  - do not consume food or drinks fortified with vitamin B12
  - have an allergy to some foods such as eggs, milk or fish
  - find it difficult to buy or prepare food (for example, people who have dementia or frailty, or those with mental health conditions)
  - find it difficult to obtain or afford foods rich in vitamin B12 (for example, people on low income)
  - have a restricted diet (for example, because of an eating disorder)
- family history of vitamin B12 deficiency or an autoimmune condition
- health conditions:
  - atrophic gastritis affecting the gastric body
  - coeliac disease or another autoimmune condition (such as thyroid disease, Sjögren's syndrome or type 1 diabetes)
- medicines:
  - colchicine
  - H2-receptor antagonists
  - metformin (see the MHRA safety advice on metformin and reduced vitamin B12)
  - phenobarbital
  - pregabalin
  - primidone”[42]

Regarding initial testing, NICE recommends “either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) as the initial test for suspected vitamin B12 deficiency unless the test needs to be done during pregnancy, or recreational nitrous oxide use is the suspected cause of deficiency.”[42]

For individuals with indeterminate test results who show no symptoms, NICE advises them to seek care if symptoms develop. If the initial test result suggests that a deficiency is unlikely, NICE recommends that "if they are still experiencing symptoms 3 to 6 months later, consider a repeat of the initial test."[42]

The British Medical Journal (BMJ)

The British Medical Journal (BMJ) published a 2023 study on diagnosing and managing vitamin B12 deficiency. Regarding testing, the BMJ notes, “Diagnosing B12 deficiency can be challenging because no single specific measurement exists to reliably diagnose or refute the presence of B12 deficiency.” For

patients with neurological symptoms, the BMJ states, “Serum B12, homocysteine, and methylmalonic acid (MMA) levels are unreliable predictors of B12 responsive neuropathy.”[43]

The BMJ also highlights, “Neurological symptoms may take several months or even years to resolve completely,” and that “Biomarkers normalize more rapidly than an improvement or reversal of (neurological) symptoms. Additionally, symptoms may reappear without changes in biomarker status.” For treatment, they recommend that providers “monitor symptoms regularly (eg, every two to three months) as they may reappear, even after several months, if injection frequency is reduced. Measuring serum biomarkers such as B12 or MMA is neither helpful nor indicated in assessing or monitoring clinical improvement. Base the injection frequency on symptoms, and not on biomarker assessment.”[43]

In 2024, the BMJ reviewed the NICE guideline for vitamin B12 deficiency diagnosis and management, agreeing with the recommendations for testing. They noted that “Vitamin B12 deficiency is a complex condition with significant variability in the type and severity of symptoms that people experience.” This led to discussion on which features and risk factors should be emphasized, with the guideline committee prioritizing “the importance of timely testing while not increasing the volume of testing unnecessarily in people who are unlikely to be deficient.”[44]

VI. Applicable State and Federal Regulations

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

CPT	Code Description
82607	Cyanocobalamin (Vitamin B-12)
83090	Homocysteine
83921	Organic acid, single, quantitative
84999	Unlisted chemistry procedure

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IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
05/23/2022	Updated background, guidelines, and evidence-based scientific references. Remove Coverage Criteria 8 and code 84999
04/04/2023	Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC3.a.iv changed to allow for B12 screening in those scheduled for bariatric surgery. Previously read: “Patients that have undergone bariatric procedures such as Roux-en-Y gastric bypass, sleeve gastrectomy, or biliopancreatic diversion/duodenal switch.” Now reads: “Having undergone, or for those who have been scheduled for, bariatric procedures such as Roux-en-Y gastric bypass, sleeve gastrectomy, or biliopancreatic diversion/duodenal switch.” All CC edited for clarity and consistency. Committee approved 04/04/2023

02/12/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Committee approved: 02/12/2024
02/06/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Added a three month testing frequency for all vitamin B testing/screening. Results in a new main criterion 1 and former CC1, CC2, and CC3 before subcriteria under the main criterion, which reads: "1) Total vitamin B12 (serum cobalamin) testing MEETS COVERAGE CRITERIA once every three months for any of the following situations:" New CC7: "7) For all other situations not described above, total vitamin B12 (serum cobalamin) testing DOES NOT MEET COVERAGE CRITERIA. Committee approved: 02/06/2025
06/17/2026	CAB Review Q1 2026: Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Committee Approved: 06/17/2026