

## Vitamin B12 and Methylmalonic Acid Testing

Policy Number: AHS –G2014 – Vitamin B12 and Methylmalonic Acid Testing	Prior Policy Name and Number, as applicable:
Effective Date: 01/01/2023	

### 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 (Oh & Brown, 2003).

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 (Sobczynska-Malefora et al., 2014).

Holotranscobalamin (holoTC) is the metabolically active fraction of B12 and is an emerging marker of impaired vitamin B12 status (Langan & Goodbred, 2017).

### II. Related Policies

Policy Number	Policy Title
AHS-G2154	Folate Testing
AHS-M2141	Testing of Homocysteine Metabolism-Related Conditions

### III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website <https://www.cms.gov/medicare-coverage-database/search.aspx> or [the manual website](#).

- 1) Vitamin B12 testing **MEETS COVERAGE CRITERIA** in individuals being evaluated for clinical manifestations of Vitamin B12 deficiency including:
  - a) Cutaneous
    - i) Hyperpigmentation
    - ii) Jaundice
    - iii) Vitiligo
  - b) Gastrointestinal
    - i) Glossitis
  - c) Hematologic
    - i) Anemia (macrocytic, megaloblastic)
    - ii) Leukopenia
    - iii) Pancytopenia
    - iv) Thrombocytopenia
    - v) Thrombocytosis
  - d) Neuropsychiatric
    - i) Areflexia
    - ii) Cognitive impairment (including dementia-like symptoms and acute psychosis)
    - iii) Gait abnormalities
    - iv) Irritability
    - v) Loss of proprioception and vibratory sense
    - vi) Olfactory impairment
    - vii) Peripheral neuropathy
- 2) Vitamin B12 testing **MEETS COVERAGE CRITERIA** when performed no sooner than 3 months after initiation of therapy for individuals undergoing treatment for vitamin B12 deficiency.
- 3) Screening for Vitamin B12 deficiency **MEETS COVERAGE CRITERIA** for individuals with one or more of the following risk factors:
  - a) Decreased ileal absorption
    - i) Crohn disease
    - ii) Ileal resection
    - iii) Tapeworm infection
    - iv) Patients that have undergone bariatric procedures such as Roux-en-Y gastric bypass, sleeve gastrectomy, or biliopancreatic diversion/duodenal switch
  - b) Decreased intrinsic factor

- i) Atrophic gastritis
  - ii) Pernicious anemia
  - iii) Postgastrectomy syndrome
  - c) Genetic
    - i) Transcobalamin II deficiency
  - d) Inadequate intake
    - i) Alcohol abuse
    - ii) Patients older than 75 years or elderly individuals being evaluated for dementia
    - iii) Vegans or strict vegetarians (including exclusively breastfed infants of vegetarian/vegan mothers)
    - iv) Eating disorders
  - e) Prolonged medication use
    - i) Histamine H2 blocker use for more than 12 months
    - ii) Metformin use for more than four months
    - iii) Proton pump inhibitor use for more than 12 months
- 4) Methylmalonic acid testing **MEETS COVERAGE CRITERIA** to confirm vitamin B12 deficiency in asymptomatic high-risk patients 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.
- 5) Methylmalonic acid testing **MEETS COVERAGE CRITERIA** for the evaluation of inborn errors of metabolism.
- 6) Screening for Vitamin B12 deficiency in healthy, asymptomatic individuals **DOES NOT MEET COVERAGE CRITERIA.**
- 7) Homocysteine testing **DOES NOT MEET COVERAGE CRITERIA** for the confirmation of vitamin B12 deficiency.

#### **IV. Scientific Background**

Vitamin B12 cannot be synthesized by human cells (Means Jr & Fairfield, 2019); rather, it is obtained from animal-derived dietary sources, such as meat, eggs, and dairy products (Hunt et al., 2014), as well as fortified cereals and supplements (Zeuschner et al., 2013). 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 (Means Jr & Fairfield, 2019).

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 (Hunt et al., 2014). 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) (Langan & Goodbred, 2017).

Vitamin B12 plays an essential role in nucleic acid synthesis. Deficiency can result in cell cycle arrest in the S phase or cause apoptosis (Green, 2017) and ultimately bone marrow failure and demyelinating nervous system disease (Stabler, 2013). 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 (Fan et al., 2020; Hama et al., 2020).

Clinical manifestations of Vitamin B12 deficiency vary in their presence and severity from mild fatigue to severe neurologic impairment (Langan & Goodbred, 2017). 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. Recent literature also suggests a relationship between Vitamin B12 and depression (Sangle et al., 2020).

Vitamin B12 deficiency can cause glossitis and other gastrointestinal symptoms that vary with underlying diseases, such as inflammatory bowel disease or celiac disease (Means Jr & Fairfield, 2019). 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 (Sobczynska-Malefora et al., 2014).

### *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 (Hunt et al., 2014); 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 (Sobczynska-Malefora et al., 2014). 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 (Langan & Zawistoski, 2011). 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 (Langan & Zawistoski, 2011).

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” (Willis et al., 2011). The test measures total serum cobalamin including both serum holohaptocorrin and serum holotranscobalamin, which may mask true deficiency or falsely imply a deficient state (Hunt et al., 2014).

Vitamin B12 deficiency is present in both infant and pregnant female populations, 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 (Rogne et al., 2017). It seems that current pregnancy-specific cutoffs for vitamin B12 biomarkers are inadequate in the medical field (Schroder et al., 2019). 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  $\mu\text{mol/L}$  (68.4% sensitivity, 58.3% specificity,  $p = .012$ ) for the detection of vit-B12 deficiency” (Yetim et al., 2019). 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  $<84.0$   $\text{pmol/L}$ , holoTC  $<29.5$  and  $<26.0$   $\text{pmol/L}$  and MMA  $>371$  and  $>374$   $\text{nmol/L}$ , in the first and second trimesters, respectively, may indicate B-12 deficiency in pregnant women. 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  $<180$   $\text{pmol/L}$  and holoTC  $<62.2$  and  $<67.5$   $\text{pmol/L}$  in the first and second trimesters, respectively, suggested an increased probability of impaired intracellular B-12 status, with no difference between ethnicities (Schroder et al., 2019).”

Elevated levels of downstream metabolites, MMA and Hcy, are commonly used as adjuvant diagnostics to confirm a suspected diagnosis of cobalamin deficiency (Berg & Shaw, 2013). 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 (Hunt et al., 2014). In a study by Rozmarič et al. (2020) the cutoff for MMA as an indicator of B12 deficiency was  $0.423$   $\mu\text{M}$  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 (Oberley & Yang, 2013). It also is not yet clinically validated or available for widespread use (Langan & Goodbred, 2017).

Criteria	Sensitivity	Specificity	Pitfalls
Serum total cobalamin ( $<200$ $\text{pg/mL}$ )	95–97%	Uncertain, possibly $<80\%$	<p><i>Elevated levels seen with:</i></p> <ul style="list-style-type: none"> <li>Assay technical failure</li> <li>Occult malignancy</li> <li>Alcoholic liver disease</li> <li>Renal disease</li> </ul> <p><i>Decreased levels also seen with:</i></p> <ul style="list-style-type: none"> <li>Haptocorrin deficiency</li> <li>Folate deficiency</li> <li>Plasma cell myeloma</li> <li>HIV</li> <li>Pregnancy</li> </ul>

Criteria	Sensitivity	Specificity	Pitfalls
Elevated serum methylmalonic acid	>95%	Uncertain	<i>Elevated levels seen with:</i> Renal insufficiency Hypovolemia Congenital metabolic defects Amyotrophic lateral sclerosis
Elevated serum homocysteine	>95%	Uncertain, less specific than methylmalonic acid	<i>Elevated levels seen with:</i> Folate or pyridoxine deficiency Renal insufficiency Hypovolemia Hypothyroidism Psoriasis Congenital metabolic defects Neurodegenerative disease Malignancy Medications
Decreased serum holotranscobalamin	Similar to total cobalamin	Uncertain	<i>Levels may be affected by:</i> 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 (HQO, 2013). 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” (HQO, 2013).

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 (Li et al., 2015). 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 (Li et al., 2015). 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” (Langan & Goodbred, 2017).

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 6 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” (Gebremicael et al., 2019). 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.

## **V. Guidelines and Recommendations**

### **American Academy of Family Physicians (AAFP) (Langan & Goodbred, 2017)**

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” (Langan & Goodbred, 2017).

The AAFP comments on pernicious anemia, stating that “Patients diagnosed with vitamin B<sub>12</sub> 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” (Langan & Goodbred, 2017).



**American College of Gastroenterology (ACG) (Rubio-Tapia et al., 2013)**

The ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease (Rubio-Tapia et al., 2013) 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.”

**Centers for Disease Control and Prevention (CDC, n.d.)**

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” (CDC, n.d.).

**British Committee for Standards in Haematology (Devalia et al., 2014)**

“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” (Devalia et al., 2014).

**The Doctors of BC (formerly the British Columbia Medical Association) (BCMA, 2013)**

The Doctors of BC recommend vitamin B12 testing for individuals with “unexplained neurologic symptoms, such as paresthesias, numbness, poor motor coordination, memory lapses or cognitive and personality changes,” and anemia. They also recommend consideration of testing of elderly individuals (>75 years old), those with inflammatory bowel disease (of small intestine), gastric or small intestine resection, prolonged vegan diet, and long-term use of H2 receptor antagonists or proton pump inhibitors (at least 12 months), or metformin (at least 4 months).

**American Association of Clinical Endocrinology (AACE), the American College of Endocrinology (ACE) and The Obesity Society (TOS) (Gonzalez-Campoy et al., 2013)**

“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)” (Gonzalez-Campoy et al., 2013).

**American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE) (Garber et al., 2020)**

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” (Garber et al., 2020).

**American Association of Clinical Endocrinology (AACE), the Obesity Society, and American Society for Metabolic & Bariatric Surgery (ASMBS) (Mechanick et al., 2013)**

“Baseline and postoperative evaluation for vitamin B12 deficiency is recommended in all bariatric surgery and annually in those with procedures that exclude the lower part of the stomach (e.g., LSG, RYGB) (Grade B; BEL 2)” (Mechanick et al., 2013).

**American Society for Metabolic and Bariatric Surgery (ASMBS) Integrated Health Nutritional Guidelines (2016 Update) (Parrott et al., 2017)**

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.” (Parrott et al., 2017).

**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) (Mechanick et al., 2019)**

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 preprocedure 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 postprocedure 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)” (Mechanick et al., 2019). 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 3 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)” (Mechanick et al., 2019).

#### **American Society for Metabolic & Bariatric Surgery (ASMBS) (Pratt et al., 2018)**

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 2 months postsurgery and all should be checked at 6 months and then yearly thereafter.” Finally, “standard supplementation recommended for adolescents includes vitamin B1 preoperatively and for at least 6 months postoperatively, vitamin B12 sublingual, multivitamin with iron, and calcium citrate with vitamin D daily.”

#### **British Obesity & Metabolic Surgery Society (BOMSS) (2020 Update) (O’Kane et al., 2020)**

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 women 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 (O’Kane et al., 2020).

### **Guidelines for Diagnosis and Management of the Cobalamin-related Remethylation Disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR Deficiency (Huemer et al., 2017).**

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” (Huemer et al., 2017).

### **The American Diabetes Association (ADA) (ADA, 2020a, 2020b, 2021)**

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 measurement of vitamin B12 levels in metformin-treated patients, especially in those with anemia or peripheral neuropathy” (ADA, 2021). The ADA also recommended that “measurement of vitamin B12 levels should be considered in patients with type 1 diabetes and peripheral neuropathy or unexplained anemia” (ADA, 2020b).

### **American Psychiatric Association (APA) (Yager et al., 2006)**

The APA released guidelines which include a table of the physical complications of anorexia nervosa and potential laboratory testing methods. This table contains a few vitamin assays that may be used to monitor endocrine or metabolic processes including vitamin B12 assays “in severe cases” (Yager et al., 2006).

### **U.S. Preventative Services Task Force (USPSTF) (Langan & Zawistoski, 2011)**

Currently, the USPSTF has not published guidelines for vitamin B12 deficiency screenings of asymptomatic or low-risk adults.

## VI. State and Federal Regulations, as applicable

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

A search of the FDA Device database on 10/25/2021 using the term “vitamin B12” yielded 253 results. Another search using the term “methylmalonic” yielded 23 results. Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; 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.

Code Number	Code Description
82607	Cyanocobalamin (Vitamin B-12)
83090	Homocysteine
83921	Organic acid, single, quantitative

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## VIII. Evidence-based Scientific References

- ADA. (2020a). 3. Prevention or Delay of Type 2 Diabetes: <em>Standards of Medical Care in Diabetes—2020</em>. *Diabetes Care*, 43(Supplement 1), S32-S36. <https://doi.org/10.2337/dc20-S003>
- ADA. (2020b). 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: <em>Standards of Medical Care in Diabetes—2020</em>. *Diabetes Care*, 43(Supplement 1), S37-S47. <https://doi.org/10.2337/dc20-S004>
- ADA. (2021). 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care*, 44(Suppl 1), S34-S39. <https://doi.org/10.2337/dc21-S003>
- BCMA. (2013, May 1). *Cobalamin (vitamin B12) Deficiency - Investigation & Management - Province of British Columbia*. British Columbia Medical Association. Retrieved October 26 from <https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12>

- Berg, R. L., & Shaw, G. R. (2013). Laboratory evaluation for vitamin B12 deficiency: the case for cascade testing. *Clin Med Res*, *11*(1), 7-15. <https://doi.org/10.3121/cmr.2012.1112>
- CDC. (n.d., August 26, 2021). *Vitamin B12*. Retrieved October 25 from <https://www.cdc.gov/breastfeeding/breastfeeding-special-circumstances/diet-and-micronutrients/vitamin-b12.html>
- Devalia, V., Hamilton, M. S., & Molloy, A. M. (2014). Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *Br J Haematol*, *166*(4), 496-513. <https://doi.org/10.1111/bjh.12959>
- Fan, X., Zhang, L., Li, H., Chen, G., Qi, G., Ma, X., & Jin, Y. (2020). Role of homocysteine in the development and progression of Parkinson's disease. *Ann Clin Transl Neurol*. <https://doi.org/10.1002/acn3.51227>
- Garber, A. J., Handelsman, Y., Grunberger, G., Einhorn, D., Abrahamson, M. J., Barzilay, J. I., Blonde, L., Bush, M. A., DeFronzo, R. A., Garber, J. R., Garvey, W. T., Hirsch, I. B., Jellinger, P. S., McGill, J. B., Mechanick, J. I., Perreault, L., Rosenblit, P. D., Samson, S., & Umpierrez, G. E. (2020). Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. *Endocr Pract*, *26*(1), 107-139. <https://doi.org/10.4158/CS-2019-0472>
- Gebremicael, G., Alemayehu, M., Sileshi, M., Geto, Z., Gebreegziabxier, A., Tefera, H., Ashenafi, N., Tadese, C., Wolde, M., & Kassa, D. (2019). The serum concentration of vitamin B12 as a biomarker of therapeutic response in tuberculosis patients with and without human immunodeficiency virus (HIV) infection. *Int J Gen Med*, *12*, 353-361. <https://doi.org/10.2147/ijgm.S218799>
- Gonzalez-Campoy, J. M., St Jeor, S. T., Castorino, K., Ebrahim, A., Hurley, D., Jovanovic, L., Mechanick, J. I., Petak, S. M., Yu, Y. H., Harris, K. A., Kris-Etherton, P., Kushner, R., Molinari-Blandford, M., Nguyen, Q. T., Plodkowski, R., Sarwer, D. B., & Thomas, K. T. (2013). Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. *Endocr Pract*, *19* Suppl 3, 1-82. <https://doi.org/10.4158/ep13155.gl>
- Green, R. (2017). Vitamin B12 deficiency from the perspective of a practicing hematologist. *Blood*, *129*(19), 2603-2611. <https://doi.org/10.1182/blood-2016-10-569186>
- Hama, Y., Hamano, T., Shirafuji, N., Hayashi, K., Ueno, A., Enomoto, S., Nagata, M., Kimura, H., Matsunaga, A., Ikawa, M., Yamamura, O., Ito, T., Kimura, Y., Kuriyama, M., & Nakamoto, Y. (2020). Influences of Folate Supplementation on Homocysteine and Cognition in Patients with Folate Deficiency and Cognitive Impairment. *Nutrients*, *12*(10). <https://doi.org/10.3390/nu12103138>
- HQO. (2013). Vitamin B12 and cognitive function: an evidence-based analysis. *Ont Health Technol Assess Ser*, *13*(23), 1-45. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3874776/>
- Huemer, M., Diodato, D., Schwahn, B., Schiff, M., Bandeira, A., Benoist, J. F., Burlina, A., Cerone, R., Couce, M. L., Garcia-Cazorla, A., la Marca, G., Pasquini, E., Vilarinho, L., Weisfeld-Adams, J. D., Kožich, V., Blom, H., Baumgartner, M. R., & Dionisi-Vici, C. (2017). Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. *J Inherit Metab Dis*, *40*(1), 21-48. <https://doi.org/10.1007/s10545-016-9991-4>
- Hunt, A., Harrington, D., & Robinson, S. (2014). Vitamin B12 deficiency. *Bmj*, *349*, g5226. <https://doi.org/10.1136/bmj.g5226>
- IOM. (1998). In *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. <https://doi.org/10.17226/6015>

- Knopman, D. S., DeKosky, S. T., Cummings, J. L., Chui, H., Corey–Bloom, J., Relkin, N., Small, G. W., Miller, B., & Stevens, J. C. (2001). Practice parameter: Diagnosis of dementia (an evidence-based review). *Neurology*, 56(9), 1143-1153. <https://doi.org/10.1212/WNL.56.9.1143>
- Langan, R. C., & Goodbred, A. J. (2017). Vitamin B12 Deficiency: Recognition and Management. *Am Fam Physician*, 96(6), 384-389. <http://dx.doi.org/>
- Langan, R. C., & Zawistoski, K. J. (2011). Update on vitamin B12 deficiency. *Am Fam Physician*, 83(12), 1425-1430.
- Li, J., Li, B., Qi, J., & Shen, B. (2015). [Meta-analysis of clinical trials of folic acid, vitamin B12 and B6 supplementation on plasma homocysteine level and risk of cardiovascular disease]. *Zhonghua Xin Xue Guan Bing Za Zhi*, 43(6), 554-561.
- Means Jr, R. T., & Fairfield, K. M. (2019, October 22). *Causes and pathophysiology of vitamin B12 and folate deficiencies*. Retrieved October 20 from [https://www.uptodate.com/contents/causes-and-pathophysiology-of-vitamin-b12-and-folate-deficiencies?source=see\\_link](https://www.uptodate.com/contents/causes-and-pathophysiology-of-vitamin-b12-and-folate-deficiencies?source=see_link)
- Mechanick, J. I., Apovian, C., Brethauer, S., Garvey, W. T., Joffe, A. M., Kim, J., Kushner, R. F., Lindquist, R., Pessah-Pollack, R., Seger, J., Urman, R. D., Adams, S., Cleek, J. B., Correa, R., Figaro, M. K., Flanders, K., Grams, J., Hurley, D. L., Kothari, S., Seger, M. V., & Still, C. D. (2019). CLINICAL PRACTICE GUIDELINES FOR THE PERIOPERATIVE NUTRITION, METABOLIC, AND NONSURGICAL SUPPORT OF PATIENTS UNDERGOING BARIATRIC PROCEDURES - 2019 UPDATE: COSPONSORED BY AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY, THE OBESITY SOCIETY, AMERICAN SOCIETY FOR METABOLIC & BARIATRIC SURGERY, OBESITY MEDICINE ASSOCIATION, AND AMERICAN SOCIETY OF ANESTHESIOLOGISTS - EXECUTIVE SUMMARY. *Endocr Pract*, 25(12), 1346-1359. <https://doi.org/10.4158/gl-2019-0406>
- Mechanick, J. I., Youdim, A., Jones, D. B., Garvey, W. T., Hurley, D. L., McMahon, M. M., Heinberg, L. J., Kushner, R., Adams, T. D., Shikora, S., Dixon, J. B., & Brethauer, S. (2013). Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocr Pract*, 19(2), 337-372. <https://doi.org/10.4158/ep12437.gl>
- O'Kane, M., Parretti, H. M., Pinkney, J., Welbourn, R., Hughes, C. A., Mok, J., Walker, N., Thomas, D., Devin, J., Coulman, K. D., Pinnock, G., Batterham, R. L., Mahawar, K. K., Sharma, M., Blakemore, A. I., McMillan, I., & Barth, J. H. (2020). British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery—2020 update. *Obesity Reviews*, 21(11), e13087. <https://doi.org/10.1111/obr.13087>
- Oberley, M. J., & Yang, D. T. (2013). Laboratory testing for cobalamin deficiency in megaloblastic anemia. *Am J Hematol*, 88(6), 522-526. <https://doi.org/10.1002/ajh.23421>
- Oh, R., & Brown, D. L. (2003). Vitamin B12 deficiency. *Am Fam Physician*, 67(5), 979-986. <http://dx.doi.org/>
- Parrott, J., Frank, L., Rabena, R., Craggs-Dino, L., Isom, K. A., & Greiman, L. (2017). American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. *Surg Obes Relat Dis*, 13(5), 727-741. <https://doi.org/10.1016/j.soard.2016.12.018>
- Pratt, J. S. A., Browne, A., Browne, N. T., Bruzoni, M., Cohen, M., Desai, A., Inge, T., Linden, B. C., Mattar, S. G., Michalsky, M., Podkameni, D., Reichard, K. W., Stanford, F. C., Zeller, M. H., & Zitsman, J. (2018). ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. *Surg Obes Relat Dis*, 14(7), 882-901. <https://doi.org/10.1016/j.soard.2018.03.019>

- Rogne, T., Tielemans, M. J., Chong, M. F., Yajnik, C. S., Krishnaveni, G. V., Poston, L., Jaddoe, V. W., Steegers, E. A., Joshi, S., Chong, Y. S., Godfrey, K. M., Yap, F., Yahyaoui, R., Thomas, T., Hay, G., Hogeveen, M., Demir, A., Saravanan, P., Skovlund, E., Martinussen, M. P., Jacobsen, G. W., Franco, O. H., Bracken, M. B., & Risnes, K. R. (2017). Associations of Maternal Vitamin B12 Concentration in Pregnancy With the Risks of Preterm Birth and Low Birth Weight: A Systematic Review and Meta-Analysis of Individual Participant Data. *Am J Epidemiol*, *185*(3), 212-223. <https://doi.org/10.1093/aje/kww212>
- Rozmarič, T., Mitulović, G., Konstantopoulou, V., Goeschl, B., Huemer, M., Plecko, B., Spenger, J., Wortmann, S. B., Scholl-Bürgi, S., Karall, D., Greber-Platzer, S., & Zeyda, M. (2020). Elevated Homocysteine after Elevated Propionylcarnitine or Low Methionine in Newborn Screening Is Highly Predictive for Low Vitamin B12 and Holo-Transcobalamin Levels in Newborns. *Diagnostics (Basel)*, *10*(9). <https://doi.org/10.3390/diagnostics10090626>
- Rubio-Tapia, A., Hill, I. D., Kelly, C. P., Calderwood, A. H., & Murray, J. A. (2013). ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol*, *108*(5), 656-676; quiz 677. <https://doi.org/10.1038/ajg.2013.79>
- Sangle, P., Sandhu, O., Aftab, Z., Anthony, A. T., & Khan, S. (2020). Vitamin B12 Supplementation: Preventing Onset and Improving Prognosis of Depression. *Cureus*, *12*(10), e11169. <https://doi.org/10.7759/cureus.11169>
- Schroder, T. H., Tan, A., Mattman, A., Sinclair, G., Barr, S. I., Vallance, H. D., & Lamers, Y. (2019). Reference intervals for serum total vitamin B12 and holotranscobalamin concentrations and their change points with methylmalonic acid concentration to assess vitamin B12 status during early and mid-pregnancy. *Clin Chem Lab Med*. <https://doi.org/10.1515/cclm-2018-1337>
- Sobczynska-Malefora, A., Gorska, R., Pelisser, M., Ruwona, P., Witchlow, B., & Harrington, D. J. (2014). An audit of holotranscobalamin ("Active" B12) and methylmalonic acid assays for the assessment of vitamin B12 status: application in a mixed patient population. *Clin Biochem*, *47*(1-2), 82-86. <https://doi.org/10.1016/j.clinbiochem.2013.08.006>
- Stabler, S. P. (2013). Clinical practice. Vitamin B12 deficiency. *N Engl J Med*, *368*(2), 149-160. <https://doi.org/10.1056/NEJMcp1113996>
- Willis, C. D., Elshaug, A. G., Milverton, J. L., Watt, A. M., Metz, M. P., & Hiller, J. E. (2011). Diagnostic performance of serum cobalamin tests: a systematic review and meta-analysis. *Pathology*, *43*(5), 472-481. <https://doi.org/10.1097/PAT.0b013e3283486435>
- Wolffebuttel, B. H. R., Heiner-Fokkema, M. R., Green, R., & Gans, R. O. B. (2020). Relationship between serum B12 concentrations and mortality: experience in NHANES. *BMC Medicine*, *18*(1), 307. <https://doi.org/10.1186/s12916-020-01771-y>
- Yager, J., Devlin, M., Halimi, K., Herzog, D., Mitchell, J., Powers, P., & Zerbe, K. (2006). Treatment of patients with eating disorders, third edition. American Psychiatric Association. *Am J Psychiatry*, *163*(7 Suppl), 4-54. <https://www.ncbi.nlm.nih.gov/pubmed/?term=PRACTICE+GUIDELINE+FOR+THE+Treatment+of+Patients+With+Eating+Disorders+Third+Edition>
- Yetim, A., Aygun, E., Yetim, C., Ucar, A., Karakas, Z., Gokcay, G., Demirkol, M., Omer, B., Gokcay, G., Bas, F., Erginoz, E., & Dagoglu, T. (2019). Measurement of serum vitamin B12-related metabolites in newborns: implications for new cutoff values to detect B12 deficiency. *J Matern Fetal Neonatal Med*, 1-9. <https://doi.org/10.1080/14767058.2019.1633301>
- Zeuschner, C. L., Hokin, B. D., Marsh, K. A., Saunders, A. V., Reid, M. A., & Ramsay, M. R. (2013). Vitamin B(1)(2) and vegetarian diets. *Med J Aust*, *199*(4 Suppl), S27-32. <http://dx.doi.org/>





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## **IX. Revision History**

<b>Revision Date</b>	<b>Summary of Changes</b>
01/01/2023	Initial Effective Date