Vitamin B12 and Methylmalonic Acid Testing AHS – G2014

Description of Procedure or Service

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 often can be reversed by early diagnosis and prompt treatment (Oh & Brown, 2003).

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

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

Policy

BCBSNC will provide coverage for Vitamin B12 and Methylmalonic Acid Testing when it is determined the medical criteria or reimbursement guidelines below are met

Benefits Application

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

When Vitamin B12 and Methylmalonic Acid Testing is covered

1. Reimbursement for vitamin B12 testing is allowed in individuals being evaluated for clinical manifestations of Vitamin B12 deficiency including:
   A. Cutaneous
      1. Hyperpigmentation
      2. Jaundice
      3. Vitiligo
   B. Gastrointestinal
      1. Glossitis
   C. Hematologic
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1. Anemia (macrocytic, megaloblastic)
2. Leukopenia
3. Pancytopenia
4. Thrombocytopenia
5. Thrombocytosis

D. Neuropsychiatric
1. Areflexia
2. Cognitive impairment (including dementia-like symptoms and acute psychosis)
3. Gait abnormalities
4. Irritability
5. Loss of proprioception and vibratory sense
6. Olfactory impairment
7. Peripheral neuropathy

2. Reimbursement for vitamin B12 testing is allowed when performed no sooner than 3 months after initiation of therapy for individuals undergoing treatment for vitamin B12 deficiency.
3. Reimbursement for screening for Vitamin B12 deficiency is allowed for individuals with one or more of the following risk factors:
   A. Decreased ileal absorption
      1. Crohn disease
      2. Ileal resection
      3. Tapeworm infection
   B. Decreased intrinsic factor
      1. Atrophic gastritis
      2. Pernicious anemia
      3. Postgastrectomy syndrome
   C. Genetic
      1. Transcobalamin II deficiency
   D. Inadequate intake
      1. Alcohol abuse
      2. Patients older than 75 years or elderly individuals being evaluated for dementia
      3. Vegans or strict vegetarians (including exclusively breastfed infants of vegetarian/vegan mothers)
      4. Eating disorders
   E. Prolonged medication use
      1. Histamine H2 blocker use for more than 12 months
      2. Metformin use for more than four months
      3. Proton pump inhibitor use for more than 12 months
4. Reimbursement for methylmalonic acid testing is allowed 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. Reimbursement for methylmalonic acid testing is allowed for the evaluation of inborn errors of metabolism, which is out of scope for this policy.

When Vitamin B12 and Methylmalonic Acid Testing is not covered

Reimbursement is not allowed for screening for Vitamin B12 deficiency in healthy, asymptomatic individuals.

Reimbursement is not allowed for homocysteine testing for the confirmation of vitamin B12 deficiency.
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Reimbursement is not allowed for holotranscobalamin testing for the screening, testing or confirmation of vitamin B12 deficiency.

**Policy Guidelines**

Vitamin B12 cannot be synthesized by human cells (Schrier, 2017), rather is obtained from animal derived dietary sources such as meat, eggs and dairy products (Hunt, Harrington, & Robinson, 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 a minority of cases and vitamin B12 deficiency now occurs most often due to malabsorption (Schrier, 2017). Reflecting this, 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. Whereas 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 (Langan & Goodbred, 2017): decreased ileal absorption (Crohn disease, ileal resection, tapeworm infection), decreased intrinsic factor (atrophic gastritis, pernicious anemia, postgastrectomy 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).

Vitamin B12 plays an essential role in nucleic acid synthesis, and deficiency can result in cell cycle arrest in the S phase or apoptosis (Green, 2017) and ultimately bone marrow failure and demyelinating nervous system disease (Stabler, 2013). Clinical manifestations vary in their presence and severity (Langan & Goodbred, 2017) from mild fatigue to severe neurologic impairment. Mild deficiency can present as fatigue and anemia, but an absence of neurological features. Moderate deficiency may include an 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. Early detection and correction of vitamin B12 deficiency with supplementation prevents progression to macrocytic anemia, elevated homocysteine, potentially irreversible peripheral neuropathy, memory loss and other cognitive deficits (Sobczynska-Malefora et al., 2014).

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). 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). Elevated levels of downstream metabolites, methylmalonic acid and homocysteine 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). Serum holotranscobalamin may be a better indicator of B12-deficiency states than serum cobalamin because it represents the biologically active fraction of cobalamin in humans and may be depleted first in subclinical cobalamin deficiency. Holotranscobalamin 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).

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Pitfalls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95–97%</td>
<td></td>
<td>Elevated levels seen with:</td>
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</tbody>
</table>
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<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum total cobalamin (&lt;200 pg/mL)</td>
<td>Uncertain, possibly &lt;80%</td>
<td>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 levels seen with: Renal insufficiency Hypovolemia Congenital metabolic defects Amyotrophic lateral sclerosis Elevated levels seen with: Folate or pyridoxine deficiency Renal insufficiency Hypovolemia Hypothyroidism Psoriasis Congenital metabolic defects Neurodegenerative disease Malignancy Medications Levels may be affected by: Liver disease Macrophage activation Autoantibodies</td>
</tr>
<tr>
<td>Elevated serum methylmalonic acid</td>
<td>&gt;95%</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Elevated serum homocysteine</td>
<td>&gt;95%</td>
<td>Uncertain, less specific than methylmalonic acid</td>
</tr>
<tr>
<td>Decreased serum holotranscobalamin</td>
<td>Similar to total cobalamin</td>
<td>Uncertain</td>
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### Applicable Federal Regulations
N/A

### Guidelines and Recommendations

**American Academy of Family Physicians (Langan & Goodbred, 2017)**
The American Academy of Family Physician 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.

The recommended laboratory evaluation for patients with suspected vitamin B12 deficiency includes a complete blood count and serum vitamin B12 level. 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.
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American College of Gastroenterology (Rubio-Tapia, Hill, Kelly, Calderwood, & Murray, 2013)
People with newly diagnosed celiac disease should undergo testing and treatment for micronutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12 (Conditional recommendation, low level of evidence)

American Academy of Neurology (Knopman et al., 2001)
The American Academy of Neurology recommends serum vitamin B12 testing as part of the assessment of elderly patients with dementia.

British Committee for Standards in Haematology (Devalia, Hamilton, & Molloy, 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.

British Columbia Medical Association (Committee, 2013)
The British Columbia Medical Association recommends 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 Endocrinologists/the American College of Endocrinology and the Obesity Society (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)

American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery (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).

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

Applicable service codes: 82607, 83921, 84999

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


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assessment of vitamin B12 status: application in a mixed patient population. *Clin Biochem, 47*(1-2), 82-86. doi:10.1016/j.clinbiochem.2013.08.006


Specialty Matched Consultant Advisory Panel review 02/2020

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>1/1/2019</td>
<td>New policy developed. BCBSNC will provide coverage for Vitamin B12 and Methylmalonic Acid Testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)</td>
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<tr>
<td>10/29/19</td>
<td>Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)</td>
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<td>02/11/20</td>
<td>Reviewed by Avalon 4th Quarter CAB. When Covered section updated to include bullet 3D4 - Eating disorders. (eel)</td>
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<tr>
<td>03/10/20</td>
<td>Specialty Matched Consultant Advisory Panel 02/19/2020. No change to policy statement. (eel)</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.