Corporate Medical Policy

Vitamin D Testing AHS – G2005

Description of Procedure or Service

Vitamin D is a precursor to steroid hormones and plays a key role in calcium absorption and mineral metabolism. Vitamin D promotes enterocyte differentiation and the intestinal absorption of calcium. Other effects include a lesser stimulation of intestinal phosphate absorption, suppression of parathyroid hormone (PTH) release, regulation of osteoblast function, osteoclast activation, and bone resorption (Pazirandeh & Burns, 2017).

Vitamin D is present in nature in two major forms. Ergocalciferol, or vitamin D$_2$, is found in fatty fish (e.g., salmon and tuna) and egg yolks, although very few foods naturally contain significant amounts of vitamin D. Cholecalciferol, or vitamin D$_3$, is synthesized in the skin via exposure to ultraviolet radiation present in sunlight. Some foods are also fortified with vitamin D, most notably milk and cereals (Sahota, 2014).

***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 D 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 D Testing is covered

1. Reimbursement for 25-hydroxyvitamin D serum testing is allowed in individuals with an underlying disease or condition which is specifically associated with vitamin D deficiency or decreased bone density (see Guideline 1 below).
2. Reimbursement for testing for D2 and D3 fractions of 25-hydroxyvitamin D is allowed as part of the total 25-hydroxyvitamin D analysis.
3. Reimbursement for repeat testing for serum 25-hydroxyvitamin D is allowed in individuals who have documented vitamin D deficiency, at least 12 weeks after initiation of vitamin D supplementation therapy.
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A. Repeat testing for monitoring of supplementation therapy should not exceed 2 testing instances per year until the therapeutic goal is achieved.

B. Once therapeutic range has been reached, annual testing, meets coverage criteria.

4. Reimbursement for 1,25-dihydroxyvitamin D serum testing is allowed in the evaluation or treatment of conditions that are associated with defects in vitamin D metabolism (see Guideline 2 below).

**Guideline 1**: Indications that support coverage criteria for serum measurement of 25 hydroxy-vitamin D are as follows:

A. Biliary cirrhosis and other specified disorders of the biliary tract
B. Blind loop syndrome
C. Celiac Disease
D. Coronary artery disease in individuals where risk of disease progression is being considered against benefits of chronic vitamin D and calcium therapy
E. Dermatomyositis
F. Hypercalcemia, hypocalcemia or other disorders of calcium metabolism
G. Hyperparathyroidism or hypoparathyroidism
H. Hypervitaminosis of vitamin D
I. Individuals receiving hyperalimentation
J. Intestinal malabsorption
K. Liver cirrhosis
L. Long term use of anticonvulsants, glucocorticoids and other medications known to lower vitamin D levels
M. Lymphoma
N. Malnutrition
O. Myalgia and other myositis not specified
P. Myopathy related to endocrine diseases
Q. Obesity
R. Osteogenesis imperfecta
S. Osteomalacia
T. Osteopetrosis
U. Osteoporosis
V. Pancreatic steatorrhea
W. Primary or miliary tuberculosis
X. Psoriasis
Y. Regional enteritis
Z. Renal, ureteral or urinary calculus
AA. Rickets
BB. Sarcoidosis
CC. Stage III-V Chronic Kidney Disease and End Stage Renal Disease
DD. Systemic lupus erythematosus

**Guideline 2**: Indications that support coverage criteria for serum testing of 1,25 dihydroxy-vitamin D are as follows:

A. Disorders of calcium metabolism
B. Familial hypophosphatemia
C. Fanconi syndrome
D. Hyperparathyroidism or hypoparathyroidism
E. Individuals receiving hyperalimentation
F. Neonatal hypocalcemia
G. Osteogenesis imperfecta
H. Osteomalacia
I. Osteopetrosis
J. Primary or miliary tuberculosis
K. Renal, ureteral or urinary calculus
L. Rickets
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M. Sarcoidosis  
N. Stage III-V Chronic Kidney Disease and End Stage Renal Disease

**When Vitamin D Testing is not covered**

Reimbursement is not allowed for 1,25-dihydroxyvitamin D serum testing for and screening of vitamin D deficiency.

Reimbursement is not allowed for routine screening for vitamin D deficiency with serum testing.

**Policy Guidelines**

The vitamin D that is consumed or formed in the skin must then be activated, via addition of hydroxyl groups, in order to be used in metabolic processes. Two forms of activated vitamin D are found in human circulation: 25-hydroxyvitamin D (calcidiol or 25OHD) and 1,25-dihydroxyvitamin D (calcitriol). 25-hydroxyvitamin D is the predominant and most stable form, but 1,25-dihydroxyvitamin D is the metabolically active form. The initial activation step occurs in the liver, where 25OHD is synthesized, and the second hydroxyl group is added in the kidney, creating the fully activated 1,25-dihydroxy form (Sahota, 2014).

25OHD has a half-life of 15 days in the circulation, whereas 1,25-dihydroxyvitamin D has a much shorter, 15 hour, circulating half-life; consequently, measurement of serum 25OHD is generally accepted as the preferred test to evaluate an individual’s vitamin D status despite lack of standardization between methods and laboratories (Glendenning & Inderjeeth, 2012; Sahota, 2014; Scott et al., 2015).

Vitamin D deficiency typically is defined as a serum 25OHD level less than 20 ng/ml, and certain organizations consider <30 ng/ml as insufficient. Trials of vitamin D supplementation (Chapuy et al., 2002; B. Dawson-Hughes, Harris, Krall, & Dallal, 1997; Sanders et al., 2010; Trivedi, Doll, & Khaw, 2003) and the Institute of Medicine (IOM) systematic review (Ross et al., 2011) recommend maintaining the serum 25OHD concentration between 20 and 40 ng/mL (50 to 100 nmol/L), whereas other experts favor maintaining 25OHD levels between 30 and 50 ng/mL (75 to 125 nmol/L). Experts agree that levels lower than 20 ng/mL are suboptimal for skeletal health. The optimal serum 25OHD concentrations for extraskeletal health have not been established (Bess Dawson-Hughes, 2017). Approximately 15% of the U.S. pediatric population suffers from either vitamin D deficiency or insufficiency. Limited sun exposure and the use of sunscreen that prohibits creation of vitamin D by sunlight radiation in the skin contribute to low vitamin D levels (Madhusmita, 2018). Also, “vitamin D deficiency has been reported in dark-skinned immigrants from warm climates to cold climates in North America and Europe (Drezner, 2017).” For example, a study by Awumey and colleagues found that Asian Indians who immigrated to the U.S. still were considered vitamin D insufficient or deficient even after the administration of 25OHD. “Thus, Asian Indians residing in the U.S. are at risk for developing vitamin D deficiency, rickets, and osteomalacia (Awumey, Mitra, Hollis, Kumar, & Bell, 1998).”

Vitamin D deficiency has been associated with important short and long-term health effects such as rickets, osteomalacia and the risk of osteoporosis (Sahota, 2014). Rickets in children can result in skeletal deformities. In adults, osteomalacia, can result in muscular weakness in addition to weak bones and osteoporosis, creating increased risk for falls and fractures (Granado-Lorencio, Blanco-Navarro, & Perez-Sacristan, 2016).

A role for vitamin D has been suggested in several other conditions and metabolic processes, such as cancer, cardiovascular disease, hypertension, diabetes, and preeclampsia, as well as others. However, conclusive evidence for vitamin D’s role in these conditions is not available (Aspray et al., 2014; Ross et al., 2011).
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Certain other conditions may impact an individual’s ability to absorb or activate vitamin D, thereby resulting in vitamin D deficiency. These include, but are not limited to, celiac disease, liver cirrhosis, chronic kidney disease, and bariatric surgery. Vitamin D is fat soluble, so anything that impacts fat absorption or storage may have an effect on circulating vitamin D levels (Drezner, 2017).

According to the Institute of Medicine (IOM), routine dietary supplementation with vitamin D is recommended for most individuals. The IOM recommends a dietary allowance of 600 IU for males and females 1-70 years of age and 800 IU for adults 71 years and older (Ross et al., 2011), although these recommendations have been met with some criticism as being too low to adequately impact vitamin D levels in some individuals. The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D3 and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women (Moyer, 2013).

Vitamin D toxicity is very rare and occurs only when levels of 25 hydroxy-vitamin D as >500 nmol/L [>200 ng/mL], well above the level considered to be sufficient. Vitamin D toxicity may cause hypercalciuria, hypercalcemia, renal stones, renal calcification with renal failure (Moyer, 2013).

Analytical Validity
Serum or plasma concentration of 25OHD can be measured using a number of assays, including ELISA, radioimmunoassay (RIA), mass spectrometry, and HPLC. Assays using LC-MS/MS can differentiate between D2 and D3. These methods “can individually quantitate and report both analytes, in addition to providing a total 25-hydroxyvitamin D concentration (Krasowski, 2011).” RIA-based assays for 25OHD can have intra- and interassay variations of 8 – 15%, and the IDS-developed RIA has a reported 100% specificity for D3 and 75% for D2 (Holick, 2009). “For most HPLC and LC-MS/MS methods extraction and procedural losses are corrected for by the inclusion of an internal standard which, in part, may account for higher results compared to immunoassay (Wallace, Gibson, de la Hunty, Lamberg-Allardt, & Ashwell, 2010).” Even though LC-MS/MS is considered to be the gold standard of measuring 25OHD and its metabolites, only approximately 20% of labs report using it (Avenell, Bolland, & Grey, 2018). One study reports that 46% of samples measured using LC-MS/MS were classified as vitamin D-deficient whereas, when the samples were measured using an immunoassay method, 69% were vitamin D-deficient (<30 nmol/L) (Annema, Nowak, von Eckardstein, & Saleh, 2018).

Clinical validity and utility
A retrospective study of 32,363 tests of serum 25OHD found that “A significant proportion of the requests was unjustified by clinical or biochemical criteria”, and “that clinical and biochemical criteria may be necessary to justify vitamin D testing but not sufficient to indicate the presence of vitamin D deficiency” (Granado-Lorencio et al., 2016).

The table below lists the criteria used for vitamin D testing in the study by Granado-Lorencio et al.
A meta-analysis study by Bolland and colleagues of 81 randomized controlled trials with a combined total of 53,537 participants measured the effects, if any, vitamin D supplementation had on fractures, falls, and bone density. They found that there was no clinically relevant difference in bone mineral density at any site between the control and experimental groups; moreover, “for total fracture and falls, the effect estimate lay within the futility boundary for relative risks of 15%, 10%, 7.5%, and 5% (total fracture only), suggesting that vitamin D supplementation does not reduce fractures or falls by these amounts... Our findings suggest that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. There were no differences between the effects of higher and lower doses of vitamin D. There is little justification to use vitamin D supplements to maintain or improve musculoskeletal health. This conclusion should be reflected in clinical guidelines (Bolland, Grey, & Avenell, 2018).”

State and Federal Regulations, as applicable
A search of the FDA Device database on 10/25/2018 for “vitamin D” yielded 39 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.

Guidelines and Recommendations

The Endocrine Society (Holick et al., 2011)
The Endocrine Society recommends serum testing of 25-hydroxyvitamin D for evaluation of vitamin D status in individuals who are at risk of deficiency, including those with osteoporosis, obesity, or a history of falls. 1,25-dihydroxyvitamin D testing is not recommended for screening of at-risk individuals, due to its very short half-life in circulation, but is recommended for a few conditions in which formation of the 1,25-dihydroxy form may be impaired (Holick et al., 2011).

Institute of Medicine (Ross et al., 2011)
After an extensive evaluation of published studies and testimony from investigators, the Institute of Medicine determined that supplementation with vitamin D is appropriate; however, guidelines regarding the use of serum markers of vitamin D status for medical management of individual
patients and for screening were beyond the scope of the Committee’s charge, and evidence-based consensus guidelines are not available (Ross et al., 2011).

**National Osteoporosis Society (Aspray et al., 2014)**
The National Osteoporosis Society recommends the measurement of serum 25 (OH) vitamin D (25OHD) to estimate vitamin D status in the following clinical scenarios: bone diseases that may be improved with vitamin D treatment; bone diseases, prior to specific treatment where correcting vitamin D deficiency is appropriate; musculoskeletal symptoms that could be attributed to vitamin D deficiency. The guideline also states that routine vitamin D testing is unnecessary where vitamin D supplementation with an oral antiresorptive treatment is already planned and sets the following serum 25OHD thresholds: <30 nmol/l is deficient; 30-50 nmol/l may be inadequate in some people; >50 nmol/l is sufficient for almost the whole population (Aspray et al., 2014).

**United States Preventive Services Task Force (LeFevre, 2015; Moyer, 2013; USPSTF, 2018)**
The USPSTF recently issued the guideline *Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults*, which recommends the following:

“The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in community-dwelling, asymptomatic men and premenopausal women. (I statement) The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. (I statement) The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. (D recommendation) These recommendations do not apply to persons with a history of osteoporotic fractures, increased risk for falls, or a diagnosis of osteoporosis or vitamin D deficiency (USPSTF, 2018).”

In the 2013 update to the USPSTF recommendation concerning the use of vitamins for the primary prevention of cardiovascular disease and cancer, they concluded that there was insufficient evidence to assess the efficacy of multivitamins, including those containing vitamin D, in the prevention of cardiovascular disease or cancer (Moyer, 2013).

The USPSTF published their recommendation concerning screening of vitamin D deficiency in asymptomatic community-dwelling, nonpregnant adults in 2015. “The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. (I statement) (LeFevre, 2015)” It should be noted that this guideline is currently undergoing review in 2018.

**American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery (Mechanick et al., 2013)**
Minimal daily nutritional supplementation for patients with RYGB and LSG all in chewable form initially should be at least 3000 international units of vitamin D (titrated to therapeutic 25-hydroxyvitamin D levels >30 ng/ml). Minimal daily nutritional supplementation for patients with LAGB should include at least 3000 international units of vitamin D (titrated to therapeutic 25-dihydroxyvitamin D levels). “Alternatively, in lieu of routine screening with relatively costly biochemical testing, the above routine micronutrient supplementation may be initiated preoperatively (Mechanick et al., 2013).”

**American Academy of Pediatrics (Golden & Abrams, 2014)**
“Evidence is insufficient to recommend universal screening for vitamin D deficiency... In the absence of evidence supporting the role of screening healthy individuals at risk for vitamin D deficiency in reducing fracture risk and the potential costs involved, the present AAP report...
advise screening for vitamin D deficiency only in children and adolescents with conditions associated with reduced bone mass and/or recurrent low-impact fractures. More evidence is needed before recommendations can be made regarding screening of healthy black and Hispanic children or children with obesity. The recommended screening is measuring serum 25-OH-D concentration, and it is important to be sure this test is chosen instead of measurement of the 1,25-OH$_2$-D concentration, which has little, if any, predictive value related to bone health (Golden & Abrams, 2014).”

American College of Obstetricians and Gynecologists (ACOG, 2011) (and reaffirmed in 2017)
“At this time, there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency. For pregnant women thought to be at increased risk of vitamin D deficiency, maternal serum 25-hydroxyvitamin D levels can be considered and should be interpreted in the context of the individual clinical circumstance (ACOG, 2011).”

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: 82306, 82652, 0038U

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

Scientific Background and Reference Sources


Chapuy, M. C., Pamphile, R., Paris, E., Kempf, C., Schlichting, M., Arnaud, S., Meunier, P. J. (2002). Combined calcium and vitamin D3 supplementation in elderly women: confirmation of
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reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study.
Osteoporos Int, 13(3), 257-264. doi:10.1007/s001980200023


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Specialty Matched Consultant Advisory Panel review 02/2020

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Update Information</th>
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<tbody>
<tr>
<td>1/1/19</td>
<td>New policy developed. BCBSNC will provide coverage for Vitamin D Testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. 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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<tr>
<td>02/11/20</td>
<td>Coding section updated per Avalon Q4 CAB review. (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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