

Medical Coverage Policy



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Vitamin D Testing

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Related Coverage Resources

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Overview

This Coverage Policy addresses serum Vitamin D testing.

Coverage Policy

Vitamin D testing is considered medically necessary in a non-pregnant individual age 18 – 64 years for any of the following:

- condition or medical diagnosis associated with Vitamin D deficiency (See Appendix A)
- previously documented Vitamin D deficiency
- known or suspected excessive Vitamin D blood levels (i.e., toxicity)

Vitamin D testing for any other indication including screening in the general population is considered not medically necessary.

Vitamin D testing (CPT® 82306) more frequently than twice in 12 rolling months is considered not medically necessary for any diagnosis other than chronic kidney disease (CKD) or intestinal malabsorption.

Vitamin D testing utilizing both CPT® 82306 and CPT® 82652 in combination is considered not medically necessary.

General Background

Vitamin D is a fat-soluble vitamin. Very few foods naturally contain Vitamin D (fatty fish and eggs are the exception), so Vitamin D is obtained primarily through fortified foods or supplements and dermal synthesis from exposure to sunlight. Vitamin D has two forms, ergocalciferol (Vitamin D₂) and cholecalciferol (Vitamin D₃), and several metabolites. Estimates of Vitamin D requirements vary and depend in part upon sun exposure and the standards used to define a deficient state. In 2010, the Institute of Medicine (IOM) released a report on dietary intake requirements for calcium and Vitamin D. Once an individual has been shown to be Vitamin D deficient, further testing may be indicated only to ensure adequate replacement has been accomplished.

25(OH)D and 1,25(OH)₂D

Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D is converted enzymatically:

- in the liver to 25-hydroxyvitamin D (25[OH]D), the major circulating form of Vitamin D; and then
- in the kidney to 1,25-dihydroxyvitamin D (1,25[OH]₂D), the active form of Vitamin D.

The concentration of 25(OH)D is almost 1000-fold that of 1,25(OH)₂D, and the half-life of 25(OH)D is much longer, implying that its concentration is more stable.

The most common type of vitamin D deficiency is 25-OH vitamin D. A much smaller percentage of 1, 25-dihydroxy vitamin D deficiency exists; mostly, in those with renal disease. Although it is not the active form of the hormone, 25-OH vitamin D is more commonly measured. It better reflects the sum total of vitamin D produced endogenously and absorbed from the diet than does the level of the active hormone 1, 25-dihydroxy vitamin D. Deficiency of 1, 25-dihydroxy vitamin D, which is present at much lower concentrations, does not necessarily reflect deficiency of 25-OH vitamin D. Its measurement should be limited to specific diseases such as acquired and inherited disorders in the metabolism of 25(OH)D and phosphate, including chronic kidney disease.

25(OH)D (CPT® code 82306)

The best laboratory indicator of Vitamin D adequacy is the serum 25(OH)D concentration. It is the measurement of choice to diagnose Vitamin D deficiency and to assess Vitamin D status. The lower limit of normal for 25(OH)D levels varies depending on the geographic location and sunlight exposure of the reference population. There is no consensus on the optimal 25(OH)D concentration for skeletal or extraskeletal health. The IOM concluded that a serum 25(OH)D concentration of 20 ng/mL (50 nmol/L) is sufficient for most individuals. Other experts (Endocrine Society, National Osteoporosis Foundation, and American Geriatrics Society) suggest that a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults to minimize the risk of falls and fracture. Additionally, 25(OH)D measurements have had wide spread variation in the results. Serum 25-OH-D assays fall into two main categories: (1) those based on a separation step of chromatography, the most popular of which is liquid chromatography–tandem mass spectrometry (LC-MS/MS) and (2) nonchromatographic methods based on antibody or protein binding, such as radioimmunoassays.

Serum 25(OH)D should be assessed in persons at risk for Vitamin D deficiency or insufficiency. Vitamin D deficiency may result from:

- inadequate exposure to sunlight or intake of Vitamin D
- reduced absorption of Vitamin D (e.g., malabsorption* syndromes)
- medications or disorders that affect the metabolism of Vitamin D and phosphate (e.g., glucocorticoids, chronic kidney disease)
- resistance to the effects of Vitamin D

*Causes of malabsorption may include:

- diseases of the gallbladder, liver, or pancreas
- some conditions such as cystic fibrosis
- damage to the intestine from infection, inflammation, trauma, or surgery

- parasitic diseases
- certain congenital defects such as biliary atresia

Vitamin D Toxicity: Another reason to measure serum 25(OH)D is when there is a suspicion of excessive Vitamin D blood levels (toxicity). Vitamin D toxicity, also called hypervitaminosis D, is a rare but potentially serious condition. The main consequence of vitamin D toxicity is a buildup of calcium in your blood (hypercalcemia), which can cause nausea, vomiting, weakness, and frequent urination. More seriously, hypercalcemia can lead to vascular and tissue calcification, with subsequent damage to the heart, blood vessels, and kidneys. The use of supplements of both calcium (1,000 mg/day) and vitamin D (400 IU) by postmenopausal women was associated with a 17% increase in the risk of kidney stones over seven years in the Women's Health Initiative. A serum 25(OH)D concentration consistently >500 nmol/L (>200 ng/mL) is considered to be potentially toxic (National Institute of Health, 2018).

1,25(OH)2D (CPT® code 82652)

Serum 1,25(OH)2D is not suitable to assess Vitamin D status because it is kept within reference limits as long as possible by hormonal mechanisms (e.g., parathyroid hormone for stimulation and serum calcium and phosphate for suppression). Serum measurement of 1,25(OH)2D is useful in monitoring certain conditions, such as acquired and inherited disorders in the metabolism of 25(OH)D and phosphate, including chronic kidney disease, hereditary phosphate-losing disorders, oncogenic osteomalacia, pseudovitamin D-deficiency rickets, Vitamin D-resistant rickets, as well as chronic granuloma-forming disorders such as sarcoidosis and some lymphomas (Dawson-Hughes, et al., 2017; National Institute of Health, 2017; Merck Manual, 2016; Pazirandeh, et al., 2016; Enko, et al., 2015; Jones, 2015; Holick, et al., 2011; Lip, et al., 2007).

Testing – Literature Review

There is a paucity of evidence evaluating the benefit and harm of testing for Vitamin D. Peer-reviewed scientific literature primarily investigates the effects of Vitamin D supplementation, not testing. LeBlanc et al. (2015) conducted a systematic review for the U.S. Preventive Services Task Force (USPSTF) to assess the benefits and harms of Vitamin D screening in asymptomatic adults. LeBlanc et al. (2015) found “No study evaluated clinical outcomes or harms in persons screened versus not screened for Vitamin D deficiency”. Limited evidence in persons not known to have conditions associated with Vitamin D deficiency demonstrated that treating this deficiency with Vitamin D may be associated with decreased risk for death in institutionalized elderly adults and a reduction in the average number of falls but not fractures. The authors conclude that future research is needed to reduce assay variability; determine appropriate thresholds for Vitamin D deficiency; and clarify effects of screening, subsequent treatment, and the subpopulations most likely to benefit.

The Washington State Health Care Authority Health Technology Assessment Program (HTA) published a technology assessment on Vitamin D Screening and Testing in 2012. It was determined that no definitive conclusions can be drawn about the effectiveness of Vitamin D screening or testing since no trials have been conducted to directly assess the impact of screening or testing on health outcomes, patient behavior, or clinical decision making. However, for some populations and outcomes, an association between serum levels and health outcomes and/or a positive effect of supplementation on health outcomes has been demonstrated. Thus, Vitamin D screening has potential utility for identifying individuals who could benefit from the preventive or disease-modifying effects of supplementation in these clinical situations. Both Vitamin D screening/testing and Vitamin D supplementation are generally safe interventions.

Testing – Professional Societies/Organizations

Endocrine Society: The Endocrine Society Clinical Practice Guideline on Evaluation, Treatment, and Prevention of Vitamin D Deficiency (Holick, et al., 2011) makes the following recommendations specific to Vitamin D testing:

- Recommend screening for Vitamin D deficiency in individuals at risk for deficiency.
- Do not recommend population screening for Vitamin D deficiency in individuals who are not at risk.
- Recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate Vitamin D status in patients who are at risk for Vitamin D deficiency.
- Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter), and Vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (525–725 nmol/liter).

- Recommend against using the serum 1,25-dihydroxyvitamin D [1,25(OH)2D] assay for this purpose (patients at risk) and are in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of Vitamin D and phosphate metabolism.

Rationale/Evidence: There is no evidence demonstrating benefits of screening for Vitamin D deficiency at a population level. Such evidence would require demonstration of the feasibility and cost-effectiveness of such a screening strategy, as well as benefits in terms of important health outcomes. In the absence of this evidence, it is premature to recommend screening at large at this time.

Currently, 25(OH)D measurement is reasonable in groups of people at high risk for Vitamin D deficiency and in whom a prompt response to optimization of Vitamin D status could be expected (Holick et al., Table 2).

Indications for 25(OH)D measurement (candidates for screening) (Holick et al., Table 2):

- Rickets
- Osteomalacia
- Osteoporosis
- Chronic kidney disease
- Hepatic failure
- Malabsorption syndromes
 - Cystic fibrosis
 - Inflammatory bowel disease
 - Crohn's disease
 - Bariatric surgery
 - Radiation enteritis
- Hyperparathyroidism
- Medications
 - Antiseizure medications
 - Glucocorticoids
 - AIDS/HIV medications
 - Antifungals, e.g. ketoconazole
 - Cholestyramine
- African-American and Hispanic children and adults
- Pregnant and lactating women
- Older adults with history of falls
- Older adults with history of nontraumatic fractures
- Obese children and adults (BMI > 30 kg/m²)
- Granuloma-forming disorders
 - Sarcoidosis
 - Tuberculosis
 - Histoplasmosis
 - Coccidiomycosis
 - Berylliosis
- Some lymphomas

The Endocrine Society Clinical Practice Guideline on Pediatric Obesity-Assessment, Treatment, and Prevention (Styne, 2017) states the following re pediatric bariatric surgery: Vitamin deficiencies are common, including deficiencies of vitamins B12, B1, and folate, as Roux-en-Y gastric bypass and vertical sleeve gastrectomy both reduce the surface of the distal portion of the stomach, resulting in inadequate secretion of intrinsic factor. Annual screening is recommended for patients at risk for developing vitamin deficiencies.

U.S. Preventive Services Task Force (USPSTF): The USPSTF Final Recommendation Statement Vitamin D Deficiency: Screening (November 2014) states:

- For community-dwelling, non-pregnant, asymptomatic adults age 18 years and older: 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. Grade I – Insufficient.

This recommendation applies to community-dwelling, nonpregnant adults aged 18 years or older who are seen in primary care settings and are not known to have signs or symptoms of Vitamin D deficiency or conditions for which Vitamin D treatment is recommended. This recommendation focuses on screening (that is, testing for Vitamin D deficiency in asymptomatic adults and treating those who are found to have a deficiency), which is different from other USPSTF recommendation statements on supplementation (that is, recommending preventive medication for patients at increased risk for a specific negative health outcome, such as falls, regardless of whether they have a deficiency).

The USPSTF recognizes that there is no consensus on how to define Vitamin D deficiency and does not endorse the use of a specific threshold to identify it. The evidence reviewed by the USPSTF used varying cut points. For the purposes of this recommendation statement, the term “Vitamin D deficiency” is used to reflect evidence from study populations generally representing total serum 25(OH)D levels of 75 nmol/L (30 ng/mL) or less or subpopulations of studies with levels less than 50 nmol/L (<20 ng/mL).

Harms: Screening may misclassify persons with a Vitamin D deficiency because of the uncertainty about the cut point for defining deficiency and the variability of available testing assays. Misclassification may result in overdiagnosis (which may lead to nondeficient persons receiving unnecessary treatment) or underdiagnosis (which may lead to deficient persons not receiving treatment).

Risk factors: Although there is not enough evidence to support screening for Vitamin D deficiency, some evidence suggests factors that may increase risk for Vitamin D deficiency. Persons with low Vitamin D intake, decreased Vitamin D absorption, and little or no sun exposure (for example, due to the winter season, high latitude, or physical sun avoidance) may be at increased risk for Vitamin D deficiency. Obesity and darker skin pigmentation may also be associated with low levels of total serum 25-(OH)D, but whether these factors reflect Vitamin D deficiency or increase the risk for adverse clinical outcomes is unclear. Some evidence suggests that older age and female sex may also be associated with increased risk for Vitamin D deficiency; however, these findings are inconsistent.

American Academy of Neurology (AAN): The Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2 (Schoser, et al., 2019) lists Vitamin D under Severe Symptoms, Endocrine and metabolic, under Recommendations to test for. The Consensus-based Care Recommendations for Children with Myotonic Dystrophy Type 1 (Johnson, et al., 2019) does not address Vitamin D testing.

American Academy of Pediatrics (AAP): The AAP Committee on Nutrition (Golden, et al., 2014) states that evidence is insufficient to recommend universal screening for Vitamin D deficiency. The AAP report advises 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-OH₂-D concentration, which has little, if any, predictive value related to bone health.”

American Association of Clinical Endocrinologists and American College of Endocrinology: These organizations have published a Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis (Camacho, et al., 2016) which includes the following recommendation: R9. Measure serum 25-hydroxyvitamin D (25[OH]D) in patients who are at risk for Vitamin D insufficiency, particularly those with osteoporosis (Grade B).

American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery (ASMBS), Obesity Medicine Association, and American Society of Anesthesiologists: The 2020 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 Clinical Practice Guidelines for the

Perioperative nutrition, metabolic, and nonsurgical support of patients undergoing Bariatric procedures recommends:

- Baseline and annual postoperative evaluation for vitamin D deficiency is recommended after Roux-en-Y gastric bypass, sleeve gastrectomy, or laparoscopic biliopancreatic diversion without or with duodenal switch (Recommendation 53) (Mechanick, 2020).

American Association of Clinical Endocrinologists and American College of Endocrinology: The AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity does not address Vitamin D testing (Garvey, 2016).

American Association of Endocrine Surgeons (AAES): The AAES Guideline for Definitive Management of Primary Hyperparathyroidism (Wilhelm, et al., 2016) includes the following recommendation: 1-1: The biochemical evaluation of suspected primary hyperparathyroidism should include serum total calcium, PTH, creatinine, and 25-hydroxyvitamin D levels (strong recommendation; moderate quality evidence).

American College of Cardiology/American Heart Association/Obesity Society: The American College of Cardiology/American Heart Association Guideline for the Management of Overweight and Obesity in Adults (Jensen, 2013) does not address vitamin D testing.

American College of Gastroenterology (ACG): The ACG Clinical Guideline Management of Crohn's Disease recommendations include "Routine laboratory investigation: Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition" (Lichtenstein, et al., 2018).

The ACG Clinical Guideline on Primary Sclerosing Cholangitis (Lindor, et al., 2015) provides this recommendation: Patients with advanced liver disease should be screened and monitored for fat-soluble vitamin deficiencies. Fat-soluble vitamin deficiencies can occur in late stages of primary sclerosing cholangitis when patient becomes jaundiced. Levels of Vitamins A, E, and D should be assessed in patients with advanced disease (Conditional recommendation, moderate quality of evidence).

The ACG Clinical Guideline on the Diagnosis and Management of Celiac Disease (Rubio-Tapia, et al., 2013) recommends: 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 College of Obstetricians and Gynecologists (ACOG): The ACOG Committee Opinion on Vitamin D screening and supplementation during pregnancy (2011, reaffirmed 2019) states that 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.

American College of Physicians: The American College of Physicians Clinical Practice Guideline Update on Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women (Qaseem, et al., 2017) does not address testing for Vitamin D.

American College of Rheumatology (ACR): The ACR Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (Buckley, et al., 2017) does not address Vitamin D testing.

American Society for Metabolic and Bariatric Surgery (ASMBS): The ASMBS Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients (Parrott, et al., 2017) recommends routine pre- and post-weight loss surgery (WLS) vitamin D screening. The ASMBS states routine post-WLS screening refers to performing a nutrient assessment every 3–6 months in the first year and annually thereafter, unless otherwise specified.

National Osteoporosis Foundation (NOF): The NOF's Clinician's Guide to Prevention and Treatment of Osteoporosis (Cosman, et al., 2014) notes the following specific to Vitamin D testing:

- Consider the following diagnostic studies for secondary causes of osteoporosis:
 - serum 25-hydroxyvitamin D (25[OH]D)
- Since Vitamin D intakes required to correct Vitamin D deficiency are so variable among individuals, serum 25(OH)D levels should be measured in patients at risk of deficiency. Vitamin D supplements should be recommended in amounts sufficient to bring the serum 25(OH)D level to approximately 30 ng/ml (75 nmol/L) and a maintenance dose recommended to maintain this level, particularly for individuals with osteoporosis. Definition of Vitamin D insufficiency is serum 25-hydroxyvitamin D (25[OH]D) < 30 ng/ml (75 nmol/L).

Supplementation – Literature Review

The Agency for Healthcare Research and Quality (AHRQ) published a technology assessment (Newberry, et al., 2014) updating a previous technology assessment (Chung, et al., 2009) that assessed numerous factors related to Vitamin D. Data from nearly 250 new studies published between 2009 and 2013 was reviewed. The report concluded that it is not possible to specify a relationship between vitamin D and health outcomes other than bone health (National Institute of Health, 2018; Newberry, et al., 2014).

Theodoratou et al. (2014) conducted an assessment of the evidence across systematic reviews and meta-analyses of observational studies of plasma 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D concentrations and randomized controlled trials of vitamin D supplementation. A total of 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma Vitamin D concentrations and 87 meta-analyses of randomized controlled trials of Vitamin D supplementation were identified. The relation between Vitamin D and 137 outcomes has been explored, covering a wide range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases. The authors concluded that despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of Vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable.

The Vitamin D and Omega-3 Trial (VITAL) is a randomized, double-blind, placebo-controlled trial including 25,871 men who were 50 years of age or older and women who were 55 years of age or older (Manson, et al., (2019). Primary end points were invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes). Secondary end points included site-specific cancers, death from cancer, and additional cardiovascular events. Randomization to receive vitamin D3 (cholecalciferol) at a dose of 2000 IU per day or placebo took place from November 2011 through March 2014. The trial intervention ended as planned on December 31, 2017, which yielded a median follow-up of 5.3 years. Manson et al. (2019) reports the VITAL trial results of the comparison of vitamin D (n = 12,927) with placebo (n = 12,944). Cancer was diagnosed in 1617 participants (793 in the vitamin D group and 824 in the placebo group; p= 0.47). A major cardiovascular event occurred in 805 participants (396 in the vitamin D group and 409 in the placebo group; p= 0.69).

- Supplementation with vitamin D3 (at a dose of 2000 IU per day) did not lead to a significantly lower incidence of invasive cancer of any type or a composite of major cardiovascular events (myocardial infarction, stroke, and death from cardiovascular causes) than placebo.
- The intervention also did not lead to a lower incidence of total deaths from cancer or a lower incidence of breast, prostate, or colorectal cancer than placebo.
- The use of vitamin D did not lead to a significant difference in any of the secondary cardiovascular end points or in the rate of death from any cause in the overall cohort or in subgroups.
- It was reported that in both an analysis that excluded 1 year of follow-up and an analysis that excluded 2 years of follow-up, neither of which was specified in the protocol, the rate of death from cancer was significantly lower with vitamin D than with placebo (hazard ratio, 0.79, and hazard ratio, 0.75, respectively).

The authors concluded that supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo.

Cochrane reviews: Several recent Cochrane reviews address the following topics and general conclusions:

- Vitamin D for the management of multiple sclerosis (Jagannath, et al., 2018)
 - To date, very low-quality evidence suggests no benefit of vitamin D for patient-important outcomes among people with MS.

- Vitamin D appears to have no effect on recurrence of relapse, worsening of disability measured by the Expanded Disability Status Scale (EDSS), and MRI lesions.
- Effects on health-related quality of life and fatigue are unclear. Vitamin D at the doses and treatment durations used in the included trials appears to be safe, although available data are limited.
- Vitamin D in reducing the risk of severe asthma exacerbations (Martineau, et al., 2016)
 - People given Vitamin D experienced fewer asthma attacks needing treatment with oral steroids (high-quality evidence).
 - Vitamin D reduced the risk of attending hospital with an acute asthma attack (high-quality evidence).
 - Vitamin D had little or no effect on lung function or day-to-day asthma symptoms (high-quality evidence).
 - Vitamin D did not increase the risk of serious adverse events at the doses that were tested (moderate quality evidence).
- Vitamin D in chronic painful conditions (Straube, et al., 2015)
 - Found no consistent pattern that Vitamin D treatment was better than placebo for any chronic painful condition (low quality evidence).
- Vitamin D for prevention of mortality in healthy adults and adults in a stable phase of disease (Bjelakovic, et al., 2014)
 - Vitamin D3 may reduce mortality, showing that about 150 participants need to be treated over five years for one additional life to be saved.
 - Found comparable effects of Vitamin D3 in studies that included only women compared with studies including both women and men.
 - Vitamin D3 may decrease cancer mortality, showing a reduction in mortality of 4 per 1000 persons treated for five to seven years. Adverse effects included renal stone formation (seen for Vitamin D3 combined with calcium) and elevated blood levels of calcium (seen for both alfacalcidol and calcitriol).
 - A large number of study participants left the trials before completion, raising concerns regarding the validity of the results.

Numerous studies and meta-analyses evaluating Vitamin D supplementation have been published. Some of the areas analyzed include:

- atopic dermatitis
- blood pressure
- bone health
- cancer mortality
- cardiovascular mortality
- COPD
- Crohn's disease
- dementia
- diabetes mellitus
- non-alcoholic fatty liver disease
- obesity
- pancreatitis
- postpartum depression
- preterm birth
- respiratory tract infections
- rheumatic diseases

Supplementation – Professional Societies/Organizations

Endocrine Society: The Endocrine Society Clinical Practice Guideline on Evaluation, Treatment, and Prevention of Vitamin D Deficiency (Holick, et al., 2011) states “We suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500 –2000 IU/d. In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at

least 6000 –10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of 3000 6000 IU/d.”

The Endocrine Society Clinical Practice Guideline on Treatment of Cushing's Syndrome (Nieman, et al., 2015) states they recommend “adequate calcium and vitamin D intake”.

U.S. Preventive Services Task Force (USPSTF): The USPSTF Final Recommendation Statement Vitamin D Deficiency: Screening (November 2014) found adequate evidence that treatment of asymptomatic vitamin D deficiency has no benefit on cancer, type 2 diabetes mellitus, risk for death in community-dwelling adults, and risk for fractures in persons not selected on the basis of being at high risk for fractures. The USPSTF found inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency on other outcomes, including psychosocial and physical functioning. Although the evidence is adequate for a few limited outcomes, the overall evidence on the early treatment of asymptomatic, screen-detected vitamin D deficiency in adults to improve overall health outcomes is inadequate. The USPSTF found no studies that evaluated the direct harms of screening for vitamin D deficiency. The USPSTF found adequate evidence that the harms of treatment of vitamin D deficiency are small to none. No studies reporting on the harms of treatment of vitamin D deficiency identified a significant increase in total adverse events, hypercalcemia, kidney stones, or gastrointestinal symptoms.

In April 2018, the USPSTF released recommendations on Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults:

- Men and premenopausal women:
 - 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 men and premenopausal women. (Grade Insufficient, The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.)
- For Postmenopausal women:
 - 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. (Grade D, The USPSTF recommends against the service.)
 - 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. (Grade Insufficient, The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.)

American Academy of Neurology (AAN): The AAN published a Practice Guideline titled Disease-modifying therapies for adults with multiple sclerosis (Rae-Grant, 2018). The AAN reviewed evidence on starting, switching, and stopping disease-modifying therapies (DMTs) for multiple sclerosis (MS) in people with clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and progressive forms of MS. The guideline addresses pharmaceutical therapies, not vitamin supplementation (Rae-Grant, et al., 2018).

American College of Rheumatology (ACR): The ACR Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (Buckley, et al., 2017) notes that optimizing calcium intake (1,000– 1,200 mg/day) and Vitamin D intake (600–800 IU/day; serum level \geq 20 ng/ml) as well as lifestyle modifications are conditionally recommended for all patients receiving glucocorticoid treatment.

The ACR Guideline for the Treatment of Rheumatoid Arthritis (Singh, et al., 2015) does not address Vitamin D testing or supplementation.

American Heart Association (AHA): The American Heart Association, American College of Cardiology, and American Geriatrics Society published a Scientific Statement on Knowledge Gaps in Cardiovascular Care of the Older Adult Population (Rich, et al., 2016). One of the Recommendations to Close Knowledge Gaps stated:

- Studies are needed to evaluate specific dietary patterns (e.g., sodium and potassium intake, fluid intake), as well as the role of dietary supplements (e.g., coenzyme Q10, Vitamin D) in older patients with

heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) and whether optimal intake of these and other nutrients varies as a function of age, renal function, and hepatic function.

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

- American Academy of Pediatrics – Section on Endocrinology: Avoid ordering Vitamin D concentrations routinely in otherwise healthy children, including children who are overweight or obese (October 2017).
- Endocrine Society: Don't routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function (October 2013)
- American Society for Clinical Pathology: Don't perform population based screening for 25-OH-Vitamin D deficiency (Last reviewed 2019)

Centers for Medicare & Medicaid Services (CMS)

- **National Coverage Determinations (NCD):** No applicable NCD found.
- **Local Coverage Determinations (LCDs):** Multiple LCDs found. Refer to the LCD table of contents link in the reference section.

Use Outside of the US

The National Institute for Clinical Excellence (NICE) Public Health Guideline [PH56] on Vitamin D: supplement use in specific population groups (updated August 2017) includes Recommendation 7: Only test vitamin D status if someone has symptoms of deficiency or is at very high risk. Health professionals should not routinely test people's vitamin D status unless:

- they have symptoms of deficiency
- they are considered to be at particularly high risk of deficiency (for example, they have very low exposure to sunlight)
- there is a clinical reason to do so (for example, they have osteomalacia or have had a fall)

The European Society for Pediatric Endocrinology examined the current global best practice in nutritional rickets and formulated evidence-based recommendations. The consensus document titled Global Consensus Recommendations on Prevention and Management of Nutritional Rickets (Munns, et al., 2016) makes the following statements specific to vitamin D testing:

- In healthy children, routine 25OHD screening is not recommended, and consequently, no specific 25OHD threshold for Vitamin D supplementation is targeted in this population.
- Screening for nutritional rickets should be based on clinical features, followed by radiographic confirmation of suspected cases. Population-based screening with serum 25OHD, serum alkaline phosphatase (ALP), or radiographs is not indicated.

NICE Clinical guideline [CG186] on Multiple Sclerosis in Adults: Management (Last updated November 2019) recommendations include: 'Do not offer vitamin D solely for the purpose of treating MS'.

- There were no direct measures of quality of life, which was considered the most critical outcome.
- Relapse rates were not affected by vitamin D, when compared to placebo. However, two studies looking at high-dose and low-dose vitamin D found that relapse rates were significantly higher with high-dose vitamin D, suggesting a potential harm of higher doses.
- Overall, the benefits observed for vitamin D were not felt to be large or consistent enough by the GDG to outweigh the harms.
- Further studies are needed to assess the benefit or harm of using vitamin D. Studies thus far have excluded people with primary progressive and secondary progressive MS, and these populations should also be investigated separately.

An Ontario Health Technology Assessment on the Clinical Utility of Vitamin D Testing (2010) noted the following conclusions:

- Given the limitations associated with serum Vitamin D measurement, ambiguities in the definition of a 'target serum level', and the availability of clear guidelines on Vitamin D supplementation from Health Canada, Vitamin D testing is not warranted for the average risk population.

- Individuals with medical conditions such as renal and liver disease, osteoporosis, and malabsorption syndromes, as well as those taking medications that may affect Vitamin D absorption/metabolism, should follow their physician's guidance concerning both Vitamin D testing and supplementation.

Appendix A

Condition or medical diagnosis associated with Vitamin D deficiency:

- Rickets
- Osteomalacia
- Osteoporosis
- Chronic kidney disease
- Hepatic failure
- Malabsorption syndromes:
 - Cystic fibrosis
 - Inflammatory bowel disease
 - Crohn's disease
 - Bariatric surgery
 - Radiation enteritis
- Hyperparathyroidism
- Medications:
 - Antiseizure medications
 - Glucocorticoids
 - AIDS/HIV medications
 - Antifungals, e.g. ketoconazole
 - Cholestyramine
- Older adults with history of falls
- Older adults with history of nontraumatic fractures
- Granuloma-forming disorders:
 - Sarcoidosis
 - Tuberculosis
 - Histoplasmosis
 - Coccidiomycosis
 - Berylliosis
- Lymphomas

Coding/Billing Information

- Note:** 1) This list of codes may not be all-inclusive.
 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed
0038U	Vitamin D, 25 hydroxy D2 and D3, by LC-MS/MS, serum microsample, quantitative

ICD-10-CM Diagnosis Codes	Description
A15.0-A19.9	Tuberculosis
C22.0-C22.9	Malignant neoplasm of liver and intrahepatic bile ducts
C23	Malignant neoplasm of gallbladder
C24.0-C24.9	Malignant neoplasm of other and unspecified parts of biliary tract

C25.0-C25.9	Malignant neoplasm of pancreas
C26.0-C26.9	Malignant neoplasm of other and ill-defined digestive organs
D13.0-D13.9	Benign neoplasm of other and ill-defined parts of digestive system
D86.0-D86.89	Sarcoidosis
E20.0	Idiopathic hypoparathyroidism
E20.8	Other hypoparathyroidism
E20.9	Hypoparathyroidism, unspecified
E21.0-E21.5	Hyperparathyroidism and other disorders of parathyroid gland
E24.0	Pituitary-dependent Cushing's disease
E24.1	Nelson's syndrome
E24.2	Drug-induced Cushing's syndrome
E24.3	Ectopic ACTH syndrome
E24.4	Alcohol-induced pseudo-Cushing's syndrome
E24.8	Other Cushing's syndrome
E24.9	Cushing's syndrome, unspecified
E41	Nutritional marasmus
E55.0-E55.9	Vitamin D deficiency
E64.3	Sequelae of rickets
E67.2	Megavitamin-B6 syndrome
E67.3	Hypervitaminosis D
E67.8	Other specified hyperalimentation
E68	Sequelae of hyperalimentation
E83.30-E83.39	Disorders of phosphorus metabolism and phosphatases
E83.50-E83.59	Disorders of calcium metabolism
E84.0-E84.9	Cystic fibrosis
E89.2	Postprocedural hypoparathyroidism
K50.00-K50.919	Crohn's disease [regional enteritis]
K51.00-K51.919	Ulcerative colitis
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.30-K70.31	Alcoholic cirrhosis of liver
K74.0-K74.69	Fibrosis and cirrhosis of liver
K75.81	Nonalcoholic steatohepatitis (NASH)
K76.0	Fatty (change of) liver, not elsewhere classified
K76.89	Other specified diseases of liver
K82.0	Obstruction of gallbladder
K82.8	Other specified diseases of gallbladder
K82.9	Disease of gallbladder, unspecified
K83.01-K83.9	Other diseases of biliary tract
K85.10-K85.12	Biliary acute pancreatitis
K86.2	Cyst of pancreas
K86.3	Pseudocyst of pancreas
K86.81-K86.89	Other specified diseases of pancreas
K86.9	Disease of pancreas, unspecified
K87	Disorders of gallbladder, biliary tract and pancreas in diseases classified elsewhere
K90.0-K90.49	Intestinal malabsorption
K90.89	Other intestinal malabsorption
K90.9	Intestinal malabsorption, unspecified
K91.2	Postsurgical malabsorption, not elsewhere classified
L90.0	Lichen sclerosus et atrophicus
L94.0	Localized scleroderma [morphea]
L94.1	Linear scleroderma
L94.3	Sclerodactyly
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor

M06.00-M06.9	Other rheumatoid arthritis
M32.0-M32.9	Systemic lupus erythematosus (SLE)
M33.01-M33.09	Juvenile dermatomyositis
M33.11-M33.19	Other dermatomyositis
M33.91-M33.99	Dermatopolymyositis
M36.0	Dermato(poly)myositis in neoplastic disease
M81.0-M81.8	Osteoporosis without current pathological fracture
M83.0-M83.9	Adult osteomalacia
M85.80	Other specified disorders of bone density and structure, unspecified site
M85.811	Other specified disorders of bone density and structure, right shoulder
M85.812	Other specified disorders of bone density and structure, left shoulder
M85.821	Other specified disorders of bone density and structure, right upper arm
M85.822	Other specified disorders of bone density and structure, left upper arm
M85.831	Other specified disorders of bone density and structure, right forearm
M85.832	Other specified disorders of bone density and structure, left forearm
M85.841	Other specified disorders of bone density and structure, right hand
M85.842	Other specified disorders of bone density and structure, left hand
M85.851	Other specified disorders of bone density and structure, right thigh
M85.852	Other specified disorders of bone density and structure, left thigh
M85.861	Other specified disorders of bone density and structure, right lower leg
M85.862	Other specified disorders of bone density and structure, left lower leg
M85.871	Other specified disorders of bone density and structure, right ankle and foot
M85.872	Other specified disorders of bone density and structure, left ankle and foot
M85.88	Other specified disorders of bone density and structure, other site
M85.89	Other specified disorders of bone density and structure, multiple sites
M85.9	Disorder of bone density and structure, unspecified
M88.0	Osteitis deformans of skull
M88.1	Osteitis deformans of vertebrae
M88.811	Osteitis deformans of right shoulder
M88.812	Osteitis deformans of left shoulder
M88.821	Osteitis deformans of right upper arm
M88.822	Osteitis deformans of left upper arm
M88.831	Osteitis deformans of right forearm
M88.832	Osteitis deformans of left forearm
M88.841	Osteitis deformans of right hand
M88.842	Osteitis deformans of left hand
M88.851	Osteitis deformans of right thigh
M88.852	Osteitis deformans of left thigh
M88.861	Osteitis deformans of right lower leg
M88.862	Osteitis deformans of left lower leg
M88.871	Osteitis deformans of right ankle and foot
M88.872	Osteitis deformans of left ankle and foot
M88.88	Osteitis deformans of other bones
M88.89	Osteitis deformans of multiple sites
M88.9	Osteitis deformans of unspecified bone
N18.2-N18.9	Chronic kidney disease (CKD)
N25.81	Secondary hyperparathyroidism of renal origin
O99.841-O99.845	Bariatric surgery status complicating pregnancy, childbirth and the puerperium
Q78.0	Osteogenesis imperfecta
Q78.2	Osteopetrosis
T30.0-T30.4	Burn and corrosion, body region unspecified
Z32.00-Z32.3	Encounter for pregnancy test and childbirth and childcare instruction
Z33.1-Z33.3	Pregnant state

Z34.00-Z34.93	Encounter for supervision of normal pregnancy
Z36.0-Z36.9	Encounter for antenatal screening of mother
Z3A.00-Z3A.49	Weeks of gestation
Z37.0-Z37.9	Outcome of delivery
Z38.00-Z38.8	Liveborn infants according to place of birth and type of delivery
Z39.0-Z39.2	Encounter for maternal postpartum care and examination
Z79.3	Long term (current) use of hormonal contraceptives
Z79.51-Z79.52	Long term (current) use of steroids
Z79.811	Long term (current) use of aromatase inhibitors
Z79.891	Long term (current) use of opiate analgesic
Z79.899	Other long term (current) drug therapy
Z98.84	Bariatric surgery status

Considered Not Medically Necessary:

ICD-10-CM Diagnosis Codes	Description
	All other codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
82652	Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed

ICD-10-CM Diagnosis Codes	Description
A15.0-A19.9	Tuberculosis
C83.80-C83.89	Other non-follicular lymphoma
C84.00-C84.09	Mycosis fungoides
C84.10-C84.19	Sezary disease
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
D86.0-D86.89	Sarcoidosis
E20.0	Idiopathic hypoparathyroidism
E20.8	Other hypoparathyroidism
E20.9	Hypoparathyroidism, unspecified
E21.0-E21.5	Hyperparathyroidism and other disorders of parathyroid gland
E55.0-E55.9	Vitamin D deficiency
E64.3	Sequelae of rickets
E67.2	Megavitamin-B6 syndrome
E67.8	Other specified hyperalimentation
E68	Sequelae of hyperalimentation
E83.30-E83.39	Disorders of phosphorus metabolism and phosphatases
E83.50-E83.59	Disorders of calcium metabolism
E89.2	Postprocedural hypoparathyroidism
M83.0-M83.9	Adult osteomalacia
N18.2-N18.9	Chronic kidney disease (CKD)
N25.81	Secondary hyperparathyroidism of renal origin
Q78.0	Osteogenesis imperfecta
Q78.2	Osteopetrosis
Z32.00-Z32.3	Encounter for pregnancy test and childbirth and childcare instruction
Z33.1-Z33.3	Pregnant state
Z34.00-Z34.93	Encounter for supervision of normal pregnancy
Z36.0-Z36.9	Encounter for antenatal screening of mother

Z3A.00-Z3A.49	Weeks of gestation
Z37.0-Z37.9	Outcome of delivery
Z38.00-Z38.8	Liveborn infants according to place of birth and type of delivery
Z39.0-Z39.2	Encounter for maternal postpartum care and examination

Considered Not Medically Necessary:

ICD-10-CM Diagnosis Codes	Description
	All other codes

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