Vitamin D screening

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Policy contains: Vitamin D assay testing, Vitamin D screening, Vitamin D supplementation.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Annual screening for vitamin D deficiency is clinically proven and therefore medically necessary for members who exhibit any sign or symptom of vitamin D deficiency (Holick, 2011), or asymptomatic members who are at risk for vitamin D deficiency, defined as having one or more of the following:

- chronic kidney disease stage III or greater
- cirrhosis
- hypocalcemia
- hypercalcemia
- hypercalciuria
- hypervitaminosis D
- parathyroid disorders
- malabsorption states
- obstructive jaundice
- osteomalacia
- osteoporosis if:
    - T score on dual energy x-ray absorptiometry scan <-2.5 or
    - History of fragility fractures or
    - Fracture risk assessment tool > 3% 10-year probability of hip fracture or 20% 10-year probability of other major osteoporotic fracture or

    - Fracture risk assessment tool > 3% (any fracture) with T-score <-1.5 or
    - hInitiating bisphosphanate therapy (Vitamin D level and serum calcium levels should be determined and managed as necessary before bisphosphonate is initiated.)
- osteosclerosis/petrosis
- pregnancy
- rickets
- vitamin D deficiency on replacement therapy related to a condition listed above; to monitor the efficacy of treatment.
- unexplained hypercalcemia (suspected granulomatous disease or lymphoma)
- unexplained hypercalciuria (suspected granulomatous disease or lymphoma)
- suspected genetic childhood rickets
- suspected tumor-induced osteomalacia
- nephrolithiasis or hypercalciuria (Centers for Medicare & Medicaid Services, 2019).

Limitations

- Both assays of vitamin D need not be performed for each of the above conditions.
- Once a member has been shown to be vitamin D deficient, further testing may be medically necessary only to ensure adequate replacement has been accomplished.
- If the Vitamin D level is between 20 and 50 ng/dl and the member is clinically stable, repeat testing is often unnecessary; if performed, documentation must clearly indicate the necessity of the test.
- If level <20 ng/dl or > 50 ng/dl are noted, a subsequent level(s) may be considered medically necessary until the level is within the normal range.
- Testing may not be used for routine or other screening (Centers for Medicare & Medicaid Services, 2019).

Screening for vitamin D deficiency is investigational, and therefore not medically necessary in asymptomatic adults age 18 years and older (Holick, 2011; U.S. Preventive Services Task Force, 2014).

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Vitamin D is a fat-soluble vitamin that is ingested through foods, sun exposure, and supplements. It promotes calcium absorption and normal growth of bone. Without adequate levels of vitamin D, bone can become thin, brittle, or misshapen. In addition, the vitamin helps modulate cell growth, enhance neuromuscular and immune function, and reduce inflammation. Vitamin D deficiency can lead to rickets in children and osteomalacia/osteoporosis in adults.

The Institute of Medicine considers any human with levels of less than 30 nanomoles per liter serum 25-hydroxyvitamin D to have vitamin D deficiency. The Institute also recommends daily intakes of vitamin D, which vary by age (persons over age 70 require 800 international units a day, while infants under age 1 require just 400; the remainder between ages 1 and 70 years require 600). Foods with the most vitamin D include cod liver oil, certain fishes (sockeye salmon, swordfish, tuna), orange juice, milk, and yogurt (National Institutes of Health, 2020).

The U.S. 2015-2016 average daily intake of Vitamin D from food and beverages were 204, 168, and 196 international units in men, women, and children age 2-19. An estimated 92% of men and 97% of women consume less than the recommended levels (National Health and Nutrition Examination Survey, 2019).

The prevalence of Vitamin D deficiency in the U.S. in 2005-2006 was 41.6%. Rates are highest among blacks (82.1%) and Hispanics (69.2%). Risk is elevated ($P < .001$) in persons with no college education, obesity, poor health status, hypertension, low high-density lipoprotein cholesterol, and those who do not consume milk daily (Forrest, 2011). The 2011-2012 rate of Vitamin D deficiency measured in 4,962 hospitalized patients over age 20 was 39.92%, essentially unchanged from the prior estimate (Parva, 2018).

A federal survey revealed 37% of Americans use Vitamin D supplements (Bailey, 2010). An Institute of Medicine expert panel found vitamin D supplements beneficial for bone, but not for extra-skeletal health. The panel added that any daily supplement over > 4000 international units may lead to possible harm, e.g., hypercalcemia and soft tissue or vascular calcification (Ross, 2011).

A review of 39,243 U.S. adults documented an increase in the proportion taking vitamin D supplements of at least 1,000 international units per day, from 0.3% to 18.2% between 1999-2000 to 2013-2014 ($P < .001$). Recent rates are much greater for females and non-Hispanic whites. Those taking at least 4,000 unites per day rose from 0.2% to 3.2% during this time, which raises concern over potential health risks (Rooney, 2017).

Vitamin D testing has increased greatly in recent years. From 2000 to 2014, the proportion of Americans over age 70 taking a vitamin D test rose from 4/1,000 to 4/10 — a 100-fold increase (Rooney, 2017). Increases such as this have prompted a discussion about when this test is medically necessary.

Medicare paid $224 million for vitamin D assay testing in 2014, a sharp increase from just a decade earlier (Rockwell, 2014). An estimated 7.5 million outpatient visits occurred in the U.S. in the four-year period 2007-2010 with a diagnosis of vitamin D deficiency (Huang, 2014), while an estimated 10% to 16% of Medicare patients and 5% to 10% of commercially insured patients were tested for vitamin D levels in the two-year period 2009-2011 (Colla, 2017).

Findings

A guideline from the Endocrine Society recommends Vitamin D screening for individuals with risk factors (Holick, 2011).

Another guideline, issued by the U.S. Preventive Services Task Force, recommends against universal screening for vitamin D deficiency. The task force found no references that assessed benefits or harms of screening for the deficiency in asymptomatic adults. The Task Force noted commonly reported risk factors for low vitamin D levels, including decreased dietary vitamin D intake, absorption, or synthesis due to decreased sun exposure or darker skin pigmentation. Other factors include older age, inflammatory bowel disease, malabsorptive conditions, history of gastric bypass, being homebound or institutionalized, routinely wearing clothing that prevents sun exposure on most of the skin, and living at high latitudes.

Finally, the group 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. It also found inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency on other outcomes, including psychosocial and physical functioning (U.S. Preventive Services Task Force, 2014).

A Centers for Medicare & Medicaid Services Local Coverage Determination, in effect starting November 14, 2019, lists the conditions for which serum 25-hydroxyvitamin testing is indicated. See the Local Coverage Determination citation later in this policy, and the list of conditions for testing in the coverage section (Centers for Medicare & Medicaid Services, 2019).

The American College of Obstetrics and Gynecology stated testing for maternal serum 25-hydroxyvitamin D levels may be considered in pregnant women believed to be at elevated risk of deficiency, and recommended 1,000–2,000 international units per day of vitamin D. However, the committee did not recommend screening all pregnant women. The recommendation was last affirmed in 2017 (American College of Obstetrics and Gynecology, 2017).

The U.S. Preventive Services Task Force guideline was supported by a systematic review of 11 studies. None of these studies addressed the effects of Vitamin D screening programs on health outcomes, and the research on Vitamin D treatment efficacy was limited (LeBlanc, 2015).

A systematic review of 12 studies analyzed the ability of screening programs to identify persons with Vitamin D deficiency through self-reported data. Authors documented the prediction models or questionnaires had sensitivity and specificity ranging from 55% to 91% and from 35% to 84%, respectively. No evidence exists that any of these existing tools have been translated into clinical practice (Naureen, 2020).

A study of 587,506 primary care encounters in family medicine and internal medicine reduced the rate of Vitamin D test orders from 6.9% to 5.2% after an educational memo distributed to providers and removal of the vitamin D test from the providers' quick order screen in the electronic health record (Rozario, 2020).

Numerous systematic reviews and meta-analyses, plus other large-scale studies, have analyzed associations between vitamin D supplements and health outcomes. Below are results of some of these studies, mostly published in 2018 or 2019. Results are mixed; some show improved outcomes, some do not, and some include both.

<u>Showed Improvements in Most/All Indicators:</u>

- Cancer (colorectal), 11 trials (n = 7,718). Increased serum 25-hydroxyvitamin D concentrations improved survival in patients with colorectal cancer, and recommended supplementation be the subject of randomized trials (Maalmi, 2018).
- Cancer (prostate), 22 trials. Men taking supplements had insignificantly lower prostate cancer mortality, but 19% had at least a 50% reduction in prostate-specific antigen, which was statistically significant (Shahvazi, 2018).
- Diabetes, 28 trials. Supplements given to non-diabetics showed no effects on fasting plasma glucose levels or insulin resistance. However, significant improvements were observed for patients with diabetes for those with low body mass index or low serum 25-hydroxyvitamin D, and risk of type 2 diabetes mellitus was lower for pre-diabetic individuals (He, 2018).
- Diabetes, 20 trials (n = 2,703). Supplementation’s effects on diabetes risk significantly improved .Vitamin D levels in short-term, high dose, non-obese, baseline vitamin D-deficient individuals, as well as reducing insulin resistance effectively (Li, 2018).
- Diabetes (type 2), 20 trials (n = 1,270). Supplements reduced levels of chronic low-grade inflammation, including C-reactive protein, tumor necrosis factor α, and erythrocyte sedimentation rate, in persons

with diabetes, compared with placebo (Mousa, 2018).

- Diabetes (gestational), 16 trials. Six trials showed that supplements reduced the level of fasting plasma glucose and the incidence of gestational diabetes. Ten other trials found vitamin D supplements significantly reduced the level of fasting plasma glucose and fasting insulin and improved the homeostasis model of assessment-estimated insulin resistance (Yin, 2019).
- Diabetes (type 2), 19 trials (n = 1,374). Compared with the control group, persons with type 2 diabetes given short-term vitamin D supplements had a decline in hemoglobin A1c, insulin resistance, and insulin (Hu, 2019).
- Diabetes (diabetic nephropathy), 20 trials (n = 1,464). In patients with diabetic nephropathy, vitamin D supplements significantly reduced 24-hour urine protein ($P < .00001$); urinary albumin excretion rate ($P < .0001$); high sensitivity C reactive protein ($P < .00001$), and interleukin-6 ($P < .00001$), but had no impact on other indicators (Wang, 2019).
- Falls (four trials, n = 4,512). A Cochrane review showed supplementation "probably" reduced falls among the institutionalized elderly (Cameron, 2018).
- Falls and fractures, 28 trials. Supplementation was highly effective in preventing falls and fractures (Poscia, 2018).
- Fractures and falls, numerous randomized trials. Supplements reduce fractures when administered with calcium in the institutionalized elderly; reduce acute respiratory tract infections if not given as bolus monthly or annual doses; and may reduce falls in those with the lowest serum 25-hydroxyvitamin D (25OHD) levels (Ebeling, 2018).
- Physical activity among elderly (36 trials, n = 4,947). Supplementation of adults age 55 and older resulted in a small positive effect on physical fitness ("get up and go"), and an increased effect when the daily dose was increased to 400 – 1,000 international units (Dewansingh, 2018).
- Pregnant women, 24 trials (n = 5,405). Supplements to pregnant women were associated with a (significant) 28% reduction in small for gestational age with no risk of fetal or neonatal mortality, along with higher birth weights (Bi, 2018).
- Asthma (n = 308,000). A review of Israeli adults age 22 – 50, including 21,737 with asthma and with known Vitamin D levels, showed a 6.9% rate of the disease, compared to 5.7% in the general population. In addition, asthmatics with Vitamin D deficiency had a 25% greater chance of exacerbation compared with persons with normal levels (Confino-Cohen, 2014).
- A systematic review of 84 articles assessed the association between circulating 25-hydroxyvitamin D concentration and all-cause or cause-specific mortality in generally healthy populations. The vast majority of studies reported inverse associations between the two variables (higher vitamin D linked with lower mortality), up to a point. This association appeared to be non-linear, with progressively lower mortality with increasing 25(OH)D up to a point, beyond which there was no further decrease. There is moderate evidence of this inverse association with lung cancer mortality, and weak evidence of this inverse association of cardiovascular deaths (Heath, 2019).

<u>Showed No Improvements</u>:

- Active tuberculosis (n = 1,787). Supplements could be used in conjunction with standard treatment based on significantly higher sputum smear and culture proportions, but did not impact adverse events and mortality (Wu, 2018)
- Cancer (all), 30 trials (n = 30,808). No evidence that supplementation was associated with a decrease in cancer-related incidence or mortality was found (Goulao, 2018).
- Falls and fractures, 81 trials (n = 53,537). Supplements had no effect on total fractures (36 studies), hip fractures (20 studies), or falls (37 studies) (Bolland, 2018).

- Fracture incidence, two trials (n = 36,727). An insignificantly lower rate of fracture incidence resulted after supplementation with vitamin D and calcium. Vitamin D alone had no significant effect on all-cause mortality (Kahwati, 2018).
- Multiple sclerosis, 12 trials (n = 933). Supplements had no apparent effect on recurrence of relapse, worsening of disability, and magnetic resonance imaging lesions, while effects on health-related quality of life and fatigue are unclear (Jaqannath, 2018).

Showed Mixed/Equivocal Results:

- Cancer (all). A systematic review of 52 trials (n = 75,454) revealed a significant reduction between reduced risk of cancer death (RR = 0.84), but non-significant reductions for all causes (RR = 0.98) and cardiovascular disorders (RR = 0.98), and all non-cancer, non-cardiovascular causes (RR = 1.05) (Zhang, 2019).
- Diabetes, 19 trials (n = 5,214) compared pregnant women taking levels of Vitamin D above versus below the recommended amount. While children of women taking higher amounts reduced the risk of gestational diabetes, but did not reduce rates of pre-eclampsia, preterm births, and low-weight births (Palacios, 2019).
- Fall risk, seven trials (n = 7,531). Results of this study on the risk of falls after taking supplements were mixed — some found higher risk, some found lower risk (Giurgis-Blake, 2018).
- Fall risk, 30 trials (n = 10,000). No evidence existed on the ability of supplements to reduce the risk of falls, but attributed this to data quality problems, stopping short of concluding vitamin D supplementation is ineffective (Tang, 2018).

Other systematic reviews and meta-analyses documented improvements in various biomarkers, and recommended that future trials of vitamin D supplementation be compared with morbidity and mortality outcomes.

A review of 175,830 persons over ager 40 documented that a significantly lower proportion of outpatient visits among African-Americans were related to Vitamin D supplements ($P < .05$). Authors suggest more focused strategies targeting blacks are needed to maintain adequate vitamin D supplements (Lee, 2016).

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On February 11, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were Vitamin D assay testing, Vitamin D screening, and Vitamin D supplementation. We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

3/2019: initial review date and clinical policy effective date: 6/2019

5/2020: Policy references updated.

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