Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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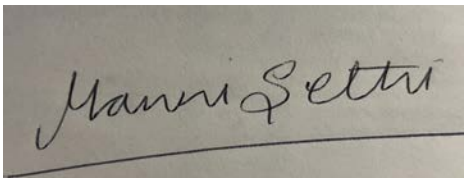
Plan: AmeriHealth Caritas Pennsylvania	**Submission Date**: 02/22/2023
Policy Number: CCP.1414	**Effective Date:** 7/2019 **Revision Date:** 02/203
Policy Name: Vitamin D screening	
Type of Submission – Check all that apply: ☐ **New Policy** **X Revised Policy*** ☐ **Annual Review – No Revisions** ☐ **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** Please see revisions with tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD,MBA, CHCQM	**Signature of Authorized Individual:** 

Vitamin D screening

Clinical Policy ID: CCP.1414

Recent review date: 2/2023

Next review date: 6/2024

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

AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas' 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 AmeriHealth Caritas 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. AmeriHealth Caritas' 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. AmeriHealth Caritas' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas' clinical policies are not guarantees of payment.

Coverage policy

Annual screening for vitamin D deficiency using the 25-hydroxyvitamin D assay is clinically proven and, therefore, medically necessary for members who exhibit any sign or symptom of vitamin D deficiency or for asymptomatic members who are at risk for vitamin D deficiency, defined as having one or more of the following conditions, when results will be used to institute more aggressive therapy (American Academy of Pediatrics, 2017; American College of Obstetrics and Gynecology, 2021; Holick, 2011):

- Chronic kidney disease stage III or greater.
- Cirrhosis/chronic liver failure.
- Hypercalcemia.
- Hypercalciuria.
- Hypervitaminosis D.
- Hypocalcemia.
- Long-term use of medications known to lower vitamin D levels (e.g., antiseizure drugs, antifungals, glucocorticosteroids, cholestyramine, and drugs for acquired immunodeficiency syndrome/human immunodeficiency virus).
- Malabsorption states.
- Obstructive jaundice.
- Osteomalacia.
- Osteoporosis if either:

  - T score on dual energy x-ray absorptiometry scan < -2.5.
  - History of fragility fractures.
  - Fracture risk assessment tool > 3% 10-year probability of hip fracture or 20% 10-year probability of other major osteoporotic fracture.
  - Fracture risk assessment tool > 3% (any fracture) with T-score < -1.5.
  - Initiating bisphosphanate therapy (Vitamin D level and serum calcium levels should be determined and managed as necessary before bisphosphonate is initiated.)
- Osteosclerosis/petrosis.
- Parathyroid disorders.
- Pregnancy.
- Rickets.
- Vitamin D deficiency on replacement therapy related to a condition listed above; to monitor the efficacy of treatment.

The serum 1,25 dihydroxyvitamin D assay is clinically proven and, therefore, medically necessary for monitoring certain acquired and inherited disorders of vitamin D and phosphate metabolism, including but not limited to (Holick, 2011):

- 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.

Limitations

Both assays of vitamin D (25-hydroxyvitamin D and 1,25-dihydroxyvitamin 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. Thereafter, annual testing may be medically necessary depending on the indication and other mitigating factors.

If the vitamin D level is between 20 and 50 nanograms per milliliter and the member is clinically stable, repeat testing is often unnecessary; if performed, documentation must clearly indicate the medical necessity of the test.

If a vitamin D level is < 20 nanograms per milliliter or > 50 nanograms per milliliter, repeat testing may be considered medically necessary until the level is within the normal range.

Vitamin D testing is investigational/not clinically proven and, therefore, not medically necessary for routine or other screening.

Annual screening for vitamin D deficiency is investigational/not clinically proven and, therefore, not medically necessary in asymptomatic members who are not at risk for vitamin D deficiency (American Academy of Pediatrics, 2017; Holick, 2011; U.S. Preventive Services Task Force, 2021).

Alternative covered services

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

Background

Vitamin D is a fat-soluble vitamin 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 National Institutes of Health recommend 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 require between ages 1 and 70 years require 600. Foods with the most vitamin D include cod liver oil, certain fishes (sockeye salmon, swordfish, and tuna), orange juice, milk, and yogurt (National Institutes of Health, 2022).

An estimated 92% of men and 97% of women in the United States consume less than the recommended daily levels of vitamin D (National Health and Nutrition Examination Survey, 2019). The prevalence of vitamin D deficiency in the United States 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).

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 (Institute of Medicine, 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 and 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). Medicare paid $224 million for vitamin D assay testing in 2014, a sharp increase from just a decade earlier (Rockwell, 2014). 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). Increases such as this have prompted a discussion about when this test is medically necessary.

Findings

The purpose of screening to identify and treat the condition before potential adverse clinical outcomes occur. The total serum 25-hydroxyvitamin D level is currently considered the best marker of vitamin D deficiency status,

and liquid chromatography with tandem mass spectrometry is considered the reference assay. A variety of assays can be used to measure serum 25-hydroxyvitamin D levels, but these levels can be difficult to measure accurately. The uncertainty in the cutoff for defining deficiency and variations in testing assays, testing laboratories, and subgroups defined by race, ethnicity, or gender further complicate test interpretation (Holick, 2011).

There is a lack of consensus on the serum concentrations of 25-hydroxyvitamin D associated with deficiency and adequacy for bone health and overall health. The Institute of Medicine considers any human with levels of less than 30 nanomoles per liter (12 nanograms per milliliter) serum 25-hydroxyvitamin D to have vitamin D deficiency, whereas the Endocrine Society defines the threshold for vitamin D deficiency as less than 20 nanograms per milliliter. Levels of 50 nanomoles per liter (20 nanograms per milliliter) or more are considered sufficient for most people (National Institutes of Health, 2022).

A guideline from the Endocrine Society recommends vitamin D screening for individuals with risk factors and in whom a swift response to optimization of vitamin D status could be expected. They recommend using the serum 1,25 dihydroxyvitamin D assay only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism (Holick, 2011).

The Choosing Wisely campaign issued the following testing recommendations for vitamin D deficiency (American Family Physician, 2022):

- Test children linked with low bone mass (e.g., rickets or a history of repeated, low-trauma bone fractures). Avoid ordering vitamin D concentrations routinely in otherwise healthy children, including children who are overweight or obese. Vitamin D supplements are a cost-effective option for children with insufficient dietary intake or for obese children, who often have low vitamin D levels (Source: American Academy of Pediatrics).
- Test higher risk patients when results will be used to institute more aggressive therapy (e.g., osteoporosis, chronic kidney disease, malabsorption, some infections, obese individuals). While vitamin D deficiency is common in many populations (e.g., patients with limited sun exposure, at higher latitudes, and during winter months), over-the-counter vitamin D supplements and increased summer sun exposure are sufficient for most otherwise healthy patients (Source: The Endocrine Society).
- Do not routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function (Source: The Endocrine Society).

An updated U.S. Preventive Services Task Force recommendation found insufficient evidence supporting vitamin D screening in community-dwelling, nonpregnant adults who have no signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended. This recommendation does not apply to persons who are hospitalized or living in institutions such as nursing homes. The Task Force noted little to no ultraviolet B exposure, older age, obesity, and being non-Hispanic Black as commonly reported risk factors for low vitamin D levels (Krist, 2021).

For treating asymptomatic vitamin D deficiency, there was sufficient evidence that treatment has no benefit on mortality, risk for fractures in persons selected solely on the basis of low vitamin D levels (as opposed to clinical

risks such as low bone density), or incidence of type 2 diabetes mellitus. There was insufficient evidence on the benefit of treatment on other outcomes, including falls, cancer, cardiovascular events, depression, infection, or physical functioning. There is sufficient evidence that the harms of treatment of vitamin D deficiency are small to none (Krist, 2021).

The systematic review on which the update was based found no studies that directly evaluated the benefits and harms of screening for vitamin D deficiency. Current evidence enrolled participants at risk for deficiency based on low serum vitamin D levels using various assays that may not have been standardized according to current testing standards (Kahwati, 2021).

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 reaffirmed in 2021 (American College of Obstetrics and Gynecology, 2021).

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 authors 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 participants 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 reduced 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 participants 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 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-hydroxyvitamin 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 (relative risk = .84), but non-significant reductions for all causes (0.98) and cardiovascular disorders (0.98), and all non-cancer, non-cardiovascular causes (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).

In 2022, we updated the U.S. Preventive Services Task Force recommendations (2021) and added recommendations from the Choosing Wisely Campaign (American Family Physician, 2022). We added two systematic reviews/meta-analyses that found insufficient evidence of a protective or therapeutic effect of vitamin D supplementation for COVID-19 (Bassatne, 2021; Stroehlein, 2021). We added chronic use of medications known to lower vitamin D levels as a risk factor for vitamin D deficiency that may warrant periodic screening. We identified acquired and inherited disorders involved in the metabolism of 25-hydroxyvitamin D and phosphate for which monitoring of 1, 25-dihydroxyvitamin D testing may be medically necessary (Holick, 2011).

In 2023, we added one systematic review and meta-analysis of four randomized controlled trials (n = 666 women) and six observational studies (n = 6,997 women) of generally low quality. The investigators found an association between vitamin D deficiency/insufficiency and miscarriage (odds ratio 1.60; 95% confidence interval 1.11 to 2.30; 6 studies; n = 6,338), but a protective effect of preconception vitamin D treatment against pregnancy loss in women at risk of miscarriage remains unknown (Tamblyn, 2022).

References

On January 3, 2023, 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 deficiency/diagnosis (MeSH)," "vitamin d deficiency/analysis (MeSH)," "vitamin D assay testing," and "vitamin D screening." 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.

7/2021: Policy references updated.

7/2022: Policy references updated.