Policy Statement

I. Testing vitamin D levels in individuals with signs and/or symptoms of vitamin D deficiency or toxicity (see Policy Guidelines section) may be considered medically necessary.

II. Testing vitamin D levels in asymptomatic individuals may be considered medically necessary in individuals who have risk factors for vitamin D deficiency (see Policy Guidelines section).

III. Repeat testing vitamin D levels to assess response to treatment may be considered medically necessary when at least 3 months have passed after beginning treatment, and generally not more than twice in a year after an initial test shows a Vitamin D deficiency (see Policy Guidelines section).

IV. Testing vitamin D levels in asymptomatic individuals is considered investigational when the above criteria are not met.

V. Testing for 1,25 dihydroxy vitamin D levels is considered not medically necessary except in some rare cases such as renal disease (see Policy Guidelines section).

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Signs and symptoms of vitamin D deficiency are largely manifested by changes in bone health and biochemical markers associated with bone production and resorption. In most cases, a clinical diagnosis of an abnormality in bone health (e.g., rickets, osteomalacia, osteoporosis) will lead to a decision to test vitamin D levels. Symptoms related to the clinical condition may be present (e.g., pain, low-impact fractures), but these symptoms are usually not indications for testing prior to a specific diagnosis. Some biochemical markers of bone health may indicate an increased risk for vitamin D deficiency, and testing of vitamin D levels may, therefore, be appropriate. These biochemical markers include unexplained abnormalities in serum calcium, phosphorus, alkaline phosphatase, and/or parathyroid hormone.

Signs and symptoms of vitamin D toxicity (hypervitaminosis D) generally result from induced hypercalcemia. Acute intoxication can cause symptoms of confusion, anorexia, vomiting, weakness, polydipsia, and polyuria. Chronic intoxication can cause bone demineralization, kidney stones, and bone pain.

“Institutionalized” as used herein refers to individuals who reside at long-term facilities where some degree of medical care is provided. These circumstances and facilities can include long-term hospital stays, nursing homes, assisted living facilities, and similar environments.

1,25 dihydroxy vitamin D levels can vary rapidly and are subject to influence by parathyroid (PTH) and other hormones. While it is a potent metabolite, it usually does not reflect body stores of vitamin D as accurately as 25-OH vitamin D levels.
Liquid chromatography (LC) tandem mass spectrometry (MS/MS) or LC-MS/MS testing uses two mass spectrometers sequentially. It is accurate and becoming more common but may not always be cost effective.

There are no standardized lists of factors denoting high risk for vitamin D deficiency, and published lists of high-risk factors differ considerably. Certain factors tend to be present on most lists, however, and they may constitute a core set of factors for which there is general agreement that testing is indicated. The Endocrine Society guidelines form the basis for the following list of high-risk factors for vitamin D deficiency. (see also Appendix 1)

- Chronic kidney disease stage ≥3
- Cirrhosis and chronic liver disease
- Malabsorption states
- Osteomalacia
- Osteoporosis
- Rickets
- Hypo- or hypercalcemia
- Granulomatous diseases
- Vitamin D deficiency, on replacement
- Obstructive jaundice and biliary tract disease
- Osteogenesis imperfecta
- Osteosclerosis and osteopetrosis
- Chronic use of anticonvulsant medications or corticosteroids
- Parathyroid disorders
- Osteopenia

The need for repeat testing may vary by condition. A single test may be indicated for diagnostic purposes; a repeat test may be appropriate to determine whether supplementation has been successful in restoring normal serum levels. More than 1 repeat test may occasionally be indicated, such as in cases where supplementation has not been successful in restoring levels (another example might include an instance in which continued or recurrent signs and symptoms may indicate ongoing deficiency, and/or when inadequate absorption or noncompliance with replacement therapy is suspected). It is recommended that retesting be done when at least 3 months have passed after beginning treatment, and generally not more than twice in a year after an initial test shows a Vitamin D deficiency.

**Coding**

There are specific CPT codes for vitamin D testing:

- **82306**: Vitamin D; 25 hydroxy, includes fraction(s), if performed
- **82652**: Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed

There is a PLA code for vitamin D testing:

- **0038U**: Vitamin D, 25 hydroxy D2 and D3, by LC-MS/MS, serum microsample, quantitative

**Description**

Vitamin D, also known as calciferol, is a fat-soluble vitamin that has a variety of physiologic effects, most prominently in calcium homeostasis and bone metabolism. In addition to the role it plays in bone metabolism, other physiologic effects include inhibition of smooth muscle proliferation, regulation of the renin-angiotensin system, a decrease in coagulation, and a decrease in inflammatory markers.
Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The U.S. Food and Drug Administration (FDA) has cleared a number of immunoassays for in vitro diagnostic devices for the quantitative measurement of total 25-hydroxyvitamin D through the 510(k) process.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Lab tests for vitamin D are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Rationale

Background

Vitamin D

Vitamin D, also known as calciferol, is a fat-soluble vitamin that has a variety of physiologic effects, most prominently in calcium homeostasis and bone metabolism. In addition to the role vitamin D plays in bone metabolism, other physiologic effects include inhibition of smooth muscle proliferation, regulation of the renin-angiotensin system, a decrease in coagulation, and a decrease in inflammatory markers.¹

Vitamin D Replacement

The Institute of Medicine (now the National Academy of Medicine [NAM]) has recommended reference values for the intake of vitamin D and serum levels, based on available literature and expert consensus.² Recommended daily allowances are 600 IU/d for individuals between 1 and 70 years of age, and 800 IU/d for individuals older than 70 years.

Estimates of vitamin D requirements are complicated by the many other factors that affect serum levels. Sun exposure is the most prominent of factors that affect serum levels, and this is because individuals can meet their vitamin D needs entirely through adequate sun exposure. Other factors such as age, skin pigmentation, obesity, physical activity, and nutritional status also affect vitamin D levels and can result in variable dietary intake requirements to maintain adequate serum levels. Excessive intake of vitamin D can be toxic. Toxic effects are usually due to hypercalcemia and may include confusion, weakness, polyuria, polydipsia, anorexia, and vomiting. In addition, high levels of
vitamin D may promote calcium deposition and have the potential to exacerbate conditions such as calcium kidney stones and atherosclerotic vascular disease.

The Institute of Medicine defined 3 parameters of nutritional needs for vitamin D, on the assumption of minimal sun exposure. These parameters were the estimated average requirement, defined as the minimum intake required to maintain adequate levels; the recommended daily allowance, defined as the optimal dose for replacement therapy; and the upper-level intake, defined as the maximum daily dose to avoid toxicity. These recommendations are summarized in Table 1.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Estimated Average Requirement, IU/d</th>
<th>Recommended Daily Allowance, IU/d</th>
<th>Upper Limit Intake, IU/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3 years old</td>
<td>400</td>
<td>600</td>
<td>2500</td>
</tr>
<tr>
<td>4 to 8 years old</td>
<td>400</td>
<td>600</td>
<td>3000</td>
</tr>
<tr>
<td>9 to 70 years old</td>
<td>400</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>&gt;70 years old</td>
<td>400</td>
<td>800</td>
<td>4000</td>
</tr>
</tbody>
</table>

Adapted from Institute of Medicine (2011).2

### Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

### Vitamin D Deficiency

Vitamin D deficiency is best assessed by measuring serum levels of 25-hydroxyvitamin D. However, there is no consensus on the minimum vitamin D level or on the optimal serum level for overall health. A 2011 Institute of Medicine (IOM) report concluded that a serum level of 20 ng/mL is sufficient for most healthy adults.2 Some experts, such as the Bone Health and Osteoporosis Foundation (formerly the National Osteoporosis Foundation), have recommended a higher level (30 ng/mL) in some patient populations.3

Vitamin D deficiency, as defined by suboptimal serum levels, is common in the U.S. In the National Health and Nutrition Examination Survey covering the period of 2011 to 2014, 5% of patients aged 1 year and older were at risk of vitamin D deficiency (25-hydroxyvitamin D levels <12 ng/mL) and 18.3% of patients were at risk of vitamin D inadequacy (25-hydroxyvitamin D levels 12 to 19.6 ng/mL).4 Vitamin D deficiency occurs most commonly as a result of inadequate dietary intake coupled with inadequate sun exposure. Evidence from the National Nutrition Monitoring System and the National Health and Nutrition Examination Survey has indicated that the average vitamin D consumption is below recommended levels of intake. Yetley (2008) estimated that the average daily intake for U.S. adults ranged from 228 to 335 IU/d, depending on gender and ethnicity.5 This level is below the average daily requirement, estimated by IOM (400 IU/d for healthy adults), and well below IOM’s required daily allowance (estimated to be 600 IU for nonelderly adults and 800 IU for elderly adults).

Vitamin D deficiency may occur less commonly for other reasons. Kidney or liver disease can cause deficiency as a result of the impaired conversion of inactive vitamin D to its active products. In rare situations, there is vitamin D resistance at the tissue level, which causes a functional vitamin D deficiency despite "adequate" serum levels.
The safe upper level for serum vitamin D is also not standardized. The IOM report concluded there is potential harm associated with levels greater than 50 ng/mL and recommended that serum levels be maintained in the 20 to 40 ng/mL range.\(^2\) However, conclusions on this point have differed. A 2011 Agency for Healthcare Research and Quality systematic review of vitamin D and bone health concluded that “There is little evidence from existing trials that vitamin D above current reference intakes is harmful.”\(^6\) The Women’s Health Initiative concluded that hypercalcemia and hypercalciuria in patients receiving calcium and vitamin D were not associated with adverse clinical events.\(^7\) The Women’s Health Initiative did find a small increase in kidney stones for women ages 50 to 79 years who received vitamin D and calcium.

Associations of vitamin D levels with various aspects of health have been noted over the last several decades,\(^8,9,10,11,12\) and these findings have led to the question of whether supplementation improves health outcomes. For example, a relation between vitamin D levels and overall mortality has been reported in most observational studies examining this association.\(^13,14\) Mortality is lowest at vitamin D levels in the 25 to 40 nmol/L range. At lower levels of serum vitamin D, mortality increases steeply, and overall mortality in the lowest quintile was more than 3 times that in the middle quintiles. Theodoratou et al (2014) identified 107 systematic reviews of observational studies examining the association between vitamin D levels and more than 100 different outcomes.\(^15\)

**Clinical Context**

The purpose of measuring vitamin D levels is to guide a treatment option that is an alternative to or an improvement on existing management in patients who are asymptomatic without conditions or risk factors for which vitamin D supplementation is recommended.

The following PICO was used to select literature to inform this review.

**Populations**

The relevant population of interest is individuals who are asymptomatic without conditions or risk factors for which vitamin D supplement is recommended.

**Interventions**

The therapy being considered is testing of vitamin D levels.

**Comparators**

The following practice is currently being used to manage vitamin D deficiency: routine care without testing for vitamin D deficiency. Routine care may include recommendations for increased ultraviolet B exposure, dietary intake of vitamin D, or vitamin D supplementation in the absence of known vitamin D deficiency.

**Outcomes**

Relevant outcomes of interest are overall survival, test validity, symptoms, morbid events, and treatment-related morbidity.

The length of time needed to correct subclinical vitamin D deficiency and improve outcomes is unknown and likely varies for different clinical situations.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for randomized controlled trials (RCTs);
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Analytic Framework

Figure 1 summarizes the approach to this evidence review. The diagram demonstrates the framework for how vitamin D testing affects outcomes. Using this framework, the main question is whether testing individuals for vitamin D deficiency improves outcomes.

Figure 1. Analytic Framework

Based on this analytic framework, the most relevant studies for showing the clinical utility of vitamin D testing are trials that directly compare care including testing vitamin D levels against care without testing vitamin D levels. Should vitamin D screening in an asymptomatic, general population be shown to be effective, guidelines would then be needed to establish criteria for screening, screening intervals, and appropriate follow-up for positive tests. Indirect evidence of the utility of vitamin D testing would include evidence of the effectiveness of supplementation from trials testing supplementation to no supplementation in patients who are vitamin D deficient. Many of the existing RCTs, including the largest trial (Women’s Health Initiative), did not test vitamin D levels prior to treatment. Rather, they treated all patients enrolled regardless of vitamin D levels. Results of some of the main systematic reviews that take this approach will be reviewed, but this evidence is indirect and must be extrapolated from the treatment of all patients to the treatment of patients who are vitamin D deficient.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

There is no consensus on how to define vitamin D deficiency or inadequacy, and there is no accepted reference standard. Available cutoffs for deficiency are neither standardized nor based on rigorous scientific studies. Therefore, despite the availability of many tests that measure total serum 25-
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hydroxyvitamin D (25(OH)D) levels, their sensitivities and specificities for detecting clinically important
deficiency are currently unknown.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net
health outcome of care. The net health outcome can be improved if patients receive correct therapy,
more effective therapy, or avoid unnecessary therapy or testing.

No RCTs were found that evaluated clinical outcomes or harms in patients tested for vitamin D
deficiency versus not tested for vitamin D deficiency. In the absence of direct evidence of the utility of
testing, evidence of the effectiveness of vitamin D supplementation could indirectly support the utility
of testing by identifying a group of patients in which baseline serum 25(OH)D is a predictor of
supplement effect so that testing might be useful.

A large number of RCTs have evaluated the impact of vitamin D supplementation on outcomes.
Theodoratou et al (2014) identified 87 meta-analyses of RCTs on vitamin D supplementation; there
were 21 meta-analyses on skeletal health, 7 on metabolic disease, 4 on pediatric outcomes, 3 on
cardiovascular disease, 3 on pregnancy-related outcomes, and 18 on other outcomes. Because of the
large literature base, this review of evidence will focus on the largest and most recent systematic
reviews and meta-analyses of RCTs. Individual trials will be reviewed separately if they were not
included in the meta-analyses or if particular features need highlighting. The evidence review
includes use of vitamin D testing and supplementation in the following indications: skeletal health,
cardiovascular disease, cancer, asthma, pregnancy, multiple sclerosis (MS), and overall mortality.

Review of Evidence
Skeletal Health

Systematic Reviews
Numerous systematic reviews and meta-analyses of RCTs have been published evaluating the
impact of vitamin D supplementation on skeletal health outcomes. The relevant health outcomes
considered for this evidence review include fractures and falls. Studies that looked at bone mineral
density and/or other physiologic measures of bone health were not included. Table 2 summarizes the
results of systematic reviews performing quantitative meta-analyses on the relevant outcomes.
Among the trials included in the meta-analyses, few were large studies; most were small or moderate
in size and limited by a small number of outcome events. Doses of vitamin D varied widely from 400
to 4800 IU/d; treatment and follow-up durations varied from 2 months to 7 years. Some studies
limited enrollment to participants with low serum vitamin D. Most studies excluded
institutionalized patients, but some included them. There was inconsistency in the results, especially
for studies of fracture prevention, as evidenced by the relatively large degree of heterogeneity
among studies.

Table 2. Systematic Reviews Assessing the Impact of Vitamin D Supplementation on Skeletal
Health

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>P, %*</th>
<th>RR for Outcome (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with vitamin D deficiency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hip fracture</td>
<td>4</td>
<td>1619</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Falls: total</td>
<td>5</td>
<td>1677</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Falls: person</td>
<td>5</td>
<td>1809</td>
<td>64.5</td>
<td></td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ling et al (2021)18</td>
<td>Falls</td>
<td>21</td>
<td>51,984</td>
<td>NR</td>
<td>1.00 (0.95 to 1.05)</td>
</tr>
<tr>
<td>Cranney et al (2011)6; AHRQ</td>
<td>Any fracture</td>
<td>14</td>
<td>58,712</td>
<td>48.3</td>
<td>0.90 (0.81 to 1.01)</td>
</tr>
<tr>
<td></td>
<td>Hip fracture</td>
<td>8</td>
<td>46,072</td>
<td>16.2</td>
<td>0.83 (0.68 to 1.0)</td>
</tr>
<tr>
<td>Study</td>
<td>Outcome</td>
<td>No. of Studies</td>
<td>No. of Participants</td>
<td>P, %a</td>
<td>RR for Outcome (95% CI)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Avenell et al (2009)</td>
<td>Falls</td>
<td>9</td>
<td>9262</td>
<td>0</td>
<td>0.84 (0.76 to 0.93)</td>
</tr>
<tr>
<td></td>
<td>All fractures</td>
<td>10</td>
<td>25,016</td>
<td>NR</td>
<td>1.01 (0.93 to 1.09)</td>
</tr>
<tr>
<td></td>
<td>Hip fractures</td>
<td>9</td>
<td>24,749</td>
<td>NR</td>
<td>1.15 (0.99 to 1.33)</td>
</tr>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td>5</td>
<td>9138</td>
<td>NR</td>
<td>0.90 (0.97 to 1.1)</td>
</tr>
<tr>
<td>Bischoff-Ferrari et al (2009)</td>
<td>Non-vertebral fracture</td>
<td>5</td>
<td>7130</td>
<td>NR</td>
<td>0.79 (0.63 to 0.99)</td>
</tr>
<tr>
<td>Palmer et al (2009)</td>
<td>All fractures (CKD-RD)</td>
<td>4</td>
<td>181</td>
<td>NR</td>
<td>1.0 (0.06 to 15.41)</td>
</tr>
<tr>
<td>Bischoff-Ferrari et al (2005)</td>
<td>Hip fracture</td>
<td>700 to 800 IU/d</td>
<td>3</td>
<td>5572</td>
<td>0.74 (0.61 to 0.88)</td>
</tr>
<tr>
<td></td>
<td>400 IU/d</td>
<td>2</td>
<td>3722</td>
<td>NR</td>
<td>1.15 (0.88 to 1.50)</td>
</tr>
<tr>
<td></td>
<td>Non-vertebral fracture</td>
<td>700 to 800 IU/d</td>
<td>5</td>
<td>6098</td>
<td>0.77 (0.68 to 0.87)</td>
</tr>
<tr>
<td></td>
<td>400 IU/d</td>
<td>2</td>
<td>3722</td>
<td>NR</td>
<td>1.03 (0.86 to 1.24)</td>
</tr>
</tbody>
</table>

AHRQ: Agency for Healthcare Research and Quality; CI: confidence interval; CKD-RD: chronic kidney disease on renal dialysis; NR: not reported; RR: relative risk.

a Heterogeneity value.

Cranney et al (2011) conducted a review for the Agency for Healthcare Research and Quality (AHRQ) on the effectiveness and safety of vitamin D in relation to bone health. Reviewers concluded that:

- The evidence on the reduction in fractures was inconsistent. The combined results of trials using vitamin D3 with calcium were consistent with a benefit on fractures, although the benefit was primarily found in the subgroup of elderly institutionalized women, which was a subgroup not included in this review.
- The evidence on a benefit in fall risk was also inconsistent. The results showed benefit in subgroups of postmenopausal women and in trials that used vitamin D in combination with calcium. There was a reduction in fall risk with vitamin D when 6 trials that adequately ascertained falls were combined.

A meta-analysis of double-blind RCTs by Bischoff-Ferrari et al (2005) estimated the benefit of vitamin D supplementation on fracture risk and examined the dose-response relation between vitamin D and outcomes. Based on a meta-analysis of 5 RCTs that used high-dose vitamin D, reviewers concluded that supplementation at 700 to 800 IU/d reduced the incidence of hip fractures by 26%, and reduced any non-vertebral fracture by 23%. In this same review, based on the results of 2 RCTs, lower doses of vitamin D at 400 IU/d did not significantly reduce the fracture risk.

Randomized Controlled Trials
The STURDY Collaborative Research Group (Appel et al 2021) was a large (N=688) RCT evaluating 4 doses of vitamin D in individuals at least 70 years of age at elevated fall risk and a serum vitamin D level of 25 to 72.5 nmol/L. The primary outcome was time to first fall or death over 2 years. The primary outcome during the confirmatory stage was not significantly different between those receiving the control dose of vitamin D (200 IU/day) and those receiving what was considered the optimal dose of 1000 IU/day. Doses of 1000 IU/day or greater were associated with safety concerns. The study is limited by the use of vitamin D 200 IU/day as a control group rather than use of a placebo.

An RCT not included in most of the systematic reviews (by Sanders et al [2010]) reported results inconsistent with some of the previous trials and conclusions of meta-analyses. In this trial, 2256 community-dwelling elderly individuals at high-risk for falls were treated with high-dose vitamin D 500,000 IU orally once per year for 3 to 5 years. There was a 15% increase in falls for the group treated with vitamin D (p=.03) and a 26% increase in fractures (p=.02). In addition, there was a
temporal relation to the increase in fall risk, with the greatest risk in the period immediately after vitamin D administration. It is unclear whether the specific regimen used in this study (e.g., high-dose vitamin D once/year) was responsible for the different results seen in this study compared with prior research.

Section Summary: Skeletal Health
Numerous RCTs and meta-analyses of RCTs have been published on the effect of vitamin D supplementation on skeletal health. The most direct evidence consists of trials that selected patients for vitamin D deficiency and randomized patients to vitamin D or placebo. A meta-analysis of these trials showed no reduction in fractures and an uncertain reduction in falls. In meta-analyses that treated all patients regardless of vitamin D levels, there are inconsistent findings on the effect of supplementation on fractures and falls. There is some evidence that subgroups (e.g., elderly women) may benefit from supplementation and that higher doses may provide a benefit whereas lower doses do not; however, very high doses may increase the risk of falls. Therefore, the evidence does not convincingly demonstrate an improvement in skeletal health outcomes with vitamin D supplementation.

Cardiovascular Disease
Systematic Reviews
A large number of trials have reported on the impact of vitamin D supplementation on cardiovascular events. A number of systematic reviews have examined the relation between vitamin D and cardiovascular outcomes.

Elamin et al (2011) published a systematic review and meta-analysis evaluating cardiovascular outcomes.\(^\text{25}\) It included 51 trials that used various forms of vitamin D with or without calcium. There was minimal heterogeneity among the studies. Combined analysis showed no significant impact on cardiovascular death (relative risk [RR]=0.96; 95% confidence interval [CI], 0.93 to 1.0), myocardial infarction (RR=1.02; 95% CI, 0.93 to 1.13), or stroke (RR=1.05; 95% CI, 0.88 to 1.25). No significant effects were found on the physiologic outcomes of lipids, glucose, or blood pressure.

A systematic review by Pittas et al (2010) assessed 5 RCTs evaluating the impact of vitamin D supplementation on incident cardiovascular disease.\(^\text{26}\) None of the 5 trials reported a significant reduction in cardiovascular outcomes in the vitamin D group. Combined analysis of these trials found a RR for cardiovascular outcomes of 1.08 (95% CI, 0.99 to 1.19) in the vitamin D group.

An AHRQ report by Chung et al (2009) concluded that\(^\text{27}\):

- The evidence on the impact of vitamin D on cardiovascular outcomes is inconsistent, and conclusions are difficult to make because of the marked heterogeneity of the evidence.
- The RCTs that have evaluated the impact of vitamin D on cardiovascular outcomes use cardiovascular events as a secondary outcome, not as a prespecified primary outcome.
- These analyses have been hampered by low numbers of cardiovascular events and imperfect methods for the ascertainment of cardiovascular events.

Wang et al (2008) also performed a systematic review of whether vitamin D and calcium prevent cardiovascular events.\(^\text{28}\) Eight RCTs of vitamin D supplementation in the general population evaluated cardiovascular outcomes as a secondary outcome. A combined analysis of studies that used high-dose vitamin D supplementation (>1000 IU/d) found a 10% reduction in cardiovascular events, but this reduction was not statistically significant (RR=0.90; 95% CI, 0.77 to 1.05). When studies that combined vitamin D plus calcium supplementation were included, there was no trend toward a benefit (RR=1.04; 95% CI, 0.92 to 1.18).

A systematic review by Pittas et al (2010) included 10 intervention trials that evaluated the relation between vitamin D and hypertension.\(^\text{26}\) Most did not report a decrease in incident hypertension associated with vitamin D supplementation.
A systematic review by Su et al (2021) assessed 36 studies that included cohort studies, RCTs, and case-control analyses for the association between serum levels of vitamin D and risk of stroke. Lower levels of serum vitamin D were associated with an elevated risk of stroke in both Asian and White populations, however, vitamin D supplementation did not show benefit in decreasing the risk of stroke. In a meta-analysis limited to RCTs, Fu et al (2022) had similar findings; vitamin D did not reduce stroke risk compared with placebo (RR=1.02; 95% CI, 0.93 to 1.13; p=.65). 30

Section Summary: Cardiovascular Disease

The available evidence does not support a benefit of vitamin D supplementation on cardiovascular events. Numerous RCTs have assessed this outcome; however, in most studies, it is a secondary outcome with a limited number of events, thus limiting the power to detect a difference. Furthermore, it is difficult to separate the impact of vitamin D from the impact of calcium in many of these studies. It is common to use vitamin D and calcium supplementation together. Research has also highlighted a potential increase in cardiovascular outcomes associated with calcium supplementation. 31 Thus, if there are beneficial effects of vitamin D, they may be obscured or attenuated by the concomitant administration of calcium supplements. Another possibility is that vitamin D and calcium act synergistically, promoting either a greater protective effect against cardiovascular disease or an increase in cardiovascular risk.

Cancer

Systematic Reviews

Systematic reviews have evaluated the effect of vitamin D supplementation on the prevention of cancer. Table 3 contains characteristics of 2 systematic reviews, and Table 4 summarizes the results of the meta-analyses performed in the reviews. The individual RCTs included in the systematic reviews are listed in Table 5. Both systematic reviews by Keum et al (2019) and Bjelakovic et al (2014) found that vitamin D supplementation did not reduce cancer incidence compared to placebo or no intervention; however, total cancer mortality was reduced. In the systematic review by Bjelakovic et al, there was no substantial difference in the effect of vitamin D on cancer in subgroup analyses of trials only including participants with vitamin D levels less than 20 ng/mL at enrollment compared with trials including participants with vitamin D levels of 20 ng/mL or greater at enrollment. Notably, most included studies were not designed to assess cancer incidence or mortality. The authors of the systematic review by Bjelakovic et al (2014) noted that the estimates that were significantly different were at high risk of type I error due to sample size and potential attrition bias.

Table 3. Characteristics of Systematic Reviews Assessing Vitamin D and Cancer

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keum et al (2019)</td>
<td>To November 2018</td>
<td>10</td>
<td>People with baseline 25-(OH)D</td>
<td>NR</td>
<td>RCTs</td>
<td>3 to 10 years</td>
</tr>
<tr>
<td>Bjelakovic et al (2014)</td>
<td>To February 2014</td>
<td>18</td>
<td>Adults (over 18 years) (healthy, with stable disease, or diagnosed with vitamin D deficiency)</td>
<td>50,623</td>
<td>RCTs</td>
<td>5 months to 7 years</td>
</tr>
</tbody>
</table>

25-(OH)D: 25-hydroxyvitamin D; NR: not reported; RCT: randomized controlled trial.

Table 4. Results of Systematic Reviews Assessing Vitamin D and Cancer

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Total Cancer Incidence</th>
<th>Total Cancer Mortality</th>
<th>Total Mortality</th>
<th>Nephrolithiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keum et al (2019)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total N</td>
<td>RR=0.98</td>
<td>RR=0.87</td>
<td>RR=0.93</td>
<td>NR</td>
</tr>
<tr>
<td>P</td>
<td>0.93 to 1.03</td>
<td>0.79 to 0.96</td>
<td>0.88 to 0.98</td>
<td>NR</td>
</tr>
<tr>
<td>Bjelakovic et al (2014)</td>
<td>50,623</td>
<td>44,492 (Vitamin D only)</td>
<td>49,866</td>
<td>42,573</td>
</tr>
<tr>
<td>Total N</td>
<td>RR=1.00</td>
<td>RR=0.88</td>
<td>RR=0.93</td>
<td>RR=1.17</td>
</tr>
</tbody>
</table>
Section Summary: Cancer
Systematic reviews of many RCTs have examined the effect of vitamin D supplementation on cancer outcomes, although cancer was not the prespecified primary outcome in most RCTs. The current evidence does not demonstrate that vitamin D supplementation reduces the incidence of cancer.

Asthma
Systematic Reviews
Several systematic reviews of vitamin D supplementation for the prevention of asthma exacerbations have been published. Four recent reviews are summarized in Tables 6 and 7. Eighteen unique RCTs were included in these systematic reviews (see Table 8). Reviews by Liu et al (2022)\textsuperscript{58}, Jolliffe et al (2017)\textsuperscript{59}, and Martineau et al (2016)\textsuperscript{60} concluded that the RCTs were generally at low risk of bias. The RCTs included children and adults, as well as variable doses of vitamin D, routes and lengths of administration, and variable levels of asthma severity. The RCTs also included patients with variable baseline 25(OH)D levels and patients were not generally selected by baseline 25(OH)D. The Jolliffe et al (2017) and Martineau et al (2016) reviews found that vitamin D supplementation reduced the rate (or proportion) of asthma exacerbations requiring treatment with systemic corticosteroids, while Liu et al (2022) found vitamin D supplementation to reduce overall asthma exacerbations. The reviews by Martineau et al (2016)\textsuperscript{60} and Luo et al (2015)\textsuperscript{61} found that vitamin D had no effect on Asthma Control Test (ACT) scores, forced expiratory volume in 1-second (FEV1) outcomes, or rates of adverse events. Liu et al (2022) found no benefit to vitamin D supplementation on ACT scores, FEV1, or Fractional Exhaled Nitric Oxide (FENO).\textsuperscript{58} The review by Jolliffe et al (2017) used individual participant data.
and was, therefore, able to test for patient-level subgroup effects. For the outcome of “rate of asthma exacerbations treated with systemic corticosteroids,” the protective effect of vitamin D was larger in patients with a baseline 25(OH)D levels of less than 25 nmol/L (rate ratio=0.33; 95% CI, 0.11 to 0.98) compared with patients who had higher a baseline 25(OH)D levels (rate ratio=0.77; 95% CI, 0.58 to 1.03). However, the subgroup by treatment group interaction was not statistically significant (p=.25).

Table 6. Characteristics of Systematic Reviews Assessing Vitamin D and Asthma

<table>
<thead>
<tr>
<th>Study, Trial, Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al (2022)59.</td>
<td>The decade prior to publication</td>
<td>Asthma patients who received any form or dose of vitamin D</td>
<td>1349</td>
<td>RCT</td>
<td>9 wks to 12 mo</td>
</tr>
<tr>
<td>Jolliffe et al (2017)59; PROSPERO CRD42014013953</td>
<td>To Oct 2016</td>
<td>People with asthma, all ages, and baseline 25(OH)D levels included</td>
<td>1078</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>15 wk to 12 mo</td>
</tr>
<tr>
<td>Martineau et al (2016)60.</td>
<td>To Jan 2016</td>
<td>People with asthma, all ages, and baseline 25(OH)D levels included</td>
<td>1093</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>4 to 12 mo</td>
</tr>
<tr>
<td>Luo et al (2015)61.</td>
<td>1946 to 2015</td>
<td>People with asthma, all ages, and baseline 25(OH)D levels included</td>
<td>903</td>
<td>RCT</td>
<td>9 wk to 12 mo</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; 25-(OH)D: 25-hydroxyvitamin D.

Table 7. Results of Systematic Reviews Assessing Vitamin D and Asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Asthma Exacerbation</th>
<th>Asthma Exacerbation Requiring SCS</th>
<th>ACT Score</th>
<th>FEV1</th>
<th>Proportion of Patients With AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al (2022)59.</td>
<td>Total N 944</td>
<td>526</td>
<td>651</td>
<td>Risk ratio=0.60</td>
<td>SMD=0.04</td>
</tr>
<tr>
<td>Total effect</td>
<td>95% CI 0.41 to 0.88</td>
<td>-0.13 to 0.21</td>
<td>-0.35 to 0.43</td>
<td>64%</td>
<td>0%</td>
</tr>
<tr>
<td>Total effect</td>
<td>95% CI 0.55 to 1.10</td>
<td>0.56 to 0.97</td>
<td>0.46 to 1.63</td>
<td>HR=0.78</td>
<td>RR=0.74</td>
</tr>
<tr>
<td>Total effect</td>
<td>95% CI 0.55 to 1.10</td>
<td>0.56 to 0.97</td>
<td>0.46 to 1.63</td>
<td>HR=0.78</td>
<td>RR=0.74</td>
</tr>
<tr>
<td>Martineau et al (2016)60.</td>
<td>Total N 999</td>
<td>963</td>
<td>713</td>
<td>387</td>
<td>879</td>
</tr>
<tr>
<td>Total effect</td>
<td>95% CI 0.28 to 0.99, favoring vitamin D</td>
<td>0.19 to 0.78, favoring vitamin D</td>
<td>-0.70 to 0.54, 0.93 to 1.89</td>
<td>53%</td>
<td>65%</td>
</tr>
<tr>
<td>Total effect</td>
<td>95% CI 0.28 to 0.99, favoring vitamin D</td>
<td>0.19 to 0.78, favoring vitamin D</td>
<td>-0.70 to 0.54, 0.93 to 1.89</td>
<td>53%</td>
<td>65%</td>
</tr>
<tr>
<td>Total effect</td>
<td>95% CI 0.32 to 1.37</td>
<td>0.30 to 1.37</td>
<td>0.15 to 1.11</td>
<td>74%</td>
<td>81%</td>
</tr>
</tbody>
</table>

ACT: Asthma Control Test; AE: adverse event; Diff: difference; CI: confidence interval; FEV1: forced expiratory volume in 1 second; HR: hazard ratio; NA: not applicable; NR: not reported; OR: odds ratio; RR: rate ratio; SCS: systemic corticosteroid; SMD: standard mean difference.

a Outcome was proportion with ≥1 exacerbation.
b FEV1, % predicted.
c At 12 months.
d Serious adverse events.
Table 8. Comparison of Randomized Controlled Trials Included in the Systematic Reviews

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Worth et al (1994)62</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Majak et al (2009)63</td>
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<tr>
<td>Urashima et al (2010)64</td>
<td></td>
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<td></td>
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<tr>
<td>Majak et al (2011)65</td>
<td></td>
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<td></td>
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<tr>
<td>Lewis et al (2012)66</td>
<td></td>
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<tr>
<td>Baris et al (2014)67</td>
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<td></td>
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<tr>
<td>Castro et al (2014)68</td>
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<td></td>
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<tr>
<td>Yadav et al (2016)69</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>de Groot et al (2015)70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martineau et al (2015)71</td>
<td></td>
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<td></td>
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<tr>
<td>Tachimoto et al (2016)72</td>
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<tr>
<td>Jensen et al (2016)73</td>
<td></td>
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<td></td>
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<tr>
<td>Kerley et al (2016)74</td>
<td></td>
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<td></td>
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<tr>
<td>Musharraf et al (2017)75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dodamani et al (2019)76</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shabana et al (2019)77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jat et al (2021)78</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thakur et al (2021)79</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Randomized Controlled Trials

An RCT of prenatal supplementation in 881 pregnant women at high-risk of having children with asthma was published in 2016.80 Women between gestational ages of 10 and 18 weeks were randomized to daily vitamin D 4000 IU plus a multivitamin containing vitamin D 400 IU (4400 IU group) or daily placebo vitamin D plus a multivitamin containing vitamin D 400 IU (400 IU group). Coprimary outcomes were (1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age and (2) third trimester maternal 25-OH(D) levels. Analysis of infant outcomes included 806 infants, 218 of whom developed asthma by age 3 years. The proportion of infants with asthma or recurrent wheeze was 24% in the 4400 IU group vs 30% in the 400 IU group (difference= -6%; 95% CI, -30% to 18%). There were no differences in the proportion of infants experiencing eczema or lower respiratory tract infections.

Andujar–Espinosa (2021) published an RCT assessing the efficacy of vitamin D supplementation in adult asthmatic patients.81 Adult asthmatic patients who had serum 25–OH(D) levels <30 ng/mL were randomized to receive either 16,000 IU (n=56) or placebo (n=56) weekly along with their regular asthma treatments for a period of 6 months. The primary outcome was the degree of asthma control as defined by the ACT scores, self-administered by patients. There was a significant difference between the 2 study groups, with clinical improvement seen in the vitamin D supplementation group compared to placebo (difference of 3.66 (95% CI, 0.89 to 5.43); p<.001) as measured using ACT scores.

Section Summary: Asthma

Results of systematic reviews have reported mixed findings with respect to the effect of vitamin D supplementation on asthma outcomes. Populations included in studies varied by baseline vitamin D deficiency levels, administration of vitamin D, and the severity of asthma. In general, patients were not selected based on a low baseline 25(OH)D level. While there is some evidence that vitamin D supplementation reduces the rate of asthma exacerbations, it is unclear if baseline 25(OH)D level is related to treatment benefit. The current evidence is insufficient to determine the effect of vitamin D supplementation on asthma outcomes.
Pregnancy Systematic Reviews

A systematic review of studies examining the role of vitamin D supplementation in pregnancy is summarized in Table 9 and Table 10. The individual studies included in the systematic review are listed in Table 11. Vitamin D supplementation during pregnancy probably reduces risk of pre-eclampsia (moderate-certainty evidence), gestational diabetes (moderate-certainty evidence), severe postpartum hemorrhage (low-certainty evidence), and low birthweight in infants (moderate-certainty evidence)\(^82\). However, not all studies measured baseline 25(OH)D levels and analyses based on initial 25(OH)D concentrations were not performed. Most studies were considered to have a low-moderate risk of bias.

Table 9. Characteristics of Systematic Review Assessing Vitamin D and Pregnancy

<table>
<thead>
<tr>
<th>Study, Trial</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palacios et al (2019)(^82),</td>
<td>To July 2018</td>
<td>22(^a) (vitamin D supplementation alone)</td>
<td>Pregnant women; most studies included baseline 25-(OH)D levels</td>
<td>3725</td>
<td>RCTs</td>
<td>NR (most studies started supplementation at or after 20 weeks gestation)</td>
</tr>
</tbody>
</table>

25-(OH)D: 25-hydroxyvitamin D; NR: not reported; RCT: randomized controlled trial.
\(^a\) Results of meta-analysis evaluating vitamin D supplementation + calcium not reported.

Table 10. Results of Systematic Review Assessing Vitamin D and Pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-eclampsia</th>
<th>Gestational diabetes</th>
<th>Maternal AE: Severe postpartum hemorrhage</th>
<th>Preterm birth (&lt;37 weeks' gestation)</th>
<th>Low birthweight (&lt;2500 gram)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palacios et al (2019)(^82),</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>499</td>
<td>446</td>
<td>1134</td>
<td>1640</td>
<td>697</td>
</tr>
<tr>
<td>Pooled effect</td>
<td>RR=0.48</td>
<td>RR=0.51</td>
<td>RR=0.68</td>
<td>RR=0.66</td>
<td>RR=0.55</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.30 to 0.79</td>
<td>0.27 to 0.97</td>
<td>0.51 to 0.91</td>
<td>0.34 to 1.3</td>
<td>0.35 to 0.87</td>
</tr>
</tbody>
</table>

AE: adverse event; CI: confidence interval; RR: relative risk.

Table 11. Randomized Controlled Trials Included in the Systematic Review

<table>
<thead>
<tr>
<th>Primary Study (Year)</th>
<th>Palacios et al (2019)(^82),</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brooke et al (1980)(^83),</td>
<td>●</td>
</tr>
<tr>
<td>Delvin et al (1986)(^84),</td>
<td>●</td>
</tr>
<tr>
<td>Mallet al al (1986)(^85),</td>
<td>●</td>
</tr>
<tr>
<td>Marya et al (1988)(^86),</td>
<td>●</td>
</tr>
<tr>
<td>Kaur et al (1991)(^87),</td>
<td>●</td>
</tr>
<tr>
<td>Yu et al (2008)(^88),</td>
<td>●</td>
</tr>
<tr>
<td>Roth et al (2010)(^89),</td>
<td>●</td>
</tr>
<tr>
<td>Sabet et al (2012)(^90),</td>
<td>●</td>
</tr>
<tr>
<td>Asemi et al (2013)(^91),</td>
<td>●</td>
</tr>
<tr>
<td>Grant et al (2013)(^92),</td>
<td>●</td>
</tr>
<tr>
<td>Tehrani et al (2014)(^93),</td>
<td>●</td>
</tr>
<tr>
<td>Mirghafourvand et al (2015)(^94),</td>
<td>●</td>
</tr>
<tr>
<td>Rodda et al (2015)(^95),</td>
<td>●</td>
</tr>
<tr>
<td>Sablok et al (2015)(^96),</td>
<td>●</td>
</tr>
<tr>
<td>Singh et al (2015)(^97),</td>
<td>●</td>
</tr>
<tr>
<td>Khan et al (2016)(^98),</td>
<td>●</td>
</tr>
<tr>
<td>Cooper et al (2016)(^99),</td>
<td>●</td>
</tr>
<tr>
<td>Naghshineh et al (2016)(^100),</td>
<td>●</td>
</tr>
<tr>
<td>Shahghheibi et al (2016)(^101),</td>
<td>●</td>
</tr>
<tr>
<td>Vaziri et al (2016)(^102),</td>
<td>●</td>
</tr>
<tr>
<td>Sasan et al (2017)(^103),</td>
<td>●</td>
</tr>
<tr>
<td>Samimi et al (2017)(^104),</td>
<td>●</td>
</tr>
</tbody>
</table>
Section Summary: Pregnancy
A systematic review found vitamin D supplementation in pregnancy reduced the risk of pre-eclampsia, gestational diabetes, low birthweight, and possibly severe postpartum hemorrhage; however, the significance of baseline 25(OH)D levels was not defined.

Multiple Sclerosis
Three systematic reviews have examined the effect of vitamin D supplementation in patients with MS. Reviewers described 6 RCTs, all of which were small (N<100). Patient follow-up ranged from 6 months to 2 years, and the dosing and administration of vitamin D varied. None of the trials reported improvement in MS relapse rates; most trials showed no effect of vitamin D on any of the surrogate or clinical outcomes. Only 1 trial reported improvement in magnetic resonance imaging of lesions in the vitamin D supplementation group. The evidence for vitamin D supplementation in MS is poor.

Overall Mortality
Systematic Reviews
A number of meta-analyses of RCTs of vitamin D supplementation have examined the benefit of vitamin D supplementation on overall mortality. Table 12 summarizes the most recent meta-analyses. The individual studies ranged in size from fewer than 100 to several thousand patients. No significant heterogeneity was reported for these trials.

The most relevant information comes from a meta-analysis of patients with vitamin D deficiency by LeBlanc et al (2015). This report included 11 studies and found a marginally significant reduction in overall mortality, with a CI that approached 1.0. When the subgroup analysis was performed, it became apparent that most of the benefit was specific to institutionalized patients whereas, in community-dwelling patients, the data revealed no reduction in mortality.

The AHRQ report by Newberry et al (2014), assessing the health effects of vitamin D supplementation, updated the original 2007 report. A quantitative synthesis of all trials was not performed in the 2014 update. Rather reviewers identified areas where the new trials might change previous conclusions. Their main conclusions were that the results did not support a benefit on overall mortality associated with vitamin D supplementation. No important trials identified in the update would potentially change this conclusion.

For meta-analyses including RCTs that treated all patients with vitamin D, most analyses have not shown a significant reduction in mortality. The single analysis that did show a significant reduction was that by Chowdhury et al (2014), who reported a marginally significant result for vitamin D3 supplementation but not for vitamin D2 supplementation.

Table 12. Results of Systematic Reviews of Randomized Controlled Trials Assessing the Impact of Vitamin D Supplementation on Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>I², %</th>
<th>RR for Outcome (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with vitamin D deficiency</td>
<td>Mortality (all patients)</td>
<td>11</td>
<td>4126</td>
<td>0</td>
<td>0.83 (0.70 to 0.99)</td>
</tr>
<tr>
<td></td>
<td>Mortality (noninstitutionalized patients)</td>
<td>8</td>
<td>2947</td>
<td>0</td>
<td>0.93 (0.73 to 1.18)</td>
</tr>
<tr>
<td>LeBlanc et al (2015)</td>
<td>Mortality (vitamin D3)</td>
<td>13</td>
<td>12,609</td>
<td>5%</td>
<td>0.92 (0.85 to 1.00)</td>
</tr>
<tr>
<td></td>
<td>Mortality (vitamin D2)</td>
<td>8</td>
<td>17,079</td>
<td>14%</td>
<td>1.03 (0.96 to 1.12)</td>
</tr>
<tr>
<td>Bjelakovic et al (2014)</td>
<td>Mortality (vitamin D3)</td>
<td>14</td>
<td>13,367</td>
<td>0</td>
<td>0.89 (0.80 to 0.99)</td>
</tr>
<tr>
<td></td>
<td>Mortality (vitamin D2)</td>
<td>8</td>
<td>17,079</td>
<td>0</td>
<td>1.04 (0.97 to 1.11)</td>
</tr>
<tr>
<td>Chowdhury et al (2014)</td>
<td>Mortality (vitamin D3)</td>
<td>14</td>
<td>13,367</td>
<td>0</td>
<td>0.89 (0.80 to 0.99)</td>
</tr>
<tr>
<td>Palmer et al (2009)</td>
<td>Mortality (CKD-RD)</td>
<td>5</td>
<td>233</td>
<td>1.34</td>
<td>(0.34 to 5.24)</td>
</tr>
<tr>
<td>Palmer et al (2009)</td>
<td>Mortality (CKD)</td>
<td>4</td>
<td>477</td>
<td>1.40</td>
<td>(0.38 to 5.15)</td>
</tr>
</tbody>
</table>
Section Summary: Overall Mortality
Evidence from a number of systematic reviews and meta-analyses does not support a benefit of vitamin D supplementation on overall mortality for the general, noninstitutionalized population. Populations included in the studies varied by baseline vitamin D deficiency and administration of vitamin D.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Bone Health and Osteoporosis Foundation
The Bone Health and Osteoporosis Foundation updated recommendations for the prevention and treatment of osteoporosis in 2021. They recommended monitoring serum 25-hydroxy vitamin D levels in postmenopausal women and men 50 years of age and older, and vitamin D supplementation as necessary to maintain levels between 30 and 50 ng/mL.

Endocrine Society
In 2011, the Endocrine Society published clinical practice guidelines on the evaluation, treatment, and prevention of vitamin D deficiency. The following recommendations were made regarding testing vitamin D levels:
- 25-hydroxy vitamin D serum level testing is recommended: “to evaluate vitamin D status only in patients who are at risk of deficiency.” The guideline did not recommend screening of individuals not at risk of vitamin D deficiency.
- 1,25-dihydroxyvitamin D testing was not recommended to evaluate vitamin D status. However, the guideline did recommend monitoring calcitriol levels under certain conditions.

American College of Obstetrics and Gynecology
The American College of Obstetrics and Gynecology (2011, reaffirmed 2021) issued a committee opinion on the testing of vitamin D levels and vitamin D supplementation in pregnant women. The following recommendation was made concerning testing vitamin D levels:
“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. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000-2,000 international units per day of vitamin D is safe.”

American Academy of Family Physicians
The American Academy of Family Physicians supports the U.S. Preventative Task Force recommendation on vitamin D screening.
In 2018, key recommendations for practice concluded that there was insufficient information to recommend screening the general population for vitamin D deficiency and that treating asymptomatic individuals with identified deficiency has not been shown to improve health.\textsuperscript{116}

**National Osteoporosis Society**
The National Osteoporosis Society issued a patient management clinical guideline for vitamin D and bone health in 2014.\textsuperscript{117} It recommended that serum 25-hydroxyvitamin D levels should be measured to estimate vitamin D status in certain clinical scenarios such as: bone diseases that may improve with vitamin D treatment; bone diseases, prior to specific treatment where correcting vitamin D deficiency is appropriate; and musculoskeletal symptoms that could be due to vitamin D deficiency.

**U.S. Preventive Services Task Force Recommendations**
The U.S. Preventive Services Task Force published an updated recommendation\textsuperscript{118} and associated evidence report and systematic review in 2021\textsuperscript{119}, on vitamin D screening. The Task Force concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic individuals (grade I [insufficient evidence]).

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing or unpublished trials that might influence this review are listed in Table 13.

<table>
<thead>
<tr>
<th>Table 13. Summary of Key Trials</th>
</tr>
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<tbody>
<tr>
<td>NCT No.</td>
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<td></td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
Appendix 1

Appendix 1. High-Risk Factors for Vitamin D Deficiency
The following list summarizes selected high-risk factors for vitamin D deficiency113,120:

- Chronic kidney disease stage ≥3
- Cirrhosis and chronic liver disease
- Malabsorption states
- Osteomalacia
- Osteoporosis
- Rickets
- Hypo- or hypercalcemia
- Granulomatous diseases
- Vitamin D deficiency, on replacement
- Obstructive jaundice and biliary tract disease
- Osteogenesis imperfecta
- Osteosclerosis and osteopetrosis
- Chronic use of anticonvulsant medication or corticosteroids
- Parathyroid disorders
- Osteopenia.

References


15. Theodoratou E, Tzoulaki I, Zgaga L, et al. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. Apr 01 2014; 348: g2035. PMID 24690624


24. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. May 12 2010; 303(18): 1815-22. PMID 20460620


38. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. Mar 01 2003; 326(7387): 469. PMID 12609940


**Documentation for Clinical Review**

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Signs/symptoms/duration/test results related to reason for Vitamin D testing
  - Comorbidities or diagnoses related to the need for testing
  - Activity and functional limitations including institutionalization if applicable
  - Main reason for performing test
  - Past and present diagnostic testing and results as applicable
  - Prior treatments, duration, and response if applicable
  - Treatment plan (i.e., dose and duration of treatment) as applicable
  - Type of vitamin D test being requested (including CPT codes)

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>0038U</td>
<td>Vitamin D, 25 hydroxy D2 and D3, by LC-MS/MS, serum microsample, quantitative</td>
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<td></td>
<td>82306</td>
<td>Vitamin D; 25 hydroxy, includes fraction(s), if performed</td>
</tr>
<tr>
<td></td>
<td>82652</td>
<td>Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed</td>
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<tr>
<td>HCPCS</td>
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<td>None</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>12/04/2015</td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>02/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>05/01/2018</td>
<td>Coding update</td>
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<tr>
<td>02/01/2019</td>
<td>Policy revision without position change</td>
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<tr>
<td>08/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>05/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
<tr>
<td>02/01/2021</td>
<td>Annual review. Policy statement, guidelines and literature updated.</td>
</tr>
<tr>
<td>02/01/2022</td>
<td>Annual review. Policy statement and literature updated.</td>
</tr>
<tr>
<td>02/01/2023</td>
<td>Annual review. Policy statement, guidelines and literature updated.</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member’s illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with
generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer:* This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.
### POLICY STATEMENT

#### BEFORE

Red font: Verbiage removed

Testing Serum Vitamin D Levels 2.04.135

Policy Statement:
Testing vitamin D levels in patients with signs and/or symptoms of vitamin D deficiency or toxicity (see Policy Guidelines section) may be considered medically necessary.

Testing vitamin D levels in asymptomatic patients may be considered medically necessary in the following patient populations:  
I. Individuals who have risk factors for vitamin D deficiency (see Policy Guidelines section)

Repeat testing vitamin D levels to assess response to treatment may be considered medically necessary when at least 3 months have passed after beginning treatment, and generally not more than twice in a year after an initial test shows a Vitamin D deficiency (see Policy Guidelines section).

Testing vitamin D levels in asymptomatic patients are considered not medically necessary when the above criteria are not met.

Testing for 1,25 dihydroxy vitamin D levels is considered not medically necessary except in some rare cases such as renal disease (see Policy Guidelines section).

#### AFTER

Blue font: Verbiage Changes/Additions

Testing Serum Vitamin D Levels 2.04.135

Policy Statement:

I. Testing vitamin D levels in individuals with signs and/or symptoms of vitamin D deficiency or toxicity (see Policy Guidelines section) may be considered medically necessary.

II. Testing vitamin D levels in asymptomatic individuals may be considered medically necessary in individuals who have risk factors for vitamin D deficiency (see Policy Guidelines section)

III. Repeat testing vitamin D levels to assess response to treatment may be considered medically necessary when at least 3 months have passed after beginning treatment, and generally not more than twice in a year after an initial test shows a Vitamin D deficiency (see Policy Guidelines section).

IV. Testing vitamin D levels in asymptomatic individuals is considered investigational when the above criteria are not met.

V. Testing for 1,25 dihydroxy vitamin D levels is considered not medically necessary except in some rare cases such as renal disease (see Policy Guidelines section).