Testing Serum Vitamin D Levels

Policy Number: 2.04.135  Last Review: 12/2018
Origination: 12/2015  Next Review: 12/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Testing Serum Vitamin D Levels when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Testing vitamin D levels in patients with signs and/or symptoms of vitamin D deficiency or toxicity (see Considerations section) may be considered medically necessary.

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

When Policy Topic is not covered
Testing vitamin D levels in asymptomatic patients is considered not medically necessary when the above criteria are not met.

Considerations
If the test or procedure is not listed in the member’s list of benefits, and Blue Cross and Blue Shield of Kansas City determines that it was done on an individual without specific symptoms of a condition or disease for which the test was done, it will be considered a non-covered screening test.

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 (eg, rickets, osteomalacia, osteoporosis) will lead to a decision to test vitamin D levels. Symptoms related to the clinical condition may be present, such as pain or 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, phosphorous, 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 patients 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.

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 following list of high-risk factors was compiled from numerous sources (see Appendix 1 for citations).

- Chronic kidney disease, stage ≥3
- Cirrhosis/chronic liver disease
- Malabsorption states
- Osteomalacia
- Osteoporosis
- Rickets
- Hypo- or hypercalcemia
- Granulomatous diseases
- Vitamin D deficiency, on replacement
- Obstructive jaundice/biliary tract disease
- Osteogenesis imperfecta
- Osteosclerosis/osteopetrosis
- Chronic use of anticonvulsant medication 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 be indicated occasionally, such as in cases where, eg, supplementation has not been successful in restoring levels, continued or recurrent signs and symptoms may indicate ongoing deficiency, and/or inadequate absorption or noncompliance with replacement therapy is suspected.

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
### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• Who are asymptomatic without conditions or risk factors for which vitamin D treatment is recommended</td>
<td>• Testing of vitamin D levels</td>
<td>• Routine care without testing vitamin D levels</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
</tbody>
</table>

### Summary

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, decrease in coagulation, and decrease in inflammatory markers.

For individuals who are asymptomatic without conditions or risk factors for which vitamin D treatment is recommended who receive testing of vitamin D levels, the evidence includes no randomized controlled trials (RCTs) of clinical utility (ie, evidence that patient care including testing vitamin D levels vs care without testing vitamin D levels improves outcomes). Indirect evidence of potential utility of testing includes many RCTs and systematic reviews of vitamin D supplementation. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, morbid events, and treatment-related morbidity. There is a lack of standardized vitamin D testing strategies and cutoffs for vitamin D deficiency are not standardized or evidence-based. In addition, despite the large quantity of evidence, considerable uncertainty remains about the beneficial health effects of vitamin D supplementation. Many RCTs have included participants who were not vitamin D deficient at baseline and did not stratify results by baseline 25-hydroxyvitamin D level. Nonwhite race/ethnic groups are underrepresented in RCTs but have increased risk of vitamin D deficiency. For skeletal health, there may be a small effect of vitamin D supplementation on falls, but there does not appear to be an impact on reducing fractures for the general population. The effect on fracture reduction may be significant in elderly women, and with higher doses of vitamin D. For overall mortality, there is also no benefit for the general population. RCTs evaluating extraskeletal, asthma, and multiple sclerosis outcomes have not reported a benefit for vitamin D supplementation. Although vitamin D toxicity and adverse events appear to be rare, few data on risks have been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Background

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, decrease in coagulation, and decrease in inflammatory markers.¹

**Vitamin D Levels**

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 2010 Institute of Medicine (IOM) report concluded that a level of 20 ng/mL is sufficient for most healthy adults.² Some experts, such as the National Osteoporosis Foundation and the American Geriatrics Society, recommend a higher level (30 ng/mL).²

Vitamin D deficiency, as defined by suboptimal serum levels, is common in the United States. In the National Health and Nutrition Examination Survey (NHANES) survey covering the period of 2000-2004, a total of 30% of individuals over the age of 12 had 25-hydroxyvitamin D levels less than 20 ng/mL.³ 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 (NNMS) and the NHANES has indicated that the average consumption is below recommended levels of intake. Yetley³ estimated that average daily intake for U.S. adults ranged from 228 to 335 IU/d, depending on gender and ethnicity. This is below the average daily requirement, estimated by IOM (400 IU/d for healthy adults), and well below IOM’s required daily allowance, which was 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 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 report² concluded that 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. However, other conclusions on this point have differed. The Agency for Healthcare Research and Quality (AHRQ) systematic review on vitamin D and bone health concluded that “There is little evidence from existing trials that vitamin D above current reference intakes is harmful.”⁴ The Women’s Health Initiative (WHI) concluded that hypercalcemia and hypercalciuria in patients receiving calcium and vitamin D were not associated with adverse clinical events.⁵ The WHI did find a small increase in kidney stones for women aged 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,⁶-¹⁰ and these findings have led to the question of whether supplementation improves health outcomes. For example, a relationship between vitamin D levels and overall mortality has been reported in most observational studies examining this relationship.¹¹,¹² Mortality is lowest at vitamin
D levels D 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 identified 107 systematic reviews of observational studies examining the association between vitamin D levels and more than 100 different outcomes.\textsuperscript{13}

**Vitamin D Replacement**

The IOM document recommended reference values for intake of vitamin D and serum levels, based on available literature and expert consensus.\textsuperscript{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, 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.

On the other hand, excessive intake of vitamin D can have toxic effects. These 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 has the potential to exacerbate conditions such as calcium kidney stones and atherosclerotic vascular disease.

IOM defined 3 parameters of nutritional needs for vitamin D, on the assumption of minimal sun exposure. They 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>1-3 years old</td>
<td>400</td>
<td>600</td>
<td>2500</td>
</tr>
<tr>
<td>4-8 years old</td>
<td>400</td>
<td>600</td>
<td>3000</td>
</tr>
<tr>
<td>9-70 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>

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) of 1988. Lab tests for vitamin D are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S.
Food and Drug Administration has chosen not to require any regulatory review of these tests.

**Rationale**
This evidence review was created in September 2015 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 16, 2017.

**Vitamin D deficiency**

**Clinical Context and Test Purpose**
The purpose of vitamin D testing in patients who are asymptomatic for vitamin D deficiency is to inform a decision about whether vitamin D supplementation is needed to replenish serum vitamin D levels to optimal levels for maintaining or improving health outcomes.

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant populations of interest are patients who are not known to have signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended.

Vitamin D testing and supplementation are standard of care in symptomatic patients and patients with conditions for which vitamin D treatment is recommended; these clinical scenarios will not be discussed further. A list of high-risk factors not covered in this review is available in Appendix 1.

**Interventions**
Relevant interventions focus on testing for vitamin D deficiency in asymptomatic adults with the goal of treating patients found to have a deficiency. Treating vitamin D deficiency is usually accomplished through vitamin D supplementation.

**Comparators**
The comparator of interest is 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 even in the absence of known vitamin D deficiency.

**Outcomes**
Through a chain of evidence, test performance characteristics would be linked to health outcomes if individuals with abnormal vitamin D levels were identified and received vitamin D supplementation and if vitamin D supplementation were associated with improved health outcomes. Beneficial or adverse events on health outcomes may be associated with such treatment. Potential outcomes of interest postulated to be associated with decreased vitamin D levels include fractures, falls, cancer, cardiovascular disease, diabetes, and death.
**Timing**
The length of time needed for correction of subclinical vitamin D deficiency to improve outcomes is unknown and probably varies between outcomes.

**Setting**
The setting of interest is primary care. Testing performed in specialty care for patients known to have conditions that are caused by or lead to vitamin D deficiency are not covered here.

**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 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 nonsymptomatic, 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 effectiveness of supplementation from trials testing supplementation to no supplementation in patients who are vitamin D–deficient. Many of the existing randomized controlled trials (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 treatment of all patients to treatment of patients who are vitamin D–deficient.

**Technical Reliability**
The technical reliability of a test is its ability to accurately and reliably measure the marker of interest. Measures of analytic validity include sensitivity (detection rate), specificity (1–false-positive rate), reliability (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables).

Many testing methods are available to measure total serum 25-hydroxyvitamin D (25(OH)D) levels, including competitive protein binding, immunoassay, high performance liquid chromatography, and combined high performance liquid chromatography and mass spectrometry (LC-MS). Concerns over interlaboratory variability in measurement of 25(OH)D led to creation of external quality assurance organizations such as the Vitamin D External Quality Assurance Scheme. The Vitamin D External Quality Assurance Scheme publishes performance characteristics (precision, accuracy, variability) for the tests performed in labs it monitors; results suggest that some methods for measuring 25(OH)D have biases in terms of accuracy and precision as well as variability as high as 15% to 20%. The National Institute of Standards and Technology has reference standards calibrated using a validated liquid chromatography and tandem mass spectrometer (LC-MS/MS) method. Yearly, interlaboratory comparison studies are performed including participating labs and reports are provided on the website. The reports would suggest that median results for serum and plasma materials that are predominantly 25-(OH)D3 in participating labs for both immunoassay and liquid chromatographic techniques are higher than the National Institute of Standards and Technology expanded uncertainty range. Coefficients of variation for all methods combined consistently range from 7% to 19%.

**Clinically Valid**
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(OH)D levels, their sensitivities and specificities for detecting clinically important deficiency are currently unknown.

**Clinically Useful**
No RCTs were found that evaluated clinical outcomes or harms in patients tested for vitamin D deficiency vs 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\(^{13}\); 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.

**Skeletal Health**

Numerous systematic reviews and meta-analyses of RCTs have been published evaluating the impact of vitamin D supplementation on skeletal health outcomes. 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 outcomes 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>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>I(^2), %(^a)</th>
<th>RR for Outcome (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with vitamin D deficiency</td>
<td>Any fracture</td>
<td>5</td>
<td>3551</td>
<td>32</td>
<td>0.98 (0.82 to 1.16)</td>
</tr>
<tr>
<td>LeBlanc et al (2015)(^{12})</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>0.96 (0.72 to 1.29)</td>
</tr>
<tr>
<td></td>
<td>Falls: total</td>
<td>5</td>
<td>1677</td>
<td>70</td>
<td>0.84 (0.69 to 1.02)</td>
</tr>
<tr>
<td></td>
<td>Falls: person</td>
<td>5</td>
<td>1809</td>
<td>64.5</td>
<td>0.66 (0.50 to 0.88)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHRQ (2011)(^{4})</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></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>Avenell et al (2009)(^{18})</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)(^{19})</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</td>
<td>All fractures</td>
<td>4</td>
<td>181</td>
<td>NR</td>
<td>1.0 (0.06 to 15.41)</td>
</tr>
<tr>
<td>Study</td>
<td>Outcome</td>
<td>No. of Studies</td>
<td>No. of Participants</td>
<td>$I^2$, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR for Outcome (95% CI)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>(2009)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>(CKD-RD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bischoff-Ferrari et al (2005)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Hip fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>700-800 IU/d</td>
<td></td>
<td>3</td>
<td>5572</td>
<td>NR</td>
<td>0.74 (0.61 to 0.88)</td>
</tr>
<tr>
<td>400 IU/d</td>
<td></td>
<td>2</td>
<td>3722</td>
<td>NR</td>
<td>1.15 (0.88 to 1.50)</td>
</tr>
<tr>
<td>Non‒vertebral fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>700-800 IU/d</td>
<td></td>
<td>5</td>
<td>6098</td>
<td>NR</td>
<td>0.77 (0.68 to 0.87)</td>
</tr>
<tr>
<td>400 IU/d</td>
<td></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; RCT: randomized controlled trial; RR: relative risk.

<sup>a</sup> Heterogeneity value.

An Agency for Healthcare Research and Quality (AHRQ) review was completed in 2011 on the effectiveness and safety of vitamin D in relation to bone health.<sup>4</sup> Reviewers concluded that:

- The evidence on reduction in fractures was inconsistent. The combined results of trials using vitamin D<sub>3</sub> 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.

One 2005 meta-analysis of double-blind RCTs published estimated the benefit of vitamin D supplementation on fracture risk and examined the dose-response relation between vitamin D and outcomes.<sup>21</sup> 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.

One 2010 RCT (not included in most of the systematic reviews) reported results inconsistent with some of the previous trials and conclusions of meta-analyses.<sup>22</sup> 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=0.03) and a 26% increase in fractures (p=0.02). 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 (eg, 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 randomize 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**
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, including a 2009 AHRQ report.\textsuperscript{23}

The AHRQ report concluded that:

- 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 ascertainment of cardiovascular events.

A 2010 systematic review assessed 5 RCTs evaluating the impact of vitamin D supplementation on incident cardiovascular disease.\textsuperscript{24} None of the 5 trials reported a significant reduction in cardiovascular outcomes in the vitamin D group. Combined analysis of these trials found a relative risk (RR) for cardiovascular outcomes of 1.08 (95% confidence interval [CI], 0.99 to 1.19) in the vitamin D group.

Wang et al (2008) also performed a systematic review on whether vitamin D and calcium prevent cardiovascular events.\textsuperscript{25} 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).
Elamin et al published a systematic review and meta-analysis of cardiovascular outcomes in 2011. 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 (RR=0.96; 95% 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.

**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. Thus, if there are beneficial effects of vitamin D, they may be obscured or attenuated by 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.

**Hypertension**

A 2010 systematic review by Pittas et al included 10 intervention trials that evaluated the relation between vitamin D and hypertension. Most did not report a decrease in incident hypertension associated with vitamin D supplementation. The largest trial with the longest follow-up was the Women’s Health Initiative, which included over 36000 patients. The Women’s Health Initiative trial did not show a reduction in the incidence of hypertension in vitamin D–treated individuals. There was a small, nonsignificant decrease in systolic blood pressure for patients in the vitamin D group (-1.9 mmHg; 95% CI, -4.2 to 0.4 mm Hg) and no change in diastolic blood pressure (-0.1 mm Hg; 95% CI, -0.7 to 0.5 mm Hg).

**Cancer**

In 2014, a Cochrane systematic review assessed the benefits and harms of vitamin D supplementation on prevention of cancer in adults. Reviewers included 18 RCTs (50,623 participants) that compared vitamin D at any dose, duration, and route of administration with placebo or no intervention in healthy adults or diagnosed with a specific disease. Cancer occurred in 1927 (7.6%) of 25,275 participants assigned to vitamin D and in 1943 (7.7%) of 25,348 participants assigned to control interventions (RR=1.00; 95% CI, 0.94 to 1.06) based on GRADE moderate quality evidence. 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. Vitamin D₃ combined with calcium was associated with increased nephrolithiasis (RR=1.17; 95% CI, 1.03 to 1.34).
A 2014 AHRQ report summarized the evidence on vitamin D supplementation and cancer outcomes. Based on a limited number of RCTs, the following conclusions were made:

- One RCT reported no effect of vitamin D on overall cancer mortality in healthy postmenopausal women.
- One RCT reported no effect of vitamin D on overall cancer mortality for elderly men or women.

The evidence on the association between vitamin D levels and cancer was reviewed by the Institute of Medicine in 2011, with the following conclusions:

- A small number of studies addressed this question and they showed a lack of consistency in associations between vitamin D intake, or levels, and all cancer mortality.
- Most available RCTs did not have cancer as a prespecified primary outcome; thus, the validity of the data was less than optimal.
- Overall, the evidence was insufficient to form conclusions about the association of vitamin D with cancer.

In 2015, Baron et al published results of a 2×2 factorial RCT of supplementation with vitamin D and/or calcium for the prevention of colorectal adenomas. The trial enrolled 2259 patients with recently diagnosed adenomas and no known colorectal polyps remaining after complete colonoscopy. Patients received treatment and continued follow-up for 3 to 5 years and the primary outcome was adenomas diagnosed through colonoscopy. Overall, 1301 (43%) of patients had 1 or more adenomas. Relative risks for recurrent adenomas were adjusted for age, clinical center, anticipated surveillance interval (3 or 5 years), sex, type of randomization, and number of baseline adenomas. The adjusted relative risk for recurrent adenomas was 0.99 (95% CI, 0.89 to 1.09) with vitamin D vs no vitamin D. The findings for advanced adenomas were similar. There were few serious adverse events, and rates of hypercalcemia did not differ between vitamin D and no vitamin D.

Lappe et al (2017) reported results of the Clinical Trial of Vitamin D3 to Reduce Cancer Risk in Postmenopausal Women (CAPS). CAPS was a double-blind, placebo-controlled randomized trial of vitamin D3 and calcium including 2303 healthy, postmenopausal, noninstitutionalized women in 31 rural counties in Nebraska. The women were randomized to vitamin D 2000 IU/d plus calcium 1500 mg/d (n=1156) or matching placebos (n=1147) for a period of 4 years. The primary outcome was time to first diagnosis of any type of cancer (excluding nonmelanoma skin cancers) over 4 years. The trial was conducted from June 2009 to August 2015. A total of 2064 (90%) women completed the 4 years of study and 2197 (95%) provided at least 6 months of follow-up data. Mean baseline 25(OH)D level was 32.8 ng/mL. Mean achieved 25(OH)D levels during follow-up were 43.6 ng/mL (95% CI, 42.9 to 44.3 ng/mL) in the vitamin D3 plus calcium group and 31.6 ng/mL (95% CI, 31.0 to 32.2 ng/mL) in the placebo group. Ninety-three women in the vitamin D3 plus calcium group discontinued their intervention early.
due to adverse events compared with 76 in the placebo group. Kaplan-Meier estimated cancer incidence was 4.2% (95% CI, 3.2% to 5.6%) in the vitamin D3 plus calcium group and 6.0% (95% CI, 4.8% to 7.6%) in the placebo group (HR=0.70; 95% CI, 0.47 to 1.02; p=0.06). In a post hoc analysis of achieved 25(OH)D levels, the estimated HR for cancer incidence for 25(OH)D levels between 30 ng/mL and 55 ng/mL compared with 30 ng/mL was 0.65 (95% CI, 0.44 to 0.97). Breast cancer was the most commonly first diagnosed cancer, with 16 diagnoses in the vitamin D$_3$ plus calcium group and 23 diagnoses in the placebo group. There were no serious supplement-related adverse events. Because of the study design, the separate effects of interventional calcium and vitamin D$_3$ cannot be assessed. The women in this trial had higher baseline 25(OH)D levels than the U.S. population based on the U.S. National Health and Nutrition Examination Surveys and therefore might not be representative of the target population. Moreover, the participants were almost entirely non-Hispanic, white women, which limits generalizability to men and other racial/ethnic groups. The trial was powered to detect a 50% risk reduction; however, a 50% reduction is unlikely to be the minimally clinically important difference. Smaller risk reductions in all-cause cancer (eg, the 30% estimated reduction) would also be clinical important.

**Section Summary: Cancer**

Many RCTs have been examined the effect of vitamin D supplementation on cancer outcomes, although cancer was not the prespecified primary outcome in most. The CAPS trial was designed with all-cause cancer as the primary outcome. The current evidence does not demonstrate that vitamin D supplementation reduces the incidence of cancer.

**Asthma**

Several systematic reviews of vitamin D supplementation for prevention of asthma exacerbations have been published. Three recent reviews are summarized in Tables 3 and 4. Thirteen unique RCTs were included in the 3 systematic reviews (see Table 5). The Jolliffe (2017) and Martineau (2016) reviews 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 (2017) and Martineau (2016) reviews found that vitamin D supplementation reduced the rate (or proportion) of asthma exacerbations requiring treatment with systemic corticosteroids. The Martineau (2016) and Luo (2015) reviews found that vitamin D had no effect on Asthma Control Test scores, forced expiratory volume in 1-second outcomes, or rates of adverse events. The Jolliffe review 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=0.25).
### Table 3. Vitamin D and Asthma Systematic Review Characteristics

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jolliffe et al (2017) [33]; PROSPERO CRD42014013953</td>
<td>Up to Oct 2016</td>
<td>8</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) [34]</td>
<td>Up to Jan 2016</td>
<td>9</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>4-12 mo</td>
</tr>
<tr>
<td>Luo et al (2015) [35]</td>
<td>1946 to July 2015</td>
<td>7</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 4. Vitamin D and Asthma Systematic Review Results

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Asthma Exacerbation</th>
<th>Asthma Exacerbation Requiring SCS</th>
<th>ACT Score</th>
<th>FEV(_1)</th>
<th>Proportion of Patients With AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jolliffe et al (2017) [33]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>868</td>
<td>955</td>
<td>NR</td>
<td>NR</td>
<td>955</td>
</tr>
<tr>
<td>Pooled effect</td>
<td>HR=0.78</td>
<td>RR=0.74</td>
<td></td>
<td>OR=0.87(^d)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.55 to 1.10</td>
<td>0.56 to 0.97</td>
<td></td>
<td>0.46 to 1.63</td>
<td></td>
</tr>
<tr>
<td>I(^2)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Martineau et al (2016) [34]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>999</td>
<td>963</td>
<td>713</td>
<td>387</td>
<td>879</td>
</tr>
<tr>
<td>Pooled effect</td>
<td>OR=0.53</td>
<td>OR=0.39(^a)</td>
<td>Diff = - 0.08</td>
<td>Diff=0.48 (%b)</td>
<td>OR=1.01(^d)</td>
</tr>
<tr>
<td>95% CI</td>
<td>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</td>
<td>0.93 to 1.89</td>
<td>0.54 to 1.89</td>
</tr>
<tr>
<td>I(^2)</td>
<td>65%</td>
<td>0%</td>
<td>21%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Luo et al (2015) [35]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>820</td>
<td>NR</td>
<td>250</td>
<td>316</td>
<td>326</td>
</tr>
<tr>
<td>Pooled effect</td>
<td>OR=0.66</td>
<td>Diff = - 0.05</td>
<td>Diff = - 0.02(^c)</td>
<td>OR=1.16</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.32 to 1.37</td>
<td>-0.30 to 0.20</td>
<td>-0.15 to 0.11</td>
<td>0.74 to 1.81</td>
<td></td>
</tr>
<tr>
<td>I(^2)</td>
<td>81%</td>
<td>NA</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

ACT: Asthma Control Test; AE: adverse event; Diff: difference; FEV\(_1\): forced expiratory volume in 1 second; HR: hazard ratio; NA: not applicable; NR: not reported; OR: odds ratio; RR: relative risk; SCS: systemic corticosteroid.

\(^a\) Outcome was proportion with ≥1 exacerbations.
\(^b\) FEV\(_1\), % predicted.
\(^c\) At 12 months.
\(^d\) Serious adverse events.
Table 5. Comparison of Randomized Controlled Trials Included in the Systematic Reviews

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Worth et al (1994)</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Majak et al (2009)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Urashima et al (2010)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Majak et al (2011)</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Lewis et al (2012)</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Baris et al (2014)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Castro et al (2014)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Yadav et al (2014)</td>
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<td>●</td>
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<tr>
<td>Martineau et al (2015)</td>
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<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Tachimoto et al (2016)</td>
<td></td>
<td>●</td>
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<tr>
<td>Jensen et al (2016)</td>
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<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Kerley et al (2016)</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>

●: included in systematic review.

An RCT of prenatal supplementation in 881 pregnant women at high risk of having children with asthma was published in 2016. 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. The proportion of infants with asthma or recurrent wheeze was 24% in the 4400 IU group versus 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.

Section Summary: Asthma
Results of RCTs 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 severity of asthma. In general, patients were not selected based on 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.

Multiple Sclerosis
Three systematic reviews have examined the effect of vitamin D supplementation in patients with multiple sclerosis. Reviewers described 6 RCTs, all of which were small (n<100). Patient follow-up ranged from 6 months to 2 years, and
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**

A number of meta-analyses of RCTs of vitamin D supplementation have examined the benefit of vitamin D supplementation on overall mortality. Table 6 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 2015 meta-analysis of patients with vitamin D deficiency. This report included 11 studies and found a marginally significant reduction in overall mortality, with a confidence interval 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.

An AHRQ performed 2 evidence reports on the health effects of vitamin D supplementation. The most recent was published in 2014, updating 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 6. Systematic Reviews of RCTs on 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, %ᵃ</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>Leblanc et al (2015)⁽¹²⁾</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><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chowdhury et al (2014)⁽³⁴⁾</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>
</tbody>
</table>
Section Summary: Overall Mortality
Evidence from a number of systematic reviews and meta-analyses does not support a benefit on overall mortality for the general, noninstitutionalized population. Populations included in the studies varied by baseline vitamin D deficiency and administration of vitamin D.

Summary of Evidence
For individuals who are asymptomatic without conditions or risk factors for which vitamin D treatment is recommended who receive testing of vitamin D levels, the evidence includes no RCTs of clinical utility (ie, evidence that patient care including testing vitamin D levels vs care without testing vitamin D levels improves outcomes). Indirect evidence of the potential utility of testing includes many RCTs and systematic reviews of vitamin D supplementation. Relevant outcomes are overall survival, test accuracy and validity, symptoms, morbid events, and treatment-related morbidity. There is a lack of standardized vitamin D testing strategies and cutoffs for vitamin D deficiency are not standardized or evidence-based. In addition, despite the large quantity of evidence, considerable uncertainty remains about the beneficial health effects of vitamin D supplementation. Many RCTs have included participants who were not vitamin D deficient at baseline and did not stratify results by baseline 25(OH)D level. Nonwhite race/ethnic groups are underrepresented in RCTs but have increased risk of vitamin D deficiency. For skeletal health, there may be a small effect of vitamin D supplementation on falls, but there does not appear to be an impact on reducing fractures for the general population. The effect on fracture reduction may be significant in elderly women, and with higher doses of vitamin D. For patients with asthma, there may be a reduction in severe exacerbations with vitamin D supplementation, but there does not appear to be an effect on other asthma outcomes. For overall mortality, there is also no benefit for the general population. RCTs evaluating extraskeletal, cancer, cardiovascular, and multiple sclerosis outcomes have not reported a statistically significant benefit for vitamin D supplementation. Although vitamin D toxicity and adverse events appear to be rare, few data on risks have been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements
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(OH)D (25-hydroxyvitamin 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(OH)2D (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 issued a committee opinion (2011) 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
In 2014, the American Academy of Family Physicians concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force published a recommendation in 2014 and associated guidelines in 2015 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 unpublished trials that might influence this review are listed in Table 7.
<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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</thead>
<tbody>
<tr>
<td>Ongoing</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NCT01169259</td>
<td>Vitamin D and Omega-3 Trial (VITAL)</td>
<td>25,871</td>
<td>Jun 2018</td>
</tr>
<tr>
<td>NCT01490502</td>
<td>A Randomized Controlled Trial of Vitamin D Supplementation in Multiple Sclerosis (VIDAMS)</td>
<td>172</td>
<td>Mar 2019</td>
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<tr>
<td>NCT00920621</td>
<td>Randomized Trial: Maternal Vitamin D Supplementation to Prevent Childhood Asthma (VDAART)</td>
<td>876</td>
<td>Jun 2019</td>
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<tr>
<td>NCT02166333</td>
<td>Vitamin D Supplements to Prevent Falls in Older Adults: A Dose-Response Trial (STURDY)</td>
<td>1200</td>
<td>Dec 2019</td>
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<tr>
<td>Unpublished</td>
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<tr>
<td>NCT01153568</td>
<td>Vitamin D and Osteoporosis Prevention in Elderly African American Women: A 4-year Randomized, Double-blind, Placebo-controlled Study to Investigate the Effect of Vitamin D Status in Elderly African American Women</td>
<td>260</td>
<td>Oct 2016 (completed)</td>
</tr>
<tr>
<td>NCT02424552</td>
<td>EVITA Trial: Effect of Vitamin D as add-on Therapy for Vitamin D Insufficient Patients With Severe Asthma: a Randomized, Double-blind, Placebo-controlled Trial</td>
<td>54</td>
<td>Feb 2017 (terminated)</td>
</tr>
<tr>
<td>NCT02750293</td>
<td>The Effect of Vitamin D Supplementation on Cardiovascular Risk Factors in Subjects With Low Serum 25-hydroxyvitamin D Levels (D-COR)</td>
<td>411</td>
<td>Sep 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References

13. 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


22. 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):1815-1822. PMID 20460620


**Billing Coding/Physician Documentation Information**

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<tr>
<th>Code</th>
<th>Description</th>
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<td>82306</td>
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</tr>
<tr>
<td>82652</td>
<td>Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed</td>
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</tbody>
</table>

**ICD-10 Codes**

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<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A15.9</td>
<td>Respiratory tuberculosis code range</td>
</tr>
<tr>
<td>A17.9</td>
<td>Tuberculosis of nervous system code range</td>
</tr>
<tr>
<td>A18.89</td>
<td>Tuberculosis of other organs code range</td>
</tr>
<tr>
<td>A19.9</td>
<td>Miliary tuberculosis code range</td>
</tr>
<tr>
<td>B18.2</td>
<td>Chronic viral hepatitis C code range</td>
</tr>
<tr>
<td>C18.9</td>
<td>Malignant neoplasm of colon, unspecified</td>
</tr>
<tr>
<td>C43.9</td>
<td>Malignant melanoma of skin code range</td>
</tr>
<tr>
<td>C44.99</td>
<td>Other and unspecified malignant neoplasm of skin code range</td>
</tr>
<tr>
<td>C50.912</td>
<td>Malignant neoplasm of unspecified site of left female breast</td>
</tr>
<tr>
<td>C50.919</td>
<td>Malignant neoplasm of unspecified site of unspecified female breast</td>
</tr>
<tr>
<td>C53.9</td>
<td>Malignant neoplasm of cervix uteri, unspecified</td>
</tr>
<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
</tr>
</tbody>
</table>
C73  Malignant neoplasm of thyroid gland
C81-  Hodgkin lymphoma code range
C81.99  Follicular lymphoma code range
C82-  Non-follicular lymphoma code range
C83-  Mature T/NK-cell lymphomas code range
C84.79  Other specified and unspecified types of non-Hodgkin lymphoma code range
C85-  Other specified types of T/NK-cell lymphoma code range
C86.6  Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C88.4  Other malignant immunoproliferative diseases
C88.9  Malignant immunoproliferative disease, unspecified
C90.00  Multiple myeloma not having achieved remission
C90.01  Multiple myeloma in remission
C91.01  Acute lymphoblastic leukemia, in remission
C91.40  Hairy cell leukemia not having achieved remission
C91.41  Hairy cell leukemia, in remission
C92.01  Acute myeloblastic leukemia, in remission
C93.11  Chronic myelomonocytic leukemia, in remission
C96.0  Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.2  Malignant mast cell tumor
C96.4  Sarcoma of dendritic cells (accessory cells)
C96.9  Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
C96.A  Histiocytic sarcoma
C96.Z  Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D04-  Carcinoma in situ of skin code range
D04.9  Functional disorders of polymorphonuclear neutrophils (includes chronic granulomatous disease)
D86-  Sarcoidosis code range
D86.9  Acute thyroiditis
E06.0  Subacute thyroiditis
E06.1  Chronic thyroiditis with transient thyrotoxicosis
E06.3  Autoimmune thyroiditis
E06.5  Other chronic thyroiditis
E06.9  Thyroiditis, unspecified
E20.0-  Hypoparathyroidism code range
E20.9 Hyperparathyroidism and other disorders of parathyroid gland
E21.5 Vitamin D deficiency codes
E55.9 Moderate protein-calorie malnutrition
E56.9 Mild protein-calorie malnutrition
E45 Retarded development following protein-calorie malnutrition
E46 Unspecified protein-calorie malnutrition
E67.3 Hypervitaminosis D
E67.8 Other specified hyperalimentation
E70- Disorders of aromatic amino acid metabolism code range
E71- Disorders of branched-chain amino acid metabolism and fatty-acid metabolism code range
E72- Other disorders of amino-acid metabolism code range
E72.4 Disorder of glycine metabolism, unspecified
E72.50 Non-ketotic hyperglycinemia
E72.59 Other disorders of glycine metabolism
E72.8 Other specified disorders of amino-acid metabolism
E72.9 Disorder of amino-acid metabolism, unspecified
E83.30 Disorder of phosphorus metabolism, unspecified
E83.31 Familial hypophosphatemia
E83.32 Hereditary vitamin D-dependent rickets (type 1) (type 2)
E83.39 Other disorders of phosphorus metabolism
E83.50 Unspecified disorder of calcium metabolism
E83.51 Hypocalcemia
E83.52 Hypercalcemia
E83.59 Other disorders of calcium metabolism
E84- Cystic fibrosis code range
E89.2 Postprocedural hypoparathyroidism
G35 Multiple sclerosis
G73.7 Myopathy in diseases classified elsewhere
K20.0 Eosinophilic esophagitis
K50- Crohn's disease [regional enteritis] code range
K50.919 Ulcerative colitis code range
K51- Eosinophilic gastritis or gastroenteritis
K52.81 Eosinophilic colitis
K70.0- Diseases of liver code range (chronic codes are distributed throughout the section – such as K72.10, K73.0-K73.9, K76.1 and cirrhosis codes include
K70.30-K70.31, K71.7, K74.60, K74.69)

K83.0- Other diseases of biliary tract code range (includes obstructive jaundice
K83.1)

K87 Disorders of gallbladder, biliary tract and pancreas in diseases classified elsewhere

K90.0- Intestinal malabsorption code range (K90.0 is celiac disease)
K90.9

L40- Psoriasis code range
L40.9

L56- Other acute skin changes due to ultraviolet radiation
L56.9

L57- Skin changes due to chronic exposure to nonionizing radiation code range
L57.9

L85.3 Xerosis cutis

M32- Systemic lupus erythematosus (SLE) code range
M32.9

M33- Dermatopolymyositis code range
M33.19

M33.9- Dermatopolymyositis, unspecified code range
M33.99

M60.8- Other myositis code range
M60.9

M79.1 Myalgia
M79.7 Fibromyalgia

M80- Osteoporosis with current pathological fracture code range
M80.88XS

M81- Osteoporosis without current pathological fracture code range
M81.8

M83- Adult osteomalacia code range
M83.9

M85.8- Other specified disorders of bone density and structure (includes osteosclerosis and osteopenia)
M85.9

M89.9 Disorder of bone, unspecified
M94.9 Disorder of cartilage, unspecified

N18.1- Chronic kidney disease (CKD) code range
N18.9

N20- Calculus of kidney and ureter code range
N20.9

N21- Calculus of lower urinary tract code range
N21.9

N25.0 Renal osteodystrophy

P71- Transitory neonatal disorders of calcium and magnesium metabolism code range
P71.9

Q44.2 Atresia of bile ducts
Q61- Cystic kidney disease code range
Q61.9

Q78.0 Osteogenesis imperfect
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Q78.2 Osteopetrosis
Q98.4 Klinefelter syndrome, unspecified
Q98.0 Klinefelter syndrome karyotype 47, XXY
Q98.1 Klinefelter syndrome, male with more than two X chromosomes
Q98.3 Other male with 46, XX karyotype
R17 Unspecified jaundice
R25.2 Cramp and spasm
R41- Other symptoms and signs involving cognitive functions and awareness code range
R41.9 Other malaise and fatigue
R53.8- Other long term (current) drug therapy
R53.83
Z21 Asymptomatic human immunodeficiency virus [HIV] infection status
Z51.11 Encounter for antineoplastic chemotherapy
Z79.51 Long term (current) use of inhaled steroids
Z79.52 Long term (current) use of systemic steroids
Z79.899 Other long term (current) drug therapy
Z94.4 Liver transplant status

Additional Policy Key Words
N/A

Policy Implementation/Update Information

12/1/15 New policy. may be considered medically necessary for patients with signs or symptoms of vitamin D deficiency or excess, in patients at high risk for vitamin D deficiency
9/1/16 Added ICD-10 Codes
12/1/16 No policy statement changes.
9/22/17 Added additional ICD-10 Codes
12/1/17 No policy statement changes.
12/1/18 No policy statement changes.

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