Introduction

Vitamin D is an important nutrient for maintaining good health. It is especially important for good bone health and calcium metabolism. Many studies and articles have been published in scientific journals and in lay magazines about the benefits of vitamin D. Despite all of this interest, there is very little data about optimal levels of vitamin D, and most published studies are of low quality. The endocrine society and public health experts strongly recommend against measuring vitamin D levels in healthy individuals. Vitamin D is found in some foods, has been added to other foods (cereals and milk), and is increased with exposure to the sun. The U.S. National Institutes of Health (NIH) has recommended vitamin D supplementation for Americans based on age (600 IU per day for ages 1 to 70 years of age). Testing for vitamin D levels is covered when a person has signs or symptoms of vitamin D deficiency or risk factors for vitamin D deficiency.

Claims for vitamin D tests are reviewed after submission based on the diagnosis listed. The diagnoses considered medically necessary, that are covered, are listed in this medical policy.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
# Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Testing Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Asymptomatic      | Testing vitamin D levels is considered not medically necessary for asymptomatic patients when criteria in this policy are not met. Testing vitamin D levels is considered medically necessary for asymptomatic patients when:  
  - The patient has risk factors for vitamin D deficiency:  
    - Chronic kidney disease, stage >3  
    - Cirrhosis/chronic liver disease  
    - Malabsorption states  
    - Osteomalacia  
    - Osteoporosis  
    - Rickets  
    - Hypo- or hyper-calcemia  
    - 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 patient is institutionalized (see Definition of Terms) |

<table>
<thead>
<tr>
<th>Testing Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Symptomatic = Vitamin D Deficiency | Testing vitamin D levels may be considered medically necessary when the patient presents with signs and symptoms of vitamin D deficiency.  
  - 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 |
Testing Condition | Medical Necessity
---|---
a decision to test vitamin D levels.
o 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.
o 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.

**Symptomatic = Vitamin D Toxicity** (hypervitaminosis D)

Testing vitamin D levels may be considered medically necessary when the patient presents with signs and symptoms of vitamin D toxicity (hypervitaminosis D).

- Signs and symptoms of vitamin D toxicity 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.

**Repeat testing**
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 is rarely necessary, however, in cases where, 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.

**Coding**
The following codes are specific to vitamin D testing and related to medically necessary diagnoses:
<table>
<thead>
<tr>
<th>Code</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>82306</td>
<td>Vitamin D; 25 hydroxy, includes fraction(s), if performed</td>
</tr>
<tr>
<td>82652</td>
<td>Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed</td>
</tr>
<tr>
<td>ICD-10 Diagnosis Codes - Covered</td>
<td></td>
</tr>
<tr>
<td>D71</td>
<td>Functional disorders of polymorphonuclear neutrophils</td>
</tr>
<tr>
<td>D86.0 – D86.9</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>E20.0 – E20.9</td>
<td>Hypoparathyroidism, code range</td>
</tr>
<tr>
<td>E21.0 – E21.5</td>
<td>Hyperparathyroidism and other disorders of parathyroid gland</td>
</tr>
<tr>
<td>E41</td>
<td>Nutritional marasmus</td>
</tr>
<tr>
<td>E43</td>
<td>Unspecified severe protein-calorie malnutrition</td>
</tr>
<tr>
<td>E55.0; E55.9</td>
<td>Vitamin D deficiency codes</td>
</tr>
<tr>
<td>E67.3</td>
<td>Hypervitaminosis D</td>
</tr>
<tr>
<td>E72.0 – E72.09</td>
<td>Disorders of amino-acid transport, unspecified</td>
</tr>
<tr>
<td>E74.21</td>
<td>Galactosemia</td>
</tr>
<tr>
<td>E83.30 – E83.39</td>
<td>Disorder of phosphorus metabolism</td>
</tr>
<tr>
<td>E83.50 – E83.59</td>
<td>Disorder of calcium metabolism</td>
</tr>
<tr>
<td>E89.2</td>
<td>Postprocedural hypoparathyroidism</td>
</tr>
<tr>
<td>K70.0 – K77</td>
<td>Disorders of the liver, code range</td>
</tr>
<tr>
<td>K83.0 – K83.9</td>
<td>Other diseases of biliary tract</td>
</tr>
<tr>
<td>K90.0 – K90.9</td>
<td>Intestinal malabsorption, code range</td>
</tr>
<tr>
<td>K91.2</td>
<td>Postsurgical malabsorption, not elsewhere classified</td>
</tr>
<tr>
<td>M80.00 – M81.8</td>
<td>Osteoporosis, code range</td>
</tr>
<tr>
<td>M83.0 – M83.9</td>
<td>Osteomalacia, code range</td>
</tr>
<tr>
<td>M85.80 – M85.9</td>
<td>Other specified disorders of bone density and structure</td>
</tr>
<tr>
<td>N18.1 – N18.9</td>
<td>Chronic kidney disease (CKD), code range</td>
</tr>
<tr>
<td>N20.0 – N20.9</td>
<td>Calculus of kidney and ureter</td>
</tr>
<tr>
<td>N22</td>
<td>Calculus of urinary tract in diseases classified elsewhere</td>
</tr>
<tr>
<td>Code</td>
<td>Descriptor</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------------------------------</td>
</tr>
<tr>
<td>N25.81</td>
<td>Secondary hyperparathyroidism of renal origin</td>
</tr>
<tr>
<td>P71.0 – P71.9</td>
<td>Transitory neonatal disorders of calcium and magnesium metabolism</td>
</tr>
<tr>
<td>Q78.0</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>Q78.2</td>
<td>Osteopetrosis</td>
</tr>
<tr>
<td>R17</td>
<td>Unspecified jaundice</td>
</tr>
<tr>
<td>Z79.52</td>
<td>Long term (current) use of systemic steroids</td>
</tr>
<tr>
<td>Z79.899</td>
<td>Other long term (current) drug therapy</td>
</tr>
</tbody>
</table>

**Related Information**

**Definition of Terms**

**Institutionalized**: For the purposes of this policy, refers to patients who live in long-term care facilities where some degree of medical care is provided. Examples include long-term care hospitals, nursing homes, assisted living facilities, and similar environments.

**Benefit Application**

Consistent with federal mandates, vitamin D supplements are covered as preventive care for individuals age 65 and older (without cost sharing) when the member’s contract is subject to those mandates. A written prescription is needed for coverage.

The USPSTF recommends exercise or physical therapy and vitamin D supplementation to prevent falls in community-dwelling adults aged 65 years or older who are at increased risk for falls. (Grade B recommendation)

**Note**: The USPSTF does not recommend routine testing of vitamin D levels as a preventive strategy. (See Practice Guidelines and Position Statements).
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 (i.e., 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.

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. Some experts, such as the National Osteoporosis Foundation and the American Geriatrics Society, recommend a higher level (30 ng/mL).
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. 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. Yetley 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 the Institute of Medicine (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 report 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.” 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. 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, 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. 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 identified 107 systematic reviews of observational studies examining the association between vitamin D levels and more than 100 different outcomes.
Vitamin D Replacement

The IOM document recommended reference values for intake of vitamin D and serum levels, based on available literature and expert consensus. 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 1. Institute of Medicine Recommendations for Vitamin D Dietary Intake

<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>
Review of Evidence

This policy was updated with literature review through October 10, 2016.

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.

Intervention

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.

Comparator

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 effects 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.

Time

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.
Based on this analytic framework, the most relevant studies are those trials that test vitamin D levels and enroll only patients who are vitamin D deficient. Many of the existing RCTs, including the largest trial (Women’s Health Initiative [WHI]), did not test vitamin D levels prior to treatment. Rather, they treated all patients who are 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.

The evidence on vitamin D supplementation for particular outcomes is reviewed next.

**Analytic Validity**

Analytic validity is the ability of a test 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 (DEQAS).¹⁴ DEQAS 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 (NIST) has reference standards calibrated using a validated liquid chromatography and tandem mass spectrometer (LC-MS/MS) method.¹⁵ Yearly, interlaboratory comparison studies are performed including participating labs and reports are provided on the website. The reports 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 NIST expanded uncertainty range. Coefficients of variation (CV) for all methods combined consistently range from 7% to 19%.

**Clinical Validity**

There is no consensus on how to define vitamin D deficiency or an accepted reference standard. Available cutoffs for deficiency are neither standardized nor based on rigorous scientific studies.¹⁶ 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.

**Clinical Utility**

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 testing might be useful.

A large number of RCTs have evaluated the impact of vitamin D supplementation on outcomes. Theodoratou et al 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 look at bone mineral density and/or other physiologic measures of bone health are not included. Table 2 gives a summary of the results of systematic reviews that performed quantitative meta-analyses on the relevant outcomes.

Among the trials included in the meta-analyses, few are large studies; most are small or moderate in size and limited by a small number of outcomes events. There is inconsistency in the results, especially for studies of fracture prevention, as evidenced by the relative large degree of heterogeneity among the studies.

Table 2. Systematic Reviews of RCTs on 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>Heterogeneity, $I^2$</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 (2015)</td>
<td>Any fracture</td>
<td>5</td>
<td>3,551</td>
<td>32%</td>
<td>0.98a (0.82 to 1.16)</td>
</tr>
<tr>
<td></td>
<td>Hip fracture</td>
<td>4</td>
<td>1,619</td>
<td>46%</td>
<td>0.96a (0.72 to 1.29)</td>
</tr>
<tr>
<td></td>
<td>Falls: total</td>
<td>5</td>
<td>1,677</td>
<td>70%</td>
<td>0.84a (0.69 to 1.02)</td>
</tr>
<tr>
<td></td>
<td>Falls: person</td>
<td>5</td>
<td>1,809</td>
<td>64.5%</td>
<td>0.66a (0.50 to 0.88)</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHRQ (2011)</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>9,262</td>
<td>0%</td>
<td>0.84 (0.76 to 0.93)</td>
</tr>
<tr>
<td>Avenell (2009)</td>
<td>All fractures</td>
<td>10</td>
<td>25,016</td>
<td></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></td>
<td>1.15 (0.99 to 1.33)</td>
</tr>
<tr>
<td>Study</td>
<td>Outcome</td>
<td>No. of Studies</td>
<td>No. of Participants</td>
<td>Heterogeneity, $I^2$</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></td>
<td>Vertebral fracture</td>
<td>5</td>
<td>9,138</td>
<td></td>
<td>0.90 (0.97 to 1.1)</td>
</tr>
<tr>
<td>Bischoff-Ferrari (2009)$^{19}$</td>
<td>Non-vertebral fracture</td>
<td>5</td>
<td>7,130</td>
<td></td>
<td>0.79 (0.63 to 0.99)</td>
</tr>
<tr>
<td>Palmer (2009)$^{20}$</td>
<td>All fractures (CKD-RD)</td>
<td>4</td>
<td>181</td>
<td></td>
<td>1.0 (0.06 to 15.41)</td>
</tr>
<tr>
<td>Bischoff-Ferrari (2005)$^{21}$</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>700-800 IU/d</td>
<td>Non-vertebral fracture</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>1.30 (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; RCT: randomized controlled trial; RR: relative risk. $^a$ Risk ratio reported rather than relative risk.

An AHRQ review was completed in 2011 on the effectiveness and safety of vitamin D in relation to bone health.$^4$ This review concluded that:

- The evidence on reduction in fractures is 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 is 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 systematic review of double-blind RCTs published in 2005 estimated the benefit of vitamin D supplementation on fracture risk and examined the dose-response relationship between vitamin D and outcomes.$^{21}$ Based on meta-analysis of 5 RCTs that used high-dose vitamin D, this review 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 RCT published in 2010 (not included in most of the systematic reviews) reported results that are 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=0.03) and a 26% increase in fractures (p=0.02). In addition, there was a temporal relationship to the increase in fall risk, with the risk greatest in the time 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 select patients for vitamin D deficiency and randomize 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 treat all patients regardless of vitamin D levels, results were similar. There is no association overall between vitamin D supplementation and reduction in fracture risk, and there is a small reduction in 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. This evidence demonstrates that, overall, there is little if any reduction in fractures after vitamin D supplementation. Therefore, the evidence does not demonstrate an improvement in skeletal health outcomes with vitamin D supplementation.

**Cardiovascular Disease**

A large number of trials report on the impact of vitamin D supplementation on cardiovascular events. A number of systematic reviews have examined the relationship between vitamin D and cardiovascular outcomes, including an AHRQ report in 2009.

- 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 pre-specified primary outcome.

• These analyses have been hampered by low numbers of cardiovascular events and imperfect methods for ascertainment of cardiovascular events.

In another systematic review published in 2010, 5 RCTs evaluating the impact of vitamin D supplementation on incident cardiovascular disease were reviewed. 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 also performed a systematic review on whether vitamin D and calcium prevent cardiovascular events. There were 8 RCTs of vitamin D supplementation in the general population that 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 and 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 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, but 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. Recent research has 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 systematic review by Pittas et al24 included 10 intervention trials that evaluated the relationship 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 WHI, which included over 36,000 patients.28 The WHI study 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).

Cancer

In 2014, a Cochrane systematic review and meta-analysis assessed the benefits and harms of vitamin D supplementation on prevention of cancer in adults.29 Reviewers included 18 RCTs (50,623 participants) that compared vitamin D at any dose, duration, and route of administration to 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 receive vitamin D versus 1943 (7.7%) of 25,348 participants assigned to receive 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 to 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).

The 2014 AHRQ report summarized the evidence on vitamin D supplementation and cancer outcomes.30 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 IOM2 with the following conclusions:
• There are a small number of studies that address this question which show a lack of consistency in associations between vitamin D intake, or levels, and all cancer mortality.

• Most available RCTs do not have cancer as a pre-specified primary outcome, thus the validity of the data is less than optimal.

• Overall, the evidence is 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 versus no vitamin D. The findings for advanced adenomas were similar. There were few serious adverse events, and hypercalcemia did not differ between vitamin D and no vitamin D.

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 current evidence suggests that vitamin D supplementation does not reduce the incidence of cancer.

Asthma

A 2015 meta-analysis of the effect of vitamin D supplementation plus asthma controller medication on acute asthma exacerbation and lung function was published. Seven RCTs from 7 countries (total N=903 patients) published up to July 2015 were selected. Three studies included children and 4 included adults. Doses as well as routes and lengths of administration of vitamin D varied by study, as did asthma severity. Mean baseline 25-OH(D) levels ranged from 19 to 21 ng/mL. The pooled relative risk (vitamin D vs control) of asthma exacerbation was 0.66 (95% CI, 0.32 to 1.37). There was no effect of vitamin D on difference in mean in forced expiratory volume in 1 second) or Asthma Control Test score.
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 been mixed 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. 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 (MS). 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 3 summarizes the most recent meta-analyses. The individual studies range in size from fewer than 100 to several thousand patients. No significant heterogeneity was reported for these included trials.
The most relevant information comes from the meta-analysis of patients with vitamin D deficiency. This report included 11 total studies and reported a marginally significant reduction in overall mortality, with a confidence interval that approached 1.0. When subgroup analysis was performed, it appeared that most of the benefit was restricted to patients who were institutionalized, whereas in community-dwelling patients there was no reduction in mortality.

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 the 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 did not show a significant reduction in mortality. The single analysis that did show a significant reduction was that by Chowdhury et al, who reported a marginally significant result for vitamin D₃ supplementation but not for vitamin D₂ supplementation.

### Table 3. Systematic Reviews of RCTs on 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>Heterogeneity, I²</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 (2015)</td>
<td>Mortality (all patients)</td>
<td>11</td>
<td>4,126</td>
<td>0%</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Mortality (noninstitutionalized patients)</td>
<td>8</td>
<td>2,947</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 (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>Bjelakovic (2011)</td>
<td>Mortality (vitamin D₂)</td>
<td>8</td>
<td>17,079</td>
<td></td>
<td>1.04 (0.97 to 1.11)</td>
</tr>
<tr>
<td></td>
<td>Mortality (vitamin D₁)</td>
<td>9</td>
<td>12,824</td>
<td></td>
<td>0.91 (0.82 to 1.02)</td>
</tr>
<tr>
<td>Study</td>
<td>Outcome</td>
<td>No. of Studies</td>
<td>No. of Participants</td>
<td>Heterogeneity, $I^2$</td>
<td>RR for Outcome (95% CI)</td>
</tr>
<tr>
<td>----------------</td>
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<td>---------------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>Palmer (2009)</td>
<td>Mortality (CKD-RD)</td>
<td>5</td>
<td>233</td>
<td></td>
<td>1.34 (0.34 to 5.24)</td>
</tr>
<tr>
<td>Palmer (2009)</td>
<td>Mortality (CKD)</td>
<td>4</td>
<td>477</td>
<td></td>
<td>1.40 (0.38 to 5.15)</td>
</tr>
</tbody>
</table>

CI: confidence interval; CKD: chronic kidney disease; CKD-HD: chronic kidney disease on renal dialysis; RCT: randomized controlled trial; RR: relative risk

**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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td></td>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02805907</td>
<td>Efficacy of Calcifediol Supplementation in Asthma Control in Asthmatic Patients With Vitamin D Deficiency (ACViD)</td>
<td>100</td>
<td>Jan 2017</td>
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<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>600</td>
<td>Sep 2017</td>
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<tr>
<td>NCT01169259</td>
<td>Vitamin D and Omega-3 Trial (VITAL)</td>
<td>25874</td>
<td>Dec 2017</td>
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<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>160</td>
<td>Mar 2018</td>
</tr>
</tbody>
</table>
Practice Guidelines and Position Statements

Endocrine Society

In 2011, the Endocrine Society published clinical practice guidelines for 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 does not recommend screening of individuals who are not at risk of vitamin D deficiency.

- 1,25(OH)2D [1,25-dihydroxyvitamin D] testing is not recommended to evaluate vitamin D status. However, the guideline does recommend monitoring calcitriol levels in certain conditions.
American College of Obstetrics and Gynecology

The American College of Obstetrics and Gynecology issued guidelines on the testing of vitamin D levels and vitamin D supplementation in pregnant women. The following recommendation was made about 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 25-OH-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 are 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 (USPSTF) published a recommendation in 2014 and associated guidelines in 2015 on vitamin D screening. USPSTF 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 Decision (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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 this test.

References


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


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>01/12/16</td>
<td>New policy, add to Pathology/Laboratory testing section. Replaces 2.04.507; testing of</td>
</tr>
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<td>vitamin D serum levels may be considered medically necessary when criteria are met.</td>
</tr>
<tr>
<td>02/04/16</td>
<td>Coding update. Added ICD10 diagnosis code E74.21.</td>
</tr>
<tr>
<td>02/19/16</td>
<td>Coding update. Minor clarifications to osteomalacia code range and correction to code K70.0.</td>
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<tr>
<td>08/01/16</td>
<td>Interim Update, approved July 12, 2016. Policy published in new template with introduction added. Clarified institutional information. Intent remains the same.</td>
</tr>
<tr>
<td>03/01/17</td>
<td>Annual review, approved February 14, 2017. Policy updated literature review through October 10, 2016; references 14-16, 29, 31-36, 43, and 45 added. Policy statements unchanged.</td>
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<tr>
<td>08/15/17</td>
<td>Minor formatting updates.</td>
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</tbody>
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Complaint forms are available at

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