Testing Serum Vitamin D Levels

Policy Number: 2.04.135  Last Review: 12/2016
Origination: 12/2015  Next Review: 12/2017

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 of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: • With signs and/or symptoms of vitamin D deficiency or toxicity</td>
<td>Interventions of interest are: • Testing vitamin D levels</td>
<td>Routine care without testing vitamin D levels</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity, Symptoms, Morbid events, Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With high risk for vitamin D deficiency</td>
<td>Interventions of interest are: • Testing vitamin D levels</td>
<td>Routine care without testing vitamin D levels</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity, Symptoms, Morbid events, Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • Who are asymptomatic, without risk factors for vitamin D deficiency</td>
<td>Interventions of interest are: • Testing vitamin D levels</td>
<td>Routine care without testing vitamin D levels</td>
<td>Overall survival, Test accuracy, Test validity, Symptoms, Morbid events, 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.

The evidence on testing vitamin D levels for skeletal health and overall mortality includes many randomized controlled trials (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. Despite the large quantity of evidence, considerable uncertainty remains regarding the beneficial health effects of vitamin D. 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, in institutionalized individuals, and with higher doses of vitamin D. For overall mortality, there is also no benefit for the general population. Evidence from a systematic review that included trials of patients with vitamin D deficiency reported a small reduction in overall mortality for institutionalized patients. The
evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence on the impact of vitamin D on extraskeletal health benefits, including cardiovascular disease, hypertension, diabetes, and cancer, includes many RCTs. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, morbid events, and treatment-related morbidity. RCTs evaluating extraskeletal outcomes have not reported a benefit for vitamin D supplementation. In the available RCTs, extraskeletal outcomes were mostly secondary and occurred uncommonly. Therefore, the studies may not have had adequate power to detect a benefit, and ascertainment of outcomes may not have been optimal. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 report\(^2\) 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.\(^3\) 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.

**Vitamin D Replacement**

The IOM document recommended reference values for intake of vitamin D and serum levels, based on available literature and expert consensus.\(^2\) Recommended daily allowances are 600 IU/d for individuals between 1 and 70 years of age and 800 IU/d for individuals older than 70 years.

Estimates of vitamin D requirements are complicated by the many other factors that affect serum levels. Sun exposure is the most prominent, 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>

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 with literature review through July 1, 2015

Review of Evidence
There is a very large quantity of literature on vitamin D and health outcomes. The majority of the published evidence consists of observational studies on the association of vitamin D levels with outcomes. For example, Theodoratou et al identified 107 systematic reviews of observational studies examining the association between vitamin D levels and more than 100 different outcomes. These observational studies do not prove causation, however, and are prone to confounding, because many of the same factors correlate with vitamin D levels also correlate with outcomes. For example, obesity, physical activity, and sun exposure all correlate with both vitamin D levels and cardiovascular outcomes. These confounding factors present a challenge when interpreting results of the observational studies. These observational studies will not be reviewed further.

There are a large number of randomized controlled trials (RCTs) that evaluate the impact of vitamin D supplementation on outcomes. Theodoratou et al identified 87 meta-analyses of RCTs on vitamin D supplementation. There were 21 meta-analyses on skeletal health, 7 on metabolic disease, 4 on pediatric outcomes, 3 on cardiovascular disease, 3 on pregnancy-related outcomes, and 18 on other outcomes.

Because of the large literature base, this review of evidence will focus on the largest and most recent systematic reviews and meta-analyses of RCTs. Individual
trials will be reviewed separately if they were not included in the meta-analyses or if there were particular features that need to be highlighted.

Figure 1 summarizes the approach to this evidence review. Vitamin D levels may be tested in various populations, both symptomatic and asymptomatic. If levels are normal, no further workup or treatment occurs; and if levels are low, supplemental vitamin D treatment is given. Using this framework, the main question is whether individuals who are identified as deficient by vitamin D testing have improved outcomes when treated with supplemental vitamin D therapy.

**Figure 1. Analytic Framework**

- Testing vitamin D levels
  - Normal → No further treatment
  - Low → No treatment
- Treatment with vitamin D → Health outcomes
- Using this 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.

**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>3551</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>1619</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>1677</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>1809</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>9262</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></td>
<td>Vertebral fracture</td>
<td>5</td>
<td>9138</td>
<td></td>
<td>0.90 (0.97 to 1.1)</td>
</tr>
<tr>
<td>Bischoff-Ferrari (2009)</td>
<td>Non-vertebral fracture</td>
<td>5</td>
<td>7130</td>
<td></td>
<td>0.79 (0.63 to 0.99)</td>
</tr>
<tr>
<td>Palmer (2009)</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>
</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. 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.
- 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. 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 (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 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 (eg, 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.

**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 report was published in 2014, and consisted of
an update to the original 2007 report. A quantitative synthesis of all the trials was not performed in the 2014 update. Rather they identified areas where the new trials might change previous conclusions. The main conclusions of this document on overall mortality were that the results of the available studies do not support a benefit on overall mortality associated with vitamin D supplementation. There were no important trials identified in the update that would potentially change this conclusion.

For meta-analyses that included 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 the Chowdhury study that reported a marginally significant result for vitamin D$_3$ supplementation but not for vitamin D$_2$ 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 ($I^2$)</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)$^{14}$</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 (institutionalized patients)</td>
<td>4</td>
<td>1134</td>
<td>0%</td>
<td>0.72 (0.56 to 0.94)</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 (2014)$^{21}$</td>
<td>Mortality (vitamin D$_3$)</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 D$_2$)</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)$^{22}$</td>
<td>Mortality (vitamin D$_2$)</td>
<td>8</td>
<td>17,079</td>
<td>0%</td>
<td>1.04 (0.97 to 1.11)</td>
</tr>
<tr>
<td></td>
<td>Mortality (vitamin D$_3$)</td>
<td>9</td>
<td>12,824</td>
<td></td>
<td>0.91 (0.82 to 1.02)</td>
</tr>
<tr>
<td>Palmer (2009)$^{17}$</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)$^{23}$</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 population. However, the best available evidence (ie, a meta-analysis of RCTs that treat patients with vitamin D deficiency) reports that mortality is reduced for institutionalized patients. For this group, there was a 36% relative reduction in mortality. Although this conclusion is based on a relatively small number of studies of institutionalized...
patients, it likely represents a clinically significant effect. For supplementation in all patients regardless of vitamin D levels, the meta-analyses do not show a significant reduction in mortality.

**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 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.

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 al. 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. 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**
The 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 IOM, with the following conclusions:

- There are a small number of studies that address this question and they 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 prespecified 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.

**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>
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<th>Completion Date</th>
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<td>Ongoing</td>
<td>NCT02422784  A Double-Blind, Randomized, Control Study to Examine the Effects of Vitamin Fortification on Vitamin D Metabolite Profiles and Status in Vitamin D Insufficient Individuals</td>
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<td>Jun 2016</td>
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</table>

NCT: national clinical trial.

### Summary of Evidence

The evidence on testing vitamin D levels for skeletal health and overall mortality includes many randomized controlled trials (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. Despite the large quantity of evidence, considerable uncertainty remains regarding the beneficial health effects of vitamin D. 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, in institutionalized individuals, and with higher doses of vitamin D. For overall mortality, there is also no benefit for the general population. Evidence from a systematic review that included trials of patients with vitamin D deficiency reported a small reduction in overall mortality for institutionalized patients. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence on the impact of vitamin D on extraskeletal health benefits, including cardiovascular disease, hypertension, diabetes, and cancer, includes many RCTs. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, morbid events, and treatment-related morbidity. RCTs evaluating extraskeletal outcomes have not reported a benefit for vitamin D supplementation. In the available RCTs, extraskeletal outcomes were mostly secondary and occurred uncommonly. Therefore, the studies may not have had adequate power to detect a benefit, and ascertainment of outcomes may not have been optimal. The evidence is insufficient to determine the effects of the technology on health outcomes.

### 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 is safe.

**U.S. Preventive Services Task Force Recommendations**
The U.S. Preventive Services Task Force (USPSTF) published a recommendation in 2014 on vitamin D screening. USPSTF concluded that the current evidence is 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References
19. 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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<td>82652</td>
<td>Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed</td>
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### ICD-10 Codes

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E83.50  Disorders of calcium metabolism code range
E83.59
E84-  Cystic Fibrosis code range.
E84.9
E20-  Hypoparathyroidism code range
E20.9
E21-  Hyperparathyroidism and other disorders of parathyroid gland
E21.5
E44.0  Moderate protein-calorie malnutrition
E44.1  Mild protein-calorie malnutrition
E45  Retarded development following protein-calorie malnutrition
E46  Unspecified protein-calorie malnutrition
E55-  Vitamin D deficiency code range
E55.9
E56.9  Vitamin deficiency, unspecified
E64.3  Sequelae of rickets
E67.3  Hypervitaminosis D
E67.8  Other specified hyperalimentation
E70-  Disorders of aromatic amino-acid metabolism code range
E70.9
E71-  Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism code range
E71.2
E72-  Other disorders of amino-acid metabolism code range
E72.4
E72.50  Disorder of glycine metabolism, unspecified
E72.51  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
E84.9
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
K51-  Ulcerative colitis code range
K51.919
K52.81  Eosinophilic gastritis or gastroenteritis
K52.82  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)
L40-   Psoriasis code range
L56-   Other acute skin changes due to ultraviolet radiation
L57-   Skin changes due to chronic exposure to nonionizing radiation code range
L85.3  Xerosis cutis
M32-   Systemic lupus erythematosus (SLE) code range
M33-   Dermatopolymyositis code range
M33.19 Dermatopolymyositis, unspecified code range
M33.9- 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  Osteoporosis without current pathological fracture code range
M81-   Adult osteomalacia code range
M83-   Other specified disorders of bone density and structure (includes osteosclerosis and osteopenia)
M85.8- 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
Testing Serum Vitamin D Levels 2.04.135

P71.9  code range
Q78.0  Osteogenesis imperfect
Q78.2  Osteopetrosis
R17    Unspecified jaundice
R41-   Other symptoms and signs involving cognitive functions and awareness code range
R41.9  Other malaise and fatigue
R53.8- Other malaise and fatigue
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

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