Medical Policy

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Title: Testing Serum Vitamin D Levels

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

DESCRIPTION

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

OBJECTIVE

The objective of this evidence review is to examine whether testing for vitamin D deficiency improves net health outcomes in asymptomatic individuals.

BACKGROUND

Vitamin D

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

Vitamin D Replacement

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

Estimates of vitamin D requirements are complicated by the many other factors that affect serum levels. Sun exposure is the most prominent of factors that affect serum levels, and this is because individuals can meet their vitamin D needs entirely through adequate sun exposure. Other factors such as age, skin pigmentation, obesity, physical activity, and nutritional status also affect vitamin D levels and can result in variable dietary intake requirements to maintain adequate serum levels.

Excessive intake of vitamin D can be toxic. Toxic effects are usually due to hypercalcemia and may include confusion, weakness, polyuria, polydipsia, anorexia, and vomiting. In addition, high

levels of vitamin D may promote calcium deposition and have the potential to exacerbate conditions such as calcium kidney stones and atherosclerotic vascular disease.

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

Table 1. Institute of Medicine Recommendations for Vitamin D Dietary Intake

Patient Group	Estimated Average Requirement, IU/d	Recommended Daily Allowance, IU/d	Upper Limit Intake, IU/d
1 to 3 years old	400	600	2500
4 to 8 years old	400	600	3000
9 to 70 years old	400	600	4000
>70 years old	400	800	4000

Adapted from Institute of Medicine (2011).[2,]

REGULATORY STATUS

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

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

POLICY

A. Testing for vitamin D deficiency may be considered **medically necessary** in individuals with signs and/or symptoms of vitamin D deficiency or toxicity (see Policy Guidelines) when one of the high-risk factors is present:
   1. Chronic kidney disease, stage ≥3
   2. Granulomatous diseases
   3. Parathyroid disorders
   4. Cirrhosis and chronic liver disease
   5. Malabsorption states
   6. Chronic use of anticonvulsant medications or systemic corticosteroids
   7. Osteomalacia
   8. Osteopenia
   9. Osteoporosis
   10. Rickets
   11. Vitamin D deficiency, on replacement
   12. Hypo- or hypercalcemia
   13. Obstructive jaundice/biliary tract disease
   14. Osteogenesis imperfecta
   15. Osteosclerosis and osteopetrosis

B. Testing vitamin D levels in asymptomatic individuals may be considered **medically necessary** in the following individual populations:
   1. Individuals who have risk factors for vitamin D deficiency (as listed in Item A above)
   2. Institutionalized individuals (see Policy Guidelines)

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

D. Routine screening for vitamin D deficiency is **not medically necessary**

POLICY GUIDELINES

A. Signs and symptoms of vitamin D deficiency are largely manifested by changes in bone health and biochemical markers associated with bone production and resorption. In most cases, a clinical diagnosis of an abnormality in bone health (e.g., rickets, osteomalacia, osteoporosis) will lead to a decision to test vitamin D levels. Symptoms related to the clinical condition may be present, 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.

B. 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.

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

D. 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 supplementation has not been successful in restoring levels (another example might include an instance in which continued or recurrent signs and symptoms may indicate ongoing deficiency, and/or when inadequate absorption or noncompliance with replacement therapy is suspected).

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RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 24, 2022 .

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

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

Vitamin D Deficiency

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

Vitamin D deficiency, as defined by suboptimal serum levels, is common in the U.S. In the National Health and Nutrition Examination Survey covering the period of 2011 to 2014, 5% of patients aged 1 year and older were at risk of vitamin D deficiency (25-hydroxyvitamin D levels <12 ng/mL) and 18.3% of patients were at risk of vitamin D inadequacy (25-hydroxyvitamin D levels 12 to 19.6 ng/mL).[4,] Vitamin D deficiency occurs most commonly as a result of inadequate dietary intake coupled with inadequate sun exposure. Evidence from the National

Nutrition Monitoring System and the National Health and Nutrition Examination Survey has indicated that the average vitamin D consumption is below recommended levels of intake. Yetley (2008) estimated that the average daily intake for U.S. adults ranged from 228 to 335 IU/d, depending on gender and ethnicity.[5,] This level is below the average daily requirement, estimated by IOM (400 IU/d for healthy adults), and well below IOM's required daily allowance (estimated to be 600 IU for nonelderly adults and 800 IU for elderly adults).

Vitamin D deficiency may occur less commonly for other reasons. Kidney or liver disease can cause deficiency as a result of the impaired conversion of inactive vitamin D to its active products. In rare situations, there is vitamin D resistance at the tissue level, which causes a functional vitamin D deficiency despite "adequate" serum levels.

The safe upper level for serum vitamin D is also not standardized. The IOM report concluded there is potential harm associated with levels greater than 50 ng/mL and recommended that serum levels be maintained in the 20 to 40 ng/mL range.[2,] However, conclusions on this point have differed. A 2011 Agency for Healthcare Research and Quality systematic review of vitamin D and bone health concluded that "There is little evidence from existing trials that vitamin D above current reference intakes is harmful."[6,] The Women's Health Initiative concluded that hypercalcemia and hypercalciuria in patients receiving calcium and vitamin D were not associated with adverse clinical events.[7,] The Women's Health Initiative did find a small increase in kidney stones for women ages 50 to 79 years who received vitamin D and calcium.

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

Clinical Context

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

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

Populations

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

Interventions

The therapy being considered is testing of vitamin D levels.

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

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

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

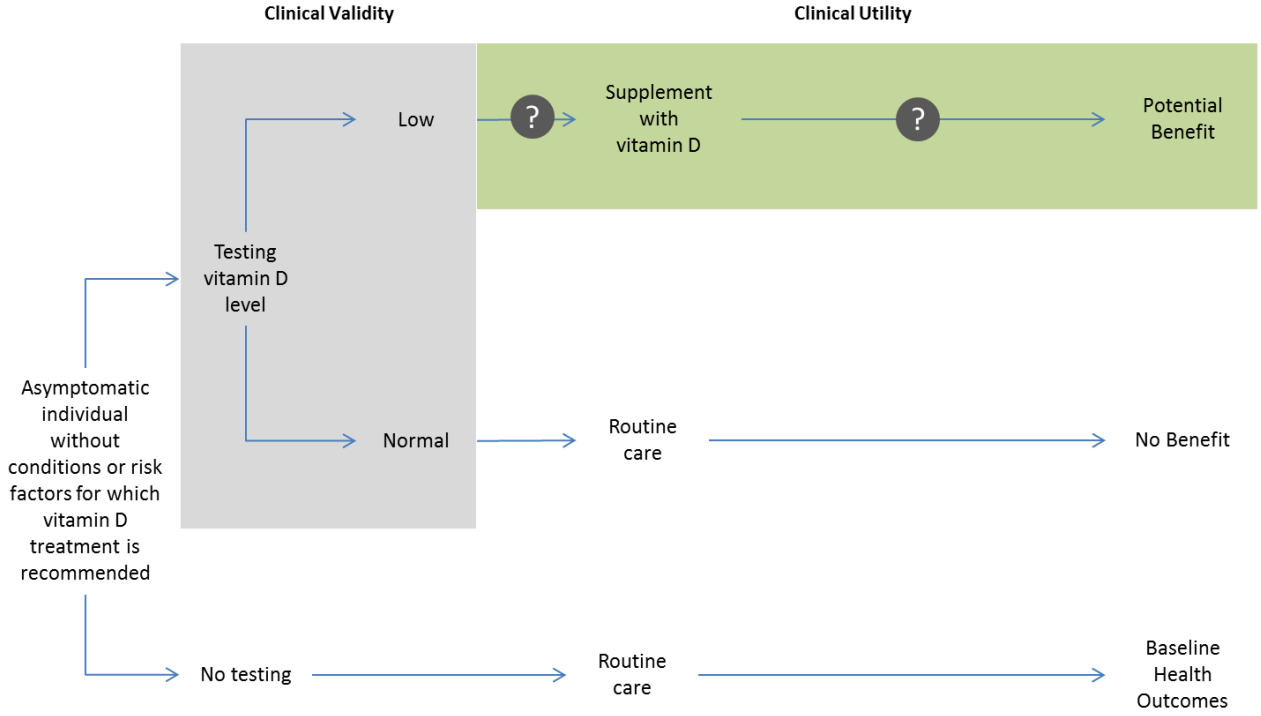
Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Studies with duplicative or overlapping populations were excluded.

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

Figure 1. Analytic Framework



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

Clinically Valid

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

There is no consensus on how to define vitamin D deficiency or inadequacy, and there is no accepted reference standard. Available cutoffs for deficiency are neither standardized nor based on rigorous scientific studies.[16,] Therefore, despite the availability of many tests that measure total serum 25-hydroxyvitamin D (25(OH)D) levels, their sensitivities and specificities for detecting clinically important deficiency are currently unknown.

Clinically Useful

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

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

A large number of RCTs have evaluated the impact of vitamin D supplementation on outcomes. Theodoratou et al (2014) identified 87 meta-analyses of RCTs on vitamin D supplementation[15,]; there were 21 meta-analyses on skeletal health, 7 on metabolic disease, 4 on pediatric outcomes, 3 on cardiovascular disease, 3 on pregnancy-related outcomes, and 18 on other outcomes. Because of the large literature base, this review of evidence will focus on the largest and most recent systematic reviews and meta-analyses of RCTs. Individual trials will be reviewed separately if they were not included in the meta-analyses or if particular features need highlighting. The evidence review includes use of vitamin D testing and supplementation in the following indications: skeletal health, cardiovascular disease, cancer, asthma, pregnancy, multiple sclerosis (MS), and overall mortality.

REVIEW OF EVIDENCE

SKELETAL HEALTH

Systematic Reviews

Numerous systematic reviews and meta-analyses of RCTs have been published evaluating the impact of vitamin D supplementation on skeletal health outcomes. The relevant health outcomes considered for this evidence review include fractures and falls. Studies that looked at bone mineral density and/or other physiologic measures of bone health were not included. Table 2 summarizes the results of systematic reviews performing quantitative meta-analyses on the relevant outcomes.

Among the trials included in the meta-analyses, few were large studies; most were small or moderate in size and limited by a small number of outcome events. Doses of vitamin D varied widely from 400 to 4800 IU/d; treatment and follow-up durations varied from 2 months to 7 years. Some studies limited enrollment to participants with low serum vitamin D. Most studies excluded institutionalized patients, but some included them. There was inconsistency in the results, especially for studies of fracture prevention, as evidenced by the relatively large degree of heterogeneity among studies.

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

Study	Outcome	No. of Studies	No. of Participants	I^2, %[a]	RR for Outcome (95% CI)
Patients with vitamin D deficiency					
LeBlanc et al (2015)[17,]	Any fracture	5	3551	32	0.98 (0.82 to 1.16)
	Hip fracture	4	1619	46	0.96 (0.72 to 1.29)
	Falls: total	5	1677	70	0.84 (0.69 to 1.02)
	Falls: person	5	1809	64.5	0.66 (0.50 to 0.88)
All patients					
Ling et al (2021)[18,]	Falls	21	51,984	NR	1.00 (0.95 to 1.05)
Cranney et al (2011)[6,]; AHRQ	Any fracture	14	58,712	48.3	0.90 (0.81 to 1.01)
	Hip fracture	8	46,072	16.2	0.83 (0.68 to 1.0)
	Falls	9	9262	0	0.84 (0.76 to 0.93)
Avenell et al (2009)[19,]	All fractures	10	25,016	NR	1.01 (0.93 to 1.09)
	Hip fractures	9	24,749	NR	1.15 (0.99 to 1.33)
	Vertebral fracture	5	9138	NR	0.90 (0.97 to 1.1)

Study	Outcome	No. of Studies	No. of Participants	I^2, %[a]	RR for Outcome (95% CI)
Bischoff-Ferrari et al (2009)[20,]	Non-vertebral fracture	5	7130	NR	0.79 (0.63 to 0.99)
Palmer et al (2009)[21,]	All fractures (CKD-RD)	4	181	NR	1.0 (0.06 to 15.41)
Bischoff-Ferrari et al (2005)[22,]	Hip fracture				
700 to 800 IU/d		3	5572	NR	0.74 (0.61 to 0.88)
400 IU/d		2	3722	NR	1.15 (0.88 to 1.50)
	Non-vertebral fracture				
700 to 800 IU/d		5	6098	NR	0.77 (0.68 to 0.87)
400 IU/d		2	3722	NR	1.03 (0.86 to 1.24)

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

Cranney et al (2011) conducted a review for the Agency for Healthcare Research and Quality (AHRQ) on the effectiveness and safety of vitamin D in relation to bone health.[6,] Reviewers concluded that:

- The evidence on the reduction in fractures was inconsistent. The combined results of trials using vitamin D_3 with calcium were consistent with a benefit on fractures, although the benefit was primarily found in the subgroup of elderly institutionalized women, which was a subgroup not included in this review.
- The evidence on a benefit in fall risk was also inconsistent. The results showed benefit in subgroups of postmenopausal women and in trials that used vitamin D in combination with calcium. There was a reduction in fall risk with vitamin D when 6 trials that adequately ascertained falls were combined.

A meta-analysis of double-blind RCTs by Bischoff-Ferrari et al (2005) estimated the benefit of vitamin D supplementation on fracture risk and examined the dose-response relation between vitamin D and outcomes.[22,] Based on a meta-analysis of 5 RCTs that used high-dose vitamin D, reviewers concluded that supplementation at 700 to 800 IU/d reduced the incidence of hip fractures by 26%, and reduced any non-vertebral fracture by 23%. In this same review, based on the results of 2 RCTs, lower doses of vitamin D at 400 IU/d did not significantly reduce the fracture risk.

Randomized Controlled Trials

The STURDY Collaborative Research Group (Appel et al 2021) was a large (N=688) RCT evaluating 4 doses of vitamin D in individuals at least 70 years of age at elevated fall risk and a serum vitamin D level of 25 to 72.5 nmol/L.[23,] The primary outcome was time to first fall or death over 2 years. The primary outcome during the confirmatory stage was not significantly different between those receiving the control dose of vitamin D (200 IU/day) and those receiving what was considered the optimal dose of 1000 IU/day. Doses of 1000 IU/day or greater were associated with safety concerns. The study is limited by the use of vitamin D 200 IU/day as a control group rather than use of a placebo.

An RCT not included in most of the systematic reviews (by Sanders et al [2010][24,]) reported results inconsistent with some of the previous trials and conclusions of meta-analyses. In this trial, 2256 community-dwelling elderly individuals at high-risk for falls were treated with high-dose vitamin D 500,000 IU orally once per year for 3 to 5 years. There was a 15% increase in falls for the group treated with vitamin D (p=.03) and a 26% increase in fractures (p=.02). In addition, there was a temporal relation to the increase in fall risk, with the greatest risk in the period immediately after vitamin D administration. It is unclear whether the specific regimen used in this study (e.g., high-dose vitamin D once/year) was responsible for the different results seen in this study compared with prior research.

Section Summary: Skeletal Health

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

CARDIOVASCULAR DISEASE

Systematic Reviews

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

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

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

An AHRQ report by Chung et al (2009) concluded that[27,]:

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

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

A systematic review by Pittas et al (2010) included 10 intervention trials that evaluated the relation between vitamin D and hypertension.[26,] Most did not report a decrease in incident hypertension associated with vitamin D supplementation.

A systematic review by Su et al (2021) assessed 36 studies that included cohort studies, RCTs, and case-control analyses for the association between serum levels of vitamin D and risk of stroke. [29,] Lower levels of serum vitamin D were associated with an elevated risk of stroke in both Asian and White populations, however, vitamin D supplementation did not show benefit in decreasing the risk of stroke. In a meta-analysis limited to RCTs, Fu et al (2022) had similar findings; vitamin D did not reduce stroke risk compared with placebo (RR=1.02; 95% CI, 0.93 to 1.13; p=.65).[30,]

Section Summary: Cardiovascular Disease

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

CANCER

Systematic Reviews

Systematic reviews have evaluated the effect of vitamin D supplementation on the prevention of cancer. Table 3 contains characteristics of 2 systematic reviews, and Table 4 summarizes the results of the meta-analyses performed in the reviews. The individual RCTs included in the systematic reviews are listed in Table 5. Both systematic reviews by Keum et al (2019) and Bjelakovic et al (2014) found that vitamin D supplementation did not reduce cancer incidence compared to placebo or no intervention; however, total cancer mortality was reduced. [32,33,] In the systematic review by Bjelakovic et al, there was no substantial difference in the effect of vitamin D on cancer in subgroup analyses of trials only including participants with vitamin D levels less than 20 ng/mL at enrollment compared with trials including participants with vitamin D levels of 20 ng/mL or greater at enrollment. Notably, most included studies were not designed to assess cancer incidence or mortality. The authors of the systematic review by Bjelakovic et al (2014) noted that the estimates that were significantly different were at high risk of type I error due to sample size and potential attrition bias.

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

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Keum et al (2019)[32,]	To November 2018	10	People with baseline 25-(OH)D	NR	RCTs	3 to 10 years
Bjelakovic et al (2014)[33,]	To February 2014	18	Adults (over 18 years) (healthy, with stable disease, or diagnosed with vitamin D deficiency)	50,623	RCTs	5 months to 7 years

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

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

Study	Total Cancer Incidence	Total Cancer Mortality	Total Mortality	Nephrolithiasis
Keum et al (2019)[32,]				
Total N	***NR***	***NR***	***NR***	***NR***
Pooled effect	RR=0.98	RR=0.87	RR=0.93	NR
95% CI	0.93 to 1.03	0.79 to 0.96	0.88 to 0.98	NR
I^2	0	0	0	NR
Bjelakovic et al (2014)[33,]				
Total N	***50,623***	***44,492 (Vitamin D_3 only)***	***49,866***	***42,573***
Pooled effect	RR=1.00	RR=0.88	RR=0.93	RR=1.17
95% CI	0.94 to 1.06	0.78 to 0.98	0.88 to 0.98	1.03 to 1.34

Study	Total Cancer Incidence	Total Cancer Mortality	Total Mortality	Nephrolithiasis
I^2	0	0	0	0

CI: confidence interval; NR: not reported; RR: relative risk.

Table 5. Comparison of Randomized Controlled Trials Included in the Systematic Reviews

Primary Study (Year)	Keum et al (2019)[32,]	Bjelakovic et al (2014)[33,]
Ott et al (1989)[34,]		●
Grady et al (1991)[35,]		●
Komulainen et al (1999)[36,]		●
Gallagher et al (2001)[37,]		●
Trivedi et al (2003)[38,]	●	●
Wactawski-Wende et al (2006)[39,]	●	
Daly et al (2008)[40,]		●
LaCroix et al (2009)[41,]	●	
Bolton-Smith et al (2007)[42,]		●
Lappe et al (2007)[43,]	●	●
Prince et al (2008)[44,]		●
Janssen et al (2010)[45,]		●
Sanders et al (2010)[24,]	●	●
Brunner et al (2011)[46,]		●
Avenell et al (2012)[47,]	●	●
Glendenning et al (2012)[48,]		●
Larsen et al (2012)[49,]		●
Murdoch et al (2012)[50,]		●
Wood et al (2012)[51,]		●
Witham et al (2013)[52,]		●
Baron et al (2015)[53,]	●	
Jorde et al (2016)[54,]	●	
Lappe et al (2017)[55,]	●	
Scragg et al (2018)[56,]	●	

Primary Study (Year)	Keum et al (2019)[32,]	Bjelakovic et al (2014)[33,]
Manson et al (2019)[57,]	●	

Section Summary: Cancer
Systematic reviews of many RCTs have examined the effect of vitamin D supplementation on cancer outcomes, although cancer was not the prespecified primary outcome in most RCTs. The current evidence does not demonstrate that vitamin D supplementation reduces the incidence of cancer.

ASTHMA

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

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

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Liu et al (2022)[58,]	The decade prior to publication	10	Asthma patients who received any form or dose of vitamin D	1349	RCT	9 wks to 12 mo
Jolliffe et al (2017)[59,]; PROSPERO CRD42014013953	To Oct 2016	8	People with asthma, all ages, and baseline 25(OH)D levels included	1078	Randomized, double-blind, placebo-controlled	15 wk to 12 mo

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Martineau et al (2016)[60,]	To Jan 2016	9	People with asthma, all ages, and baseline 25(OH)D levels included	1093	Randomized, double-blind, placebo-controlled	4 to 12 mo
Luo et al (2015)[61,]	1946 to 2015	7	People with asthma, all ages, and baseline 25(OH)D levels included	903	RCT	9 wk to 12 mo

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

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

Study	Asthma Exacerbation	Asthma Exacerbation Requiring SCS	ACT Score	FEV_1	Proportion of Patients With AEs
Liu et al (2022)[58,]					
Total N	**944**		**526**	**651**	
Pooled effect	Risk ratio=0.60		SMD=0.04	SMD=0.04	
95% CI	0.41 to 0.88		-0.13 to 0.21	-0.35 to 0.43	
I^2	64%		0%	78%	
Jolliffe et al (2017)[59,]					
Total N	***868***	***955***	***NR***	***NR***	***955***
Pooled effect	HR=0.78	RR=0.74			OR=0.87[d]
95% CI	0.55 to 1.10	0.56 to 0.97			0.46 to 1.63
I^2	NA	NA			
Martineau et al (2016)[60,]					
Total N	***999***	***963***	***713***	***387***	***879***
Pooled effect	OR=0.53	OR=0.39[a]	Diff = -0.08	Diff=0.48%[b]	OR=1.01[d]
95% CI	0.28 to 0.99, favoring vitamin D	0.19 to 0.78, favoring vitamin D	-0.70 to 0.54	0.93 to 1.89	0.54 to 1.89
I^2	65%	0%	21%	0%	0%
Luo et al (2015)[61,]					

Total N	***820***	***NR***	***250***	***316***	***326***
Pooled effect	OR=0.66		Diff = -0.05	Diff = -0.02[c]	OR=1.16
95% CI	0.32 to 1.37		-0.30 to 0.20	-0.15 to 0.11	0.74 to 1.81
I^2	81%		NA	0%	0%

ACT: Asthma Control Test; AE: adverse event; Diff: difference; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; HR: hazard ratio; NA: not applicable; NR: not reported; OR: odds ratio; RR: rate ratio ; SCS: systemic corticosteroid; SMD: standard mean difference.
[a] Outcome was proportion with ≥1 exacerbation.
[b] FEV_1, % predicted.
[c] At 12 months.
[d] Serious adverse events.

Table 8. Comparison of Randomized Controlled Trials Included in the Systematic Reviews

Primary Study (Year)	**Liu et al (2022)[58],**	**Jolliffe et al (2017)[59],**	**Martineau et al (2016)[60],**	**Luo et al (2015)[61],**
Worth et al (1994)[62],				●
Majak et al (2009)[63],			●	●
Urashima et al (2010)[64],		●	●	
Majak et al (2011)[65],	●	●	●	
Lewis et al (2012)[66],			●	
Baris et al (2014)[67],				●
Castro et al (2014)[68],	●	●	●	●
Yadav et al (2014)[69],	●		●	●
de Groot et al (2015)[70],	●			●
Martineau et al (2015)[71],	●	●	●	●
Tachimoto et al (2016)[72],		●	●	
Jensen et al (2016)[73],		●	●	
Kerley et al (2016)[74],		●		

Primary Study (Year)	Liu et al (2022)[58,]	Jolliffe et al (2017)[59,]	Martineau et al (2016)[60,]	Luo et al (2015)[61,]
Musharraf et al (2017)[75,]	●			
Dodamani et al (2019)[76,]	●			
Shabana et al (2019)[77,]	●			
Jat et al (2021)[78,]	●			
Thakur et al (2021)[79,]	●			

Randomized Controlled Trials

An RCT of prenatal supplementation in 881 pregnant women at high-risk of having children with asthma was published in 2016.[80,] Women between gestational ages of 10 and 18 weeks were randomized to daily vitamin D 4000 IU plus a multivitamin containing vitamin D 400 IU (4400 IU group) or daily placebo vitamin D plus a multivitamin containing vitamin D 400 IU (400 IU group). Coprimary outcomes were (1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age and (2) third trimester maternal 25-OH(D) levels. Analysis of infant outcomes included 806 infants, 218 of whom developed asthma by age 3 years. The proportion of infants with asthma or recurrent wheeze was 24% in the 4400 IU group vs 30% in the 400 IU group (difference= -6%; 95% CI, -30% to 18%). There were no differences in the proportion of infants experiencing eczema or lower respiratory tract infections.

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

Section Summary: Asthma

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

PREGNANCY

Systematic Reviews

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

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

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Palacios et al (2019)[82,]	To July 2018	22[a] (vitamin D supplementation alone)	Pregnant women; most studies included baseline 25-(OH)D levels	3725	RCTs	NR (most studies started supplementation at or after 20 weeks gestation)

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

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

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

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

Table 11. Randomized Controlled Trials Included in the Systematic Review

Primary Study (Year)	Palacios et al (2019)[82,]
Brooke et al (1980)[83,]	●
Delvin et al (1986)[84,]	●
Mallet al (1986)[85,]	●
Marya et al (1988)[86,]	●
Kaur et al (1991)[87,]	●
Yu et al (2008)[88,]	●

Primary Study (Year)	Palacios et al (2019)[82,]
Roth et al (2010)[89,]	●
Sabet et al (2012)[90,]	●
Asemi et al (2013)[91,]	●
Grant et al (2013)[92,]	●
Tehrani et al (2014)[93,]	●
Mirghafourvand et al (2015)[94,]	●
Rodda et al (2015)[95,]	●
Sablok et al (2015)[96,]	●
Singh et al (2015)[97,]	●
Khan et al (2016)[98,]	●
Cooper et al (2016)[99,]	●
Naghshineh et al (2016)[100,]	●
Shahgheibi et al (2016)[101,]	●
Vaziri et al (2016)[102,]	●
Sasan et al (2017)[103,]	●
Samimi et al (2017)[104,]	●

Section Summary: Pregnancy
A systematic review found vitamin D supplementation in pregnancy reduced the risk of pre-eclampsia, gestational diabetes, low birthweight, and possibly severe postpartum hemorrhage; however, the significance of baseline 25(OH)D levels was not defined.

Multiple Sclerosis
Three systematic reviews have examined the effect of vitamin D supplementation in patients with MS.[105,106,107,] Reviewers described 6 RCTs, all of which were small (N<100). Patient follow-up ranged from 6 months to 2 years, and the dosing and administration of vitamin D varied. None of the trials reported improvement in MS relapse rates; most trials showed no effect of vitamin D on any of the surrogate or clinical outcomes. Only 1 trial reported improvement in magnetic resonance imaging of lesions in the vitamin D supplementation group. The evidence for vitamin D supplementation in MS is poor.

OVERALL MORTALITY

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

The most relevant information comes from a meta-analysis of patients with vitamin D deficiency by LeBlanc et al (2015).[108,] This report included 11 studies and found a marginally significant reduction in overall mortality, with a CI that approached 1.0. When the subgroup analysis was performed, it became apparent that most of the benefit was specific to institutionalized patients whereas, in community-dwelling patients, the data revealed no reduction in mortality.

The AHRQ report by Newberry et al (2014),[109,] assessing the health effects of vitamin D supplementation, updated the original 2007 report. A quantitative synthesis of all trials was not performed in the 2014 update. Rather reviewers identified areas where the new trials might change previous conclusions. Their main conclusions were that the results did not support a benefit on overall mortality associated with vitamin D supplementation. No important trials identified in the update would potentially change this conclusion.

For meta-analyses including RCTs that treated all patients with vitamin D, most analyses have not shown a significant reduction in mortality. The single analysis that did show a significant reduction was that by Chowdhury et al (2014), who reported a marginally significant result for vitamin D_3 supplementation but not for vitamin D_2 supplementation.[110,]

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

Study	Outcome	No. of Studies	No. of Participants	I^2, %[a]	RR for Outcome (95% CI)
Patients with vitamin D deficiency					
Leblanc et al (2015)[108,]	Mortality (all patients)	11	4126	0	0.83 (0.70 to 0.99)
	Mortality (noninstitutionalized patients)	8	2947	0	0.93 (0.73 to 1.18)
All patients					
Bjelakovic et al (2014)[111,]	Mortality (vitamin D_3)	13	12,609	5%	0.92 (0.85 to 1.00)
	Mortality (vitamin D_2)	8	17,079	14%	1.03 (0.96 to 1.12)
Chowdhury et al (2014)[110,]	Mortality (vitamin D_3)	14	13,367	0	0.89 (0.80 to 0.99)
	Mortality (vitamin D_2)	8	17,079	0	1.04 (0.97 to 1.11)
Palmer et al (2009)[21,]	Mortality (CKD-RD)	5	233		1.34 (0.34 to 5.24)
Palmer et al (2009)[112,]	Mortality (CKD)	4	477		1.40 (0.38 to 5.15)

CI: confidence interval; CKD: chronic kidney disease; CKD-RD: chronic kidney disease on renal dialysis; RCT: randomized controlled trial; RR: relative risk.
[a] Heterogeneity value.

Section Summary: Overall Mortality
Evidence from a number of systematic reviews and meta-analyses does not support a benefit of vitamin D supplementation on overall mortality for the general, noninstitutionalized population. Populations included in the studies varied by baseline vitamin D deficiency and administration of vitamin D.

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

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

Bone Health and Osteoporosis Foundation
The Bone Health and Osteoporosis Foundation updated recommendations for the prevention and treatment of osteoporosis in 2021.[3,] They recommended monitoring serum 25-hydroxy vitamin D levels in postmenopausal women and men 50 years of age and older, and vitamin D supplementation as necessary to maintain levels between 30 and 50 ng/mL.

Endocrine Society
In 2011, the Endocrine Society published clinical practice guidelines on the evaluation, treatment, and prevention of vitamin D deficiency.[113,] The following recommendations were made regarding testing vitamin D levels:

- 25-hydroxy vitamin D serum level testing is recommended: "to evaluate vitamin D status only in patients who are at risk of deficiency." The guideline did not recommend screening of individuals not at risk of vitamin D deficiency.
- 1,25-dihydroxyvitamin D testing was not recommended to evaluate vitamin D status. However, the guideline did recommend monitoring calcitriol levels under certain conditions.

American College of Obstetrics and Gynecology
The American College of Obstetrics and Gynecology (2011, reaffirmed 2021) issued a committee opinion on the testing of vitamin D levels and vitamin D supplementation in pregnant women.[114,] The following recommendation was made concerning testing vitamin D levels:

"At this time there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency. For pregnant women thought to be at increased risk of vitamin D deficiency, maternal serum 25-hydroxyvitamin D levels can be considered and should be interpreted in the context of the individual clinical circumstance. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000-2,000 international units per day of vitamin D is safe."

American Academy of Family Physicians
The American Academy of Family Physicians supports the U.S. Preventative Task Force recommendation on vitamin D screening.[115,]

In 2018, key recommendations for practice concluded that there was insufficient information to recommend screening the general population for vitamin D deficiency and that treating asymptomatic individuals with identified deficiency has not been shown to improve health.[116,]

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

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

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

Table 13. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05431920	Effects of Vitamin D3 Supplementation in Asthma Control, Pulmonary Function and Th17 Inflammatory Biomarkers in Adolescents With Asthma, Obesity and Vitamin D Deficiency: a Randomized Clinical Trial	264	Aug 2024
NCT05043116	High-dose Vitamin D Supplement for the Prevention of Acute Asthma-like Symptoms in Preschool Children - a Double-blind, Randomized, Controlled Trial	320	Oct 2031
NCT05329428	PREDIN: Pregnancy and Vitamin D Intervention Study - A Randomized Controlled Trial	102	Dec 2024
NCT05208827	A Multicenter Randomized Controlled Study of Vitamin D Supplementation in Pregnant Women for the Prevention of Gestational Diabetes.	1600	Jan 2025

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04291313	Vitamin D Deficiency in Pregnancy - Identifying Associations and Mechanisms Linking Maternal Vitamin D Deficiency to Placental Dysfunction and Adverse Pregnancy Outcomes	2000	May 2023
NCT00856947	Vitamin D Supplementation During Pregnancy for Prevention of Asthma in Childhood: An Interventional Trial in the ABC (Asthma Begins in Childhood) Cohort	600	Jul 2027
NCT04117581	A Daily 5000 IU Vitamin D Supplement for the Improvement of Lung Function and Asthma Control in Adults With Asthma: a Randomised Controlled Trial	32	Jul 2022
Unpublished			
NCT01490502	A Randomized Controlled Trial of Vitamin D Supplementation in Multiple Sclerosis (VIDAMS)	172	May 2021

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed
82652	Dihydroxyvitamin D, 1, 25 dihydroxy, includes fraction(s), if performed
0038U	Vitamin D, 25 hydroxy D2 and D3, by LCMS/MS, serum microsample, quantitative

ICD-10 DIAGNOSES	
D71	Functional disorders of polymorphonuclear neutrophils
E20.0-E20.9	Hypoparathyroidism code range
E21.0-E21.5	Hyperparathyroidism and other disorders of parathyroid gland
E55.0-E55.9	Vitamin D deficiency codes (includes Rickets)
E83.50-E83.59	Disorders of calcium metabolism code range
K70.0-K77	Diseases of liver code range
K83.0-K83.9	Other diseases of biliary tract code range
K90.0-K90.9	Intestinal malabsorption code range (K90.0 is celiac disease)
K91.2	Postsurgical malabsorption, not elsewhere classified
M80.00-M81.8	Osteoporosis code range
M83.0-M83.9	Osteomalacia code range
M85.80-M85.9	Other specified disorders of bone density and structure (includes osteosclerosis and osteopenia)
N18.1-N18.9	Chronic kidney disease (CKD) code range
Q78.0	Osteogenesis imperfecta
Q78.2	Osteopetrosis
Z59.3	Problems related to living in residential institution
Z79.52	Long term (current) use of systemic steroids
Z79.899	Other long term (current) drug therapy

REVISIONS	
03-08-2010	Updated Description section
	In Coding Section: ▪ Removed CPT code: 82307 (effective 01/01/2010) ▪ Updated wording for CPT codes: 82306, 82652 (effective 01/01/2010)

REVISIONS	
	Updated References
10-26-2010	Updated Description section
	In Policy section: ▪ To emphasize the need for recommended vitamin D supplementation prior to testing, revised the wording from: "A. Conditions for which testing for vitamin D deficiency may be considered medically necessary, include:" to: "A. Testing for vitamin D deficiency is considered not medically necessary except when: 1. The recommended vitamin D supplementation is being taken AND 2. One of the following conditions is present:"
	In Coding section: ▪ Updated diagnosis coding from 345.0-345.9 to 345.00-345.91
01-28-2011	Updated Description section.
	Updated Reference section.
	In Coding section: ▪ Addition of diagnosis codes: 252.1 and 775.4.
03-28-2011	In Coding section: ▪ Addition of Diagnosis codes: 242.00-242.31, 242.90, 242.91. ▪ Removed Diagnosis code 268.9.
	Updated Reference section
09-29-2011	Updated the Description section.
	In the Policy Language section: ▪ In Item A, #2, h, added "oral anti-fungals," ▪ In Item A, #2, added the following: ○ "o. muscle weakness ○ p. history of falls ○ q. history of vitamin D deficiency"
	In the Coding section: ▪ Added the following diagnosis codes: 135, 263-263.8, 268.9, 275.41, 275.49, 555.0-555.9, 556.0, 556.1, 556.2, 556.3, 556.6, 556.8, 556.9, 577.1, 579.0-579.9, 728.87
	Updated the Reference section.
12-20-2011	In the Coding Section: ▪ Added the following diagnosis codes: 277.00, 277.02, 277.03, 277.9
02-05-2014	Policy reviewed.
	In Policy section: ▪ In Item A, 2, inserted "r. Post-transplant"
	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
10-01-2015	Policy published 11-25-2015. Effective 10-01-2015 with ICD-10 coding implementation.
	In Coding section: ▪ Added ICD-10 codes: E55.9, Z79.52.
10-01-2015	Policy published 01-13-2016. Effective 10-01-2015 with ICD-10 coding implementation.
	In Coding section: ▪ Added ICD-10 code: M85.89.
10-01-2015	Policy published 03-25-2016. Effective 10-01-2015 with ICD-10 coding implementation.
	In Coding section: ▪ Added ICD-10 code Z91.81

REVISIONS	
	Updated References section.
06-10-2016	Updated Description section.
	In Policy section: ▪ In Item A, removed "is", "not", and "except", and added "may be", "in patients with signs and/or symptoms of vitamin D deficiency or toxicity (see Policy Guidelines)", and "one of the high-risk factors is present" to read "Testing for Vitamin D deficiency may be considered medically necessary in patients with signs and/or symptoms of vitamin D deficiency or toxicity (see Policy Guidelines) when one of the high-risk factors is present:" ▪ Removed previous Item A 1, "The recommended vitamin D supplementation is being taken AND" ▪ Removed previous Item A 2, "One of the following conditions is present" ▪ Removed previous Item A 2 c, "hyperthyroidism" ▪ Removed previous Item A 2 e, "heritable disorders of Vitamin D metabolism" ▪ Removed previous Item A 2 i, "obesity" ▪ Removed previous Item A 2 m, "phosphaturia" ▪ Removed previous Item A 2 o, "muscle weakness" ▪ Removed previous Item A 2 p, "history of falls" ▪ In current Item A 1, added ", stage ≥3" to read "chronic kidney disease, stage ≥3" ▪ In current Item A 2, removed "disorder" and added "diseases" to read "granulomatous diseases" ▪ In current Item A 3, removed "hyperparathyroidism" and added "parathyroid disorders" ▪ In current Item A 4, removed "liver failure" and added "cirrhosis/chronic liver disease" ▪ In current Item A 5, added "states" to read "malabsorption states" ▪ In current Item A 6, removed "(oral antifungals, AIDS medications)" and added "chronic use of" to read "chronic use of anticonvulsant medications or corticosteroids" ▪ In current Item A 11, removed "history of vitamin D deficiency" and added "vitamin D deficiency, in replacement" ▪ Added Item A 12, "hypo- or hypercalcemia" ▪ Added Item A 13, "obstructive jaundice/biliary tract disease" ▪ Added Item A 14, "osteogenesis imperfecta" ▪ Added Item A 15, "osteosclerosis/osteopetrosis" ▪ Added Item B, Item B 1, and Item B 2, "Testing vitamin D levels in asymptomatic patients may be considered medically necessary in the following patient populations: 1. Individuals who have risk factors for vitamin D deficiency (as listed in Item A above) 2. Institutionalized patients (see Policy Guidelines)" ▪ Added Item C, "Testing vitamin D levels in asymptomatic patients is considered not medically necessary when the above criteria are not met." ▪ Added Policy Guidelines
	Added Rationale section.
	In Coding section: ▪ Removed ICD-10 codes B20, D86.0, D86.1, D86.2, D86.3, D86.81, D86.82, D86.83, D86.84, D86.85, D86.86, D86.87, D86.89, D86.9, E05.00, E05.01, E05.10, E05.11, E05.20, E05.21, E44.0, E44.1, E45, E64.3, E66.01, E66.09, E66.1, E66.8, E83.30, E83.31, E83.32, E83.39, E84.0, E84.19, E84.8, E84.9, E89.2, G40.001, G40.009, G40.011, G40.019, G40.101, G40.109, G40.111, G40.119, G40.201, G40.209, G40.211, G40.219, G40.301, G40.309, G40.401, G40.409, G40.411, G40.419,

REVISIONS	
	G40.501, G40.509, G40.801, G40.802, G40.811, G40.812, G40.813, G40.814, G40.821, G40.822, G40.823, G40.824, G40.89, G40.901, G40.909, G40.911, G40.919, G40.A01, G40.A09, G40.A11, G40.A19, G40.B01, G40.B09, G40.B11, G40.B19, K50.00, K50.018, K50.019, K50.10, K50.118, K50.119, K50.80, K50.818, K50.819, K50.90, K50.918, K50.919, K51.00, K51.018, K51.019, K51.20, K51.218, K51.219, K51.30, K51.318, K51.319, K51.80, K51.818, K51.819, K51.90, K51.918, K51.919, K73.9, K86.0, K86.1, K90.9, M62.81, M89.9, M94.9, N18.2, P71.0, P71.1, P71.2, P71.3, P71.4, P71.8, P71.9, R17, Z91.81 ▪ Added ICD-10 codes E20.0, E20.1, E20.8, E21.4, E83.52, K71.0, K71.10, K71.11, K71.2, K71.3, K71.4, K71.50, K71.51, K71.6, K71.7, K71.8, K72.10, K72.11, K74.0, K74.60, K74.69, K75.3, K75.4, K75.89, K76.0, K76.1, K76.2, K76.3, K76.4, K76.5, K76.7, K76.81, K76.89, K77, K83.0, K83.1, K83.2, K83.3, K83.4, K83.5, K83.8, K90.81, M80.011A-S, M80.012A-S, K80.021A-S, M80.022A-S, M80.031A-S, M80.032A-S, M80.041A-S, M80.042A-S, M80.051A-S, M80.052A-S, M80.061A-S, M80.062A-S, M80.071A-S, M80.072A-S, M80.08XA-S, M80.811A-S, M80.812A-S, M80.821A-S. M80.822A-S. M80.831A-S, M80.832A-S, M80.841A-S, M80.842A-S, M80.851A-S, M80.952A-S, M80.861A-S, M80.862A-S, M80.871A-S, M80.872A-S, M80.88XA-S, M83.0, M83.1, M83.2, M83.3, M83.4, M83.5, M83.8, M85.811, M85.812, M85.821, M85.822, M85.831, M85.832, M85.841, M85.842, M85.851, M85.852, M85.861, M85.862, M85.871, M85.872, M85.88, N18.3, N18.4, N18.5, N18.6, Q78.0, Q78.2, Z59.3, Z79.52, Z79.899
	Updated References section.
	Added Appendix section.
10-01-2016	In Coding section: ▪ Added ICD-10 code effective 10-01-2016: K90.49 ▪ Termed ICD-10 code effective 09-30-2016: K90.4
01-25-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 code: K90.9.
	Updated References section.
02-15-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
	Updated Appendix section.
03-28-2018	In Coding section: ▪ Added CPT code: 0038U.
10-01-2018	In Coding section: ▪ Added ICD-10 codes: K83.01, K83.09. ▪ Removed ICD-10 code: K83.0.
02-01-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
	Removed Appendix section.
10-01-2020	In Coding Section: Added ICD-10: K74.00, K74.01, K74.02, N18.31, N18.32 Removed ICD-10: K74.0, N18.3
04-19-2021	Updated Description section.

REVISIONS	
	Updated Rationale section.
	Updated References section.
2-25-2022	Changed Title to Testing Serum Vitamin D Levels
	Updated Description Section
	Updated Policy Section ▪ Section A4 changed to read Cirrhosis "and" chronic liver disease ▪ Section A6 changed to read "systemic" corticosteroids ▪ Section A15 changed to read osteosclerosis "and" osteopetrosis ▪ Section C word "is" was changed to "are"
	Updated Rationale Section
	In the Coding section ▪ Changed ICD-10 codes to code ranges
	Updated References Section
01-24-2023	Updated Description Section
	Updated Rationale Section
	Updated References Section

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