Medical Policy

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Title: Testing for Vitamin D Deficiency

Professional
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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, decrease in coagulation, and 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 patients.

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.[2,]

Vitamin D Replacement

The Institute of Medicine has recommended reference values for the intake of vitamin D and serum levels, based on available literature and expert consensus.[3,] 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).[3,]

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 patients 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/chronic liver disease
   5. malabsorption states
   6. chronic use of anticonvulsant medications or 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/osteopetrosis

B. 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)

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

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

Policy Guidelines

1. 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.
2. 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.

3. "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.
4. 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).

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 16, 2020.

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.[3,] Some experts, such as the National Osteoporosis Foundation and the American Geriatrics Society, have recommended a higher level (30 ng/mL).[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.[3,] 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 question addressed in this evidence review is: Does testing and measurement of vitamin D levels and supplement of deficiency in asymptomatic patients improve the net health outcome?

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. Patients with vitamin D deficiency are managed by primary care providers in an outpatient setting.

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.

Patients with vitamin D deficiency are managed by primary care providers in an outpatient setting.

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:

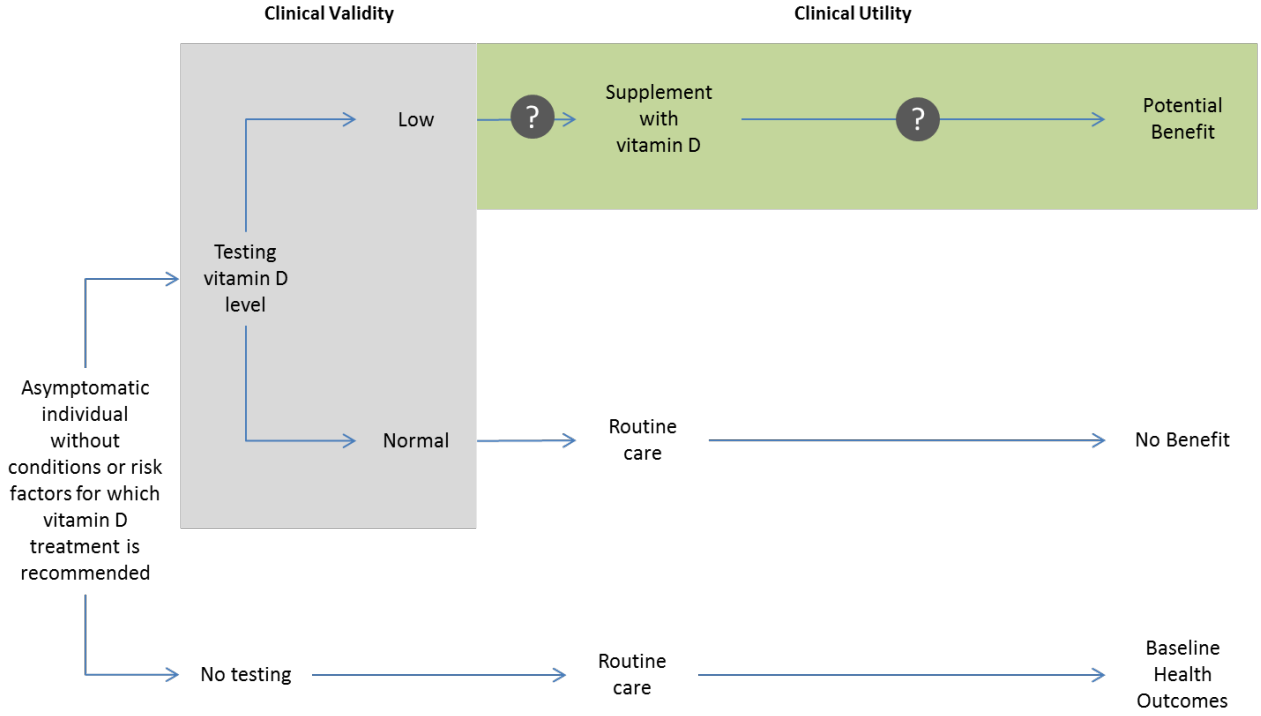
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer term outcomes and adverse effects, single-arm studies 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 randomized controlled trials (RCTs), including the largest trial (Women's Health Initiative), did not test vitamin D levels prior to treatment. Rather, they treated all patients enrolled regardless of vitamin D levels. Results of some of the main systematic reviews that take this approach will be reviewed, but this evidence is indirect and must be extrapolated from the treatment of all patients to the treatment of patients who are vitamin D deficient.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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.

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					
Cranney et al (2011)[6,]; AHRQ	Any fracture	14	58,712	48.3	0.90 (0.81 to 1.01)

Study	Outcome	No. of Studies	No. of Participants	I^2, %[a]	RR for Outcome (95% CI)
	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)[18,]	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)
Bischoff-Ferrari et al (2009)[19,]	Non-vertebral fracture	5	7130	NR	0.79 (0.63 to 0.99)
Palmer et al (2009)[20,]	All fractures (CKD-RD)	4	181	NR	1.0 (0.06 to 15.41)
Bischoff-Ferrari et al (2005)[21,]	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.[21,] 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

An RCT not included in most of the systematic reviews (by Sanders et al [2010][22,]) 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 ($p=0.03$) and a 26% increase in fractures ($p=0.02$). In addition, there was a temporal relation to the increase in fall risk, with the greatest risk in the period immediately after vitamin D administration. It is unclear whether the specific regimen used in this study (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 randomize patients to vitamin D or placebo. A meta-analysis of these trials showed no reduction in fractures and an uncertain reduction in falls. In meta-analyses that treated all patients regardless of vitamin D levels, there are inconsistent findings on the effect of supplementation on fractures and falls. There is some evidence that subgroups (e.g., elderly women) may benefit from supplementation and that higher doses may provide a benefit whereas lower doses do not; however, very high doses may increase the risk of falls. Therefore, the evidence does not convincingly demonstrate an improvement in skeletal health outcomes with vitamin D supplementation.

CARDIOVASCULAR DISEASE

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.[23,] 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.[24,] None of the 5 trials reported a significant reduction in cardiovascular outcomes in the vitamin D group. Combined analysis of these trials found a 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[25,]:

- 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.[26,] 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.[24,] Most did not report a decrease in incident hypertension associated with vitamin D supplementation.

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.[27,] 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 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. [28,29,] 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)[28,]	To November 2018	10	People with baseline 25-(OH)D	NR	RCTs	3 to 10 years
Bjelakovic et al (2014)[29,]	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)[28,]				
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)[29,]				
Total N	***50,623***	***44,492 (Vitamin D_3 only)***	***49,866***	***42,573***

Study	Total Cancer Incidence	Total Cancer Mortality	Total Mortality	Nephrolithiasis
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
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)[28,]	Bjelakovic et al (2014)[29,]
Ott et al (1989)[30,]		●
Grady et al (1991)[31,]		●
Komulainen et al (1999)[32,]		●
Gallagher et al (2001)[33,]		●
Trivedi et al (2003)[34,]	●	●
Wactawski-Wende et al (2006)[35,]	●	
Daly et al (2008)[36,]		●
LaCroix et al (2009)[37,]	●	
Bolton-Smith et al (2007)[38,]		●
Lappe et al (2007)[39,]	●	●
Prince et al (2008)[40,]		●
Janssen et al (2010)[41,]		●
Sanders et al (2010)[22,]	●	●
Brunner et al (2011)[42,]		●
Avenell et al (2012)[43,]	●	●
Glendenning et al (2012)[44,]		●
Larsen et al (2012)[45,]		●
Murdoch et al (2012)[46,]		●
Wood et al (2012)[47,]		●
Witham et al (2013)[48,]		●
Baron et al (2015)[49,]	●	
Jorde et al (2016)[50,]	●	
Lappe et al (2017)[51,]	●	

Primary Study (Year)	Keum et al (2019)[28,]	Bjelakovic et al (2014)[29,]
Scragg et al (2018)[52,]	●	
Manson et al (2019)[53,]	●	

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. Three recent reviews are summarized in Tables 6 and 7. Thirteen unique RCTs were included in the 3 systematic reviews (see Table 8). Reviews by Jolliffe et al (2017)[54,] and Martineau et al (2016)[55,] 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. The reviews by Martineau et al (2016)[55,] and Luo et al (2015)[56,] found that vitamin D had no effect on Asthma Control Test scores, forced expiratory volume in 1-second outcomes, or rates of adverse events. The 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=0.25).

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

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Jolliffe et al (2017)[54,]; 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
Martineau et al (2016)[55,]	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

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Luo et al (2015)[56,]	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
Jolliffe et al (2017)[54,]					
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 1.97			0.46 to 1.63
I^2	NA	NA			
Martineau et al (2016)[55,]					
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)[56,]					
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: relative risk; SCS: systemic corticosteroid.

[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)	Jolliffe et al (2017)[54,]	Martineau et al (2016)[55,]	Luo et al (2015)[56,]
Worth et al (1994)[57,]			●
Majak et al (2009)[58,]		●	●
Urashima et al (2010)[59,]	●	●	
Majak et al (2011)[60,]	●	●	
Lewis et al (2012)[61,]		●	
Baris et al (2014)[62,]			●
Castro et al (2014)[63,]	●	●	●
Yadav et al (2014)[64,]		●	●
de Groot et al (2015)[65,]			●
Martineau et al (2015)[66,]	●	●	●
Tachimoto et al (2016)[67,]	●	●	
Jensen et al (2016)[68,]	●	●	
Kerley et al (2016)[69,]	●		

Randomized Controlled Trials

An RCT of prenatal supplementation in 881 pregnant women at high-risk of having children with asthma was published in 2016.[70,] 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.

Section Summary: Asthma

Results of RCTs have reported mixed findings with respect to the effect of vitamin D supplementation on asthma outcomes. Populations included in studies varied by baseline vitamin D deficiency levels, administration of vitamin D, and 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).[71,] 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)[71,]	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)[71,]					
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)[71,]
Brooke et al (1980)[72,]	●
Delvin et al (1986)[73,]	●
Mallet et al (1986)[74,]	●
Marya et al (1988)[75,]	●
Kaur et al (1991)[76,]	●

Primary Study (Year)	Palacios et al (2019)[71,]
Yu et al (2008)[77,]	●
Roth et al (2010)[78,]	●
Sabet et al (2012)[79,]	●
Asemi et al (2013)[80,]	●
Grant et al (2013)[81,]	●
Tehrani et al (2014)[82,]	●
Mirghafourvand et al (2015)[83,]	●
Rodda et al (2015)[84,]	●
Sablok et al (2015)[85,]	●
Singh et al (2015)[86,]	●
Khan et al (2016)[87,]	●
Cooper et al (2016)[88,]	●
Naghshineh et al (2016)[89,]	●
Shahgheibi et al (2016)[90,]	●
Vaziri et al (2016)[91,]	●
Sasan et al (2017)[92,]	●
Samimi et al (2017)[93,]	●

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.[94,95,96,] 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).[97,] 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),[98,] 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.[99,]

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)[97,]	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)[100,]	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)[99,]	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)[20,]	Mortality (CKD-RD)	5	233		1.34 (0.34 to 5.24)
Palmer et al (2009)[101,]	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.

Summary of Evidence

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

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Endocrine Society

In 2011, the Endocrine Society published clinical practice guidelines on the evaluation, treatment, and prevention of vitamin D deficiency.[1,] 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 2017) issued a committee opinion on the testing of vitamin D levels and vitamin D supplementation in pregnant women.[102,] 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.[103,]

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.[104,]

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force published a recommendation in 2014[105,] and associated guidelines in 2015[106,] 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]). In the 2020 draft of the updated evidence review, the final recommendation upholds the same conclusion; however, the final version is not yet published.[107,]

Ongoing and Unpublished Clinical Trials
Some currently 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			
NCT01490502	A Randomized Controlled Trial of Vitamin D Supplementation in Multiple Sclerosis (VIDAMS)	172	Mar 2021
Unpublished			
NCT02166333	Vitamin D Supplements to Prevent Falls in Older Adults: A Dose-Response Trial (STURDY)	1200; enrollment terminated at 688	Jun 2019

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02750293	The Effect of Vitamin D Supplementation on Cardiovascular Risk Factors in Subjects With Low Serum 25-hydroxyvitamin D Levels (D-COR)	411	Sep 2017 (completed; last update posted 10/26/17)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

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	Idiopathic hypoparathyroidism
E20.1	Pseudohypoparathyroidism
E20.8	Other hypoparathyroidism
E21.0	Primary hyperparathyroidism
E21.1	Secondary hyperparathyroidism, not elsewhere classified
E21.2	Other hyperparathyroidism
E21.4	Other specified disorders of parathyroid gland
E55.0	Rickets, active
E55.9	Vitamin D deficiency, unspecified
E83.51	Hypocalcemia
E83.52	Hypercalcemia
E83.59	Other disorders of calcium metabolism
K70.0	Alcoholic fatty liver
K70.10	Alcoholic hepatitis without ascites
K70.11	Alcoholic hepatitis with ascites
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.30	Alcoholic cirrhosis of liver without ascites
K70.31	Alcoholic cirrhosis of liver with ascites
K70.40	Alcoholic hepatic failure without coma
K70.41	Alcoholic hepatic failure with coma
K71.0	Toxic liver disease with cholestasis
K71.10	Toxic liver disease with hepatic necrosis, without coma
K71.11	Toxic liver disease with hepatic necrosis, with coma
K71.2	Toxic liver disease with acute hepatitis
K71.3	Toxic liver disease with chronic persistent hepatitis
K71.4	Toxic liver disease with chronic lobular hepatitis

K71.50	Toxic liver disease with chronic active hepatitis without ascites
K71.51	Toxic liver disease with chronic active hepatitis with ascites
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.7	Toxic liver disease with fibrosis and cirrhosis of liver
K71.8	Toxic liver disease with other disorders of liver
K72.10	Chronic hepatic failure without coma
K72.11	Chronic hepatic failure with coma
K73.0	Chronic persistent hepatitis, not elsewhere classified
K73.1	Chronic lobular hepatitis, not elsewhere classified
K73.2	Chronic active hepatitis, not elsewhere classified
K73.8	Other chronic hepatitis, not elsewhere classified
K74.00	Hepatic fibrosis, unspecified
K74.01	Hepatic fibrosis, early fibrosis
K74.02	Hepatic fibrosis, advanced fibrosis
K74.1	Hepatic sclerosis
K74.2	Hepatic fibrosis with hepatic sclerosis
K74.3	Primary biliary cirrhosis
K74.4	Secondary biliary cirrhosis
K74.60	Unspecified cirrhosis of liver
K74.69	Other cirrhosis of liver
K75.3	Granulomatous hepatitis, not elsewhere classified
K75.4	Autoimmune hepatitis
K75.81	Nonalcoholic steatohepatitis (NASH)
K75.89	Other specified inflammatory liver diseases
K76.0	Fatty (change of) liver, not elsewhere classified
K76.1	Chronic passive congestion of liver
K76.2	Central hemorrhagic necrosis of liver
K76.3	Infarction of liver
K76.4	Peliosis hepatitis
K76.5	Hepatic veno-occlusive disease
K76.7	Hepatorenal syndrome
K76.81	Hepatopulmonary syndrome
K76.89	Other specified diseases of liver
K77	Liver disorders in diseases classified elsewhere
K83.01	Primary sclerosing cholangitis
K83.09	Other cholangitis
K83.1	Obstruction of bile duct
K83.2	Perforation of bile duct
K83.3	Fistula of bile duct
K83.4	Spasm of sphincter of Oddi
K83.5	Biliary cyst
K83.8	Other specified diseases of biliary tract
K90.0	Celiac disease
K90.1	Tropical sprue
K90.2	Blind loop syndrome, not elsewhere classified
K90.3	Pancreatic steatorrhea
K90.49	Malabsorption due to intolerance, not elsewhere classified
K90.81	Whipple's disease
K90.89	Other intestinal malabsorption
K90.9	Intestinal malabsorption, unspecified
K91.2	Postsurgical malabsorption, not elsewhere classified
M80.011A-S	Age-related osteoporosis with current pathologic fracture, right shoulder
M80.012A-S	Age-related osteoporosis with current pathological fracture, left shoulder

M80.021A-S	Age-related osteoporosis with current pathological fracture, right humerus
M80.022A-S	Age-related osteoporosis with current pathological fracture, left humerus
M80.031A-S	Age-related osteoporosis with current pathological fracture, right forearm
M80.032A-S	Age-related osteoporosis with current pathological fracture, left forearm
M80.041A-S	Age-related osteoporosis with current pathological fracture, right hand
M80.042A-S	Age-related osteoporosis with current pathological fracture, left hand
M80.051A-S	Age-related osteoporosis with current pathological fracture, right femur
M80.052A-S	Age-related osteoporosis with current pathological fracture, left femur
M80.061A-S	Age-related osteoporosis with current pathological fracture, right lower leg
M80.062A-S	Age-related osteoporosis with current pathological fracture, left lower leg
M80.071A-S	Age-related osteoporosis with current pathological fracture, right ankle and foot
M80.072A-S	Age-related osteoporosis with current pathological fracture, left ankle and foot
M80.08XA-S	Age-related osteoporosis with current pathological fracture, vertebra(e)
M80.811A-S	Other osteoporosis with current pathological fracture, right shoulder
M80.812A-S	Other osteoporosis with current pathological fracture, left shoulder
M80.821A-S	Other osteoporosis with current pathological fracture, right humerus
M80.822A-S	Other osteoporosis with current pathological fracture, left humerus
M80.831A-S	Other osteoporosis with current pathological fracture, right forearm
M80.832A-S	Other osteoporosis with current pathological fracture, left forearm
M80.841A-S	Other osteoporosis with current pathological fracture, right hand
M80.842A-S	Other osteoporosis with current pathological fracture, left hand
M80.851A-S	Other osteoporosis with current pathological fracture, right femur
M80.852A-S	Other osteoporosis with current pathological fracture, left femur
M80.861A-S	Other osteoporosis with current pathological fracture, right lower leg
M80.862A-S	Other osteoporosis with current pathological fracture, left lower leg
M80.871A-S	Other osteoporosis with current pathological fracture, right ankle and foot
M80.872A-S	Other osteoporosis with current pathological fracture, left ankle and foot
M80.88XA-S	Other osteoporosis with current pathological fracture, vertebra(e)
M81.0	Age-related osteoporosis without current pathological fracture
M81.6	Localized osteoporosis [Lequesne]
M81.8	Other osteoporosis without current pathological fracture
M83.0	Puerperal osteomalacia
M83.1	Senile osteomalacia
M83.2	Adult osteomalacia due to malabsorption
M83.3	Adult osteomalacia due to malnutrition
M83.4	Aluminum bone disease
M83.5	Other drug-induced osteomalacia in adults
M83.8	Other adult osteomalacia
M85.811	Other specified disorders of bone density and structure, right shoulder
M85.812	Other specified disorders of bone density and structure, left shoulder
M85.821	Other specified disorders of bone density and structure, right upper arm
M85.822	Other specified disorders of bone density and structure, left upper arm
M85.831	Other specified disorders of bone density and structure, right forearm
M85.832	Other specified disorders of bone density and structure, left forearm
M85.841	Other specified disorders of bone density and structure, right hand
M85.842	Other specified disorders of bone density and structure, left hand
M85.851	Other specified disorders of bone density and structure, right thigh
M85.852	Other specified disorders of bone density and structure, left thigh
M85.861	Other specified disorders of bone density and structure, right lower leg
M85.862	Other specified disorders of bone density and structure, left lower leg
M85.871	Other specified disorders of bone density and structure, right ankle and foot
M85.872	Other specified disorders of bone density and structure, left ankle and foot
M85.88	Other specified disorders of bone density and structure, other site

M85.89	Other specified disorders of bone density and structure, multiple sites
M85.9	Disorder of bone density and structure, unspecified
N18.31	Chronic kidney disease, stage 3a
N18.32	Chronic kidney disease, stage 3b
N18.4	Chronic kidney disease, stage 4 (severe)
N18.5	Chronic kidney disease, stage 5
N18.6	End stage renal disease
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)
	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
01-28-11	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 "o. muscle weakness o p. history of falls o 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
	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, 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.
	Updated Rationale section.
	Updated References section.

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