02.04.34 Vitamin D Testing

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Summary

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.

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. However, high doses of vitamin D may be associated with safety concerns in patients at risk for falls. 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 certain maternal and fetal outcomes. For overall mortality, there is also no benefit to the general population. RCTs evaluating extraskeletal, cancer, cardiovascular, and multiple sclerosis outcomes have not reported a statistically significant benefit for vitamin D supplementation. Although vitamin D toxicity and adverse events appear to be rare, few data on risks have been reported. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. However, for certain carefully selected individuals who have an associated defect risk in vitamin D metabolism, vitamin D testing may be considered medically necessary when the policy criteria is met.

Additional Information

Not applicable.

OBJECTIVE

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

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary: 25-hydroxyvitamin D (82306 or 0038U)

25-hydroxyvitamin D serum testing may be considered **medically necessary** in individuals in the evaluation of **one of the following** conditions with an associated defect risk in vitamin D metabolism:

- Chronic kidney disease stage III or greater
- Chronic liver disease
- Granuloma forming disorders to include but not limited to:
    - Berylliosis
    - Coccidiomycosis
    - Histoplasmosis
    - Sarcoidosis
    - Tuberculosis
- Glycogen storage disease
- Graft versus host disease
- HIV
- Hypercalcemia
- Hypocalcemia
- Hyperparathyroidism
- Hypoparathyroidism
- Hypervitaminosis of vitamin D
- Individuals receiving hyperalimentation

- Intestinal malabsorption to include but not limited to:
    - Bariatric surgery
    - Celiac Disease
    - Crohn's (regional enteritis)
    - Cystic Fibrosis
- Institutionalized individuals
- Liver cirrhosis
- Medication known to lower vitamin D levels to include but not limited to:
    - Anticonvulsants
    - Glucocorticoids
- Myalgia
- Myopathy related to endocrine disease
- Myositis
- Neoplastic hematologic disorders to include but not limited to:
    - Leukemia
    - Lymphoma
- Obesity (Adults with a BMI $\geq$ 30; Pediatrics with a BMI $\geq$ 95th percentile)
- Osteogenesis imperfecta
- Osteopetrosis
- Osteoporosis
- Osteomalacia
- Osteopenia
- Pancreatic steatorrhea
- Primary or miliary tuberculosis
- Psoriasis
- Renal, ureteral or urinary calculus
- Rickets
- Sarcoidosis
- Systemic Lupus Erythematosus
- Transplants

Medically Necessary: 1,25-dihydroxyvitamin D (82652)

1,25-dihydroxyvitamin D may be considered **medically necessary no more frequently than annually** in the evaluation and monitoring of **one of the following** conditions with an associated defect risk in vitamin D metabolism:

- Cat-scratch disease
- Chronic kidney disease stage III or greater
- Granuloma forming disorders to include but not limited to:
    - Berylliosis
    - Coccidiomycosis
    - Histoplasmosis
    - Sarcoidosis
    - Tuberculosis
- Familial hypophosphatemia
- Fontan surgery for congenital heart disease (i.e., Hypoplastic left heart syndrome, Tricuspid atresia, and Double outlet right ventricle)
- Hypercalcemia of malignancy
- Hyperparathyroidism
- Hypoparathyroidism

- Individuals receiving hyperalimentation
- Lymphoma
- Neonatal hypocalcemia
- Osteogenisis imperfecta
- Osteomalacia
- Osteopetrosis
- Primary or miliary tuberculosis
- Pseudohypoparathyroidism
- Renal, ureteral, or urinary calculus
- Rickets
- Sarcoidosis
- Systemic connective tissue disorder
- Transplants

Investigational: **25-hydroxyvitamin D and 1,25-dihydroxyvitamin D**

The use of 1,25 dihydroxyvitamin D and 25-hydroxyvitamin D serum testing is considered **investigational** when the above criteria is not met and for all other indications to include but not limited to the following because the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes:

- Asymptomatic/General population screening
- Routine testing

Frequency Testing: **Medically Necessary 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D**

The evaluation and monitoring of vitamin D may be considered **medically necessary** when the above criteria has been met, no more frequently than annually.

Frequency Testing: Not Medically Necessary 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D

The evaluation and monitoring of vitamin D when testing occurs more frequently than annually is considered **not medically necessary.**

POLICY GUIDELINES

Note

- Iowa House File 2668 (Iowa Code section 514C.36) requires that certain health plans issued or renewed on or after January 1, 2025 “provide coverage for biomarker testing for the purposes of diagnosing, treating, appropriately managing, or monitoring a disease or condition in a covered person when the biomarker testing has demonstrated clinical utility.” Iowa House File 2668 defines clinical utility as ”sufficient medical and scientific evidence indicating that the use of a biomarker test will provide meaningful information that affects treatment decisions and guides improvement of net health outcomes, including an improved quality of life or longer survival.” Wellmark has reviewed this Medical Policy in light of Iowa House File 2668.

- *There are no standardized lists of factors denoting high risk for vitamin D deficiency, and published lists of high-risk factors differ considerably. Certain factors tend to be present on most lists, however, and they may constitute a core set of factors for which there is general agreement that testing is indicated.*

- Serum concentration of 25 hydroxyvitamin D is the optimal clinical indicator of vitamin D metabolism due to the rapid conversion of vitamin D to 25-hydroxyvitamin D with only a small fraction converted to 1,25 hydroxyvitamin D.
- 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 (e.g., pain, 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, phosphorus, alkaline phosphatase, and/or parathyroid hormone.
- Signs and symptoms of vitamin D toxicity (hypervitaminosis D) generally result from induced hypercalcemia. Acute intoxication can cause symptoms of confusion, anorexia, vomiting, weakness, polydipsia, and polyuria. Chronic intoxication can cause bone demineralization, kidney stones, and bone pain.

Definitions

- Vitamin D - A nutrient that helps the body absorb calcium in the intestines. Calcium and vitamin D can help prevent bone loss, lower the risk of fracture, and perform other functions in the body. Sources of vitamin D include sun exposure, foods such as fortified dairy products, and dietary supplements.
- Vitamin D deficiency - There is too little vitamin D in the blood. Low vitamin D levels can cause problems such as bone loss or softening. Low vitamin D in the blood can be caused by not eating foods that contain vitamin D or not getting enough sun exposure. Low vitamin D can also be caused by certain health conditions, such as some liver, kidney, and intestinal diseases.
- “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.
- Serum 25-hydroxyvitamin D test for vitamin D – A blood test which measures level of 25-hydroxyvitamin D, a form of Vitamin D that circulates in the body. This form of Vitamin D is considered the most accurate way to determine that the body’s vitamin D levels are too low or too high. It is the test commonly used to measure overall vitamin D levels.
- Serum 1,25-dihydroxyvitamin D test for vitamin D - A blood test which measures levels of 1,25-dihydroxyvitamin D, a potent form of vitamin D that is used quickly in the body. It is not considered an accurate way to measure the body’s overall reserves of vitamin D. Measurement of this type of vitamin D is useful for a small number of diseases, such as chronic kidney disease.

The CDC Defined Childhood Weight Status:

CDC Growth Charts are commonly used to measure the size and growth patterns of children and teens in the United States. BMI-for-age weight status categories and the corresponding percentiles, based on expert committee recommendations, and are in the following table:

BMI-for-age weight status categories and the corresponding percentiles	
Weight Status Category	**BMI Range**
Underweight	Less than the 5th percentile

BMI-for-age weight status categories and the corresponding percentiles	
Weight Status Category	**BMI Range**
Healthy Weight	5th percentile to less than the 85th percentile
Overweight	85th percentile to less than the 95th percentile
Obesity	95th percentile or greater
Severe Obesity	120% of the 95th percentile or greater OR 35 kg/m^2 or greater

Coding
See the Codes table for details.

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.

Vitamin D Levels
Vitamin D deficiency is best assessed by measuring serum levels of 25-hydroxyvitamin D. However, there is no consensus on the minimum vitamin D level or on the optimal serum level for overall health. A 2011 Institute of Medicine (IOM) report concluded that a serum level of 20 ng/mL is sufficient for most healthy adults. Some experts, such as the National Osteoporosis Foundation and the American Geriatrics Society, have recommended a higher level (30 ng/mL). Vitamin D deficiency, as defined by suboptimal serum levels, is common in the United States. In the National Health and Nutrition Examination Survey covering the period of 2000-2004, 30% of individuals over the age of 12 had 25-hydroxyvitamin D levels less than 20 ng/mL. Vitamin D deficiency occurs most commonly because 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 consumption is below recommended levels of intake. Yetley (2008) estimated that average daily intake for U.S. adults ranged from 228 to 335 IU/d, depending on gender and ethnicity. 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. 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." The Women's Health Initiative concluded that hypercalcemia and hypercalciuria in patients receiving calcium

and vitamin D were not associated with adverse clinical events. 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 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. 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.

There are no standardized lists of factors denoting high risk for vitamin D deficiency and published lists of high-risk factors differ considerably. Conditions which may support vitamin D screening generally include, but are not limited to:

- Chronic kidney disease stage ≥ 3
- Cirrhosis and chronic liver disease
- Malabsorption states
- Osteomalacia
- Osteoporosis
- Rickets
- Hypo- or hypercalcemia
- Granulomatous diseases
- Vitamin D deficiency, on replacement
- Obstructive jaundice and biliary tract disease
- Osteogenesis imperfecta
- Osteosclerosis and osteopetrosis
- Chronic use of anticonvulsant medications or corticosteroids
- Parathyroid disorders
- Osteopenia.

25-hydroxyvitamin D and 1,25-dihydroxyvitamin D

Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D is converted enzymatically:

- in the *liver* to 25-hydroxyvitamin D, the major *circulating* form of Vitamin D
- in the *kidney* to 1,25-dihydroxyvitamin D, the *active* form of Vitamin D.

The concentration of 25-hydroxyvitamin D is almost 1000-fold that of 1,25-hydroxyvitamin D, and the half-life of 25-hydroxyvitamin D is much longer, implying that its concentration is more stable.

The most common type of vitamin D deficiency is 25-hydroxyvitamin D vitamin D. A much smaller percentage of 1,25-dihydroxyvitamin D deficiency exists; mostly, in those with renal disease. Although it is not the active form of the hormone, 25-hydroxyvitamin D is more commonly measured. It better reflects the sum total of vitamin D produced endogenously and absorbed from the diet than does the level of the active hormone 1,25-dihydroxyvitamin D. Deficiency of 1,25-dihydroxyvitamin D, which is present at much lower concentrations, does not necessarily reflect deficiency of 25-hydroxyvitamin D vitamin D. Its measurement should be limited to specific diseases such as acquired and inherited disorders in the metabolism of 25-hydroxyvitamin D and phosphate, including chronic kidney disease.

25-hydroxyvitamin D

The best laboratory indicator of Vitamin D adequacy is the serum 25-hydroxyvitamin D concentration. It is the measurement of choice to diagnose Vitamin D deficiency and to assess Vitamin D status. The lower limit of normal for 25-hydroxyvitamin D levels varies depending on the geographic location and sunlight exposure of the reference population. There is no consensus on the optimal 25-hydroxyvitamin D concentration for skeletal or extra skeletal health. 25-hydroxyvitamin D measurements have had widespread variation in the results.

Serum 25-hydroxyvitamin D assays fall into two main categories:

(1) those based on a separation step of chromatography, the most popular of which is liquid chromatography–tandem mass spectrometry (LC-MS/MS) and
(2) nonchromatographic methods based on antibody or protein binding, such as radioimmunoassays.

25-hydroxyvitamin D should be assessed in persons at risk for Vitamin D deficiency or insufficiency. Vitamin D deficiency may result from inadequate exposure to sunlight or intake of Vitamin D, reduced absorption of Vitamin D (e.g., malabsorption* syndromes) or medications or disorders that affect the metabolism of Vitamin D and phosphate (e.g., glucocorticoids, chronic kidney disease) resistance to the effects of Vitamin D. Causes of malabsorption may include:

- diseases of the gallbladder, liver, or pancreas
- some conditions such as cystic fibrosis
- damage to the intestine from infection, inflammation, trauma, or surgery
- parasitic diseases
- certain congenital defects such as biliary atresia

1,25-dihydroxyvitamin D

Serum 1,25-dihydroxyvitamin D is not suitable to assess Vitamin D status because it is kept within reference limits as long as possible by hormonal mechanisms (e.g., parathyroid hormone for stimulation and serum calcium and phosphate for suppression). It also has a short half-life measured in hours. Levels of 1,25-dihydroxyvitamin D do not typically decrease until vitamin D deficiency is severe. Serum measurement of 1,25-dihydroxyvitamin D is useful in monitoring certain conditions, such as acquired and inherited disorders in the metabolism of 1,25-dihydroxyvitamin D and phosphate, including chronic kidney disease, hereditary phosphate losing disorders, oncogenic osteomalacia, pseudovitamin D-deficiency rickets, Vitamin D-resistant rickets, as well as chronic granuloma-forming disorders such as sarcoidosis and some lymphomas. Some patients with vitamin D deficiency have coexisting primary hyperparathyroidism that is not recognized until vitamin D is repleted. Hypercalcemia may not be evident initially if the vitamin D deficiency is severe. Calcium concentrations are normal or at the upper end of the normal range and PTH concentrations are elevated. Vitamin D replacement in these individuals should be provided cautiously as hypercalcemia may develop. In this scenario: 1,25-dihydroxy vitamin D levels may be needed.

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. 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.

The Institute of Medicine defined three 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 the below table.

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 of age	400	600	2500
4 to 8 years of age	400	600	3000
9 to 70 years of age	400	600	4000
> 70 years of age	400	800	4000

Adapted from Institute of Medicine (2011).

Vitamin D Toxicity

Another reason to measure serum 25-hydroxyvitamin D is when there is a suspicion of excessive Vitamin D blood levels (toxicity). Because vitamin D increases calcium absorption in the gastrointestinal tract, vitamin D toxicity results in marked hypercalcemia (total calcium greater than 11.1 mg/dL, beyond the normal range of 8.4 to 10.2 mg/dL), hypercalciuria, and high serum 25-hydroxyvitamin D levels (typically greater than 375 nmol/l [150 ng/mL]) [155]. Hypercalcemia, in turn, can lead to nausea, vomiting, muscle weakness, neuropsychiatric disturbances, pain, loss of appetite, dehydration, polyuria, excessive thirst, and kidney stones (National Institute of Health, 2020).

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.

RATIONALE

This evidence review was created in May 2011 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 2025.

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. 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.

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). 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. 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. 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." The Women's Health Initiative concluded that hypercalcemia and hypercalciuria in individuals receiving calcium and vitamin D were not associated with adverse clinical events. 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 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. 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.

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 individuals who are asymptomatic without conditions or risk factors, asymptomatic with conditions/risk factors, or symptomatic individuals 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, asymptomatic with conditions/risk factors, or symptomatic individuals 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

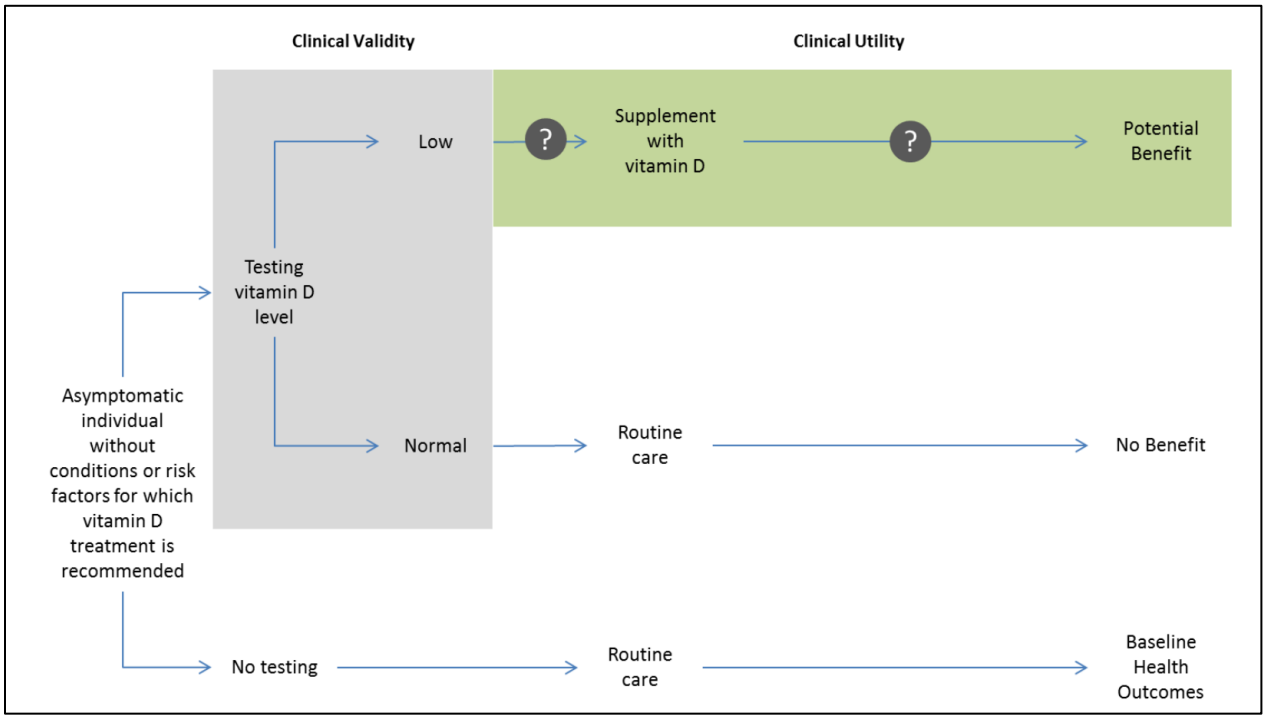
Methodologically credible studies were selected using the following principles:

- 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 individuals 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 individuals to the treatment of individuals 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. 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 outcomes of care. The net health outcome can be improved if individuals 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 individuals 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, there were 21 meta-analyses on skeletal health, 7 on metabolic disease, 4 on pediatric outcomes, three on cardiovascular disease, three 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)	Any fracture	5	3551	32	0.98 (0.82 to 1.16)
	Hip fracture	4	1619	46	0.96 (0.72 to 1.29)

Study	Outcome	No. of Studies	No. of Participants	I^2, %[a]	RR for Outcome (95% CI)
	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					
Tan et al (2024)	Falls				
800 to 1000 IU/d vs placebo or no treatment		35	58,937	11%	0.85 (0.74 to 0.95)
≤ 500 IU/d vs 800 to 1000 IU/d		NR	NR	NR	1.2 (1.02 to 1.45
1100 to 1900 IU/d vs 800 to 1000 IU/d		NR	NR	NR	1.22 (1.04 to 1.47
≥ 2000 IU/d vs 800 to 1000 IU/d					
Ling et al (2021)	Falls	21	51,984	NR	1.00 (0.95 to 1.05)
Cranney et al (2011); 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)	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)	Non-vertebral fracture	5	7130	NR	0.79 (0.63 to 0.99)

Study	Outcome	No. of Studies	No. of Participants	I^2, %[a]	RR for Outcome (95% CI)
Palmer et al (2009)	All fractures (CKD-RD)	4	181	NR	1.0 (0.06 to 15.41)
Bischoff-Ferrari et al (2005)	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. 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. 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.

Similarly, a meta-analysis of RCTs by Tan et al (2024) examined the dose-response relationship between vitamin D supplementation and falls in elderly individuals. The study found that when compared to Vitamin D supplementation at a dose of 800 to 1000 IU/day, the following doses significantly increased the risk of falls: $\leq$ 500 IU/d (relative risk [RR]=1.2; 95% confidence interval [CI], 1.02 to 1.45), 1100 to 1900 IU/d (RR=1.22; 95% CI, 1.04 to 1.47), and $\geq$ 2000 IU/d (RR=1.23; 95% CI, 1.06 to 1.45).

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. 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]) 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. It included 51 trials that used various forms of vitamin D with or without calcium. There was minimal heterogeneity among the studies. Combined analysis showed no significant impact on cardiovascular death (RR=0.96; 95% CI, 0.93 to 1.0), myocardial infarction (RR=1.02; 95% CI, 0.93 to 1.13), or stroke (RR=1.05; 95% CI, 0.88 to 1.25). No significant effects were found on the physiologic outcomes of lipids, glucose, or blood pressure.

A systematic review by Pittas et al (2010) assessed 5 RCTs evaluating the impact of vitamin D supplementation on incident cardiovascular disease. 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:

- 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. 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. 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. 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).

Section Summary: Cardiovascular Disease

The available evidence does not support a benefit of vitamin D supplementation on cardiovascular events. Numerous RCTs have assessed this outcome; however, in most studies, it is a secondary outcome with a limited number of events, thus limiting the power to detect a difference. Furthermore, it is difficult to separate the impact of vitamin D from the impact of calcium in many of these studies. It is common to use vitamin D and calcium supplementation together. Research has also highlighted a potential increase in cardiovascular outcomes associated with calcium supplementation. Thus, if there are beneficial effects of vitamin D, they may be obscured or attenuated by 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 contain 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. 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)	To November 2018	10	People with baseline 25-(OH)D	NR	RCTs	3 to 10 years
Bjelakovic et al (2014)	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)				
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)				
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
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)	Bjelakovic et al (2014)
Ott et al (1989)		●
Grady et al (1991)		●
Komulainen et al (1999)		●
Gallagher et al (2001)		●
Trivedi et al (2003)	●	●
Wactawski-Wende et al (2006)	●	
Daly et al (2008)		●
LaCroix et al (2009)	●	
Bolton-Smith et al (2007)		●
Lappe et al (2007)	●	●
Prince et al (2008)		●
Janssen et al (2010)		●
Sanders et al (2010)	●	●
Brunner et al (2011)		●
Avenell et al (2012)	●	●
Glendenning et al (2012)		●
Larsen et al (2012)		●
Murdoch et al (2012)		●
Wood et al (2012)		●
Witham et al (2013)		●
Baron et al (2015)	●	
Jorde et al (2016)	●	
Lappe et al (2017)	●	
Scragg et al (2018)	●	
Manson et al (2019)	●	

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 below. Twenty-six unique RCTs were included in these systematic reviews. Reviews by Williamson et al (2023), Liu et al (2022), and Jolliffe et al (2017) 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 most recent Cochrane systematic review evaluating vitamin D for asthma management by Williamson et al (2023) failed to find improved outcomes with vitamin D use, reversing conclusions of a 2016 Cochrane review by Martineau et al (2016). The Jolliffe et al (2017) review 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 review by Luo et al (2015) 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). 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
Williamson et al (2023)	To Sep 2022	20	People with asthma, all ages, and baseline 25(OH)D levels included	2474	RCT	3 mo to 40 mo
Liu et al (2022)	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); 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
Luo et al (2015)	1946 to 2015	7	People with asthma, all ages, and baseline	903	RCT	9 wk to 12 mo

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Williamson et al (2023)	To Sep 2022	20	People with asthma, all ages, and baseline 25(OH)D levels included	2474	RCT	3 mo to 40 mo
			25(OH)D levels included			

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
Williamson et al (2023)					
Total N	1070	1778	1271	1286	1556
Pooled effect	OR=0.56	OR=1.04[a]	SMD=0.23 higher	Diff=0.2% higher[b]	OR=0.89[d]
95% CI	0.81 to 1.34	0.26 to 1.21	0.26 lower to 0.73 higher	1.24 lower to 1.63 higher	0.56 to 1.41
I^2	33%	60%	29%	25%	0%
Liu et al (2022)					
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)					
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			
Luo et al (2015)					
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)	Williamson et al (2023)	Liu et al (2022)	Jolliffe et al (2017)	Luo et al (2015)
Ramos-Martinez et al (2018)	●			
Jiang et al (2017)	●			
Jerzynska et al (2016)	●			
Forno et al (2020)	●			
Ducharme et al (2019)	●			
Camargo et al (2021)	●			
Andújar-Espinosa et al (2021)	●			
Aglipay et al (2019)	●			
Worth et al (1994)				●
Majak et al (2009)	●			●
Urashima et al (2010)	●		●	
Majak et al (2011)	●	●	●	
Lewis et al (2012)	●			
Baris et al (2014)				●
Castro et al (2014)	●	●	●	●
Yadav et al (2014)	●	●		●
de Groot et al (2015)		●		●
Martineau et al (2015)	●	●	●	●
Tachimoto et al (2016)	●		●	

Jensen et al (2016)	●		●	
Kerley et al (2016)	●		●	
Musharraf et al (2017)		●		
Dodamani et al (2019)		●		
Shabana et al (2019)		●		
Jat et al (2021)	●	●		
Thakur et al (2021)	●	●		

Randomized Controlled Trials

A RCT of prenatal supplementation in 881 pregnant women at high-risk of having children with asthma was published in 2016. Women between gestational ages of 10 and 18 weeks were randomized to daily vitamin D 4000 IU plus a multivitamin containing vitamin D 400 IU (4400 IU group) or daily placebo vitamin D plus a multivitamin containing vitamin D 400 IU (400 IU group). Coprimary outcomes were (1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age and (2) third trimester maternal 25-OH(D) levels. Analysis of infant outcomes included 806 infants, 218 of whom developed asthma by age 3 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 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 2019 and updated Cochrane 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 review are listed in Table 111. 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). 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. In the 2024 update, a trustworthy assessment tool removed most of the studies that were previously included in the 2019 review. In the updated analyses, the evidence was very uncertain about Vitamin D supplementation for the outcome of pre-eclampsia (very low certainty evidence), gestational diabetes (very low certainty evidence), and pre-term birth (very low certainty evidence). However, the authors found that supplementation with Vitamin D during pregnancy may reduce the risk of severe

postpartum hemorrhage (low-certainty evidence) and low birth weight (low-certainty evidence). The risk of bias was high for blinding in 4 studies and for attrition in 4 studies. Additionally, not all studies measured baseline 25(OH)D levels.

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

Study; Trial	Dates	Trials	Participants	N	Design	Duration
Palacios et al (2024)	To December 2022	8[a] (vitamin D supplementation alone)	Pregnant women; most studies included baseline 25(OH)D levels	2313	RCTs	NR (most studies started supplementation at or after 20 weeks gestation)
Palacios et al (2019)	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 (2024)					
Total N	165	165	1134	1368	371
Pooled effect	RR=0.53	RR=0.53	RR=0.68	RR=0.76	RR=0.69
95% CI	0.21 to 1.33	0.03 to 8.28	0.51 to 0.91	0.25 to 2.33	0.44 to 1.08
Palacios et al (2019)					
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)	Palacios et al (2024)
Brooke et al (1980)	●	
Delvin et al (1986)	●	
Mallet et al (1986)	●	
Marya et al (1988)	●	
Kaur et al (1991)	●	
Yu et al (2008)	●	●
Roth et al (2010)	●	●
Sabet et al (2012)	●	
Asemi et al (2013)	●	
Grant et al (2013)	●	●
Tehrani et al (2014)	●	
Mirghafourvand et al (2015)	●	
Rodda et al (2015)	●	●
Sablok et al (2015)	●	●
Singh et al (2015)	●	
Khan et al (2016)	●	●
Cooper et al (2016)	●	●
Naghshineh et al (2016)	●	
Shahgheibi et al (2016)	●	
Vaziri et al (2016)	●	
Sasan et al (2017)	●	
Samimi et al (2017)	●	
Vafaei (2019)		●

Section Summary: Pregnancy

A 2019 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. A 2024 update of this review excluded less

reputable studies and found that Vitamin D during pregnancy may reduce the risk of severe postpartum hemorrhage and low birth weight.

Multiple Sclerosis

Three systematic reviews by Pozuelo-Moyano et al, James et al, and Jagannath et al have examined the effect of vitamin D supplementation in patients with MS. 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. The table below 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). 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), 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.

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)	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)	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)	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)	Mortality (CKD-RD)	5	233		1.34 (0.34 to 5.24)
Palmer et al (2009)	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;; 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.

American Academy of Neurology (AAN)

In 2019, the AAN affirmed the Myotonic Dystrophy Foundations Consensus-Based Care Recommendations for Adults with Myotonic Dystrophy Type 2 vitamin D is recommended to test for “Severe Symptoms, Endocrine and metabolic”.

In 2019, the AAN affirmed the Myotonic Dystrophy Foundations Consensus-Based Care Recommendations for Adults with Myotonic Dystrophy Type 1 recommendation does not address Vitamin D testing.

American Academy of Pediatrics (AAP)

In 2017, the American Academy of Pediatrics contributed to Choosing Wisely® #354 – Section on Endocrinology, on "Avoid Ordering Vitamin D Concentrations Routinely in Otherwise Healthy Children, including Children who are Overweight or Obese" which stated: "Although a 25-hydroxyvitamin D concentration, reflecting both vitamin D synthesis and intake, is the correct screening lab to monitor for vitamin D deficiency, current evidence is not sufficient to suggest that screening in otherwise healthy children who are overweight or obese is necessary or safe. Global consensus recommendations caution against population-based screening for vitamin D deficiency. The U.S. Preventive Services Task Force also has noted that variability of current assays and unclear cutoffs for deficiency may lead to "misclassification" of persons as having vitamin D deficiency, and that this misclassification could outweigh any benefits if there are harms. The AAP report on Optimizing Bone Health in Children and Adolescents advises screening for vitamin D deficiency only in patients with disorders associated with low bone mass such as rickets and/or a history of recurrent, low-trauma fractures. It has been shown that children who are overweight or obese have a greater likelihood of having low vitamin D levels. If the history suggests an obese child has insufficient dietary intake of vitamin D (e.g., little milk intake), a vitamin D supplement should be recommended, which is more cost-effective than 25-hydroxyvitamin D measurements for both screening and monitoring therapy."

American Association of Clinical Endocrinologists and American College of Endocrinology

In 2020, the American Association of Clinical Endocrinologists and American College of Endocrinology published their "Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis" which includes the following recommendations:

- "Measure serum 25-hydroxyvitamin D (25[OH]D) in patients who are at risk for vitamin D insufficiency, particularly those with osteoporosis (Grade B, BEL2)."
- "Maintain serum 25-hydroxyvitamin D (25[OH]D) ≥ 30 ng/mL in patients with osteoporosis (preferable range, 30 to 50 ng/mL) (Grade A; BEL 1)."
- "Supplement with vitamin D3 if needed, with a daily dose of 1,000 to 2,000 international units (IU) typically required to maintain an optimal serum 25(OH)D level (Grade A; BEL 1)."
- "Higher doses of vitamin D3 may be necessary in patients with present factors such as obesity, malabsorption, and older age (Grade A; BEL 1)."

American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery (ASMBS), Obesity Medicine Association, and American Society of Anesthesiologists

In 2019, the Clinical Practice Guidelines for the Perioperative nutrition, metabolic, and nonsurgical support of patients undergoing Bariatric procedures recommended: "Baseline and annual postoperative evaluation for vitamin D deficiency is recommended after Roux-en-Y gastric bypass, sleeve gastrectomy, or laparoscopic biliopancreatic diversion without or with duodenal switch." (Recommendation 53)

American College of Obstetrics and Gynecology (ACOG)

The American College of Obstetrics and Gynecology (2011, reaffirmed 2024) issued a committee opinion on the testing of vitamin D levels and vitamin D supplementation in pregnant women. The following recommendation was made concerning testing vitamin D levels:

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

American College of Rheumatology (ACR)

In 2022, the ACR provided a guideline for the recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. It provided the following recommendations “For individuals of all ages (adults and children) who are initiating or continuing long-term GC therapy at a dose of at least 2.5 mg/day for greater than 3 months, the ACR conditionally recommends considering the optimization of age-appropriate dietary and supplemental intake of calcium and vitamin D, in conjunction with making lifestyle modifications.”

- “Vitamin D supplementation to sustain serum vitamin D 25(OH)D levels of at least 30 to 50 ng/mL, typically requiring 600 to 800 international units daily or further supplementation as needed”

American Family Physician

The American Society of Clinical Pathology contributed the following recommendation to Choosing Wisely® #67 which stated, “Don’t perform population-based screening for 25-OH vitamin D deficiency.” “Vitamin D deficiency is common in many populations, particularly in patients at higher latitudes, during winter months and in those with limited sun exposure. Over the counter Vitamin D supplements and increased summer sun exposure are sufficient for most otherwise healthy patients. Laboratory testing is appropriate in higher risk patients when results will be used to institute more aggressive therapy (e.g., osteoporosis, chronic kidney disease, malabsorption, some infections, obese individuals).”

The Endocrine Society

In 2024, the Endocrine Society has a clinical practice guideline on Vitamin D for the prevention of disease. The 2024 guideline updates and replaces a 2011 Endocrine Society guideline on the evaluation, treatment, and prevention of vitamin D deficiency. The 2024 guideline suggests *against* routine testing vitamin D levels in the following populations who do not otherwise have established indications for 25(OH)D testing (e.g., hypocalcemia):

- General adult population younger than age 50 years, aged 50 to 74 years, and aged 75 years and older
- Pregnant individuals
- Healthy adults
- Adults with dark complexion
- Adults with obesity

For these populations, the guideline notes that: "25(OH)D levels that provide outcome-specific benefits have not been established in clinical trials."

United States Preventive Services Task Force (USPSTF)

The U.S. Preventive Services Task Force published an updated recommendation, and associated evidence report and systematic review in 2021, 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 and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed
	82652	Vitamin D; 1,25 dihydroxy, includes fraction(s), if performed
	0038U	Vitamin D, 25 hydroxy D2 and D3, by LC-MS/MS, serum microsample, quantitative (*Proprietary Test: Sensieva™ Droplet 25OH Vitamin D2/D3 Microvolume LC/MS Assay. Lab/Manufacturer: InSource Diagnostics*)
HCPCS		
	No code(s)	
Type of Service	Laboratory	

Codes	Number	Description
Place of Service	Outpatient	

POLICY HISTORY

Date	Reason	Action
February 2025	Annual Review	Policy Renewed
February 2024	Annual Review	Policy Revised
February 2023	Annual Review	Policy Revised
January 2022	Annual Review	Policy Revised
January 2021	Annual Review	Policy Revised
January 2020	Annual Review	Policy Revised
January 2019	Annual Review	Policy Revised
January 2018	Annual Review	Policy Revised
February 2017	Annual Review	Policy Revised
March 2016	Annual Review	Policy Renewed
January 2016	Interim Review	Policy Revised
March 2015	Annual Review	Policy Revised
March 2014	Annual Review	Policy Revised
March 2013	Annual Review	Policy Renewed
March 2012	Annual Review	Policy Renewed
May 2011	Literature Review	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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