Vitamin D Testing

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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.

The term, vitamin D, is broad and includes several metabolically interrelated sterol substances that have hormonal activity. Vitamin D has two distinctive forms: Vitamin D_2 and Vitamin D_3. Ergocalciferol, or vitamin D_2, is found in fatty fish (e.g., salmon and tuna) and egg yolks, although very few foods naturally contain significant amounts of vitamin D. Cholecalciferol, or vitamin D_3, is synthesized in the skin via exposure to ultraviolet radiation present in sunlight. Some foods are also fortified with vitamin D, most notably milk and cereals.

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

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).

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 phosphatelosing 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.

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

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 question addressed in this evidence review is: Does testing and measurement of vitamin D levels and supplement of deficiency in individuals who are asymptomatic without conditions or risk factors, asymptomatic with conditions/risk factors, or symptomatic individuals 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, 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.

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 outcome of care. The net health outcome can be improved if

individuals receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

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, 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.

Asthma

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

(2017) Jolliffe et al. completed a systematic review and meta-analysis of individual participant data on vitamin D supplementation to prevent asthma exacerbations which noted they identified 483 unique studies, eight of which were eligible randomized controlled trials (total 1078 participants). We sought individual participant data for each and obtained it for seven studies (955 participants). Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (adjusted incidence rate ratio [aIRR] 0·74, 95% CI 0·56-0·97; p=0·03; 955 participants in seven studies; high-quality evidence). There were no significant differences between vitamin D and placebo in the proportion of participants with at least one exacerbation or time to first exacerbation. Subgroup analyses of the rate of asthma exacerbations treated with systemic corticosteroids revealed that protective effects were seen in participants with baseline 25(OH)D of less than 25 nmol/L (aIRR 0·33, 0·11-0·98; p=0·046; 92 participants in three studies; moderate-quality evidence) but not in participants with higher baseline 25(OH)D levels (aIRR 0·77, 0·58-1·03; p=0·08; 764

participants in six studies; moderate-quality evidence; interaction=0·25). P values for interaction for all other subgroup analyses were also higher than 0·05; therefore, we did not show that the effects of this intervention are stronger in any one subgroup than in another. Six studies were assessed as being at low risk of bias, and one was assessed as being at unclear risk of bias. The two-step meta-analysis did not reveal evidence of heterogeneity of effect (I2=0·0, p=0·56). The interpretation or conclusion was vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids overall. They did not find definitive evidence that effects of this intervention differed across subgroups of patients.

(2016) Litonjua et al. completed 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.

(2016) Martineau et al. completed a systematic review of double-blind, randomized, placebo-controlled trials of vitamin D in children and adults with asthma evaluating exacerbation risk or asthma symptom control or both. The authors' concluded meta-analysis of a modest number of trials in people with predominantly mild to moderate asthma suggests that vitamin D is likely to reduce both the risk of severe asthma exacerbation and healthcare use. It is as yet unclear whether these effects are confined to people with lower baseline vitamin D status; further research, including individual patient data meta-analysis of existing datasets, is needed to clarify this issue. Children and people with frequent severe asthma exacerbations were under-represented; additional primary trials are needed to establish whether vitamin D can reduce the risk of severe asthma exacerbation in these groups.

(2015) Lou et al. completed a meta-analysis review on if vitamin D supplementation in addition to asthma controllers improve clinical outcomes in patients with asthma and concluded Vitamin D supplementation in addition to asthma controllers cannot decrease asthma exacerbation and FeNO, nor improve lung function and asthma symptoms, although it can be safely applied to increase serum 25-hydroxyvitamin D levels. More large double-blind RCTs are needed, particularly in identical medication doses and administration routines and durations, to further determine the role of vitamin D, including the cost-effectiveness, in patients with asthma. They also noted the following study limitations First, the name, dose, administration routine, and duration of the intervention drugs were not identical in the enrolled studies, which may result in

performance biases. Second, the baseline characteristics of the patients were not completely provided, and we included all trials conducted in adults and children, which may lead to selection biases. Third, the total number of studies and patients enrolled was relatively small. And finally, these trials relied on a single measurement of vitamin D status or intake with asthmatic outcomes assessed up to 31 years later; therefore, it is impossible to discount variables other than vitamin D contributing to the development of asthma.

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.

Cancer
(2019) Keum et al. completed an updated meta-analysis on randomized control trials for vitamin D supplementation and total cancer incidence and mortality which noted. For total cancer incidence, 10 trials were included [6537 cases; 3-10 years of follow-up; 54-135 nmol/l of attained levels of circulating 25(OH) vitamin D [25(OH)D] in the intervention group]. The summary RR was 0.98 (95% CI, 0.93-1.03; P = 0.42; I2 = 0%). The results remained null across subgroups tested, including even when attained 25(OH)D levels exceeded 100 nmol/l (RR, 0.95; 95% CI, 0.83-1.09; P = 0.48; I2 = 26%). For total cancer mortality, five trials were included [1591 deaths; 3-10 years of follow-up; 54-135 nmol/l of attained levels of circulating 25(OH)D in the intervention group]. The summary RR was 0.87 (95% CI, 0.79-0.96; P = 0.005; I2 = 0%), which was largely attributable to interventions with daily dosing (as opposed to infrequent bolus dosing). No statistically significant heterogeneity was observed by attained levels of circulating 25(OH)D (Pheterogeneity = 0.83), with RR being 0.88 (95% CI, 0.78-0.98; P = 0.02; I2 = 0%) for ≤100 nmol/l and 0.85 (95% CI, 0.70-1.03; P = 0.11; I2 = 0%) for >100 nmol/l. The authors concluded vitamin D supplementation significantly reduced total cancer mortality but did not reduce total cancer incidence.

(2014) Bjelakovic et a.l completed a systematic review which included randomized trials that compared vitamin D at any dose, duration, and route of administration versus placebo or no intervention in adults who were healthy or were recruited among the general population or diagnosed with a specific disease. Vitamin D could have been administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)), or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol), or 1,25-dihydroxyvitamin D (calcitriol)).

The main results for 18 randomized trials with 50,623 participants provided data for the analyses. All trials came from high-income countries. Most of the trials had a high risk of bias, mainly for-profit bias. Most trials included elderly community-dwelling women (aged 47 to 97 years). Vitamin D was administered for a weighted mean of six years. Fourteen trials tested vitamin D_3, one trial tested vitamin D_2, and three trials tested calcitriol supplementation. Cancer occurrence was observed in 1927/25,275 (7.6%) recipients of vitamin D versus 1943/25,348 (7.7%) recipients of control interventions (RR 1.00 (95% confidence interval (CI) 0.94 to 1.06); P = 0.88; I^2 = 0%; 18 trials; 50,623 participants; moderate quality evidence according to the GRADE instrument). Trial sequential analysis (TSA) of the 18 vitamin D trials shows that the futility area is reached after the 10th trial, allowing us to conclude that a possible intervention effect, if any, is lower than a 5% relative risk reduction. We did not observe substantial differences in the effect of vitamin D on cancer in subgroup analyses of trials at low risk of bias compared to trials at high risk of bias; of trials with no risk of for-profit bias compared to trials with risk of for-profit bias; of trials assessing primary prevention compared to trials assessing secondary prevention; of trials including participants with vitamin D levels below 20 ng/mL at entry compared to trials including participants with vitamin D levels of 20 ng/mL or more at entry; or of trials using concomitant calcium supplementation compared to trials without calcium. Vitamin D decreased all-cause mortality (1854/24,846 (7.5%) versus 2007/25,020 (8.0%); RR 0.93 (95% CI 0.88 to 0.98); P = 0.009; I^2 = 0%; 15 trials; 49,866 participants; moderate quality evidence), but TSA indicates that this finding could be due to random errors. Cancer occurrence was observed in 1918/24,908 (7.7%) recipients of vitamin D_3 versus 1933/24,983 (7.7%) in recipients of control interventions (RR 1.00 (95% CI 0.94 to 1.06); P = 0.88; I^2 = 0%; 14 trials; 49,891 participants; moderate quality evidence). TSA of the vitamin D_3 trials shows that the futility area is reached after the 10th trial, allowing us to conclude that a possible intervention effect, if any, is lower than a 5% relative risk reduction. Vitamin D_3 decreased cancer mortality (558/22,286 (2.5%) versus 634/22,206 (2.8%); RR 0.88 (95% CI 0.78 to 0.98); P = 0.02; I^2 = 0%; 4 trials; 44,492 participants; low quality evidence), but TSA indicates that this finding could be due to random errors. Vitamin D_3 combined with calcium increased nephrolithiasis (RR 1.17 (95% CI 1.03 to 1.34); P = 0.02; I^2 = 0%; 3 trials; 42,753 participants; moderate quality evidence). TSA, however, indicates that this finding could be due to random errors. We did not find any data on health-related quality of life or health economics in the randomized trials included in this review.

Authors' conclusions noted there is currently no firm evidence that vitamin D supplementation decreases or increases cancer occurrence in predominantly elderly community-dwelling women. Vitamin D_3 supplementation decreased cancer mortality and vitamin D supplementation decreased all-cause mortality, but these estimates are at risk of type I errors due to the fact that too few participants were examined, and to risks of attrition bias originating from substantial dropout of participants. Combined vitamin D_3 and calcium supplements increased nephrolithiasis, whereas it remains unclear from the included trials whether vitamin D_3, calcium, or both were responsible for this effect. We need more trials on vitamin D supplementation, assessing the benefits and harms

among younger participants, men, and people with low vitamin D status, and assessing longer duration of treatments as well as higher dosages of vitamin D. Follow-up of all participants is necessary to reduce attrition bias.

(2015) Baron et al. completed a randomized controlled trial on a trail of calcium and vitamin D for the prevention of colorectal adenomas. The results were the participants who were randomly assigned to receive vitamin D had a mean net increase in serum 25-hydroxyvitamin D levels of 7.83 ng per milliliter, relative to participants given placebo. Overall, 43% of participants had one or more adenomas diagnosed during follow-up. The adjusted risk ratios for recurrent adenomas were 0.99 (95% confidence interval [CI], 0.89 to 1.09) with vitamin D versus no vitamin D, 0.95 (95% CI, 0.85 to 1.06) with calcium versus no calcium, and 0.93 (95% CI, 0.80 to 1.08) with both agents versus neither agent. The findings for advanced adenomas were similar. There were few 11serious adverse events. The author's conclusions noted daily supplementation with vitamin D3 (1000 IU), calcium (1200 mg), or both after removal of colorectal adenomas did not significantly reduce the risk of recurrent colorectal adenomas over a period of 3 to 5 years. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00153816.).
(2012) Avenell et al. completed a randomized controlled trial review on the long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D (3) and/or calcium. The results noted in intention-to-treat analyses, mortality [hazard ratio (HR) = 0.93; 95% confidence interval (CI) = 0.85-1.02], vascular disease mortality (HR = 0.91; 95% CI = 0.79-1.05), cancer mortality (HR = 0.85; 95% CI = 0.68-1.06), and cancer incidence (HR = 1.07; 95% CI = 0.92-1.25) did not differ significantly between participants allocated vitamin D and those not. All-cause mortality (HR = 1.03; 95% CI = 0.94-1.13), vascular disease mortality (HR = 1.07; 95% CI = 0.92-1.24), cancer mortality (HR = 1.13; 95% CI = 0.91-1.40), and cancer incidence (HR = 1.06; 95% CI = 0.91-1.23) also did not differ significantly between participants allocated calcium and those not. In a post hoc statistical analysis adjusting for compliance, thus with fewer participants, trends for reduced mortality with vitamin D and increased mortality with calcium were accentuated, although all results remain nonsignificant. The conclusions noted daily vitamin D or calcium supplementation did not affect mortality, vascular disease, cancer mortality, or cancer incidence.

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.

Cardiovascular Disease
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.

(2021) Su et al. completed a systematic review by 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.

(2011) Elamin et al. 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 (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.

(2010) Pittas et al. assessed 5 RCTs in a systematic review by 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.

(2010) Pittas et al. completed a systematic review which 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.

(2009) Chung et al. report in AHRQ concluded 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.

(2008) Wang et al. 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).

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.

Endocrine Disorders

(2018; Last reviewed 2021) The Endocrine Society released a Choosing Wisely and provided information on Vitamin D testing: Don't routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function. Many practitioners become confused when ordering a vitamin D test. Because 1,25-dihydroxyvitamin D is the active form of vitamin D, many practitioners think that measuring 1,25-dihydroxyvitamin D is an accurate means to estimate vitamin D stores and test for vitamin D deficiency, which is incorrect.

Current Endocrine Society guidelines recommend screening for vitamin D deficiency in individuals at risk for deficiency. Serum levels of 1,25-dihyroxyvitamin D have little or no relationship to vitamin D stores but rather are regulated primarily by parathyroid hormone levels, which in turn are regulated by calcium and/or vitamin D. In vitamin D deficiency, 1,25-dihydroxyvitamin D levels go up, not down.

Unregulated production of 1,25-dihydroxyvitamin D (i.e., sarcoidosis, granulomatous diseases) is an uncommon cause of hypercalcemia; this should be suspected if blood calcium levels are high and parathyroid hormone levels are low and confirmed by measurement of 1,25-dihydroxyvitamin D. The enzyme that activates vitamin D is produced in the kidney, so blood levels of 1,25-dihydroxyvitamin D are sometimes of interest in patients on dialysis or with end-stage kidney disease. There are few other circumstances, if any, where 1,25-dihydroxyvitamin D testing would be helpful.

Serum 25-hydroxyvitamin D levels may be overused, but when trying to assess vitamin D stores or diagnose vitamin D deficiency (or toxicity), 25-hydroxyvitamin D is the correct test. (*Accessed January 2022*)

(2017: Last reviewed 2019) American Academy of Pediatrics contributed to the following Choosing Wisely® – Section on Endocrinology, Five Things Physician and Patients Should Question: Avoid ordering Vitamin D concentrations routinely in otherwise healthy children, including children who are overweight or obese.

- 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.

(*Accessed January 2022*)

(2014; Updated 2021) The American Society of Clinical Pathology contributed the following recommendation to Choosing Wisely®:

- 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). (*Accessed January 2022*)

(2016) Jorde et al. completed a study with five hundred eleven subjects (mean age 62 y, 314 males) with prediabetes diagnosed with an oral glucose tolerance test as part of the Tromso Study 2007–2008 were included. A total of 256 were randomized to vitamin D and 255 to placebo. Twenty-nine subjects in the vitamin D and 24 in the placebo group withdrew because of adverse events. Interventions included vitamin D (cholecalciferol) 20 000 IU/wk vs placebo for 5 years. Annual oral glucose tolerance tests were performed. They measured outcomes by progression to T2DM was the main outcome measure. Secondary outcomes were change in glucose levels, insulin resistance, serum lipids, and blood pressure. The mean baseline serum 25-hydroxyvitamin D level was 60 nmol/L (24 ng/mL). One hundred three in the vitamin D and 112 in the placebo group developed T2DM (hazard risk 0.90; 95% confidence interval 0.69–1.18, Cox regression, P = .45, intention to treat analysis). No consistent significant effects on the other outcomes were seen. Subgroup analyses in subjects with low baseline 25-hydroxyvitamin D yielded similar results. No serious side effects related to the intervention were recorded.
The authors concluded in subjects without vitamin D deficiency, vitamin D supplementation is unlikely to prevent progression from prediabetes to diabetes. Very large studies with inclusion of vitamin D-deficient subjects will probably be needed to

show such a putative effect. This study tested if supplementation with vitamin D to subjects with prediabetes will prevent progression to type 2 diabetes (T2DM).

Miscellaneous
(2014) Avitable et al. completed a cross-sectional study included whole body dual energy X-ray absorptiometry scans in 50 Fontan participants ≥5 years, and measures of peak oxygen consumption (VO2) in 28. Whole body and leg LM (a measure of skeletal muscle) were converted to sex- and race-specific Z-scores, relative to age and stature, based on 992 healthy reference participants. The results noted a median age was 11.5 (range 5.1-33.5) years at 9.3 (1.1-26.7) years from Fontan. Height Z-scores were lower in Fontan compared with reference participants (-0.47±1.08 vs 0.25±0.93, p<0.0001). Body mass index Z-scores were similar (0.15±0.98 vs 0.35±1.02, p=0.18). LM Z-scores were lower in Fontan compared with reference participants (whole body LM -0.33±0.77 vs 0.00±0.74, p=0.003; leg LM -0.89±0.91 vs 0.00±0.89, p<0.0001). LM Z-scores were not associated with age or Fontan characteristics. Leg LM Z-scores were lower in vitamin D deficient versus sufficient Fontan participants (-1.47±0.63 vs -0.71±0.92, p=0.01). Median per cent predicted peak VO2 was 81% (range 13%-113%) and was associated with leg LM Z-scores (r=0.54, p=0.003). The author's concluded Fontan, children and young adults are shorter than their peers and have significant LM deficits. Skeletal muscle deficits were associated with vitamin D deficiency and reduced exercise capacity. Future studies should examine the progression of these deficits to further understand the contribution of peripheral musculature to Fontan exercise capacity.

Multiple Sclerosis
(2010-2013) 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.

Pregnancy
(2019) Palacios et al. completed a systematic review of 300 trials (7033 women) across three separate comparisons on vitamin D supplementation for women during pregnancy. GRADE assessments ranged from moderate to very low, with downgrading decisions based on limitations in study design, imprecision and indirectness. Supplementing pregnant women with vitamin D alone probably reduces the risk of pre-eclampsia, gestational diabetes, low birthweight and may reduce the risk of severe postpartum hemorrhage. It may make little or no difference in the risk of having a preterm birth < 37 weeks' gestation. Supplementing pregnant women with vitamin D and calcium probably reduces the risk of pre-eclampsia but may increase the risk of preterm births < 37 weeks (these findings warrant further research). Supplementing pregnant women with vitamin D and other nutrients may make little or no difference in the risk of preterm birth < 37

weeks' gestation or low birthweight (less than 2500 g). Additional rigorous high quality and larger randomized trials are required to evaluate the effects of vitamin D supplementation in pregnancy, particularly in relation to the risk of maternal adverse events.

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. Most studies were considered to have a low-moderate risk of bias.

Skeletal Health
(2021) Ling et al. completed an updated meta-analysis which results noted 31 eligible studies involving 57 867 participants met inclusion criteria, reporting 17 623 falls. A total of 21 RCTs of vitamin D alone and 10 RCTs of vitamin D plus calcium were included in the meta-analysis. The meta-analysis of 21 RCTs (51 984 participants) of vitamin D supplementation alone (daily or intermittent doses of 400-60 000 IU) did not show a reduced risk of falls (The risk ratio [RR] 1.00, 95% confidence intervals [CI] 0.95 to 1.05) compared to placebo or no treatment. Subgroup analyses showed that the baseline of serum 25(OH)D concentration less than 50 nmol/L resulted in a reduction of fall risk (RR 0.77, 95% CI 0.61 to 0.98). In contrast, the meta-analysis of 10 RCTs (5883 participants) of combined supplementation of vitamin D (daily doses of 700-1000 IU) and calcium (daily doses of 1000-1200 mg) showed a 12% reduction in the risk of fall (RR 0.88, 95% CI 0.80 to 0.97). In conclusion the combination of vitamin D and calcium have beneficial effects on prevention falls in old adults. Although vitamin D supplementation alone has no effect on fall risk in old adults with 25(OH)D levels higher than 50 nmol/L, vitamin D supplementation alone does have a benefit on prevention of falls in old adults with 25(OH)D levels lower than 50 nmol/L.

(2015) LeBlanc et al. completed a systemic review of randomized trials of screening for and treatment of vitamin D deficiency and case-control studies nested within the Women's Health Initiative. No study examined the effects of vitamin D screening versus no screening on clinical outcomes. Vitamin D treatment was associated with decreased mortality versus placebo or no treatment (11 studies; risk ratio [RR], 0.83 [95% CI, 0.70 to 0.99]), although benefits were no longer seen after trials of institutionalized persons were excluded (8 studies; RR, 0.93 [CI, 0.73 to 1.18]). Vitamin D treatment was associated with possible decreased risk for having at least 1 fall (5 studies; RR, 0.84 [CI, 0.69 to 1.02]) and falls per person (5 studies; incidence rate ratio, 0.66 [CI, 0.50 to 0.88]) but not fractures (5 studies; RR, 0.98 [CI, 0.82 to 1.16]). Vitamin D treatment was not associated with a statistically significant increased risk for serious adverse events (RR, 1.17 [CI, 0.74 to 1.84]). In conclusion treatment of vitamin D deficiency in asymptomatic persons might reduce mortality risk in institutionalized elderly persons and risk for falls but not fractures. Limitations included variability across studies in 25-hydroxyvitamin D assays and baseline levels, treatment doses, use of calcium, and duration of follow-up.

(2014) Theodoratou et al. completed a systemic review and meta-analysis which noted 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of randomized controlled trials of vitamin D supplementation were identified. The relation between vitamin D and 137 outcomes has been explored, covering a wide range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases. Ten outcomes were examined by both meta-analyses of observational studies and meta-analyses of randomized controlled trials, but the direction of the effect and level of statistical significance was concordant only for birth weight (maternal vitamin D status or supplementation). On the basis of the available evidence, an association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis is probable, but further studies and better designed trials are needed to draw firmer conclusions. In contrast to previous reports, evidence does not support the argument that vitamin D only supplementation increases bone mineral density or reduces the risk of fractures or falls in older people. In conclusions despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable.

(2009) Bishoff-Ferrari et al. performed a meta-analysis on the efficacy of oral supplemental vitamin D in preventing nonvertebral and hip fractures among older individuals (> or =65 years). We included 12 double-blind randomized controlled trials (RCTs) for nonvertebral fractures (n = 42 279) and 8 RCTs for hip fractures (n = 40 886) comparing oral vitamin D, with or without calcium, with calcium or placebo. To incorporate adherence to treatment, we multiplied the dose by the percentage of adherence to estimate the mean received dose (dose x adherence) for each trial.

the results included a pooled relative risk (RR) was 0.86 (95% confidence interval [CI], 0.77-0.96) for prevention of nonvertebral fractures and 0.91 (95% CI, 0.78-1.05) for the prevention of hip fractures, but with significant heterogeneity for both end points. Including all trials, antifracture efficacy increased significantly with a higher dose and higher achieved blood 25-hydroxyvitamin D levels for both end points. Consistently, pooling trials with a higher received dose of more than 400 IU/d resolved heterogeneity. For the higher dose, the pooled RR was 0.80 (95% CI, 0.72-0.89; n = 33 265 subjects from 9 trials) for nonvertebral fractures and 0.82 (95% CI, 0.69-0.97; n = 31 872 subjects from 5 trials) for hip fractures. The higher dose reduced nonvertebral fractures in community-dwelling individuals (-29%) and institutionalized older individuals (-15%), and its effect was independent of additional calcium supplementation. In conclusion, nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older.

(2009) Palmer et al. completed a systemic review assessing the effects of vitamin D compounds on clinical, biochemical, and bone outcomes in people with CKD and receiving dialysis. Results included sixty studies (2773 patients) were included. No formulation, route, or schedule of administration was associated with altered risks of

death, bone pain, or parathyroidectomy. Marked heterogeneity in reporting of outcomes resulted in few data available for formal meta-analysis. Compared with placebo, vitamin D compounds lowered serum PTH at the expense of increasing serum phosphorus. Trends toward increased hypercalcaemia and serum calcium did not reach statistical significance but may be clinically relevant. Newer vitamin D compounds (paricalcitol, maxacalcitol, doxercalciferol) lowered PTH compared with placebo, with increased risks of hypercalcaemia, although inadequate data were available for serum phosphorus. Intravenous vitamin D may lower PTH compared with oral treatment and be associated with lower serum phosphorus and calcium levels, although limitations in the available studies precludes a conclusive statement of treatment efficacy. Few studies were available for intermittent versus daily and intraperitoneal versus oral administration or directly comparative studies of newer versus established vitamin D compounds.

The author's confirmed vitamin D compounds suppress PTH in people with CKD and requiring dialysis although treatment is associated with clinical elevations in serum phosphorus and calcium. All studies were inadequately powered to assess the effect of vitamin D on clinical outcomes and until such studies are conducted the relative importance of changes in serum PTH, phosphorus and calcium resulting from vitamin D therapy remain unknown. Observational data showing vitamin D compounds may be associated with improved survival in CKD need to be confirmed or refuted in specifically designed RCTs.

(2007) Cranney et al. completed a review in the effectiveness and safety of vitamin D in relation to bone health and found the following in the One hundred and six RCTs were included in the review questions addressed here.

Effect of fortified foods on circulating 25(OH)D concentrations (13 RCTs): there was good evidence of a positive effect of supplementation, based on 11 trials (of which six were high quality), although the magnitude of the effect varied (range 15-40nmol/L).

Effect of UV light on circulating 25(OH)D concentrations (eight RCTs): there was fair evidence that sun exposure or artificial UV-B radiation increased serum 25(OH)D in participants with low or normal baseline levels (based on eight studies, of which two were high quality).

Effect of vitamin D supplementation on circulating 25(OH)D concentrations (74 RCTs): a meta-analysis showed a dose response effect of vitamin D3 supplementation on serum 25(OH)D when doses of less than 400 IU (two RCTs) were compared with doses over 400 IU (14 RCTs) (11.36, 95% CI: 8.6, 14). There was a high degree of clinical and statistical heterogeneity across all trials.

Effect of vitamin D supplementation on bone density, falls and fractures in elderly men and postmenopausal women (17 RCTs): small increases in bone mineral density were associated with supplementation, although synthesis was limited by heterogeneity. Fifteen RCTs showed inconsistent evidence for fracture reduction associated with

supplementation, but fair evidence for a subgroup of older individuals in institutional settings (OR 0.69, 95% CI: 0.53, 0.90, two RCTs). The evidence of 14 RCTs was inconsistent for the effect on falls with a small overall benefit (OR 0.89, 95% CI: 0.80, 0.99, 12 RCTs). However, subgroup analysis suggested that there were benefits in postmenopausal women (OR 0.80, 95% CI: 0.66, 0.98, six RCTs) and when vitamin D3 was combined with calcium supplementation (OR0.84, 95% CI: 0.76, 0.93, eight RCTs).

Toxicity resulting from vitamin D intake above current reference level (22 RCTs): there was little evidence that vitamin D intake above the current reference intake was harmful.

In conclusion most trials the effects of vitamin D and calcium supplementation could not be separated. Vitamin D3 at a dose of at least 700 IU/day with calcium supplementation had a small beneficial effect on bone mineral density compared to placebo and reduced the risk of fractures and falls, although the benefit may be restricted to specific subgroups. There was no increased risk of adverse events associated with vitamin D intakes above current reference intakes, although further research was needed to confirm this. Recommendations for further research included validation of laboratory assays of 25(OH)D measurement; consensus on meaningful outcome measures for vitamin D adequacy in groups of interest; the dose response relationship for vitamin D in these groups; high quality RCTs to determine bone health and safety outcomes in infants, children and adolescents; clear reporting of all outcome data, including safety data; high quality studies in minority ethnic populations in North America; research on modifiers of the effect of 25(OH)D status; development of sensitive and specific indices of the risk of vitamin D toxicity; and a systematic review of the safety and efficacy of sun exposure that provides adequate vitamin D photosynthesis.

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.

Transplants
(2019) Kenny et al. reported on the impact of a replacement algorithm for vitamin D deficiency in adult hematopoietic stem cell transplant patients and noted Adults undergoing hematopoietic stem cell transplant (HSCT) are at risk for vitamin D deficiency. After HSCT, exposure to sunlight is restricted, and patients may experience poor nutrition and malabsorption from HSCT-related side effects. Vitamin D affects bone

health and immunologic processes. The aim of this project is to establish a process for monitoring and treating vitamin D deficiency and to evaluate if therapeutic vitamin D levels are attainable posttransplant using an HSCT vitamin D replacement algorithm. A multidisciplinary group led by advanced practice providers established a workflow for monitoring and supplementing vitamin D and created an HSCT vitamin D replacement guideline. The medical records of 144 adult HSCT patients were reviewed, and the records of another 72 patients were reviewed a year later. Historical baseline data before the intervention found that 81% of patients were vitamin D deficient and 30% received supplementation. Postintervention and at 1-year follow-up, 76% and 65% of patients were vitamin D deficient before transplant and 97.1% and 100%, respectively, received supplementation for vitamin D deficiency. Post-HSCT compliance with monitoring demonstrated that approximately 91% of patients had a vitamin D level checked within 6 months of transplant. After implementation of the algorithm, there was a statistically significant difference ($p < .001$) between deficient vitamin D levels pretransplant (72.9%) and posttransplant (26.4%). Results demonstrate sustained compliance over a 2-year period with monitoring and supplementation of vitamin D pre- and peritransplant. Aggressive vitamin D repletion posttransplant decreased the incidence of vitamin D deficiency in HSCT patients. Further study is needed to investigate the long-term effects of vitamin D repletion on posttransplant complications.

In conclusion, the current recommendations for daily vitamin D supplementation in the United States may not be adequate to meet the needs of the HSCT population. The implications for practice include recommendations for pre- and posttransplant screening with 25(OH)D levels and aggressive supplementation based on specific vitamin D replacement guidelines for adult HSCT patients. The appropriate level of vitamin D supplementation given various clinical situations remains unknown and can be guided by the measurement of 25(OH)D levels.

This QI project demonstrates that pre- and posttransplant monitoring and treatment of vitamin D deficiency is relatively easy to implement. Vitamin D deficiency remains a long-term issue for this population that is counseled to reduce the risk of secondary skin malignancy by limiting unprotected sun exposure. In the HSCT setting, vitamin D deficiency is a potentially modifiable risk factor that is correctable and may positively impact outcomes. More aggressive replacement of vitamin D with higher dosing than recommended for the general population may be indicated in this population given the population's reduced sun exposure, medications that interfere with the metabolism of vitamin D, malabsorption of vitamin D due to gastrointestinal GVHD, and impaired renal and hepatic function posttransplant. Maintaining vitamin D sufficiency pre- and posttransplant may decrease HSCT-associated morbidity and improve long-term outcomes and quality of life for survivors. Advanced practice providers in oncology have a unique opportunity to impact practice and patient outcomes in this setting. Further investigation is warranted to determine the impact of long-term effects of early repletion of vitamin D on posttransplant complications of bone loss and GVHD**.**

(2014) Stein et al. reported vitamin D insufficiency and deficiency are extremely common among patients with end-stage organ failure; insufficient vitamin D levels have been documented in organ transplant candidates with congestive heart failure, end-stage pulmonary disease, liver failure, and chronic kidney disease. Several factors place patients with end-stage organ failure at particular risk for vitamin D deficiency. These include limited sunlight exposure and low dietary intake of vitamin D-containing foods. In addition, hepatic dysfunction, which can result from intrinsic liver disease or from hepatic congestion in heart failure patients, may contribute to vitamin D deficiency. For the purposes of this review, we will define insufficiency as 25-OHD <30 ng/mL, deficiency as 25-OHD <20 ng/mL, and severe deficiency as 25-OHD <10 ng/mL. As categorization of vitamin D status differs in the various published reports, it is not always possible to ascertain the percentage of subjects in each of these categories. We have tried to present the data available in a uniform manner.

Risk factors for vitamin D deficiency in organ transplant patients

- African American race
- Limited sunlight exposure, northern latitude, and winter months
- Low dietary intake of vitamin D
- Low fat mass
- Low serum albumin
- Hepatic dysfunction
- Obstructive pulmonary disease
- Renal insufficiency
- Diabetes
- Malabsorption
- Poor general health
- Female sex
- Glucocorticoid use—increases catabolism of 25-OHD
- Organ transplanted—liver transplant recipients may be at increased risk
- Recent transplantation
- Proteinuria
- Use of ACE inhibitors or aldosterone receptor blockers

In conclusion, the authors noted Given the high prevalence of 25-OHD deficiency in patients with organ failure prior to and following transplantation, patients should be assessed before transplantation and receive treatment for vitamin D insufficiency and deficiency, if present. In addition, long-term transplant recipients should be monitored and treated for vitamin D deficiency as part of broader management of bone disease. We recommend treatment with parent vitamin D for patients with insufficient 25-OHD (<30 ng/mL) regardless of the type of underlying disease. In patients with stage 3 and 4 CKD (estimated GFR 15–60 mL/min), therapy with an active oral vitamin D analogue (calcitriol, alfacalcidol, or doxercalciferol) should be initiated when serum levels of 25-OHD are sufficient (>30 ng/mL) and plasma levels of intact PTH are above the target range for the CKD stage, as outlined in the K/DOQI guidelines [102]. Patients treated

with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL should receive an active vitamin D sterol to reduce the serum levels of PTH to a target range of 150–300 pg/mL. For patients with other types of end-organ failure, including liver disease, we suggest replacement with parent vitamin D alone. If monitoring during treatment reveals that 25-OHD is not increasing by the expected amount and is suggestive of a significant impairment in 25-hydroxylase activity, we would consider adding an active vitamin D analogue.

Pharmacologic doses of vitamin D and its analogues have clear utility after renal transplant but should be utilized as adjunctive rather than primary therapy for osteoporosis in patients after other types of solid organ transplantation because of their narrow therapeutic window and inconsistent efficacy.

Epidemiologic studies and one randomized controlled clinical trial suggest that adequacy of vitamin D is associated with lower incidence of malignancy as well as cardiovascular disease and mortality in healthy populations; these data may be applicable to transplant patients as well. At present, physicians who care for transplant patients should screen all patients for 25-OHD deficiency. Treatment of this condition and subsequent improvement in vitamin D status may reduce skeletal and extraskeletal morbidity in transplant patients. There is a need for longitudinal studies to evaluate the efficacy of different repletion regimens to restore 25-OHD levels after transplantation and to examine whether restoring 25-OHD at the time of transplant reduces the development of infectious complications and immunosuppressant requirements.

Overall Mortality

(2015) LeBlanc et al. submitted recommendations for screening for vitamin D deficiency with the following comment/response:

The U.S. Preventive Services Task Force has concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. As LeBlanc and colleagues' review (1) shows, this current evidence comprises studies whereby supplementation (variable doses of vitamin D2 or D3 with or without calcium) has been monitored mainly by measuring total concentrations of 25-(OH)D. Instead, future studies should focus on assessing concentrations of bioavailable vitamin D. Concentrations of total 25-(OH) D and 1,25-dihydroxyvitamin D measured routinely in daily practice are known to differ from those of bioavailable vitamin D. Free and bioavailable vitamin D concentrations depend on the vitamin D–binding protein and ethnicity (2). In addition, we need evidence of techniques to increase concentrations of bioavailable vitamin D, such as obtaining more outdoor physical activity, which might increase biosynthesis and bioavailable concentrations of vitamin D3 and circumvent hypervitaminosis D (3). Harmful effects of hypervitaminosis D might be due solely to excess biosynthesized sequestrated vitamin D as a result of inappropriate oral supplementations and of not being converted to active bioavailable vitamin D. Excess vitamin D is arteriotoxic and causes elastocalcinosis, which induces destruction of elastic fibers, which leads to arterial stiffness and causes arterial

calcification through upregulation of 1,25-dihydroxyvitamin D3 receptors and increased calcium uptake in smooth-muscle cells of the arteries.

(2014) Chowdhury et al. completed a systematic review and meta-analysis of observational cohort and randomized intervention studies on vitamin D and risk of cause specific death and the author's concluded evidence from observational studies indicates inverse associations of circulating 25-hydroxyvitamin D with risks of death due to cardiovascular disease, cancer, and other causes. Supplementation with vitamin D3 significantly reduces overall mortality among older adults; however, before any widespread supplementation, further investigations will be required to establish the optimal dose and duration and whether vitamin D3 and D2 have different effects on mortality risk.

(2014) Newberry et al completed an updated systematic review of the health outcomes for vitamin D and calcium. Their conclusions noted in solid agreement with the findings of the original report, the majority of the findings concerning vitamin D, alone or in combination with calcium, on the health outcomes of interest were inconsistent. Associations observed in prospective cohort and nested case-control studies were inconsistent, or when consistent, were rarely supported by the results of randomized controlled trials. Clear dose-response relationships between intakes of vitamin D and health outcomes were rarely observed. Although a large number of new studies (and longer follow-ups to older studies) were identified, particularly for cardiovascular outcomes, all-cause mortality, several types of cancer, and intermediate outcomes for bone health, no firm conclusions can be drawn. Studies identified for the current report suggest a possible U-shaped association between serum 25(OH)D concentrations and both all-cause mortality and hypertension and also suggest that the level of supplemental vitamin D and calcium administered in the Women's Health Initiative Calcium-Vitamin D Trial are not associated with an increased risk for cardiovascular disease or cancer among postmenopausal women who are not taking additional supplemental vitamin D and calcium. Studies suggest the method used to assay 25(OH)D may influence the outcomes of dose-response assessments. Beyond these observations, it is difficult to make any substantive statements on the basis of the available evidence concerning the association of either serum 25(OH)D concentration, vitamin D supplementation, calcium intake, or the combination of both nutrients, with the various health outcomes because most of the findings were inconsistent. Limitations were noted as follows: Studies on vitamin D and calcium were not specifically targeted at life stages (except for pregnant and postmenopausal women) specified for the determination of DRI and were often underpowered for their intended outcomes. Studies vary widely in methodological quality and in the assays used to measure vitamin D status.

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 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. Randomized controlled trials 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. Although there is inadequate data in the published peer reviewed literature vitamin D testing will be considered as outlined under the policy criteria section of this document below to determine medical necessity or investigational and whether the vitamin D testing is/are eligible for reimbursement under the member's medical health insurance benefits.

The central question today is not whether the body needs vitamin D, it absolutely does, but whether the average person should be taking a supplement or be tested for deficiency. There is widespread public belief that it's a good idea. The scientific evidence on the value of supplementation and testing in the asymptomatic, as well as numerous diseases and conditions, is minimal overall. 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, only a clinical diagnosis of an abnormality in bone health (e.g., rickets, osteomalacia, osteoporosis) should lead to a decision to test vitamin D levels and thus are medically necessary. Although there is inadequate data in the published peer reviewed literature vitamin D testing will be considered as outlined under the policy criteria section of this document below to determine medical necessity

or investigational and whether the vitamin D testing is/are eligible for reimbursement under the member's medical health insurance benefits.

Practice Guidelines and Position Statements

American Academy of Family Physicians (2018)
(2018) The American Academy of Family Physicians supports the U.S. Preventative Task Force recommendation on vitamin D screening and concluded 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 (*Accessed January 2022*)

American Academy of Neurology (AAN)
(2019) The Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2:

- Vitamin D is listed under Severe Symptoms, Endocrine and metabolic, under Recommendations to test for. (*Accessed January 2022*)

(2019) The Consensus-based Care Recommendations for Children with Myotonic Dystrophy Type 1:

- The recommendation does not address Vitamin D testing. (*Accessed January 2022*)

American College of Obstetrics and Gynecology (ACOG)
(Reaffirmed 2021) The following recommendation was made about Vitamin D: Screening and Supplementation During Pregnancy:

- At this time there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency. For pregnant women thought to be at increased risk of vitamin D deficiency, maternal 25-OH-D levels can be considered and should be interpreted in the context of the individual clinical circumstance. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000-2,000 international units per day of vitamin D is safe. Higher dose regimens used for treatment of vitamin D deficiency have not been studied during pregnancy. Recommendations concerning routine vitamin D supplementation during pregnancy beyond that contained in a prenatal vitamin should await the completion of ongoing randomized clinical trials. (*Accessed January 2022*)

The Endocrine Society
(2011) The Endocrine Society has a clinical practice guideline for the Evaluation, Treatment, and Prevention of Vitamin D Deficiency as it recommends the following:

- We recommend vitamin D deficiency in individuals at risk for deficiency. We do not recommend population screening for vitamin D deficiency in individuals who are not at risk.

- We recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency.
- We recommend against using the serum 1,25-dihydroxyvitamin D [1,25(OH)2D] assay for this purpose and are in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism.
- There is no evidence demonstrating benefits of screening for vitamin D deficiency at a population level. Such evidence would require demonstration of the feasibility and cost-effectiveness of such a screening strategy, as well as benefits in terms of important health outcomes. In the absence of this evidence, it is premature to recommend screening at large at this time.

(*Accessed January 2022*)

Joint Guidance

- **American Association of Clinical Endocrinologists and American College of Endocrinology**
    - (2020) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis which includes the following recommendation:
        - Measure serum 25-hydroxyvitamin D (25[OH]D) in patients who are at risk for vitamin D insufficiency, particularly those with osteoporosis (Grade B) (Grade A, Strong; Grade B, Intermediate; Grade C, Weak; Grade D, No conclusive evidence/expert opinion).
- **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**
    - (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) (*Accessed January 2022*)
- **American Society for Bone and Mineral Research (ASBMR), Endocrine Society, American Association of Clinical Endocrinologists (AACE), European Calcified Tissue Society (ECTS), the National Osteoporosis Foundation (NOF), and the International Osteoporosis Foundation (IOF)** (2020) Released joint guidance on vitamin D in the era of COVID-19 with the following information:
    - To date, no clinical trials studying a potential effect of vitamin D supplementation on preventing COVID-19 disease have been completed.

Although recent epidemiologic (observational) studies have suggested associations between low 25(OH)-vitamin D concentrations and higher rates of COVID-19 infection, these are likely related to ethnicity, age, and general health rather than a causal relationship.

- The current data do not provide any evidence that vitamin D supplementation will help prevent or treat COVID-19 infection; however, our guidance does not preclude further study of the potential effects of vitamin D on COVID-19. Research to date suggests that vitamin D may play a role in enhancing the immune response and given prior work demonstrating a role for the activated form of vitamin D [1,25(OH)2D] in immune responses, further research into vitamin D supplementation in COVID-19 disease is warranted.

(*Accessed January 2022)*

American Heart Association (AHA)

(2019) Rychik et al completed a Scientific Statement for the American Heart Association (AHA) on the evaluation and management of the Child and Adult with Fontan Circulation and it noted:

- It is not known whether there is something unique about the Fontan circulation that affects the absorption of vitamin D, although one may speculate that alterations in gut circulation may affect essential element and vitamin absorption. Differences in renal perfusion and microcirculation that are present in the Fontan circulation may also affect vitamin D production in the kidney. Understanding the impact of the Fontan operation on vitamin D levels may have implications for simple therapies such as the timing of supplementation to help promote long-term muscle and bone development and to improve strength and physical functioning. (*Accessed January 2022*)

Medical Services Commission of British Columbia

(2019) Vitamin D Testing Key Recommendations Guideline:

- Routine vitamin D testing or screening for vitamin D deficiency is not recommended.
- Measurement of vitamin D levels is not generally required prior to or after initiating vitamin D supplementation.
- Vitamin D testing is indicated in patients who are at high risk for vitamin D deficiency such as those with malabsorption syndromes, renal failure, unexplained bone pain, unusual fractures, or other evidence of metabolic bone disorders.
    - **25-hydroxyvitamin D (25(OH)D)**
        - 25(OH)D is the preferred test for assessing vitamin D status. Measuring 25(OH)D is the best way to determine the adequacy of vitamin D production by skin (D_3) and oral intake (D_2 or D_3).
        - The test may be considered in the following clinical scenarios:
            - significant liver disease
            - significant renal disease

- osteomalacia
- osteopenia or osteoporosis
- history of non-traumatic ("fragility") fractures
- malabsorption syndromes
- hypo- or hypercalcemia/hyperphosphatemia
- hypo- or hyperparathyroidism
- medications affecting vitamin D metabolism (e.g., phenobarbital, carbamazepine, phenytoin and valproate)
- unexplained elevation of alkaline phosphatase
- high dose vitamin D combined with evidence of vitamin D toxicity

- There are a variety of testing methods measuring total serum 25(OH)D and to minimize assay variation, international reference standards have been developed. There is substantial assay variation which contributes to the lack of consensus on the laboratory values defining vitamin D deficiency.

25(OH)D Levels and Health	
<30 nmol/L	Risk of vitamin D deficiency (rickets or osteomalacia)
30-50 nmol/L	Clinical features of inadequacy in some individuals
≥50 nmol/L	Adequate for bone health in practically all individuals
> 125 nmol/L	Concern for vitamin D toxicity

- **1,25-dihydroxyvitamin D (1,25(OH)2D)**
  - 1,25(OH)2D should not be used for the investigation of vitamin D nutritional status. Measurement of 1,25 dihydroxyvitamin D levels is recommended only in isolated circumstances such as the investigation of parathyroid hormone independent hypercalcemia.

(*Accessed January 2022*)

National Osteoporosis Society (NOS)
(2014) The National Osteoporosis Society issued a patient management clinical guideline for vitamin D and bone health.

- Recommends serum 25-hydroxyvitamin D levels should be measured to estimate vitamin D status in certain clinical scenarios such as: bone diseases that may improve with vitamin D treatment; bone diseases, prior to specific treatment where correcting vitamin D deficiency is appropriate; and musculoskeletal symptoms that could be due to vitamin D deficiency. (*Accessed January 2022)*

United States Preventive Services Task Force (USPSTF)
(2021) Vitamin D Deficiency in Adults: Screening Final Recommendation Statement:

        - For community-dwelling, non-pregnant, asymptomatic adults age 18 years and older:
- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for Vitamin D deficiency in asymptomatic adults. Grade I – Insufficient.
- This recommendation applies to community-dwelling, nonpregnant adults aged 18 years or older who are seen in primary care settings and are not known to have signs or symptoms of Vitamin D deficiency or conditions for which Vitamin D treatment is recommended.
    - It does not apply to persons who are hospitalized or living in institutions such as nursing homes.
- This recommendation focuses on screening (that is, testing for Vitamin D deficiency in asymptomatic adults and treating those who are found to have a deficiency), which is different from other USPSTF recommendation statements on supplementation (that is, recommending preventive medication for patients at increased risk for a specific negative health outcome, such as falls, regardless of whether they have a deficiency).

The USPSTF recognizes that there is no consensus on how to define Vitamin D deficiency and does not endorse the use of a specific threshold to identify it. The evidence reviewed by the USPSTF used varying cut points. For the purposes of this recommendation statement, the term "Vitamin D deficiency" is used to reflect evidence from study populations generally representing total serum 25(OH)D levels of 75 nmol/L (30 ng/mL) or less or subpopulations of studies with levels less than 50 nmol/L (<20ng/mL).

- Harms: Screening may misclassify persons with a Vitamin D deficiency because of the uncertainty about the cut point for defining deficiency and the variability of available testing assays. Misclassification may result in overdiagnosis (which may lead to nondeficient persons receiving unnecessary treatment) or underdiagnosis (which may lead to deficient persons not receiving treatment).

- Risk factors: Although there is not enough evidence to support screening for Vitamin D deficiency, some evidence suggests factors that may increase risk for Vitamin D deficiency. Persons with low Vitamin D intake, decreased Vitamin D absorption, and little or no sun exposure (for example, due to the winter season, high latitude, or physical sun avoidance) may be at increased risk for Vitamin D deficiency. Obesity and darker skin pigmentation may also be associated with low levels of total serum 25-(OH)D, but whether these factors reflect Vitamin D deficiency or increase the risk for adverse clinical outcomes is unclear. Some evidence suggests that older age and female sex may also be associated with increased risk for Vitamin D deficiency; however, these findings are inconsistent.

(*Accessed January 2022*)

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.

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 risk in defects in vitamin D metabolism, when monitoring plays a role in halting disease progression:

- Chronic kidney disease stage III or greater
- Disorders of calcium metabolism
- Follicular lymphoma
- Granuloma forming Disorders (e.g., Sarcoidosis, Tuberculosis, histoplasmosis, coccidiomycosis, berylliosis)
- Glycogen storage disease
- Graft versus host disease
- HIV
- Hypercalcemia
- Hypocalcemia
- Hyperparathyroidism
- Hypoparathyroidism
- Hypervitaminosis of vitamin D
- Individuals receiving hyperalimentation
- Intestinal malabsorption (e.g., Cystic fibrosis, Crohn's, Celiac disease, Bariatric surgery)
- Liver cirrhosis

- Medication known to lower vitamin D levels (i.e., chronic use of anticonvulsants, glucocorticoids)
- Myalgia
- Myopathy related to endocrine disease
- Myositis
- Neoplastic hematologic disorders
- Obesity
- Osteogenesis imperfecta
- Osteoporosis/Osterpetrosis
- Osteomalacia
- Osteopenia
- Pancreatic steatorrhea
- Primary or miliary tuberculosis
- Psoriasis
- Regional enteritis
- Renal, ureteral or urinary calculus
- Rickets
- Sarcoidosis
- Systemic lupus erythematosus

Medically Necessary: 1,25-dihydroxyvitamin D (82652)
1,25-dihydroxyvitamin D may be considered **medically necessary** in the evaluation and monitoring of **one of the following** conditions associated with defects in vitamin D metabolism:

- Cat-scratch disease
- Disorders of calcium metabolism
- Granulomatous diseases
- Familial hypophosphatemia
- Follicular lymphoma
- 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
- Neonatal hypocalcemia
- Osteogenisis imperfecta
- Osteomalacia
- Osteopetrosis
- Primary or miliary tuberculosis
- Pseudohypoparathyroidism
- Renal failure
- Renal, ureteral, or urinary calculus

- Rickets
- Sarcoidosis
- Solid organ transplants
- Systemic connective tissue disorder

Not Medically Necessary: **25-hydroxyvitamin D and 1,25-dihydroxyvitamin D**
The use of vitamin D deficiency with 1,25 dihydroxyvitamin D and 25-hydroxyvitamin D serum testing is considered **not medically necessary** when the above criteria is not met and for all other indication to include but not limited to the following:

- General population screening
- Routine testing

Repeat Testing:
Testing of Vitamin D levels may be considered **medically necessary** to monitor therapy when criteria have been met above *and* Vitamin D deficiency is diagnosed.

Policy Guidelines
Note:

- ***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.

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.
- 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.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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*)

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POLICY HISTORY

Date	Reason	Action
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
Des Moines, IA 50306-9232

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