Commercial Medical
Coverage Policy Highlights

Quest Diagnostics™

aetna®

Vitamin D Testing

CPT(s): 82306 / 82652

The purpose of this guide is to highlight the **Aetna** coverage policy for **Vitamin D** testing, including a brief overview, instructions for use, medical necessity, general background information, and top ICD-10 codes currently utilized by ordering physicians which are defined by the policy as medically supportive. Individual plans may vary. For the most accurate coverage policy for each patient, please contact the patient's health plan. See the full **Vitamin D Aetna** coverage policy here.

Medical coverage policy	
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Full vitamin D Aetna coverage policy ►

Policy

Aetna considers measurements of serum 25-hydroxyvitamin D experimental and investigational for routine preventive screening.

Background

Vitamin D (calciferol) refers to a group of lipid-soluble prohormones; the 2 major forms of which are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The term vitamin D also refers to metabolites and other analogs of these substances. Calcitriol (1,25-dihydroxycholecalciferol [1,25-OH(2)D]) is the biologically active form of vitamin D found in the body. Vitamin D that is synthesized in the skin via photo-isomerization or ingested in the diet via intestinal absorption is biologically inert and requires 2 successive hydroxylations. First, in the liver on carbon 25 to form 25-hydroxyvitamin D (25-OHD). Second, in the kidney on carbon 1 to form 1,25-OH(2)D. Vitamin D and its metabolites have a significant clinical role because of their interrelationship with calcium (Ca) homeostasis and bone metabolism. Serum 25-OHD is the best index for vitamin D status; while serum 1,25-OH(2)D provides no information about vitamin D status and is often normal or even increased as the result of secondary hyper-parathyroidism associated with vitamin D deficiency. The lower limit of normal 25-OHD levels is dependent on the geographical location and sunlight exposure of the reference population (range of 8 to 15 ng/ml). Moreover, there is no consensus on the optimal 25-OHD concentration for skeletal or extra-skeletal health. Most experts, however, agree that 25-OHD of less than 20 ng/ml is considered to be vitamin D deficiency, whereas a 25-OHD concentration of 21 to 29 ng/ml is considered to be insufficient. The serum parathyroid hormone (PTH) level typically is inversely related to 25-OHD levels, and is a useful secondary laboratory indicator of vitamin D insufficiency. Recent studies suggested that vitamin D is important not only for promoting bone health in children and adults, but also for other health benefits, including reducing the risk of chronic diseases. Sub-clinical vitamin D deficiency may be associated with an increased risk of falls and fractures in the elderly, decreased immune function, bone pain, and possibly cancer and cardiovascular health. It has been suggested that for both children and adults, 25-OHD should be maintained at a level of greater than 30 ng/ml (Holick, 2009; Pazirandeh and Burns, 2018). However, the clinical value of routine vitamin D testing is unclear.

Allan and colleagues (2016) stated that over the last 10 years, a large body of observational evidence has suggested an association between lower vitamin D status (25-hydroxyvitamin D) and multiple acute and chronic disorders, including cancer, multiple sclerosis, depression and respiratory tract infections. This evidence has fostered the hypothesis that increasing vitamin D intake may treat and prevent such disorders. These investigators carried out a critical analysis of the highest-level evidence for 10 common beliefs regarding vitamin D for the prevention of falls, fractures and respiratory tract infections, the reduction of cancer incidence/mortality and overall mortality, and the prevention or treatment of depression/mental well-being, rheumatoid arthritis (RA) and multiple sclerosis (MS), as well as maximum dosing and regular testing. These investigators searched the Cochrane Database of Systematic Reviews and PubMed (up to August 2014) for RCTs and systematic reviews/meta-analyses based on those studies. All searches were performed, all evidence reviewed and each section written by at least 2 authors. The evidence showed that vitamin D supplementation provided some benefit in fracture prevention (likely approximately 10 to 15 % relative reduction), particularly at a dose greater than or equal to 800 IU and with calcium; a likely benefit in the rate of falls, though it is less clear whether the number of fallers changes; and a possible small (approximately 5 %) relative reduction in mortality. Evidence did not support the use of vitamin D supplementation for the prevention of cancer, respiratory infections or RA. Similarly, evidence did not support vitamin D supplementation for the treatment of MS and RA or for improving depression/mental well-being. Regular testing of 25-hydroxyvitamin D is generally not required, and mega-doses (greater than or equal to 300,000 IU) appeared to increase harms. Much of the evidence as at high risk of bias, with multiple flaws, including analyses of secondary end-points, small and under-powered studies, inconsistent results and numerous other issues. The authors concluded that enthusiasm for a vitamin D panacea should be tempered.

Chronic Kidney Disease (CKD)

Since vitamin D is biologically inactive and requires sequential hydroxylations in the liver and kidney to form 1,25-OH(2)D, this explains why patients with renal failure are often resistant to vitamin D and suffer from secondary hyper-parathyroidism and renal osteodystrophy. In patients with CKD, phosphate excretion is impaired and vitamin D production is decreased, resulting in hypocalcemia. In response, the level of PTH rises to increase reabsorption of Ca from the kidney and transfer of Ca from the bone. This may result in hypercalcemia, bone fragility, fractures and pain, which increase morbidity and mortality. Vitamin D status is best determined by the measurement of circulating levels of 25-OHD. Vigilance for maintaining a 25-OHD level of at least 20 ng/ml and preferably 30 to 50 ng/ml has important benefits for children and adults suffering from CKD (NKF, 2003; Holick, 2005).

Beckman and Downs (2006) stated that maintenance of adequate vitamin D status is important in patients with CKD because vitamin D deficiency is a major complication in these patients and facilitates the development of hyper-parathyroidism. Vitamin D deficiency develops as early as stage 3 of CKD due to loss of a threshold mass of functioning proximal tubules, which contain 25-OHD-1-alpha-hydroxylase (an enzyme that catalyzes the synthesis of 1,25OH(2)D), and some patients with stage 3 CKD (glomerular filtration rate [GFR] of 30 to 59 ml/min) can begin to develop secondary hyper-parathyroidism with low serum Ca, vitamin D deficiency and accumulation of serum phosphate as the core contributing factors. In patients with CKD, 25-OHD levels should be maintained at greater than 30 ng/ml, and if PTH rises despite adequate 25-OHD stores, then treatment with an active vitamin D sterol may be indicated.

Chandra et al (2008) examined the effectiveness of vitamin D3 in raising serum 25-OHD levels and reducing PTH levels in patients with CKD. Subjects with CKD stage 3 and 4 (estimated GFR of 15 to 59 ml/min/1.73 m2), vitamin D insufficiency (serum 25-OHD less than 30 ng/ml), and serum intact PTH (iPTH) levels greater than 70 pg/ml were randomly assigned to receive either 50,000 International Unit (IU) of vitamin D3 or placebo once-weekly for 12 weeks. Primary outcomes (25-OHD and PTH levels) were measured at baseline, week 6, and week 12. Secondary outcomes (1,25-OH(2)D and bone turnover markers) were measured at baseline and week 12. Because of skewed data distribution, statistical analyses were performed on a logarithmic scale. The difference between the group means was exponentiated to provide the geometric mean ratio. A linear mixed model using an unstructured variance-covariance matrix was used to examine change in the primary and secondary outcomes over time. Geometric mean serum 25-OHD concentrations of the study groups were similar at baseline ($p = 0.77$). At week 6, a significant difference between the treatment and placebo groups was detected ($p = 0.001$); this difference was maintained at week 12 ($p = 0.002$). Among vitamin D3-treated participants, serum 25-OHD concentration increased on average from 17.3 ng/ml (95 % confidence interval [CI]: 11.8 to 25.2) at baseline to 49.4 ng/ml (95 % CI: 33.9 to 72.0) at week 12. As-treated analysis indicated a trend toward lower PTH levels among vitamin D3-treated participants ($p = 0.07$). The authors concluded that weekly vitamin D3 supplementation appeared to be an effective treatment to correct vitamin D status in patients with CKD.

Kooienga and colleagues (2009) performed post-hoc analysis of the randomized clinical trial "Vitamin D, Calcium, Lyon Study II" to assess the effects of combined Ca and vitamin D3 supplementation on serum iPTH in patients with moderate CKD according to baseline estimated GFR (eGFR). Patients received placebo or Ca (1,200 mg) and vitamin D3 (800 IU) in fixed or separate combination. Major outcome measure was proportion of participants with a mean decrease in iPTH level of 30 % or greater. Estimated GFR was calculated using the 4-variable "Modification of Diet in Renal Disease Study" equation and categorized as 60 or greater, 45 to 59, and less than 45 ml/min/1.73 m(2). A total of 610 participants had an eGFR at baseline: 288 (47.2 %), 222 (36.4 %), and 100 (16.4 %) were in each decreasing eGFR category. Across decreasing eGFR groups, 88 %, 86 %, and 89 % had 25-OHD levels less than 15 ng/ml at baseline. On treatment, similar improvements in the proportion of participants achieving 25-OHD levels greater than 30 ng/ml at 6 months were seen in all kidney function groups (43 %, 49 %, and 41 %, respectively). Active regimens versus placebo increased mean 25-OHD levels from baseline in all eGFR groups at all times ($p < 0.001$ for all). The proportion with a 30 % or greater decrease in iPTH level at 6 months was 50 % in all eGFR groups on treatment versus 6 % to 9 % for placebo ($p < 0.001$ for all). The effects of the intervention on iPTH levels did not differ according to baseline eGFR (interaction $p > 0.1$ for all times). The authors concluded that vitamin D3 was effective in increasing 25-OHD and decreasing iPTH levels in patients with moderate CKD.

The National Kidney Foundation (NKF)'s clinical practice guideline on "Prevention and treatment of vitamin D deficiency in CKD patients" (2004) stated that if plasma iPTH is above the target range for the stage of CKD, serum 25-OHD should be measured at first encounter. If it is normal, measurement of serum 25-OHD should be repeated annually; if the serum level of 25-OHD is less than 30 ng/ml (75 nmol/L), supplementation with vitamin D2 should be initiated, and once patients are replete with vitamin D, continued supplementation with a vitamin-D-containing multi-vitamin preparation should be used with annual reassessment of serum levels of 25-OHD, and the continued assessment of corrected total Ca and phosphorus every 3 months. Lorenzo Sellares and Torregrosa (2008) stated that for patients with CKD (stage 3, 4, and 5), it is important to maintain adequate levels of 25-OHD (greater than 30 ng/ml), since they will be the substrate for the production of 1,25-OH(2)D, and their deficiency aggravates hyperthyroidism. These investigators noted that determining 25-OHD levels every 6 to 12 months is a recommended guideline.

Hypervitaminosis D/Hypercalcemia

An excess of vitamin D can result in intoxication, with manifestations that may entail anorexia, confusion, hypercalcemia, polydipsia, polyuria, vomiting, muscle weakness, as well as bone demineralization with pain. The intake at which the dose of vitamin D becomes toxic is unclear. The Institute of Medicine has defined the "tolerable upper intake level" (UL) for vitamin D as 50 micrograms (2000 IU) daily for healthy adults and children aged 1 to 18 years. This is also the UL for pregnant and lactating women. However, newer data indicate that higher doses may be safe, at least for a period of several months. Vitamin D intoxication may happen in dieters who consume "megadoses" of supplements or in patients on vitamin D replacement therapy for malabsorption, renal osteodystrophy, osteoporosis, or psoriasis. It has been reported in individuals consuming more that 60,000 IU/day (Pazirandeh and Burns, 2018).

Certain disorders/diseases can increase the risk of hypercalcemia in response to vitamin D, including Hodgkin's lymphoma, granulomatous disease sarcoidosis, primary hyperparathyroidism, and tuberculosis. Measurement of serum levels of 25-OHD will aid to diagnose hypervitaminosis D/hypercalcemia (Vieth, 1999; Carroll and Schade, 2003).

Osteoporosis

In a review on "the prevention and treatment of senile osteoporosis and hip fractures", Dugue and colleagues (2009) stated that vitamin D combined with Ca has a role in primary prevention. This is in agreement with the position statement by the Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, and the Endocrine Society of Australia (Sanders et al, 2009), which noted that currently, the balance of evidence remains in favor of fracture prevention from combined Ca and vitamin D supplementation in elderly men and women. Adequate vitamin D status is essential for active Ca absorption in the gut and for bone development and remodeling. In adults with a baseline Ca intake of 500 to 900 mg/day, increasing or supplementing this intake by a further 500 to 1000 mg/day has a beneficial effect on bone mineral density (BMD). Briot et al (2009) stated that the measurement of the serum 25-OHD level is the only way to determine the vitamin D status. These researchers recommended measuring the serum 25-OHD level in patients with osteoporosis or at risk of osteoporosis, and to correct the deficiency. Furthermore, the National Comprehensive Cancer Network (NCCN)'s task force on bone health in cancer care (Gralow et al, 2009) suggested checking 25-OHD level for cancer patients at increased risk for bone loss and fracture due to therapy or age with a T score [BMD] of lesser than -1.0 (a T score of -1.0 to -2.5 is classified as osteopenia; a T score of less than -2.5 is classified as osteoporosis).

Rickets/Osteomalacia

Okazaki (2007) noted that for differential diagnosis of rickets/osteomalacia, it is essential to evaluate the level of circulating vitamin D metabolites. Although many other metabolites are present, it is clinically sufficient to assess 25-OHD and 1,25-OH(2)D. Low "normal" serum 25-OHD level does not cause rickets/osteomalacia, but could harm bone health. Such vitamin D insufficiency or inadequacy can not be recognized unless serum 25-OHD is measured. The NKF's clinical practice guideline on "Treatment of bone disease in CKD patients" (2003) stated that osteomalacia due to vitamin D2 or D3 deficiency or phosphate depletion, though uncommon, should be treated with vitamin D2 or D3 supplementation and/or phosphate administration, respectively. In a review on the diagnosis of disorders of vitamin D metabolism and osteomalacia, Scharla (2008) noted that the presence of vitamin D deficiency can be proven by measuring the serum concentration of 25-OHD. During the treatment of vitamin D deficiency with drugs consisting of vitamin D/vitamin D supplements, the measurement of serum 25-OHD is very useful for monitoring of therapy and follow-up.

Other Health Issues

In an evidence-based review on vitamin D safety and effectiveness in relation to bone health, Cranney et al (2008) completed an extensive literature search of multiple databases and a multi-level selection process with synthesis of results from 167 studies. These researchers included a variety of outcomes such as falls, BMD, fractures, and adverse events (AEs). They provided an overview of the methods and a summary of the key findings. In addition, they discussed areas where the evidence was inconclusive, as well as methodological issues that were encountered. There was inconsistent evidence of an association between serum 25-OHD concentration and bone mineral content (BMC) in infants and fair evidence of an association with BMC or BMD in older children and older adults. The evidence of an association between serum 25-OHD concentration and some clinical outcomes (e.g., fractures, performance measures) in post-menopausal women and older men was inconsistent, and the evidence of an association with falls was fair. These investigators found good evidence of a positive effect of consuming vitamin D-fortified foods on 25-OHD concentrations. The evidence for a benefit of vitamin D on falls and fractures varied. They found fair evidence that adults tolerated vitamin D at doses above current dietary reference intake levels, but they had no data on the association between long-term harms and higher doses of vitamin D.

In a Cochrane review, Gillespie et al (2009) evaluated the effects of interventions to reduce the incidence of falls in older people living in the community. These investigators searched various databases for randomized trials of interventions to reduce falls in community-dwelling older people were selected. Primary outcomes were rate of falls and risk of falling. Two review authors independently assessed trial quality and extracted data. Data were pooled where appropriate. A total of 111 trials (55,303 subjects) were included. Multiple-component group exercise reduced rate of falls and risk of falling (rate ratio [RaR] 0.78, 95 % CI: 0.71 to 0.86; risk ratio/relative risk (RR) 0.83, 95 % CI: 0.72 to 0.97), as did Tai Chi (RaR 0.63, 95 % CI: 0.52 to 0.78; RR 0.65, 95 % CI: 0.51 to 0.82), and individually prescribed multiple-component home-based exercise (RaR 0.66, 95 % CI 0.53 to 0.82; RR 0.77, 95 % CI 0.61 to 0.97). Assessment and multi-factorial intervention reduced rate of falls (RaR 0.75, 95 % CI 0.65 to 0.86), but not risk of falling. Overall, vitamin D did not reduce falls (RaR 0.95, 95 % CI: 0.80 to 1.14; RR 0.96, 95 % CI: 0.92 to 1.01), but may do so in people with lower vitamin D levels. The authors concluded that exercise interventions reduce risk and rate of falls. They stated that more research is needed to confirm the contexts in which multi-factorial assessment and intervention, home safety interventions, vitamin D supplementation, and other interventions are effective.

Janssens and colleagues (2009) noted that the discovery that the vitamin D endocrine system regulates a very large number of genes and their associated biological processes improves the understanding of the fundamental role of vitamin D and sun exposure for human health. Approximately 50 % of the world's elderly, and to a lesser extent the adult population, have insufficient to deficient 25-OHD serum levels, and several intervention studies are being undertaken to study the impact of adequate vitamin D supplementation in chronic diseases. In this perspective, the authors claimed that chronic obstructive pulmonary disease (COPD) is a candidate disease for which vitamin D supplementation might be beneficial. Epidemiological studies revealed a dose-dependent association between serum 25-OHD levels and pulmonary function so that adequate vitamin D supplementation may extend beyond its protection against osteoporotic fractures. In line with the novel insights on its immune function, it is tempting to speculate that vitamin D may down-regulate the inflammatory immune response in the airways while boosting innate immune defense against different microorganisms. Apart from its affects on osteoporosis, vitamin D may also interfere with other co-morbidities of COPD such as skeletal muscle weakness, cardiovascular disease, and cancer. Because respiratory treatments in COPD fail to reverse disease progression, interventional trials that may exploit the broader potential of vitamin D are warranted. A further challenge of such studies is to define optimal serum 25-OHD levels for such non-calcemic end-points.

In addition to its role in maintaining Ca and phosphate homeostasis, vitamin D is thought to play a role in a host of conditions including Alzheimer's disease/dementia, cancers, diabetes mellitus, fibromyalgia, multiple sclerosis, Parkinson's disease, and psoriasis. However, Grant (2009) noted that although there are reports suggesting that vitamin D can lower the risk of developing dementia, there do not appear to be observational studies of incidence of dementia with respect to pre-diagnostic serum 25-OHD or vitamin D supplementation. The author stated that such studies now appear to be warranted.

In a population-based cross-sectional study, Lee et al (2009) examined the association between 25-OHD levels and cognitive performance in middle-aged and older European men. A total of 3,369 men aged 40 to 79 years from 8 centers enrolled in the European Male Ageing Study. Cognitive function was assessed using the Rey-Osterrieth Complex Figure (ROCF) test, the Camden Topographical Recognition Memory (CTRM) test and the Digit Symbol Substitution Test (DSST). Serum 25-OHD levels were measured by radioimmunoassay. Additional assessments included measurement of mood/depression, functional performance, as well as physical activity. Associations between cognitive function and 25-OHD levels were explored using locally weighted and linear regression models. In total, 3,133 men (mean age of 60 +/- 11 years) were included in the analysis. The mean 25-OHD concentration was 63 +/- 31 nmol/L. In age-adjusted linear regressions, high levels of 25-OHD were associated with high scores on the copy component of the ROCF test (beta per 10 nmol/L = 0.096; 95 % CI: 0.049 to 0.144), the CTRM test (beta per 10 nmol/L = 0.075; 95 % CI: 0.026 to 0.124) and the DSST (beta per 10 nmol/L = 0.318; 95 % CI: 0.235 to 0.401). After adjusting for additional confounders, 25-OHD levels were associated with only score on the DSST (beta per 10 nmol/L = 0.152; 95 % CI: 0.051 to 0.253). Locally weighted and spline regressions suggested the relationship between 25-OHD concentration and cognitive function was most pronounced at 25-OHD concentrations below 35 nmol/L. The authors concluded that lower 25-OHD levels were associated with poorer performance on the DSST. Moreover, they stated that further research is needed to ascertain if vitamin D sufficiency might have a role in preserving cognitive function in older adults.

Slinin et al (2010) tested the hypothesis that lower 25-OHD levels are associated with a greater likelihood of cognitive impairment and risk of cognitive decline. These investigators measured 25-OHD and assessed cognitive function using the Modified Mini-Mental State Examination (3MS) and Trail Making Test Part B (Trails B) in a cohort of 1,604 men enrolled in the Osteoporotic Fractures in Men Study and followed them for an average of 4.6 years for changes in cognitive function. In a model adjusted for age, season, and site, men with lower 25-OHD levels seemed to have a higher odds of cognitive impairment, but the test for trend did not reach significance (impairment by 3MS: odds ratio [OR] 1.84, 95 % CI 0.81 to 4.19 for quartile [Q] 1; 1.41, 0.61 to 3.28 for Q2; and 1.18, 0.50 to 2.81 for Q3, compared with Q4 [referent group; p trend = 0.12]; and impairment by Trails B: OR 1.66, 95 % CI: 0.98 to 2.82 for Q1; 0.96, 0.54 to 1.69 for Q2; and 1.30, 0.76 to 2.22 for Q3, compared with Q4 [p trend = 0.12]). Adjustment for age and education further attenuated the relationships.

There was a trend for an independent association between lower 25-OHD levels and odds of cognitive decline by 3MS performance (multi-variable OR 1.41, 95 % CI: 0.89 to 2.23 for Q1; 1.28, 0.84 to 1.95 for Q2; and 1.06, 0.70 to 1.62 for Q3, compared with Q4 [p = 0.10]), but no association with cognitive decline by Trails B. The authors concluded that there was little evidence of independent associations between lower 25-OHD level and baseline global and executive cognitive function or incident cognitive decline.

Jorde and colleagues (2010) noted that vitamin D receptors have been detected in vascular smooth muscle cells, and 1,25-OH(2)D inhibits the renin mRNA expression. Epidemiological studies show an inverse relation between serum 25-OHD levels and blood pressure (BP), and low serum 25-OHD levels are reported to be predictors of future development of hypertension. This may indicate an important role for vitamin D in BP regulation. In the present study, 25-OHD was measured in sera collected in 1994 from 4,125 subjects who did not use BP medication, and thereafter measurement was repeated in 2008 for 2,385 of these subjects. In sera from 1994 there was a significant decrease in age, body mass index (BMI), and systolic BP and a significant increase in physical activity score across increasing 25-OHD quartiles. After adjusting for sex, age, BMI, and physical activity, the difference in systolic BP between the lowest and highest serum 25-OHD quartiles was 3.6 mm Hg. After adjustment for confounders, serum 25-OHD from 1994 did not predict future hypertension or increase in BP, nor was there any significant association between change in serum 25-OHD from 1994 to 2008 and change in BP. The authors concluded that these findings do not support a causal role for vitamin D in BP regulation, and large randomized clinical trials, preferably including subjects with hypertension and/or low serum 25-OHD levels, are greatly needed to clarify whether vitamin D supplementation affects the BP.

Pittas et al (2010) examined the association between vitamin D status, including the effect of vitamin D supplementation, and cardio-metabolic outcomes in generally healthy adults. A total of 11 reviewers screened citations to identify longitudinal cohort studies that reported associations between vitamin D status and cardio-metabolic outcomes, including randomized trials of vitamin D supplementation; 5 independent reviewers extracted data about study conduct, participant characteristics, outcomes, and quality. Differences were resolved by consensus. A total of 13 observational studies (14 cohorts) and 18 trials were eligible. Three of 6 analyses (from 4 different cohorts) reported a lower incident diabetes risk in the highest versus the lowest vitamin D status groups; 8 trials found no effect of vitamin D supplementation on glycemia or incident diabetes. In meta-analysis of 3 cohorts, lower 25-OHD concentration was associated with incident hypertension (RR, 1.8 [95 % CI:1.3 to 2.4]). In meta-analyses of 10 trials, supplementation non-significantly reduced systolic BP (weighted mean difference [WMD], −1.9 mm Hg [95 % CI: −4.2 to 0.4 mm Hg]) and did not affect diastolic BP (WMD, −0.1 mm Hg [95 % CI: −0.7 to 0.5 mm Hg]). Lower 25-OHD concentration was associated with incident cardiovascular disease in 5 of 7 analyses (6 cohorts); 4 trials found no effect of supplementation on cardiovascular outcomes. The authors concluded that the association between vitamin D status and cardio-metabolic outcomes is uncertain. Trials showed no clinically significant effect of vitamin D supplementation at the dosages given.

Moreover, it is interesting to note that a recent Agency for Healthcare Research and Quality's systematic review on health outcomes of vitamin D and Ca (Chung et al, 2009) noted that there appeared to be considerable uncertainty as to the benefits of vitamin D and Ca largely because of conflicting study findings or because specific health outcomes have not been studied. Also, currently, the NCCN's oncological guidelines do not address the issue of vitamin D assay testing.

Cancers

The active form of vitamin D (1,25-OH(2)D3) acts as an effective regulator of cell growth and differentiation in various cell types, including cancer cells. It has been suggested that vitamin D malnutrition may be linked to an increased susceptibility to certain cancers (e.g., breast, colorectal, endometrial, pancreatic, prostate, and skin). However, vitamin D's mechanism of action in the prevention or progression of various cancers has not been established definitively. Available evidence also does not support an association between vitamin D status and cancer development. In a review on epidemiology of vitamin D insufficiency and cancer mortality, Pilz and colleagues (2009) stated that while there is growing evidence that vitamin D exerts anti-carcinogenic effects, there is still a need for further investigations to assess the association of vitamin D insufficiency and cancer incidence and mortality.

Breast

Knight and co-workers (2007) noted that current evidence in humans is limited with some suggestion that vitamin D-related factors may reduce the risk of breast cancer. These researchers conducted a population-based case-control study to evaluate the evidence for a relationship between sources of vitamin D and breast cancer risk. Women with newly diagnosed invasive breast cancer were identified from the Ontario Cancer Registry. Women without breast cancer were identified through randomly selected residential telephone numbers. Telephone interviews were completed for 972 cases and 1,135 controls; ORs and 95 % CI for vitamin D-related variables were estimated using unconditional logistic regression with adjustment for potential confounders. Reduced breast cancer risks were associated with increasing sun exposure from ages 10 to 19 (e.g., OR, 0.65; 95 % CI, 0.50 to 0.85 for the highest quartile of outdoor

activities versus the lowest; p = 0.0006). Reduced risk was also associated with the use of cod liver oil (OR, 0.76; 95 % CI, 0.62 to 0.92) and increasing milk consumption (OR, 0.62 95 % CI: 0.45 to 0.86 for greater than or equal to 10 glasses per week versus none; p = 0.0004). There was weaker evidence for associations from ages 20 to 29 and no evidence for ages 45 to 54. The authors concluded that there is strong evidence to support the hypothesis that vitamin D could help prevent breast cancer. However, their results suggested that exposure earlier in life, particularly during breast development, maybe most relevant; and these results needed to be confirmed.

Freedman et al (2008) stated that experimental and epidemiological studies suggested that vitamin D metabolites (1,25-OH(2)D and its precursor 25-OHD) may reduce breast cancer risk. These investigators examined subsequent breast cancer risk related to serum levels of these metabolites. In a cohort of women aged 55 to 74 years who donated blood at baseline (1993 to 2001) in the "Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial", these researchers identified 1,005 incident breast cancer cases during follow-up through 2005 (mean time between blood draw and diagnosis was 3.9 years). Non-cases (n = 1,005) were frequency-matched to the cases based on age and year of entry. Sample weights that accounted for unequal probabilities of selecting cases and non-cases were applied to make inferences that reflected the entire "Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial" cohort. Using Cox proportional hazards modeling, these investigators computed breast cancer RR and 95 % CI by quintile for each metabolite. The RR of breast cancer for the highest quintile of 25-OHD concentration versus the lowest was 1.04 (95 % CI: 0.75 to 1.45; p = 0.81). Similarly, the breast cancer RR for the highest quintile of 1,25-OH(2)D compared with the lowest was 1.23 (95 % CI: 0.91 to 1.68; p = 0.14). Excluding the first 2 years of follow-up did not materially alter these estimates. There was also no evidence of inverse risk in older women (greater than or equal to 60 years of age) versus younger women (less than 60 years of age). The authors concluded that in this prospective study of post-menopausal women, they did not observe an inverse association between circulating 25-OHD or 1,25-OH(2)D and breast cancer risk, although they could not exclude an association in younger women or with long-term or earlier exposure.

Mahoney et al (2008) noted that due to the high incidence of breast cancer among women in the United States, risk-reduction strategies are essential. These investigators summarized information on potential nutritional, pharmacological, surgical, and behavioral approaches to reducing breast cancer risk. While there is no clear evidence that specific dietary components can effectively reduce breast cancer risk, weight gain and obesity in adulthood are risk factors for the development of post-menopausal breast cancer. Alcohol consumption, even at moderate levels, increases breast cancer risk, although some of the detrimental effects may be reduced by sufficient folate intake. Women at increased risk of breast cancer can opt to reduce their breast cancer risk through the use of tamoxifen or raloxifene; other chemo-preventive agents remain under investigation. Surgical approaches to risk reductions are restricted to women with a substantially increased risk of developing breast cancer. Patients should be encouraged to maintain a healthy lifestyle for their overall well-being and to remain up-to-date with recommendations for screening and surveillance. Vitamin D assay testing is not mentioned as an option of risk reduction in breast cancer.

Chlebowski and associates (2008) examined the role of Ca plus vitamin D supplementation and the risk of breast cancer. Post-menopausal women (n = 36,282) who were enrolled in a "Women's Health Initiative" clinical trial were randomly assigned to 1,000 mg of elemental Ca with 400 IU of vitamin D3 daily or placebo for a mean of 7.0 years to determine the effects of supplement use on incidence of hip fracture. Mammograms and breast examinations were serially conducted. Invasive breast cancer was a secondary outcome. Baseline serum 25-OHD levels were assessed in a nested case-control study of 1,067 case patients and 1,067 control subjects. A Cox proportional hazards model was used to estimate the risk of breast cancer associated with random assignment to Ca with vitamin D3. Associations between 25-OHD serum levels and total vitamin D intake, BMI, recreational physical activity, and breast cancer risks were evaluated using logistic regression models. Statistical tests were 2-sided. Invasive breast cancer incidence was similar in the 2 groups (528 supplement versus 546 placebo; HR = 0.96; 95 % CI: 0.85 to 1.09). In the nested case-control study, no effect of supplement group assignment on breast cancer risk was seen. Baseline 25-OHD levels were modestly correlated with total vitamin D intake (diet and supplements) (r = 0.19, p < 0.001) and were higher among women with lower BMI and higher recreational physical activity (both p < 0.001). Baseline 25-OHD levels were not associated with breast cancer risk in analyses that were adjusted for BMI and physical activity (p (trend) = 0.20). The authors concluded that Ca and vitamin D supplementation did not reduce invasive breast cancer incidence in post-menopausal women. In addition, 25-OHD levels were not associated with subsequent breast cancer risk. These findings do not support a relationship between total vitamin D intake and 25-OHD levels with breast cancer risk.

In a meta-analysis, Gissel et al (2008) studied the association between vitamin D intake and risk of breast cancer. These investigators searched various databases using the terms "vitamin D" and "breast cancer". A total of 1,731 studies were identified, but only 6 studies contained original data on the association between intake of vitamin D and risk of breast cancer. Overall, there was no association between amount of vitamin D and risk of breast cancer (RR = 0.98, 95 % CI: 0.93 to 1.03, test for heterogeneity p < 0.01). However, most studies reported on very low intakes of vitamin D (typically in the range of 100 to 400 IU/day). Restricting the analyses to intakes greater than or equal to 400 IU/day yielded a more homogenous result with a trend towards less breast cancer with greater than or equal to 400 IU/day versus the lowest intake (typically less than 50 to 150 IU/day, RR = 0.92, 95 % CI: 0.87 to 0.97, p for heterogeneity = 0.14). The authors concluded that there may be a trend towards fewer cases of breast cancer with higher intakes of vitamin D (greater than or equal to 400 IU/day). However, more research is needed, preferably in the form of randomized controlled trials (RCTs).

Goodwin et al (2009) noted that vitamin D has been linked to breast cancer risk, but prognostic effects are unknown. Such effects are biologically plausible given the presence of vitamin D receptor (VDR) in breast cancer cells, which act as nuclear transcription factors to regulate gene activity. The study was conducted in a prospective inception cohort of 512 women with early breast cancer diagnosed in 1989 to 1996. Vitamin D levels were measured in stored blood. Clinical, pathological, and dietary data were accessed to examine prognostic effects of vitamin D. Mean age was 50.4 years, mean vitamin D was 58.1 +/- 23.4 nmol/L. Vitamin D levels were deficient (less than 50 nmol/L) in 37.5 % of patients, insufficient (50 to 72 nmol/L) in 38.5 % of patients, and sufficient (greater than 72 nmol/L) in 24.0 % of patients. There was little variation in mean vitamin D levels between summer and winter months. Mean follow-up was 11.6 years; 116 women had distant recurrences, and 106 women died. Women with deficient vitamin D levels had an increased risk of distant recurrence (HR = 1.94; 95 % CI: 1.16 to 3.25) and death (HR = 1.73; 95 % CI: 1.05 to 2.86) compared with those with sufficient levels. The association remained after individual adjustment for key tumor and treatment related factors but was attenuated in multi-variate analyses (HR = 1.71; 95 % CI: 1.02 to 2.86 for distant recurrence; HR = 1.60; 95 % CI: 0.96 to 2.64 for death). The authors stated that "[o]ur observations provide the first direct evidence that vitamin D may be an important host factor influencing breast cancer prognosis. Although encouraging, they require replication in large independent data sets. Translation of previous observational findings of potential beneficial effects of vitamins to clinical benefits in the field of cancer has not been straightforward. For example, observational data suggesting that B-carotene supplements would reduce lung cancer risk in smokers were refuted in subsequent randomized trials. Although women with breast cancer will likely benefit in terms of overall health from having sufficient vitamin D levels, we believe caution is needed in recommending that vitamin D intake in patients with breast cancer be increased to high levels with the goal of improving breast cancer outcomes until further research has been undertaken".

Furthermore, in a review on vitamin D and breast cancer, Bertone-Johnson (2009) stated that prospective studies are needed to determine if vitamin D may have important potential for breast cancer prevention. Of note, the NCCN's practice guideline on breast cancer screening and diagnosis (2018) does not mention vitamin D assay testing.

Colorectal

Huncharek et al (2009) stated that in-vivo as well as in-vitro studies suggested that dairy products, Ca, and dietary vitamin D inhibits the development of colorectal cancer (CRC). These investigators performed a meta-analysis to evaluate this relationship in observational studies. Data from 60 epidemiological studies enrolling 26,335 CRC cases were pooled using a general variance-based meta-analytic method. Summary RR estimates and 95 % CIs were calculated for the highest versus the lowest intake categories. Sensitivity analyses tested the robustness of these summary effect measures and the statistical heterogeneity. The summary RR for high milk and dairy product intake, respectively, on colon cancer risk was 0.78 (95 % CI: 0.67 to 0.92) and 0.84 (95 % CI: 0.75 to 0.95), respectively. Milk intake was unrelated to rectal cancer risk. High Ca intake had a greater protective effect against tumors of the distal colon and rectal cancer versus proximal colon. The risk reduction associated with Ca was similar for dietary and supplemental sources. Vitamin D was associated with a non-significant 6 % reduction in CRC risk. Higher consumption of milk/dairy products reduces the risk of colon cancer, and high Ca intake reduces the risk of CRC. Low vitamin D intake in the study populations may limit the ability to detect a protective effect if one exists.

Endometrial

McCullough and associates (2008) presented the epidemiological evidence on the relation between intake of vitamin D and Ca, and the occurrence of endometrial cancer. Random and fixed effects summary estimates were computed. Pooled analyses of the 3 case-control studies of dietary vitamin D and endometrial cancer uncovered heterogeneous results that were insignificant in random or fixed effects analyses. Cut-points for the highest vitamin D intakes ranged from greater than 244 to greater than 476 IU/day. Qualitatively similar findings were observed for dietary Ca. Only 2 studies provided estimates for Ca supplements (random effects OR = 0.62, 95 % CI: 0.39 to 0.99; fixed effects OR = 0.62, 95 % CI: 0.42 to 0.93, for top versus bottom category, p for heterogeneity = 0.25). The authors concluded that the limited epidemiological evidence suggested no relation between endometrial cancer in the ranges of dietary vitamin D examined, and suggested a possible inverse association for Ca from supplements. They stated that prospective studies, ideally including plasma 25-OHD to estimate vitamin D input from diet and sun exposure, are needed to further explore these hypotheses.

Melanoma

Gandini et al (2009) performed a comprehensive bibliographical search of the literature to identify studies on cutaneous malignant melanoma (CMM) and non-melanoma skin cancer (NMSC), VDR polymorphisms, vitamin D intake and 25-OHD serum levels. Fully adjusted risk estimates were found and extracted for the 2 polymorphisms FokI and BsmI and vitamin D intake. A total of 10 studies were included in the meta-analysis, with a total of 6,805 skin cancer cases. These researchers found an association with CMM for both polymorphisms. The summary RR (SRR) for the studies on CMM were: 1.21 (1.03 to 1.42) and 1.21 (0.95 to 1.54) for the Ff and ff

versus wild-type of FokI, respectively. The SRR for ff versus wild-type became significant with the inclusion of NMSC. The SRR for the studies on CMM were: 0.78 (0.65 to 0.92) and 0.75 (0.59 to 0.95) for the Bb and BB versus wild-type of BsmI, respectively. There was also a slight indication of a role of dietary vitamin D in CMM development. The authors concluded that this meta-analysis suggested a possible significant role of VDR FokI and BsmI polymorphism in CMM and NMSC risk. The association with vitamin D intake was less clear and further studies could be useful to clarify the role of diet.

Pancreatic

Stolzenberg-Solomon et al (2009) performed a nested case-control study in the "Prostate, Lung, Colorectal, and Ovarian Screening Trial" cohort of men and women 55 to 74 years of age at baseline to test whether pre-diagnostic serum 25-OHD concentrations were associated with pancreatic cancer risk. Between 1994 and 2006, 184 incident cases of pancreatic adenocarcinoma occurred (follow-up to 11.7 years). Two controls who were alive at the time the case was diagnosed were selected for each case and matched by age, race, sex, and calendar date of blood draw (to control for seasonal variation). These researchers calculated ORs and 95 % CI using conditional logistic regression, adjusting for smoking and BMI. Vitamin D concentrations were not associated with pancreatic cancer overall (highest versus lowest quintile, greater than 82.3 versus less than 45.9 nmol/L: OR, 1.45; 95 % CI: 0.66 to 3.15; p = 0.49). However, positive associations were observed among subjects with low estimated annual residential solar UVB exposure, but not among those with moderate-to-high annual UVB exposure (p = 0.015). The authors concluded that these findings did not confirm the previous strong positive association between 25-OHD and pancreatic cancer; however, the increased risk among participants with low residential UVB exposure is similar.

Prostate

Li and colleagues (2007) stated that despite intriguing results from laboratory studies, previous epidemiological studies showed inconsistent associations of circulating levels of 25-OHD, 1,25-OH(2)D, and several VDR polymorphisms with prostate cancer risk. Few studies have explored the joint association of circulating vitamin D levels with VDR polymorphisms. During 18 years of follow-up of 14,916 men initially free of diagnosed cancer, these investigators identified 1,066 men with incident prostate cancer (including 496 with aggressive disease, defined as stage C or D, Gleason 7 to 10, metastatic, and fatal prostate cancer) and 1,618 cancer-free, age- and smoking-matched control participants in the Physicians' Health Study. They examined the associations of pre-diagnostic plasma levels of 25-OHD and 1,25-OH(2)D, individually and jointly, with total and aggressive disease, and explored whether relations between vitamin D metabolites and prostate cancer were modified by the functional VDR FokI polymorphism, using conditional logistic regression. Among these United States physicians, the median plasma 25-OHD levels were 25 ng/ml in the blood samples collected during the winter or spring and 32 ng/ml in samples collected during the summer or fall. Nearly 13 % (summer/fall) to 36 % (winter/spring) of the control participants were deficient in 25-OHD (less than 20 ng/ml) and 51 % (summer/fall) and 77 % (winter/spring) had insufficient plasma 25-OHD levels (less than 32 ng/ml). Plasma levels of 1,25-OH(2)D did not vary by season. Men whose levels for both 25-OHD and 1,25-OH(2)D were below (versus above) the median had a significantly increased risk of aggressive prostate cancer (OR = 2.1, 95 % CI: 1.2 to 3.4), although the interaction between the 2 vitamin D metabolites was not statistically significant (p = 0.23). These investigators observed a significant interaction between circulating 25-OHD levels and the VDR FokI genotype (p < 0.05). Compared with those with plasma 25-OHD levels above the median and with the FokI FF or Ff genotype, men who had low 25-OHD levels and the less functional FokI ff genotype had increased risks of total (OR = 1.9, 95 % CI: 1.1 to 3.3) and aggressive prostate cancer (OR = 2.5, 95 % CI: 1.1 to 5.8). Among men with plasma 25-OHD levels above the median, the ff genotype was no longer associated with risk. Conversely, among men with the ff genotype, high plasma 25-OHD level (above versus below the median) was related to significant (about 60 % to 70 %) lower risks of total and aggressive prostate cancer. The authors concluded that these findings suggested that a large proportion of men in the United States had sub-optimal vitamin D status (especially during the winter/spring season), and both 25-OHD and 1,25-OH(2)D may play an important role in preventing prostate cancer progression. Moreover, vitamin D status, measured by 25-OHD in plasma, interacts with the VDR FokI polymorphism and modifies prostate cancer risk. Men with the less functional FokI ff genotype (14 % in the European-descent population of this cohort) are more susceptible to this cancer in the presence of low 25-OHD status.

On the other hand, in a meta-analysis, Huncharek et al (2008) reported that the data from observational studies do not support an association between dairy product use and an increased risk of prostate cancer. These investigators examined the available evidence and sources of heterogeneity for studies of dairy products, Ca, and vitamin D intake and the risk of prostate cancer. These researchers pooled data from 45 observational studies using a general variance-based, meta-analytic method employing CIs. Summary RRs were calculated for specific dairy products such as milk and dairy micronutrients. Sensitivity analyses were performed to test the robustness of these summary measures of effect. Cohort studies showed no evidence of an association between dairy [RR = 1.06; 95 % CI: 0.92 to 1.22] or milk intake (RR = 1.06; 95 % CI: 0.91 to 1.23) and risk of prostate cancer. This was supported by pooled results of case-control analyses (RR = 1.14; 95 % CI: 1.00 to 1.29), although studies using milk as the exposure of interest were heterogeneous and could not be combined. Calcium data from cohort studies were heterogeneous. Case-control analyses using Ca as the exposure of interest

demonstrated no association with increased risk of prostate cancer (RR = 1.04; 95 % CI: 0.90 to 1.15). Dietary intake of vitamin D also was not related to prostate cancer risk (RR = 1.16; 95 % CI: 0.98 to 1.38).

Ahn and colleagues (2008) examined the association between vitamin D status, as determined by serum 25-OHD level, and risk of prostate cancer in a case-control study nested within the "Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial". The study included 749 case patients with incident prostate cancer who were diagnosed 1 to 8 years after blood draw and 781 control subjects who were frequency matched by age at cohort entry, time since initial screening, and calendar year of cohort entry. All study participants were selected from the trial screening arm (which includes annual standardized prostate cancer screening). Conditional logistic regression was used to estimate adjusted ORs with 95 % CIs by quintile of season-standardized serum 25-OHD level; statistical tests were 2-sided. No statistically significant trend in overall prostate cancer risk was observed with increasing season-standardized serum 25-OHD level. However, serum 25-OHD concentrations greater than the lowest quintile (Q1) were associated with increased risk of aggressive (Gleason sum greater than or equal to 7 or clinical stage III or IV) disease (in a model adjusting for matching factors, study center, and history of diabetes, ORs for Q2 versus Q1 = 1.20, 95 % CI: 0.80 to 1.81, for Q3 versus Q1 = 1.96, 95 % CI: 1.34 to 2.87, for Q4 versus Q1 = 1.61, 95 % CI: 1.09 to 2.38, and for Q5 versus Q1 = 1.37, 95 % CI: 0.92 to 2.05; p (trend) = 0.05). The rates of aggressive prostate cancer for increasing quintiles of serum 25-OHD were 406, 479, 780, 633, and 544 per 100,000 person-years. In exploratory analyses, these associations with aggressive disease were consistent across sub-groups defined by age, family history of prostate cancer, diabetes, BMI, vigorous physical activity, Ca intake, study center, season of blood collection, and assay batch. The authors concluded that the findings of this large prospective study did not support the hypothesis that vitamin D is associated with decreased risk of prostate cancer; indeed, higher circulating 25-OHD concentrations may be associated with increased risk of aggressive disease.

Travis et al (2009) examined if vitamin D concentrations were associated with prostate cancer risk in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (1994 to 2000). Serum concentrations of 25-OHD were measured in 652 prostate cancer cases matched to 752 controls from 7 European countries after a median follow-up time of 4.1 years. Conditional logistic regression models were used to calculate ORs for prostate cancer risk in relation to serum 25-OHD after standardizing for month of blood collection and adjusting for co-variates. No significant association was found between 25-OHD and risk of prostate cancer (highest versus lowest quintile: OR = 1.28, 95 % CI: 0.88 to 1.88; p = 0.188). Sub-group analyses showed no significant heterogeneity by cancer stage or grade, age at diagnosis, BMI, time from blood collection to diagnosis, or Ca intake. In summary, the results of this large nested case-control study provided no evidence in support of a protective effect of circulating concentrations of vitamin D on the risk of prostate cancer.

Pre-Bariatric Surgery Screening

Peterson (2016) stated that obesity is the most widespread nutritional problem globally. Bariatric surgery is the preeminent long-term obesity treatment. Bariatric procedures manipulate the intestines to produces malabsorption and/or restrict the size of the stomach. The most enduring bariatric procedure is the Roux-en-Y gastric bypass, which utilizes both restriction (small stomach pouch) and malabsorption (duodenum bypass). The in-vogue procedure is the vertical sleeve gastrectomy -- resection of the greater curvature of the stomach (predominantly restrictive). Malabsorptive procedures function by decreasing nutrient absorption, primarily fat and fat-soluble nutrients (vitamins A, D, E, and K). Most studies of vitamin D status in bariatric surgery candidates reported a prevalence of over 50 % vitamin D deficiency (less than 50 nmol/L), enduring post-operatively with one study reporting 65 % deficient at 10 years post-bariatric surgery. Obesity is associated with chronic inflammation, which may contribute to adverse surgical outcomes (e.g., poor healing and infection). Since vitamin D deficiency is also associated with chronic inflammation, obese individuals with vitamin D deficiency have extraordinary risk of adverse surgical outcomes, particularly delayed wound healing and infection due to the role of vitamin D in re-epithelialization and innate immunity. When the risk of adverse surgical outcomes in obesity is combined with that of vitamin D deficiency, there is likely an additive or potentially a synergistic effect. Furthermore, deficiency in fat-soluble vitamins, such as vitamin D, is considered a metabolic complication of bariatric surgery. Thus, determining the vitamin D status of bariatric surgery candidates and amending it preoperatively may prove greatly beneficial acutely and lifelong.

Furthermore, an UpToDate review on “Bariatric surgery: Postoperative nutritional management” (Kushner et al, 2018) states that “Presurgical screening -- It is common for patients with obesity preparing for bariatric surgery to have at least one vitamin or mineral deficiency preoperatively. Thus, the American Society for Metabolic and Bariatric Surgery (ASMBS) intergraded health nutritional guides for the surgical weight loss patient recommend routine baseline pre-surgical screening for levels of thiamin, vitamin B12, folate, iron, vitamin D and calcium, fat-soluble vitamins (A, E, K), zinc, and copper. These screening laboratory tests can be performed as an integral part of the preoperative clinical nutrition evaluation by a registered dietitian”.

Pregnancy Care

Pike and associates (2012) noted that studies exploring the relationship between prenatal vitamin D exposure and childhood asthma have yielded conflicting results. Higher vitamin D intake during pregnancy has been shown to lower the risk of childhood wheeze, yet a study of maternal late-pregnancy serum 25-hydroxyvitamin D suggested higher serum concentrations may be associated with increased childhood asthma. These researchers evaluated the relationship between mothers' serum 25-hydroxyvitamin D status and asthma and wheeze phenotypes in their children at age 6 years. They also examined the relationship between maternal 25-hydroxyvitamin D status and objective measures of childhood atopy and lung function. Serum 25-hydroxyvitamin D was measured at 34 weeks' gestation in the mothers of 860 children born at term. Wheeze was classified as either transient or persistent/late using questionnaire data collated from 6, 12, 24 and 36 months and 6 years. At 6 years, spirometry was performed and atopic status was determined by skin prick testing, exhaled nitric oxide was measured in 451 children and bronchial hyper-responsiveness in 216 children. There were no significant associations between maternal late-pregnancy 25-hydroxyvitamin D status and either asthma or wheeze at age 6 years. Maternal vitamin D status was not associated with transient or persistent/late wheeze; no significant association was found between persistent/late wheeze when sub-divided according to atopic status. No associations were found with skin sensitization or lung function. The authors concluded that the findings of this study provided no evidence that exposure to higher concentrations of 25-hydroxyvitamin D in maternal serum during late pregnancy increased the risk of childhood asthma, wheeze or atopy.

Wei and co-workers (2016) stated that maternal vitamin D status has been reported to be associated with childhood allergic diseases. However, this association remains to be fully elucidated. These investigators performed a systematic review and meta-analysis using prospective cohort studies that examined the association between maternal vitamin D status and childhood allergic diseases including wheeze, eczema and asthma. They searched electronic databases of PubMed, Embase, the Cochrane library, the Wanfang (Chinese) database, the VIP (Chinese) database, and Chinese National Knowledge Infrastructure (CNKI) up to August 2014; ORs and 95 % CIs from individual studies were synthesized using a fixed effects model. A total of 4 studies on the association between maternal vitamin D status and childhood asthma (3,666 mother-child pairs), 4 studies on the association between maternal vitamin D status and childhood wheeze (2,225 mother-child pairs) and 3 papers on the association between maternal vitamin D status and childhood eczema (2,172 mother-child pairs) met the inclusion criteria. Maternal vitamin D status during pregnancy was associated with childhood eczema (pooled OR = 0.904, 95 % CI: 0.831 to 0.983). However, the meta-analysis showed no statistical association between maternal vitamin D status and childhood asthma (pooled OR = 0.981, 95 % CI: 0.944 to 1.019) or childhood wheeze (pooled OR = 0.995, 95 % CI: 0.982 to 1.009). The authors concluded that the findings of this meta-analysis showed that lower maternal vitamin D during pregnancy was associated with an increased risk of childhood eczema; but was not associated with childhood asthma or wheeze. Moreover, they stated that the role of maternal vitamin D as an important protective factor for the development of childhood eczema remains to be elucidated.

Pacheco-Gonzalez and associates (2018) noted that pre-natal vitamin D status may influence offspring's respiratory and allergic outcomes; however, evidence is inconclusive. These investigators carried out a systematic review and meta-analysis on the association between 25-hydroxyvitamin D [25(OH)D] levels in maternal blood in pregnancy or cord blood at birth with the risk of offspring's respiratory and allergic conditions. Two independent researchers conducted systematic searches for observational studies published until May 2017 using defined keywords on vitamin D and health outcomes, including respiratory tract infections (RTIs), wheeze, asthma, atopic eczema, allergic rhinitis, allergic sensitization, and lung function. Random-effects meta-analyses were conducted. A total of 34 from 547 retrieved articles were included. Increased pre-natal exposure to 25(OH)D was inversely associated with risk of RTIs. Comparing the highest with the lowest category of 25(OH)D levels, the pooled OR was 0.64 (95 % CI: 0.47 to 0.87). A positive borderline association was found for lung function at school age (forced expiratory volume in 1 second [FEV1] z-score coefficient 0.07, 95 % CI: -0.01 to 0.15). No associations were found for wheeze, asthma, atopic eczema, allergic rhinitis, and allergic sensitization. The authors concluded that the introduction of public health measures to tackle vitamin D status in pregnancy may reduce the burden of RTIs in offspring; however, current evidence does not support an impact on asthma and allergy.

Homer and colleagues (2018) stated that the clinical practice guidelines on pregnancy care have been developed to provide reliable and standardized guidance for health professionals providing ante-natal care in Australia. They were originally released as the Clinical Practice Guidelines: Antenatal Care in 2 separate editions (modules 1 and 2) in 2012 and 2014. These modules have now been combined and updated to form a single set of consolidated guidelines that were publicly released in February 2018 as the Clinical Practice Guidelines: Pregnancy Care. A total of 11 topics have been updated and new guidance on substance use in pregnancy has been added. Main recommendations: The updated guidelines include the following key changes to practice: recommend routine testing for hepatitis C at the 1st ante-natal visit; recommend against routine testing for vitamin D status in the absence of a specific indication; recommend discussing weight change, diet and physical activity with all pregnant women; and recommend offering pregnant women the opportunity to be weighed at every ante-natal visit and encouraging women to self-monitor weight gain. Changes in management as a result of the guidelines: The guidelines will enable pregnant women diagnosed with hepatitis C to be identified and thus avoid invasive procedures that increase the risk of mother-to-baby transmission. Women can be treated post-partum, reducing the risk of liver disease

and removing the risk of perinatal infection for subsequent pregnancies. Routine testing of all pregnant women for vitamin D status and subsequent vitamin D supplementation is not supported by evidence and should cease as the benefits and harms of vitamin D supplementation remain unclear. The recommendation for health professionals to provide advice to pregnant women about weight, diet and physical activity, and the opportunity to be weighed will help women to make changes leading to better health outcomes for themselves and their babies.

Guidelines and Recommendations

Health Quality Ontario (2010) stated that with regards to non-bone health outcomes, there is no high or even moderate quality evidence that supports the effectiveness of vitamin D in outcomes such as cancer, cardiovascular outcomes, and all-cause mortality. Even if there is any residual uncertainty, there is no evidence that testing vitamin D levels encourages adherence to Health Canada's guidelines for vitamin D intake. A normal serum vitamin D threshold required to prevent non-bone health related conditions cannot be resolved until a causal effect or correlation has been demonstrated between vitamin D levels and these conditions. This is as an ongoing research issue around which there is currently too much uncertainty to base any conclusions that would support routine vitamin D testing. For patients with CKD, there is again no high or moderate quality evidence supporting improved outcomes through the use of calcitriol or vitamin D analogs. In the absence of such data, the authors of the guidelines for CKD patients considered it best practice to maintain serum calcium and phosphate at normal levels, while supplementation with active vitamin D should be considered if serum PTH levels are elevated. As previously stated, the authors of guidelines for CKD patients believed that there is inadequate evidence to support routine vitamin D [25(OH)D] testing. According to what is stated in the guidelines, decisions regarding the commencement or discontinuation of treatment with calcitriol or vitamin D analogs should be based on serum PTH, calcium, and phosphate levels. Limitations associated with the evidence of vitamin D testing included ambiguities in the definition of an "adequate threshold level" and both inter- and intra- assay variability. The Medical Advisory Secretariat considered both the lack of a consensus on the target serum vitamin D levels and assay limitations directly affected and undermined the clinical utility of testing. The evidence supporting the clinical utility of vitamin D testing is thus considered to be of very low quality.

The National Osteoporosis Society's guideline on "Vitamin D and Bone Health" (Aspray et al, 2014) stated that "There has been no clear consensus in the UK on vitamin D deficiency its assessment and treatment, and clinical practice is inconsistent. This guideline is aimed at clinicians, including doctors, nurses and dieticians. It recommends the measurement of serum 25 (OH) vitamin D (25OHD) to estimate vitamin D status in the following clinical scenarios: bone diseases that may be improved with vitamin D treatment; bone diseases, prior to specific treatment where correcting vitamin D deficiency is appropriate; musculoskeletal symptoms that could be attributed to vitamin D deficiency. The guideline also states that routine vitamin D testing is unnecessary where vitamin D supplementation with an oral anti-resorptive treatment is already planned and sets the following serum 25OHD thresholds: less than 30 nmol/L is deficient; 30 to 50 nmol/L may be inadequate in some people; greater than 50 nmol/L is sufficient for almost the whole population. For treatment, oral vitamin D3 is recommended with fixed loading doses of oral vitamin D3 followed by regular maintenance therapy when rapid correction of vitamin D deficiency is required, although loading doses are not necessary where correction of deficiency is less urgent or when co-prescribing with an oral anti-resorptive agent. For monitoring, serum calcium (adjusted for albumin) should be checked 1 month after completing a loading regimen, or after starting vitamin D supplementation, in case primary hyperparathyroidism has been unmasked. However, routine monitoring of serum 25OHD is generally unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected. The guideline focused on bone health as, although there are numerous putative effects of vitamin D on immunity modulation, cancer prevention and the risks of cardiovascular disease and multiple sclerosis, there remains considerable debate about the evaluation of extra-skeletal factors and optimal vitamin D status in these circumstances".

The Agency for Healthcare Research and Quality (AHRQ)'s systematic review on "Vitamin D and calcium" (Newberry et al, 2014) concluded that "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 post-menopausal 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".

The Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE)'s position statement: on "Clinical Management of Vitamin D Deficiency in Adults" (Cesareo et al, 2018) reviewed literature about vitamin D deficiency in adults; and 4 topics were identified as worthy for the practicing clinicians. For each topic recommendations based on scientific evidence and clinical practice were issued according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) System. First, what cut-off defines vitamin D deficiency: even though 20 ng/ml (50 nmol/L) can be considered appropriate in the general population, the authors recommended to maintain levels above 30 ng/ml (75 nmol/L) in categories at risk. Second, whom, when, and how to perform screening for vitamin D deficiency: categories at risk (patients with bone, liver, kidney diseases, obesity, malabsorption, during pregnancy and lactation, some elderly); but not healthy people should be screened by the 25-hydroxy-vitamin D assay. Third, whom and how to treat vitamin D deficiency: beyond healthy lifestyle (mostly sun exposure), the authors recommended oral vitamin D (vitamin D2 or vitamin D3) supplementation in patients treated with bone active drugs and in those with demonstrated deficiency. Dosages, molecules and modalities of administration can be profitably individually tailored. Fourth, how to monitor the efficacy of treatment with vitamin D: no routine monitoring is suggested during vitamin D treatment due to its large therapeutic index. In particular conditions, 25-hydroxy-vitamin D can be assayed after at least a 6-month treatment.

An UpToDate review on "Overview of vitamin D" (Pazirandeh and Burns, 2018) states that "The best laboratory indicator of vitamin D adequacy is the serum 25(OH)D concentration. The lower limit of normal for 25(OH)D levels varies depending on the geographic location and sunlight exposure of the reference population (range 8 to 15 ng/mL). However, there is no consensus on the optimal 25(OH)D concentration for skeletal or extra-skeletal health. The IOM concluded that a serum 25(OH)D concentration of 20 ng/mL (50 nmol/L) is sufficient for most individuals, but other experts (Endocrine Society, National Osteoporosis Foundation [NOF], International Osteoporosis Foundation [IOF], American Geriatrics Society [AGS]) suggest that a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults to minimize the risk of falls and fracture".

Furthermore, National Comprehensive Cancer Network's clinical practice guidelines on "Breast cancer" (Version 3.2018) and "Breast cancer screening and diagnosis" (Version 3.2018) do not mention vitamin D assay / testing.

Summary of Guidelines/Recommendations

- Health Quality Ontario (2010) stated that "Given the limitations associated with serum vitamin D measurement, ambiguities in the definition of a 'target serum level', and the availability of clear guidelines on vitamin D supplementation from Health Canada, vitamin D testing is not warranted for the average risk population. Individuals with medical conditions such as renal and liver disease, osteoporosis, and malabsorption syndromes, as well as those taking medications that may affect vitamin D absorption/metabolism, should follow their physician's guidance concerning both vitamin D testing and supplementation".
- The American Society for Clinical Pathology (2013) stated that "Don't perform population based screening for 25-OH-Vitamin D deficiency".
- The Endocrine Society (2013) stated that "Don't routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function".
- The National Osteoporosis Society's guideline on "Vitamin D and Bone Health" (2014) stated that "Routine vitamin D testing is unnecessary where vitamin D supplementation with an oral anti-resorptive treatment is already planned".
- The United States Preventive Services Task force's review on "Vitamin D deficiency: Screening" (USPSTF, 2014) concluded that "The current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults".
- The American Society for Metabolic and Bariatric Surgery's "Integrated health nutritional guidelines for the surgical weight loss patient 2016 update" (2017) recommended "Routine baseline pre-surgical screening for levels of thiamin, vitamin B12, folate, iron, vitamin D and calcium, fat-soluble vitamins (A, E, K), zinc, and copper for candidates of bariatric surgery".
- The Australian Clinical Practice Guidelines: Pregnancy Care (2018) recommended against "Routine testing for vitamin D status in the absence of a specific indication".
- The USPSTF (2018) recommends against "Daily supplementation with 400 IU or less of vitamin D and 1,000 mg or less of calcium for the primary prevention of fractures in community-dwelling, post-menopausal women".
- The Washington State Health Care Authority's review on "Vitamin D screening and testing" (2018) states that "There are questions about the accuracy and usefulness of tests for Vitamin D levels, especially in healthy subjects. Assessing vitamin D levels may be useful to influence diagnostic or treatment decisions in some circumstances, though the usefulness of testing is uncertain in others".
- The Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE)'s position statement: on "Clinical Management of Vitamin D Deficiency in Adults" (Cesareo et al, 2018) stated that "Healthy people should not be screened by the 25-hydroxy-vitamin D assay; and no routine monitoring 25-hydroxy-vitamin D is suggested during vitamin D treatment due to its large therapeutic index".

Commercial Medical Coverage Policy Highlights
aetna®

Vitamin D Testing

CPT(s): 82306 / 82652

Quest Diagnostics™

The ICD-10 codes listed below are the top diagnosis codes currently utilized by ordering physicians for the tests highlighted above that are also listed as medically supportive under **Aetna** coverage policy. **If you are ordering these tests for diagnostic reasons that are not covered under the Aetna policy, patients may be responsible for payment.**

Medical coverage policy

Effective Date	02/18/2019
Next Review Date	11/11/2019
Coverage Policy Number	0945

Full vitamin D Aetna coverage policy ►

Code	Description
E55.9	Vitamin D deficiency, unspecified
Z79.899	Other long term (current) drug therapy
M81.0	Age-related osteoporosis without current pathological fracture
N18.3	Chronic kidney disease, stage 3 (moderate)
E66.9	Obesity, unspecified Obesity
E66.01	Morbid (severe) obesity due to excess calories
Z98.84	Bariatric surgery status
E83.52	Hypercalcemia
E66.3	Overweight
E21.3	Hyperparathyroidism, unspecified
N18.2	Chronic kidney disease, stage 2 (mild)
N18.4	Chronic kidney disease, stage 4 (severe)
E05.90	Thyrotoxicosis, unspecified without thyrotoxic crisis or storm
M06.9	Rheumatoid arthritis, unspecified
B20	Human immunodeficiency virus [HIV] disease
N18.9	Chronic kidney disease, unspecified
K91.2	Postsurgical malabsorption, not elsewhere classified
E66.09	Other obesity due to excess calories
E83.51	Hypocalcemia
M81.0	Other osteoporosis without current pathological fracture

Visit **QuestDiagnostics.com/commercialcoverage** to view additional commercial insurance limited coverage tests, reference guides, and policy information.

Last updated: 4/1/2019

Disclaimer:
This diagnosis code reference guide is provided as an aid to physicians and office staff to help inform you of the limited coverage policy. Diagnosis codes must be applicable to the patient's symptoms or conditions and must be consistent with documentation in the patient's medical record. Quest Diagnostics does not recommend any diagnosis codes and will only submit diagnosis information provided to us by the ordering physician or his/her designated staff. The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed. Please see the payer's full vitamin D coverage policy for a complete list of references.

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