In 2014, the United States Preventive Services Task Force (USPSTF) concluded that among community-dwelling asymptomatic adults aged 18 years and older, there was insufficient evidence (i.e., I statement) to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. Over the past 7 years, many randomized clinical trials (RCTs) have evaluated vitamin D supplementation for improving primary or secondary outcomes of cardiovascular disease, cancer, diabetes, depression, bone health, and falls, necessitating a reevaluation of whether screening for vitamin D insufficiency might be worthwhile. The evidence is still not there to inform this decision.

Screening is the routine evaluation of an asymptomatic population with the goal of detection of a disease, when the natural course of that disease can be altered by early intervention. The benefits of screening in a population need to outweigh any potential harms that might arise from false positive tests, inappropriate downstream testing, and overtreatment of so-called pseudodisease. Thus, the rationale for screening a broad population by measuring blood 25-hydroxyvitamin D (25(OH)D) levels would be to identify a deficiency state, with the expectation that eliminating the deficiency in individuals (through an intervention) will improve health.

In epidemiological studies, low blood levels of 25(OH)D have consistently been a factor strongly associated with many health outcomes, such as depression, fractures, frailty, falls, diabetes, hypertension, cardiovascular diseases, cancer, and others. However, associations do not equal causation, and low 25(OH)D status might reflect a poorer health status in general owing to reverse causation or confounding by other health or behavioral factors. For example, individuals with obesity, reduced outdoor physical activity, and less healthy diets are more likely to have lower 25(OH)D levels. Importantly, high quality RCTs have not found that supplementation with vitamin D meaningfully mitigates these outcomes. Even the benefit of vitamin D on bone health and musculoskeletal outcomes has been challenged, and its efficacy may depend on whether concomitant calcium supplementation is given. While many of these RCTs did not specifically enroll individuals with a documented deficiency state, post hoc subgroup analyses failed to find outcome benefit for vitamin D supplementation among those with low 25(OH)D levels (i.e., <20 ng/mL [to convert to nanomoles per liter, multiply by 2.496]), with less data available for the subgroup of those below 12 ng/mL.

Might the commonly used vitamin D measure be the wrong measure? In the blood, 25(OH)D is the major circulating form and reflects both endogenous and exogenous sources. It has a half-life of 2 to 3 weeks and has long been considered to be the best marker of vitamin D status, although 25(OH)D is largely biologically inert. The activated form, 1,25-dihydroxyvitamin D (also known as calcitriol), confers the biological activity through the binding of the vitamin D nuclear receptor in the small intestine, kidneys, and other tissues. However, given its short half-life and tightly controlled regulation, calcitriol levels do not adequately reflect vitamin D stores. Furthermore, it has been challenging to measure 25(OH)D accurately, with substantial overestimation or underestimation of 25(OH)D levels with the most commonly used immunoassays. This has improved with implementation of the Vitamin D Standardization Program and, currently, liquid chromatography-mass spectrometry is the criterion standard, although it is unknown how broadly this is used across commercial laboratories. Additionally, 25(OH)D circulates predominately in the bound form, with...
only 10% to 15% being bioavailable; current clinical assays do not discern between bound and bioavailable states. Other novel vitamin D markers, such as free vitamin D, may more adequately reflect vitamin D status and thus more accurately identify those who would benefit from vitamin D supplementation; this has been an active area of investigation.3,7

Yet, what constitutes 25(OH)D sufficiency? The guidelines are generally in agreement that evidence is scant for better health, aside from skeletal health, in individuals with higher 25(OH)D levels; thus, recommendations for optimal 25(OH)D levels are benchmarked for optimizing bone health. Vitamin D deficiency results in decreased intestinal absorption of calcium and phosphate from dietary sources, leading to increased parathyroid hormone levels. Secondary hyperparathyroidism in turn results in calcium mobilization from the skeleton and phosphate wasting from the kidney, adversely impacting bone health. Vitamin D deficiency is also associated with muscle weakness, which may further contribute to an increased risk of fracture.

The Institute of Medicine16 has defined vitamin D deficiency as 25(OH)D less than 12 ng/mL, with levels greater than 20 ng/mL being considered adequate for bone and overall health; whereas the Endocrine Society14 has classified 25(OH)D less than 20 ng/mL as deficient and greater than 30 ng/mL as optimal. These cutoffs for vitamin D deficiency have been defined, in part, based on levels at which parathyroid hormone levels begin to normalize. A prominent issue with using 25(OH)D as a marker of bone health status is the paradoxical findings by race. Black adults living at northern latitudes have lower 25(OH)D levels than lighter-skinned individuals owing to reduced UV-B absorption, yet Black women generally have lower rates of fracture and higher bone mineral density than similarly aged White women.17 Thus, sufficiency may be hard to define at a population level.

Approximately half of adults would be considered vitamin D deficient or insufficient using current definitions, with higher rates in racial/ethnic minorities, including Black and Hispanic individuals,18 suggesting wide-spread vitamin D deficiency.15 There are unclear harms associated with assigning a diagnosis of vitamin D deficiency to asymptomatic people in regards to patient anxiety, costs of treatment for vitamin D repletion and monitoring of follow-up levels, and the pill burden of supplementation.11 Additionally there is the rare but real potential for vitamin D toxic effects with overtreatment, leading to the adverse clinical manifestations that stem from hypercalcemia and hypercalciuria. Even without overt hypercalcemia, some studies have suggested that daily vitamin D supplementation of greater than 4000 IU may even reduce bone health and increase fall risk.5,6 Combined vitamin D and calcium supplementation may increase the risk for kidney stones. Thus, vitamin D supplementation above the recommended daily allowances should not be considered as a benign intervention.

We note that the latest USPSTF statement about insufficient evidence relates to population-based screening.9,10 The recommendation does not preclude targeted measurement of 25(OH)D in the individual patient, where it is thought that the risk-to-benefit ratio may favor testing to guide intervention or risk stratification.9,10 This might include individuals with osteoporosis, chronic kidney disease, malabsorption syndromes, or medication use (ie, glucocorticoids) and pregnant and lactating women. This is concordant with recommendations from the Endocrine Society,14 which also concluded that there was insufficient evidence for broad screening of populations but that measurement could be considered selectively among individuals at high risk for deficiency.

Thus, in 2021, the USPSTF recommendation remains an I statement: the evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.9,10 The biggest challenge remains that no studies have specifically evaluated the direct benefits or harms of screening for vitamin D deficiency. To move the needle, further data are needed to determine whether a broad populated-based screening approach is superior to a selective targeted measurement approach or to no measurement of 25(OH)D at all. Ideally, an RCT evaluating such a screening approach would generate the strongest evidence, yet would be challenging to conduct. A screening trial would need to carefully choose the clinical outcomes to target for evidence of benefit (bone health vs other). Additionally, the needed duration of a trial is uncertain, and there is likely to be substantial heterogeneity in benefits of screening among subgroups. Over the past 7
years, despite RCTs of vitamin D supplementation, everything has changed and yet nothing has changed regarding the approach to screening for vitamin D deficiency.

REFERENCES

