Increasing requests for vitamin D measurement: costly, confusing, and without credibility

"Sunbathing boosts men's sex drives" proclaimed newspaper reports.[1,2] This headline was extrapolated from a cross-sectional study showing that serum 25-hydroxyvitamin D (25OHD) concentrations—a biochemical measure of vitamin D status—correlate to circulating testosterone concentrations in men referred for angiography, but neither sun exposure nor sex drive was directly assessed.[3] This anecdote epitomises what has become a bandwagon of vitamin-D-related epidemiological research fuelling easily accessible headlines in lay media. Such frequent and prominent headlines have cast vitamin D in the role of a putative miracle cure that can prevent and treat a burgeoning list of chronic disorders such as cardiovascular disease, diabetes, and cancer.

This media coverage has caused a massive rise in demand for measurement of blood concentrations of 25OHD from the public and physicians. Glasgow Royal Infirmary—the main provider of 25OHD tests in Scotland—has seen a rise in vitamin D test requests from 18 682 in 2008, to 37 830 in 2010, which has resulted in a longstanding backlog of 2000 tests. Similarly, a hospital in London, UK, had a sixfold increase in 25OHD test requests over 4 years, rising from 7537 tests in 2007, to nearly 46 000 in 2010 (personal communication). Similar trends have been noted in other countries—eg, Canada and the USA.[4,5] To match demand, manufacturers (eg, Abbott, Roche, and Siemens) are developing immunoassays (similar to liquid chromatography tandem mass spectrometry gold standard) for clinical use, and promoting them widely in North America, Europe, and elsewhere. A 25OHD test costs the UK National Health Service around £20. The economic burden of widespread routine vitamin D testing in the UK and elsewhere is therefore substantial.

But is this skyrocketing of 25OHD test requests and related costs justified? The prevalence of apparent vitamin D inadequacy is high in the UK.[6,7] For example, roughly 50% of 45-year-old UK adults (1958 British birth cohort) were vitamin D insufficient during winter months, with the greatest inadequacy recorded in Scotland (average concentration 35 nmol/L).[7] A patient in the UK attending a general practitioner in winter is therefore likely to be vitamin D insufficient (serum concentrations <50 nmol/L) or deficient (serum concentrations <25 nmol/L). But how should general practitioners interpret such test results? The key question is: does knowing the result usefully improve clinical practice and patient wellbeing?

To address this issue, whether vitamin D inadequacy has a predisposing relation with health consequences that could be avoided by intervention (eg, supplementation, diet, or sun exposure) needs to be established. Most evidence promoting a role for vitamin D in chronic disease has been extrapolated from epidemiological studies, but these results are often limited by factors such as potential reverse causality and residual confounding—particularly relevant limitations for vitamin D as a biomarker of health (table). Therefore, any conclusions about causality extrapolated from observational data are premature.[10]

The only reliable tests of causality are randomised trials. The effectiveness of vitamin D supplementation in rickets and osteomalacia has been proven.

	Why important for vitamin D?	Examples
Confounding and residual confounding	Many risk factors are related to both low 25OHD and poor health outcomes; statistical models might be incomplete if such factors are not measured, or measured imprecisely	Little physical activity (outdoor activity often related to sunlight exposure); low socioeconomic status; obesity; smoking; season
Reverse causality	Sunlight exposure is a major determinant of circulating-25OHD concentrations; pain or illness can limit sunlight exposure through inactivity, and thus disease could cause inadequacy rather than the reverse	Clinical diagnosis of many disorders (eg, multiple sclerosis) can be preceded by a period of preclinical disease when little time is spent outdoors; acute inflammation can drive down circulating 25OHD concentrations so that in acute illnesses or many hospitalised patients, low measurements are secondary to an acute-phase response
Publication and citation bias	Null or negative findings are less likely to be published, especially when overwhelming perception is of a positive association; thus, investigators are less likely to pursue publication or persist after manuscript rejection than if results were positive; null findings that are published are not frequently cited and result in little media interest, and therefore perception of the weight of evidence can be heavily skewed	Marniemi and colleagues' 2005 report[8] of no association of 25OHD with 130 cases of myocardial infarction in elderly people has been cited 33* times in Web of Science; by contrast, Wang and co-workers' 2008 article[9] reporting 25OHD inadequacy associated with 120 cases of cardiovascular disease in Framingham offspring has been cited 409* times

25OHD=serum 25-hydroxyvitamin D. *As of Nov 28, 2011.

Table: **Potential limitations in making causal inferences from observational epidemiology for vitamin D**

Vitamin D supplementation in appropriate doses with concomitant calcium supplements might reduce the risk of fractures in elderly people at risk of osteoporosis.[11] However, the need to measure circulating vitamin D in people with osteoporosis (diagnosed on the basis of dual energy x-ray imaging scans) is questionable because treatment is likely to include vitamin D supplements irrespective of the result. Meanwhile, convincing evidence that vitamin D supplements reduce the risk of cardiovascular disease or diabetes, or lower glucose concentrations in patients with diabetes, does not exist.[12] Proponents argue that longer trials with higher doses of vitamin D than have been tested heretofore are needed, and we agree. However, until the investigators of such trials report their results, we must remain cautious about the recommendation of widespread supplementation for chronic disease prevention. The reports[13] of increased rates of infantile hypercalcaemia in the UK in the 1950s after overenthusiastic food fortification with vitamin D show the importance of caution—a point re-emphasised in 2011.[14]

In short, widespread testing of asymptomatic people's vitamin D status is unhelpful. Economic constrictions are a concern for health-care providers worldwide. Until the results of large randomised trials are reported, we urge all clinicians to stop and think critically before measuring 25OHD, particularly in conditions not linked to bone disease. Such practice will avoid many unnecessary tests, reduce laboratory backlog, and save a lot of health-service time and money without affecting patients' health.

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1 The Telegraph. Sunbathing "boosts men's sex drive". http://www.telegraph.co.uk/health/healthnews/7127197/Sunbathing-boosts-mens-sex-drive.html (accessed Dec 19, 2011).

2 Mail Online. Sunbathing "boosts men's sex drives": testosterone levels rise with vitamin D increase. http://www.dailymail.co.uk/health/article-1247793/Sunbathing-boosts-mens-sex-drives-Testosterone-levels-rise-Vitamin-D-increase.html (accessed Dec 19, 2011).

3 Wehr E, Pilz S, Boehm BO, März W, Obermayer-Pietsch B. Association of vitamin D status with serum androgen levels in men. *Clin Endocrinol (Oxf)* 2010; **73:** 243–48.

4 Brophy Marcus M. Vitamin D tests soar as deficiency, diseases linked. July 14, 2008. http://www.usatoday.com/news/health/2008-07-13-vitamin-d-tests_N.htm (accessed Nov 18, 2011).

5 CBC News. Calgary vitamin D test numbers soar. http://www.cbc.ca/news/canada/calgary/story/2011/01/28/calgary-vitamin-d-blood-testing.html (accessed Nov 18, 2011).

6 Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010; **340:** b5664.

7 Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr* 2007; **85:** 860–68.

8 Marniemi J, Alanen E, Impivaara O, et al. Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr Metab Cardiovasc Dis* 2005; **15:** 188–97.

9 Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; **117:** 503–11.

10 Welsh P, Peters MJ, Sattar N. Is vitamin D in rheumatoid arthritis a magic bullet or a mirage? The need to improve the evidence base prior to calls for supplementation. *Arthritis Rheum* 2011; **63:** 1763–69.

11 DIPART (vitamin D individual patient analysis of randomized trials) group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ* 2010; **340:** b5463.

12 Shapses SA, Manson JE. Vitamin D and prevention of cardiovascular disease and diabetes: why the evidence falls short. *JAMA* 2011; **305:** 2565–66.

13 Lightwood R. Hypercalcaemia in infants and vitamin D. *BMJ* 1956; **2:** 149.

14 Schlingmann KP, Kaufmann M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *N Engl J Med* 2011; **365:** 410–21.

Idrabiotaparinux treatment for venous thromboembolism

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Standard treatment of venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is started with a rapidly acting parenteral anticoagulant such as heparin or low-molecular-weight heparin for at least 5 days and is overlapped with a vitamin K antagonist such as warfarin.[1] Warfarin is then continued for at least 3 months. Although effective, this drug has important limitations. Lifestyle changes are necessary because of interactions with food, alcohol, and other drugs, and the unpredictable anticoagulant effect of warfarin necessitates frequent coagulation monitoring and dose adjustments to optimise the balance between efficacy and safety. Warfarin reduces the risk of recurrent venous thromboembolism by up to 90%, but there is a catch-up effect if warfarin is stopped in patients with unprovoked venous thromboembolism. This effect means that, by 2 years, the risk of recurrence in patients treated for 3 months is akin to that in patients treated for 12 months.[2] Consequently, some experts recommend life-long warfarin therapy for patients with unprovoked venous thromboembolism. The complexity of such treatment