MBS Review

Vitamin D Testing

Protocol

July 2013
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,25-(OH)2D</td>
<td>1,25 Dihydroxy vitamin D</td>
</tr>
<tr>
<td>25-(OH)D</td>
<td>25 Hydroxy vitamin D</td>
</tr>
<tr>
<td>µg</td>
<td>Micro gram (unit of measurement)</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CMFM</td>
<td>Comprehensive Management Framework for the MBS</td>
</tr>
<tr>
<td>CRC</td>
<td>Consultation Review Committee</td>
</tr>
<tr>
<td>Department</td>
<td>Department of Health and Ageing</td>
</tr>
<tr>
<td>HTA</td>
<td>Health technology assessment</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography-Mass spectrometry</td>
</tr>
<tr>
<td>MSAC</td>
<td>Medical Services Advisory Committee</td>
</tr>
<tr>
<td>MBS</td>
<td>Medicare Benefits Schedule</td>
</tr>
<tr>
<td>MESP</td>
<td>MSAC Expert Standing Panel</td>
</tr>
<tr>
<td>NIST</td>
<td>National Institute of Standards and Technology</td>
</tr>
<tr>
<td>nmol/L</td>
<td>Nano mole per litre (unit of measurement)</td>
</tr>
<tr>
<td>OHTAC</td>
<td>Ontario Health technology advisory committee</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>PICO</td>
<td>Population, intervention, comparator, outcome</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid Hormone</td>
</tr>
<tr>
<td>RCPAQAP</td>
<td>Royal College of Pathologists of Australasia Quality Assurance Program</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trials</td>
</tr>
<tr>
<td>RDA</td>
<td>Recommended Dietary Allowance</td>
</tr>
<tr>
<td>UVB</td>
<td>Ultraviolet B</td>
</tr>
</tbody>
</table>
INTRODUCTION TO MBS REVIEWS

In the 2011-12 Budget, the Australian Government committed to continue the systematic review of Medicare Benefits Schedule (MBS) items to ensure that they reflect contemporary evidence, improve health outcomes for patients and represent value for money under the Comprehensive Management Framework for the MBS (CMFM).

Reviews support the public funding of evidence-based, cost-effective clinical practice through the MBS.

The MBS Reviews process includes the consideration of policy issues related to services funded under the MBS and is designed to have flexibility depending on the complexity of the issues pertaining to the particular review. For example, where there is a single MBS item or service the review may be focussed and timeframes may not be as exhaustive as a review that include multiple MBS items with related policy issues or non MBS issues. Non MBS issues that require a different process (such as pharmaceuticals or prostheses), and policy issues that are not appropriately dealt with by the Medical Services Advisory Committee (MSAC) process will be identified and addressed in separate processes which will feed into the MBS process where appropriate.

The first stage of a review is the identification of the scope. Reviews with single MBS services/issues will follow the MBS pathway and will be considered by MSAC using the MSAC process. For reviews with multiple MBS services or a specialty and policy issues, the scope and pathway (MBS pathway and policy pathway) will be confirmed by the Consultation Review Committee (CRC), a time limited committee of nominated experts, determined and chaired by the Department of Health and Ageing (the Department).

The MBS pathway will follow the MSAC process and include the:
- development of a protocol;
- collection and evaluation of evidence; and
- advice and recommendations to the Minister through the Department.

The pathway for policy and other issues depends on the issues identified in the scope. The CRC will provide expertise to the Department in the development of the policy issues paper. There will be interactions between the MBS and policy pathways and stakeholders will be consulted throughout the review process; ensuring alignment of processes and consistency in deliberations.

The engagement with stakeholders is a critical component of the reviews process and issues will be dealt with in a consultative fashion. The role of the CRC is advising the Department on policy issues and the MSAC and its subcommittees is advising on MBS matters. The review process is flexible, ensuring that new and emerging issues and feedback from the CRC, MSAC or public consultations can be incorporated into the reports.

The advice and recommendations provided by the CRC and MSAC to the Department informs the advice for the Minister.
Reviews will:
- have a primary focus on improving health outcomes and the financial sustainability of the MBS, through consideration of areas potentially representing:
  - patient safety risk;
  - limited health benefit; and/or
  - inappropriate use (under or over use)
- be evidence-based and fit-for-purpose;
- be conducted in consultation with key stakeholders including, but not limited to, the medical profession and consumers;
- include opportunities for public submission;
- be published; and
- use Government resources efficiently.

Objectives of the Review
To ensure the clinical and financial sustainability of the MBS, reviews will assess specific services or MBS item(s) and associated policy issues in a focused, fit-for-purpose, evidence based process. Findings will recognise that MBS funding should align with contemporary evidence, reflecting appropriate patient groups and best clinical practice.

Purpose of the Protocol
This document outlines the methodology for providing evidence based analysis to support the review of services for the vitamin D testing, specifically the frequency of testing and the appropriate patient population for testing. The Protocol outlines the review methodology, clinical research questions the review will focus on, methods to identify and appraise the evidence and key stakeholder groups and experts to be consulted during the conduct of the review.

Stakeholder Consultations
The Department is responsible for the review process including documents developed for policy and MBS issues and contractual arrangements for the development of the protocol and other report documents for the review. This includes ensuring that the relevant documents are available online for public consultation at the appropriate time and that comments are incorporated into informing the review process.

The Department’s management of stakeholder engagement and negotiations with the relevant medical craft groups and key stakeholders will ensure the review findings are informed by consultations.

Following the finalisation of the review process, the advice to the Minister for Health on the findings of the review will be informed by the review reports, advice and recommendations from MSAC and CRC, public consultations and also other information that is relevant to the review including budgetary considerations.

The following questions, to be addressed as part of the stakeholder consultations, are:
(1) What are the appropriate clinical indications for medically necessary vitamin D testing?
(2) What is the strength of evidence for the effectiveness of vitamin D testing in improving outcomes in each target population across the patient journey?
(3) What are the safety and quality implications (including morbidity, mortality and patient satisfaction) associated with vitamin D testing in each target population?

(4) How do safety and quality outcomes of vitamin D testing vary according to:
   a. the difference in testing methodologies?
   b. frequency of testing?

(5) What is the evidence regarding the cost implications associated with vitamin D testing in each target population compared with not testing?

(6) Is the current MBS fee appropriate?

Public Consultations
The invitations to the general public (which include all stakeholders - patients, consumer groups, individual service providers, health professionals and manufacturers) to provide comment on the draft documents during the review process are critical to the review process. The documents will be available on the MSAC website (www.msac.gov.au) inviting the public to submit written comments over a four week period. The purpose of the feedback is to inform the final report and recommendations to the Minister.

Medical Craft Groups / Key Stakeholders
The following clinical craft groups and key stakeholders have been identified as having an interest in this review:
- Osteoporosis Australia;
- IVD Australia;
- Australia and New Zealand Bone and Mineral Society;
- Endocrine Society of Australia;
- National Prescribing Network;
- Australian Association of Pathology Practices;
- Australian Medical Association;
- Consumers Health Forum of Australia;
- National Coalition of Public Pathology;
- Royal Australian College of General Practitioners; and
- Royal College of Pathologists of Australasia.
BACKGROUND

Vitamin D metabolism and function

Vitamin D is a lipid soluble vitamin that acts as a hormone. It is synthesised in the skin through exposure to ultraviolet B light (UVB) radiation from sunlight and may also be obtained from dietary sources and supplements. There are two forms of vitamin D:

- vitamin D2 (also known as ergocalciferol), which is present in plants (e.g. mushrooms); and
- vitamin D3 (also known as cholecalciferol), which is the main form obtained from animal sources (such as some fish) and exposure to sunlight. Vitamin D supplements are composed of the D3 form and are manufactured by the irradiation of 7-D dehydrocholesterol extracted from lanolin found in sheep's wool.

Figure 1 shows that cutaneous synthesis of vitamin D is triggered by the skin’s exposure to UVB (wavelength 290-315 nm) which converts 7-D dehydrocholesterol present in the skin into previtamin D3, and which is then converted into vitamin D3. Experimental data indicates that exposure of around 15% of the body surface (arms and hands or equivalent) near the middle of the day will result in the production of about 1000 IU (25 μg) of vitamin D. Achieving this exposure on most days should generally, though not always, be sufficient to maintain vitamin D levels in the body. Factors such as seasons and latitude can play a role in vitamin D synthesis, for example less vitamin D is synthesised in winter, particularly at latitudes further from the equator.

![Figure 1: Synthesis of vitamin D](http://gardenofeaden.blogspot.com.au/2012/02/what-is-vitamin-d-deficiency.html)

Vitamin D from diet, supplements, or sunlight exposure first undergoes a hydroxylation reaction in the liver (Figure 1), producing 25-hydroxyvitamin D (25-(OH)D) (also known as...
calcidiol). This is the major circulating form and the metabolite routinely used to assess overall vitamin D status. Further hydroxylation occurs in the kidney to form the hormonal and biologically active 1,25-Dihydroxyvitamin D, also known as calcitriol.\(^5\) This hydroxylation step can also occur in other tissues.\(^2, 8\) The renal synthesis of 1,25-dihydroxyvitamin D is regulated by plasma parathyroid hormone (PTH), serum calcium and phosphorus levels.\(^9\)

The active compound of vitamin D promotes intestinal calcium and phosphate absorption and is important in maintaining adequate calcium levels for bone mineralisation, bone growth and remodelling, and to prevent hypocalcemic tetany (i.e. this is an uncommon condition caused by an abnormally low level of calcium in the blood).\(^1, 3, 10\) Serum PTH has an inverse correlation with absorbed calcium.\(^11\) Vitamin D deficiency reduces the efficiency of calcium absorption from the intestines and therefore indirectly result in increased serum PTH\(^11\), which may lead to the mobilisation of calcium from the bone.\(^12\)

**Vitamin D dietary sources, fortification and supplements**

Vitamin D (D3) is naturally present in small quantities in certain food such as fatty fish (salmon, herring, tuna, sardines etc.), egg yolks, fish liver oil, and certain types of mushrooms (see Table 1).\(^3, 13\) However, most adults are unlikely to obtain more than 5%–10% of their vitamin D requirement from dietary foods and is therefore insufficient to meet daily requirements.\(^14\) Thus, most vitamin D is obtained from exposure to sunlight, some fortified or unfortified foods, and/or vitamin D supplements.

<table>
<thead>
<tr>
<th>Type of food</th>
<th>Estimated vitamin D content (International Unit IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon (fresh, farmed), 3.5 oz (99 grams)</td>
<td>100-250 IU vitamin D3</td>
</tr>
<tr>
<td></td>
<td>600 – 1,000 IU vitamin D3 (wild)</td>
</tr>
<tr>
<td>Mackerel, (canned), 3.5 oz (99 grams)</td>
<td>250 IU vitamin D3</td>
</tr>
<tr>
<td>Cod liver oil, 1 teaspoon (also contains vitamin A)</td>
<td>400-1,000 IU vitamin D3</td>
</tr>
<tr>
<td>Tuna (canned), 3.6 oz (100 grams)</td>
<td>230 IU vitamin D3</td>
</tr>
<tr>
<td>Shiitake mushrooms (fresh), 3.5 oz</td>
<td>100 IU vitamin D2 (fresh)</td>
</tr>
<tr>
<td></td>
<td>1,600 IU vitamin D2 (sun-dried)</td>
</tr>
<tr>
<td>Egg yolk (1 unit)</td>
<td>20 IU vitamin D3 or D2</td>
</tr>
</tbody>
</table>

Food fortification is defined as the process of adding micronutrients, such as vitamins and minerals, to food as permitted by the Food Standards Code.\(^15\) Regulations regarding the fortification of foods with vitamin D varies between countries. In Australia, mandatory fortification regulations require the addition of vitamin D to margarines and spreads.\(^15\) In Canada, which has similar regulations to the United States, vitamin D fortification of milk (including evaporated and powdered milk), soy milk, and margarine is mandatory.\(^13\) One serving (250 ml) of milk contains approximately 44% of the 200 IU adequate daily intake of vitamin D.\(^13\) Vitamin D fortification is also permitted for orange juice, meal replacements, nutritional supplements, and formulated liquid diet.\(^13, 16\) However, and despite vitamin D mandatory fortification of foods in North America, a large proportion of the American and Canadian populations are vitamin D deficient, indicating that limited voluntary fortification has little impact at a population level.\(^13, 17\)

It is acknowledged that the current (2006) guidelines for recommended dietary intakes (i.e. adequate intakes) of vitamin D in Australia and New Zealand\(^18\) are out of date.\(^19\) The recently revised recommended daily allowances (RDAs) for vitamin D in the US are 600 IU
(15 μg) for people aged 1–70 years and 800 IU (20 μg) for those aged ≥ 71 years, with an upper limit (that includes a generous safety factor) of 4000 IU (100 μg).\(^{(20)}\)

Vitamin D synthesis through the skin can be influenced by several factors such as number of sunshine hours, time of day, season, latitude and skin colour (due to the amount of melanin in skin). All these factors determine the amount of UBV that reaches the skin. The season is an important predictor of serum 25-(OH)D levels.\(^{(21, 22)}\) In an Australian study that looked at three populations of women in three locations across Australia and covering a broad latitudinal range (Tasmania, Geelong, and Queensland), vitamin D insufficiency was common in winter and spring regardless of latitude.\(^{(22)}\) However, latitude plays a significant role in serum 25-(OH)D levels, and higher prevalence of vitamin D deficiencies is reported in people living at increasing distances from the Equator.\(^{(23)}\)

Vitamin D toxicity is a rare condition that can be caused by excess oral or intramuscular administration of vitamin D. The current policy of the Institute of Medicine (IOM) has set the tolerable upper intake level for vitamin D at 100 micrograms (µg) (4000 IU)/d, defining this as “the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population”.\(^{(20)}\) Vitamin D toxicity cannot be caused by prolonged exposure of the skin to sunlight, which produces 25-(OH)D amounts equivalent to daily oral consumption of 250 μg (10,000 IU)/d. The main symptoms with hypervitaminosis D are hypercalciuria (i.e. a condition of elevated calcium in the urine), hypercalcaemia (i.e. a condition of elevated calcium in the blood), and calcification of soft tissues and kidney.\(^{(24)}\) Hypercalcaemia is not seen until serum 25-(OH)D concentrations have consistently been above 375–500 nmol/L.\(^{(25, 26)}\)

**Vitamin D testing**

A vitamin D test measures either 25-(OH)D, the major circulating metabolite to assess vitamin D status, or 1,25-Dihydroxyvitamin D\(^{(27)}\), to assess serum vitamin D level and metabolism. The 25-(OH)D metabolite has an estimated half-life of approximately two to three weeks, \(^{(5, 27, 28)}\) and provides a measure of the vitamin D originating from both cutaneous production and dietary/supplement sources.\(^{(5)}\) Vitamin D stored in other body tissues are, however, not reflected in the serum 25(OH)D levels.\(^{(5)}\) The 1,25-dihydroxyvitamin D has a half-life of 15 hours and therefore serum levels of this metabolite do not accurately indicate the individual’s vitamin D status. Since it is closely regulated by PTH and the intake of calcium and phosphate, serum levels of 1,25-Dihydroxyvitamin D\(^{(5, 13)}\) may be normal in individuals with vitamin D deficiency\(^{(29)}\).

There are two different assays for measuring serum levels of 25-(OH)D \(^{(30-32)}\):

- **liquid chromatography-tandem mass spectrometry (LC-MS):** this is a sensitive and reasonably specific method for the detection of 25-(OH) D (in its two analyte forms D2 and D3) based on their respective chemical properties. This method has been referred to as a ‘gold standard’ test, but it is slow and requires expensive equipment and skilled staff.
- **commercial immunoassays either using radioactive markers or chemical markers** (e.g. the Abbott Architect, Diasorin Liaison and the Siemens Centaur): are automated immunoassays to measure total vitamin D levels. These assays may be cheaper and quicker to conduct (about half the cost of liquid chromatography). Most are less sensitive as they do not distinguish between the two metabolites of vitamin D.
It is not clear from the literature if the detection of both D2 and D3 metabolites has any clinical relevance. A systematic review and meta-analysis on the comparison of vitamin D2 and D3 supplementation in raising serum 25-(OH)D status indicated that vitamin D3 is more efficacious at raising serum 25-(OH)D concentrations than is vitamin D2. Moreover, some current automated immunoassays have a limited capacity to detect 25-(OH)D2. It is currently accepted in Australia that total 25-(OH)D measurement is appropriate to judge a patient’s vitamin D status.

**Accuracy and precision of Vitamin D testing**

Different immunoassays are readily available for measurement of 25-(OH)D3. Prior to the recent introduction of the standard reference material for 25-(OH)D, called SRM 972 introduced from the National Institute of Standards and Technology (NIST), there were numerous publications reporting that different immunoassays may be yielding different results, with inter-assay variation reaching up to 25% at low serum 25-(OH)D levels (15 nmol/L). However, with the introduction of the reference standard, the accuracy of the different immunoassays for the measurement of 25-(OH)D in serum should serve as an adjunct to quality assurance programs for vitamin D measurements.

The performance of radioimmunoassay and enzyme-linked assays is acceptable, however, the bias and imprecision of many automated methods may be problematic at the lower, clinically important and analytically important range (< 50 nmol/L) of the assay. The new reference standard is available at four different concentrations (called Level 1 – Level 4 by the manufacturer).

The first SRM 972 concentration (Level 1) is prepared from “normal” human serum and is the only standard that has not been altered through dilutions or enrichments (59.6 nmol/L). The second concentration (called Level 2) was prepared by diluting Level 1 with horse serum to achieve a lower 25(OH)D concentration, whereas Level 3 and Level 4 had 25 (OH)D3 added to them. The development of this reference standard for vitamin D in blood serum has assisted laboratories to validate the accuracy of their test methods, as well as to validate new analytical methods as they are developed.

In addition, all Australian and New Zealand laboratories (including those offering 25-(OH)D testing) are required to be enrolled in external proficiency programs (such as the Royal College of Pathologists of Australasia Quality Assurance Program (RCPAQAP)), which allow each laboratory to monitor its performance compared with its peers. These standardisation efforts are essential to the reliable diagnosis, evaluation, and treatment of vitamin D deficiency in a population and help clinicians to more accurately interpret the results from vitamin D testing.

**Serum Vitamin D target values**

Some evidence suggests that optimal mineral metabolism, bone density and muscle function is achieved at serum 25-(OH)D concentrations of greater than 50-60 nmol/L. However, an optimal serum concentration of vitamin D has not been established and this value may vary across different stages of life. Some authors believe that target serum levels should be above 50 nmol/L, others believe that it should be above 75 nmol/L. One study indicated that 25-(OH)D concentrations <75 nmol/L showed increased unmineralised bone matrix, making this value an appropriate cut-off for optimal bone health. This however may require vitamin D supplementation.
Vitamin D deficiency is defined as a serum 25-(OH)D levels below 25 nmol/L \(^{(3, 4, 27)}\), based primarily on the risk of rickets in infants and osteomalacia in adults.\(^{(44)}\) Although mild Vitamin D deficiency is defined as a serum level below 50 nmol/L.\(^{(19)}\) Severe deficiency has also been defined as a serum level below 12.5 nmol/L.\(^{(1, 2, 10)}\) Table 2 summarises serum vitamin D concentrations and health.

```
<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>Serum vitamin D concentrations nmol/L*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Sufficient</td>
<td>50-75</td>
</tr>
<tr>
<td>Mild deficiency</td>
<td>25-49</td>
</tr>
<tr>
<td>Moderate deficiency</td>
<td>12.5-24</td>
</tr>
<tr>
<td>Severe deficiency</td>
<td>&lt; 12.5</td>
</tr>
</tbody>
</table>
```

*1 nmol/L = 0.4 ng/ml

Prevalence of Vitamin D Deficiency in Australia

Two publications have attempted to measure the prevalence of vitamin D deficiency in the Australian population. The first study was conducted by the Baker IDI Heart and Diabetes Institute. The population included 11,218 adults aged 25-95 years. The study reported an estimated 31% of adults in Australia have inadequate vitamin D status (serum 25-(OH)D levels < 50 nmol/L) and that 4% of the population had severely deficient levels (serum 25-(OH)D levels < 25 nmol/L). Individuals at greatest risk for deficiency were identified to be women, the elderly, the obese, people doing less than 2.5 hours of physical activity a week, and people of non-European background.\(^{(47)}\) The second study, which assessed 24,819 samples taken from a large reference laboratory in NSW between 1\(^{st}\) July 2008 and 30\(^{th}\) July 2010, reported that up to 58% of Australians are deficient in vitamin D.\(^{(48)}\)

Conditions that may cause vitamin D deficiency

There are several factors reported in the literature that can cause vitamin D deficiency in a diverse group of individuals. Table 3 summarises the risk factors for vitamin D deficiency.

```
<table>
<thead>
<tr>
<th>Reduced sun exposure</th>
<th>Dietary intake</th>
<th>Age and disease conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly(^{(49)})</td>
<td>Exclusive breastfeeding (risk for the infant)(^{(52)})</td>
<td>Obesity(^{(53)})</td>
</tr>
<tr>
<td>Darker skin pigmentation(^{(50)})</td>
<td></td>
<td>Older age worsened by immobility and aging kidneys</td>
</tr>
<tr>
<td>Winter season(^{(51)})</td>
<td></td>
<td>Chronic kidney disease(^{(54, 55)})</td>
</tr>
<tr>
<td>Sunscreen(^{(22)})</td>
<td></td>
<td>Malabsorption syndromes/other conditions: Crohn’s disease, cystic fibrosis, severe liver disease(^{(56)})</td>
</tr>
<tr>
<td>Shift and indoor workers</td>
<td></td>
<td>Drug interactions: anticonvulsants, cimetidine, thiazides, corticosteroids(^{(57, 58)})</td>
</tr>
<tr>
<td>People who habitually wear long sleeves, modest dress</td>
<td></td>
<td>Drugs that decrease absorption: mineral oil, laxatives orlistat, cholestiramine etc.(^{(59)})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genetics(^{(60)})</td>
</tr>
</tbody>
</table>
```
Incidence and prevalence of diseases relevant to the vitamin D testing review

Table 4 presents the incidence and prevalence of clinical conditions where the literature indicates that vitamin D testing is recommended.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Prevalence/incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>The condition where bone is lost at a higher rate than its replacement causing to loss of bone mineral density(^{(61)})</td>
<td>692,000 cases (3.4)(^{(62)})</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Softening of bones, inadequate mineralization of bone matrix, caused by vitamin D deficiency(^{(5, 63)})</td>
<td>Data on prevalence is not available</td>
</tr>
<tr>
<td>Rickets</td>
<td>Inadequate bone mineralisation, disorder affecting growth plate, caused by vitamin D deficiency, leading to soft bones, skeletal deformities, and growth retardation(^{(64)})</td>
<td>Australian Paediatric Surveillance Unit (APSU) study suggests that the overall incidence in children (&lt;\sim 15) years of age in Australia was 4.9/100 000/year(^{(65)})</td>
</tr>
<tr>
<td>Chronic kidney disease (CKD)</td>
<td>Refers to all conditions of the kidney, lasting at least three months, where a person has had evidence of kidney damage and/or reduced kidney function, regardless of the specific diagnosis of disease or condition causing the disease. There are five stages depending on the level of damage(^{(66)})</td>
<td>Stages 1-2: 5.6%(^{(66)}) Stages 3-5: 7.8%(^{(66)})</td>
</tr>
<tr>
<td>Crohn’s disease (and any malabsorption)</td>
<td>An autoimmune disease (where the body’s immune system attacks its own healthy body tissues) affecting the intestines and resulting in chronic inflammation of the gastrointestinal tract(^{(67)})</td>
<td>29.3/100,000 (incidence rate)(^{(68)})</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>A genetic disease affecting the secretory organs, causing thick, sticky mucus to build up in the lungs, digestive tract, and other areas of the body. It is one of the most common chronic lung diseases in children and young adults(^{(69)})</td>
<td>3,200 cases (prevalence)(^{(70)})</td>
</tr>
</tbody>
</table>

There is an increasing number of medical conditions associated with low vitamin D status. Prolonged vitamin D deficiency causes rickets in children\(^{(44)}\) and osteomalacia in adults.\(^{(5)}\) Other symptoms associated with vitamin D deficiency, such as bone pain and muscle weakness, may be attributed to the decline of vitamin D receptors in skeletal muscle associated with ageing.\(^{(71)}\)

Vitamin D deficiency is classified as one of the risk factors for osteoporosis.\(^{(62)}\) Even though osteoporosis does not cause death, osteoporotic fractures can lead to premature deaths among the elderly. In 2007, osteoporosis was listed as the underlying cause of 240 deaths in Australia. Fractures of hip and pelvis (40.5%) and wrist and forearm (17.1%) were the most common sites of minimal trauma fractures in 2007–08. The total direct health expenditure for osteoporosis in 2004-05 was $304 million (Table 5). Over 70% of this was spent to cover the cost of pharmaceutical medicines ($215 million). Surgical and non-surgical procedures to treat fractures in hospitals constitute another large component of this outlay ($35 million, 11.5%).
### Table 5: Direct health expenditure for osteoporosis, 2001-01 and 2004-05\(^{(62)}\)

<table>
<thead>
<tr>
<th>Health service area</th>
<th>2000-01</th>
<th>2004-05</th>
<th>Percent growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted patient services</td>
<td>31.8 m</td>
<td>35.0 m</td>
<td>10.1</td>
</tr>
<tr>
<td>Out-of-hospital medical services</td>
<td>29.4 m</td>
<td>47.3 m</td>
<td>60.8</td>
</tr>
<tr>
<td>Prescription pharmaceuticals</td>
<td>75.5 m</td>
<td>215.0 m</td>
<td>184.8</td>
</tr>
<tr>
<td>Research</td>
<td>2.6 m</td>
<td>7.0 m</td>
<td>169.2</td>
</tr>
<tr>
<td>Total</td>
<td>139.3 m</td>
<td>304.3 m</td>
<td>118.5</td>
</tr>
</tbody>
</table>

Source: AIHW 2009. AIHW Disease Expenditure Database

### Effects of vitamin D on fractures

There are five published meta-analyses studies examining the effect of vitamin D, alone or in combination with calcium on the reduction in the risk of hip fractures.\(^{(72-76)}\) The results of a 2009 systematic review and meta-analysis of postmenopausal women and men over 65 years of age with involutional or post-menopausal osteoporosis found a statistically significant reduction in the risk of hip fractures among those treated with a combination of vitamin D and calcium, versus control.\(^{(73)}\) The authors concluded that there was an indication that vitamin D3 doses between 400 IU and 800 IU plus 1,000 mg of calcium daily result in a decreased risk of hip fractures.\(^{(73)}\) These results were corroborated by four other meta-analyses in the same age group.\(^{(72, 74-76)}\) Two meta-analyses did not find a statistically significant effect of vitamin D alone on hip or non-vertebral fractures, however completing the studies with calcium and vitamin D was stated to be a confounding factor.\(^{(72, 73)}\) An attempt was made in one of the meta-analyses to evaluate the effect of vitamin D in the prevention of osteoporosis in younger women (19-49 years old) but no RCTs conducted among this age group could be identified.\(^{(72)}\)

### Effect of vitamin D on falls

There are several systematic reviews and meta-analysis reporting that circulating 25-(OH)D levels < 60–75 nmol/L have been associated with lower-extremity muscle weakness and impaired balance, and accelerated losses in muscle mass, strength and physical function.\(^{(41, 77)}\)

A minimum serum 25-(OH)D level of 60 nmol/L is required to effectively reduce the rate of falls.\(^{(78)}\) Most evidence indicates that vitamin D (at daily doses of > 800 IU) needs to be combined with adequate calcium (> 1000 mg/day) to reduce the risk of falls (and fractures). Therefore, older people would be recommended to maintain adequate vitamin D and calcium levels to reduce risk of falls.

Annual megadoses of vitamin D are not recommended. A large RCT in older Australian women found that a single annual dose of 500,000 IU vitamin D3 for three to five (3–5) years resulted in a 15% increase in falls and 26% increase in fractures. The increased risk of falls was pronounced in the first three months after taking the dose and three-month post-dose period, when serum 25-(OH)D levels would have been highest.\(^{(79)}\)

### Vitamin D and other diseases

A wide range of diseases have been associated with low levels of circulating serum 25-(OH)D, including cardiovascular,\(^{(80)}\) diabetes,\(^{(81, 82)}\) some cancers,\(^{(83, 84)}\) autoimmune disease,\(^{(85)}\) and some neurological and mental health conditions including schizophrenia.\(^{(87)}\) Three RCTs and two cohort studies evaluated the effects of vitamin D (with or without calcium) on cancer incidence or cancer mortality risk with a mean follow-up of four to seven years. However, many of the studies were observational and their results were inconsistent. Accordingly, proposals that recommend serum 25-(OH)D levels of
75–80 nmol/L or higher, and which serve as a protective factor that prevents the development of diabetes and other diseases are not supported by a significant amount of data from RCTs.\(^{20}\) There are however a few reports that identify vitamin D deficiency as a risk factor to the development of type 2 diabetes. One recent Australian study reported that lower 25(OH)D concentrations were associated with increased Metabolic Syndrome\(^1\) risk and higher waist circumference, serum triglyceride, fasting glucose, and insulin resistance.\(^{81}\)

Another Australian study that evaluated the association between serum 25-(OH)D on five-year incidence of diabetes and insulin sensitivity reported that higher serum 25-(OH)D levels were associated with significantly reduced risk of diabetes in adult men and women.\(^{82}\)

**Service providers claiming MBS benefits for vitamin D testing**

Most pathology in Australia is provided in comprehensive laboratories that provide a wide range of testing services at a single location. Only approved pathology practitioners are eligible to claim MBS items for vitamin D testing.

**Previous assessment of vitamin D testing**

One of the two health technology assessments (HTA) identified in the literature reviewed the clinical utility of vitamin D testing performed by the Ontario Health Technology Advisory Committee (OHTAC) in 2010.\(^{92}\) The assessment was initiated due to the increased volume of laboratory vitamin D tests from 2004 to 2009 in Canada. The purpose of the assessment was to evaluate the clinical utility of vitamin D testing, with specific reference to the prevalence rates of vitamin D deficiency in both the general population and in patients with kidney disease. The assessment focused primarily on bone health. It was noted that the use of vitamin D with or without calcium has been shown to reduce the risk of fractures and falls in elderly men and postmenopausal women. With respect to non-bone related health this HTA concluded that as of August of 2009 there were insufficient data to support a link between vitamin D and different non-bone health outcomes such as cancer, all-cause mortality and some cardiovascular outcomes. OHTAC recommended that routine testing of vitamin D levels should be endorsed for patients with certain bone related conditions, renal disease or malabsorption syndromes and not the general population.

The second HTA reviewing vitamin D screening and testing prepared by Hayes Inc. for Washington State Health Care Authority, HTA program published in November 2012\(^{93}\) concluded that higher serum 25-(OH)D levels have a protective association with bone health, but evidence to date has not demonstrated an association with health outcomes such as fractures or falls. There was also very little evidence that healthy vitamin D levels in younger adults protected this population group from the development of osteoporosis later in life. With respect to non-bone related health, this HTA concluded that higher levels of serum 25-(OH)D may protect adults against cardiovascular disease (CVD), type 2 diabetes, colorectal cancer, ovarian cancer, and all-cause mortality. However, there was insufficient evidence regarding a link between high serum vitamin D levels and with the reduced risk of obesity, gestational diabetes or multiple sclerosis (MS). The assessment concluded that the literature does not provide direct evidence that vitamin D screening in healthy populations as well as patients with chronic disease improves health outcomes.

---

\(^1\) Metabolic Syndrome is defined as a combination of medical disorders that when occurring together increase the risk of developing cardiovascular disease and type 2 diabetes.
Clinical Flow Chart
The clinical decision pathway which determines whether vitamin D testing should be undertaken is provided in Figure 2.

Figure 2: Clinical flow chart for vitamin D testing

Patient presents to General Practitioner

Does the patient have any of the following clinical symptoms of vitamin D deficiency?
- Widespread bone pain or tenderness
- Nonspecific myalgia
- Myalgia on strain
- Proximal muscle weakness
- Non-stress fracture
- Stress fracture e.g. femoral neck, scapula, ribs or vertebrae
- Rickets
- Low serum calcium or high Alkaline Phosphatase
- Low serum phosphates
- Low bone density on DEXA or osteopenia on x ray

Yes No

Does the patient have any of the following risk factors associated with vitamin D deficiency?
- Housebound or in residential aged care facility
- Patients >65
- Indoor worker
- Long sleeve clothing, staying in the shade
- Dark skinned
- Vegetarians
- Diabetes
- Renal/liver disease
- Pregnancy or breast feeding
- Gastrointestinal disorders e.g. Crohn’s, Coeliac, gastrectomy
- Obesity

Yes No

Is Vitamin D testing medically necessary?

Yes
- Measure serum Vitamin D
- Claim MBS item numbers 66608 or 66609

No
- No MBS claim for vitamin D testing

Is Vitamin D testing medically necessary?

Yes
- Measure serum Vitamin D
- Claim MBS item numbers 66608 or 66609

No
- No MBS claim for vitamin D testing
METHODOLOGY

The review will be primarily based on a fit-for-purpose, evidence based methodology. Fit-for-purpose in this context means that where comprehensive, high quality literature is found which clearly addresses the clinical questions, less work will be undertaken to find and analyse lower quality evidence or grey papers. The less comprehensive or lower quality the evidence relating to a clinical question (or where the evidence is not directly comparable to the Australian context), more work will be undertaken in finding and analysing lower quality evidence to ensure robust findings.

The main methodology for the review will be Mini-health technology assessments:

- a comprehensive systematic search of the scientific literature will be conducted to identify relevant studies addressing the key clinical/research questions.

To translate the evidence into the Australian context, the review will consider:

- Secondary data analysis:
  - MBS will be analysed to examine the existing population utilisation of services and assess whether existing MBS item numbers for the services are appropriate.
- Guideline concordance:
  - an analysis of the MBS services will be assessed relative to ‘best practice’ as recommended in relevant Clinical Practice Guidelines and relevant practice in Australia.
- Stakeholder consultation:
  - clinician engagement (e.g. RCC, MESP and submission authors) to understand existing services and practices in Australia; and
  - consumer engagement to determine consumer experiences with the services under review.
- Economic evaluation
  - preliminary economic evaluation will be conducted as part of the review, relying on studies identified through the systematic literature review.

The above information will take on additional significance when there is a lack of clear, high quality evidence.

Population, Intervention, Comparator, Outcomes (PICO)

The PICO (Population, Intervention, Comparator, Outcomes) criteria (94) are used to develop well-defined questions for this review. This involves focusing the question on the following four elements:

- the target population for the intervention;
- the intervention being considered;
- the comparator for the existing MBS service (where relevant); and
- the clinical outcomes that are most relevant to assess safety and effectiveness.

The PICO criteria have been determined on the basis of information provided in the literature, as well as clinical advice. These criteria will be applied when selecting literature for these mini-HTAs. Additional criteria for selecting literature have also been outlined (i.e. relevant study designs for assessing the safety and effectiveness of the service, time period
within which the literature will be sourced, and language restrictions as discussed above and in appendix C). The PICO for the review of vitamin D testing are shown in Table 6.

### Table 6: Clinical and research questions for the vitamin D testing items under review

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| (1) General health population (includes pregnant women, elderly, dark-skinned people, indoor workers etc.) | Serum vitamin D testing | Supplementation | Safety  
- Complications associated with Vitamin D testing (e.g. infection, needle injuries)  
Effectiveness  
- Physical health outcome as a consequence of the vitamin D testing (e.g. all-cause mortality, anaemia, NTDs, CVD, neuropathy, depression, dementia) |
| (2) Patients diagnosed with osteoporosis and osteomalacia | | | |
| (3) Children with rickets | | | |
| (4) Patients with chronic disease (kidney disease, multiple sclerosis, diabetes, CVD disease, gastrointestinal and malabsorption disorders etc.) | | | |

**Literature review**

A comprehensive search of the scientific literature will be conducted to identify relevant studies addressing the key questions. The databases to be included in the search are: MEDLINE® (from 1966 to present), MEDLINE® In-Process & Other Non-Indexed Citations, EMBASE (Excerpta Medica published by Elsevier), the Cumulative Index to Nursing & Allied Health Literature (CINAHL) and Cochrane databases. The search will be restricted to English language studies of humans. In electronic searches we will use various terms for, limited to humans, and relevant research designs as shown in Appendix 1.

Reference lists of related systematic reviews and selected narrative reviews and primary articles should be reviewed. Databases maintained by health technology assessment (HTA) agencies should be reviewed to identify existing assessments of vitamin D testing. In terms of supplementary search strategies, as part of consultations with pathologists and general practitioners, they should be asked if they are aware of any clinical guidelines, unpublished studies, and reviews relevant to the review of vitamin D testing.

The research questions to be addressed as part of the review protocol using the literature review include:

1. What are the appropriate clinical indications for medically necessary vitamin D testing?
2. What is the effectiveness of vitamin D testing in improving outcomes in each target population?
3. What are the safety and quality implications (including morbidity, mortality and patient satisfaction) associated with vitamin D testing in each target population?
4. How do safety and quality outcomes of vitamin D testing vary according to:
   a. the difference in testing methodologies?
   b. frequency of testing?
5. What is the evidence regarding the cost implications associated with vitamin D testing services in each target population?
MBS data
MBS data are available for MBS item numbers 66608 and 66609 since the early 1990s. A brief review of the available MBS data for the purposes of drafting the Vitamin D Testing Protocol identified an overall increase in claims for vitamin D testing, particularly for item number 66608. The clinical/research questions to be addressed as part of the review using MBS data include:

   a. How frequent are claims for the MBS item numbers 66608 and 66609?
   b. Are there any age, sex, temporal or geographic trends associated with usage of these item numbers?
   c. What are the characteristics of patients undergoing vitamin D testing?
   d. Are the Medicare claims data consistent with trends in the incidence/prevalence of the conditions/diseases being addressed by the services?
   e. Are there other pathology tests claimed in association with vitamin D testing?

Guideline concordance
An analysis of the two vitamin D testing MBS item numbers will be assessed relative to ‘best practice’ as recommended in relevant clinical practice guidelines and relevant practice in Australia. Where formalised clinical practice guidelines do not exist, the review should take account of other guidelines in operation in comparable health systems overseas. Differences in the purpose and intended audience of any such guidelines should be considered, documented and acknowledged in the process of undertaking the review.

The clinical/research questions to be addressed as part of the review using guideline concordance include:

   (1) Are the existing MBS item for services (66608 and 66609), including the associated explanatory notes appropriate?
      a. Is the descriptor for the MBS item number/service under review consistent with evidence-based (or in the absence of evidence, consensus-based) recommendations provided in relevant clinical practice guidelines?

Economic evaluation
Only a preliminary economic evaluation will be conducted as part of conducting the review, relying on studies identified through the systematic literature review. In the literature searches, acceptable evidence would include trial-based costing studies, cost analyses and economic modelling studies. Acceptable outcomes would include: cost, incremental cost-effectiveness ratio e.g. cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year. The applicability of any identified economic analyses to the Australian health system will be assessed.

The clinical/research questions to be addressed as part of the review using the economic evaluation component include:

   (1) What is the evidence regarding the cost implications associated with vitamin D testing in each target population across the patient journey?
   (2) Is the current fee structure for the items under review appropriate?
REFERENCES

7. Rhodes LE, Webb AR, Fraser HI, Kift R, Durkin MT, Allan D, et al. Recommended summer sunlight exposure levels can produce sufficient (> or =20 ng ml(-1)) but not the proposed optimal (> or =32 ng ml(-1)) 25(OH)D levels at UK latitudes. J Invest Dermatol. 2010 May;130(5):1411-8.

18
64. N. DPaB. Rickets. Paediatric and Child Health. 2007;17(7).
77. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab. 2003 Dec;88(12):5766-72.


95. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. BMC Med Res Methodol. 2009;9:34.

APPENDIX A – MBS DATA

The MBS item numbers relevant to vitamin D testing

Table A.1 shows the two in-scope MBS item number for vitamin D testing.

Table A.1: Description of vitamin D testing funded under the MBS

<table>
<thead>
<tr>
<th>Item Number</th>
<th>MBS Item Number description</th>
</tr>
</thead>
<tbody>
<tr>
<td>66608</td>
<td>Vitamin D or D fractions (Schedule fee: $42.55)</td>
</tr>
<tr>
<td>66609</td>
<td>A test described in item 66608 if rendered by a receiving Approved Pathology Practitioner (APP) - 1 or more tests (Item is subject to rule 18) (Schedule Fee: $42.55)</td>
</tr>
</tbody>
</table>

**Description of Rule 18**: The term "Episode Cone" describes an arrangement under which Medicare benefits payable in a patient episode for a set of pathology services, containing more than three items, ordered by a general practitioner for a non-hospitalised patient, will be equivalent to the sum of the benefits for the three items with the highest Schedule fees. Item 66609 is not included in the count of the items performed when applying the episode cone.

Source: Department of Human Services Medicare

**MBS usage and expenditure**

Table A.2 shows that the volume of vitamin D tests performed in Australia has steadily increased over the past ten years, from 73,330 tests in 2002 to more than three million tests in 2012 (nearly up 4,600%). The annual number of claims for MBS item number 66609 has been variable since May 2007.

Table A.2: Number of claims for Vitamin D testing MBS items since 2000/2001

<table>
<thead>
<tr>
<th>MBS item no</th>
<th>Financial year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>02/03</td>
</tr>
<tr>
<td>66608</td>
<td>73,330</td>
</tr>
<tr>
<td>66609</td>
<td>743</td>
</tr>
<tr>
<td>Total</td>
<td>73,330</td>
</tr>
</tbody>
</table>

Source: Department of Human Services Medicare

The pattern of use for item number 66608 is further analysed in Figure A.1 showing different patterns of usage by age, gender and time period. This analysis shows that vitamin D testing claimed under MBS item number 66608 is performed for both genders. However, the number of claims for vitamin D testing is particularly significant for females aged between 24 and 84, showing a marked increase from 2008 to 2012 (green line) compared to 2004-2008 (red line) and 2000 to 2004 (blue line).
Figure A.1: Usage of MBS item 66608 by age and gender since 2000

Figure A.2 shows that the annual MBS benefits paid for vitamin D testing (item numbers 66608 and 66609) has increased significantly from $2.6 million in 2002 to $126.5 million in 2012. The significant increase in the benefits paid for both item numbers is consistent with the increase in the volume of claims.

Figure A.2: Benefits paid for MBS item number 66608 and 66609 since 2002/2003

Source: Department of Human Services Medicare
APPENDIX B - SEARCH TERM STRATEGY

Clinical questions

1. What is the safety and effectiveness of vitamin D testing?

Table B.1: Search term strategy for clinical question one

<table>
<thead>
<tr>
<th>Population</th>
<th>Search Terms</th>
</tr>
</thead>
</table>
| Healthy population        | **Embase and Medline**  
Population – ('preeclampsia'/exp OR 'preeclampsia' OR 'pregnancy'/exp OR 'pregnancy' OR 'infant'/exp OR 'infant' OR 'human milk'/exp OR 'human milk' OR 'lactation'/exp OR 'lactation' OR 'dark skin'/exp OR 'dark skin' OR 'obesity'/exp OR 'obesity' OR 'elderly'/exp OR 'elderly' OR 'aged'/exp OR 'aged' OR 'indoor workers') AND Intervention – ('Vitamin D' OR 'vitamin D'/exp OR '25-OHD' OR '25-OHD3' OR '25-(OH)D3' OR '25-hydroxyvitamin D'/exp OR '25-hydroxyvitamin D' OR '25-hydroxycholecalciferol'/exp OR '25-hydroxycholecalciferol' OR '25-hydroxyergocalciferol'/exp OR '25-hydroxyergocalciferol' OR 'calcidiol'/exp OR 'calcidiol' OR 'cholecalciferol'/exp OR 'cholecalciferol' OR 'ergocalciferol'/exp OR 'ergocalciferol') AND ('testing'/exp OR 'testing' OR 'haematologic test*'/exp OR 'haematologic test*') AND **Cochrane**  
Population – ((MeSH descriptor Preeclampsia explode all trees) OR (MeSH descriptor Pregnancy explode all trees) OR (MeSH descriptor Infant explode all trees) OR (MeSH descriptor Human Milk explode all trees) OR (MeSH descriptor Lactation explode all trees) OR (MeSH descriptor Obesity explode all trees) OR (MeSH descriptor Aged explode all trees) OR (preeclampsia) OR (preeclampsia):ti,ab,kw) OR ((pregnancy) OR (pregnancy):ti,ab,kw) OR ((infant) OR (infant):ti,ab,kw) OR ((human milk) OR (human milk):ti,ab,kw) OR ((lactation) OR (lactation):ti,ab,kw) OR ((dark skin) OR (dark skin):ti,ab,kw) OR ((obesity) OR (obesity):ti,ab,kw) OR ((indoor worker) OR (indoor worker):ti,ab,kw)) AND Intervention – ((MeSH descriptor Vitamin D explode all trees) OR (Vitamin D):ti,ab,kw OR (MeSH descriptor 25-OHD explode all trees) OR (25-OHD):ti,ab,kw OR (MeSH descriptor 25OHD3 explode all trees) OR (25OHD3):ti,ab,kw OR (MeSH descriptor (OH)D3 explode all trees) OR ((OH)D3):ti,ab,kw OR (MeSH descriptor 25-Hydroxyvitamin D explode all trees) OR (25-Hydroxyvitamin D):ti,ab,kw OR (MeSH descriptor 25-Hydroxycholecalciferol explode all trees) OR (25-Hydroxycholecalciferol):ti,ab,kw OR (MeSH descriptor 25-Hydroxyergocalciferol):ti,ab,kw OR (MeSH descriptor Calcidiol explode all trees) OR (Calcidiol):ti,ab,kw OR (MeSH descriptor Cholecalciferol explode all trees) OR (Cholecalciferol):ti,ab,kw OR (MeSH descriptor Ergocalciferol explode all trees) OR (Ergocalciferol):ti,ab,kw AND ((MeSH descriptor Testing explode all trees) OR (Testing):ti,ab,kw OR (MeSH descriptor Haematologic test* explode all trees) OR (Haematologic test*):ti,ab,kw) AND Limits [humans]/lim AND [english]/lim}
<table>
<thead>
<tr>
<th>Population</th>
<th>Search Terms</th>
</tr>
</thead>
</table>
| 2. Patients diagnosed with osteoporosis and osteomalacia                   | **Embase and Medline**  
Population – (‘osteoporosis’/exp OR ‘osteoporosis’ OR ‘osteomalacia’/exp OR ‘osteomalacia’ OR ‘bone density’/exp OR ‘bone density’ OR ‘bone’/exp OR ‘bone’ OR ‘fractures’/exp OR ‘fractures’ OR ‘falls’/exp OR ‘falls’ OR osteopor* OR osteomalac*) AND  
Intervention – (Vit*D OR ‘vitamin D’/exp OR ‘vitamin D’ 25-OHD OR 25OHD3 OR 25(OH)D3 OR 25-(OH)D3 OR ‘25-hydroxyvitamin D’/exp OR ‘25-hydroxycholecalciferol’/exp OR ‘25-hydroxycholecalciferol’ OR ‘25-hydroxyergocalciferol’/exp OR ‘25-hydroxycholecalciferol’ OR ‘calcidiol’/exp OR ‘calcidiol’ OR ‘cholecalciferol’/exp OR ‘cholecalciferol’ OR ‘ergocalciferol’/exp OR ‘ergocalciferol’) AND (‘testing’/exp OR ‘testing’ OR ‘haematologic test*’/exp OR ‘haematologic test*’) AND  
Limits – [humans]/lim AND [english]/lim  
**Cochrane**  
Population – ((MeSH descriptor Osteoporosis explode all trees) OR (MeSH descriptor Osteomalacia explode all trees) OR (MeSH descriptor Bone density explode all trees) OR (MeSH descriptor Bone explode all trees) OR (MeSH descriptor Falls explode all trees) OR (osteoporosis) OR (osteomalacia):ti,ab,kw) AND ((‘bone density’ OR ‘bone density’):ti,ab,kw OR ((‘bone’ OR ‘bone’):ti,ab,kw) OR ((‘fractures’ OR ‘fractures’):ti,ab,kw) OR ((‘falls’ OR ‘falls’):ti,ab,kw) OR osteopor* OR osteomalac*) AND  
Intervention – ((MeSH descriptor Vitamin D explode all trees) OR (Vitamin D):ti,ab,kw OR (MeSH descriptor 25-OHD explode all trees) OR (25-OHD):ti,ab,kw OR (MeSH descriptor 25OHD3 explode all trees) OR (25OHD3):ti,ab,kw OR (MeSH descriptor 25(OH)D3 explode all trees) OR (25(OH)D3):ti,ab,kw OR (MeSH descriptor 25-OHD3 explode all trees) OR (25(OH)D3):ti,ab,kw OR (MeSH descriptor 25-(OH)D3 explode all trees) OR (25-(OH)D3):ti,ab,kw OR (MeSH descriptor 25-Hydroxyvitamin D explode all trees) OR (25-Hydroxyvitamin D):ti,ab,kw OR (MeSH descriptor 25-Hydroxycholecalciferol explode all trees) OR (25-Hydroxycholecalciferol):ti,ab,kw OR (MeSH descriptor 25-Hydroxycholecalciferol explode all trees) OR (25-Hydroxycholecalciferol):ti,ab,kw OR (MeSH descriptor Calcidiol explode all trees) OR (Calcidiol):ti,ab,kw OR (MeSH descriptor Cholecalciferol explode all trees) OR (Cholecalciferol):ti,ab,kw OR (MeSH descriptor Ergocalciferol explode all trees) OR (Ergocalciferol):ti,ab,kw) AND ((MeSH descriptor Testing explode all trees) OR (Testing):ti,ab,kw OR (MeSH descriptor Haematologic test* explode all trees) OR (Haematologic test*):ti,ab,kw) AND  
Limits [humans]/lim AND [english]/lim  
| 3. Children diagnosed with rickets                                           | **Embase and Medline**  
Population – (‘rickets’/exp OR ‘rickets’) OR (‘rachitis’/exp OR ‘rachitis’) OR (‘bone development’/exp OR ‘bone development’) AND  
Limits [humans]/lim AND [english]/lim |
<table>
<thead>
<tr>
<th>Population</th>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limits – [humans]/lim AND [english]/lim</td>
<td></td>
</tr>
</tbody>
</table>

**Cochrane**

**Population** – ((MeSH descriptor Rickets explode all trees) OR (MeSH descriptor rickets explode all trees) OR (MeSH descriptor Bone Development explode all trees) OR (rickets) OR (rickets):ti,ab,kw) OR ((rachitis) OR (rachitis):ti,ab,kw) OR ((bone development) OR (bone development):ti,ab,kw)

AND

**Intervention** – ((MeSH descriptor Vitamin D explode all trees) OR (Vitamin D):ti,ab,kw OR (MeSH descriptor 25-OHD explode all trees) OR (25-OHD):ti,ab,kw OR (MeSH descriptor 25OHD3 explode all trees) OR (25OHD3):ti,ab,kw OR (MeSH descriptor 25(OH)D3 explode all trees) OR (25(OH)D3):ti,ab,kw OR (MeSH descriptor 25-Hydroxyvitamin D explode all trees) OR (25-Hydroxyvitamin D):ti,ab,kw OR (MeSH descriptor 25-Hydroxycholecalciferol explode all trees) OR (25-Hydroxycholecalciferol):ti,ab,kw OR (MeSH descriptor 25-Hydroxyergocalciferol explode all trees) OR (25-Hydroxyergocalciferol):ti,ab,kw OR (MeSH descriptor Calcidiol explode all trees) OR (Calcidiol):ti,ab,kw OR (MeSH descriptor Cholecalciferol explode all trees) OR (Cholecalciferol):ti,ab,kw OR (MeSH descriptor Ergocalciferol explode all trees) OR (Ergocalciferol):ti,ab,kw) AND ((MeSH descriptor Testing explode all trees) OR (Testing):ti,ab,kw OR (MeSH descriptor Haematologic test* explode all trees) OR (Haematologic test*):ti,ab,kw)

AND

**Limits** [humans]/lim AND [english]/lim
<table>
<thead>
<tr>
<th>Population</th>
<th>Embase and Medline</th>
</tr>
</thead>
</table>
| Cochrane | Population – ((MeSH descriptor Cardiovascular Disease explode all trees) OR (MeSH descriptor Coronary Disease explode all trees) OR (MeSH descriptor Myocardial Infarction explode all trees) OR (MeSH descriptor Stroke explode all trees) OR (MeSH descriptor Peripheral Vascular Disease explode all trees) OR (MeSH descriptor Ischemia explode all trees) OR (MeSH descriptor Pulmonary Embolism explode all trees) OR (MeSH descriptor Kidney Failure explode all trees) OR (MeSH descriptor Diabetes Mellitus explode all trees) OR (MeSH descriptor Rheumatoid Arthritis explode all trees) OR (MeSH descriptor Multiple Sclerosis explode all trees) OR (MeSH descriptor Breast Cancer explode all trees) OR (MeSH descriptor Prostate Cancer explode all trees) OR (MeSH descriptor Inflammatory Bowel Disease explode all trees) OR (MeSH descriptor Crohn’s Disease explode all trees) OR (MeSH descriptor Ulcerative Colitis explode all trees) OR (Cardiovascular disease OR cardiovascular disease):ti,ab,kw OR (coronary disease):ti,ab,kw OR (heart disease):ti,ab,kw OR (myocardial infarction) OR (myocardial infarction):ti,ab,kw OR (stroke):ti,ab,kw OR (ischemia):ti,ab,kw OR (ischemia):ti,ab,kw OR (heart failure):ti,ab,kw OR (peripheral vascular disease):ti,ab,kw OR (kidney disease):ti,ab,kw OR (diabetes mellitus):ti,ab,kw OR (rheumatoid arthritis):ti,ab,kw OR (multiple sclerosis):ti,ab,kw OR (inflammatory bowel disease):ti,ab,kw OR (Crohn’s disease):ti,ab,kw OR (ulcerative colitis):ti,ab,kw) AND Intervention – ((MeSH descriptor Vitamin D explode all trees) OR (Vitamin D):ti,ab,kw OR (MeSH descriptor 25-OHD explode all trees) OR (25-OHD):ti,ab,kw OR (MeSH descriptor 25(OH)D3 explode all trees) OR (25(OH)D3):ti,ab,kw OR (MeSH descriptor 25-(OH)D3 explode all trees) OR (25-(OH)D3):ti,ab,kw)
### Table B.2: Search term strategy for clinical question two

**Population** | **Search Terms**
---|---
1. Patients undertaking serum vitamin D testing | **Embase and Medline**
   - AND
   - Economic Terms – (‘economic aspect’/exp OR ‘cost benefit analysis’ OR cost* OR ‘cost effectiveness’)
   - AND
   - Limits – [humans]/lim AND [english]/lim

**Cochrane**
   - Intervention – ((MeSH descriptor Vitamin D explode all trees) OR (Vitamin D):ti,ab,kw OR (MeSH descriptor 25-OHD explode all trees) OR (25-OH):ti,ab,kw OR (MeSH descriptor 25OH3D explode all trees) OR (25(OH)D3):ti,ab,kw OR (MeSH descriptor 25-OHD3 explode all trees) OR (25-(OH)D3):ti,ab,kw OR (MeSH descriptor 25-OHD3 explode all trees) OR (25-(OH)D3):ti,ab,kw OR (MeSH descriptor 25(OH)D3 explode all trees) OR (25-(OH)D3):ti,ab,kw OR (MeSH descriptor 25-OHD3 explode all trees) OR (25-OHD3):ti,ab,kw OR (MeSH descriptor 25-Hydroxyvitamin D explode all trees) OR (25-Hydroxycholecalciferol explode all trees) OR (25-Hydroxyergocalciferol explode all trees) OR (Calcidiol):ti,ab,kw OR (MeSH descriptor Cholecalciferol explode all trees) OR (Cholecalciferol):ti,ab,kw OR (MeSH descriptor Ergocalciferol explode all trees) OR (Ergocalciferol):ti,ab,kw OR (MeSH descriptor Haematologic test* explode al trees) OR (Haematologic test*):ti,ab,kw)
   - AND
   - Economic Terms – (((economic aspect) OR (economic aspect):kw) OR ((cost benefit) OR (cost benefit):kw)) OR (((cost effectiveness) OR (cost effectiveness):kw) OR (MeSH descriptor Cost-Benefit Analysis explode all trees) OR (Costs and Cost Analysis:kw) OR (Costs and Cost Analysis explode all trees))
   - AND
   - Limits [humans]/lim AND [english]/lim
APPENDIX C – SEARCH STRATEGY CRITERIA

Search strategies generally include a combination of indexing terms (e.g. MeSH or Emtree headings) and text word terms. Tables C.1 and C.2 set out proposed terms to identify papers in EMBASE. These terms would also be adopted to search other databases as described above. Limits will be employed in a hierarchical manner according to the type of literature being sourced (i.e. Limit 1, and if no relevant literature then Limit 2 and if no relevant literature, then Limit 3).

The selection criteria in Table C.1 will be applied to all publications identified by the literature search to identify studies eligible for inclusion in the systematic review. Study eligibility will be assessed by at least two reviewers.

Table C.1: Inclusion/exclusion criteria for identification of relevant studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Publication type</strong></td>
<td>Clinical studies included. Non-systematic reviews, letters, editorials, animal, in vitro and laboratory studies excluded.</td>
</tr>
<tr>
<td><strong>Systematic reviews</strong></td>
<td>Systematic reviews that have been superseded will be excluded</td>
</tr>
<tr>
<td><strong>Primary studies</strong></td>
<td>Primary studies published during the search period of included systematic reviews excluded</td>
</tr>
<tr>
<td><strong>Effectiveness studies</strong></td>
<td>Emphasis will be placed on identifying comparative trials however in the absence of such evidence other study designs may be included such as cohort or case series studies (&gt; 20? Patients)</td>
</tr>
<tr>
<td>• prospective, comparative trial</td>
<td></td>
</tr>
<tr>
<td>• &gt;20 patients</td>
<td></td>
</tr>
<tr>
<td><strong>Safety studies</strong></td>
<td>included if:</td>
</tr>
<tr>
<td>• &gt;50 patients included</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Vitamin D testing</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>No vitamin D testing</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Studies must report on at least one of the following outcomes:</td>
</tr>
<tr>
<td>• Patient outcomes: (morbidity, mortality, quality of life )</td>
<td></td>
</tr>
<tr>
<td>• Safety: (adverse physical health outcomes Of Complications associated with the procedure )</td>
<td></td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>Non-English language articles excluded</td>
</tr>
</tbody>
</table>

All eligible studies will be assessed according to the National Health and Medical Research Council (NHMRC) Dimensions of Evidence (Table C.2). There are three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular intervention. The last two require expert clinical input as part of their determination.

Table C.2: Dimensions of Evidence

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of the evidence</strong></td>
<td>The study design used, as an indicator of the degree to which bias has been eliminated by design.</td>
</tr>
<tr>
<td>• Level</td>
<td>The methods used by investigators to minimise bias within a study design.</td>
</tr>
<tr>
<td>• Quality</td>
<td>The p-value or, alternatively, the precision of the estimate of the effect (as indicated by the confidence interval). It reflects the degree of certainty about the existence of a true effect.</td>
</tr>
<tr>
<td>• Statistical precision</td>
<td>The distance of the study estimate from the “null” value and the inclusion of only clinically important effects in the confidence interval.</td>
</tr>
<tr>
<td><strong>Size of effect</strong></td>
<td>The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.</td>
</tr>
</tbody>
</table>
One aspect of the ‘strength of the evidence’ domain is the level of evidence, which will be assigned using the NHMRC levels of evidence outlined in Merlin et al 2009. Study quality will be evaluated and reported using the NHMRC Quality Criteria (Table C.3) for randomised controlled trials, cohort studies, case control studies and systematic reviews.

Table C.3: Quality criteria for RCTs, cohort studies, case-control studies and systemic reviews

<table>
<thead>
<tr>
<th>Study type</th>
<th>Quality criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trials³</td>
<td>Was the study double blinded? Was allocation to treatment groups concealed from those responsible for recruiting the subjects? Were all randomised participants included in the analysis?</td>
</tr>
<tr>
<td>Cohort studies²</td>
<td>How were subjects selected for the ‘new intervention’? How were subjects selected for the comparison or control group? Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the design or analysis? Was the measurement of outcomes unbiased (i.e. blinded to treatment group and comparable across groups)? Was follow-up long enough for outcomes to occur? Was follow-up complete and were there exclusions from the analysis?</td>
</tr>
<tr>
<td>Case-control studies²</td>
<td>How were cases defined and selected? How were controls defined and selected? Does the study adequately control for demographic characteristics and important potential confounders in the design or analysis? Was measurement of exposure to the factor of interest (e.g. the new intervention) adequate and kept blinded to case/control status? Were all selected subjects included in the analysis?</td>
</tr>
<tr>
<td>Systematic reviews²</td>
<td>Was an adequate search strategy used? Were the inclusion criteria appropriate and applied in an unbiased way? Was a quality assessment of included studies undertaken? Were the characteristics and results of the individual studies appropriately summarised? Were the methods for pooling the data appropriate? Were sources of heterogeneity explored?</td>
</tr>
</tbody>
</table>


Data will be extracted from individual studies using a standardised data extraction form designed specifically for this review. Data extraction will be performed by one reviewer and checked by a second reviewer.