Bone mineral density analyses using dual energy X-ray absorptiometry (DXA) for women in their 50th year

June 2014

MSAC application no. 1162

Assessment report

This report was commissioned for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee that has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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An application requesting Medicare Benefits Schedule (MBS) listing of bone mineral density (BMD) analyses using dual energy X-ray absorptiometry (DXA) for women in their 50th year was received from Professor Christopher Nordin by the Australian Government Department of Health. The decision analytic protocol to guide the assessment was finalised on 1 August 2013.

Osteoporosis, BMD and DXA

Osteoporosis is defined by the World Health Organization (WHO) as *'a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase of fracture risk'*. One of the main characteristics of osteoporosis is a fracture that occurs following no or little trauma, known as a 'minimal trauma fracture'. Osteoporosis is often underdiagnosed as it is usually not discovered until a minimal trauma fracture occurs, most commonly in the hip and pelvis. In Australia it is estimated that 5.9% of men and 22.8% of women aged 50 years or older would be classified as having osteoporosis.

DXA is a method of measuring BMD using two X-ray beams of different energy levels. It is currently the most widely used method for informing an osteoporosis diagnosis. A BMD T-score that is 2.5 standard deviations below the young adult mean is considered diagnostic. Women diagnosed with low BMD usually receive lifestyle and dietary advice to improve bone health, with the aim of preventing future minimal trauma fractures. The advice usually concerns sufficient calcium and vitamin D intake, adequate exercise, smoking cessation and limited alcohol intake. The Applicant suggests that DXA can be used in combination with lifestyle and dietary advice to encourage women in their 50th year with osteoporosis, or those with a low BMD and at risk of osteoporosis, to change their lifestyle, comply with dietary advice and thus prevent future minimal trauma fractures.

Clinical need

As bone loss in elderly women is related to the level of peak bone mass in earlier life and to the amount of bone lost since then, it is important to know when the most bone loss occurs in order to determine the optimal time for prevention. An acceleration of bone loss is seen around and after (female) menopause, at a rate of 2–5% per year in perimenopausal women. It is estimated that 4.7% of women aged 50–54 years have osteoporotic bone and a

further 40.6% have osteopenic bone. Although osteoporosis is rarely a direct cause of death, half the patients who sustain a hip fracture will be unable to gain their previous independence. Osteoporotic fractures (e.g. of the hip) are also associated with a risk of premature death in the years following the fracture (AIHW 2011). Hip or pelvic fractures were reported as associated causes in 1,668 deaths in Australia in 2007, and older adults have a 5- to 8-fold increased risk for all-cause mortality during the first 3 months after a hip fracture.

Other risk assessment tools for calculating fracture risk

Only three externally validated risk assessment tools (FRAX®, Garvan and QFracture) have been developed to predict fractures. FRAX® was developed in 2008 by the University of Sheffield on behalf of the WHO: the tool provides an algorithm that calculates a 10-year probability of minimal trauma fracture based on individual patient models that integrate the risks associated with specific clinical factors. It can be used in combination with or without DXA results. The Garvan Fracture Risk Calculator is based on an Australian population; it is only applicable to men and women older than 60 years of age and provides a 5- and 10-year risk of hip fracture or any other fracture. QFracture estimates the 10-year risk of developing hip or major fractures (without BMD measurement), and is applicable to people aged 30–99 years. No tool performs consistently better than the others. There are currently no specific MBS items associated with the use of these tools—it is likely that they would be administered as part of a medical consultation with a general practitioner (GP) around the time that a woman is perimenopausal.

Current arrangements for public reimbursement

There have been no previous MSAC considerations of DXA for women in their 50th year (without risk factors). However, DXA is currently reimbursed for people older than 70 years of age, and women who have suffered from a minimal trauma fracture, other pre-defined conditions or osteoporosis risk factors. The conditions under which DXA services can be reimbursed under the MBS are provided in Table 1. The currently available MBS item numbers for DXA are shown in Table 4.

Results of assessment

Safety—Due to the lack of evidence on women in their 50th year alone, the inclusion criteria were broadened to capture all women in the perimenopausal period (i.e. women aged 40–65 years). No studies were identified that assessed the safety of DXA in women in

this age bracket. DXA is considered safe as radiation doses are smaller than most diagnostic X-ray examinations (e.g. X-ray mammography).

Effectiveness—Studies meeting the pre-specified inclusion criteria and assessing the direct health impact of DXA versus no risk assessment in women aged 40–65 years were not available. Another recent systematic review (Nelson et al. 2010) on this topic was identified that confirmed that the primary research has not been done. Given the lack of evidence, the results of two studies (one with postmenopausal women and one with premenopausal women) are discussed as they provide some information on the change in BMD 1–2 years after DXA testing in women. In the study of postmenopausal women no significant change in BMD was reported; thus, the expected age-related reduction in BMD between visits was not found in the 12–18 months subsequent to DXA testing plus lifestyle counselling. In the second study (premenopausal women) there was a mean 1.1% per year increase in femoral neck BMD from baseline to 2 years, and no change in lumbar spine BMD when DXA testing was used in combination with lifestyle counselling. The study found that DXA plus informing women of the BMD results was effective at increasing hip BMD in the short term (2 years).

The linked evidence analysis considered the accuracy of DXA compared with FRAX®, as reported in two studies. Both studies had a high loss to follow-up of participants (potential for selection bias). Also, the study participants were Asian women in the right age group, so the results may not be wholly applicable to an Australian population. The studies had a 4.5±2.8- and 10-year follow-up. The length of time needed to follow 50 year old women to ascertain fracture outcomes is probably one of the major reasons why there is so little data regarding this age group. Even though one study followed a large cohort of women of an appropriate age for 10 years, there were still only 325 fractures in the cohort (around 8% of the participants experienced a fracture). The area under the curve (AUC) calculated for each of the studies showed average performance of both DXA and FRAX® in predicting fracture. DXA AUC values were 0.71 (95%CI 0.66, 0.76) and 0.64 (95%CI 0.57, 0.72) when predicting any major minimal trauma fracture, and 0.86 (95%CI 0.79, 0.92) and 0.82 (95%CI 0.67, 0.98) when predicting hip fracture, respectively. The predictive accuracy of FRAX® was very similar, with AUC values of 0.71 (95%CI 0.66, 0.76) and 0.67 (95%CI 0.59, 0.75) for any major fracture, and 0.90 (95%CI 0.83, 0.97) and 0.86 (95%CI 0.68, 1.00) for hip fracture, respectively. It would therefore appear that DXA is as accurate as clinical risk assessment (using FRAX® without DXA results).

The second step of the evidence linkage included two studies reporting lifestyle changes after DXA and lifestyle counselling in women aged 40–65 years. A significantly higher mean

daily calcium intake was reported in the DXA plus questionnaire group compared with the 'no DXA' group in one study. The second study reported an increase in adequate calcium intake from 43% at baseline to 70% at 12–18 months after the DXA testing. No significant change in exercise was reported over time in the latter study or between the intervention groups in the former study.

The third step of the evidence linkage found a considerable body of evidence on lifestyle interventions for the prevention of fracture; however, little of the evidence is applicable to the target population for this assessment as most studies were conducted in older women. Eleven systematic reviews were included on the effect of exercise, vitamin D and/or calcium supplementation on fracture. A large and high-quality systematic review of randomised controlled trials (RCTs) and observational studies undertaken by the Agency for Healthcare Research and Quality (AHRQ) in the US reported that the evidence for both calcium and vitamin D supplementation in preventing fracture was uncertain. Other reviews also indicated that the evidence regarding the impact of vitamin D supplementation on preventing fracture in the general population is uncertain. In contrast, a high-quality Cochrane review found that vitamin D in combination with calcium supplementation was beneficial at preventing hip fractures in institutionalised patients. A non-significant decrease in vertebral fractures was also seen after calcium supplementation alone (without vitamin D).

The AHRQ systematic review found that the evidence on exercise was too limited to draw any conclusions. Other systematic reviews of RCTs alone did not find an effect of exercise on fracture risk, although it is possible that this was because the RCTs were not conducted for a sufficient duration to capture all the fracture risk. Systematic reviews of observational studies reported that exercise had a protective effect on the risk of fracture. However, confounding factors might have affected this result; although the direction of effect in the meta-analysis was very consistent across the studies, and the heterogeneity between the studies was low, it is possible that the magnitude of the protective effect of exercise might not be as large as observed. Lifestyle interventions are recommended in Australian and international osteoporosis guidelines.

Economic and financial considerations

There was inadequate evidence available to determine the safety and effectiveness of BMD screening with DXA. Given the important impact of age on bone loss in women, it is difficult to determine whether the results described above would be replicated in women in their 50th year, and it is unclear how the BMD results could be extrapolated to predict fracture

risk in an economic model without information on the individual osteoporotic risk factors present in Australian women aged 49 or 50 years. Further, as test accuracy was similar between DXA and clinical assessment, it is likely that similar impacts on health outcomes would be obtained using both methods, but that using a clinical assessment tool such as FRAX® would be less costly and without additional risk. Information was not available on whether the level of compliance with lifestyle advice differs if a DXA test is used to determine osteoporotic risk when compared with a clinical assessment tool. Therefore, an evidence-based assessment of the cost-effectiveness of DXA for analysing BMD in women in their 50th year was not undertaken, as the resulting incremental cost-effectiveness ratio would be subject to an unacceptable level of uncertainty.

Were the proposed listing to be implemented, after achieving a stable uptake over 4 years it might be expected to cost the MBS approximately $9.5 million per year (increasing annually). As the uptake is highly uncertain and depends on the extent of promotion of BMD screening using DXA, the financial impact may be in the range $2.5–$20 million.

Other relevant considerations

Guidelines—Current clinical practice guidelines do not recommend DXA screening for women in the perimenopausal period. Australian guidelines only recommend DXA for men and women over 50 years of age with one or more risk factors or when there is a history of minimal trauma fracture. The WHO concluded in 2006 that there was no evidence to support widespread screening programs for BMD testing, and a report in 2012 by the National Clinical Guideline Centre (NCGC) stated that fracture risk should not be routinely assessed in people aged under 50 years of age as they are unlikely to be at high risk unless major risk factors are present (NICE 2012a).

Other considerations—With implementation of the intervention, women in their 50th year who are diagnosed with osteoporosis would not be eligible for osteoporosis medication, as the relevant PBS-listed pharmaceuticals are only accessible for women with a diagnosed minimal trauma fracture or who are older than 70 years of age.

Conclusions

Safety—Ionising radiation levels associated with DXA are low and no safety concerns or serious adverse events have been reported in the literature. DXA is considered safe, although not as safe as clinical assessment tools that predict fracture risk (i.e. not including imaging).

Effectiveness—There was a considerable lack of evidence on effectiveness: studies of women younger than 40 years and older than 65 years of age were generally excluded due to the inability to generalise results to a perimenopausal population. There was no evidence available that specifically assessed the impact of DXA testing on fracture risk at 49 or 50 years of age. Similarly, there were no studies with a sufficient follow-up period to capture outcomes such a fracture risk, morbidity/mortality or quality of life, and studies with the appropriate comparator were lacking.

Although there was some evidence that the use of DXA and lifestyle counselling may stabilise BMD over the short term in postmenopausal or premenopausal women, the use of DXA testing appears to be no more accurate at predicting fracture risk than the use of a clinical assessment tool (FRAX®). FRAX® is likely to be a cheaper, safer and more accessible option than DXA testing. No evidence on the effectiveness of repeat testing in the correct population was identified. Similarly, no evidence was identified to determine whether compliance with lifestyle advice differed as a consequence of an osteoporosis risk assessment using DXA compared with the use of a clinical assessment tool. The evidence that lifestyle change affects fracture risk was inconsistent for interventions such as vitamin D supplementation or dietary calcium, and was uncertain for exercise interventions.

Glossary and abbreviations

Abbreviation	Description
AHRQ	Agency for Healthcare Research and Quality
AHTA	Adelaide Health Technology Assessment
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
AUC	area under the curve
BMD	bone mineral density
CI	confidence interval
DAP	decision analytic protocol
DXA	dual energy X-ray absorptiometry
FRAX®	WHO Fracture Risk Assessment Tool
GP	general practitioner
HESP	Health Expert Standing Panel
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NOF	National Osteoporosis Foundation
NPV	negative predictive value
ORAI	Osteoporosis Risk Assessment Instrument
OST	Osteoporosis self-assessment screening tool
PASC	Protocol Advisory Sub-Committee (of MSAC)
PBS	Pharmaceutical Benefits Schedule
PPV	positive predictive value
QCT	quantitative computed tomography
QUS	quantitative ultrasound
RCT	randomised controlled trial
SCORE	Simple Calculated Osteoporosis Risk Estimation Score
WHO	World Health Organization

Introduction

This assessment report is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on systematic reviews of the scientific literature (such as the information provided in this document) and other information sources, including clinical expertise.

Adelaide Health Technology Assessment (AHTA), from the School of Population Health, University of Adelaide, has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of bone mineral density (BMD) analyses using dual energy X-ray absorptiometry (DXA) for women in their 50th year. This evaluation has been undertaken in order to inform MSAC's decision-making regarding public funding of the intervention.

The proposed use of DXA screening for women in their 50th year in Australian clinical practice was outlined in a decision analytic protocol (DAP) that guided the evaluation. The DAP was released for public comment on 11 June 2013 and closed for comments on 19 July 2013. No public consultation responses were received. The DAP was finalised on 1 August 2013.

Rationale for assessment

Professor Christopher Nordin submitted an application requesting MBS listing for BMD analyses using dual energy X-ray absorptiometry (DXA) for women in their 50th year. The purpose of the intervention is to identify individuals with a low or low–normal BMD who may be at an increased risk for 'minimal trauma fractures'. These individuals would then receive appropriate dietary and lifestyle (healthy bone) advice to prevent osteoporosis and the occurrence of minimal trauma fracture at an older age.

The hypothesis is that when people are identified as having low BMD using DXA, they would be more likely to comply with lifestyle and dietary advice to prevent fracture risk, compared with women who underwent a risk assessment without the use of DXA testing.

This would essentially be a screening item as it is for an unselected population of (healthy) women in their 50th year without major osteoporosis risk factors. The use of DXA as a screening tool on the MBS would pose a policy issue, as Medicare rebates generally cannot

be paid for screening services: section 19(5) of the *Health Insurance Act 1973* states: 'Unless the Minister otherwise directs, a Medicare benefit is not payable in respect of a health screening service, that is to say, a professional service that is a medical examination or test that is not reasonably required for the management of the medical condition of the patient' (Australian Government 1973).

It should be noted that there are currently no MBS items pertaining to the use of clinical risk assessment tools for identifying patients at risk of minimal trauma fracture (i.e. the comparator). It is likely that the use of these tools (if routinely undertaken) would occur during a standard medical consultation.

Eligibility for the proposed DXA screening service would be very similar to the breast cancer screening program that is jointly funded by the Commonwealth and states and territories.

Background

Osteoporosis and low bone mineral density

Osteoporosis is a skeletal disorder characterised by low BMD that causes the bones to weaken, resulting in high risk of fracture (AIHW 2011). It is defined by the World Health Organization (WHO) as *'a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk'* (WHO 1994). A major characteristic of osteoporosis is fractures that occur following little or no trauma, known as 'minimal trauma fractures'. The disorder itself is usually silent and only becomes clinically evident when these fractures occur. Although osteoporosis is rarely a direct cause of death, osteoporotic fractures (e.g. hip fractures) can be associated with premature deaths in the years following the fracture (AIHW 2011). The disease was associated with more than 8.9 million fractures worldwide in 2000, of which 34.8%, 28.6% and 17.4% were in Europe, the Western Pacific[1] and South-East Asia, respectively (WHO 2007).

Risk factors

Factors identified that increase the risk of developing osteoporosis are shown in Table 1.

Table 1   Risk factors for the development of osteoporosis (DAP 1162)

Type	Risk factors
Fixed (non-modifiable) risk factors	- Age (risk increases after 40–50 years of age) - Sex (osteoporosis affects women more than men) - Menopause - Family history of osteoporosis (genetic predisposition) - Previous minimal trauma fracture, particularly of the hip, spine or wrist [a]
Lifestyle (modifiable) risk factors	- Physical inactivity - Diet: low calcium intake - Vitamin D deficiency - Tobacco smoking - Excessive alcohol consumption - Low Body Mass Index (BMI <18.5) - Anorexia/exercise-induced amenorrhea - Excessively high BMI
Diseases implicated in osteoporosis	- Rheumatoid arthritis [a] - Hyperthyroidism [a] - Hyperparathyroidism [a] - Hypogonadism, including early menopause (younger than 45 years of age) [a]

[1] Includes Australia, China, Japan, New Zealand and the Republic of Korea

Type	Risk factors
	- Cushing's syndrome [a]
	- Chronic gut conditions including coeliac disease, and inflammatory bowel disease (malabsorptive disorders) [a]
	- Chronic liver disease [a]
	- Chronic renal disease [a]
	- Some cancers (e.g. myeloma)
	- Type 1 diabetes
	- Gastrectomy
	- Ankylosing spondylitis
Drug therapies implicated in osteoporosis	- Chemotherapy
	- Aromatase inhibitors for the treatment of breast cancer
	- Long-term corticosteroid use (e.g. glucocorticoid therapy [a])
	- Anti-androgenic treatments for prostate cancer

Source: AIHW (2011)

[a] DXA testing is currently reimbursed through the MBS in women with these risk factors

Prevalence, morbidity and mortality of osteoporosis in Australia

In Australia, osteoporosis is often underdiagnosed, predominantly because it is usually not discovered until a fracture occurs. An estimated 692,000 Australians (3.4% of the total population) have diagnosed osteoporosis, based on the 2007–08 National Health Survey. The disease mostly occurs in females (81.9%) and most osteoporosis patients are aged 55 years or older (AIHW 2011). The Geelong Osteoporosis Study recruited a random population-based sample of individuals from an area surrounding Geelong, Victoria. After standardising for age and sex to the 2006 Australian population, they reported that 5.9% of men and 22.8% of women aged 50 years or older, and 12.9% of men and 42.5% of women aged 70 years or older, would be classified as having osteoporosis (Henry et al. 2011). They reported that 4.7% of the women in the 50–54 years age group are osteoporotic, and a further 40.6% are osteopenic (Henry et al. 2011).

Minimal trauma fracture is a major cause of morbidity in osteoporosis patients. In 2007–08 there were 52,730 hospital separations for these fractures in people aged 40 years or older. Hip and pelvis fractures were the most common, with 21,360 separations (40.5 %). Wrist and forearm, shoulder, spine and ankle fractures occurred 9,038, 4,320, 2,952 and 2,553 times, respectively (AIHW 2011). Osteoporosis Australia (2012) estimates that half of all patients who sustain a hip fracture will be unable to gain their previous independence. Although the overall number of minimal trauma hip fractures is on the increase (from 14,671 in 1998–99 to 17,192 in 2007–08), the hospital separation rate appears to be decreasing, an outcome possibly partly explained by a greater awareness of osteoporosis and bone density testing, increased uptake of anti-resorptive medications and lifestyle

preventive actions. The incidence rate of hip fractures in 2007–08 was 252 per 100,000 in females, and 100 per 100,000 in males, aged 40 years or older (AIHW 2011).

As osteoporotic fractures increase the risk of death but do not directly cause death, the role of minimal trauma fracture is usually assessed as an associated cause of death. Hip or pelvic fractures were associated with 1,688 deaths in 2007 (AIHW 2011). A systematic review conducted in 2010 reports that older adults have a 5- to 8-fold increased risk for all-cause mortality during the first 3 months after a hip fracture; and this excess mortality risk remains constant over time for both women and men (Haentjens et al. 2010).

Dual energy X-ray absorptiometry (DXA)

Dual energy X-ray absorptiometry (DXA) is currently widely used to measure BMD to inform the diagnosis of osteoporosis. Measuring BMD is currently considered the only way to diagnose osteoporosis or osteopenia in the absence of a minimal trauma fracture. A clinical risk assessment can estimate the person's risk of fracture, but this is not the same as determining low BMD. Central DXA examinations have three major roles: diagnosis of osteoporosis, assessment of a patient's risk of fracture, and monitoring the response to treatment (Blake & Fogelman 2007). The DXA scan generates T-scores, which represent a comparison between the patient's BMD and the optimal peak bone density for the patient's gender and ethnic group (WHO 2007).

$$\text{T-score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young adult population SD}}$$

(Blake & Fogelman 2007)

Osteoporosis is defined as a BMD that is 2.5 standard deviations (SDs) below the young adult mean (T-score $\leq$–2.5); a T-score of between –1 and –2.5 is osteopenia or low bone mass, which indicates increased risk of fracture. A T-score of –1.0 or above is classified as normal BMD (WHO 1994).

The procedure

DXA testing can be performed at any location that has a DXA machine and a qualified technician. The tests should be critically assessed by a densitometrist and interpreting physician for abnormalities that can affect BMD measurements (El Maghraoui & Roux 2008).

All DXA systems have a radiation source that is aimed at a radiation detector opposite the measurement site. The patient lies on a table in the path of the radiation beam. The site of

interest is scanned, and the attenuation of radiation in these sites is determined and related to BMD (El Maghraoui & Roux 2008). Diagnosis of low BMD depends on the measurement site and the number of sites measured; normally, a diagnosis is only made after measuring BMD at two or more sites.

The effective radiation dose per site scanned is negligible for first-generation pencil beam scanners (which use a singular X-ray beam)—this means that it is well below the effective dose from natural background radiation of 7 µSv per day. The newer fan beam scanners (wide angle fan beam with multiple detectors) have higher radiation doses. An adult patient who has a spine and hip scan performed on a Hologic fan beam DXA scanner (Hologic, Waltham, Massachusetts) receives an effective dose of approximately 10–20 µSv. These radiation doses, however, are still smaller than most diagnostic X-ray examinations (e.g. X-ray mammography) (Damilakis & Guglielmi 2010). The dose of radiation is affected by the scanning technique, efficiency of the detection system, X-ray tube filtration, number of scans, exposure parameters, scan size, scan speed and body size of the patient (Damilakis & Guglielmi 2010).

Lifestyle and dietary advice

Women with a low T-score usually receive lifestyle and dietary advice to improve bone health and increase their BMD in order to prevent minimal trauma fracture in later life. According to current guidelines and recommendations, this advice should consist of:

- **Dietary calcium**. Calcium has an important role in maintaining bone mass; the main sources of calcium are dairy milk, cheese and yoghurt, and women who cannot achieve adequate calcium intake may require additional supplementation. An intake of 1,000 mg of dietary calcium daily is associated with a 24% lower rate of hip fractures. Guidelines support the importance of dietary calcium in preventing osteoporosis, and the Australian recommendation is 1,300 mg/day for women aged 50 years or older (Ebeling et al. 2013; NHMRC 2010).

- **Vitamin D**. Vitamin D plays a role in maintaining bone mass by promoting the absorption of calcium. The primary source of vitamin D is sunlight but it can also be found in dietary sources such as fatty fish, and vitamin D supplements are also available. The Australian osteoporosis guidelines recommend sunlight exposure of around 15% of the body (i.e. face, hands and arms) for 6–8 minutes, four to six times a week in summer, and before 10 am or after 2 pm for moderately fair skinned people. Darker skinned people require more sunlight exposure to achieve the same vitamin D uptake (Ebeling et al. 2013; NHMRC 2010).

- **Exercise.** Exercise programs have a positive effect on BMD in the spine. For healthy women without major risk factors for fracture, the key focus of exercise and physical activity is to improve or maintain BMD, muscle mass, strength and functional capacity. A combination of weight-bearing and impact training is recommended, including muscle strengthening exercises. Exercises that are highly osteogenic are basketball, netball, impact aerobics, dancing/gymnastics, tennis and (rope) skipping. These activities are recommended (for all stages of life) for at least 30 minutes three to five times a week (Ebeling et al. 2013).

- **Alcohol and smoking.** Smoking cessation and moderate alcohol intake are important in maintaining an overall healthy lifestyle, as excessive alcohol intake impairs bone formation and smoking is associated with a reduction in bone structure and strength (Ebeling et al. 2013; NHMRC 2010). If alcohol is consumed it should be in moderation (up to one standard drink per day for women). Smoking is not recommended.

Intended purpose

It is proposed that DXA would be used in combination with lifestyle and dietary advice to encourage women in their 50th year with a BMD lower than the mean (T-score <0) to change their lifestyle to prevent future osteoporosis and/or minimal trauma fracture. As postmenopausal osteoporosis is both predictable and preventable, the Applicant suggests that a change in lifestyle and diet at age 50 years in those who are at risk of developing osteoporosis could significantly reduce the fracture burden.

Indications for DXA

As DXA is already available for patients with a wide range of risk factors and in all people aged ≥70 years, the proposed new item number would be for *all* Australian women in their 50th year, in order to determine future fracture risk.

Contraindications for DXA

According to the Royal Australian and New Zealand College of Radiologists, contraindications for DXA in (healthy) women in their 50th year would be (Hendrich 2013):

Absolute contraindication:

- Pregnancy, due to ionising radiation.

Relative contraindications:

- Weight—women heavier than 120–130 kg may not be able to be tested with DXA, depending on the manufacturer. Newer DXA machines can accommodate greater weights.

- Carrying out a DXA in the week after other radiological investigations using contrast media (e.g. barium meals/enemas, intravenous pyelograms, CT scans), as this might interfere with the observed results.

- Inability to transfer from a wheelchair to the scanning table (height of the table is unadjustable).

Clinical need

Bone loss

Bone mass in elderly women is related to the level of peak bone mass in earlier life and the amount of bone lost since then. As low bone mass is the most important determinant of osteoporotic fractures, it is important to know when this bone loss occurs to determine the optimal time for prevention programs. Bone loss in pre- and perimenopausal women was investigated in a longitudinal study with a 3-year follow-up (Chapurlat et al. 2000). Over the 3 years, premenopausal women (n=196) had no significant bone loss at any site (total body, femoral neck, trochanter, anteroposterior and lateral spine, and forearm) as measured on a DXA. However, perimenopausal women (n=76) significantly lost bone from cancellous and cortical sites (i.e. the femoral neck, trochanter and lumbar spine), showing a rapid and diffuse bone loss related to a reduction in oestrogen.

Other studies also report bone loss around this time, with a rate of 0.3–0.5% per year around the age of 40 years. An acceleration of bone loss is seen after menopause, with an initial annual rate of 2–3%, decreasing exponentially over a period of 8–10 years (Elders et al. 1988). A cross-sectional study has reported a mean bone loss rate of 5.1% per year in the first 2 postmenopausal years (Elders et al. 1988). A longitudinal study of 438 Chinese women aged 45–55 years also showed that menopausal status was the strongest determinant of bone changes (Ho et al. 2008). An annual bone loss of around 0.5% was seen among premenopausal women (follow-up of 30 months), whereas bone loss in perimenopausal women and postmenopausal women was around 2–2.5% and 1.5% per year, respectively.

As a rapid acceleration of bone loss occurs around menopause, this could be considered the optimal time to start osteoporosis prevention behaviour. As DXA testing around menopause

would facilitate the early detection of those with (already) low BMD, individuals would know if they are at increased risk of osteoporosis and future minimal trauma fracture. Knowledge of low BMD (negative T-score) could improve compliance with preventive lifestyle and dietary changes in this population, so as to maintain good bone health.

Other existing tests for calculating fracture risk

Risk assessment tools

Many risk assessment tools have been developed to determine the risk of low BMD or fracture. However, only 20 tools have been externally validated and only 6 tools—Osteoporosis self-assessment screening tool (OST), Osteoporosis Risk Assessment Instrument (ORAI), Simple Calculated Osteoporosis Risk Estimation Score (SCORE), Garvan Fracture Risk Calculator, WHO Fracture Risk Assessment Tool (FRAX®) and QFracture—were validated in a population-based setting with a proper methodological quality (Rubin et al. 2013). According to a 2013 systematic review, no tool performed consistently better than others, and simple tools with fewer risk factors often did as well or even better than more-complex tools with more risk factors (Rubin et al. 2013). However, only three tools (FRAX®, Garvan and QFracture) predicted fractures, whereas the other three (OST, ORAI and SCORE) only predict low BMD. As fracture risk is the outcome of interest, only FRAX®, Garvan and QFracture are described below.

FRAX®

The University of Sheffield developed FRAX® in 2008 on behalf of the WHO. It provides an algorithm that gives a 10-year probability of minimal trauma fracture, based on individual patient models that integrate the risks associated with clinical risk factors (WHO undated). This tool can be used in combination with DXA results, or without DXA, as a predictor of risk of fracture. An Australian FRAX® algorithm is also available, based on the Australian population, and is applicable to people aged 40–90 years. The risk factors used in the FRAX® algorithm are shown in Table 2. FRAX® was developed using data from 9 different population-based cohorts and validated in 11 prospective population-based cohorts (NICE 2012a).

Garvan

The Garvan Fracture Risk Calculator was developed using data from the Dubbo Osteoporosis Epidemiology Study, which was conducted by the Bone and Mineral Research Program of Sydney's Garvan Institute of Medical Research. The study (which began in 1989) includes 1,693 males and 2,167 females aged 60 years or older (Simons et al. 1990). The tool is

applicable to men and women 60–96 years of age and provides 5- and 10-year fracture risk estimates for hip and any osteoporotic fracture. The risk factors used in the Garvan tool are shown in Table 2.

QFracture

QFracture was developed in 2009 and has been validated based on large primary care populations in the UK (NICE 2012a). It estimates the 10-year risk of developing hip and major osteoporotic fractures without BMD measurement, and is currently applicable to people aged 30–99 years. The tool is updated annually, and the risk factors used in the most recent update (2013) are shown in Table 2.

Table 2   Factors assessed by fracture risk assessment tools

Risk factors	FRAX®	Garvan	QFracture
Age	X	X	X
Sex	X	X	X
Weight	X	X	X
Height	X		X
Race			X
Previous fracture	X	X	X
History of falls		X	X
Parent with fractured hip or family history	X		X
Alcohol use	X		X
Smoking	X		X
Menopausal symptoms			
Endocrine disorders			X
Glucocorticoid therapy	X		X
HRT therapy			X
Oestrogen therapy			X
Antidepressants			X
Rheumatoid arthritis	X		X
Secondary osteoporosis	X		
Type 2 diabetes			X
Asthma or COPD			X
Cardiovascular disease			X
GI malabsorption			X
Chronic liver disease			X
Chronic kidney disease			X
Parkinson's disease			X
Epilepsy			X
Cancer			X
Dementia			X

Risk factors	FRAX®	Garvan	QFracture
In nursing or care home			X

Sources: ClinRisk (2013); NICE (2012b); Rubin et al. (2013)

Quantitative computed tomography (QCT)

Computed tomography (CT) was introduced in 1973 for head scanning, and a few years later it became available for whole-body scanning. The quantitative ability of CT (QCT) was applied to the skeleton soon afterwards and was subsequently used to determine BMD. However, with the introduction of DXA, the use of QCT diminished, as DXA has lower ionising radiation doses and higher reproducibility. Another limitation of QCT was that the WHO definition of osteoporosis (in terms of bone densitometry) would not be applicable. In recent years, with technical developments in QCT and recognition of some advantages of QCT over DXA (i.e. separate measures of cortical and trabecular BMD, information on bone morphometry from which biomechanical parameters can be extracted), the use of QCT is again increasing (Adams 2009). It can be performed on conventional CT scanners, and at peripheral sites (e.g. radius and tibia) using smaller and cheaper peripheral CT scanners. Due to the broader use and technical developments, QCT may be considered as an alternative to DXA in the future.

Quantitative ultrasound (QUS)

QUS for bone assessment typically involves placing ultrasound transducers on either side of the calcaneus (heel bone), one as a wave transmitter and the other as a receiver. The devices assess multiple parameters in which values are lower in osteoporotic bone than in healthy bone. QUS is used in clinical practice, but with this technique there are no universal guidelines establishing normal versus abnormal measurements, and no consensus criteria with which to diagnose osteoporosis. The diagnostic accuracy of QUS was determined in a systematic review with DXA as the reference standard (Nayak et al. 2006). For the QUS index parameter T-score cut-off threshold of −1, sensitivity was 79% (95%CI 69%, 86%) and specificity 58% (95%CI 44%, 70%) for identifying people with a DXA T-score of ≤−2.5 at the hip or spine. The systematic review concluded that results of QUS at commonly used cut-off thresholds do not definitively exclude or confirm DXA-determined osteoporosis. However, there are some advantages with QUS: it is less expensive than DXA, is portable, does not involve radiation and does not require trained personnel.

Marketing status of device/technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). Four DXA devices, listed on the ARTG as category IIb devices

(medium–high level of risk), are shown under the items in Table 3. They are listed in the ARTG.

Table 3   DXA devices listed on the ARTG

ARTG item no.	Manufacturer	Product name	Indication/purpose
97975	GE Medical Systems Lunar	GE Medical Systems Australia Pty Ltd—X-ray system, diagnostic, bone absorptiometer, dual-energy	X-ray imaging for bone densitometry
119491	Medilink	InMed Pty Ltd—X-ray system, diagnostic, bone absorptiometer, dual-energy	For the estimation of bone density and other structural parameters of bones using X-ray absorptiometry for the purpose of aiding in the diagnosis of osteoporosis including bone regeneration and loss
158772	Hologic Inc.	Cytyc Australia Pty Ltd—X-ray system, diagnostic, bone absorptiometer, dual-energy	Intended to be used to estimate bone density; the data can then be used to calculate BMD
199129	BM Tech Worldwide Co. Ltd	Central Medical Pty Ltd—X-ray system, diagnostic, bone absorptiometer, dual-energy	BMD measurement and assessing the efficacy of drug treatment

Source: Therapeutic Goods Administration, accessed 18 March 2014, <https://www.ebs.tga.gov.au/>

Current reimbursement arrangements

DXA services are currently reimbursed for people 70 years or older (MBS item number 12323), women who suffer from a minimal trauma fracture and other pre-defined conditions and/or risk factors for osteoporosis. The conditions that relate to 'high osteoporosis risk', and that are currently eligible for reimbursement under the MBS, can be found in Table 1. Currently available MBS item numbers for DXA are shown in Table 4. For notes regarding these items, see Appendix G.

Table 4   Current MBS items for DXA scanning

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry
MBS 12306
Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), **using dual energy X-ray absorptiometry**, for:
- the confirmation of a presumptive diagnosis of low bone mineral density made on the basis of 1 or more fractures occurring after minimal trauma; or   - the monitoring of low bone mineral density proven by bone densitometry at least 12 months previously.
Measurement of 2 or more sites – **1 service only in a period of 24 months** – including interpretation and report; not being a service associated with a service to which item 12309, 12312, 12315, 12318 or 12321 applies (Ministerial Determination).
Fee: $100.50 Benefit: 75% = $75.40   85% = $85.45
Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry
MBS 12312

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using **dual energy X-ray absorptiometry**, for the diagnosis and monitoring of bone loss associated with 1 or more of the following conditions:

- prolonged glucocorticoid therapy;
- conditions associated with excess glucocorticoid secretion;
- male hypogonadism; or
- female hypogonadism lasting more than 6 months before the age of 45 years.

Where the bone density measurement will contribute to the management of a patient with any of the above conditions – measurement of 2 or more sites – 1 service only in a period of 12 consecutive months – including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12315, 12318 or 12321 applies (Ministerial Determination)

Fee: $100.50 Benefit: 75% = $75.40   85% = $85.45

Relevant explanatory notes

'Prolonged glucocorticoid therapy' is defined as the commencement of:

(a) a dosage of inhaled glucocorticoid equivalent to or greater than 800 micrograms beclomethasone, dipropionate or budesonide per day; or

(b) a supraphysiological glucocorticoid dosage equivalent to or greater than 7.5 mg prednisolone in an adult taken orally per day;

for a period anticipated to last for at least 4 months.

Glucocorticoid therapy must be contemporaneous with the current scan. Patients no longer on steroids would not qualify for benefits.

(a) Male hypogonadism is defined as serum testosterone levels below the age matched normal range.

(b) Female hypogonadism is defined as serum oestrogen levels below the age matched normal range.

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry

MBS 12315

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using **dual energy X-ray absorptiometry**, for the diagnosis and monitoring of bone loss associated with 1 or more of the following conditions:

- primary hyperparathyroidism;
- chronic liver disease;
- chronic renal disease;
- proven malabsorptive disorders;
- rheumatoid arthritis; or
- conditions associated with thyroxine excess.

Where the bone density measurement will contribute to the management of a patient with any of the above conditions – measurement of 2 or more sites – 1 service only in a period of 24 consecutive months – including interpretation and report; not being a service associated with a service to which items 12306, 12309, 12312, 12318 or 12321 applies (Ministerial Determination)

Fee: $100.50 Benefit: 75% = $75.40   85% = $85.45

Relevant explanatory notes

A malabsorptive disorder is defined as one or more of the following:

(a) malabsorption of fat, defined as faecal fat estimated at greater than 18 gm per 72 hours on a normal fat diet; or

(b) bowel disease with presumptive vitamin D malabsorption as indicated by a sub-normal circulating 25-hydroxyvitamin D level; or

(c) histologically proven coeliac disease.

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry

MBS 12321

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using **dual energy X-ray absorptiometry**, for the measurement of bone density 12 months following a significant change in therapy for:

- established low bone mineral density; or
- the confirmation of a presumptive diagnosis of low bone mineral density made on the basis of 1 or more fractures occurring after minimal trauma.

Measurement of 2 or more sites – 1 service only in a period of 12 consecutive months – including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12312, 12315 or 12318 applies (Ministerial Determination)

Fee: $100.50 Benefit: 75% = $75.40   85% = $85.45

Relevant explanatory notes

Item 12321 is intended to allow for bone mineral density measurement following a significant change in therapy—e.g. a change in the class of drugs—rather than a change in the dosage regimen.

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry

MBS 12323

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using **dual energy X-ray absorptiometry** or quantitative computerised tomography, for the measurement of bone mineral density, for a person aged 70 years or older.

Measurement of 2 or more sites – including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12312, 12315, 12318 or 12321 applies (Ministerial Determination)

Fee: $100.50 Benefit: 75% = $75.40 85% = $85.45

Relevant explanatory notes

Item 12323 enables the payment of a Medicare benefit for a bone densitometry service performed on a patient aged 70 years or older. The Government has decided to expand access to Medicare-subsidised bone mineral density testing to coincide with the expanded eligibility for the osteoporosis medication 'alendronate' under the Pharmaceutical Benefits Scheme.

QCT is also listed on the MBS for measuring BMD, for mostly the same indications. The currently available MBS items for QCT are shown in Table 5 and item number 12323 in Table 4.

Table 5   Current MBS items for QCT

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry

MBS 12309

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using quantitative computerised tomography, for:

- the confirmation of a presumptive diagnosis of low bone mineral density made on the basis of 1 or

---

more fractures occurring after minimal trauma; or

- the monitoring of low bone mineral density proven by bone densitometry at least 12 months previously.

Measurement of 2 or more sites – 1 service only in a period of 24 months – including interpretation and report; not being a service associated with a service to which item 12306, 12312, 12315, 12318 or 12321 applies (Ministerial Determination)

Fee: $100.50 Benefit: 75% = $75.40   85% = $85.45

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry

MBS 12318

Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using quantitative computerised tomography, for the diagnosis and monitoring of bone loss associated with 1 or more of the following conditions:

- prolonged glucocorticoid therapy;
- conditions associated with excess glucocorticoid secretion;
- male hypogonadism;
- female hypogonadism lasting more than 6 months before the age of 45 years;
- primary hyperparathyroidism;
- chronic liver disease;
- chronic renal disease;
- proven malabsorptive disorders;
- rheumatoid arthritis; or
- conditions associated with thyroxine excess.

Where the bone density measurement will contribute to the management of a patient with any of the above conditions - measurement of 2 or more sites - 1 service only in a period of 24 consecutive months - including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12312, 12315 or 12321 applies (Ministerial Determination)

Fee: $100.50 Benefit: 75% = $75.40   85% = $85.45

The usage of MBS items for DXA testing in females is shown in Table 6. MBS items regarding DXA scanning in women were used 262,482 times in 2012–13, of which 62.4% occurred in women 65 years of age or older. In women aged 45–54 years, only 27,507 DXA services were conducted. Of these women, 62.1% (17,082) had a DXA scan because they were considered 'high risk' (MBS items 12312 and 12315), and 32.2% (8,861) had a scan after suffering a minimal trauma fracture or for the monitoring of low BMD.

Table 6   MBS items used for DXA scanning of females between July 2012 and June 2013

	MBS 12306 (after fracture or monitoring low BMD)	MBS 12312 (hypogonadism, glucocorticoid secretion or therapy)	MBS 12315 (other indications associated with low BMD)	MBS 12321 (after significant change in therapy)	MBS 12323 (DXA + QCT aged 70 years or older)	All DXA
0–4 years	12	4	0	3	0	19
5–14 years	103	232	81	64	0	480
15–24 years	350	1,135	470	74	0	2029
25–34 years	925	1,436	862	113	0	3336
35–44 years	2,349	4,191	1,856	283	0	8,679
45–54 years	8,861	11,539	5,543	1,564	0	27,507
55–64 years	24,696	17,257	9,076	5,669	0	56,698
65–74 years	20,582	11,943	5,527	4,969	42,845	85,866
75–84 years	6,393	2,343	877	1,410	53,392	64,415
85 years or older	1,453	328	134	250	11,288	13,453
All ages	65,724	50,408	24,426	14,399	107,525	262,482

Source: https://www.medicareaustralia.gov.au/statistics/mbs_item.shtml, accessed 18 March 2014
Notes:
1: The low figures provided for 12306, 12312, 12315 and 12321 for patients aged 75 years or older may not reflect the true incidence of DXA scans clinically included under these item numbers, but instead may have been processed under the 70 years of age or older MBS item (12323).
2: MBS 12323 includes both QCT and DXA. However, the current usage of MBS item numbers for QCT is low, so we assumed that the usage of QCT in this item number would be negligible.

Proposal for public funding

The proposed MBS item is summarised in Table 7. As DXA services are already on the MBS for other indications, the fee is the same as for the existing MBS item numbers. The proposed item number relates to all women in their 50th year. As women with a T-score of ≤–2.5 would be eligible for repeat testing (monitoring) under item number 12306, it is expected that usage of this item number would increase after the introduction of the proposed new item (see 'Financial implications' section). The proposed item number would be used in addition to the existing MBS items for DXA and QCT. It is intended that it would only be used once in a woman's lifetime, in their 50th year; this limit may need to be made explicit in the item descriptor.

Table 7   Proposed MBS item descriptor for DXA scanning of women in their 50th year

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry
MBS XXXX
Bone densitometry (performed by a specialist or consultant physician where the patient is referred by another medical practitioner), using **dual energy X-ray absorptiometry**, for the measurement of hip and

spine bone mineral density in women in their 50th (or 55th or 60th) year.

Measurement of 2 or more sites – 1 service only – including interpretation and report; not being a service associated with a service to which item 12306, 12309, 12312, 12315, 12318, 12321 or 12323 applies (Ministerial Determination).

Fee: $100.50 Benefit: 75% = $75.40   85% = $85.45

Other relevant notes from D1.27, Bone Densitometry – (Items 12306 to 12323)

Consumer impact statement

There were no consumer responses received during the public consultation period.

Approach to assessment

The objective of this assessment was to determine whether there is sufficient evidence, in relation to safety, effectiveness and cost-effectiveness, to have DXA listed on the MBS for the screening of women in their 50th year. A structured assessment was carried out to assess:

- **clinical effectiveness**

  - *direct evidence*: <u>impact on health outcomes</u>—do women who are DXA tested in their 50th year have better health outcomes?

  - *linked evidence*:

    - <u>diagnostic accuracy</u>—this involves comparing DXA test results against a reference standard ('truth'), which may be determined by the rate of minimal trauma fracture

    - <u>impact on clinical decision making</u>—measured as the change in treatment decision made by clinicians, or the change in compliance rates in patients in response to the information provided by a DXA test

    - <u>effectiveness of treatment</u>—does treatment of those people with a diagnosis, or a change in rate of compliance, change the health outcomes of women determined to have low BMD?

- **safety**

- **economic considerations**

Clinical pathway

A flowchart can help define the place of a proposed new intervention in the clinical management of a patient (Figure 1). The dotted lines in Figure 1 show the proposed clinical pathway (with the intervention), whereas the solid lines show the current clinical pathway (with the comparator). In this case, management options are the same for both the comparator and the intervention, but the proportions of patients in the various branches may change. First, this may occur if DXA is more accurate, as more women who would normally develop a minimal trauma fracture would be provided with lifestyle advice, possibly preventing subsequent fractures. Second, the Applicant has claimed that this could occur if a larger proportion of women adhere to lifestyle and dietary advice following the results of a DXA, compared with a clinical fracture assessment without DXA.

An additional comparator for women who do not quality for DXA on the MBS is self-funded DXA, paid for by the patient and undertaken by private radiologists. Should the proposed new item be MBS funded, women who may have previously paid for their own DXA testing would now be eligible for an MBS-funded scan.
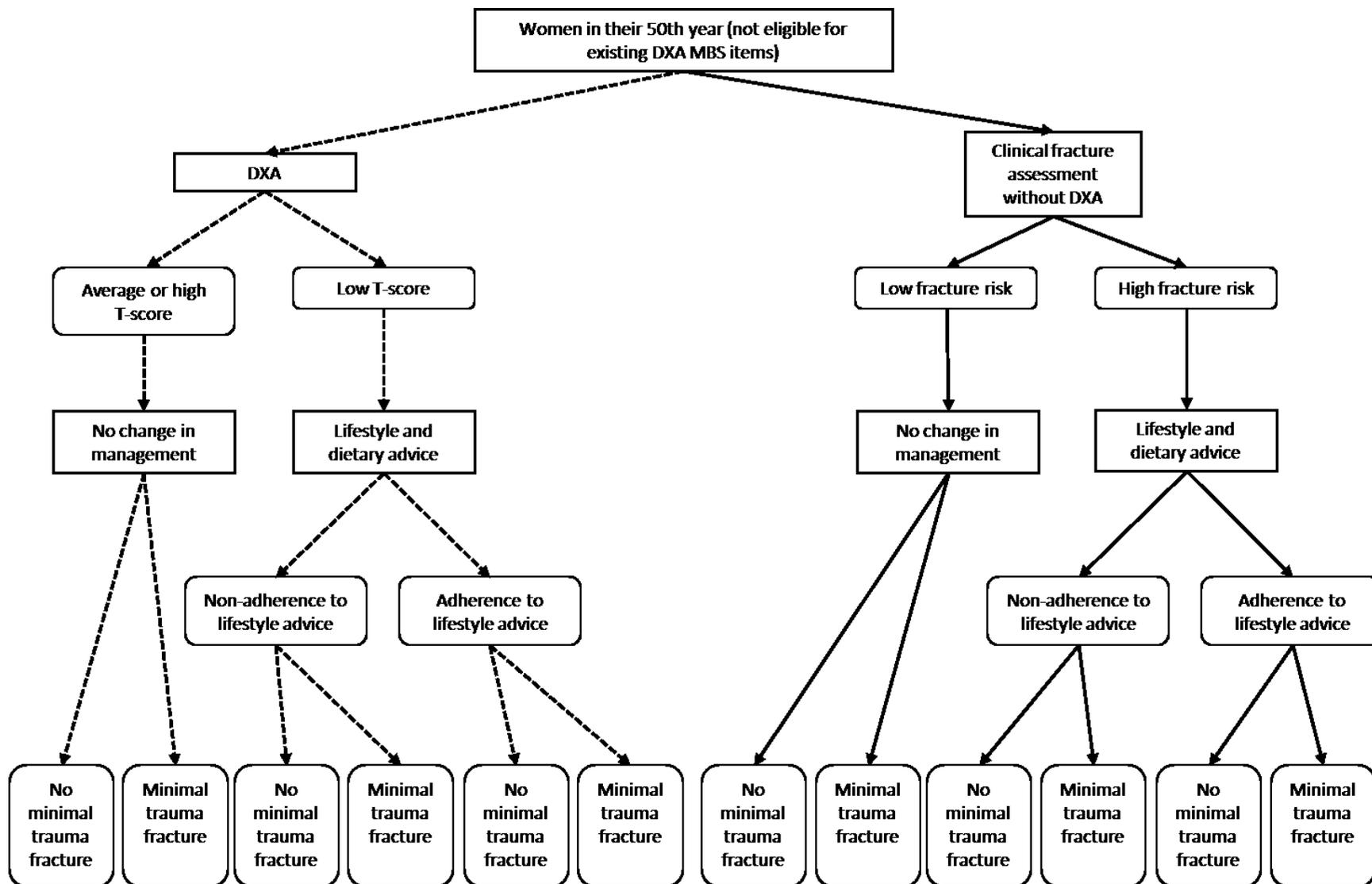
Figure 1   Clinical management algorithm for the proposed new intervention

Comparator

Comparators are usually selected by determining the test that is most likely to be replaced (or added to) by the technology submitted for a new MBS item number. Currently, most women in their 50th year will not receive a DXA test to measure BMD. Fracture risk may be assessed, however, through a clinical assessment provided by a general practitioner (GP) and conducted using existing fracture risk tools. Tools such as FRAX® can be used in combination with DXA results, or without DXA, as a predictor of risk of fracture.

Lifestyle and dietary advice will be offered if a patient is considered at risk of low BMD, irrespective of the method of determining fracture risk. Therefore, the comparator is:

- Lifestyle and dietary advice (calcium and vitamin D) based on a general clinical assessment by a GP using existing fracture risk assessment tools (for example the FRAX® algorithm) without the results of a BMD test.

The reference standard

As the aim of the intervention and comparator is to prevent minimal trauma fracture, the reference standard for determining the accuracy of DXA and fracture risk assessment tools is the occurrence of minimal trauma fracture (clinically diagnosed).

Research questions

In the event that direct evidence was available to assess the safety, effectiveness and cost-effectiveness of BMD analyses using DXA for women in their 50th year, the following research question was to be addressed by this evaluation:

- For women in their 50th year, what is the safety, effectiveness and cost-effectiveness of DXA to determine low or low–normal BMD, compared with clinical assessment (including the use of existing fracture risk assessment tools but no DXA), for preventing minimal trauma fracture?

In the event that linked evidence (see 'Diagnostic assessment framework' on page 38) was the only evidence available to assess the safety, effectiveness and cost-effectiveness of BMD analyses using DXA for women in their 50th year, the following research questions were also to be addressed:
Safety

- What is the safety of DXA compared with a clinical assessment (using existing fracture risk assessment tools but no DXA) for women in their 50th year ?

<u>Accuracy</u>

- What is the diagnostic accuracy of DXA compared with clinical assessment tools without DXA for women in their 50th year ?

<u>Change in patient management</u>

- Does having a low BMD identified through DXA testing, rather than a risk assessment without DXA, result in better adherence to preventive lifestyle advice?

<u>Effectiveness in case of a change in management</u>

- Does adherence to preventive lifestyle advice in women in their 50th year have an impact on health outcomes?

Diagnostic assessment framework

This assessment uses the theoretical framework outlined in the MSAC *Guidelines for the Assessment of Diagnostic Technologies* (MSAC 2005).

This means that evidence of the clinical effectiveness of BMD analyses using DXA requires either one or other of the following:

- evidence of the effectiveness of DXA from high-quality comparative studies (direct evidence). The use of DXA and subsequent lifestyle and dietary advice would be compared with clinical risk assessment (without DXA) and subsequent lifestyle and dietary advice. RCTs provide the highest quality evidence for this comparison

- evidence of treatment effectiveness from high-quality comparative studies that assess the change in lifestyle and diet for women in their 50th year (and its effect on minimal trauma fracture risk), linked with applicable and high-quality evidence of the accuracy of DXA at predicting the risk of fracture. This is called 'linked evidence'.

There was no direct evidence available that met all the inclusion criteria developed to determine the safety and effectiveness of DXA in women aged 40–65 years, so in this assessment a linked evidence approach was undertaken. This means that evidence from studies that report on diagnostic test performance (diagnostic accuracy), the impact on clinical decision-making, and the impact of lifestyle and dietary changes of women with a low T-score on health outcomes was narratively linked in order to infer the effect of the diagnostic test on patient health outcomes. For the last step of the linked analysis a separate search was conducted. Systematic literature reviews providing evidence on the

effectiveness of a change in lifestyle and diet in preventing minimal trauma fracture were collated.

Systematic review of the literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews addressing each of the research questions developed. DXA was first approved by the American Food and Drug Administration in 1988, so the search period was restricted to the period between 1988 and February 2014. Searches were conducted via the databases described in Table 8. Search terms are described in Table 9 and Table 10. In each database the search terms were mapped to the relevant indexing terms and exploded (e.g. MeSH for PubMed and the Cochrane Library, and EmTree for Embase.com). To identify systematic reviews, RCTs and meta-analyses, search filters were employed.

Table 8   Electronic databases searched

Electronic database	Period covered
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1988 – 2/2014
Current Contents	1988 – 2/2014
Embase	1988 – 2/2014
PubMed	1988 – 2/2014
Web of Science – Science Citation Index Expanded	1988 – 2/2014
Cinahl	1988 – 2/2014
Econlit	1988 – 2/2014
Scopus	1988 – 2/2014

Table 9   Search terms used

Element of clinical question	Search terms
Population	Osteoporosis OR osteopenia OR fractur* OR bone mineral density
Intervention	Dual energy X-ray absorptiometry
Comparator (if applicable)	N/A
Outcomes (if applicable)	N/A
Limits	Publication date from 1988 to 2014/2; Humans

N/A = not applicable

Table 10   **Search terms used to identify systematic reviews for the last step of the linked analysis (health outcomes)**

Element of clinical question	Search terms
Population	Osteoporosis OR fracture
Intervention	Lifestyle
Comparator (if applicable)	N/A
Outcomes (if applicable)	N/A
Limits	Publication date from 1988 to 2/2014; humans; systematic reviews or randomised controlled trials or meta-analyses or meta-syntheses

N/A = not applicable

Selection criteria

In general, studies were excluded from the systematic literature review if they:

- did not provide information on the pre-specified target population. This means that women younger than 40 years and older than 65 years of age were generally excluded, as the rate of bone loss in these women is very different from our target population (see 'Bone loss' at page 24), making it impossible to generalise results from older and younger populations to the population eligible for the MBS item under review;

- did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes;

- were in a language other than English and were of a lower level of evidence than the studies in English; or

- did not have an eligible study design.

If the same data were duplicated in multiple articles, only results from the most comprehensive or most recent article were included.

Search results

Figure 2 and Figure 3 provide an overview of the process of study selection for this systematic review, as per PRISMA reporting guidelines (Liberati et al. 2009).

PRISMA flowchart

```
┌──────────────────────────────────────────────────────────────────────────┐
│  Potentially relevant studies identified in the literature searches and    │
│  screened for retrieval:                                                   │
│  N=34,493                                                                  │
└──────────────────────────────────────────────────────────────────────────┘
                                    │
                                    ├──────────► ┌────────────────────────┐
                                    │            │  Duplicates removed:   │
                                    │            │  N=17,641              │
                                    │            └────────────────────────┘
┌──────────────────────────────────────────────────────────────────────────┐
│  Potentially relevant articles after duplicates removed:                   │
│  N=16,852                                                                  │
└──────────────────────────────────────────────────────────────────────────┘
                                    │
                                    ├──────────► ┌────────────────────────┐
                                    │            │  Articles excluded:    │
                                    │            │  N=16,446              │
                                    │            └────────────────────────┘
┌──────────────────────────────────────────────────────────────────────────┐
│  Full text articles retrieved for more detailed examination:               │
│  N=480                                                                     │
└──────────────────────────────────────────────────────────────────────────┘
```

- Papers identified through 'grey' literature: N=21
- Papers identified through pearling: N=3
- Papers identified via applicant: N=1

Did not meet inclusion criteria (N=498):
- Incorrect language (N=5)
- Incorrect study design (N=192)
- Incorrect population (N=93)
- Incorrect intervention (N=87)
- Incorrect comparator (N=36)
- Incorrect outcomes (N =67)
- Unable to retrieve full text (N=4)
- Duplicate study / population (N=5)
- No (extractable) data (N=9)

Included:
N=7

Figure 2   **Summary of the process used to identify and select studies for the systematic review (specifically searches for direct evidence and the first two linked evidence steps)**

```
┌─────────────────────────────────────────────────────────────────────────┐
│  Potentially relevant studies identified in the literature searches and    │
│  screened for retrieval:                                                    │
│  N=1,681                                                                    │
└─────────────────────────────────────────────────────────────────────────┘
                                    │
                                    │        ┌──────────────────────────┐
                                    ├───────▶│  Duplicates removed:      │
                                    │        │  N=66                     │
                                    │        └──────────────────────────┘
                                    ▼
┌─────────────────────────────────────────────────────────────────────────┐
│  Potentially relevant articles after duplicates removed:                    │
│  N=1,615                                                                    │
└─────────────────────────────────────────────────────────────────────────┘
                                    │
                                    │        ┌──────────────────────────┐
                                    ├───────▶│  Articles excluded:       │
                                    │        │  N=1,341                  │
                                    │        └──────────────────────────┘
                                    ▼
┌─────────────────────────────────────────────────────────────────────────┐
│  Full-text articles retrieved for more detailed examination:                │
│  N=274                                                                      │
└─────────────────────────────────────────────────────────────────────────┘
                                    │
                                    │   ┌────────────────────────────────────┐
                                    │   │ Did not meet inclusion criteria       │
                                    │   │ (N=262):                              │
                                    │   │  - incorrect language (N=1)           │
                                    ├──▶│  - incorrect study design (N=103)     │
                                    │   │  - incorrect population (N=42)        │
                                    │   │  - incorrect intervention (N=42)      │
                                    │   │  - incorrect outcomes (N =52)         │
                                    │   │  - unable to retrieve full text (N=3) │
                                    │   │  - data included elsewhere (N=2)      │
                                    │   │  - other (since updated or systematic │
                                    │   │    review postdates) (N=17)           │
                                    ▼   └────────────────────────────────────┘
┌─────────────────────────────────────────────────────────────────────────┐
│  Included:                                                                  │
│  N=12                                                                       │
└─────────────────────────────────────────────────────────────────────────┘
```

Figure 3   **Summary of the process used to identify and select systematic reviews in the last step of the linked analysis (health outcomes)**

Data extraction and analysis

A profile of key characteristics was developed for each included study (see Appendix C). Each study profile described the level of evidence, design and quality of the study, authors, publication year, location, criteria for including/excluding patients, study population characteristics, type of intervention, comparator intervention and/or reference standard (where relevant), and outcomes assessed. Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed in Appendix D. Definitions of all technical terms and abbreviations are provided in the Glossary (page 16). Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies.

Assessing diagnostic accuracy

To assess the accuracy of DXA testing to predict minimal trauma fracture, the aim was to report the sensitivity, specificity, negative and positive predictive values (NPV, PPV), and likelihood ratios of the tests with corresponding 95% confidence intervals (CIs). However, none of the included studies had data suitable for the calculation of these variables, nor to enable meta-analysis. Where diagnostic accuracy was reported in the studies, it was predominantly in the form of receiver operating characteristic (ROC) curves or area under the curve (AUC) data. These data were extracted and a narrative meta-synthesis of the data was undertaken.

Appraisal of the evidence

Appraisal of the evidence was conducted in three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review (strength of the evidence).

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results for primary outcomes in individual studies—used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Stage 1: strength of the evidence

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 11) consider important aspects of the evidence supporting a particular intervention and include 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 as informing a particular intervention; the last two each require expert clinical input as part of their determination.

Table 11   Evidence dimensions

Type of evidence	Definition
Strength of the evidence:	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design. [a]
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

[a] See Table 12

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results. The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (Table 12).

Table 12   Designations of levels of evidence according to type of research question (including table notes)

Level	Intervention [a]	Diagnostic accuracy [b]
I [c]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[d] among consecutive persons with a defined clinical presentation [e]
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[d] among non-consecutive persons with a defined clinical presentation [e]
III-2	A comparative study with concurrent controls: ▪ non-randomised, experimental trial [f] ▪ cohort study ▪ case-control study ▪ interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	A comparative study without concurrent controls: ▪ historical control study ▪ two or more single-arm studies [g] ▪ interrupted time series without a parallel control group	Diagnostic case-control study [e]
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [h]

Source: NHMRC (2009)

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Explanatory notes:

a   Definitions of these study designs are provided in NHMRC (2000; pp. 7–8) and in the accompanying Glossary.

b   These levels of evidence apply only to studies assessing the accuracy of diagnostic or screening tests. To assess the overall effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (MSAC 2005; Sackett & Haynes 2002).The evidence hierarchy given in the 'Intervention' column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis/comparator test(s). The evidence hierarchy given in the 'Screening' column should be used when assessing the impact of a screening test on health outcomes relative to no screening or alternative screening methods.

c   A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies and study designs might contribute to each different outcome.

d   The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al. 2003).

e   Well-designed population-based case-control studies (e.g. screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease is compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin & Miller 2002).

f   This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C to determine A vs C, with statistical adjustment for B).

g   Comparing single-arm studies, i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C to determine A vs C, but where there is no statistical adjustment for B).

h   Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; both physical and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarms and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Note C: Each individual study that is attributed a 'level of evidence' should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

Sources: Hierarchies adapted and modified from: Bandolier (1999); Lijmer et al. (1999); NHMRC (1999); Phillips et al. (2001)

Individual studies assessing the diagnostic effectiveness of DXA testing were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 13.

Table 13   Grading system used to rank included studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population

Quality of study	Was the study designed to avoid bias?
	High quality = no potential for bias based on pre-defined key quality criteria
	Medium quality = some potential for bias in areas other than those pre-specified as key criteria
	Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria
		Q1 high quality
		Q2 medium quality
		Q3 poor reference standard:
		  poor quality, or
		  insufficient information

The appraisal of intervention studies (trials and cohort studies) pertaining to treatment safety and effectiveness was undertaken using the Downs & Black (1998) checklist. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al. 2001). Studies of diagnostic accuracy were assessed using the QUADAS-2 quality assessment tool (Whiting et al. 2011), whereas systematic reviews included in the last step of the linked analysis were assessed with the PRISMA checklist (Liberati et al. 2009).

Stage 2: precision, size of effect and clinical importance

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000). Studies need to be appropriately powered to ensure that a real difference between groups will be detected in the statistical analysis.

For intervention studies it was important to assess whether statistically significant differences between patients receiving DXA or clinical risk assessment were also clinically important. The size of the effect needed to be determined, as well as whether the 95%CI included only clinically important effects.

The outcomes being measured in this report were assessed as to whether they were appropriate and clinically relevant (NHMRC 2000).

Stage 3: assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC on clinical practice guideline development (NHMRC 2008). Five components are considered essential by the NHMRC when judging the body of evidence:

1. the evidence-base—which includes the number of studies sorted by their methodological quality and relevance to patients;

2. the consistency of the study results—whether the better quality studies had results of a similar magnitude and in the same direction; that is, homogenous or heterogeneous findings;

3. the potential clinical impact—appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;

4. the generalisability of the evidence to the target population; and

5. the applicability of the evidence—integration of the evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 14).

Table 14 Body of evidence matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence-base [a]	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias, or an SR or several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency [b]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as target population	Population(s) studied in the body of evidence are similar to target population	Population(s) studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population [c]	Population(s) studied in body of evidence differ from target population and hard it is to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: adapted from NHMRC (2008)

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 12)

[b] If there is only one study, rank this component as 'not applicable'

[c] For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

SR = systematic review; several = more than two studies

Results of assessment

Is it safe?

Summary—For women in their 50th year, what is the safety of using DXA to diagnose low or low–normal BMD, compared with clinical assessment (including the use of existing fracture risk assessment tools but no DXA) of low BMD, in the prevention of minimal trauma fracture?

No studies were identified that evaluated the safety of DXA testing of women in their 50th year.

Studies would have been included to assess the safety of BMD analysis using DXA of women in their 50th year if they had met the criteria outlined *a priori* in Box 1.

Box 1   Criteria for selecting studies to assess the safety of DXA testing for low BMD in women in their 50th year

Selection criteria	Inclusion criteria
Population	(Healthy) women in their 50th year. Additional groups for consideration were women in their 55th year and 60th year. In the absence of studies on women in their 50th year, studies of women with a mean age of 40–65 years were considered
Intervention	Dual energy X-ray absorptiometry (DXA) for BMD, and treatment (lifestyle and dietary advice, including vitamin D test) for all women with negative T-scores
Comparators	Clinical assessment including the use of existing fracture risk assessment tools (and vitamin D test) with lifestyle and dietary advice
	No assessment and no lifestyle and dietary advice
Outcomes	Any adverse events or complications related to DXA scanning or treatments for osteoporosis
	Any adverse events arising from exposure to ionising radiation
Publication type	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports [a] or systematic reviews of these study designs
Search period	DXA was brought onto the market in 1988, so the search period was 1988 – 2/2014
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified

[a] Case reports were only assessed for safety outcomes

No studies were identified meeting the inclusion criteria and addressing the safety of DXA in women in their 50th year (or women aged 40–65 years). One high-quality systematic review that had a similar research question (although not meeting the inclusion criteria) was included due to the lack of evidence (Nelson et al. 2010). This systematic review was conducted in 2010 to update the evidence from the 2002 US Preventive Services Task Force (USPSTF) recommendation on osteoporosis screening. One of the key research questions

was: 'What are the harms associated with osteoporosis screening?' Screening included BMD measurements and mainly involved DXA testing. Unfortunately, no studies were identified in this systematic review that evaluated the potential harms from screening. The lack of empirical evidence in this high-quality systematic review on safety confirmed that we had not missed any relevant studies in our literature searches.

Is it effective?

Direct evidence of diagnostic effectiveness

Does BMD analysis using DXA for women in their 50th year improve health outcomes?

> **Summary—For women in their 50th year, what is the effectiveness of using DXA to diagnose low or low–normal BMD, compared with clinical assessment (including the use of existing fracture risk assessment tools but no DXA) of the risk of low BMD, in order to prevent minimal trauma fracture?**
>
> No studies were found that met all the inclusion criteria. A systematic review (Nelson et al. 2010) asking a similar research question identified no trials on the effectiveness of DXA screening. A further two studies that also had similar research questions were included and are described below due to the lack of evidence. In both these studies there was no information on the specified outcomes of fracture risk, quality of life or mortality/morbidity.
>
> The two studies measured change in BMD 1–2 years after a DXA test. Gutin et al. (1992) reported that the expected age-related reduction in BMD between visits was not found 12–18 months after DXA and subsequent lifestyle counselling in postmenopausal women. Winzenberg et al. (2006) reported a 1.1% increase per year (95%CI +0.9, +1.4) in femoral neck BMD from baseline to 2 years, and no change in lumbar spine BMD (+0.09% p.a.; 95%CI –0.06, +0.20) in premenopausal women. They concluded that DXA testing plus providing BMD results and lifestyle information is effective at increasing hip BMD during a 2-year follow-up.

Studies would have been included to assess the effectiveness of DXA testing of women in their 50th year if they had met the criteria outlined *a priori* in Box 2.

Box 2 Criteria for selecting studies to assess the effectiveness of BMD analyses using DXA on fracture risk, quality of life and morbidity/mortality in women in their 50th year

Selection criteria	Inclusion criteria
Population	(Healthy) women in their 50th year. Additional groups for consideration were women in their 55th year and 60th year. In the absence of studies on women in their 50th year, studies of women with a mean age of 40–65 years were considered
Intervention	Dual energy X-ray absorptiometry (DXA) for BMD, and treatment (lifestyle and dietary advice, including vitamin D test) for all women with negative T-scores
Comparators	Clinical assessment including the use of existing fracture risk assessment tools (including vitamin D test) with lifestyle and dietary advice
	No assessment and no lifestyle and dietary advice

Outcomes	Incidence of minimal trauma fracture, incidence of all fractures, patient-related quality of life, change in morbidity/mortality
Publication type	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports [a] or systematic reviews of these study designs
Search period	DXA was brought onto the market in 1988, so the search period was 1988 – 2/2014
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified

[a] Case reports were only included for safety outcomes

No studies were found that met all inclusion criteria. However, three articles that had similar research questions were included and are described below due to the lack of evidence.

The high-quality systematic review by Nelson et al. (2010) evaluated the direct effectiveness of DXA, albeit in a slightly older population. A key research question in this systematic review was: 'Does screening for osteoporosis and low bone density reduce osteoporosis-related fractures and/or fracture-related morbidity and mortality in postmenopausal women aged 50 years or older?' However, no trials were identified to assess the effectiveness of screening (using DXA).

A second study by Gutin et al. (1992) aimed to describe the impact of DXA and lifestyle counselling to achieve and maintain optimal bone health through changes in exercise and eating behaviours. The study was non-comparative, medium-quality and analysed retrospectively. Although the rate of fractures was not an outcome in the study, changes in bone density were reported. A total of 53 women were included with a mean age of 55.2 (SD = 5.14) years at first visit. They were postmenopausal without any other known osteoporosis risk factors. Before the initial DXA, patients completed a questionnaire that provided information on lifestyle, nutrition, and medical/genetic history. Upon arrival at the hospital they received a DXA (lumbar and femoral) test and a one-on-one counselling session, where osteoporosis risk factors were discussed along with ways to achieve and maintain optimal bone health.

The bone density results (in mg/cm^2) at the two visits (at baseline and 12–18 months after the intervention) are shown in Table 15. The age of the population was *inversely* and significantly correlated with femoral (r=–0.40; p=0.003) and spinal (r=–0.36; p=0.009) bone densities. However, in this study the expected age-related reduction in BMD between visits was not found 12–18 months after the intervention (DXA and counselling).

Table 15   Bone density (means (SD) in mg/cm² at both visits

BMD measurements	BMD visit 1 (SD)	BMD visit 2 (SD)	Change in mean BMD
Femoral neck (n=53)	0.81 (0.10)	0.82 (0.10)	NS
Lumbar spine (n=53)	0.95 (0.14)	0.96 (0.15)	NS
Radius (not DXA)	0.64 (0.12)	0.65 (0.10)	NS

NS = not significant, BMD = bone mineral density, SD = standard deviation

The third study aimed to determine the effects of individualised BMD feedback and two different educational interventions on osteoporosis preventive behaviour, and the 2-year change in BMD, in premenopausal women in a prospective high-quality study (Winzenberg et al. 2006). Although the study population consisted of younger women than targeted for this review (mean age was younger than 40 years), it was decided to describe the results due to the lack of available evidence. Fracture rate was not an outcome in this study and an appropriate comparator was also absent—all included participants (415/470 reached final follow-up; mean age = 37.4–38.4 years) received DXA and feedback. Those with a mean T-score at the hip or spine of ≥0 received a letter informing them that they were not at a higher risk of fracture, whereas those with a mean T-score of <0 were informed that they were at higher risk. Participants were randomised to receive either an information leaflet or the Osteoporosis Prevention and Self-management Course; women randomised to the leaflet intervention received their BMD feedback with the leaflet, whereas women randomised to the course received their BMD feedback at the first course session. Across the whole study population, there was a 1.1% per year (95%CI +0.9, +1.4) increase in femoral neck BMD from baseline to 2 years and no change in lumbar spine BMD (+0.09% p.a.; 95%CI –0.06, +0.20). Subjects in the low T-score group had a higher percentage rate of change in (femoral) BMD as well as a higher absolute change. This study therefore found that DXA and providing BMD results to premenopausal women is effective at increasing hip BMD during a 2-year follow-up. There was no difference in BMD as a consequence of the type of education implemented (information leaflet versus counselling).

Linked evidence

Evidence linkage 1: Is it accurate?

Summary—What is the diagnostic accuracy of DXA testing compared with clinical risk assessment?

Two studies were identified that compared the accuracy of DXA at predicting fracture risk relative to clinical risk assessment (FRAX® in both cases). Both studies were undertaken in Asia, in women of varying ages. The studies were both plagued by a high loss to follow-up, meaning that partial verification bias was likely in these trials. Results were not reported in a format that allowed meta-analysis; both reported AUC and found similar accuracy of DXA and FRAX® at predicting fracture risk. A further non-comparative study considered women in the appropriate age group for this assessment and followed them for 10 years subsequent to receiving DXA. It found DXA to be a poor predictor of fracture, although this was probably because of the low rate of fracture in the population.

Studies were included to assess the accuracy of DXA according to criteria outlined in Box 3.

Box 3   Criteria for selecting studies relevant to determining the accuracy of DXA testing in women in their 50th year

Selection criteria	Inclusion criteria
Population	(Healthy) women in their 50th year. Additional groups for consideration were women in their 55th year 60th year. In the absence of studies on women in their 50th year, studies of women with a mean age of 40–65 years were considered.
Intervention	Dual energy X-ray absorptiometry (DXA)
Comparator	Clinical risk assessment tool (e.g. FRAX® without DXA, QFracture)
Reference standard	Minimal trauma fracture
Outcomes	Sensitivity Specificity Positive/negative predictive value Level of agreement (concordance of data) Comparative diagnostic yield
Publication type	All study designs listed in the 'Diagnostic accuracy' column of Table 12
Search period	DXA was brought onto the market in 1988, so the search period was 1988 – 2/2014
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified

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Studies on the accuracy of DXA testing at predicting fracture risk, compared with clinical risk assessment, were rare. Only two studies (Cheung et al. 2012; Tamaki et al. 2011) were identified that directly compared the two risk assessment tools; in both cases the clinical risk assessment tool used was FRAX®. Cheung et al. (2012) conducted a prospective study of women in Hong Kong that were recruited through the community between 1995 and 2009. The study design had a low risk of bias. The mean age of the women was 62.1 ±8.5 years and participants had to be at least 1 year into the menopause, dwelling in the community and ambulatory. This means that there was likely to be some selection bias due to the exclusion of more frail and less ambulatory women. They were followed up for 4.5±2.8 years, and fracture of wrist, clinical spine, humerus or hip was ascertained by self-reporting and confirmed using medical records.

The Tamaki et al. (2011) study was undertaken in seven municipalities in Japan, with baseline measurements taken in 1996 and follow-up measures 10 years later (mean follow-up time was not reported). Women aged 15–79 years were randomly selected from a population register, but no other inclusion or exclusion criteria were described. The mean age of the participants was 56.7±9.6 years. The risk of bias in the study design was low; however, the ascertainment of fractures was based on self-reporting and the response rate at the 10-year follow-up was only 53%, so there was a high risk of partial verification bias. Moreover, fractures were not independently verified.

One other study (Stewart, Kumar & Reid 2006) considered the diagnostic accuracy of DXA relative to the reference standard but without a comparator. This study, conducted in Aberdeen in Scotland, followed 5,119 women aged 45–54 (mean 48.6±2.4) years over a 10-year period. Although there was a low risk of bias due to the study design, there was some loss at follow-up as the authors used n=3,883 when reporting their results. As with the Tamaki et al. (2011) study, this loss to follow-up would result in a high risk of partial verification bias.

The results from the three included studies are presented in Table 16. The AUC calculated for each of these studies showed that there was average fracture risk prediction performance for both DXA and a clinical risk assessment, although both were better at predicting hip fracture than any other osteoporotic fracture. The study (Stewart, Kumar & Reid 2006) that included women of an age closest to the target MBS population did not have a comparator, and found DXA to be poor at predicting fracture risk.

Table 16   Diagnostic accuracy of DXA and FRAX® in women 40–65 years of age (reference standard = minimal trauma fracture)

Study	Intervention	Comparator	Results: AUC
Cheung 2012	DXA of lumbar spine, femoral neck and total hip	FRAX® Ethnic-specific CRF	Major osteoporotic fracture: DXA 0.71 (95%CI 0.66, 0.76) FRAX® 0.71 (95%CI 0.66, 0.76) CRF 0.73 (95%CI 0.68, 0.78) Hip fracture: DXA 0.86 (95%CI 0.79, 0.92) FRAX® 0.90 (95%CI 0.83, 0.97) CRF 0.90 (95%CI 0.84, 0.96)
Tamaki 2011	DXA of femoral neck	FRAX® (Japanese version)	Major osteoporotic fracture: DXA 0.64 (95%CI 0.57, 0.72) FRAX® 0.67 (95%CI 0.59, 0.75) Hip fracture: DXA 0.82 (95%CI 0.67, 0.98) FRAX® 0.86 (95%CI 0.68, 1.00)
Stewart 2006	DXA of lumbar spine and femoral neck	none	Lumbar spine fracture: DXA 0.62 (95%CI 0.60, 0.64) Femoral neck fracture: DXA 0.59 (95%CI 0.58, 0.61)

DXA = dual X-ray absorptiometry, FRAX® = WHO Fracture Risk Assessment Tool, CRF = ethnic-specific clinical risk factors, AUC = area under the curve

There were several other studies of an appropriate design to consider for diagnostic accuracy, including a meta-analysis. However, none of these studies calculated test accuracy; the results were focused on hazard ratios per standard deviation decrease in *baseline* BMD. Other studies used peripheral DXA, which is not recommended in Australian guidelines for measuring BMD. Studies were also excluded due to inappropriate age groups; many focused on groups considerably older than the one under consideration. Due to a much higher fracture rate in older populations, it was not appropriate to apply those results to younger women. The length of time needed to follow 50 year old women to determine fracture outcomes is probably one of the major reasons why there is so little data regarding this age group. Even though the Stewart et al. (2006) study followed a large cohort of women of an appropriate age for 10 years, there were still only 325 fractures in the cohort (around 8% of the participants experienced a fracture).

The first step of the linked evidence analysis indicated that the DXA test is as accurate as a clinical risk assessment tool, although it does entail some risk, albeit small, from ionising radiation, in contrast to the negligible risk associated with a clinical risk assessment tool.

Evidence linkage 2: Does it change patient management?

Summary—Does having a low BMD identified through DXA testing, rather than a risk assessment without DXA, result in better adherence to preventive lifestyle advice?

Two studies were included that reported on a change in the management of women aged 40–65 years after a DXA test. A medium-quality RCT reported that the intervention group (n=101; received a DXA test and questionnaires at 0, 6 and 12 months) had a significantly higher mean daily calcium intake than the control group (n=102; no DXA, questionnaires at 0, 6 and 12 months) at a follow-up of 12 months (836.22 mg and 750.15 mg, respectively). However, the mean calcium intake increased in the whole participant population during the study, from 613.43 mg/day at baseline to 775.03 mg/day at 6 months and 792.97 mg/day at 12 months. The other non-comparative study reported an increase in adequate calcium intake from 43% at baseline to 70% at 12–18 months after DXA testing (n=46).

The RCT reported no significant difference in exercise activity in women over the period of the study or between the intervention and control groups. A slight increase in women reporting adequate physical activity at follow-up (p=0.06) was reported in the non-comparative study.

Studies were included to assess patient change in management, following a DXA test plus lifestyle and dietary advice, according to the criteria outlined *a priori* in Box 4.

Box 4   Criteria for selecting studies to determine changes in management following DXA testing for low BMD

Selection criteria	Inclusion criteria
Population	(Healthy) women in their 50th year. Additional groups for consideration were women in their 55th year and 60th year. In the absence of studies on women in their 50th year, studies of women with a mean age of 40–65 years were considered.
Intervention	Dual energy X-ray absorptiometry (DXA) for BMD, and treatment (lifestyle and dietary advice, including vitamin D test) for all women with negative T-scores
Comparators	Clinical assessment including the use of existing fracture risk assessment tools (and vitamin D test) with lifestyle and dietary advice, or no clinical risk assessment and no DXA
Outcomes	Proportion of women who adhered to the dietary and lifestyle change
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series or systematic reviews of these study designs

Search period	DXA was brought onto the market in 1988, so the search period was 1988 – 2/2014
Language	Studies in languages other than English were excluded unless they represented a higher level of evidence than that available in the English language evidence-base

Two studies were included to assess the impact of a DXA result on participants' adherence to diet and lifestyle advice. One study compared results of the intervention to a control arm where no risk assessment was undertaken (Sedlak et al. 2007), whereas the other study did not have a comparator (Gutin et al. 1992).

Sedlak et al. (2007) conducted a medium-quality RCT of postmenopausal women aged 50–65 years in general good health (no chronic diseases) who responded to media advertisements and were able to read and write English (study conducted in the U.S.). The mean age of the study population was 56.6 years. After inclusion, all women received questionnaires to determine their knowledge, health beliefs, behaviours and self-efficacy regarding (the prevention of) osteoporosis. The intervention group (n=101) subsequently had a DXA test, whereas the control group (n=102) did not. Women in the intervention group received a letter reporting the results of the DXA test and providing information on how the results should be interpreted. If the DXA test showed below-normal results, a follow-up with the participant's physician was recommended. Study questionnaires were completed in both groups at two more times: 6 months and 12 months after the initial questionnaire.

The study by Gutin et al. (1992) has been included in the evaluation of direct effectiveness (page 51), but it also provided some (non-comparative) information on change in management. Gutin et al. (1992) aimed to describe the changes in exercise and dietary changes resulting from DXA and the provision of counselling to prevent osteoporosis in a non-comparative retrospective study. The study population consisted of 46 women with a mean age of 55.0 (SD = 5.45) years at first visit, and the follow-up was done 12–18 months later. Although a study by Winzenberg et al. (2006) (page 53) also reports on some change in health behaviours after DXA, no extractable data were available. Furthermore, the population did not quite fit the inclusion criteria (a mean age younger than 40 years). Therefore, it was decided to exclude this study from the 'change in management' section.

Calcium intake

On average, the whole study population (n=203) in the RCT by Sedlak et al. (2007) significantly increased their calcium intake over the course of the study, from 613.43 mg/day to 775.03 mg/day and 792.97 mg/day at 6 and 12 months, respectively

(Wilks's λ F = 11.684; df=2, 200; p≤0.001). At 12 months there was also a significant difference in mean calcium intake between the intervention and control groups— 836.22 mg/day and 750.15 mg/day, respectively. In the study by Gutin et al. (1992), 20/46 women (43%) reported an adequate calcium intake (at least 750 mg/day) at the start of the study. At follow-up 2 of these women dropped to the 'inadequate calcium intake' category, whereas 14 women moved from the 'inadequate calcium' category to the 'adequate calcium' category. So, at the end of the study, 70% of women had an adequate calcium intake (p=0.02).

Exercise

In the RCT by Sedlak et al. (2007) women in both groups (n=203) reported similar amounts of exercise over time; no significant differences were observed between the groups or at the start or end of the study. The mean exercise time was 74.64 minutes/week. Gutin et al. (1992) reported adequate physical activity (at least 3 hours of weight-bearing exercise a week) in 31/46 women (67%) at the start of the study. At follow-up 5 women dropped from adequate to inadequate exercise, whereas 8 women moved from inadequate to adequate physical activity. This means that at, the end of the study, 74% reported adequate exercise (p=0.06).

Hormone therapy and osteoporosis medication

The RCT also reported on osteoporosis drug use (Sedlak et al. 2007). None of the women included in the study reported taking hormone replacement therapy or medication to treat osteoporosis at the start of the study. At 12 months there was a significant difference between groups, with 18.8% (n=19) of the intervention group and only 5.9% (n=6) of the control group taking medications to prevent or treat osteoporosis (Chi square test, χ^2=7.856; df=1; p≤0.01).

Based on these findings, the overall impact of the change in management from DXA compared with clinical risk assessment is uncertain. The analysis then proceeded to the third step of the evidence linkage.

Evidence linkage 3: Does change in management improve patient outcomes?

Summary—Do alterations in clinical management and treatment options have an impact on the health outcomes of patients with low BMD and osteoporosis?

Despite a considerable body of evidence for lifestyle interventions to prevent fracture, there is very little evidence applicable to the target population for this assessment. The majority of studies have been undertaken in older people, many in populations with previous fractures or in institutionalised populations, thus limiting their applicability to this assessment.

A large, comprehensive systematic review undertaken by the Agency for Healthcare Research and Quality (AHRQ) in the U.S. found that the evidence for benefits from both vitamin D and calcium was uncertain, and there was insufficient evidence regarding exercise. In other systematic reviews it was found that the evidence is uncertain regarding the effectiveness of vitamin D in the general population, but there is some evidence that vitamin D with calcium can be beneficial for preventing hip fracture in institutionalised patients. With regard to calcium supplementation, there was a non-significant reduction in vertebral fractures. Systematic reviews of RCTs found no effect of exercise in a few, small trials; however, a review of observational studies found a significant protective effect of exercise and consistency in results across many large studies (although the results may have been affected by confounding). Despite these variable and uncertain findings, lifestyle interventions are recommended in Australian osteoporosis guidelines, perhaps because the benefits for lifestyle change (particularly exercise) are broad reaching. The risk of harm from these interventions is probably small if supplementation is given in correct doses and the lifestyle change occurs with appropriate guidance.

A literature search was conducted to investigate the effectiveness of lifestyle interventions (exercise, and calcium and vitamin D supplementation) in preventing fractures. The search was limited to systematic reviews and RCTs; several suitable systematic reviews were identified for each intervention, so RCTs were only considered if they were published after the reviews. The PICO criteria outlined *a priori* are presented in

Box 5, and the PRISMA flowchart for this search is shown in Figure 3.

Box 5   Criteria for selecting studies to assess the impact on health outcomes of a change in management following DXA testing for low BMD

Selection criteria	Inclusion criteria
Population	(Healthy) women in their 50th year. Additional groups for consideration were women in their 55th year and 60th year. In the absence of studies on women in their 50th year, studies of women with a mean age of 40–65 years were considered
Intervention	(Adherence to) lifestyle and dietary advice for women with negative T-scores
Comparators	No intervention and no adherence to lifestyle advice in women with negative T-scores
Outcomes	(Proportion of women who adhere to the dietary and lifestyle change) Incidence of minimal trauma fracture, incidence of all fractures, patient-related quality of life, change in morbidity/mortality
Study design	Systematic reviews, meta-analyses, evidence-based clinical practice guidelines
Search period	DXA was brought onto the market in 1988, so the search period was 1988 – 2/2014
Language	Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base

There was a dearth of evidence in the age group relevant to this assessment. The studies tended to focus on older age groups, in which the majority of fractures happen.

A systematic review by the U.S. AHRQ, updated to March 2011 from a review published in 2008, looked at the performance of calcium, vitamin D and exercise interventions, as well as pharmaceutical treatments for osteoporosis, at preventing fracture (Crandall et al. 2012). This very comprehensive review considered many types of fracture outcome, and the systematic reviews identified in the AHRQ search were also identified by our review. A summary of the findings of the AHRQ report is provided below; some of the systematic reviews have also been considered separately in order to provide greater detail on specific populations.

The AHRQ review was very thorough. The 2012 publication was an update of a review published in 2008. The search strategy, data extraction, quality appraisal and methods for analysing data were all of high quality, thus ensuring that the review had a low risk of bias. For calcium, four systematic reviews including 23 RCTs were included; for vitamin D there were 16 meta-analyses that comprised 43 RCTs; and there was one systematic review that considered exercise (Crandall et al. 2012).

The study reported its findings based on the strength of the evidence developed by the AHRQ and on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Crandall et al. 2012). For calcium, the strength of the evidence was

moderate (i.e. moderate confidence that the evidence reflects the true effect, but further research may change the estimate or the confidence of the estimate). However, the effectiveness of calcium supplementation is uncertain; several large, good-quality RCTs were unable to demonstrate the effectiveness of calcium at reducing fracture risk in postmenopausal women. For vitamin D, again the effectiveness of the agent at preventing fracture was uncertain and the evidence was of low to moderate strength. Thus, despite a considerable number of trials and systematic reviews assessing the impact of calcium and vitamin D on fracture prevention, the results varied widely and there was inadequate evidence to conclusively judge the effectiveness of either intervention. There was also insufficient evidence to make a recommendation about exercise.

The authors attributed the variability in results to differing methodologies, settings and populations in the trials. Importantly, the populations in which the vast majority of these studies occurred is not the same as that for the current assessment; whereas many studies included healthy postmenopausal women, many also included women who already had low BMD or osteoporosis, had already sustained a fracture, or had any number of other risk factors for low BMD. Thus, it is difficult to apply the findings of this systematic review to the current assessment.

Each of the three lifestyle interventions are considered separately below.

<u>Exercise</u>

A Cochrane systematic review, last updated in January 2011, considered RCTs with an exercise intervention in postmenopausal women (Howe et al. 2011). This review was of high quality. A total of 43 trials were included, although fracture rate was the primary outcome in only one trial and was reported as an adverse event in three others. All the other studies used BMD as their primary outcome measure. The four trials that included fracture as an outcome comprised n=539 participants. One of these trials used dynamic weight-bearing exercise of low force (such as walking or tai chi), and two of high force (such as jogging or jumping), and the other used a combination of approaches. In the one study with fracture as the primary outcome, the mean age of participants was 70.6±8.7 years and all participants also received alendronate. The study quality was deemed to be unclear due to a lack of detailed reporting. Two of the three studies that recorded fracture as an adverse event were deemed to be at low risk of bias and were undertaken on women aged 70–79 years, whereas the third was on younger women 54±3.5 years of age but the risk of bias was unclear and only post-intervention measures without further follow-up were reported. The risk of fracture in the exercise group was lower than in the control group, but the difference

was not statistically significant and the wide confidence interval suggests that the analysis was underpowered (OR 0.61; 95%CI 0.23, 1.64).

A systematic review by Lock et al. (2006) included three RCTs of exercise, but these were all included in the ARHQ review and so have not been considered further.

A systematic review conducted by the U.S. National Osteoporosis Foundation (NOF) in 1998 found no RCTs with exercise as an intervention and fracture as an outcome; likewise, the systematic review conducted in 2008 by Moayyeri to assess exercise for preventing fractures in middle-aged and elderly people of both sexes found no RCTs with fracture as the outcome. Prospective cohort studies, where exercise was not an intervention but a measurable exposure, were then considered, and 21 were identified as relevant. This review did not report any quality assessment of the included studies; however, the possible bias associated with selecting healthy participants into the studies was discussed. The review found that exercise, variously described, was protective against hip fracture in a meta-analysis with 13 studies included (RR_p= 0.62; 95%CI 0.56, 0.69; I^2=0.7%; p=0.43). One of the major issues with these studies, some of which were very large (over 90,000 participants) and with long follow-up duration (up to 15 years), was the very low fracture rate, meaning that there was greater imprecision in the results. However, the results of the studies included in the meta-analysis were very consistent and heterogeneity between the studies was low. Given the known impact of confounding in observational studies, it is likely that, although there appears to be a protective effect from exercise, the magnitude of the effect may not be as large as observed. The more recent evidence available in the AHRQ review has not confirmed these results.

Vitamin D with or without calcium

Several reviews of vitamin D supplementation, and vitamin D in conjunction with calcium supplementation, were identified.

A Cochrane review by Avenell et al. (2009) considered vitamin D in its various states with or without calcium, as well as compared with placebo, no treatment or calcium. This high-quality review included a total of 45 trials with 84,585 participants. Various populations were included in the trials, and participants were generally older, with mean ages greater than 70 years. Some trials had a previous fracture as a selection criterion, whereas others excluded people with previous fractures, and participants were recruited from both community and institutional settings. Subgroup analyses by residence (community-dwelling versus nursing homes) were conducted, and the results showed that there was a protective effect of vitamin D and calcium against hip fracture in two trials (n=3,852) conducted in

institutionalised settings (RR_p 0.75; 95%CI 0.62, 0.92; χ^2= 0.38; df=1; p=0.0049) but not for community-dwelling participants (k=6; RR_p 0.91; 95%CI 0.76, 1.08; χ^2=2.17; df=5; p=0.27; I^2=0.0%). Additionally, people with previous fracture were not protected from hip fracture by taking a combination of vitamin D and calcium (k=4; RR 1.02; 95%CI 0.71, 1.47; χ^2=1.28; df=3; p=0.71; I^2=0.0%), but there was a protective effect in participants without a previous fracture (k=4; RR_p 0.81; 95%CI 0.71, 0.93; χ^2=1.75; df=3; p=0.0038; I^2=0.0%). The overall conclusions were that vitamin D alone was unlikely to prevent fracture, but that it may be effective in preventing hip fractures in frail older people confined to institutions. The results are shown in Table 17.

Table 17   Results from the Cochrane review of vitamin D supplementation for prevention of osteoporotic fractures

Comparison	Number of trials	Population(s)	Results
Vitamin D alone versus placebo or no treatment	10	Various populations recruited from communities (including GPs) and nursing homes; some trials had previous hip fracture as inclusion criteria, whereas others excluded previous hip fracture patients; mean ages between 74 and 85 years	Hip fracture (k=9 trials): RR_p 1.15; 95%CI 0.99, 1.33; χ^2=4.58; df=8; p=0.065; I^2=0.0% Non-vertebral fracture (k=1 trial): RR 0.96; 95%CI 0.80, 1.15 Vertebral fracture (k=5 trials): RR_p 0.90; 95%CI 0.42, 1.92; χ^2=7.54; df=3; p=0.78; I^2=60% Any fracture (k=10 trials): RR_p 1.01; 95%CI 0.93, 1.09; χ^2=14.68; df=9; p=0.77; I^2=39%
Vitamin D plus calcium versus placebo or no treatment	9	Various populations recruited from communities and nursing homes; included people with previous fractures but one study excluded people with known osteoporosis; mean ages between 69 and 85 years	Hip fracture (k=8 trials): RR_p 0.84; 95%CI 0.73, 0.96; χ^2=4.47; df=3; p=0.0082; I^2=0.0% Non-vertebral fracture (k=9 trials): RR_p 0.95; 95%CI 0.90, 1.00; χ^2=9.65; df=8; p=0.052; I^2=17% Vertebral fracture (k=3 trials): RR_p 0.91; 95%CI 0.75, 1.11; χ^2=0.37 df=1, p=0.36
Alfacalcidol versus placebo or no treatment	7	All studies except one were Japanese mixed populations; one study included patients with Parkinson's disease and two had stroke patients; some included recent fracture, some excluded recent fracture; mean ages not all reported but youngest was 50 years; one study	Hip fracture (k=4 trials): RR_p 0.18, 95%CI 0.05, 0.67, χ^2=0.49; df=3; p=0.01; I^2=0.0% Non-vertebral fracture (k=5 trials): RR_p 0.39; 95%CI 0.15, 1.00; χ^2=2.90; df=2; p=0.011; I^2=31%

Comparison	Number of trials	Population(s)	Results
		included postmenopausal women with mean age 51 years, but was a very small study (n=44) All participants had osteoporosis	Vertebral fracture (k=1 trial): RR 0.65; 95%CI 0.33, 1.27
Calcitriol versus placebo or no treatment	3	Various populations aged 54–77 years; two studies included women with previous fracture and one excluded women with osteoporosis	Hip fracture (k=1 trial): RR 0.33; 95%CI 0.01, 8.10 Non-vertebral fracture (k=1 trial): RR 0.46;95%CI 0.18, 1.18 Vertebral deformity (k=3 trials): RR_p 0.75; 95%CI 0.40, 1.41; χ^2= 3.41 df=2; p=0.37; I^2=41%

Source: Avenell et al. (2009)

Several other systematic reviews also looked at the impact of vitamin D, with or without calcium, on bone health. The NOF (1998) included three controlled studies in men and women of mean age 80 years or older, with a 3- to 4-year follow-up. One RCT found a non-significant increase in fractures in the intervention group, whereas the other two studies found a decrease. The authors concluded that the evidence was too uncertain to make conclusions about the effectiveness of vitamin D at preventing fractures. Tang et al. (2007) included RCTs in their review that investigated the impact of calcium with or without vitamin D supplementation. This review had a low risk of bias and located 17 RCTs with variable populations. The mean age of participants was 58–85 years, and the study sizes ranged from very small (n=19) to very large (n=9,605), with an average treatment duration of 3.5 years. This review found that both calcium alone and calcium with vitamin D supplementation were associated with a statistically significant reduction in fracture of all types (random effects model, RR_p 0.88; 95%CI 0.83, 0.95; I^2=20%). A further review by Boonen et al. (2007), including nine studies, assessed RCTs of vitamin D supplementation, with and without added calcium, for prevention of hip fracture. The populations were mixed, with mean ages of 62–85 years, and the study sizes were n=583 and n=36,282. This review found a reduction in hip fracture risk with vitamin D plus calcium supplementation (k=6; RR_p 0.82; 95%CI 0.71, 0.94; p=0.0005; I^2=5%), but not for vitamin D alone (k=4; RR_p 1.10; 95%CI 0.89, 1.36; p=0.38; I^2=0%). An older systematic review by Papadimitropolous (2002), which had a low risk of bias but included many small older trials in which the mean age of the participants was mostly older than 65 years, found a reduction in vertebral fractures (k=8; RR_p 0.63; 95%CI 0.45, 0.88; p<0.01; heterogeneity p=0.16) but not in non-vertebral fractures (k=6; RR 0.77; 95%CI 0.57, 1.04; p=0.09; heterogeneity p=0.09).

One RCT worth mentioning was the Women's Health Initiative, a very large trial of n=36,282 postmenopausal women aged 50–79 years who were randomised to vitamin D and calcium or placebo, and followed up for 7 years (Prentice et al. 2013). The trial's primary outcome measure was hip fracture, with all fractures and death as secondary outcomes. The hazard ratio for hip fracture occurrence following more than 5 years of calcium and vitamin D supplementation versus placebo was 0.62 (95%CI 0.38, 1.00), and the authors concluded that the overall results were null or inconclusive regarding the effectiveness of vitamin D and calcium supplementation on fracture risk.

The evidence for vitamin D supplementation with or without calcium for preventing fracture in women around the age of menopause is therefore lacking. The vast majority of the studies were in much older adults, and much of the time in people with other risk factors for fracture, such as previous fracture. It is difficult to apply this information to the population in question for this assessment.

<u>Calcium intake</u>

Four systematic reviews were identified on the effectiveness of calcium supplements and/or dietary calcium intake for the prevention of fractures in postmenopausal women. Two of these reviews were of high quality; they were by the same authors and reported similar methods and results (Shea et al. 2002, 2004).

In these systematic reviews, five studies reported fractures as an outcome and included 576 women. The average age varied from 58.0 years to 73.5 years, and follow-up was between 1.5 and 4 years. All five RCTs investigated the effect of calcium supplementation on vertebral fractures. The pooled RR indicated a trend towards a reduction in vertebral fractures in the intervention group (k=5; RR_p 0.79; 95%CI 0.55 to 1.13; p=0.2); however, this was not statistically significant. Only two RCTs also included non-vertebral fractures. These studies had very few reported fractures and the confidence interval is therefore very wide (RR_p 0.86; 95%CI 0.431.72; p=0.66; k=2). For all fractures (vertebral and non-vertebral) the effect of calcium was consistent across the different trials (heterogeneity p=0.40, 0.54 respectively).

The two remaining systematic reviews were older and of lower quality than those by Shea et al. (Cumming & Nevitt 1997; 1998). The authors included 4 RCTs, 3 non-randomised trials, 7 observational epidemiologic studies of calcium supplements, and 23 observational epidemiologic studies on dietary calcium (18 concerned with hip fractures). The RCTs included 3,638 women, but 3,270 were from one trial and recruited from nursing homes where the mean age was 84 years. A reduced fracture risk in the range 26%–70% was seen

among women randomised to receive calcium supplements. All subjects in the included non-randomised studies had at least one vertebral fracture upon entry into the study. A similar effect was seen in these studies, where a lower risk of new fractures was observed in women who were given calcium supplements compared with untreated women. Observational studies were inconsistent in their results. The NOF (1998) systematic review identified the same four RCTs as Cumming and Nevitt (mean age 58.5–84.0 years), comparing the effects of oral calcium supplements and placebo on the incidence of fracture. An additional study was included that investigated treatment with calcium plus vitamin D supplements. The studies reported widely varying results because of the differences in populations and treatments, and the small sample sizes in most of the studies. Each of the studies suggested an effect in reducing the chance of fracture by about one-third, but there was a wide range of effects and therefore a definitive statement about the magnitude of the effect could not be made.

Other relevant considerations

Current guidelines regarding DXA testing in perimenopausal women

Rossignol et al. (2002) synthesised and compared recommendations made by public agencies in Western countries concerning screening for osteoporosis. Eleven reports were included in the analysis. In the category 'women in the perimenopausal period', nine reports made an explicit recommendation: five reports (INAHTA 1996, European Commission 1999, Canadian Task Force 1993, Institut National de la Santé et de la Recherche Médicale 1996-1997 (France), and UK Department of Health 1999) made a recommendation against the use of densitometry; and the remaining four reports (U.S. Preventive Services Task Force 1996, U.S. National Institutes of Health 2000, Swedish Council of Technology Assessment in Health Care 1997, and Catalan Agency of Health Technology Assessment 1999) made no recommendation because of the lack of scientific evidence. They concluded that mass screening was generally not recommended either for the general population or the population of perimenopausal women (Rossignol et al. 2002).

More-recent Australian guidelines (Osteoporosis Australia 2013, The Royal Australian College of General Practitioners 2010) recommend DXA scanning only for men and women over 50 years of age with one or more risk factors, or when there is a history of minimal trauma fracture. Recent US recommendations are that all women 65 years of age or older should receive a DXA scan. Younger postmenopausal women (aged 50 years or older according to some guidelines) should be evaluated for risk factors and receive a DXA scan if they have at least one major or more than one minor risk factor for osteoporosis (North American Menopause Society 2010; U.S. Preventive Services Task Force (USPSTF) 2011; Lim, Hoeksema & Sherin 2009). An evidence-based guideline published by the National Clinical Guideline Centre (NICE, UK) concluded: '*Do not routinely assess fracture risk in people aged under 50 years unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture), because they are unlikely to be at high risk*' (NICE 2012a).

In conclusion, no guidelines from Western countries were found that had a positive recommendation for DXA scanning in asymptomatic women around 50 years of age. Furthermore, the WHO concluded in 2006 that indirect evidence supports screening for women 65 years of age or older, but that there is no evidence supporting widespread screening programs using BMD testing (Johnell & Hertzman 2006).

Effects of implementation of DXA for women in their 50th year

With implementation of the proposed item number, only women that are 49 years of age (i.e. in their 50th year) would be eligible for a DXA test. This raises the question of uptake: what percentage of 49 year old women would undergo a DXA scan? It is expected that this would largely depend on how women are informed of the possibility of having the test—whether they are referred by their physician or receive a letter in the mail. Furthermore, it is not known if there would be the possibility of 'leakage' beyond the intended indication. Clarification is needed on what whether a woman who is already 50 years of age or older at the time of the DXA scan would be eligible to claim the MBS item. If there is a high uptake rate of screening with DXA, it is not known if this would significantly increase waiting times for the imaging procedure.

As the proposed item number is for *all* women in their 50th year, those with confirmed osteoporosis (T-score ≤–2.5) would be eligible for repeat testing under MBS item number 12306 once every 24 months (this item number allows for monitoring of low BMD confirmed by a DXA scan). It is expected that the usage of this item number would increase 2 years after the introduction of the proposed item, as it is estimated that 4.7% of women aged 50–54 years are osteoporotic and they would usually not be diagnosed without implementation of the proposed item (Henry et al. 2011). However, on implementation of the intervention these women would be diagnosed with osteoporosis, but they would not be eligible for PBS-listed medicines for osteoporosis as these are only accessible for postmenopausal women with a diagnosed fracture or women aged 70 years or older. This is an ethical issue that should be considered, as the test would be provided and funded, whereas access to medication would not. These women would have to pay for osteoporosis drugs out of pocket.

Women whose T-score was ≥–2.5 in their 50th year would not be eligible for repeat testing under item number 12306. There is no evidence on the timing and frequency of monitoring and retesting in this population group. Without monitoring in the non-osteoporotic group, these women would not be eligible for a DXA scan until they reach the age of 70 years.

What are the economic considerations?

Economic evaluation

Overview

The systematic review of the effectiveness and safety of DXA screening was unable to identify adequate evidence, either direct or indirect, to conclude that giving any woman aged 49 (i.e. in their 50th year) a DXA test would result in different health outcomes than a general clinical assessment by a GP using existing fracture risk assessment tools (e.g. the FRAX® algorithm). The available evidence was in women in different age groups, and measures involved a surrogate outcome (i.e. BMD). The review did not identify any evidence to establish the relative safety of DXA testing over alternative techniques to assess and counsel women of this age on their osteoporotic risk.

Given the important impact of age on bone loss in women, it is difficult to determine whether the results of the two studies identified in the systematic review would be replicated in women in their 50th year. It is also unclear how the BMD results could be extrapolated to predict fracture risk in an economic model without information on the individual osteoporotic risk factors present in Australian women aged 49 years. Further, as test accuracy was similar between DXA and clinical assessment, it is likely that similar impacts on health outcomes (if any) would be obtained using both methods, but that using a clinical assessment tool such as FRAX® would be less costly and without risk. Information was not available on whether the level of compliance with lifestyle advice differs if a DXA test is used to determine osteoporotic risk when compared with a clinical assessment tool. In both instances, implementation would be provided in conjunction with lifestyle (e.g. exercise) and dietary (e.g. calcium and vitamin D supplementation) advice to improve low BMD, but the evidence on whether these lifestyle changes result in a reduced fracture risk was inconsistent and uncertain.

These findings are not consistent with those expected during the preparation of the Application and the decision analytic protocol (DAP), which had hypothesised that the systematic review might identify evidence supporting the superior effectiveness and non-inferior safety of DXA testing, and therefore had anticipated that a cost–utility analysis would be necessary (see Appendix F, Table 44).

However, as there is inadequate evidence available to demonstrate the effectiveness or safety of DXA testing of women in their 50th year relative to other clinical assessment tools,

the construction of a cost–utility model would be inappropriate. Any health outcome difference incorporated into the model would not be evidence-based and therefore could only be speculative. Subsequently, a calculation of cost-effectiveness would be inappropriate as it would generate results that do not have an evidentiary basis. Any incremental cost-effectiveness ratio would be subject to an unacceptable level of uncertainty and could be potentially misleading.

A costing assessment has been undertaken of the financial implications for the MBS and Australian governments should the proposed listing be accepted (see 'Financial implications').

Economic literature review

For completeness, the results of the background economic literature search are presented in Appendix E.

Financial implications

The estimations of the financial implications associated with the proposed listing of screening for BMD with DXA in all women in their 50th year are based on an epidemiological approach with respect to estimating the eligible population, with additional data to inform estimates of the rate of uptake.

Data sources used in the financial analysis

The eligible population is based on population data published by The Australian Bureau of Statistics (ABS; 2013).

Estimates of participation in referral for DXA screening in primary care and uptake rates of DXA are informed by data on:

- the existing uptake of DXA in women aged 70 years and older (Medicare Australia 2014)

- AIHW data on the uptake of other screening programs by Australian women (AIHW 2014).

Use and costs of the proposed listing

Proposed fee

- At the time of the assessment the MBS fee for existing listings of Bone Densitometry by dual energy X-ray absorptiometry (for other specific populations) was $102.40 (Benefits: 75% = $76.80; 85% = $87.05).

- The Applicant and the Protocol Advisory Sub-Committee (PASC) both proposed that the new listing would have the same fee as existing MBS listings, but at the time of application and PASC review this fee was $100.50 per service (Benefits: 75% = $75.40; 85% = $85.45).

Additional Medicare data (2012–13)[2] show that over 99% of existing MBS-subsidised DXA services are undertaken in the out-of-hospital setting (where the 85% benefit applies), and therefore the following analyses and discussion on financial implications relate primarily to services in this context.

The extent to which existing services are bulk-billed varies by the specific listing. MBS items for DXA screening/monitoring in high-risk or treated patients (12306, 12312, 12315, 12321) were bulk-billed 77% of the time, whereas this rate increased to >95% of the time for the existing screening item 12323, for which only patients over 70 years of age are eligible. Given the lower age and likelihood of less co-morbidity in the population eligible for the proposed listing, it might be anticipated that the extent of bulk-billing will be between 70% and 80%.

The overall average patient contribution (co-payment + 'gap') per (out-patient) service for patients who were not bulk-billed ranged from $39.24 to $51.98 across the various DXA item numbers.[2] When added to the average benefit paid for the respective service, the average total fee billed for DXA services ranged between $125.90 and $139.25. The overall average benefit paid (i.e. including the safety net) was $86.92, suggesting only a small average safety net contribution of ~$1.47/service. It is noted that various non-MBS subsidised DXA services are currently provided in Australia for a variety of purposes. A few examples of existing non-MBS listed DXA services and their publicly advertised prices are provided for general background and comparison in Table 45, Appendix F.

Associated resources

Initial DXA test

While there are no other healthcare resources directly incurred with the DXA testing procedure, there is additional resource use associated with the proposed listing.

Both the referral for the DXA test and the discussion with the patient on interpretation of the BMD results require separate medical consultations (i.e. MBS item 23). However, the

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[2] Data compiled in April 2014 by Department of Health and Ageing, provided to AHTA on request.

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initial referring consult would not constitute an additional resource use *per se*, as this is likely to occur opportunistically during a visit for other purposes or at a routine check-up. Therefore, to calculate the financial impacts of DXA testing, only a single additional medical consultation for the purposes of interpreting the results has been included in the base-case analysis. Likewise, in both existing practice (i.e. using a clinical risk assessment tool without DXA to assess osteoporotic risk) and with the proposed listing, the clinical management algorithm suggests that vitamin D testing would occur, since vitamin D deficiency is directly linked to increased bone loss. Therefore, in the base-case scenario of the proposed listing where DXA testing is used in place of an existing risk assessment, no additional vitamin D testing would be anticipated. In a scenario analysis, where the availability of the proposed listing is assumed to increase the overall population of women receiving risk assessment, it is assumed that the costs of additional medical consultations and vitamin D testing would be incurred. No change in hospital or day-facility resource use is anticipated to be associated with the proposed listing. Therefore, the only additional resource used routinely (in the base-case) with the proposed listing is MBS item 23, as detailed in Table 18.

Table 18   Additional resources used with the proposed intervention (base-case)

Nature of resource	MBS item	Description	MBS fee/ benefit	Application
Appointment with GP to discuss results	23	CONSULTATION AT CONSULTING ROOMS Professional attendance at consulting rooms	$36.30 [a]	Approximately 80% of GP consultations are bulk-billed (MBS fee); for the remaining 20% an average gap payment (out-of-pocket patient expense) of $28.58 per service applies

[a] For item 23 the MBS benefit is 100% of the MBS fee

<u>Subsequent resource consequences in patients identified as 'at risk'</u>

A patient who has a DXA test under the proposed listing that identifies them as having low BMD (identified in MBS Schedule, Section D1.19, as a T-score ≤–2.5), will become eligible for 2-yearly monitoring of their BMD under MBS item 12306. The ongoing monitoring with DXA would also be associated with a GP consultation. The prevalence of low BMD in the proposed screening population is estimated to be 4%, based on the finding of a prevalence of 4.7% in marginally older women (50–54 years of age) in the Geelong Osteoporosis Study (Henry et al. 2011). Therefore, the following additional resources (Table 19) will be potentially incurred by these patients every 2 years following the proposed initial DXA test.

Table 19   Additional MBS item resources that may be used concurrently with occasions of the proposed intervention, or for subsequent follow-up

Nature of resource	MBS item	Description	MBS fee	MBS benefit	Expected comparative extent of use
Ongoing monitoring	12306	Bone densitometry (performed by a specialist or consultant physician where the patient is	$102.40	$87.05 [a]	Based on the estimate of the underlying prevalence of

Nature of resource	MBS item	Description	MBS fee	MBS benefit	Expected comparative extent of use
of BMD in eligible patients		referred by another medical practitioner), **using dual energy X-ray absorptiometry**, for the monitoring of low BMD proven by bone densitometry at least 12 months previously Measurement of 2 or more sites – **1 service only in a period of 24 months** – including interpretation and report			osteoporosis (defined as BMD T-score ≤–2.5); 4% of patients having the initial screening will subsequently become eligible for this monitoring service, which may be repeated 2-yearly
Appoint-ment with GP to discuss results	23	CONSULTATION AT CONSULTING ROOMS Professional attendance at consulting rooms	$36.30 [b]	$36.30 [b]	At least one GP consultation would be expected to be associated with ongoing monitoring (for referral and/or results). Approx. 80% of consultations are bulk-billed (MBS fee), but a gap payment of $28.58 per service applies to the other 20% of services

[a] Assumed to occur in the out-patient setting in ~100% of occasions of service (85% benefit payable)
[b] For item 23 the MBS benefit is 100% of the MBS fee

Furthermore, patients identified through screening as having low BMD may be given prescription medications such as alendronate or etidronate. These therapies are not currently funded through Commonwealth health budgets for patients who would have been identified by screening and who have not yet sustained a fracture. Therefore, medication-related resource use following a DXA test will be a patient out-of-pocket expense. The DAP had specified that prescription medicines used for the management of osteoporosis would not be considered as part of the intervention associated with the listing (page 11 of the DAP).

In addition, a patient receiving results of a DXA test who has a bone density T-score ≤–1 (osteopenia) may be advised to use calcium or vitamin D supplementation—also an out-of-pocket patient expense. This is also likely to occur for patients who are shown to have a high risk of osteoporotic fracture through the use of clinical risk assessment tools, even without DXA scanning. A summary of potential patient-funded treatments is shown in Table 20.

Table 20   Other resource use, funded at patient expense (out-of-pocket private expenditure), that may be associated with the proposed intervention

Nature of resource	Cost	Example products and prices [a]	Expected extent of use with the proposed listing (and comparator)
Prescription medicine for osteoporosis	~$120 –$260 per year	Alendronate Sandoz 70 mg, 12 tablets (1 weekly) $32.97 (private prescription) Etidronate (Didrocal Osteo Therapy Tablets 90 Days) $64.39	May be recommended in patients identified as osteoporotic following a DXA scan (~4%) [c]; unlikely to be recommended on the basis of a clinical risk assessment only
Calcium and/or Vitamin D supplement-	~$60– $150 per year [b]	Blackmores Total Calcium Swisse Ultiboost Calcium + Vitamin D 150 Tablets (dose: 3 daily); $10.98–$21.95 Ostelin Vitamin D & Calcium 300 tablets	May be recommended to patients identified as osteopenic or osteoporotic following a DXA test (~40%?) [c] May also be recommended to women identified

Nature of resource	Cost	Example products and prices [a]	Expected extent of use with the proposed listing (and comparator)
ation		$29.99–$52.99 Bio-Organics Calcium 600 + Vitamin D3, 120 Tablets (dose: 2 daily) $9.99–$17.50	as high risk on the basis of a clinical risk assessment only

[a] Prices are advertised or recommended retail prices listed on http://www.chemistwarehouse.com.au, accessed 10/04/2014
[b] Annual costs vary substantially depending on brand of supplement, dose, pack-size and retailer. For example: women would require seven packs/year of Swisse Ultiboost at the recommended dose, which would cost $76.86-–$153.65 depending on retail price, or six packs/year of Bio-Organics, which may cost $59.94–$105
[c] Approximate rates of osteoporosis and osteopenia in Australian women aged 50–54 years (Henry et al. 2011)

Estimated volume per year

<u>Eligible population</u>

The number of women in their 50th year (i.e. eligible for the proposed listing) has been estimated using ABS population data from 2011 and 2012 (ABS 2013). An ongoing annual population growth of 1.39% is used for the projections. This growth rate is the average of the growth rates seen across the female populations aged 49–59 years from 2011 to 2012, and is reasonably consistent with recent overall Australian population growth rates (2011: 1.15%; 2012: 1.13%; 2013: 1.80%).

Table 21   Estimated annual population of women aged 49 years, 2011, 2012, with projections for 2013–19 assuming linear growth

Age group	2011	2012	2013	2014	2015	2016	2017	2018	2019
49 years	153,213 [a]	154,202 [a]	156,350	158,528	160,736	162,975	165,245	167,547	169,880

[a] Based on ABS data on the total pooled female population aged 45–54 years: assuming the number of women at each year of age reduces approximately linearly as age increases, the size of the population in their 50h year, which is central within this range, will approximate the total population aged 45–54 years divided by 10

Extrapolations for population sizes using alternative population ages are also undertaken using the same methodology, for the purposes of scenario analysis where screening is conducted in older women, as requested in the DAP (Table 22).

Table 22   Estimated annual population of women aged 54 years and 59 years, projected with linear growth from ABS data, 2011, 2012 (Sensitivity analyses)

Age group	2011	2012	2013	2014	2015	2016	2017	2018	2019
54 years	142,835[a]	145,992[a]	148,026	150,087	152,178	154,298	156,447	158,626	160,836
59 years	128,873[b]	130,578[b]	132,397	134,241	136,111	138,007	139,929	141,878	143,854

[a] Based on ABS data on the total pooled female population aged 50-59: Assuming the number of women at each year of age reduces approximately linearly as age increases, then the size of the population in their 55th ear, which is central within this range, will approximate the total population aged 50-59 divided by 10.
[b] Based on ABS data on the total pooled female population aged 55-64: Assuming the number of women at each year of age reduces approximately linearly as age increases, then the size of the population in their 60th year, which is central within this range, will approximate the total population aged 55-64 divided by 10.

While there is some uncertainty around the projected population growth rate (it may plausibly vary between approximately 1.0% and 2.0%), the parameter of 'uptake rate' is a

much more significant driver in the estimate of costs, and is also associated with considerably greater uncertainty (see discussion below). As sensitivity analyses around growth rate will not add useful information, these have not been presented.

Uptake rate within eligible population

The uptake rate of the proposed DXA screening is highly uncertain. There are no data available on the existing extent of use of clinical risk assessment tools for osteoporosis risk assessment and counselling in Australia.

The participation rate among Australian women for mammography screening for breast cancer (recommended 2-yearly between the ages of 50 and 69 years) is reported to be around 55% and Pap test screening participation is around 58% (AIHW 2014). However, these screening programs are highly organised, funded and administered by purpose-specific government bodies that actively recruit women. It may be assumed that, without equivalent promotion, the participation in DXA screening as per the proposed MBS listing would be lower than in these programs.

Another publication (Byles et al. 2014) reporting on the participation of Australian women aged 59–64 years in cholesterol screening (defined as a cholesterol test 3-yearly) claimed an 81% uptake rate. Again, although there is no purpose-specific public funding or promotion of this screening in Australia, the relatively high uptake rate for cholesterol screening may be associated with: the ease of checking cholesterol levels with a blood test (which may or may not have been necessary for other medical purposes); the high prevalence and awareness of this condition in the community; and the relatively large array of management options for patients found to have high cholesterol. These factors are not common to DXA screening for osteoporosis, so again a lower uptake rate may be expected.

Item 12323 (screening for osteoporosis using DXA for people aged 70 years or older) appears to be used annually by approximately 10% of eligible women aged 70–84 years (dropping to less than 5% in those older than 85 years of age). These estimates were calculated using Medicare data on the number of services provided to women, and on ABS female population estimates, and are shown in Table 23.

Table 23   Calculation of uptake rate of item 12323 based on ABS population data and Medicare data, financial year 2012–13

Age group (years)	65–74	75–84	85+
Female population (ABS data 2012) [a]	900,323	557,733	274,916
% eligible for MBS listing (i.e. over 70 years of age)	<50%	~100%	~100%
Estimated eligible population	<450,162	~557,733	~274,916

Age group (years)	65–74	75–84	85+
Services undertaken (Medicare Australia data FY 2012–13) [b]	42,845	53,392	11,288
Apparent annual uptake rate (services/eligible population)	>9.5%	~9.6%	~4.1%

[a] Australian Bureau of Statistics (ABS) (2013)
[b] Medicare Australia (2014)

Furthermore, it is unclear whether any accommodation for 'catch-up' or 'late' DXA screening would be available to women who do not use the proposed listing in their 49th year (apart from the current provision for eligibility for DXA testing at 70 years of age or in conjunction with a specific co-morbidity). Where the window of opportunity for screening for each individual is reduced to a single year, uptake rates may be expected to be further reduced (despite the stronger imperative to take advantage of an opportunity given with limited availability). It is also likely that screening in the 50th year would impact on uptake of the other DXA testing items, resulting in a potential increase in the monitoring item 12306 (as discussed previously) but also a potential decrease in the future use of the items associated with specific co-morbidities.

A review of the international literature identified a systematic review into the determinants of bone densitometry uptake in women aged 50 years or older (Brennan et al. 2012). This review identified five relevant publications, in which the crude rates of DXA screening were:

- 55% of Canadian women aged 65 years or older have had a DXA test at some time in their life (Cadarette et al. 2007);
- 3.25% of Canadian women aged 50–64 years have an annual DXA test (Demeter et al. 2007); and
- 6.7% of Danish women aged 40–65 years with no identified risk factors for osteoporosis have received a DXA test at some time in their life (Rubin 2011).

Further details from these studies are reported in Appendix E. The studies were highly heterogeneous in design and population. Although the studies were in healthcare systems with universal coverage, DXA screening was not routinely recommended for non-high-risk women aged 50 years in these studies. The uptake rates may therefore have little direct applicability to the proposed listing. The authors of the systematic review concluded that there was evidence that the uptake of DXA screening in women was positively associated with income, even in settings with universal healthcare, and, to a lesser degree, level of education.

Given the wide-ranging data on existing screening uptake in Australia, and the limited applicability of these rates given the varying circumstances, it is very difficult to predict an

uptake rate for the proposed listing. For the base-case financial estimations a first-year DXA uptake rate of 10% is estimated, increasing as medical and public awareness of the listing occurs, and stabilising at 40% after 4 years. This is thought to be a conservative approach but it is highly uncertain. A broad range of uptake rates has been tested in sensitivity analyses.

The number of intended services is assumed to be one per patient per lifetime (i.e. the number of patients equates to the number of services). Increased usage per patient above this level would be considered unlikely, given that MBS item 12306 would service the monitoring of women found to have low BMD (see 'Subsequent indirect MBS costs' for estimates of this impact). Consideration should perhaps be given to whether or not a limit to one service per patient should be explicit in the descriptor for the proposed MBS item, should it be listed (see 'Proposal for public funding').

Based on the estimated eligible population and the assumed uptake rate, the projected number of services per year over the next 5 years is calculated in Table 24.

Table 24 **Projected number of services of proposed listing per year, based on projected number of eligible women (i.e. in their 50th year) and estimated uptake rate (base-case)**

	2015	2016	2017	2018	2019
Estimated female population aged 49 years	160,736	162,975	165,245	167,547	169,880
Predicted uptake rate	10%	20%	30%	40%	40%
Estimated number of services	16,074	32,595	49,573	67,019	67,952

Plausible extreme upper and lower limits of uptake, for the sensitivity analyses, are considered to be 80% (similar to GP-initiated cholesterol screening) and 10% (as seen with item 12323), respectively.

Estimated MBS costs per year

Direct MBS costs associated with listing

Based on the estimated uptake rates detailed above, the direct costs associated with the proposed listing (i.e. directly associated with the proposed service item number) and its associated costs have been calculated. MBS costs were calculated assuming that all services are undertaken in the out-patient setting. Out-of-pocket patient costs are based on actual available bulk-billing and gap payment statistics, rather than theoretical co-payments based on list price.

Table 25   Total direct costs of proposed listing to the MBS (base-case)

	2015	2016	2017	2018	2019
Estimated number of services (see **Table 24**)	16,074	32,595	49,573	67,019	67,952
Listing cost					
Estimated total 'theoretical' MBS fees, assuming that the listed fee (benefit + patient co-payment) of $102.40 per service applies	$1,645,936	$3,337,724	$5,076,324	$6,862,711	$6,958,303
MBS benefits payable (85%)	**$1,399,206**	**$2,837,392**	**$4,315,371**	**$5,833,975**	**$5,915,237**
Estimated real patient out-of-pocket expenses - no co-payments to 75% of patients (bulk-billed) - $45.10 [a] out-of-pocket expense to 25% of patients	**$181,230**	**$367,508**	**$558,941**	**$755,635**	**$766,161**
Additional associated item costs					
Item 23 (GP consultation – interpretation) $36.30 per patient	**$583,471**	**$1,183,197**	**$1,799,517**	**$2,432,777**	**$2,466,664**
Estimated real patient out-of-pocket expenses associated with item 23 - no co-payments to 80% of patients (bulk-billed) [b] - $28.58 [a] average out-of-pocket gap payment to remaining 20% of patients [c]	$91,877	$186,313	$283,362	$383,079	$388,415
Total MBS costs associated with listing	**$1,982,677**	**$4,020,589**	**$6,114,889**	**$8,266,752**	**$8,381,901**
Total patient out-of-pocket costs associated with listing	$273,106	$553,821	$842,303	$1,138,714	$1,154,575

[a] Total gap of $45.10 includes the $15.10 MBS co-payment and additional ~$30 'gap' for fees billed above the proposed fee (average gap charged for existing DXA services; see discussion in 'Proposed Fee')
[b] Approximately 80% of GP attendances are bulk-billed (known to be at a higher rate than imaging services). See https://ama.com.au/ama-gaps-poster
[c] Estimate of average gap payment 2013, as reported in ABC news (http://www.abc.net.au/news/2014-05-07/catherine-king-gp-co-payment-claim-overreach/5421798)
MBS = Medicare Benefits Schedule

The estimations are quite uncertain, primarily because the annual uptake rate is difficult to predict and could be either higher or lower (explored in the sensitivity analysis).

Subsequent indirect MBS costs in patients identified as 'at risk'

As previously discussed, following the proposed screening DXA item it would be expected that approximately 4% of women who have the test might be identified as osteoporotic (based on the estimate of 4.7% in women aged 50–55 years from Henry et al. (2011)). These women would subsequently become eligible for additional MBS-funded item 12306 DXA tests every 2 years. The financial impact of the follow-up DXA tests will not be particularly significant if projected costs are only determined to 5 years (in 2019 the number of additional follow-up scans is only ~4% of the number of primary screening scans). However, over time the relative costing impact of the additional follow-up scans increases, as shown in Table 26.

Table 26   Projected number of services of proposed listing per year, based on projected number of eligible women (i.e. in their 50th year) and estimated number of follow-up tests (base-case)

	2015	2016	2017	2018	2019	2020	2021	2022
Estimated number of services of the proposed listing (see Table 24)	16,074	32,595	49,573	67,019	67,952	68,854	69,768	70,686
Women diagnosed as osteoporotic (4%)	643	1,304	1,983	2,681	2,718	2,754	2,791	2,827
1st follow-up DXA (98% of those diagnosed—2 years from Dx) [a]	-	-	630	1,278	1,943	2,627	2,664	2,699
2nd follow-up DXA (98% of patients having 1st scan—now 4 years from Dx) [a]	-	-	-	-	617	1,252	1,904	2,575
3rd follow-up DXA (98% of patients having 2nd scan—now 6 years from Dx) [a]	-	-					605	1,227
Total number of follow-up (item 12306) tests	**0**	**0**	**630**	**1,278**	**2,561**	**3,879**	**5,173**	**6,501**
# of follow-up Item 12306 tests as a % of # of services of the proposed listing	0%	0%	1.27%	1.91%	3.77%	5.63%	7.41%	9.20%

[a] A bi-annual mortality/discontinuation rate of 2% is applied, which is marginally greater than the biannual mortality rate of the Australian female population of this age, based on ABS Life Tables

Dx = diagnosis, DXA = dual X-ray absorptiometry

Note: Samples of the scans associated with cohorts from a specific screening year are tracked in different colours to aid interpretation.

Under the proposed listing, if a 49 year old woman is diagnosed with osteoporosis, she may potentially have additional bi-annual DXA tests that would not have otherwise been undertaken until either age 70 years, or on experience of a fracture (at which time the patient would have qualified for DXA under other existing listings) or death. Therefore, the number of patients and rate of use of item 12306 would accrue at a greater rate than the proposed listing or general population growth, for at least 20 years. An extended projection of costs associated with repeat DXA tests in women found to be osteoporotic is presented in Appendix F. Allowing for a discontinuation rate (due to death or other factors) of 2% bi-annually for women up to age 60 years and 5% bi-annually for women aged 60–70 years, the relative costs of follow-up screening increase from <4% of the cost of the proposed listing in 2019, to stabilise at 20–25% of the proposed listing after 25 years (beyond 2037). Naturally, the numerical accuracy of projections of cost extended this far are subject to considerable uncertainty; however, it is apparent that the cost impact of follow-up DXA tests associated with the proposed listing will become increasingly significant over the long term.

Changes in use and cost of current testing strategy

Should the proposed listing become available, it is anticipated that all doctors who already undertake clinical osteoporosis risk assessments (i.e. the comparator) would continue to do

so, but over time most would also use DXA scans in conjunction with the risk assessment tool.

Costs of existing osteoporosis risk assessment

The initial GP consultation (which may or may not be opportunistic) and the vitamin D testing component of the existing method of clinical osteoporosis risk assessment are common to all osteoporosis risk assessment scenarios. Therefore, these resources are not included in the base-case calculation of the costs of the proposed intervention, nor are they considered potential cost-offsets with respect to the existing scenario. Thus, in the base-case scenario where GPs change practice from using a clinical risk assessment alone to using a clinical risk assessment plus DXA screen to advise on osteoporosis risk, there are no aspects of the existing practice that would not occur under the proposed MBS item, and therefore there are no additional costs or cost-offsets (to the MBS or patients) to be considered at the *patient level*.

Existing uptake of osteoporosis risk assessment

There is no unique MBS item code or other data that can be used to identify the extent that osteoporosis risk assessment is being carried out by GPs for Australian women.

The base-case assumes that the proposed item number would not change the overall awareness of osteoporosis risk in the community (patient or doctor), and the proposed DXA service would be offered to a proportion of eligible women, all of whom would have received a clinical consultation and risk assessment anyway. No additional costs or cost-offsets (to the MBS or patients) would therefore need to be considered at the *population level*.

The possibility exists that there are currently lower rates of osteoporosis risk assessment than would be expected with the proposed DXA listing. Therefore, an assumption that the proposed listing increases the 'osteoporosis risk assessment / screening market' has been examined through a sensitivity analysis.

Sensitivity analysis

Increasing overall uptake in the osteoporosis risk assessment market

If the estimated existing extent of clinical osteoporosis risk assessment is, in reality, lower than estimated in the base-case, and lower than the estimated uptake rate of DXA screening, the proposed listing may result in an increased awareness of osteoporosis screening in the community. In turn, this may increase the overall rate of women having osteoporosis risk assessments (in conjunction with the proposed DXA screening). To the extent that the projected osteoporosis DXA screening usage is greater than the population

who would have otherwise had a clinical osteoporosis risk assessment, there will be further costs associated with the proposed listing. These are (i) an additional GP consultation and (ii) a vitamin D blood level test for each additional woman who would not previously have had their osteoporosis risk considered. The additional resource use for each woman that would not have been previously assessed for osteoporosis risk is shown in Table 27.

Table 27 Additional MBS resources that would be incurred in women who receive DXA under the proposed listing but who would not previously have received any osteoporosis risk assessment without the proposed listing (scenario analysis)

Nature of Resource	MBS item	Description	MBS fee	MBS benefit	Application
Appointment where referral for DXA is written	**23**	CONSULTATION AT CONSULTING ROOMS Professional attendance at consulting rooms	$36.30	$36.30 [a]	The MBS fee will be payable on all occasions where additional women receive risk assessment, and a private patient gap payment of $23.58 is assumed to apply to 20% of these patients
Concurrent clinical investigations	**66608**	Vitamin D or D fractions – 1 or more tests	$39.05	$33.20 [b]	The MBS fee will be payable on all occasions where additional women receive risk assessment, and the patient co-payment of $5.85 is also assumed to apply to all patients
Total				$69.50	Additional MBS fees of $69.50 and private costs of $11.57 (average) are anticipated with all additional women receiving DXA screening who would not have otherwise been assessed

[a] Currently the MBS benefit for item 23 is 100% (subject to change in government health policy in the future)
[b] Assuming testing occurs in the out-patient setting, where an 85% benefit is payable
MBS = Medicare Benefits Schedule

The total additional costs to the MBS and to patients, assuming the rate of osteoporosis risk assessment occurs in only 20% of eligible women (i.e. half the women that the anticipated base-case rate of DXA screening is estimated to plateau at) are calculated in Table 28. The data used in the sensitivity analysis of a constant rate of clinical risk assessment is lower than the projected maximum (plateaued) rate of DXA screening, under the proposed listing (see Table 23).

Table 28 Projected number of clinical risk assessment services (existing scenario), based on projected number of women of relevant age (using population of women in 50th year as proxy) and estimated existing assessment uptake rate

	2015	2016	2017	2018	2019
Estimated female population aged 49 years	160,736	162,975	165,245	167,547	169,880
Predicted ongoing uptake rate of existing clinical assessment	20%	20%	20%	20%	20%

Estimated number of services (existing scenario)	32,147	32,595	33,049	33,509	33,976
Predicted uptake rate of proposed DXA listing	10%	20%	30%	40%	40%
Estimated number of services (proposed listing)	**16,074**	**32,595**	**49,573**	**67,019**	**67,952**
Additional women taking up assessment under the proposed listing	(fewer)	(equal number)	16,524	33,509	33,976
Additional MBS costs associated with additional uptake (see Table 27) ($69.50/service)	-	-	$1,148,452	$2,328,899	$2,361,338
Additional patient/private costs associated with additional uptake ($11.57/service)	-	-	$191,122	$387,569	$392,967

MBS = Medicare Benefits Schedule

In the sensitivity analysis where this scenario is considered (a relatively higher uptake rate of DXA vs existing clinical risk assessment; see Table 34), the additional costs determined in Table 28 are required to be added to the base-case costs (Table 29).

Financial implications to the MBS and patient costs

The overall total financial impact to the MBS is calculated by combining the immediate costs of the listing (Table 25) with the downstream costs of additional follow-up scans (Table 28). These total costs are provided in Table 29.

Table 29   **Total costs of proposed listing to the MBS (base-case)**

	2015	2016	2017	2018	2019
Estimated number of services for proposed listing (see Table 24)	16,074	32,595	49,573	67,019	67,952
Proposed listing cost at total MBS fee: $102.40/service	$1,645,936	$3,337,724	$5,076,324	$6,862,711	$6,958,303
Proposed listing MBS benefits payable (85%)	$1,399,206	$2,837,392	$4,315,371	$5,833,975	$5,915,237
Proposed listing patient out-of-pocket expenses [a]	$181,230	$367,508	$558,941	$755,635	$766,161
Item 23 MBS costs ($36.30 per patient)	$583,471	$1,183,197	$1,799,517	$2,432,777	$2,466,664
Item 23 patient out-of-pocket expenses [b]	$91,877	$186,313	$283,362	$383,079	$388,415
Patients having follow-up item 12306 and additional Item 23	0	0	630	1,278	2,561
Item 12306 MBS benefits payable ($87.05/patient)	0	0	$54,849	$111,226	$222,914
Item 12306 patient out-of-pocket expenses [a] ($11.28/patient)	0	0	$7,104	$14,406	$28,873
Follow-up item 23 MBS benefits payable	0	0	$22,872	$46,381	$92,956
Follow-up item 23 out-of-pocket costs	0	0	$3,602	$7,303	$14,637
Total MBS costs associated with listing	**$1,982,677**	**$4,020,589**	**$6,192,610**	**$8,424,359**	**$8,697,771**
Total patient out-of-pocket costs associated with listing	$273,106	$553,821	$853,009	$1,160,424	$1,198,085
TOTAL (MBS and patient costs)	**$2,255,784**	**$4,574,410**	**$7,045,618**	**$9,584,783**	**$9,895,857**

[a] As previously, assumes 75% of patients are bulk-billed and 25% pay a total gap of $45.10 (av. $11.28/patient)

[b] Approximately 80% of GP attendances are bulk-billed (https://ama.com.au/ama-gaps-poster) and an average $28.58 out-of-pocket gap payment is applied to the remaining 20% of patients, as reported in http://www.abc.net.au/news/2014-05-07/catherine-king-gp-co-payment-claim-overreach/5421798

MBS = Medicare Benefits Schedule

No significant implications with respect to MBS safety net costs are anticipated, given the minimal safety net reimbursement associated with currently listed DXA tests.

Alternative population scenarios

As requested in the DAP, the financial implications associated with the proposed listing adjusted to women of ages 54 and 59 years have also been determined, and are presented in Table 30 and Table 31. These analyses simply change the size of the population (based on projections from ABS age-specific population data). Assumptions around DXA uptake rates—that they plateau at 40% in year 4 and are equivalent (or less) than existing risk assessment uptake rates—are applied as per the base-case.

Table 30   Total costs of proposed listing to the MBS for women aged 54 years (alternative population proposed in the DAP)

	2015	2016	2017	2018	2019
Estimated population aged 54 years (see Table 22)	152,178	154,298	156,447	158,626	160,836
Estimated number of services for proposed listing after uptake (base-case uptake pattern) *	15,218	30,860	46,934	63,450	64,334
Proposed listing cost at total MBS fee: $102.40/service	$1,558,303	$3,160,018	$4,806,051	$6,497,328	$6,587,830
Proposed listing MBS benefits payable (85%)	$1,324,710	$2,686,324	$4,085,613	$5,523,363	$5,600,299
Proposed listing patient out-of-pocket expenses [a]	$171,581	$347,941	$529,182	$715,404	$725,369
Item 23 MBS costs ($36.30 per patient)	$552,406	$1,120,202	$1,703,708	$2,303,252	$2,335,334
Item 23 patient out-of-pocket expenses [b]	$86,985	$176,393	$268,275	$362,683	$367,735
Patients having follow-up item 12306 and additional Item 23	0	0	597	1,210	2,424
Item 12306 MBS benefits payable ($87.05/patient)	0	0	$51,929	$105,304	$211,046
Item 12306 patient out-of-pocket expenses [a] ($11.28/patient)	0	0	$6,726	$13,639	$27,335
Follow-up item 23 MBS benefits payable	0	0	$21,654	$43,912	$88,007
Follow-up item 23 out-of-pocket costs	0	0	$3,410	$6,915	$13,858
Total MBS costs associated with listing	**$1,877,116**	**$3,806,525**	**$5,862,904**	**$7,975,831**	**$8,234,686**
Total patient out-of-pocket costs associated with listing	$258,566	$524,335	$807,593	$1,098,641	$1,134,297
TOTAL (MBS and patient costs)	**$2,135,682**	**$4,330,860**	**$6,670,496**	**$9,074,471**	**$9,368,983**

* Year 1: 10%, year 2: 20%, year 3: 30%, years 4–5: 40% (as per Table 24)

[a] As previously, assumes 75% of patients are bulk-billed and 25% pay a total gap of $45.10 (av. $11.28/patient)

[b] Approximately 80% of GP attendances are bulk-billed (https://ama.com.au/ama-gaps-poster) and an average $28.58 out-of-pocket gap payment is applied to the remaining 20% of patients, as reported in http://www.abc.net.au/news/2014-05-07/catherine-king-gp-co-payment-claim-overreach/5421798

MBS = Medicare Benefits Schedule

Table 31   Total costs of proposed listing to the MBS for women aged 59 years (alternative population proposed in the DAP)

	2015	2016	2017	2018	2019
Estimated population aged 59 years (see Table 22)	136,111	138,007	139,929	141,878	143,854

Estimated number of services for proposed listing (see Table 24)	13,611	27,601	41,979	56,751	57,542
Proposed listing cost at total MBS fee: $102.40/service	$1,393,776	$2,826,379	$4,298,623	$5,811,332	$5,892,280
Proposed listing MBS benefits payable (85%)	$1,184,845	$2,402,699	$3,654,249	$4,940,200	$5,009,013
Proposed listing patient out-of-pocket expenses [a]	$153,465	$311,205	$473,310	$639,871	$648,784
Item 23 MBS costs ($36.30 per patient)	$494,083	$1,001,929	$1,523,828	$2,060,072	$2,088,767
Item 23 patient out-of-pocket expenses [b]	$77,801	$157,769	$239,950	$324,390	$328,909
Patients having follow-up item 12306 and additional item 23	0	0	534	1,082	2,168
Item 12306 MBS benefits payable ($87.05/patient)	0	0	$46,446	$94,186	$188,764
Item 12306 patient out-of-pocket expenses [a] ($11.28/patient)	0	0	$6,016	$12,199	$24,449
Follow-up item 23 MBS benefits payable	0	0	$19,368	$39,276	$78,715
Follow-up item 23 out-of-pocket costs	0	0	$3,050	$6,185	$12,395
Total MBS costs associated with listing	**$1,678,928**	**$3,404,628**	**$5,243,892**	**$7,133,733**	**$7,365,258**
Total patient out-of-pocket costs associated with listing	$231,266	$468,975	$722,326	$982,645	$1,014,537
TOTAL (MBS and patient costs)	**$1,910,194**	**$3,873,603**	**$5,966,218**	**$8,116,378**	**$8,379,795**

[a] As previously, assumes 75% of patients are bulk-billed and 25% pay a total gap of $45.10 (av. $11.28/patient)

[b] Approximately 80% of GP attendances are bulk-billed (https://ama.com.au/ama-gaps-poster) and an average $28.58 out-of-pocket gap payment is applied to the remaining 20% of patients, as reported in http://www.abc.net.au/news/2014-05-07/catherine-king-gp-co-payment-claim-overreach/5421798)

MBS = Medicare Benefits Schedule

Unsurprisingly, the overall costs associated with the proposed listing decrease when it is restricted to an older age group (a smaller population).

Sensitivity analyses: alternative uptake rates and relative uptake rates

The parameters of greatest uncertainty in the financial analysis are the expected uptake rate of the proposed service and the existing rate of clinical assessment for osteoporosis for women of the relevant age.

The expected uptake of the proposed listing by 40% of the eligible population may be an underestimate or an overestimate. Extreme upper and lower estimates of a constant annual uptake rate of 80% and 10%, respectively, are examined in the following tables.

Table 32   Total costs of proposed listing to the MBS for women aged 49 years, with maximum expected uptake rate of 80% (sensitivity analysis)

	2015	2016	2017	2018	2019
Estimated population aged 49 years (see Table 22)	160,736	162,975	165,245	167,547	169,880
Estimated number of services for proposed listing at maximum expected uptake rate of 80% *	128,589	130,380	132,196	134,037	135,904
Proposed listing cost at total MBS fee:	$13,167,485	$13,350,897	$13,536,864	$13,725,422	$13,916,606

$102.40/service					
Proposed listing MBS benefits payable (85%)	$11,193,648	$11,349,567	$11,507,657	$11,667,949	$11,830,474
Proposed listing patient out-of-pocket expenses [a]	$1,449,838	$1,470,033	$1,490,509	$1,511,271	$1,532,322
Item 23 MBS costs ($36.30 per patient)	$4,667,771	$4,732,789	$4,798,713	$4,865,555	$4,933,328
Item 23 patient out-of-pocket expenses [b]	$735,013	$745,251	$755,632	$766,157	$776,829
Patients having follow-up item 12306 and additional item 23	0	0	5,041	5,111	10,122
Item 12306 MBS benefits payable ($87.05/patient)	0	0	$438,791	$444,903	$881,115
Item 12306 patient out-of-pocket expenses [a] ($11.28/patient)	0	0	$56,834	$57,625	$114,125
Follow-up item 23 MBS benefits payable	0	0	$621,768	$630,428	$1,248,542
Follow-up item 23 out-of-pocket costs	0	0	$28,813	$29,214	$57,857
Total MBS costs associated with listing	**$15,861,419**	**$16,082,355**	**$16,928,137**	**$17,163,932**	**$18,012,344**
Total patient out-of-pocket costs associated with listing	$2,184,851	$2,215,284	$2,331,787	$2,364,267	$2,481,133
TOTAL (MBS and patient costs)	**$18,046,270**	**$18,297,639**	**$19,259,925**	**$19,528,200**	**$20,493,477**

* Year 1: 10%, year 2: 20%, year 3: 30%, years 4–5: 40% (as per Table 24)

[a] As previously, assumes 75% of patients are bulk-billed and 25% pay a total gap of $45.10 (av. $11.28/patient)

[b] Approximately 80% of GP attendances are bulk-billed (https://ama.com.au/ama-gaps-poster) and an average $28.58 out-of-pocket gap payment is applied to the remaining 20% of patients, as reported in http://www.abc.net.au/news/2014-05-07/catherine-king-gp-co-payment-claim-overreach/5421798)

MBS = Medicare Benefits Schedule

Table 33   Total costs of proposed listing to the MBS for women aged 49 years, with minimum expected uptake rate of 10% (sensitivity analysis)

	2015	2016	2017	2018	2019
Estimated population aged 49 years (see Table 22)	160,736	162,975	165,245	167,547	169,880
Estimated number of services for proposed listing at maximum expected uptake rate of 80% *	16,074	16,297	16,524	16,755	16,988
Proposed listing cost at total MBS fee: $102.40/service	$1,645,936	$1,668,862	$1,692,108	$1,715,678	$1,739,576
Proposed listing MBS benefits payable (85%)	$1,399,206	$1,418,696	$1,438,457	$1,458,494	$1,478,809
Proposed listing patient out-of-pocket expenses [a]	$181,230	$183,754	$186,314	$188,909	$191,540
Item 23 MBS costs ($36.30 per patient)	$583,471	$591,599	$599,839	$608,194	$616,666
Item 23 patient out-of-pocket expenses [b]	$91,877	$93,156	$94,454	$95,770	$97,104
Patients having follow-up item 12306 and additional Item 23	0	0	630	639	1,265
Item 12306 MBS benefits payable ($87.05/patient)	0	0	$54,849	$55,613	$110,139
Item 12306 patient out-of-pocket expenses [a] ($11.28/patient)	0	0	$7,104	$7,203	$14,266
Follow-up item 23 MBS benefits payable	0	0	$22,872	$23,191	$45,928
Follow-up item 23 out-of-pocket costs	0	0	$3,602	$3,652	$7,232

Total MBS costs associated with listing	$1,982,677	$2,010,294	$2,116,017	$2,145,492	$2,251,543
Total patient out-of-pocket costs associated with listing	$273,106	$276,911	$291,473	$295,533	$310,142
TOTAL (MBS and patient costs)	**$2,255,784**	**$2,287,205**	**$2,407,491**	**$2,441,025**	**$2,561,685**

* Year 1: 10%, year 2: 20%, year 3: 30%, years 4–5:40% (as per Table 24)

a As previously, assumes 75% of patients are bulk-billed and 25% pay a total gap of $45.10 (av. $11.28/patient)

b Approximately 80% of GP attendances are bulk-billed (https://ama.com.au/ama-gaps-poster) and an average $28.58 out-of-pocket gap payment is applied to the remaining 20% of patients, as reported in http://www.abc.net.au/news/2014-05-07/catherine-king-gp-co-payment-claim-overreach/5421798)

MBS = Medicare Benefits Schedule

Another uncertain assumption in the financial estimates is that women of the relevant population are already having GP consultations and vitamin D tests as part of the existing method of assessing osteoporosis risk. If this practice is not occurring in the existing scenario, to the extent that it would under the proposed new item number, additional costs of another GP consultation and vitamin D test need to be added to the base-case scenario. The relevant additional costs required are calculated in Table 28 (assuming a rate of only 20% risk assessment occurs in current practice, but increasing to 40% under the proposed listing).

Table 34   Total costs of proposed listing, assuming underlying rate of risk assessment without proposed listing is only 20%, but increases (over 4 years) to 40% (sensitivity analysis)

	2015	2016	2017	2018	2019
Base-case MBS costs	$1,982,677	$4,020,589	$6,192,610	$8,424,359	$8,697,771
Base-case patient costs	$273,106	$553,821	$853,009	$1,160,424	$1,198,085
Base-case overall cost	$2,255,784	$4,574,410	$7,045,618	$9,584,783	$9,895,857
Additional women taking up assessment under the proposed listing (see Table 28)	(fewer)	(equal number)	16,524	33,509	33,976
Additional MBS costs associated with additional uptake (see Table 27) ($69.50/service)	-	-	$1,148,452	$2,328,899	$2,361,338
Additional patient / private costs associated with additional uptake ($11.57/service)	-	-	$191,122	$387,569	$392,967
Total MBS cost allowing for additional uptake (sensitivity analysis)	$1,982,677	$4,020,589	$7,341,062	$10,753,258	$11,059,109
Total patient costs allowing for additional uptake (sensitivity analysis)	$273,106	$553,821	$1,044,131	$1,547,993	$1,591,052
Total healthcare costs allowing for additional uptake (sensitivity analysis)	**$2,255,783**	**$4,574,410**	**$8,385,193**	**$12,301,251**	**$12,650,161**

Other Australian healthcare system costs

Costs to the state and territory health systems

The proposed listing of DXA screening would not be expected to have an impact (financial or otherwise) on hospital admissions or other state-administered health services. Over 99% of services are undertaken in the out-patient setting and any follow-up would be expected to also occur in the community setting.

Costs to the private health insurer and/or patient

Privately borne patient costs are calculated alongside the MBS costs in Table 29 and in the sensitivity analyses. Only healthcare costs are included (e.g. transport or productivity costs are not included). Non-government costs are primarily expected to be borne as out-of-pocket expenses to the consumer as nearly all episodes of service will be undertaken in the out-patient setting and therefore may not be reimbursable under all private health / hospitalisation insurance policies. There is also considerable additional uncertainty, particularly around patient out-of-pocket expenses, associated with broader potential changes to Australian government health policy; for example, the proposal in the recent Australian Government Budget 2014–15 of a patient co-payment for routine GP consultations.

Total Australian healthcare system costs

Given that there are no further healthcare costs associated with state or territory budgets, and out-of-pocket expenses have already been included, the total costs to the Australian healthcare system are as presented in Table 29 and subsequent sensitivity analyses.

Discussion

Safety

As described in the background section of the report (see page 22), ionising radiation levels associated with DXA are considered low. No safety concerns or adverse event data have been found in the existing literature. Furthermore, DXA has already been approved in other MBS items for different indications (see page 28) and has been widely used since 1988 without any reported safety concerns.

Effectiveness

There was a considerable lack of evidence regarding the effectiveness of DXA at screening for low BMD in women in their 50th year. First, studies with women aged 40 years or younger (mean) and women 65 years or older were generally excluded, as the rate of bone loss in perimenopausal women (usually aged 45–55 years) is significantly different from premenopausal and postmenopausal women (see 'Bone loss', page 24), making it impossible to generalise the results of older or younger women to the target study population. Second, there was a lack of studies with a sufficient follow-up period, leading to an absence of eligible studies with actual minimal trauma fracture or hip fracture as an outcome. Third, no studies were identified with 'clinical assessment including the use of existing fracture risk assessment tools including lifestyle and dietary advice' as a comparator, meaning that the information on the benefits of DXA was in addition to 'no testing and no lifestyle advice', rather than the comparator specified.

The few studies that were included contain some evidence regarding change in BMD after a DXA scan. A slight mean increase in BMD was seen at 1–2 years post-DXA, and a slight change in lifestyle after receiving the DXA results was also observed. However, due to the lack of comparative evidence, it is not known if a similar increase in BMD would occur in women who underwent clinical risk assessment with assessment tools such as FRAX® or QFracture (the comparator). To clarify: Winzenberg et al. (2006) reported that a low T-score was the main determinant for women to commence calcium supplementation; that is, women who were identified as 'at risk' were more likely to change their behaviour to prevent fractures. It may be that a similar effect would be observed when women were identified as 'high risk' with a risk assessment tool, which is less costly, has no radiation and could be done by the woman's GP or even by the woman herself (as the assessment tools are accessible online and are free). Furthermore, the diagnostic accuracy of DXA and FRAX®

are similar when it comes to predicting osteoporotic fractures and hip fractures, making FRAX® a cheaper, safer, more accessible and faster option.

The PASC stated that this assessment should provide evidence to inform the appropriate threshold T-score(s) for lifestyle and dietary advice, and should undertake sensitivity analyses around various relevant thresholds for therapy (lifestyle advice). However, no evidence was found to inform the threshold for advice. The assumption is that, in practice, the physician would probably provide feedback and personalised lifestyle advice based on their score.

The PASC also considered that the timing and frequency of monitoring and re-testing should be informed by the evidence of the change in BMD and consequent change in the risk of minimal trauma fracture over time. No evidence was identified informing the frequency of testing; however, women diagnosed with osteoporosis (T-score ≤−2.5) are eligible for a DXA every 2 years (see 'Other considerations' on page 69). According to the Royal Australian College of General Practitioners guidelines on osteoporosis, repeat BMD analysis is recommended at 2 years after the initial DXA when BMD is likely to be approaching −2.5 (2010). The systematic review by Nelson et al. (2010) reported that repeating a BMD test up to 8 years after an initial measurement does not significantly increase predictive performance for fracture outcomes. However, these results were based on a population of women aged 65 years or older.

Overall, the evidence was characterised by inconsistency that reflected the many and varied populations from which it was drawn. In many cases the evidence was simply not applicable to the population eligible for the proposed item number, especially in the last step of the linked evidence analysis.

For the direct evidence and the first two steps of the linked evidence analysis, the studies were limited by lack of an appropriate comparator in the design, whereas the final step was predominantly systematic reviews of RCTs. As such, these two parts have been addressed by separate matrices. A summary of the body of evidence for the non-comparative studies is provided in Table 35, and for the comparative studies in Table 36.

Table 35   Body of evidence matrix for non-comparative studies

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base [a]				Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency [b]		Most studies consistent and inconsistency may be explained		
Clinical impact				Slight or restricted
Generalisability		Population(s) studied in the body of evidence are similar to target population		
Applicability			Probably applicable to Australian healthcare context with some caveats	

Source: adapted from NHMRC (2008)

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 12)
[b] If there is only one study, rank this component as 'not applicable'

Table 36   Body of evidence matrix for comparative studies

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence–base [a]	One or more level I studies with a low risk of bias			
Consistency [b]			Some inconsistency reflecting genuine uncertainty around clinical question	
Clinical impact				Slight or restricted
Generalisability				Population(s) studied in body of evidence differ from target population and it is hard to judge whether it is sensible to generalise to target population
Applicability			Probably applicable to Australian healthcare context with some caveats	

Source: adapted from NHMRC (2008)

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 12)
[b] If there is only one study, rank this component as 'not applicable'

Despite a considerable amount of evidence identified for the third stage of the evidence linkage, we are unable to draw any conclusions from it due to the heterogeneity in the results and the lack of applicability to the population under question in this assessment. Because fractures occur predominantly in older people, this is where the focus has been in trials of lifestyle interventions. Many more studies were located in the search that did not use fracture as an outcome but rather measured BMD, a far easier and cheaper way of measuring the outcome than following up participants for decades to ascertain outcomes.

Even though the evidence is uncertain, the lifestyle interventions of exercise, vitamin D and calcium supplementation are recommended in Australian guidelines for the prevention of osteoporosis (NMHRC 2010). In most cases these lifestyle interventions are unlikely to cause harm in recommended doses and under supervision, although there is some risk related to falls or other injuries from exercise, and there can be side effects associated with the dietary supplements (e.g. gastrointestinal effects and serious cardiovascular events)(Avenell et al. 2009).

Economic considerations

Estimated cost-effectiveness

Given the lack of evidence available to demonstrate any change in health outcomes associated with the proposed use of DXA screening for osteoporosis in women aged 49 years, no assessment or conclusion regarding the cost-effectiveness of DXA testing in this population can be made.

Estimated financial impact

Assuming a moderate stabilised uptake rate of 40%, it is estimated that the proposed listing would result in increased healthcare costs of approximately $10 million per year after 5 years—with first year estimates around $2 million, and uptake expected to increase gradually over the first 4 years in line with increasing community and medical awareness. Approximately 88% of costs would be borne by the MBS and 12% as out-of-pocket consumer costs. A steady increase in costs is expected every year, well beyond the 5-year projections, due not only to population growth but also to the increased accrual of follow-up costs, which may extend to 20 years in patients who are subsequently diagnosed with osteoporosis.

The financial impact of the proposed listing is highly dependent on the uptake rate. The existing listing of DXA screening for osteoporosis in people aged 70 years and older is less than 10%. If uptake of the proposed listing is similarly low, annual costs may stabilise at

about \$2.5 million per year, but if uptake increases to around 80% (as estimated to occur with cholesterol screening), costs will exceed \$20 million per year.

Without evidence of any health benefits (i.e. decreased fracture rates) there are no cost offsets, direct or indirect, that can be applied to the costs of the listing.

Conclusions

Is BMD analysis using DXA safe for women in their 50th year?

No studies were identified on adverse events of DXA in perimenopausal women. Ionising radiation levels are low and DXA has been widely used since 1988 without any (serious) safety issues. Therefore, DXA is considered safe for women in their 50th year.

Is BMD analysis using DXA effective for women in their 50th year?

Direct evidence with fracture outcomes on BMD analyses using DXA in perimenopausal women was not available. However, limited linked evidence was identified: the limited accuracy evidence with fracture as a reference standard showed that FRAX® and DXA had a similar accuracy in perimenopausal women. A slight change in management was observed after a DXA scan (maximum 2-year follow-up) in two studies, although data comparing DXA with a risk assessment tool was lacking.

As a result of the lack of evidence, no conclusion can be drawn regarding the effectiveness of DXA for women in their 50th year. Furthermore, no national and international guidelines were identified that reported a positive recommendation for osteoporosis screening for DXA in a perimenopausal population. In fact, the majority of guidelines made a recommendation *against* osteoporosis screening with DXA in this population group.

As the accuracy of DXA and FRAX® is similar and the latter is a safer, faster, more accessible and cheaper tool, FRAX® could be considered for assessing fracture risk in perimenopausal women. However, it is not known if FRAX® results lead to a similar change in management compared with DXA.

Is BMD analysis using DXA for women in their 50th year cost-effective?

There is inadequate evidence available to produce an evidence-based assessment of the cost-effectiveness of DXA and BMD analyses for women in their 50th year, and therefore no conclusion of cost-effectiveness can be made.

Were the proposed listing to be implemented, after achieving a stable uptake over 4 years, it might be expected to cost the MBS approximately $9.5 million per year (increasing annually); however, depending on uptake, which is highly uncertain and may depend on the extent of promotion, this may range between $2.5 million and $20 million.

Appendix A   Assessment group

AHTA, University of Adelaide, South Australia

Name	Position
Ms Sharon Kessels	Research Officer
Ms Camille Schubert	Senior Health Economist
Ms Jacqueline Parsons	Team leader (Medical HTA)
Ms Judy Morona	Senior Research Officer
Assoc. Prof. Tracy Merlin	Managing Director

Noted conflicts of interest

There were no conflicts of interest.

Appendix B   Search strategies

HTA websites

AUSTRALIA

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/
Centre for Clinical Effectiveness, Monash University	http://www.monashhealth.org/page/Health_Professionals/CCE/
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/

AUSTRIA

Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita

CANADA

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications.html
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Association for Health Services and Policy Research (CAHSPR)	http://www.cahspr.ca/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca

DENMARK

Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta.aspx?sc_lang=en
Danish Institute for Health Services Research (DSI)	http://www.kora.dk/velkommen

FINLAND

Finnish Office for Health Technology Assessment (FINOHTA)	http://www.thl.fi/en_US/web/en

FRANCE

L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/

GERMANY

German Institute for Medical Documentation and Information (DIMDI) / HTA — http://www.dimdi.de/static/en/index.html

Institute for Quality and Efficiency in Health Care (IQWiG) — http://www.iqwig.de

THE NETHERLANDS

Health Council of the Netherlands Gezondheidsraad — http://www.gezondheidsraad.nl/en/

Institute for Medical Technology Assessment (Netherlands) — http://www.imta.nl/

NEW ZEALAND

New Zealand Health Technology Assessment (NZHTA) — http://www.otago.ac.nz/christchurch/research/nzhta/

NORWAY

Norwegian Knowledge Centre for the Health Services — http://www.kunnskapssenteret.no

SPAIN

Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"l/Health Technology Assessment Agency (AETS) — http://www.isciii.es/

Andalusian Agency for Health Technology Assessment (Spain) — http://www.juntadeandalucia.es/

Catalan Agency for Health Technology Assessment (CAHTA) — http://www.gencat.cat

SWEDEN

Center for Medical Health Technology Assessment — http://www.cmt.liu.se/?l=en&sc=true

Swedish Council on Technology Assessment in Health Care (SBU) — http://www.sbu.se/en/

SWITZERLAND

Swiss Network on Health Technology Assessment (SNHTA) — http://www.snhta.ch/

UNITED KINGDOM

National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) — http://www.hta.ac.uk/

NHS Quality Improvement Scotland — http://www.nhshealthquality.org/

National Institute for Clinical Excellence (NICE) — http://www.nice.org.uk/

The European Information Network on New and Changing Health Technologies — http://www.euroscan.bham.ac.uk/

University of York NHS Centre for Reviews and Dissemination (NHS CRD) — http://www.york.ac.uk/inst/crd/

UNITED STATES

Agency for Healthcare Research and Quality (AHRQ) — http://www.ahrq.gov/clinic/techix.htm

Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (U.S.)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (U.S.)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (U.S.)	http://www.oregon.gov/oha/OHPR/HRC/Pages/index.aspx
Office of Health Technology Assessment Archive (U.S.)	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/blueresources/tec/
Veteran's Affairs Research and Development Technology Assessment Program (U.S.)	http://www.research.va.gov/default.cfm

Bibliographic databases

Electronic database	Time period
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1988 – 2/2014
Current Contents	1988 – 2/2014
Embase	1988 – 2/2014
PubMed	1988 – 2/2014
Web of Science – Science Citation Index Expanded	1988 – 2/2014
Cinahl	1988 – 2/2014
Econlit	1988 – 2/2014
Scopus	1988 – 2/2014

Additional sources of literature

Source	Location
Internet	
NHMRC – National Health and Medical Research Council (Australia)	http://www.nhmrc.gov.au/
U.S. Department of Health and Human Services (reports and publications)	http://www.hhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.greylit.org/
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/

National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.nihr.ac.uk/Pages/NRRArchive.aspx
Google Scholar	http://scholar.google.com/
Australian and New Zealand Clinical Trials Registry	www.anzctr.org.au
Pearling	
All included articles will have their reference lists searched for additional relevant source material	
Specialty websites	
Osteoporosis Australia	http://www.osteoporosis.org.au/
National Osteoporosis Foundation (USA)	http://nof.org/
International Osteoporosis Foundation	http://www.iofbonehealth.org/
Australian and New Zealand Bone and Mineral Society	https://www.anzbms.org.au/Index.asp

Appendix C   Studies included in the review

Table 37   Studies included in the direct effectiveness and/or change in management section

Study setting	Study design / Quality appraisal	Study population	Selection criteria	Intervention	Comparator and/or reference standard	Outcomes
Gutin, Peterson, Galsworthy et al. (1992) Osteoporosis Center, Hospital for Special Surgery, New York, USA	Retrospective case series Level: IV Quality: Q2	N=53 Mean age at first visit: 55.2 (SD = 5.14) years Mean age at menopause: 48.9 (SD = 4.75) years	Inclusion: Women 1–10 years postmenopausal; never on oestrogen-, steroid- or chemotherapy; non-smoker; no illness known to affect BMD	BMD measurement using DXA and a questionnaire that provided information about lifestyle, nutrition and genetic/family history Second visit (follow-up DXA and questionnaire) at 12–18 months	None	Change in management (n=46): - % adequate physical activity (before/after) - % adequate calcium intake (before/after) Direct evidence (n=53): - Mean change in BMD
Sedlak et al. (2007) College of Nursing, Henderson Hall, Kent State University, Kent, OH, USA	RCT Level: II Quality: 16.5 / 26	N=203 (Treatment group n=101, Control group n=102) Mean age: 56.6 years Mean height: 163 cm Mean weight: 74.8 kg 88% Caucasian, 10.6% African American	Inclusion: Community-based women 50–65 years who responded to media advertisements and were able to read and write English, no prior BMD test, postmenopausal, general good health with no chronic diseases, not on HRT, and ability to travel to a DXA office site	Intervention group: Initial questionnaires relating to osteoporosis (preventing behaviours survey, knowledge test, health belief scale, self-efficacy scale), a DXA scan and a letter containing a description and interpretation of normal BMD, osteopenia and osteoporosis, and highlighting participant's own results. If the DXA scan showed below-normal results, follow-up with the participant's physician was recommended. Questionnaires were repeated at 6 and 12 months	Control group: Initial questionnaires relating to osteoporosis (preventing behaviours survey, knowledge test, health belief scale, self-efficacy scale) Questionnaires were repeated at 6 and 12 months	Change in management (n=203): - Calcium intake / change in calcium intake - Exercise time - % of women taking HRT or osteoporosis medication at 12 months
Winzenberg et al. (2006) Menzies Research Institute, University	Non-comparative cohort study or case series Level: IV	N=415 Mean age: 37.4–38.4 years (depending on	Inclusion: Women 25–44 years of age (population-based study)	BMD measurement using DXA at the hip and spine, with feedback on participant's T-score (leaflet or counselling)	None	Direct evidence (n=415): - Mean change in BMD

Study setting	Study design / Quality appraisal	Study population	Selection criteria	Intervention	Comparator and/or reference standard	Outcomes
of Tasmania, Hobart, Australia	Quality: Q1	intervention group)	Exclusion: Previous BMD measurement, thyroid disease, renal failure, malignancy, rheumatoid arthritis, history of hysterectomy, HRT, pregnancy, lactating			

BMD = bone mineral density/densitometry; DXA = dual X-ray absorptiometry; HRT = hormone replacement therapy; SD = standard deviation

Table 38   Systematic review included to address the safety and effectiveness of DXA testing in women aged 50 years

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
Nelson et al. (2010)	Systematic review to determine the effectiveness and harms of osteoporosis screening in reducing fractures for men and post-menopausal women without known previous fractures; the performance of risk assessment instruments and bone measurement tests in identifying persons with osteoporosis, optimal screening intervals, and efficacy and harms of medications to reduce primary fractures

Although the risk of bias of included studies was poorly | Men aged 50 years or older and postmenopausal women aged 60 years or older; 60–64 years at increased risk for osteoporotic fractures; 60–64 years not at increased risk for osteoporotic fractures; and 65 years or older | RCTs of screening or medications with fracture outcomes published in English, performance studies of validated risk-assessment instruments, and systematic reviews and population-based studies of BMD tests or medication harms | Direct evidence: No trials were identified

Safety: No trials were identified | No studies were identified |

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
	reported, other parts of the review were satisfactory Overall, a low risk of bias				

BMD = bone mineral density/densitometry; RCT = randomised controlled trial

Table 39   Studies included to assess the accuracy of DXA testing in women aged 50 years

Study setting	Study design / Quality appraisal	Study population	Selection criteria	Intervention	Comparator and/or reference standard	Outcomes
Cheung et al. (2012)

Hong Kong, China; baseline 1995–2009 | Prospective study of women recruited through community; not random sample; followed up for 4.5±2.8 years Unclear risk of bias in population selection and large age range included; otherwise low risk of bias in study design | N=2,266 community-dwelling Chinese women in Hong Kong aged 40 years or older; mean age 62.1±8.5 years | Women had to be at least 1 year menopausal and not taking any medications for osteoporosis, community-dwelling and ambulatory | DXA of lumbar spine, femoral neck and total hip | Ethnic-specific clinical risk factor assessment FRAX® (combinations of clinical risk factor assessment with and without DXA results were considered) | Fracture of wrist, clinical spine, humerus or hip, self-reported and confirmed by medical records |
| Stewart, Kumar & Reid (2006)

Aberdeen, Scotland; baseline 1990–94 | Prospective cohort of women aged 45–54 years living in Aberdeen randomly selected from population-based register; response rate approx. 75%; followed up for fracture for average of 9.7±1.1 years Low risk of bias in terms of population selection and study design; however, high risk of bias in terms of coverage of fractures as only confirmed self-reports included, and follow up not good Population highly applicable | N=5,119 at baseline; difficult to tell coverage of follow-up; n=3,142 who completed questionnaire at 2002, but authors use n=3,883 as final number; important as fractures are based on self-report Mean age 48.6±2.4 years | Women aged 45–54 years randomly selected from population-based register; no exclusion criteria described | DXA of lumbar spine and neck of femur | None | Self-reported fractures; confirmed by sighting of X-rays or with physician |
| Tamaki et al. (2011) | Prospective cohort of randomly selected women aged 15–79 years living in seven municipalities in Japan | N=1,651 at baseline; final study analysis included n=851 women; response rate 53% | Included women randomly selected from population register; no other inclusion | DXA of femoral neck | FRAX® (Japanese version) | Self-reported fractures; confirmed with |

Study setting	Study design / Quality appraisal	Study population	Selection criteria	Intervention	Comparator and/or reference standard	Outcomes
Seven municipalities in Japan; baseline 1996	recruited from the community into the Japanese Population-based Osteoporosis Cohort Study; followed up at 10 years after baseline; response rate 84.7% Low risk of bias in terms of population selection and study design; however, high risk of bias in terms of coverage of fractures as only self-reports included, and follow up not good Limited population applicability	Mean age 56.7±9.6 years Fractures based on self-reporting Surveys undertaken in 1999, 2002 and 2006; first fracture counted as end of follow-up time	criteria described Excluded from the analysis were women without baseline DXA and women who were taking HRT or osteoporosis drugs at baseline			nurse interview but no independent verification

DXA = dual X-ray absorptiometry; FRAX® = WHO Fracture Risk Calculator

Table 40   Studies included to determine whether proposed DXA testing would result in a change in management: exercise

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
Moayyeri (2008)	Systematic review of exercise interventions for preventing fracture No systematic quality appraisal of studies reported; other parts of review satisfactory; overall unclear risk of bias	Men and women (reported separately) older than 40 years of age (although some studies included younger participants)	Systematic reviews, RCTs and prospective studies featuring a measure of exercise with fracture as an outcome Studies with participants all under 40 years of age and not in English were excluded	No RCTs found; 21 prospective studies fulfilled the inclusion criteria Studies with hip fracture as an endpoint were pooled in meta-analysis; other studies not suitable Included studies were all quite large (between 1,959 and 93,676 participants), ages 35 years and older; duration of follow-up between 4 and 15 years Exercise variously categorised as walking and moderate, regular and intermediate work activity	Exercise protective against hip fracture in women (RR 0.62; 95%CI 0.56, 0.69) Low heterogeneity Association likely to be confounded by other health-related issues such as co-morbidity Problems associated with low event rates in these studies Data for other fracture sites variable; limited evidence for protective impact of exercise on vertebral fractures; possible increases in risk of wrist and other site fractures with exercise
Howe et al. (2011)	Systematic review of	Healthy postmenopausal	RCTs featuring an exercise	Only one RCT with fracture as	Risk of fracture not statistically

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
Cochrane review	exercise interventions for preventing fracture Low risk of bias	women aged 45–70 years	intervention and with fracture or BMD as an outcome	primary outcome and a further three with fracture as a secondary outcome Two with unclear risk of bias due to under-reporting and two with low risk of bias; included both high- and low-impact exercise	significantly different in exercise and control groups (OR 0.61; 95%CI 0.23, 1.64)
National Osteoporosis Foundation (1998)	Systematic review of interventions for preventing fracture; covers many interventions Quality appraisal not reported Unclear risk of bias	No restrictions on population described	RCTs featuring an exercise intervention and with fracture as an outcome	No RCTs were identified in this review	
Crandall (2012) Agency for Healthcare Research and Quality review	Systematic review of interventions for preventing fracture in people with low bone density or osteoporosis; covers many interventions (current to March 2011) Low risk of bias	Healthy populations, or populations with or at risk of low bone density or osteoporosis, aged 18 years or older	Systematic reviews, meta-analyses and RCTs with exercise intervention, and with fracture as an outcome	Reported in Lock et al. (2006)	

BMD = bone mineral density/densitometry; RCT = randomised controlled trial

Table 41   Studies included to determine whether proposed DXA testing would result in a change in management: calcium

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
Crandall et al. (2012) Agency for Healthcare Research and	Systematic review of interventions for preventing fracture in people with low bone density or osteoporosis; covers many interventions (current to	Healthy populations, or populations with or at risk of low bone density or osteoporosis, aged 18 years or older	Systematic reviews, meta-analyses and RCTs with a calcium supplementation intervention, and with fracture as an outcome	Four systematic reviews including 23 RCTs	No significant effect of calcium on reducing vertebral or non-vertebral fracture risk compared with placebo or no treatment One pooled analysis found a statistically significant increased risk of

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
Quality review	March 2011) Low risk of bias				hip fracture, but another with many more participants found a significant reduction in hip fracture One review of 9 studies found statistically significant risk reduction for calcium, greater with higher dose of calcium
Cumming & Nevitt (1997)	Systematic review to assess the effectiveness of calcium supplements and/or dietary calcium for the prevention of fractures in postmenopausal women Quality appraisal and risk of bias was not reported, unclear risk of bias	No restrictions on population described	Studies had to have fracture as an outcome Ecologic studies were excluded	Four RCTs of calcium supplements (mean age of participants was older than 70 years in 3 studies, and 58 years in 4th); 3 non-randomised trials of calcium supplements (mean age 62–65 years); 7 observational epidemiologic studies of calcium supplements; and 23 observational epidemiologic studies of dietary calcium (18 concerned with hip fractures) In RCTs number of subjects in each study were 78, 93, 197 and 3,270 Follow-up was 1.5–4.3 years	The main finding was that increased calcium intake among postmenopausal women appears to be associated with a small reduction in risk of fracture Conclusion is based on consistent findings of RCTs and a meta-analysis of 16 observational epidemiologic studies of dietary calcium and hip fractures
National Osteoporosis Foundation (1998)	Systematic review of interventions for preventing fracture; covers many interventions Quality appraisal not reported Unclear risk of bias	No restrictions on population described	RCTs with a calcium supplementation intervention, and with fracture as an outcome	Four RCTs with oral calcium supplementation, mean age of participants was older than 70 years in 3 studies, and 58.5 years in 4th; 1 study had men and women, whereas the rest had women only; mix of participants with and without previous fractures; follow-up 18 months – 4 years; all small studies (n<200)	Widely varying results due to differences in populations, treatments and small sample sizes; while each study suggests an effect in reducing fracture probabilities, range of uncertainty is too wide to make a definitive statement about magnitude of effect

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
Shea et al. (2002)	Systematic review to summarise controlled trials examining the effect of calcium on BMD and fractures in postmenopausal women High-quality systematic review	Women 45 years or older with absence of menses for a minimum of 6 months	RCTs of calcium supplementation in study population; treatment with doses of calcium at least 400 mg/day Also included RCTs in which both active and control groups received a maintenance dose of vitamin D, providing the loading dose was no more than 300,000 IU and the maintenance dose no more than 400 IU/day	Fifteen RCTs were included with fracture or BMD as outcome, with n=1,806, of which 953 received calcium supplementation Five studies including 576 women reported fracture as an outcome Mean ages of participants in various studies were between 58.0 and 73.5 years; follow-up was 1.5–4.0 years	Point estimate from meta-analysis of the 5 studies suggested a potentially important reduction in vertebral fractures and a smaller reduction in risk of non-vertebral fractures
Shea et al. (2004) Cochrane review	Systematic review to assess the effects of calcium on BMD and fractures in postmenopausal women High-quality systematic review	Women 45 years or older with absence of menses for a minimum of 6 months	RCTs of calcium supplementation in study population; treatment with doses of calcium at least 400 mg/day Also included RCTs in which both active and control groups received a maintenance dose of Vitamin D, providing the loading dose was no more than 300,000 IU and the maintenance dose no more than 400 IU/day	Five studies including 576 women reported fracture as an outcome Mean ages of participants in various studies were between 58.0 and 73.5 years; follow up was 1.5–4.0 years	Point estimate from meta-analysis of the 5 studies suggested a potentially important reduction in vertebral fractures and a smaller reduction in risk of non-vertebral fractures

BMD = bone mineral density/densitometry; RCT = randomised controlled trial

Table 42   Studies included to determine whether proposed DXA testing would result in a change in management: vitamin D with or without calcium

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
National Osteoporosis Foundation (1998)	Systematic review of interventions for preventing fracture; covers many interventions Quality appraisal not reported	No restrictions on population described	RCTs with a vitamin D supplementation intervention, and with fracture as an outcome RCTs featuring calcium and vitamin D supplementation, and with fracture as an outcome	Two controlled studies; both large (1,186>n<2,578) and in men and women, with 4-year follow-up; both in participants with a mean age of 80 years or older One large study of elderly (mean age 84 years) French women with	One trial found a non-significant increase in fractures in vitamin D arm; the other found a decrease in fractures Evidence too uncertain to draw conclusions Statistically significantly fewer fractures

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
	Unclear risk of bias			3-year follow-up	in the intervention arm
Crandall et al. (2012) Agency for Healthcare Research and Quality review	Systematic review of interventions for preventing fracture in people with low bone density or osteoporosis; covers many interventions (current to March 2011) Low risk of bias	Healthy populations, or populations with or at risk of low bone density or osteoporosis, aged 18 years or older	Systematic reviews, meta-analyses and RCTs with vitamin D with or without calcium intervention, and with fracture as an outcome	16 meta-analyses including 43 RCTs comparing fracture risk with vitamin D with or without calcium compared with placebo or no treatment	Results varied markedly across studies—according to population (e.g. prior fracture), dose of vitamin D and whether calcium included Some pooled estimates showed no significant benefit of vitamin D, whereas some showed benefit for overall fracture risk Significant reductions in risk for non-vertebral fractures in institutionalised people, but evidence not consistent among others Overall conclusion of the authors was that the evidence was of low to moderate quality and the findings inconclusive
Avenell et al. (2009) Cochrane review	Systematic review of vitamin D and vitamin D analogues, with or without calcium, for preventing fractures associated with involutional and post-menopausal osteoporosis	Men older than 65 years of age and postmenopausal women, without osteoporosis associated with corticosteroid therapy	RCTs or quasi-randomised trials of vitamin D or vitamin D-related compounds, with or without calcium, and with fracture as an outcome	Forty-five trials; 23 smaller (n<150 participants), 8 medium (150>n<500) and 14 large (610–36,282 participants) Varied populations, mostly elderly, many with pre-existing fractures and many institutionalised	Vitamin D alone versus placebo showed no statistically significant effect on hip fracture, non-vertebral fracture, vertebral fracture or any new fracture Vitamin D plus calcium versus calcium alone showed no statistically significant effect of either arm on hip fracture, non-vertebral fracture, vertebral fracture or any fracture Vitamin D plus calcium showed significantly significant reduction in hip fracture compared with placebo or no treatment; subgroup analysis showed effect in institutionalised people but not community-dwelling people; no effect on non-vertebral or vertebral fracture
Tang et al. (2007)	Systematic review of	Patients aged 50 years or	RCTs with calcium ± vitamin D	17 RCTs with fracture as an	Calcium and calcium with vitamin D

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
	interventions including calcium, vitamin D or both for preventing fracture Low risk of bias	older without secondary osteoporosis	supplementation (not dietary calcium) intervention, and with fracture as an outcome	outcome; men and women with mean age of 58–85 years; studies between n=19 and n=9,605 participants Included 8 studies with calcium and vitamin D, and 9 with calcium only (reported together) Average treatment duration 3.5 years	associated with statistically significant reduction in fractures of all types; evidence consistent across all included studies
Boonen et al. (2007)	Systematic review of interventions including vitamin D with or without calcium for preventing hip fracture Low risk of bias	Postmenopausal women and/or men aged 50 years or older	RCTs of vitamin D supplementation with or without calcium, and with hip fracture as an outcome	Nine RCTs with patients with mean age of 62–85 years; studies between n=583 and n=36,282 participants; 6 of 9 studies had vitamin D and calcium Treatment duration 24–84 months	Statistically significant reduction of hip fracture risk with vitamin D and calcium; also reported statistically significant reduction in all non-vertebral fractures Non-significant increase in hip fracture from vitamin D alone
Papadimitropolous et al. (2002)	Systematic review of interventions including standard or hydroxylated vitamin D with or without calcium for preventing fracture Low risk of bias	Women aged 45 years or older; postmenopausal for at least 6 months	RCTs of vitamin D supplementation greater than 400 IU daily, or hydroxyvitamin D, with or without calcium, and with X-ray-confirmed hip, vertebral or wrist fracture as an outcome	Ten RCTs with patients with mean age of 63.7–80.0 years; studies between n=14 and n=1,916; many older studies with small numbers and older participants	Statistically significant reduction of vertebral fracture risk with vitamin D ± calcium found in 8 studies; non-significant reduction of non-vertebral fracture risk with vitamin D ± calcium in 6 studies Authors concluded variability in study results limits any inferences that could be made
Prentice et al. (2013)	RCT of postmenopausal women in Women's Health Initiative, USA Low risk of bias	N=36,282 postmenopausal women randomised to vitamin D and calcium or placebo, and followed for an average of 7 years; population could be already taking calcium	Included women aged 50–79 years Excluded women with history of breast cancer, no mammogram in previous 2 years, daily corticosteroid use, urinary tract stones at baseline	Conducted alongside an observational study of n=93,676 women, some of whom were taking calcium and/or vitamin D supplements	All trial participants: non-significant reduction in hazard ratio for participants receiving supplements for hip fracture, total fracture and death; similar results whether population taking personal supplements were included or not Observational study found similar

Study	Study design / Quality appraisal	Study population	Selection criteria	Studies included	Findings
		and vitamin D supplements			results Authors concluded that RCT data are inconclusive concerning the health effects of calcium and vitamin D supplementation

RCT = randomised controlled trial

Appendix D   Excluded studies

First search (safety, direct evidence, diagnostic accuracy and change in management)

Duplicate study or population

Leslie, WD & Lix, LM 2010, 'Simplified 10-year absolute fracture risk assessment: a comparison of men and women', *Journal of Clinical Densitometry*, vol. 13, no. 2, pp. 141–146.

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Stewart, A, Torgerson, DJ & Reid, DM 1996, 'Prediction of fractures in perimenopausal women: a comparison of dual energy X-ray absorptiometry and broadband ultrasound attenuation', *Annals of the Rheumatic Diseases*, vol. 55, no. 2, pp. 140–142.

Incorrect language

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No (extractable) data

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prognostic thresholds in healthy postmenopausal women. The Danish Osteoporosis Prevention Study', *Osteoporosis International*, vol. 17, no. 2, pp. 245–251.

Abrahamsen, B, Vestergaard, P, Rud, B, Barenholdt, O, Jensen, JE, Nielsen, SP, Mosekilde, L & Brixen, K 2006, 'Ten-year absolute risk of osteoporotic fractures according to BMD T-score at menopause: the Danish Osteoporosis Prevention Study', *Journal of Bone and Mineral Research*, vol. 21, no. 5, pp. 796–800.

Kellie, SE 1992, 'Diagnostic and therapeutic technology assessment: measurement of bone density with dual-energy X-ray absorptiometry (DEXA)', *JAMA*, vol. 267, no. 2, pp. 286–288, 290–294.

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Ryan, PJ, Blake, GM & Fogelman, I 1992, 'Postmenopausal screening for osteopenia', *British Journal of Rheumatolpgy*, vol. 31, no. 12, pp. 823–828.

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Kirac, FS, Yuksel, D & Yaylali, OT 2001, 'Pitfalls in the measurement of bone mineral density by the dual-energy X-ray absorptiometric method', *Clinical Nuclear Medicine*, vol. 26, no. 10, pp. 874–875.

Second search (effect of change in management on health)

Duplicate data

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Studies post-dated by systematic review or update

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Nelson, ME, Fiatarone, MA, Morganti, CM, Trice, I, Greenberg, RA & Evans, WJ 1994, 'Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures: a randomized controlled trial', *JAMA*, vol. 272, no. 24, pp. 1909–1914.

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Appendix E Economic literature search

Table 43   Citations identifying health economic studies of bone densitometry

Author(s) and year	Publication title and reference	Results	Comments on applicability to the proposed MBS listing and economic evaluation questions
Harrison, EJ & Adams, JE 2006	'Application of a triage approach to peripheral bone densitometry reduces the requirement for central DXA but is not cost effective', *Calcified Tissue International*, vol. 79, no. 4, pp. 199–206.	In the DXA-referred population, treatment of all women identified by clinical screening tool without DXA was found to be more expensive than using DXA in all women to confirm risk. This was because more women were treated unnecessarily (unless an unacceptably poor tool was used). However, use of a clinical screening tool and then subsequent DXA in high-risk women to determine treatment requirements resulted in cost savings.	Not directly useful. Costing information was based on the UK health system and was not disaggregated to allow translation, and health outcomes were not included. Furthermore, the analysis was not in the relevant patient group, and the intervention used less common screening tools and did not include the FRAX® tool.
Mueller, D & Gandjour, A 2008	'Cost-effectiveness of ultrasound and bone densitometry for osteoporosis screening in postmenopausal women', *Applied Health Economics and Health Policy*, vol. 6, no. 2–3, pp. 113–135.	(In Germany) Use of QUS as a pre-test screening tool for DXA and alendronate treatment was compared with: i) screening with DXA and alendronate treatment; and ii) no screening/treatment.Cost–utility incremental cost-effectiveness ratios (ICERS) (2006 prices) in 50–60 year old women were: QUS + DXA vs no screening; was €3,529/QALY gained; DXA alone vs DXA + QUS was €5,331/QALY gained.	The 8-state Markov model used for the analysis is depicted, and the inclusion of resources and outcomes are detailed, along with transition probabilities and other population parameters. Although the interventions and findings are not directly applicable to the proposed listing, some input data and the approach may be applied.
Mueller, D & Gandjour, A 2009	'Cost-effectiveness of using clinical risk factors with and without DXA for osteoporosis screening in postmenopausal women', *Value Health*, vol. 12, no. 8, pp. 1106–1117.	(In Germany) Use of screening with a CRF tool, and age and subsequent selective DXA to allocate alendronate treatment, was compared with: i) allocating alendronate treatment on the basis of a CRF tool and age alone; and ii) no screening/ treatment. Cost–utility ICERS (2006 prices) in 60–70 year old women were: CRF tool and age vs no screening was €4,607/QALY; CRF + DXA vs CRF alone was €20,235/QALY.	Uses the same model structure as the above publication, adjusting inputs as necessary. Although the interventions and findings are not directly applicable to the proposed listing, some input data and the approach may be applied.
Nagata-Kobayashi, S, Shimbo, T & Fukui, T 2002	'Cost-effectiveness analysis of screening for osteoporosis in postmenopausal Japanese women', *Journal of Bone and Mineral Metabolism*, vol. 20, no. 6, pp. 350–357.	In a hypothetical cohort of postmenopausal 50 year old Japanese women: 3 strategies; (i) DXA screening + HRT if T-score ≤–2.5; (ii) DXA screening + HRT if T-score ≤–1; and (iii) universal HRT (no screening) were compared against no screening or HRT. DXA + HRT for patients with T-score ≤–2.5 was the most cost-effective strategy, with an ICER of 5.36 million ¥/QALY. The ICERs for other strategies were >10 million ¥/QALY.	The 5-state Markov model used for the analysis is depicted, and the inclusion of resources and outcomes are detailed, along with transition probabilities and other population parameters. Although the interventions and findings are not directly applicable to the proposed listing, some input data and the approach may be applied.
Panichkul, S, Panichkul, P, Sritara, C &	'Cost-effectiveness analysis of various screening methods for	Five screening (and selective treatment) programs were compared against 'no screening or intervention', and 'no screening and universal	A decision-analytic model is used, but the evaluation is of limited use; while some

Author(s) and year	Publication title and reference	Results	Comments on applicability to the proposed MBS listing and economic evaluation questions
Tamdee, D 2006	osteoporosis in perimenopausal Thai women', *Gynecologic and Obstetric Investigation*, vol. 62, no. 2, pp. 89–96.	treatment with HRT' in 45–55 year old Thai women. Costs to prevent 1 fracture were: with universal treatment: US$207.82; DXA: US$88.42; QUS: US$147.05; a Risk Index (clinical factors): US$127.67; QUS+DXA: US$71.33; and a Risk Index+DXA: US$60.30. The cost of fractures/population was US$8.49; therefore, 'no intervention' is concluded to be the most cost-effective strategy.	test/clinical parameters may be in common with the MBS context, the differing health systems mean that the cost inputs are not applicable and population differences would require translation. Further, 'fractures avoided' is the only health outcome assessed, which is insufficient for the requested MSAC economic evaluation.
Pfister, AK, Welch, CA, Emmett, MK & Gessford, AK 2012	'An approach to identify rural women aged 60 to 64 for osteoporosis treatment', *Southern Medical Journal*, vol. 105, no. 1, pp. 11–17.	A comparison of three screening + treatment strategies: (i) universal (forearm) DXA and treatment for T-score ≤–1; (ii) CRFs and, if ≥9.3% risk, confirmatory DXA to determine treatment; and (iii) if prior fracture or CRF ≥20%, automatic treatment, otherwise strategy (ii). A sample of US women … showed that 37.5% had CRFs indicating risk of fracture in 10 years ≥9.3%. Only osteoporotic pDXA values were significantly higher at this threshold. A cost-savings strategy non-significantly identified more women who were eligible for treatment using the three strategies (p=0.25), and significantly fewer pDXA examinations were required (p=0.001).	Only considered costs of screening. No HEALTH OUTCOMES.
Richy, F, Ethgen, O, Bruyere, O, Mawet, A & Reginster, JY 2004	'Primary prevention of osteoporosis: mass screening scenario or pre-screening with questionnaires? An economic perspective', *Journal of Bone and Mineral Research*, vol. 19, no. 12, pp. 1955–1960.	4,035 Belgium women older than 45 years of age were studied. In the first scenario women were systematically referred to DXA if older than 45, 50 or 65 years of age. The second scenario involved the validated pre-screening tools SCORE, ORAI, OST and OSIRIS, and assessed two separate ways of handling their results (theoretical and pragmatic). All strategies were compared in terms of cost per osteoporotic patient detected. Results: In the systematic DXA strategies the cost per patient detected ranged from 123€ when measuring all women aged 45 years to 91€ when focusing on women aged 65 years. The corresponding percentage of cases detected ranged from 100% (age 45 years) to 50% (age 65 years). When considering pre-screening under the theoretical and pragmatic scenarios, the OSIRIS index provided the best efficiency, with costs of 74€ (theoretical) to 85€ (pragmatic) per case detected, followed by ORAI (75€ and 96€), OST (84€ and 94€), and SCORE (96€ and 103€). The corresponding percentage of cases detected ranged from 89% (SCORE) to 75% (OSIRIS). The cost-effectiveness analysis showed that mass	Outcome per osteoporotic patient detected—not QALYs.

Author(s) and year	Publication title and reference	Results	Comments on applicability to the proposed MBS listing and economic evaluation questions
		screening strategies for those older than 50 and 65 years of age and using ORAI were best.	
Schousboe, JT 2008	'Cost effectiveness of screen-and-treat strategies for low bone mineral density: how do we screen, who do we screen and who do we treat?', *Applied Health Economics and Health Policy*, vol. 6, no. 1, pp. 1–18.	Review article only: The abstract states: 'Based on older paradigms of the pharmacological treatment of those with a bone density value below a specific threshold, bone densitometry appears to be cost-effective for postmenopausal women aged ≥65 years, regardless clinical risk factors. For younger post-menopausal women, bone densitometry is likely to be cost effective only for those with specific clinical risk factors, such as prior fracture or low bodyweight'.	

BMD = bone mineral density/densitometry; CRF = clinical risk factor; DXA = dual X-ray absorptiometry; FRAX® = WHO Fracture Risk Calculator; QALY = quality-adjusted life year; HRT = hormone replacement therapy; QUS = quantitative ultrasound; UK = United Kingdom

Appendix F Additional information relating to the economic or financial analysis

Table 44   Matrix to determine the appropriate type of economic model

CEA = cost-effectiveness analysis; CUA = cost–utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases there will be some uncertainty around such a conclusion (i.e. the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost–utility analyses

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Table 45   Advertised fees for non-MBS subsidised DXA scans in Australia, 2014

Provider	Advertised cost to public	Reference [a]
Central DXA scan for BMD for osteoporosis screening or monitoring:		
Royal Adelaide Hospital (requires Dr referral)	Private patients $40 (subsidised by SA Government) Pensioners/RAH outpatients: no charge	http://www.rah.sa.gov.au/nucmed/BMD/bmd_info.htm
Measure Up (requires Dr referral)	$80 where no Medicare rebate applies	http://www.measureup.com.au/bone-density
Peripheral EXA scan for BMD for osteoporosis screening:		
Australian Bone Density Testing Centre (no Dr referral required)	$45 [b] Ultrasound to heel of 1 foot	http://www.bonedensitytesting.com.au/pages/default.cfm?page_id=19724
DXA scan for body composition information, used for athlete training or weight-loss programs: [b]		
BodyScan	$170 total, comprising: $70.30 Medicare benefit $99.70 patient co-payment	http://www.bodyscan.com.au/pricing.php
Hall Cycle Training	$130	http://bradhall.com.au/hall-cycling-dexa-scan/

[a] Websites accessed 4 April 2014
[b] BMD information not necessarily provided

Table 46   Potential additional follow-up DXA scans in women identified as osteoporotic after taking up proposed listing, 2015–29

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
Uptake of proposed listing	16,074	32,595	49,573	67,019	67,952	68,854	69,768	70,686	71,601	72,516	73,431	74,346	75,261	76,177	77,092
Women diagnosed as osteoporotic	643	1,304	1,983	2,681	2,718	2,754	2,791	2,827	2,864	2,901	2,937	2,974	3,010	3,047	3,084
Women rescanned: 2 years later [a]	0	0	630	1,278	1,943	2,627	2,664	2,699	2,735	2,771	2,807	2,843	2,879	2,914	2,950
4 years later [a]					617	1,252	1,904	2,575	2,610	2,645	2,680	2,715	2,751	2,786	2,821
6 years later [a]							605	1,227	1,866	2,523	2,558	2,592	2,627	2,661	2,696
8 years later [a]									593	1,203	1,829	2,473	2,507	2,540	2,574
10 years later [a]											581	1,179	1,792	2,423	2,457
12 years later [a]													552	1,120	1,703
14 years later [a]															525
16 years later [a]															
Total additional screens			630	1,278	2,561	3,879	5,173	6,501	7,805	9,142	10,455	11,801	13,107	14,444	15,725
Additional screens as a % of eligibility for proposed listing			1.27%	1.91%	3.77%	5.63%	7.41%	9.20%	10.90%	12.61%	14.24%	15.87%	17.42%	18.96%	20.40%

[a] For the first additional 10 years the survival/follow-up rate has been assumed at 98% every 2 years (which is lower than the 2-year survival rate in women of the appropriate age group based on ABS Australian life tables). After 10 years (11–20 years) the survival/follow-up rate is reduced to 95% every 2 years, which better reflects (but is still lower than) the mortality rate in the increased age group.

Table 47   Potential additional follow-up DXA scans in women identified as osteoporotic after taking up proposed listing, 2030–40

	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
Uptake of proposed listing	78,007	78,922	79,837	80,752	81,667	82,582	83,497	84,412	85,327	86,242	87,158
Women diagnosed as osteoporotic	3,120	3,157	3,193	3,230	3,267	3,303	3,340	3,376	3,413	3,450	3,486
Women rescanned: 2 years later [a]	2,986	3,022	3,058	3,094	3,130	3,165	3,201	3,237	3,273	3,309	3,345
4 years later	2,856	2,891	2,926	2,962	2,997	3,032	3,067	3,102	3,137	3,172	3,208
6 years later	2,730	2,765	2,799	2,833	2,868	2,902	2,937	2,971	3,006	3,040	3,075
8 years later	2,608	2,642	2,675	2,709	2,743	2,777	2,811	2,844	2,878	2,912	2,946
10 years later	2,490	2,523	2,556	2,589	2,622	2,655	2,688	2,721	2,754	2,787	2,820
12 years later	2,302	2,334	2,365	2,396	2,428	2,459	2,491	2,522	2,554	2,585	2,617
14 years later	1,064	1,618	2,187	2,217	2,247	2,277	2,307	2,336	2,366	2,396	2,426
16 years later		498	1,010	1,537	2,078	2,107	2,134	2,163	2,191	2,220	2,248
18 years later				473	960	1,460	1,974	2,001	2,028	2,055	2,082
20 years later						450	912	1,387	1,875	1,901	1,926
Total additional screens	**17,035**	**18,292**	**19,577**	**20,811**	**22,071**	**23,284**	**24,521**	**25,286**	**26,062**	**26,378**	**26,692**
Additional screens as a % of eligibility for proposed listing	21.84%	23.18%	24.52%	25.77%	27.03%	28.19%	29.37%	29.96%	30.54%	30.59%	30.62%

[a] For the first additional 10 years the survival/follow-up rate has been assumed at 98% every 2 years (which is lower than the 2-year survival rate in women of the appropriate age group based on ABS Australian life tables). After 10 years (11–20 years) the survival/follow-up rate is reduced to 95% every 2 years, which better reflects (but is still lower than) the mortality rate in the increased age group.

Appendix G   Medicare Benefits Schedule – Note D1.27

Category 2 - DIAGNOSTIC PROCEDURES AND INVESTIGATIONS D1.27 Bone Densitometry - (Items 12306 to 12323)

Item 12321 is intended to allow for bone mineral density measurement following a significant change in therapy - e.g. a change in the class of drugs - rather than for a change in the dosage regimen.

Item 12323 enables the payment of a Medicare benefit for a bone densitometry service performed on a patient aged 70 years or over. The Government has decided to expand access to Medicare subsidised bone mineral density testing to coincide with the expanded eligibility for the osteoporosis medication 'alendronate' under the Pharmaceutical Benefits Scheme.

An examination under any of these items covers the measurement of 2 or more sites, interpretation and provision of a report. Two or more sites must include the measurement of bone density of the lumbar spine and proximal femur. If technical difficulties preclude measurement at these sites, other sites can be used for the purpose of measurements. The measurement of bone mineral density at either forearms or both heels or in combination is excluded for the purpose of Medicare benefit.

Referrals

Bone densitometry services are available on the basis of referral by a medical practitioner to a specialist or consultant physician. However, providers of bone densitometry to whom a patient is referred for management may determine that a bone densitometry service is required in line with the provisions of Items 12306, 12309, 12312, 12315, 12318, 12321 and 12323.

For Items 12306 and 12309 the referral should specify the indication for the test, namely:

   (a) 1 or more fractures occurring after minimal trauma; or

   (b) monitoring of low bone mineral density proven by previous bone densitometry.

For Item 12312 the referral should specify the indication for the test, namely:

   (a) prolonged glucocorticoid therapy;

   (b) conditions associated with excess glucocorticoid secretion;

   (c) male hypogonadism; or

   (d) female hypogonadism lasting more than 6 months before the age of 45.

For Item 12315 the referral should specify the indication for the test, namely:

   (a) primary hyperparathyroidism;

   (b) chronic liver disease;

   (c) chronic renal disease;

   (d) proven malabsorptive disorders;

   (e) rheumatoid arthritis; or

   (f) conditions associated with thyroxine excess.

For Item 12318 the referral should specify the indication for the test, namely:

   (a) prolonged glucocorticoid therapy;

(b) conditions associated with excess glucocorticoid secretion;

(c) male hypogonadism;

(d) female hypogonadism lasting more than 6 months before the age of 45;

(e) primary hyperparathyroidism;

(f) chronic liver disease;

(g) chronic renal disease;

(h) proven malabsorptive disorders;

(i) rheumatoid arthritis; or

(j) conditions associated with thyroxine excess.

Definitions

Low bone mineral density is present when the bone (organ) mineral density falls more than 1.5 standard deviations below the age matched mean or more than 2.5 standard deviations below the young normal mean at the same site and in the same gender.

For Items 12312 and 12318

(a) 'Prolonged glucocorticoid therapy' is defined as the commencement of a dosage of inhaled glucocorticoid equivalent to or greater than 800 micrograms beclomethasone dipropionate or budesonide per day; or

(b) a supraphysiological glucocorticoid dosage equivalent to or greater than 7.5 mg prednisolone in an adult taken orally per day;

for a period anticipated to last for at least 4 months.

Glucocorticoid therapy must be contemporaneous with the current scan. Patients no longer on steroids would not qualify for benefits.

For Items 12312 and 12318

(a) Male hypogonadism is defined as serum testosterone levels below the age matched normal range.

(b) Female hypogonadism is defined as serum oestrogen levels below the age matched normal range.

For Items 12315 and 12318

A malabsorptive disorder is defined as one or more of the following:

(a) malabsorption of fat, defined as faecal fat estimated at greater than 18 gm per 72 hours on a normal fat diet; or

(b) bowel disease with presumptive vitamin D malabsorption as indicated by a sub-normal circulating 25-hydroxyvitamin D level; or

(c) histologically proven Coeliac disease.

Related Items: 12306, 12309, 12312, 12315, 12318, 12321, 12323

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