

**MSAC application no 1313**

**Bone mineral density analyses using  
Dual Energy X-ray Absorptiometry  
(DXA) in breast cancer patients  
receiving aromatase inhibitor treatment**

**June 2014**

**Assessment Report - Bone mineral density analyses using Dual Energy X-ray Absorptiometry (DXA) in breast cancer patients receiving aromatase inhibitor treatment**

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This report is a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health and Ageing 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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This report should be referenced as follows:

Gordon L, Downes M, Sowa P, Tuffaha H, Scuffham P. (2014). Bone mineral density analyses using Dual Energy X-ray Absorptiometry (DXA) in breast cancer patients receiving aromatase inhibitor treatment. MSAC Application 1313, Assessment Report. Commonwealth of Australia, Canberra, ACT.

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# Executive summary

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## The procedure

Dual-energy X-ray absorptiometry (DXA) is a diagnostic procedure introduced into routine clinical practice as a method to measure bone mineral density (BMD). Clinicians use DXA to diagnose osteopenia and osteoporosis and appropriately treat individuals to prevent fractures. The DXA scan is used to generate a T-score, a comparison of a patient's bone density to that of peak bone density for the patient's gender and is the number of standard deviations above or below the normal young adult BMD means. T-scores are often taken at the lumbar spine (L2-L4), total hip and femoral neck.

## Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from Griffith University was engaged to conduct a systematic review of the literature and an economic evaluation of DXA and anti-resorptive therapy.

**Main research question:** What is the safety, effectiveness, and cost-effectiveness of DXA and anti-resorptive therapy in women taking aromatase inhibitor treatment for early breast cancer, compared with no DXA and no anti-resorptive therapy?

## Assessment of DXA

### 1. Purpose of application

An application was submitted by the Australian and New Zealand Bone Mineral Society (ANZBMS) to list bone densitometry using DXA in June 2011. In this MSAC application, a DXA scan is intended to be used to assess BMD and subsequent fracture risk specifically in post-menopausal women with early stage breast cancer who are taking or about to start a course of aromatase inhibitors. Aromatase inhibitor (AI) therapy is the mainstay treatment in post-menopausal women with breast cancer. AIs prevent oestrogen synthesis by inhibiting the aromatase enzyme which is responsible for converting androgens to oestrogen. Oestrogen is an important modulator of bone formation. So although AI therapy has been demonstrated to lengthen progression-free survival, bone loss is one detrimental consequence of this therapy.

### 2. Background

The ANZBMS has also submitted a concurrent application (MSAC 1316) to list bone densitometry using DXA for all men and women with risk factors for osteoporosis and aged 50-69. Unconditional access to DXA scanning is currently available to persons aged 70 years and over (MBS item 12323) and is funded for men and women below the age of 70 when they suffer from certain pre-defined conditions.

### 3. Prerequisites to implementation of any funding advice

DXA scanners are already approved for use in Australia through the TGA. Four DXA scanning machines currently used in Australia are: Hologic QDR, GE Medical Systems Lunar, Norland and Medilink. All DXA BMD operators require a Radiation Use licence from their respective State Radiation Health authority before they can operate a bone densitometer as the densitometer is classified as an irradiating device. Nuclear medicine physicians and radiologists can obtain Use licences on successful completion of their training as verified by their respective colleges. Other non-medical operators are required by the State Radiation Health authorities to undergo certification to document that there is sufficient expertise to operate the bone densitometer before a Use licence is issued. The ANZBMS and some universities run courses which, upon completion, award participants with a Certificate of Completion in Clinical Bone Densitometry. This satisfies the requirements of radiation safety legislation in most Australian states. Radiology and nuclear medicine trainees attend the ANZBMS course as part of their training. In terms of site accreditation, at present radiology and nuclear medicine modalities require accreditation under the Diagnostic Imaging Accreditation Scheme whereas BMD measurement does not. This is because Medicare eligible items for BMD measurement do not come in under the *Health Insurance Diagnostic Imaging Services Table Regulation*. Rather, it is regulated under the *Health Insurance (Bone Densitometry) Determination* and the BMD Medicare eligible items are found within the *Health Insurance (General Medical Services Table) Regulation*.

### 4. Proposal for public funding

The proposed new MBS item is shown below. For patients with BMD T-scores  $\leq -2.5$ , repeat scans are already available through the existing MBS item 12306. At age 70, patients will be eligible for MBS item 12323. If a patient has undergone premature menopause as a consequence of breast cancer chemotherapy treatment and is under age 45, she is eligible for MBS item 12312.

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#### Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS, Bone Densitometry

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MBS XXXXX

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 mineral density in patients with breast cancer who are currently being treated with or are about to commence treatment with aromatase inhibitors.

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, 12318, 12321 or 12323 applies

Fee: \$102.40 Benefit: 75% = \$76.80 85% = \$87.05

[Relevant explanatory notes]

D1.27, Bone Densitometry – (Items 12306 to 12323)

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Currently, all BMD Medicare eligible items within the *Health Insurance (Bone Densitometry) Determination* require BMD to be performed by a specialist or consultant physician in the practice of his or her specialty. This requirement is opposed by the ANZBMS, Osteoporosis Australia, RANZCR and others. They believe that there should not be any issue with an appropriately certified BMD operator performing BMD measurement under the supervision of a specialist physician. The test is relatively simple (relative to ECG, EEG, more complicated audiology testing etc) and can be delegated without the need for personal onsite attendance of the specialist physician. However, the specialist physician needs to review and interpret the study and report the results. The MSAC policy area agrees that this requirement needs reviewing, however the policy area requests

that minimum qualifications of BMD personnel be clarified and with the change, a review on the rebate be undertaken to ensure value for money.

## 5. Consumer Impact Statement

On 8 November 2012, the Breast Cancer Network Australia (BCNA) provided feedback on MSAC application 1313. The BCNA welcomes and supports this application in order to assist women with the significant financial burden associated with their diagnosis, treatment and care. They reported survey results that suggest 30% cent of women taking aromatase inhibitors had a DXA test every 12 months, and almost 30% every two years. Some women reported having up to six DXA tests in conjunction with their aromatase inhibitor treatment, fully paid by the patient.

## 6. Proposed intervention's place in clinical management

The proposed intervention is to be used where no current intervention is publicly funded. DXA scans are already commonly used in the proposed patient group. The clinical algorithm states that patients on aromatase inhibitors would be assessed at baseline for osteoporosis. If they have osteoporosis, patients would start anti-resorptives, or otherwise they would be re-tested after two years. If at this time patients have osteoporosis, they would start anti-resorptives or if not, would only receive a third DXA and/or anti-resorptives if they develop skeletal metastases or premature menopause. The clinical evidence addressed the requirements of the agreed Protocol.

## 7. Other options for MSAC consideration

Nil

## 8. Comparator to the proposed intervention

In the agreed final Protocol, the comparator for the intervention DXA scan plus anti-resorptive treatment is fracture risk assessment (without DXA scan) and lifestyle advice with or without vitamin supplements (without anti-resorptive treatment). Vitamin supplements include calcium and vitamin D<sub>3</sub>. The comparator is somewhat inconsistent with the clinical decision algorithm because lifestyle advice with or without supplements occurs in addition to a baseline BMD measurement by DXA. Calcium/vitamin D<sub>3</sub> supplements were also permitted in the major clinical trials presented in this report.

Current MBS items for the comparators include vitamin D testing (MBS items 66608, 66609) and physician consultations (MBS items: 23, etc). In practice, it may be usual to see fracture risk assessment and lifestyle/vitamin advice given in addition to DXA scan and anti-resorptive treatment. Anti-resorptive combination products with calcium and vitamin D<sub>3</sub> are currently prescribed on the PBS and are increasing in usage.

## 9. Comparative safety

### DXA safety

There are no studies identified that assessed the safety of DXA scans in this patient group. DXA scans are regarded as non-invasive, safe and are widely available in Australia. The main concern for DXA scans is the emission of radiation and the accumulation of radiation from multiple scans over time. The main sources of evidence on DXA safety were a) a review by Njeh CF *et al.* (1999) and b) an observational study by Bandirali *et al.* (2013). DXA scans emit negligible amounts of radiation and below background levels.

### Anti-resorptive treatment safety

In 14 randomised controlled trials on bone loss treatments for women on aromatase inhibitors, the common adverse events were arthralgia, hot flushes, fatigue, myalgia, bone pain and fever. In general, these were not statistically significantly different in the treatment and no (or delayed) treatment arms.

## 10. Comparative effectiveness

### DXA effectiveness

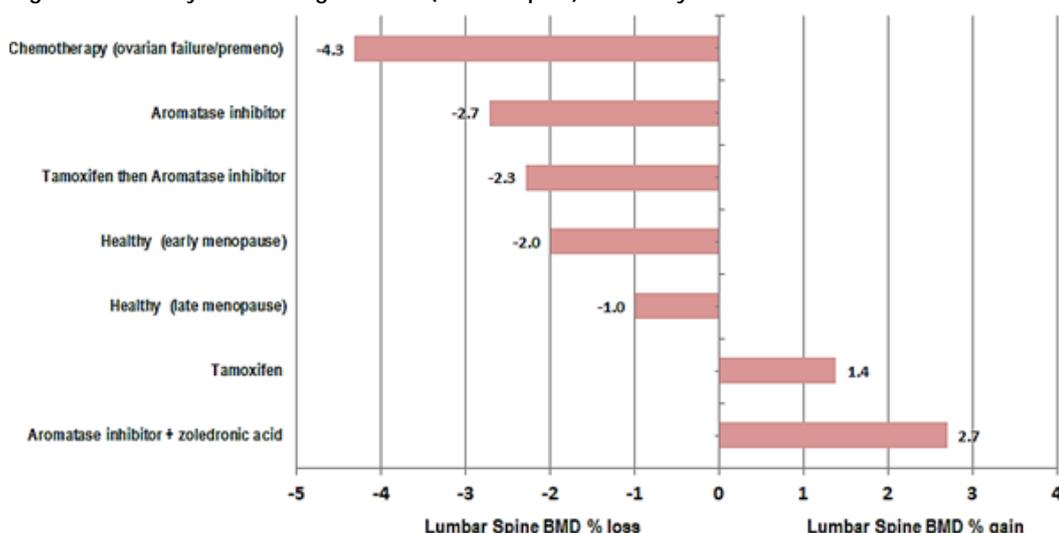
The primary sources of evidence on the effectiveness of DXA for BMD measurement were three meta-analyses, two health technology reports, one review and one case control study. The main results indicate that DXA scans predict low BMD well, better than other modalities and better than risk fracture assessment alone. The predictive performance of DXA for hip fractures shows that it has high specificity 88% but low sensitivity 37% (15 year incidence)(Marshall *et al.* 1996). The combined use of clinical risk factor assessment and BMD analysis provides the best prediction of fracture risk (Kanis *et al.* 2007).

### Anti-resorptive treatment effectiveness

The primary sources of evidence were 14 studies assessing anti-resorptives or other BMD treatments; 12 randomised controlled trials (phase II, phase III and/or open label), one comparative study and one meta-analysis. The evidence consistently showed that anti-resorptive treatment significantly improved BMD in women taking aromatase inhibitors. Studies with 60 month follow-ups showed linear increases in BMD in each successive year. Positive BMD occurred regardless of whether women were treated with prior chemotherapy or prior tamoxifen. Meta-analyses for BMD lumbar spine and total hip confirmed positive mean differences between the intervention and comparator arms but study heterogeneity was problematic. Fracture incidence was lower in anti-resorptive treatment arms but these trials were not of sufficient power or duration to detect differences in minimal trauma fractures. Clinical management with the proposed intervention is more effective than clinical management without it.

A summary of the rate of bone loss in women with breast cancer and healthy women is provided in Figure ES1.

Figure ES1: One year % change in BMD (lumbar spine) in healthy women and women with breast cancer



AI = aromatase inhibitor, BMD = bone mineral loss

Sources: Figure adapted from Fig 2 (Bauer, Bryce et al. 2012). (O'Flaherty 2000, Eastell, Adams et al. 2008, Finkelstein, Brockwell et al. 2008, Llombart, Frassoldati et al. 2012). Weighted average of Powles 1998, Saarto 1997, Delmas 1997, Shapiro 2001, Vehmanen 2001, Hines 2009.

## 11. Economic evaluation

A cost-utility analysis was undertaken with four comparison arms:

1. DXA and anti-resorptive therapy (women with osteoporosis, T-score  $\leq -2.5$ )
2. DXA and anti-resorptive therapy (women with osteopenia or osteoporosis T-score  $\leq -1.0$ )
3. DXA and anti-resorptive therapy (all women in this population)
4. No DXA and lifestyle advice only (all women in this population)

A Markov cohort model was constructed with annual cycles. The starting age of the cohort of women was 60 years and the model duration was lifetime. The main inputs were: age-related fracture risk; relative risk of fracture in women taking AIs; incidence of osteoporosis, osteopenia and normal BMD in post-menopausal women; risk of fracture when taking anti-resorptives, utilities in women with breast cancer and costs for annual DXA scans, anti-resorptive treatment (risedronate in base case), fractures (hip, vertebrae and 'other') and vitamin D testing. The key results are provided in Table ES1.

Table ES1: Key results of economic evaluation (annual DXA scan, 60 year old cohort)

Intervention	Mean Costs	Mean QALYs	Inc Costs	Inc QALYs	ICER QALYs	Fractures per 1000 women	ICER Fracture avoided
No DXA and lifestyle advice only	\$4056	11.657	ref	ref	ref	113	ref
DXA + ARTx (osteoporosis)	\$5331	11.956	\$1275	0.299	\$4,264	100	\$98,077
DXA + ARTx (osteoporosis + osteopenia)	\$10249	11.959	\$6193	0.302	\$20,507	80	\$187,667
DXA + ARTx (all women)	\$13131	11.960	\$9075	0.303	\$29,950	73	\$226,875

ARTx = Anti-resorptive therapy, DXA = dual absorptiometry X-ray, ICER = incremental cost-effectiveness ratio, QALYs = quality adjusted life years

As shown above, the ICERs are cost-effective when QALYs are used as the outcome but very high when incremental cost per fracture avoided is considered. One-way and probabilistic sensitivity analyses indicate the model is stable to variations in parameters including discount rates, frequency of DXA scans, cost of bone therapy, probability of osteoporosis, background utility for women with breast cancer.

## 11. Financial/budgetary impacts

The financial impact has been calculated for the next five years taking into account the number of new cases of (early stage) breast cancer each year (aged 50-69), repeat scans, and ongoing treatment for bone density while on AI therapy (Table ES2).

Table ES2: Results of the financial estimates over next five years

	2015	2016	2017	2018	2019
Total number of women each year	5911	11956	18138	24454	30906
No. DXA scans if annual	5911	11956	18138	24454	30906
No.women with osteoporosis on anti-resorptives	866	1752	2657	3583	4528
Estimated cost of DXA scans x uptake	\$514,510	\$1,040,770	\$1,578,913	\$2,128,721	\$2,690,367
TOTAL MBS COSTS (DXA, vit D tests, GP visits)	\$865,074	\$1,749,927	\$2,654,694	\$3,579,156	\$4,523,487
TOTAL PBS COSTS (anti-resorptives)	\$473,815	\$910,560	\$1,308,605	\$1,666,324	\$1,982,089
TOTAL STATE GOVT COST SAVINGS (fracture prevention)	-\$38,453	-\$77,787	-\$118,002	-\$159,098	-\$201,074
TOTAL GOVERNMENT COSTS	\$1,300,436	\$2,582,699	\$3,845,297	\$5,086,383	\$6,304,502

DXA = dual x-ray absorptiometry, MBS = Medical Benefits Schedule, PBS= Pharmaceutical Benefits Schedule.

The expected uptake of DXA scans is estimated at 5911 procedures for 5911 patients in Year 1 rising to 30,906 DXA scans for 30,906 patients in Year 5.

The total cost to the Medical Benefits Scheme for the DXA plus anti-resorptives for osteoporotic women is estimated to be \$13.372 million over the next five years. If DXA scans were offered every 2 years instead of annually, the total MBS cost reduces to \$10.203 million over 5 years.

Total cost to the Australian healthcare system including MBS for DXA plus anti-resorptives for osteoporotic women is estimated to be \$19.119 million over the next five years.

If DXA scans in this population are funded, patients will face a small co-payment of \$15.36 for each DXA scan received during treatment. Currently women are spending \$300-\$500 on DXA scans in addition to their overall out-of-pocket expenses for breast cancer treatment. If women are prescribed vitamin supplements, the estimated costs of taking vitamin D<sub>3</sub> and calcium tablets in women on 'lifestyle advice' is \$57.63, based on an average cost per tablet of 1000IU of vitamin D<sub>3</sub> taken once per day for 12 months.

### 13. Other significant factors

Osteoporotic medications and particularly oral bisphosphonates have been linked with poor adherence and compliance outside of trial settings (Silverman, Schousboe et al. 2011). The reasons for this are unclear but these observations are common to other chronic diseases where medications are taken in asymptomatic patients. Stomach complaints and other adverse events have been attributed to this noncompliance but other possible explanations include; the perceived lack of risk of fracture and benefit of taking the medication, scepticism of the effectiveness of the medication, forgetfulness, cost barriers or the belief that vitamin supplements may be better (Silverman, Schousboe et al. 2011). Further Australian research on the extent and nature of non-compliance is important if the potential health benefits of the intervention (DXA and bone treatment) are to be fully realised.

An additional study on vitamin D supplements provides supplementary evidence for this application. A 2014 systematic review on the effects of vitamin D supplements on bone mineral density showed an overall small benefit at the femoral neck (weighted mean difference 0.8% 95%CI 0.2-1.4%) with moderate trial heterogeneity ( $I^2=67%$   $p<0.01$ ) (Reid, Bolland et al. 2014). The authors have concluded that widespread use of vitamin D for osteoporosis prevention in adults without specific risk factors for vitamin D

deficiency is inappropriate. Further they suggest that the effects of combination calcium and vitamin D on fracture risk are similar to those for calcium alone, suggesting the negligible effect of vitamin D. The implication of this systematic review is that vitamin D supplements may be inferior to bone resorptive agents. Following on from this, vitamin D testing will be unnecessary particularly if bone medications become routinely prescribed and combined with calcium and vitamin D<sub>3</sub>.

## 14. Conclusions

There is good evidence that women with breast cancer on aromatase inhibitors have a higher risk of BMD loss and bone fractures compared to women not taking aromatase inhibitors. However the following points should be noted:

- The absolute fracture risk is low, fractures are a rare event with the number needed to harm (with aromatase inhibitors) = 46.
- The higher fracture risk for aromatase inhibitor users remains regardless of
  - prior tamoxifen or
  - the sequencing of aromatase inhibitor and tamoxifen or
  - aromatase inhibitor compliance rates or
  - type of aromatase inhibitor.
- The decline in bone density subsides when aromatase therapy stops but bone density may not return to baseline pre-therapy levels
- The risk of bone loss caused by aromatase inhibitor therapy is independent and additional to bone loss from ovarian failure secondary to chemotherapy which can subsequently cause premature menopause.

Issues that remain as sources of uncertainty relate to clinical practice in Australia and the expected role of clinicians in performing risk assessments, the non-uniform reporting requirements of BMD analyses in practice and the frequency of DXA scans needed.

Women with breast cancer can face significant out-of-pocket expenses in Australia (see Discussion). Funding DXA scans will have a favourable impact on alleviating the sometimes substantial costs of breast cancer treatment, symptoms and work disruption for this patient group.

# Introduction

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The Medical Services Advisory Committee (MSAC) has reviewed the use of dual energy x-ray absorptiometry (DXA), which is a diagnostic and monitoring test for bone mineral density. In this instance, the test is to assess bone mineral density for patients with breast cancer receiving or scheduled for aromatase inhibitors and, where appropriate, treat with anti-resorptive medications. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme 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 reviews of the scientific literature and other information sources, including clinical expertise.

MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for DXA and anti-resorptive agents for low bone mineral density in patients with breast cancer receiving aromatase inhibitors.

This application has been submitted by the Australian and New Zealand Bone Mineral Society. A parallel application is submitted MSAC 1316 for men and women aged 50-69 years with risk factors for osteoporosis.

# Background

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Women who are post-menopausal and have breast cancer are often treated with aromatase inhibitors (e.g., anastrozole, letrozole, exemestane). These endocrine medications are designed to inhibit oestrogen which effectively prevents cancer cell growth. Aromatase inhibitor treatment is now standard of care and is regarded as equal to or superior over tamoxifen. However, a well-known and classic adverse event of these hormone medications is de-mineralisation of bones which may lead to increased risk of bone fractures (Bauer, Bryce et al. 2012). Consequently, women taking aromatase inhibitors are at risk of developing bone thinning, fractures and osteoporosis. The following sub-sections provide background information on: breast cancer, bone mineral density, the role of DXA and anti-resorptive treatments for poor bone density.

## Breast cancer

Breast cancer is the most common cancer affecting women in Australia (excluding non-melanoma skin cancer) representing 28% of all female cancers (Australian Institute of Health and Welfare & Cancer Australia 2012). One in eight women is expected to develop the disease at some stage during their lives. In 2008, 13,567 new invasive breast cancers were diagnosed. The mean age of Australian women diagnosed with breast cancer is 60 years. Of all women with breast cancer, 69% of occur in women aged 40-69 years. Compared to lung, colorectal or ovarian cancers, survival rates are better and approximately 89% of women diagnosed with breast cancer survive for at least five years. As survival rates continue to improve, research is focussing on understanding and improving health-related quality of life, particularly for new treatments. Breast cancer also affects men but this is very uncommon; the number of new cases was 127 in 2010.

The economic impact of breast cancer on the health system is significant (\$331 million per year) and this represents 1.4% of all female disease expenditure (2004-05)(Australian Institute of Health and Welfare & Cancer Australia 2012). The demand for hospital services has increased by 32% between 2001/01 – 2004/05. There were a total of 113,132 hospitalisations for breast cancer as either the principal or additional diagnosis in 2008 (Australian Institute of Health and Welfare & Cancer Australia 2012).

Aromatase inhibitor (AI) therapy is the mainstay treatment in post-menopausal women with oestrogen or progesterone receptor-positive breast cancer, both in adjuvant (early) and metastatic (advanced) settings. AIs prevent oestrogen synthesis by inhibiting the aromatase enzyme which is responsible for converting androgens to oestrogen. Oestrogen is an important modulator of bone formation. Although AI therapy has been demonstrated to lengthen progression-free survival, bone loss is one detrimental consequence of this therapy. This side-effect is predictable because AIs works to deplete oestrogen that combats the cancer but simultaneously has a negative regulatory effect on bone resorption and potentially cause bone loss (Bauer, Bryce et al. 2012).

Post-menopausal women with breast cancer, before they receive AI therapy, are already at increased risk of bone loss due to: age-related failure of ovarian function, subsequent decline in oestrogen and possible disease-related bone loss. Treatment-related bone loss may also be accelerated due to various hormone and chemotherapy treatments (Bauer, Bryce et al. 2012). AI therapy is therefore an added risk factor of bone loss in women with breast cancer.

Cancer Australia published evidence-based Clinical Practice Guidelines on 'Recommendations for use of bisphosphonate in early breast cancer' in November 2011. The full recommendations are listed at: <http://canceraustralia.gov.au/publications-resources/cancer-australia-publications/recommendations-use-bisphosphonates-early-breast> . In brief, these guidelines recommend:

1. Short-term use of bisphosphonates (up to 4 years) should be considered to reduce loss of BMD in lumbar spine, hip and femoral neck associated with treatment for early breast cancer (chemotherapy, endocrine therapy).
2. In post-menopausal women with osteopenia, upfront intravenous zoledronic acid (4 mg every 6 months) should be considered over delayed treatment to prevent bone mineral density loss associated with aromatase inhibitor treatment for breast cancer.

## Bone mineral density

Bone mineral density (BMD) technologies are used in osteoporosis diagnosis and management. They are also used to provide an indicator of risk for future fractures and monitoring bone disease. An individual's BMD relies on the balance between the processes of bone formation and bone resorption. BMD reflects bone strength, mass, spatial distribution (i.e., shape and microarchitecture) and other bone properties such as density, matrix mineralisation, collagen trains and micro damage.

The DXA scan is used to generate a T-score, a comparison of a patient's bone density to that of peak bone density for the patient's gender and is the number of standard deviations above or below the normal young adult BMD means. T-scores are often taken at the lumbar spine (L2-L4), total hip and femoral neck. T-scores of 1.0, 2.0 and 2.5 relate to the normal distribution of bone mass and are the standard deviations to the normal range. Z-scores are number of standard deviations that a BMD score deviates from the mean BMD in persons of the same age and gender.

There is widespread acceptance of the World Health Organisation (WHO) definition of osteoporosis as determined by a person's BMD T-score at the femoral neck (Table 1). Osteopenia is a precursor to osteoporosis.

Table 1: Diagnosis by T-score (femoral neck) and WHO classification of osteoporosis

T-score	Diagnosis
Equal or greater than -1.0	Normal bone density
Between -1.0 to -2.5	Low bone mass 'osteopenia'
Equal or less than -2.5	Osteoporosis
Equal or less than -2.5 and minimal trauma fracture	Established osteoporosis

Source: WHO 2007

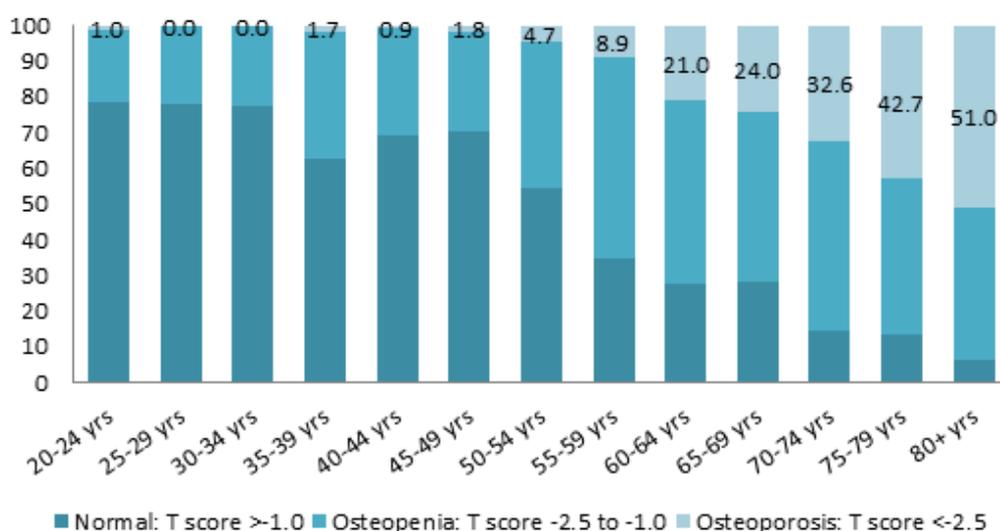
Major risk factors for osteoporosis in post-menopausal women include:

- Low BMD T-score
- Age >65 years
- Low body weight (body mass index (BMI) <20 kg/m<sup>2</sup>)
- Family history of osteoporotic fracture
- Previous fragility fracture after age 50
- Oral corticosteroid use > 6 months duration

Taking into consideration all risk factors, evaluating both BMD T-score and clinical risk factors is believed to provide the best assessment of an increased risk of fracture in women with breast cancer (Bauer, Bryce et al. 2012).

In Australia, the background population levels of BMD are provided for women in Figure 1. These data come from the Geelong Osteoporosis Study (Henry, Pasco et al. 2011) and are reported to be closely representative of all Australian women.

Figure 1: Bone mineral density of Australian women by age group (n=1467)



Source: Graph constructed using data reported in Henry 2011, (% of osteoporosis at top of bars)

Fractures in the context of osteoporosis are called fragility fractures or ‘minimal trauma fractures’. These are defined as a trauma as a result of a fall from standing height or less. Predictors of minimal trauma fracture include:

- advancing age;
- muscle weakness;
- low BMD;
- history of smoking;
- increased body sway; and
- reduced physical activity.

Common sites of minimal trauma fracture are the hip, pelvis, wrist, forearm and spine. Some mild vertebrae fractures may not come to medical attention, patients may feel a dull ache in their spine for example and the following day the pain has gone.

The management of fractures is expensive and hip fractures are the most expensive of all fracture types (Borgstrom and Kanis 2008). Fracture statistics often do not distinguish between minimal trauma fractures and other fractures.

## Dual-energy X-ray absorptiometry (DXA)

Dual-energy X-ray absorptiometry (DXA) scanners were introduced into routine clinical practice during the late 1980s. Their main purpose is to measure BMD. Nowadays DXA scans of the central skeleton are the preferred method for testing BMD compared to the peripheral DXA which measures BMD in the wrist, fingers, leg or heel. Clinicians are able to diagnose osteopenia and osteoporosis and appropriately treat individuals and prevent fractures. DXA allows bone density to be determined in the lower spine, the femur, total body and forearm (as well as other sites on special machines).

DXA scans of the lumbar spine (L2-L4) and hip have three major roles:

1. To diagnose osteoporosis
2. To assess patient's risk of fracture
3. To monitor response to treatment

The WHO provides reference ranges of BMD T- and Z-scores and these are used to make standardized diagnoses of BMD levels, osteopenia and osteoporosis. BMD reference ranges have been calibrated for the Australian population.

A lumbar spine DXA scan requires the patient to lie on a bed on their back, with a pillow under their head and cushion under their knees. For a femur scan, the cushion under their knees is removed and the foot is strapped into a positioning brace. For the scan, any metal or dense objects around the hips, spine or waist need to be removed. The duration of a DXA scan appointment can take up to 20 minutes.

Bone densitometry is performed in radiology and endocrinology departments as well as in nuclear medicine departments. A radiologist, nuclear medicine physician or other accredited specialist is required to perform the test and analyse the results. As different bone densitometer manufacturers have different calibration on their machines, it is important that any subsequent scans be done on the same machine (or at least the same brand) for results to be comparable.

## Anti-resorptive therapies

For women with low BMD as indicated by the T-score, anti-resorptive therapies may assist in the maintenance or increase of bone mass. The anti-resorptive medications considered in this assessment include:

**Oral bisphosphonates** (alendronate, risedronate, ibandronate): these treatments prevent bone loss by inhibiting osteoclast-mediated bone resorption. Oral bisphosphonates may be taken by tablet daily, weekly, or monthly, but are only available in Australia on the Pharmaceutical Benefits Scheme (PBS) for use to treat established osteoporosis with fracture or in women over 70 years with osteoporosis. The most common side effect of treatment with bisphosphonates in tablet form is gastrointestinal complaints making compliance a problem.

**Intravenous bisphosphonates** (zoledronic acid): Zoledronic acid is also known as zoledronate or zolendronate. It is taken intravenously once every six months for the prevention of skeletal-related events in patients with advanced malignancies involving bone (dose: 4 mg for 3 to 4 weeks). For the treatment of post-menopausal osteoporosis

the recommended dose is 5mg of zoledronic acid monohydrate administered once a year.

**Selective oestrogen receptor modulators (SERMs):** work by blocking the oestrogen effect at some receptor sites while prompting an oestrogen effect at others. In bone, they work like oestrogen and lead to an increase in bone mass (density), mainly in the spine (less in the hips). Potential side effects of SERMs include hot flushes and a slightly increased risk of deep vein thrombosis. It is a less potent anti-resorptive agent than bisphosphonates and denosumab.

**Strontium ranelate:** Strontium is a trace element that is naturally found within soft tissues, blood, teeth and bone. How it combats osteoporosis is unclear, but it seems to reduce bone loss and may enhance bone formation. Studies of strontium ranelate treatment for post-menopausal women have shown a reduction in vertebral (spinal), hip and other fractures. It is available through the PBS for the treatment of post-menopausal osteoporosis. Strontium ranelate is taken in the form of granules in water and should be taken at bedtime at least two hours after eating. TGA has advised strontium ranelate should be restricted to a last-line therapy for osteoporosis and strictly avoided in patients with heart disease.

**Denosumab:** is a human monoclonal antibody designed to target RANKL (a receptor activator of nuclear factor kappa-B ligand), which is a protein that acts as the primary signal to promote bone removal. This medication is available through the PBS in Australia for the treatment of post-menopausal osteoporosis. Denosumab is administered as a subcutaneous injection 60 mg once every 6 months. The main side effects include infections, rashes and joint pain.

**Vitamin D and calcium supplements:** If diet is inadequate, a woman experiencing menopause may be prescribed vitamin D and calcium supplements to improve bone mass and strength. Daily sunlight exposure can also boost vitamin D production through ultraviolet radiation B rays and contribute to bone health. Vitamin D tablets are widely available in Australia as over-the-counter supplements in chemists and supermarkets.

**Exercise advice:** Weight bearing exercise increases bone strength and mass and therefore it is important for older persons to maintain adequate levels of physical activity for ideal bone health. In relation to increasing BMD, there is still uncertainty as to which are the best types of exercise or intensities for optimal bone health (Martyn-St James and Carroll 2009).

## Intended purpose

The purpose of this report is to assess the value of DXA scans in women taking aromatase inhibitors at risk of developing bone thinning, fractures and osteoporosis. Standard management of early stage hormone receptor positive breast cancer is using adjuvant aromatase inhibitors to enhance progression-free survival. The report will assess the role of DXA scans in this population and to evaluate the subsequent treatment options of medications that have anti-resorptive bone properties.

## Clinical need

Currently, the patient population is not eligible for MBS reimbursement of a DXA scan, initial or otherwise unless they are over the age of 70, have bone conditions pertaining to the current MBS items or they have experienced a minimal trauma fracture.

As previously stated, breast cancer is a common and serious disease in the Australian community. It exerts a large toll on social, medical and economic resources. Standard hormone therapy with aromatase inhibitors is associated with reductions in BMD. The magnitude of BMD loss will be addressed later in the report in relation to all post-menopausal women.

DXA scans are used to assess BMD and guide clinical decisions about anti-resorptive treatments. DXA scans are widely used in Australia and regarded as the gold standard in BMD measurement. The clinical need and the issues around whether DXA scans are essential in these clinical decisions will be discussed later in the report.

## Existing tests

Quantitative computed tomography (QCT) and quantitative ultrasound can be used in measuring BMD. Bone mineral tests other than DXA are not considered appropriate for this evaluation (Protocol 1313) because:

- QCT results are less reproducible than DXA;
- There is less robust evidence currently available to support the use of QCT;
- Although QCT radiation doses are reducing over time, currently the use of QCT involves a higher dose of radiation than DXA so exposes patients to a greater degree of harm;
- There are no standardised Australian normative data for QCT; and
- QCT assessment of the spine may overestimate osteoporosis compared to DXA using the WHO standard definitions.

PASC recognises that QCT may be considered an alternative to DXA in the future. Peripheral DXA scanning also exists but are not considered in this assessment.

Fracture risk tools are often used to estimate 10-year fracture risk. The FRAX™ online tool was developed by the University of Sheffield (UK) on behalf of the WHO. The assessment is likely to be less accurate for pre-menopausal women, young men (<50 years) and is not validated for children. A variation of FRAX supported with Australian data is available at: <http://www.shef.ac.uk/FRAX/tool.jsp?country=31>. The tool calculates the 10-year absolute risk of hip or major osteoporotic fracture. It was derived from models of population-based cohorts in Europe, North America, Asia and Australia. FRAX™ integrates clinical risk factors to estimate risk. Although optional, the addition of BMD improves the predictive value of hip fracture risk.

Fracture risk tools will be covered in greater detail later in this report.

## Marketing status of device

A radiologist, nuclear medicine physician or other accredited specialist is required to perform the test and analyse the results under all current MBS bone mineral density

items and the proposed MBS item for this application. All DXA BMD operators require a Radiation Use licence from their respective State Radiation Health authority before they can operate a bone densitometer as the densitometer is classified as an irradiating device. Nuclear medicine physicians and radiologists can obtain Use licences on successful completion of their training as verified by their respective colleges. Trainees of these colleges have a trainee Use Licence. Other non-medical operators are required by the State Radiation Health authorities to undergo certification to document that there is sufficient expertise to operate the bone densitometer before a Use licence is issued. The ANZBMS and some universities run courses which, upon completion, award participants with a Certificate of Completion in Clinical Bone Densitometry. This satisfies the requirements of radiation safety legislation in most Australian states. Radiology and nuclear medicine trainees do attend the ANZBMS course as part of their training. In terms of site accreditation, at present radiology and nuclear medicine modalities require accreditation whereas BMD measurement does not. This is because BMD measurement does not come under the *Health Insurance (Diagnostic Imaging Services Table) Regulation*. Rather, it is regulated under the *Health Insurance (Bone Densitometry) Determination* and the BMD Medicare eligible items are found within the *Health Insurance (General Medical Services Table) Regulation*.

The following table provides the regulatory status of four DXA scanning machines used in Australia – Hologic QDR, GE Medical Systems Lunar, Norland and Medilink. All devices are listed in the ARTG as category IIb devices (medium-high level of risk).

Table 2: Regulatory status of DXA scanners in Australia

ARTG number	Approval date	Manufacturer	Product	Approved indication
97975	10/11/2003	GE Medical Systems (Lunar)	GE Medical Systems Australia Pty Ltd - X-ray system, diagnostic, bone absorptiometer, dual-energy	x-ray imaging for bone densitometry
117461	16/03/2005	Norland Corp	Inderlec Medical Systems Pty Ltd - X-ray system, diagnostic, bone absorptiometer, dual-energy	For the estimation of bone density and other structural parameters using x-ray absorptiometry for the purpose of aiding in the diagnosis of osteoporosis including bone regeneration and loss.
119491	25/05/2005	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	23/01/2009	Hologic Inc	Cytec 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 bone mineral density.

Source: <https://www.ebs.tga.gov.au/>.

## Current reimbursement arrangements

DXA scanning is not currently funded for men and women below the age of 70 unless they suffer from certain pre-defined conditions. Unconditional access to DXA scanning

is currently available to persons aged 70 years and over (MBS item 12323). The specific patient populations covered for DXA under the MBS include:

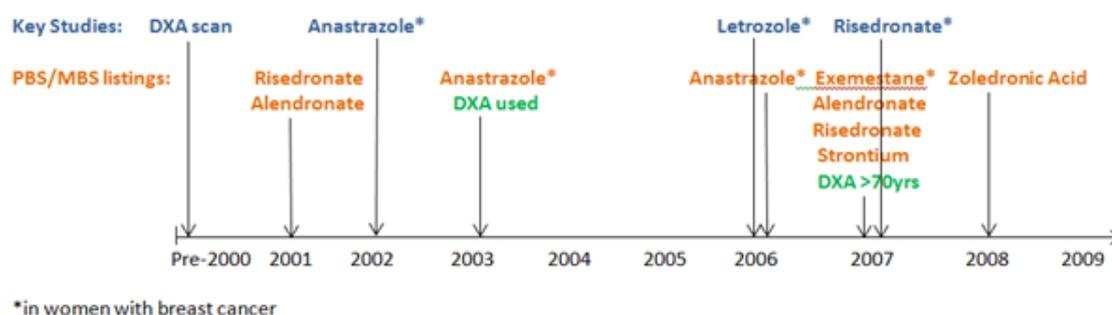
- Presumed low BMD following one or more fractures after minimal trauma;
- Who have undergone prolonged glucocorticoid therapy and conditions associated with excess glucocorticoid secretion;
- Male (all) and female (lasting > 6 months before the age of 45) hypogonadism (i.e. premature menopause in women)
- Primary hyperparathyroidism
- Chronic liver and/or renal disease
- Proven malabsorptive disorders;
- Rheumatoid arthritis; or
- Conditions associated with thyroxine excess.

Several MBS items cover indications for repeat scans every 12 or 24 months depending on the indication. According to current Australian guidelines (RACGP 2010), for patients with low risk factors and ‘normal’ T-scores, repeat scans are not required unless the patient has a minimal trauma fracture or increased risk conditions. People diagnosed with osteoporosis (T-score  $\leq -2.5$ ) are eligible for repeat testing as required under MBS item 12306. Patients with confirmed osteoporosis and receiving anti-osteoporotic treatment do not require repeat DXA scans unless there is a change in, or cessation of, anti-osteoporotic therapy (RACGP 2010b).

The current MBS reimbursement arrangements for DXA were summarised in the Protocol. In general, anti-resorptive treatments are covered by the Pharmaceutical Benefits Scheme (PBS) for men and women after fragility fracture as well as for those at high risk, without prior fracture, on the basis of age ( $\geq 70$  years) and low BMD (T score  $\leq -2.5$  or  $\leq -3.0$ ).

Figure 2 provides a time line showing the relative introduction dates of AIs, anti-resorptive medications and DXA scans in Australia.

Figure 2: Time line of studies and listings for AIs, anti-resorptive medications and DXA scans in Australia



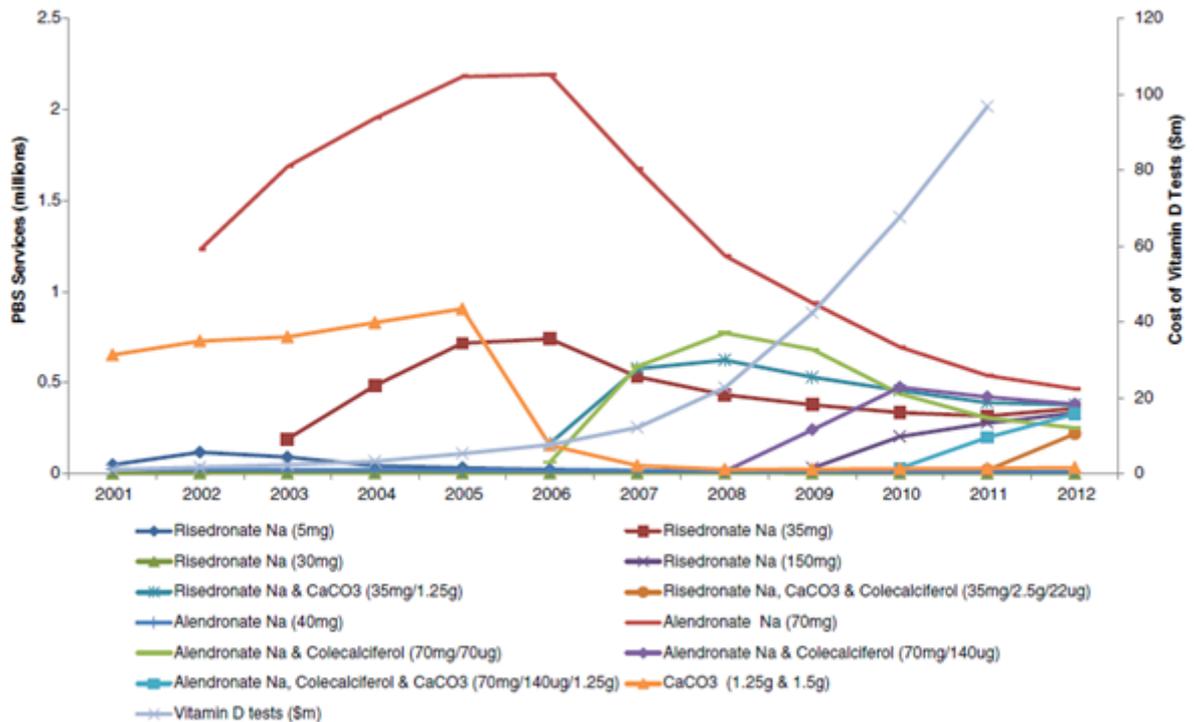
Key studies on the performance of DXA scans for BMD measurement occurred in the late 1980s and 1990s (and difficult to access). This is well before they were introduced into clinical practice in Australia. Oral bisphosphonates were introduced earlier than zoledronic acid however most of the evidence is available on the use of zoledronic acid for prevention of fractures in AI-induced bone loss in women with breast cancer.

Illustrated in Figure 3 are the trends over the last decade in Australia of PBS-listed oral bisphosphonate medications. The graph also shows the costs of vitamin D testing indicated by MBS items 66608 and 66609 (Rowell and Gordon 2013).

MSAC is currently reviewing vitamin D testing in Australia which has experienced large growth in the number of tests since 2006 <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/reviews-lp>. Over \$100 million per year is currently spent on vitamin D testing in Australia. The MBS Vitamin D testing review was discussed at the 61<sup>st</sup> MSAC Meeting on 3-4 April 2014.

In general, Figure 3 shows that single agents have declined over time while combination products (bisphosphonates with calcium and vitamin D<sub>3</sub>) have increased. Vitamin D testing has increased exponentially and is particularly high in New South Wales, Victoria and South Australia (Source: MBS item reports by State, MBS items 66608, 66609). In total MBS costs for vitamin D testing now exceeds \$100 million each year.

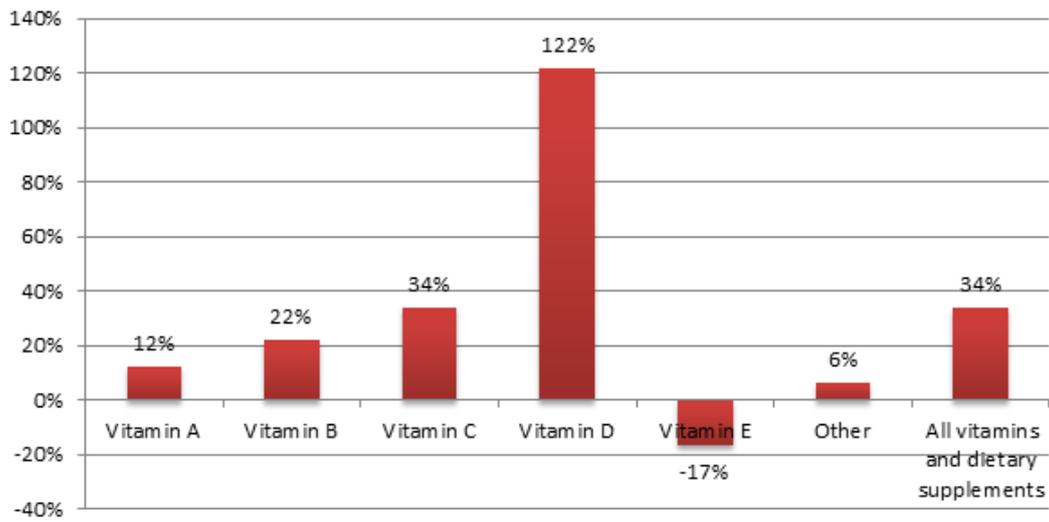
Figure 3: Changes in use of bisphosphonates and cost of Vitamin D (25OHD) testing (2001 to 2012)



PBS item codes included in Figure x: Risedronate Na (4443W, 4444X, 8481J, 8621R, 8972F, 9391G); Risedronate Na, CaCO<sub>3</sub> and Colecalciferol (4380M, 8974H); Risedronate Na and CaCO<sub>3</sub> (8899J, 8973G); Alendronate Na and Colecalciferol (9012H, 9183H); Alendronate Na, Colecalciferol and CaCO<sub>3</sub> (39351E)  
Source: (Rowell and Gordon 2013)

In line with these growth figures in bisphosphonates for bone mineralisation, Australia has also seen a marked increase over 5-years in the growth in vitamin D supplement sales (Figure 4).

Figure 4: Percentage growth in sales of over-the-counter vitamin D supplements (Australia 2006-2011)



Source: Euromonitor International – official statistics, trade associations, trade press, company research, store checks, trade interviews, trade sources.

# Approach to assessment

## Objective

The objective of this assessment is to undertake a structured evaluation of the clinical need, safety, effectiveness and cost-effectiveness of DXA scans, with treatment with anti-resorptive agents, for patients taking aromatase inhibitors for early stage breast cancer.

## Clinical decision pathway

Figure 5: Clinical decision tree

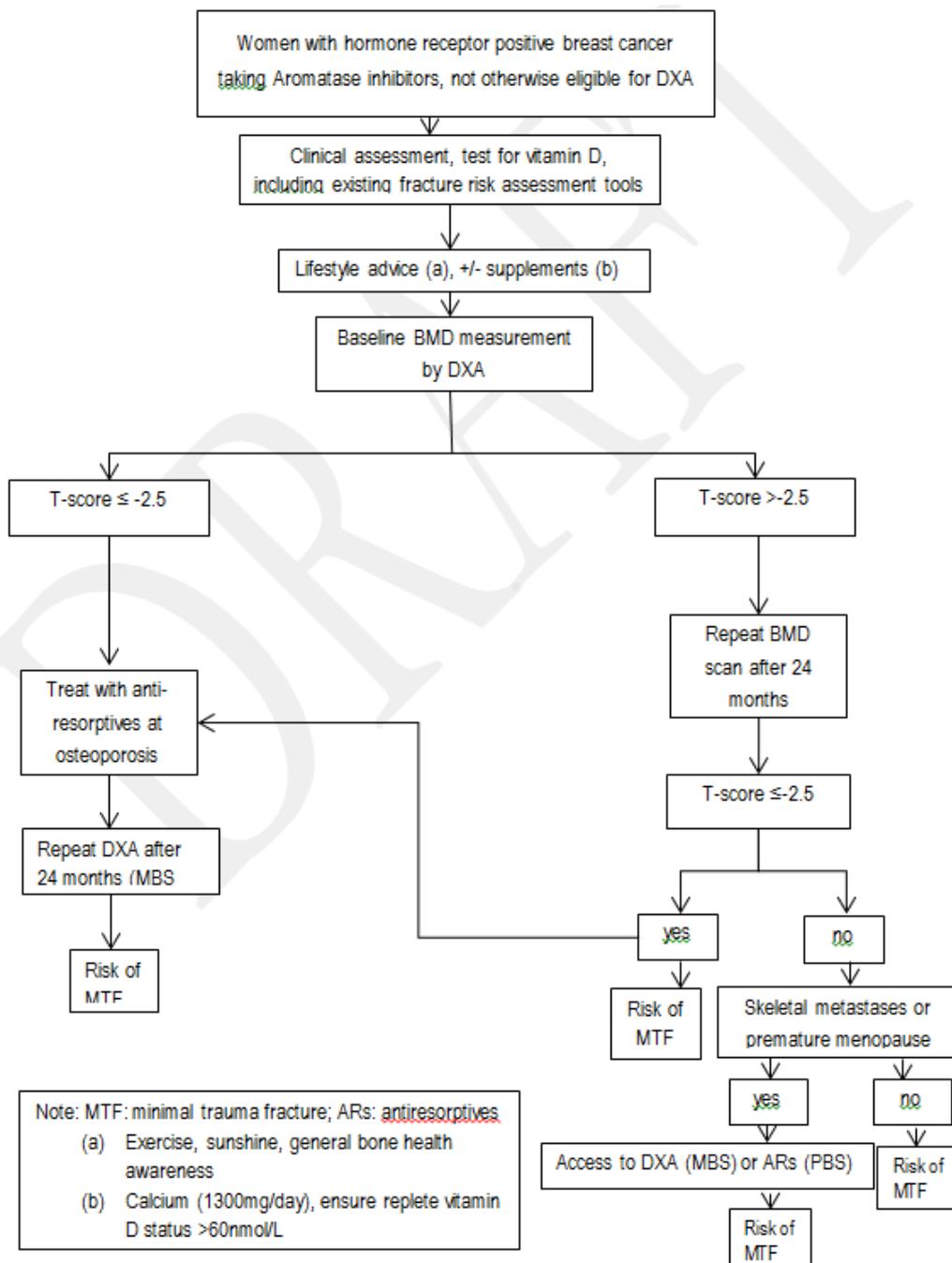


Figure 5 provides the proposed clinical management algorithm relevant for this assessment. The diagram was adapted from information provided by the applicant and Reid DM *et al.* 2008.

The clinical algorithm states that patients on aromatase inhibitors would be assessed at baseline for osteoporosis. If they have osteoporosis, patients would start anti-resorptives, or otherwise they would be re-tested after 2 years. If at this time patients have osteoporosis, they would start anti-resorptives or if not, would only receive a third DXA and/or anti-resorptives if they develop skeletal metastases or premature menopause.

Overall, the proposed algorithm targets patients at the highest risk of bone loss or fractures and only after routine clinical assessments, lifestyle advice and vitamin D/calcium supplements.

## Comparator

For the intervention *DXA scan plus anti-resorptive treatment*, the comparator is *fracture risk assessment (without DXA scan) and lifestyle and vitamin supplements (without anti-resorptive treatment)*. Vitamin supplements include calcium and vitamin D<sub>3</sub>.

## Research questions

The following clinical research questions will be addressed:

1. Is the proposed population of women being treated with aromatase inhibitors, at greater risk of minimal trauma fracture than the baseline population (i.e., post menopausal women)?
2. What is the safety of DXA and management of bone mineral density compared with no DXA and no bone loss management in women taking AIs?
3. What is the effectiveness of DXA and management of bone mineral density compared with no DXA and no bone loss management in women taking AIs? What are the long term effects of treatment on the incidence of minimal trauma fracture?
4. What is the cost-effectiveness of DXA and management of bone mineral density compared with no DXA and no bone loss management in women taking AIs?

Questions 2-4 were applied to each of the specified populations:

- a. Post-menopausal women with breast cancer taking aromatase inhibitors
- b. Women taking aromatase inhibitors who have previously been treated with tamoxifen.
- c. Sensitivity analyses should be undertaken to provide information on the range of variables identified in the Protocol.

Secondary clinical research questions include:

5. What is the appropriate threshold T-score to trigger anti-resorptive treatment in women taking aromatase inhibitors?

6. For patients reaching the threshold T-score and subsequently being treated with anti-resorptive therapy, with what frequency should women receive a repeat DXA scan?
7. For patients not reaching the threshold T-score for therapy at their initial test, with what frequency should women undergo repeat testing?

Four literature searches were undertaken on the following general areas in an effort to capture the evidence to answer all questions. The searches comprised:

**Search 1:** Risk of minimal trauma fracture in women with breast cancer taking aromatase inhibitors;

**Search 2:** Effectiveness and safety of DXA scans;

**Search 3:** Anti-resorptive therapies (pharmacotherapies and non-pharmacotherapies) for women with breast cancer taking aromatase inhibitors;

**Search 4:** Cost effectiveness of DXA and bone mineral density interventions for women with breast cancer taking aromatase inhibitors.

As noted by PASC, BMD loss was considered a reasonable surrogate for minimal trauma fracture in the literature search. Table 3 provides details of the PICO criteria for the assessment.

Table 3: PICO criteria for assessment

Patients	Intervention	Comparator	Outcomes to be assessed
Post-menopausal women with breast cancer taking aromatase inhibitors.  Women taking aromatase inhibitors who have previously been treated with tamoxifen.  Exclude: Women at age 70 and over, with a previous minimal trauma fracture, or currently eligible for MBS items for DXA scanning	DXA scan and treatment with a prescription drug at a T-score of $\leq -2.5$  Follow-up options: Sensitivity analyses should investigate options of repeat scanning as advised by the evidence. Threshold to therapy options for sensitivity analysis: T-scores of -1.0, -1.5, -2.0. Sensitivity analyses should investigate other options of threshold to therapy as advised by the evidence QCT & QUS are excluded Different thresholds of access to therapy should be investigated	Clinical assessment including the use of existing fracture risk assessment tools (including vitamin D test) with lifestyle and dietary advice  DXA and QCT or QUS are excluded	Primary outcomes: Incidence of minimal trauma fracture Incidence of all fractures Patient related quality of life  Secondary effectiveness: Change in morbidity/mortality Bone mineral density (as measured by T-score, or by Z-score in pre-menopausal women)  Safety outcomes and adverse events: Any adverse event related to scanning or treatments Any adverse event arising from exposure to ionising radiation.

## Review of literature

### Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews for the period up to 20<sup>th</sup> February 2014. Searches were conducted via Medline via Ovid Medline, Clinical Registers and HTA websites (Table 4).

Table 4: Electronic databases searched

Database	Date searched
MEDLINE via OVID MEDLINE	18 <sup>th</sup> -20 <sup>th</sup> February 2014
The Cochrane Library <ul style="list-style-type: none"> <li>• NHS-EED</li> <li>• Cochrane Reviews</li> <li>• DARE</li> <li>• HTA</li> </ul>	18 <sup>th</sup> -20 <sup>th</sup> February 2014
Clinical Registers <ul style="list-style-type: none"> <li>• Current Controlled Trials <a href="http://www.controlled-trials.com">www.controlled-trials.com</a></li> <li>• ControlledTrials.gov <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></li> <li>• Australian New Zealand Clinical Trials Registry <a href="http://www.anzctr.org.au">www.anzctr.org.au</a></li> <li>• WHO International Clinical Trials Registry Platform <a href="http://apps.who.int/trialsearch">http://apps.who.int/trialsearch</a></li> </ul>	25 <sup>th</sup> February 2014
HTA websites <ul style="list-style-type: none"> <li>• International Network of Agencies for Health Technology Assessment (INAHTA) <a href="http://www.inahta.org/">http://www.inahta.org/</a></li> <li>• NHS Centre for Reviews and Dissemination databases <a href="http://www.crd.york.ac.uk/CRDWeb/">http://www.crd.york.ac.uk/CRDWeb/</a></li> </ul>	25 <sup>th</sup> February 2014

The search terms used were extensive and are different according to the four searches. Full details are provided in Appendix A.

Reference lists of the selected studies were also manually searched for any studies that may have been overlooked in the initial searches. Title and abstracts were screened by two evaluators for potential relevance and omitted where appropriate. Of those remaining, full text articles were retrieved and examined in more depth. Further omissions were made at this second screening with reasons documented (see Appendix B). Table 5 provides the inclusion and exclusion criteria for the assessment and in particular they address Search 3, covering the core question in this assessment.

## Selection criteria

Table 5: Selection criteria for included studies

Selection criteria	Included	Excluded
Publication type	Comparative clinical studies and systematic reviews of comparative studies. Economic evaluation studies.	<ul style="list-style-type: none"> <li>– Non-systematic reviews, letters, editorials, animal, in-vitro, laboratory studies, conference abstracts, pilot studies and technical reports excluded.</li> <li>– Clinical studies or systematic reviews that have been superseded by later follow-ups. Clinical studies that are within a systematic review selected for this review.</li> </ul>
Patients	Studies with patients with <u>early stage breast cancer</u> : <ul style="list-style-type: none"> <li>– including patients who are post-menopausal</li> <li>– including patients previously treated with tamoxifen</li> </ul> and on (or considered for) aromatase inhibitors	<ul style="list-style-type: none"> <li>– Patients with mean age 70 years or over</li> <li>– Patients with a previous minimal trauma fracture</li> <li>– Patients that are eligible for current MBS items for DXA scanning (e.g., women who have undergone premature menopause, bone metastases and breast cancer).</li> <li>– Pre-menopausal women with breast cancer not previously treated with Tamoxifen.</li> <li>– Women with metastatic breast cancer</li> </ul>
Intervention/test	DXA scan and BMD management (anti-resorptive therapy) for T-score $\leq$ -2.5. Anti-resorptive therapies could include those not currently listed on the PBS Studies that assessed optimal frequency of DXA scanning.	Studies that did not include DXA as one test to determine anti-resorptive therapy.
Comparators	Comparators had to be either: Other clinical assessment of fracture risk – could include clinical fracture risk tools, vitamin D tests with Lifestyle and dietary advice	Studies comparing DXA with quantitative computer tomography or ultrasound
Outcome	Studies included if at least one of the following outcomes were reported: <ul style="list-style-type: none"> <li>– Incidence of minimal trauma fracture</li> <li>– Incidence of all fractures</li> <li>– Health related quality of life</li> <li>– Change in morbidity/mortality</li> <li>– BMD T-score or Z-score</li> <li>– Adverse event relating to DXA scanning</li> <li>– Adverse events relating to anti-resorptive therapy</li> <li>– Adverse event arising from exposure to ionising radiation (DXA scan)</li> </ul>	-
Language	English language articles	Non-English language articles

BMD = bone mineral density, DXA = dual energy X-ray absorptiometry, PBS = Pharmaceutical Benefits Schedule

## Search results

The results of the four searches are provided in Table 6.

Table 6: Overall search results

Database	Search 1 – fracture risk	Search 2 – role of DXA	Search 3 – anti-resorptives	Search 4 – cost-effects
MEDLINE (Ovid SP)	88	115	599	25
The Cochrane Library	116	241	111	13
Centre for Reviews and Dissemination	3	13	12	5
<b>Sub Total</b>	<b>207</b>	<b>369</b>	<b>722</b>	<b>43</b>
Duplicates Removed	55	35	80	7
<b>Total</b>	<b>152</b>	<b>334</b>	<b>642</b>	<b>36</b>
1 <sup>st</sup> Screen: Excluded studies from title search:	19 in meta-analysis 1 animal study 39 BMD intvns 6 duplicates 9 short follow-ups 1 metastatic brca 9 not AIs 7 not breast cancer 14 wrong outcomes 36 wrong pub	237 irrelevant 5 wrong publication 14 wrong patients 17 wrong comparator	486 wrong intvn 1 non-English 13 wrong patients 20 wrong comparator 54 wrong publication 16 irrelevant	29 wrong intvn 4 wrong patients
Papers retrieved	11	64	48	3
2 <sup>nd</sup> Screen: Excluded studies from full papers	1 superseded 1 could not get 1 wrong outcome	1 duplicate 2 could not get 4 non-English 3 not DXA 26 wrong topic 1 superseded 1 wrong comparator 19 wrong pub	4 irrelevant 1 could not get 3 duplicates 4 systematic reviews 12 trial stages 11 superseded	1 wrong patients
Included studies	8	7	13	2
Studies added	0	0	1	1
Total studies	8	7	14	3

AI = aromatase inhibitor, BMD = bone mineral density, DXA = dual energy X-ray absorptiometry,

The total number of studies found on the clinical registers and HTA websites was 76. After duplicates were removed (4), there were no relevant studies to add to the above search results.

### Data extraction and analysis

For the included studies, data were extracted from full text articles on year of publication, study type, country of research, study design, follow-up period, aromatase inhibitor, bone-loss treatment, comparative groups and key results. Summary tables were completed with appraisal of the evidence and are provided in Appendix C.

### Appraisal of the evidence

Appraisal of the evidence was conducted at 3 stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review.

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes 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.

### Validity assessment of individual studies

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) (NHMRC, 2000). These dimensions (Table 7) 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 require expert clinical input as part of its determination.

Table 7: Evidence dimensions

Type of evidence	Definition
Strength of the evidence	The study design used, as an indicator of the degree to which bias has been eliminated by design.* The methods used by investigators to minimise bias within a study design. The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Level	
Quality Statistical precision	
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.

\* See Table 8

### Strength of the evidence

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

#### Level

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 (see Table 8).

**Table 8: Designations of levels of evidence according to type of research question**

Level	Intervention	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A randomised controlled trial
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>▪ Non-randomised, experimental trial</li> <li>▪ Cohort study</li> <li>▪ Case-control study</li> <li>▪ Interrupted time series with a control group</li> </ul>	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>▪ Non-randomised, experimental trial</li> <li>▪ Cohort study</li> <li>▪ Case-control study</li> </ul>
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>▪ Historical control study</li> <li>▪ Two or more single arm study</li> <li>▪ Interrupted time series without a parallel control group</li> </ul>	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>▪ Historical control study</li> <li>▪ Two or more single arm study</li> </ul>
IV	Case series with either post-test or pre-/post-test outcomes	Case series

Table notes (please refer to original Sources)

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandalier 1999; Lijmer et al. 1999; Phillips et al. 2001.

Individual studies assessing effectiveness were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 9.

**Table 9: Grading system used to rank included studies**

Validity criteria	Description	Grading System
Appropriate comparison	Did the study evaluate a direct comparison of the test/treatment strategy versus the comparator strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the test/treatment 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 and 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 Q3 poor reference standard poor quality or insufficient information

## Quality

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (NHMRC 2000). This checklist was used for trials and cohort studies. 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, Ter Riet et al. 2001).

## **Statistical precision**

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.

## **Size of effect**

For intervention studies of intervention name it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95% confidence interval included only clinically important effects.

## **Relevance of evidence**

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000).

## **Assessment of economic evaluations**

In this report, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement is used to assess the economic evaluation studies. This statement is the minimum standards required to present health economic results comprehensively and transparently. It includes 24 criteria that should be met. Although there is no scoring system for this statement, the number of criteria met will be assessed.

## **Assessment of the body of evidence**

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

- The evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients;
- The consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction ie homogenous or heterogeneous findings;
- 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;
- The generalizability of the evidence to the target population; and
- The applicability of the evidence - integration of this 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 10) (NHMRC 2008).

Table 10: Body of evidence assessment matrix

	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	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
Generalizability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard 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

Adapted from (NHMRC 2008)

## Expert advice

An advisory panel was established to provide guidance to the evaluators to ensure that the assessment is clinically relevant and takes into account consumer interests. Membership of the advisory panel is provided at Appendix D.

# Results of assessment

## Relevant studies for assessment

The searches yielded 32 studies that were deemed relevant for this assessment. A summary of these studies is provided in Table 11.

Table 11: Summary of studies included in the assessment

Reviewed for assessment of :	Study	Study design
Search 1 Are patients with breast cancer and taking aromatase inhibitors at high risk of fractures? (and related questions)	Amir 2011 Becker 2012 Bell 2011 Eastell 2011 Edwards 2011 Goss 2013 Kalder 2013 Neuner 2011	Meta-analysis Meta-analysis Comparative study RCT Systematic review and case series RCT RCT Population study, retrospective
Search 2 Are DXA scans safe and effective? (and related questions)	Marshall 1996 Homik 1999 Rud 2007 Kanis 2009 Lim 2009 Cummins 2011 Hailey 1998	Meta-analysis HTA report Meta-analysis Meta-analysis Review and position statement Case control study, retrospective HTA report
Search 3 Are anti-resorptives or other BMD treatments safe and effective? (and related questions)	Brufsky 2012 (Z-FAST) Coleman 2013 (ZO-FAST) Llombart 2012 (E-ZO-FAST) Takahashi 2012 Nuzzo 2012 (HOBOE) Safra 2011 Lee 2011 Lester 2012 (ARIBON) Markopoulos 2010 (ARBI) Rhee 2013 Van Poznak 2010 (SABRE) Ellis 2009 Rastelli 2011 Martyn-St James 2009	RCT open label RCT open label RCT open label RCT open label RCT Phase III RCT Phase II Comparative study RCT RCT phase II open-label RCT RCT phase III RCT phase III RCT phase II Meta-analysis
Search 4 Cost-effectiveness of DXA and treatment? (and related questions)	Ito 2012 Logman 2010 Mueller 2009	Cost-utility analysis Cost-utility analysis Cost-utility analysis

Sources: (Marshall, Johnell et al. 1996, Hailey, Sampietro-Colom et al. 1998, Homik and Hailey 1999, Bell and Lewis 2007, Kanis, Oden et al. 2007, Rud, Hilden et al. 2007, Ellis, Bone et al. 2009, Lim, Hoeksema et al. 2009, Mueller and Gandjour 2009, Logman, Heeg et al. 2010, Markopoulos, Tzoracoleftherakis et al. 2010, Amir, Seruga et al. 2011, Cummins, Poku et al. 2011, Eastell, Adams et al. 2011, Edwards, Raisch et al. 2011, Lee, Hwang et al. 2011, Neuner, Yen et al. 2011, Rastelli, Taylor et al. 2011, Safra, Bernstein-Molho et al. 2011, Becker, Lipscombe et al. 2012, Brufsky, Harker et al. 2012, Ito, Blinder et al. 2012, Lester, Dodwell et al. 2012, Llombart, Frassoldati et al. 2012, Nuzzo, Gallo et al. 2012, Takahashi, Iwase et al. 2012, Coleman, Boer et al. 2013, Goss, Ingle et al. 2013, Kalder, Ziller et al. 2013, Rhee, Song et al. 2013)

## Are post-menopausal women with breast cancer on aromatase inhibitors at high risk of minimal trauma fractures?

A summary of the key features, results and quality appraisal are provided in Tables 12 and 13. Additional information on these studies is provided in Appendix C.

No studies were identified that compared the risk of fractures in women with breast cancer and those on long term corticosteroid therapies (the benchmark population). In general, the trials below excluded women who were on corticosteroid therapy.

Table 12: Key features on studies assessing fracture risk

Author/Year	Study design	Intvn/Comparator	Population	Outcome measures
Amir 2011	Systematic review and meta-analysis (7 studies)	AIs vs tamoxifen, switching options	Mean age range 59.9 to 64.5 years	OR and NNH of cardiovascular disease, bone fractures, venous thrombosis, cerebrovascular disease, endometrial cancer, death
Becker 2012	Systematic review (11 Studies)	AIs vs tamoxifen or placebo, single therapy only, no switching	Mean age range 59.9 to 65 years Median follow up: 24 to 100 months	Bone fractures, Bone turnover makers, % BMD change
Edwards 2011	Systematic review of non-RCT evidence	Observational case series of FDA Adverse Events Reporting System	Women with breast cancer and reported AEs	Fractures associated with breast cancer therapy
Bell 2007	Cross-study comparison & modelling	Healthy post-menopausal controls All women with breast ca Anastrozole Tamoxifen	Post-menopausal women aged 64-69 years (from ATAC)	RR of bone fracture risk at 5 years
Goss 2013	Phase III RCT open-label	Exemestane vs anastrozole	7576 women, median age 64 years, 4.1 years follow up	Event-free survival Adverse events including fractures Osteoporosis/ osteopenia
Kalder 2013	Prospective single bone sub-study	Anastrozole compliant ( $\geq 80\%$ ) vs anastrozole non-compliant	63 analysed, 180 in RCT core study, matched pair analysis compliant vs non compliant, postmeno brca	% BMD change (baseline to 2 yrs)
Neuner 2011	Population based prospective cohort of community dwelling women	AI (87% anastrozole) Tamoxifen No hormone therapy	2,748 women diagnosed with breast cancer in 2003, aged $\geq 65$ yrs, 28% had initial tamoxifen first, 28% initial AI Women considered high risk of fractures	Hip fractures at 36 months Non-vertebrae fractures Time to event analyses
Eastell 2011	Phase III RCT – bone sub-study	Anastrozole Tamoxifen Combined	60 Post-menopausal women with breast cancer who were participants of ATAC trial	Median % change in lumbar spine and total hip BMD from 5 to 7 years (long term follow up)

AI = aromatase inhibitors, ATAC = Arimidex, Tamoxifen Alone or in Combination, BMD = bone mineral density, NNH = number needed to harm, OR = odds ratios, RCT = randomised controlled trial

Table 13: Key results and appraisal of studies assessing fracture risk

Author/Year	Main results	Author conclusions	Quality
Amir 2011	Pooled result - Increased odds of bone fractures with longer use of Als OR 1.47 (95%CI: 1.34, 1.61) p<0.001, NNH 46	Switching from tamoxifen to Als may be the best strategy to reduce toxicity and maximise effectiveness. Tamoxifen and Als have different toxicity profiles.	HIGH
Becker 2012	Across the trials, fracture rates in trials were ~1.5 times higher in women taking AI compared to not (not statistically significant). Fractures were more frequent in women taking Als but not statistically significant in NSAS BC-03, ARNO95, ITA, MA.17 & NSASP. Fractures were more frequent and statistically sign in ATAC, BIG I-98, ABCSG, IES. ATAC is largest trial: fracture rate = 11% anastrozole arm vs 7.7% tamoxifen arm (p<0.01)	Bone markers, BMD and fractures are worse for women with early breast cancer treated with Als compared with tamoxifen or placebo. The poorer bone outcomes hold irrespective of treatment sequencing, follow-up time or type of AI.	HIGH
Edwards 2011	Of women reported to have fractures after breast cancer treatment n=229, 77 (29%) were hip or femur fractures. AI were the most common therapy associated with fractures n=149 or 65% 78 fractures were in younger women <=64 years	Fractures occur more frequently in women with early breast cancer treated with Als compared to other treatments. Evidence outside of trial conditions.	POOR
Bell 2007	Fracture risks: All women with breast cancer vs controls RR 1.15 Women on Als vs controls RR 1.36 Women on tamoxifen vs controls RR 0.91	Patients with breast cancer have an increased risk of bone fracture and women taking Als slightly adds to the risk. Absolute risk is low in each population.	POOR
Goss 2013	31.6% patients discontinued Als due to adverse events. Exemestane vs anastrozole: % osteoporosis: 31% vs 35% (p<0.001) Clinical fracture: 10% vs 9% (p=0.91) Fragility fracture: 4% vs 4% (p=0.98)	Overall compliance was poor. Exemestane is not superior to anastrozole and toxicity profiles are different. Hot flashes, arthritis, arthralgia, myalgia were not sign different between treatments. Similar rates of fractures across groups.	MEDIUM
Kalder 2013	Anastrozole compliant arm 0-2mths – BMD lumbar spine change: -2.02% (p=0.05) Anastrozole non-compliant 0-2mths – BMD lumbar spine change: -2.00% (p=0.085) No non-traumatic fractures were recorded	Compliant patients treated with anastrozole have more rapid loss of BMD during first 12 months then stabilises 12-14 mths but continues to decrease	MEDIUM
Neuner 2011	Hip fractures: 1.7% AI arm, 0.5% tamoxifen arm, 2.0% none (p=0.028) Non-vertebral fractures: 8.8% AI arm, 6.8% tamoxifen arm, 8.1% none AI vs Tamoxifen: Time to hip fracture HR 3.24 (95%CI: 1.05, 9.98) adj for age, comorb, BMI Absolute risk 1.1% inc hip fracture over 36 months	Large study of older women in a real-world setting. Patients are at higher risk of fractures with AI compared with tamoxifen but not substantial in short term (small absolute risk).	MEDIUM
Eastell 2011	Medium change in lumbar spine BMD: +4.05% 5-7 yrs anas (iqr -6.04 to 14.01) p<0.01 -0.3% 5-7 yrs tamox (iqr -7.43 to 10.22) p=0.90 No women who had normal BMD or was osteopenic in year 5 became osteoporotic in years 6 or 7 in either group.	Bone mass after 5-year treatment returns but not to baseline levels. Anastrozole treatment related bone loss does not continue after cessation of treatment	MEDIUM

AI = aromatase inhibitors, ATAC = Arimidex, Tamoxifen Alone or in Combination, BMD = bone mineral density, BMI = body mass index, HR = hazards ratio, OR = odds ratios, NNH = number needed to harm, NSAS BC-03 = National Surgical Adjuvant Study in Breast Cancer, ARNO95 = German Adjuvant Breast Cancer Group Arimidex/Nolvadex, ITA = Italian Tamoxifen Anastrozole study, NSASP = National Surgical. BIG I-98 = Breast International Group, ABCSG = Austrian Breast Cancer Study Group, IES=Intergroup Exemestane Study.

The systematic review by Amir *et al.* (2011) assessed all adverse events for women taking aromatase inhibitors (Amir, Seruga *et al.* 2011). 'Bone fractures' were one endpoint and the number needed to harm was high; 46 women treated with aromatase inhibitors resulted in 1 fracture. This suggests that the occurrence of fractures in this population is rare. The review included seven major trials and a total of 30,023 patients:

- ATAC = Arimidex, Tamoxifen Alone or in Combination
- BIG I-98 = Breast International Group
- IES=Intergroup Exemestane Study
- ITA = Italian Tamoxifen Anastrozole study
- NSAS BC-03 = National Surgical Adjuvant Study in Breast Cancer
- ARNO95 = German Adjuvant Breast Cancer Group Arimidex/Nolvadex and ABCSG8 = Austrian Breast Cancer Study Group (combined study)
- TEAM = Tamoxifen, Exemestane Adjuvant Multinational trial

The review included 5-year trials only and therefore there was sufficient time for early toxicity (while on treatment) to arise. All grades of toxicity were included. Most studies did not report baseline factors that could potentially confound the differences across treatment groups. These factors include the prior history of clinical factors for fractures and concurrent medication use, use of vitamin D and calcium supplements. The review included studies with a mix of previous treatments; tamoxifen prior and naïve patients. The BIG I-98 and ATAC trials provided information on either upfront aromatase inhibitor or upfront tamoxifen and switching. Switching agents did not appear to modify the relative risk of developing bone fractures. However, toxicities present while on tamoxifen were not recorded pre-randomisation to aromatase inhibitor therapy. The quality of the reporting of adverse events varied across the studies.

The systematic review by Becker *et al.* (2012) specifically focussed on bone health outcomes and therefore provided more specific information and in greater detail than Amir's review (Becker, Lipscombe *et al.* 2012). The key outcomes were fractures, BMD decrease and bone turnover markers. A total of 11 randomized controlled trials were included up to August 2011 and these included all 7 studies in the Amir review. The ARNO95 and ABCSG studies were separately assessed and three additional studies included were:

- MA.17 = National Clinical Institute of Cancer Clinical Trials Group
- NSASP = National Surgical Adjuvant Breast and Bowel Project
- Gonnelli *et al.* 2007

As for Amir *et al.* (2011), the review findings showed that fracture rates were higher in women taking aromatase inhibitors (about 1.5 fold) but studies were mixed on whether these were statistically significant.

Edwards *et al.* (2011) undertook a systematic review of non-trial data and grey literature as well as retrieving records from the FDA Adverse Event Reporting System. The goal of this study was to assess whether fracture rates were higher in observational reports and studies outside of trial conditions and that were not statistically powered for capturing the rare event of fractures. Their assessment confirmed the trial evidence and concluded that AIs had been commonly used among women with breast cancer and bone fractures (Edwards, Raisch *et al.* 2011).

Bell *et al.* (2007) provided a cross-study comparison of the relative risk of bone fracture using healthy post-menopausal women (aged 64-69 years) as the reference population (Bell and Lewis 2007). They undertook a modelling study to estimate and calibrate the relative risk of women using AIs to healthy post-menopausal women, women on tamoxifen and all women with breast cancer. The studies they based their modelling on were the NSABP-P trial, the Women's Health Initiative study and the ATAC trial. Women with breast cancer had a higher risk of bone fracture with those on AI therapy adding to this risk, compared to healthy post-menopausal women.

Two studies provided additional information on bone outcomes among specific aromatase inhibitor users. In an open-label RCT comparing exemestane and anastrozole, Goss *et al.* (2013) concluded that there were no significant differences in bone outcomes between the two different AI treatments at 4 years follow up. Similarly, examining compliance ( $\geq 80\%$ ) with anastrozole at 24 months, changes in BMD lumbar spine were not significantly different in the compliant and non-compliant anastrozole users (Goss, Ingle *et al.* 2013, Kalder, Ziller *et al.* 2013).

Neuner *et al.* 2011 in the US conducted a large (n=2748) retrospective analysis of population-based community dwelling women who were diagnosed with breast cancer in 2003. At 36 months, these older women already at higher fracture risk, were found to have significantly higher risk of fracture if they had received AIs compared to tamoxifen or no hormone therapy, but the absolute risk of fractures was low. This was after models adjusted for age, bone mass index and a history of previous fracture (Neuner, Yen *et al.* 2011).

Finally, the study by Eastell *et al.* (2011) provided 7-year extension follow up data from the ATAC trial, the first large trial of AIs or tamoxifen in women with early stage breast cancer (Eastell, Adams *et al.* 2011). BMD was measured in the post-hormone treatment phase from 5 to 7 years. Although there was a substantial loss to follow-up by this stage of the trial, the authors' concluded that bone loss accelerated during the time the women were on AIs but was partially restored upon treatment cessation, although not to baseline levels.

### **Quality of the studies assessing bone loss or fracture risk**

In general, the studies were of mixed quality and there existed some potential risk of bias in the medium and poor quality ranked studies. The limitations of the latter studies included:

- Poor reporting of bone outcomes at non-standard intervals;
- Outcomes were inconsistently adjusted or not adjusted for baseline fracture risk factors;
- Small sample sizes or high drop outs (missing data);
- Little detail about blinding of BMD readers to patient treatment allocation;
- Patients received vitamin D and calcium which might have affected outcomes;
- No discussion regarding background fracture risk in normal post-menopausal women; and
- Industry sponsorship that may lead to bias in favour of aromatase inhibitor treatment.

Nevertheless, two high-quality systematic reviews provided solid evidence for concluding that women taking AIs face a higher risk of adverse bone health than those not taking this therapy.

### **Rate of bone loss in different populations**

Additional searches were required to provide evidence on the *rate of bone loss* in post-menopausal women without breast cancer and in women on long-term glucocorticoid therapy.

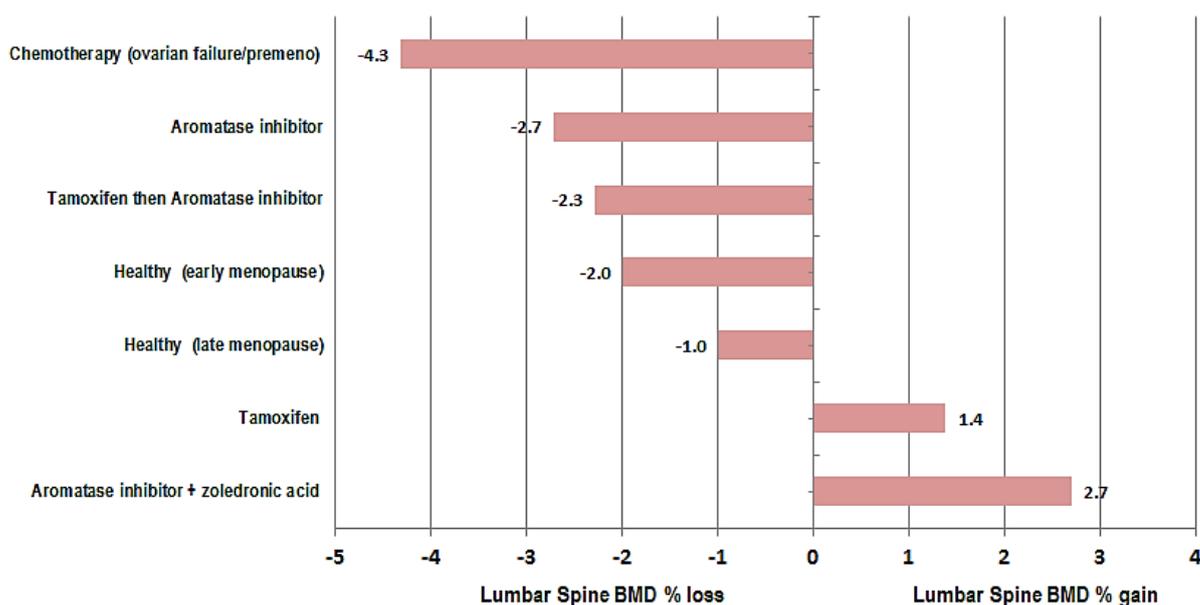
Bone loss is part of normal ageing. Bone mass peaks when an individual reaches 25-30 years, stabilises until age 40 years and declines thereafter. Bone mass generally peaks earlier in men than women and after approximately age 40, it is observed to decrease 6-10% in the decade up to 50 years (O'Flaherty 2000). The rate of bone loss in older people is a determinant of peak bone mass, diet and calcium intake, exercise and genetic factors. The rate of bone loss is a function of either a failure of bone formation and/or bone resorption processes. These various factors mean that the rate of bone loss varies by person. Bone loss is also not uniformly distributed across bone sites and more rapid loss often occurs in trabecular bone (O'Flaherty 2000).

Menopause occurs naturally for women after the age of 45. On average, a woman loses 7-10% of her lumbar spine bone density in the first five years of menopause (Finkelstein, Brockwell et al. 2008). Body weight is a strong predictor of bone density and it is independent from ethnicity (Finkelstein, Brockwell et al. 2008). Women with established menopause have slower rates of bone loss than in early menopause.

In a meta-analysis of corticosteroid use and fracture risk (Kanis, Johansson et al. 2004), involving 42,500 men and women from seven prospectively studied cohorts, previous corticosteroid use was associated with a significantly increased risk of fracture. The relationship between corticosteroid use and fracture risk was linear and increased with age, and independent of BMD. In an Australian study of young adults (20-49 years), glucocorticoid use was the most common reason for referral to DXA among women (Torpy, Brennan et al. 2012).

Figure 6 illustrates the relative bone mineral loss in the lumbar spine among groups of women over one year. As shown, unlike aromatase inhibitor therapy alone, tamoxifen alone has an early favourable effect on bone formation post-menopause but this is not the case in pre-menopausal women (not shown). In addition, evidence shows that anti-resorptives taken with aromatase inhibitor results in bone gain (shown here for zoledronic acid) (Figure 6).

Figure 6: One year % change in BMD (lumbar spine) in various populations



AI = aromatase inhibitor, BMD = bone mineral loss

Sources: Figure adapted from Fig 2 (Bauer, Bryce et al. 2012). (O'Flaherty 2000, Eastell, Adams et al. 2008, Finkelstein, Brockwell et al. 2008, Lombart, Frassoldati et al. 2012). Weighted average of Powles 1998, Saarto 1997, Delmas 1997, Shapiro 2001, Vehmanen 2001, Hines 2009.

## Are DXA scans safe and effective?

No trials were identified in Search 2 that addressed the issue of safety, necessity or effectiveness of DXA scan in women with breast cancer on aromatase inhibitor therapies. Therefore, the assessment more broadly evaluated DXA scans in all post-menopausal women. The studies retrieved provided information on the role of DXA scan in BMD measurement for osteoporosis.

Many clinical risk factor tools and their components are listed in Table 14. DXA scan analysis provides information on bone mass as an optional component of FRAX™. Risk factor tools are viewed as clinically useful when clinicians do not have access to a DXA scanner. Most risk tools do not require BMD measurement.

Table 14: Risk factors included in various fracture risk assessment tools

Risk factor	OSIRIS	OST	ORAI	SCORE	CAROC	WHI	FRAX®	QFracture	Garvan
Age	x	x	x	x	x	x	x	x	x
Gender					x		x	x	x
Body mass index						x	x	x <sup>2</sup>	
Body weight	x	x	x	x					x
Previous fracture	x			x	x	x	x		x
Family history of fracture						x	x	x	
Smoking						x	x	x	
Alcohol intake							x	x	
Glucocorticoid therapy					x	x	x	x	
Secondary osteoporosis							x	<sup>1</sup> x	
HRT	x		x	x				x	
Diabetes treatment						x		x	
Rheumatoid arthritis				x				x	
Race				x		x			
Physical activity						x			
Health status						x			
BMD required?	No	No	No	No	Yes	No	Optional	No	Optional

HRT = hormone replacement therapy, OST = Osteoporosis Self-Assessment Screening Tool, FRAX = fracture risk-assessment tool, ORAI = osteoporosis risk assessment instrument, OSIRIS = osteoporosis index of risk, SCORE simple calculated osteoporosis risk estimation score, WHI = Women's Health Initiative hip fracture risk calculator, CAROC = Osteoporosis Society of Canada and Canadian Association of Radiologists Working Group

1. In QFracture algorithms, secondary causes of osteoporosis are not recorded as a single entity but separately in the table and in addition: asthma, heart attack, stroke, falls, chronic liver disease, tricyclic antidepressants, type 2 diabetes, endocrine problems, malabsorption, menopausal symptoms.
2. Separately as height and weight.

Source: (Lim, Hoeksema et al. 2009, Cummins, Poku et al. 2011)

The Australian 'Garvan Fracture Risk Calculator' is available online:

<http://www.garvan.org.au/bone-fracture-risk>. This tool is based on the Dubbo Epidemiology Study. In addition to the risk factors in Table 14, the Garvan tool also includes falls in the past 12 months. BMD measurement can be entered as either T-score or actual (g/cm<sup>3</sup>) and the choice of DXA scanner (Hologic or Lunar GX). The results provide 5- and 10-year risk of hip and all osteoporotic fractures.

### Effectiveness of DXA vs clinical risk fracture tools

Tables 15 and 16 show the key features and results of studies considered relevant for this assessment and Appendix C provides greater detail on studies that included reviews and/or meta-analyses. The populations are generally peri- or post-menopausal women. Collectively the studies assess the predictive value of DXA with or without clinical risk factors of osteoporotic fractures.

**Table 15: Key features of studies assessing DXA vs clinical risk fracture tools**

Author/Year	Study design	DXA vs comparator	Population	Outcome measures
Marshall 1996	Systematic review and meta-analysis (11 studies)	BMD all absorptiometry MRI, ultrasound and CT methods Fractures vs none	90,000 person years, 11 prospective studies 2000 fractures Prospective cohort & case control studies Women (post-meno age)	RR of bone fractures for a decrease in BMD of 1 standard deviation below age adjusted mean
Lim 2009	Review and position statement	DXA and clinical risk tools reviewed	US adults	Sensitivity and specificity of clinical risk tools
Kanis 2007	Meta-analysis of 9 population-based cohort studies	BMD/all DXA with or without clinical risk factors to predict fractures (compared to 11 validation cohorts)	Primary cohort: n=46,340 68% women, 189,852 person years, Mean age 65	Gradient of risk = increase in fracture risk per SD increase in risk score, (95%CI)
Rud 2007	Meta-analysis of 36 studies	Performance of OST clinical risk tool vs DXA	n =72,315 women, peri and post-menopausal, median sample size 780, mean >45 years	Sensitivity and specificity, Likelihood Ratio of a Negative Test (DXA reference standard)
Cummins 2011	Case control study (retrospective)	FRAX (with DXA) vs QFractureScores (no DXA)	N=246 women who had fractures aged 50-85 years N=338 controls	Risk of fracture Correlation statistics
Hailey 1998	HTA report, collaborative review	Role of DXA & treatment for fractures	n/a	Commentary summary
Homik 1999	HTA report	Role of DXA	n/a	Commentary summary

BMD = bone mineral density, DXA = dual energy x-ray absorptiometry, MRI = magnetic resonance imaging, RR = relative risk, OST = Osteoporosis Self-Assessment Screening tool, FRAX = fracture risk-assessment tool, SD = standard deviation, CT = computer tomography, HTA = Health Technology Assessment

Table 16: Key results and appraisal of studies assessing DXA vs clinical risk fracture tools

Author/Year	Main outcomes	Author conclusions	Quality
Marshall 1996	RR fractures all sites 1.5 (95%CI: 1.4, 1.6) except: RR spine fractures 2.3 (95%CI: 1.9, 2.8) RR hip fractures 2.6 (95%CI: 2.0, 3.5) No association between RR for dec BMD 1 sd and length of follow up	BMD measurements predict fracture risk but not individuals who will have a fracture. Screening menopausal women for osteoporosis is not recommended	MEDIUM
Lim 2009	No RCTs exist for screening on fracture outcomes. OST Sensitivity = 88-92% Specificity = 37-52%, in women aged ≥45 years (better discriminative ability than ORAI or SCORE risk tools) ORAI Sensitivity = 94.4% Specificity = 41.4% SCORE Sensitivity = 93.6% Specificity = 43.3% OSIRIS Sensitivity = 78.5% Specificity = 51.4%	DXA is the most widely used and accepted method of BMD measurement. Studies on the harms related to radiation exposure from repeated DXA scans are lacking. Risk assessment tools may be useful supplements to BMD assessment and can be used when DXA is not available.	POOR
Kanis 2007	<u>Hip fracture (50 year old):</u> BMD alone - GR 3.68 (95%CI: 2.61, 5.19) Clinical risk factors alone -GR 2.05 (95%CI: 1.58, 2.65) Both - GR 4.23 (95%CI: 3.12, 5.73) <u>Other osteoporotic fractures (50 year old):</u> BMD alone - GR 1.19 (95%CI: 1.05, 1.34) Clinical risk factors alone GR 1.41 (95%CI: 1.28, 1.56) Both - GR 1.44 (95%CI: 1.30, 1.59)	Integrated BMD plus clinical risk factors better predicts fracture risk. Both are useful alone. Absolute fracture risk cannot be provided with data unless further calibration occurs.	MEDIUM
Rud 2007	Range depending on BMD location: White women: T≤-2.5 sens 84-92% specificity 34-40% Asian women: T≤-2.5 sens 82-91% specificity 40-64% White women: T≤-2.0 sens 82-88% specificity 36-44% LR- : White women: any region overall 0.37 (95%CI:0.27, 0.51) I <sup>2</sup> =88% Asian women: any region overall 0.29 (95%CI: 0.23, 0.37) I <sup>2</sup> =41%	Clinical usefulness of OST is uncertain. It could be used to rule out femoral neck T-score ≤-2.5. Quality of studies according to QUADAS assessment was generally low. Heterogeneity between studies was high.	HIGH
Cummins 2011	Significant difference<0.05 in risk estimation for Major fracture: FRAX 15.2% vs QFractureScore 9.5% Hip fractures: FRAX 4.7% vs QFractureScore 2.9% High correlation R=0.803 major fracture and R=0.857 hip fracture	Both algorithms yield similar results and could be of value in primary care. Both tools yielded high specificity but poor sensitivity. Most important factors were age, T-score femoral neck and previous falls.	MEDIUM

BMD = bone mineral density, DXA = dual energy x-ray absorptiometry, MRI = magnetic resonance imaging, RR = relative risk, OST = Osteoporosis Self-Assessment Screening Tool, FRAX = fracture risk-assessment tool, ORAI = osteoporosis risk assessment instrument, OSIRIS = osteoporosis index of risk, SCORE simple calculated osteoporosis risk estimation score, SD = standard deviation, CT = computer tomography, LR- = negative likelihood ratio, QUADAS = Quality of Diagnostic test Assessment Score, GR = gradient risk (RR/standard deviation in risk score).

Marshall *et al.* (1996) is a well-quoted seminal paper on BMD measurement and its use in predicting fractures in adult women. The majority of studies had cohorts with a mean age past menopause (Marshall, Johnell *et al.* 1996). The relationship of the type of fractures and BMD site were considered. The findings showed that BMD measurement of any method produced low sensitivity but high specificity (Table 17) for hip fractures.

Table 17: Performance of BMD measurement for hip fractures

	Lifetime incidence (%)		
	3 year	15 year	30 year
Sensitivity (%)	47	37	34
Specificity (%)	83	88	89
Positive predictive value (%)	9	36	58
Population attributable risk (%)	36	26	21

Source: Table 3 in Marshall *et al.* (1996)

Very few studies in the Marshall *et al.* (1996) review studied the predictive ability of BMD in participants aged between 50 and 60 years, an age group relevant to this assessment. Studies also lacked homogeneity. Screening for osteoporosis was not recommended by the authors since there was a wide overlap in the bone density of patients who did or did not develop a fracture.

Two health technology assessment groups provided summarised reports on the role of DXA in BMD measurement. Hailey *et al.* (1998) compared the performance of DXA compared to other BMD technologies. They concluded that the accuracy of DXA measured by the coefficient of variation was 3-6% and precision within 1-3%. It had the best performance rating compared with other technologies. They also concluded DXA could assess further fracture occurrence over the short term but not with high accuracy. Homik *et al.* (1999) highlighted a number of points in their assessment of DXA for screening for fractures. These included:

- Wide overlap exists in BMD between those with and without fractures;
- There are limited alternatives to DXA available to doctors and clinical risk factors for fractures are limited and different for younger and older age groups. Therefore both BMD measurement and clinical risk factor assessments are desirable; and
- Analytical performance of BMD is influenced by device, operator performance, and physiological composition therefore good quality control of the DXA device and use is important.

Lim *et al.* (2009) provided a review of the performance of risk factor tools and discussed their usefulness when BMD measurement was not available to clinicians. They concluded that screening should be performed with BMD and monitoring frequency should not be more frequent than every two years. This appears to be a consensus agreement. Rud *et al.* (2007) provided a meta-analysis on the Osteoporosis Screening Tool (OST) and its performance in ruling out 'false negatives' against the DXA reference standard. OST only measures age and weight to determine future fracture risk. The authors found OST performance was 'moderate' for the femoral neck and 'poor' for the lumbar spine. They determined that OST was as accurate as other tools with more complex risk factor components.

Kanis *et al.* (2007) provides strong evidence using meta-analysis and meta-regression from nine large prospective population-based studies on osteoporosis from around the world and 11 validated comparison cohorts. They combined individual data sets in a meta-regression to conclude that the combined use of clinical risk factor assessment and

BMD analysis is optimal and provides the most effective prediction of fracture risk and the need for bone resorptive medications in adult populations.

### **Quality of studies on BMD measurement using DXA**

There were no studies which directly compared DXA versus clinical risk factor assessment in a trial setting for women with breast cancer or any female population. The studies included here provide information on the ability of DXA scans or clinical risk factor tools to detect poor bone density and predict future fracture risk.

Excluding review studies by Lim, Homik and Hailey, the studies were of medium to high quality. Meta-analysis studies by Marshall, Kanis and Rud involve very large populations (of predominantly post-menopausal women), person years and from many countries.

### **DXA safety issues**

There appears to be few clinical issues around patient safety with performing DXA. On its own, the test is non-invasive, emits a negligible amount of ionizing-radiation and presents no chemical or bodily harm to the patient. Radiation levels have been stated as being one-tenth those of standard computer tomography scans (Lim 2009).

The effective radiation dose is a product of the radiation dose and the biological sensitivity of tissue, measured in millisieverts (mSv). Abdominal structures are more biologically active and imaging results in higher effective doses than other body parts. Susceptibility to higher effective doses is also found in younger age groups. High cumulative dose is considered >50 mSv over a 5-year period (Kroeker, Lam et al. 2011). Cumulative effective dose of >75 mSv is associated with an increased cancer risk of 7.3%.

The Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) state that total radiation exposure should take into account background radiation exposure received from natural sources. In Australia, this background radiation level is reported to be 1.5 mSv per year. The risk of cancer from 1 mSv of radiation is 1 in 17,000 (lower than the age-standardised incidence rate of 57 in 17,000) or the equivalent risk of getting cancer from smoking 100 cigarettes (ARPANSA, 2011). Ionizing radiation exposure from abdominal x-ray is 0.7 mSv and 10 mSv for abdominal/pelvic CT scan. The effective radiation dose for each person is highly variable due to different machine settings, the amount of radioactive material used and patient metabolism.

In the vast number of patients and person-years included in the studies in Table 15, there were no issues reported for adverse radiation safety with DXA scans. An additional search was performed in PubMed to identify studies reporting radiation levels from DXA scanning. This search was not extensive or systematic.

In a study by Bandirali *et al.* (2013), the lifetime dose and attributable risk for cancer was estimated taking into account background radiation levels and different DXA modalities (FA: fast array, A: array, HD: high definition) (Bandirali, Lanza et al. 2013). The effective dose for lumbar scans was FA = 0.018 mSv, A = 0.033 mSv, HD = 0.031 mSv; for femoral scans, FA = 0.053 mSv, A = 0.096 mSv, HD = 0.075 mSv. There was a minimal increase in cancer risk (e.g.  $4.02 \times 10^{-3}$  % [A, lumbar, female]). The lifetime dose absorption and lifetime attributable risk for cancer for a male and a female patient undergoing 36 DXA analyses (18 lumbar, 18 femoral) every 21 months for 32

years were 0.756 mSv,  $3.82 \times 10^{-3}\%$  and 0.756 mSv,  $5.11 \times 10^{-3}\%$ , respectively. The authors' concluded that DXA examinations emitted radiation levels that were comparable to the background radiation and the authors stated:

'Regardless of the scan modality or the anatomic site, a patient undergoing DXA scans for a lifetime has a negligible increased risk of developing cancer.' (Bandirali, Lanza et al. 2013)

## **Are anti-resorptives or other BMD treatments effective and safe?**

Search 3 has provided the trial-based evidence for effectiveness and safety on anti-resorptive agents in patients with breast cancer on aromatase inhibitors. Several studies with 5 year follow-up durations where anti-resorptive agents were used for 5 years (for the duration of aromatase inhibitors) may provide better profiles of adverse events than studies of shorter duration.

### **Effectiveness of BMD management (anti-resorptives, calcium, vitamin D and lifestyle advice)**

A description of the studies and the effectiveness outcomes are provided in Tables 18 and 19.

No studies were identified that directly assessed anti-resorptive agents compared with lifestyle advice with calcium/vitamin D in the population of interest. They usually combined anti-resorptives with calcium and vitamin D.

Table 18 shows the BMD treatments in various interventions (early or delayed treatment) or participant groups (risk stratified by T-score) or placebo. Zoledronic acid was the most studied bone loss treatment in post-menopausal women taking aromatase inhibitors with or without prior tamoxifen treatment.

Overall, the studies enrolled participants who included:

- Women who were post-menopausal (either spontaneous or treatment-induced);
- Women with early stage breast cancer (stage I to IIIa), hormone receptor positive;
- Women taking or scheduled for adjuvant aromatase inhibitors for 5 years treatment;
- Women who were permitted to have received adjuvant chemotherapy;
- Women who had Eastern Cooperative Oncology Group (ECOG) performance score of 0-2 (i.e., not worse than symptomatic, <50% in bed during the day);
- Women who were permitted or assigned to take vitamin D and calcium supplements;
- Women who had not previously or concurrently used aromatase inhibitors, bone resorptive agents, recent systemic corticosteroids, anabolic steroids or growth hormones; and
- Women who did not have a history of previous fractures, bone diseases or previous or concomitant malignancy  $\leq$  5 years.

A few exceptions to the list above were Markopoulos 2012 & Lester 2012 who excluded women who had chemo-induced menopause, Rastelli 2011 who also allowed women with Stage IIIb breast cancer and Rhee 2011 who restricted women with ECOG status  $\leq 1$  only (i.e., no worse than symptomatic but completely ambulatory). Studies differed in that women were sometimes stratified or excluded according to baseline lumbar spine T-Score, the interventions and aromatase inhibitor agents varied and study designs varied. Importantly, the study follow-ups were widely different and ranged from 6 to 60 months which rendered the ‘% change in BMD’ endpoint not easily comparable across studies.

All studies reported BMD using DXA scanners and the majority used the Hologic or GE Lunar scanners. The studies included in the assessment were varied in respect to the aromatase inhibitor agent (6 x letrozole, 4 x anastrozole, 3 x either), the anti-resorptive agent (7 x zoledronic acid, 2 x risedronate, 1 each of ibandronate, alendronate, denosumab) and follow up time (4 x 60 months, 1 x 36 months, 3 x 24 months, 3 x 12 months and 2 x 6 months). Studies were published between 2009 to 2013 with many reporting long-term results and superseding earlier publications of shorter follow-ups (Brufsky, Harker et al. 2012, Llombart, Frassoldati et al. 2012, Coleman, Boer et al. 2013).

Only one study was found that assessed the main comparator treatment in this assessment and in this population; vitamin D and calcium versus placebo (Rastelli, Taylor et al. 2011).

A meta-analysis was performed using a random effects model. Where BMD was recorded for different follow-up times, the BMD of the longest follow-up period was included. Study heterogeneity was assessed using the  $I^2$  statistic where  $>50-74\%$  was considered moderate heterogeneity and  $\geq 75\%$  was considered high heterogeneity. Analyses were undertaken for BMD lumbar and total hip outcomes, by early or longer follow up period ( $\leq$  or  $>$  24 months) and by zoledronic acid versus other bone treatment.

A study was further added to the assessment (Martyn-St James and Carroll 2009) to provide supporting information. This additional study was a meta-analysis of the impact of exercise (of mixed loads) on post-menopausal bone loss but was not specifically in women with breast cancer taking aromatase inhibitors. Therefore, this study was not included in the meta-analysis.

All studies reported BMD of the lumbar spine and nearly all also reported the BMD of the total hip. Nearly all studies administered, instructed or allowed calcium and vitamin D supplementation concurrently with the bone resorptive medication.

Although there were several systematic reviews and meta-analyses on this topic (Perez and Weilbaecher 2006, Hadji, Aapro et al. 2011), these were excluded from the assessment because they included many studies that were superseded by reports of longer follow-ups and outcomes. Here we have redone the meta-analyses using the latest results where data permitted. Several authors were emailed for additional data when their published reports did not supply variance statistics around ‘% BMD change over time’ (either standard deviation or 95%CI).

Table 18: Key features of studies on treatments for aromatase-inhibitor-associated bone loss

Author /Year	N	Country	Design	F/up (mths)	Aromatase inhibitor	Bone-loss Treatment (dose)	Intervention Groups
Brufsky 2012 Z-FAST	602	US	Randomized phase III open-label trial	61	Letrozole 2.5 mg/day for 5 years	Zoledronic Acid (4mg IV once every 6 months for up to 5 years). Instructed to take vitamin D (400-800 IU/day) and calcium (500 mg /day)	Upfront zoledronic acid Delayed zoledronic acid ( when T score LS <-2.0)
Coleman 2013 ZO-FAST	1065	Europe (28 countries)		60			
Llombart 2012 E-ZO-FAST	527	Europe, Latin America, Africa, Middle East (66 centres)		12			
Takahashi 2012	189	Japan multicentre	Randomized phase III open-label trial	12	Letrozole 2.5 mg/day for 5 years	Zoledronic Acid (4mg IV once every 6 months)	Upfront zoledronic acid Delayed zoledronic acid (when T score LS <-2.0)
Nuzzo 2012 HOBOE	483	Italy	Randomized phase III open-label trial	12	Letrozole	Zoledronic Acid (4mg IV once every 6 months) Could have calcium and vitamin D	Zoledronic acid Letrozole alone Tamoxifen then letrozole
Safra 2011	90	Israel	Randomized phase II	60	Letrozole 2.5 mg/day for 2.5 years after all received Tamoxifen 2.5 years	Zoledronic Acid (4mg IV once every 6 months) Vitamin D (400 IU/day) and calcium (1200 mg/day)	Zoledronic Acid Placebo
Lee 2011	107	Korea single centre	Comparative Study	36	Letrozole 2.5 mg/ day or Anastrozole 1 mg/day	Zoledronic Acid (4mg IV once every 3 or 6 months)	Zoledronic acid Placebo
Hines 2009 NO3CC	558	US	Randomized phase III open-label trial	24	Letrozole 2.5 mg/day for 5 years after all received Tamoxifen	Zoledronic Acid (4mg IV once every 6 months) Calcium 1000 mg and vitamin D 400 IU daily	Upfront zoledronic acid Delayed zoledronic acid ( when T score LS <-2.0)
Lester 2012 ARIBON	131	UK (2 centres)	Randomized phase III open-label trial	62	Anastrozole 1 mg daily	Ibandronate (oral monthly 150 mg for 5 years) Calcium 500 mg and vitamin D 400 IU daily	Osteoporosis - ibandronate Osteopenia - ibandronate Osteopenia - placebo Normal BMD – no bone tx
Markopoulos 2010 ARBI	213	Greece	Phase II, open-label and double-blind	24	Anastrozole 1 mg daily	Risedronate (oral 35 mg/week) Calcium 1000 mg and vitamin D 400 IU daily	High risk – risedronate Med risk – risedronate Med risk – placebo Low risk– no bone tx

Author /Year	N	Country	Design	F/up (mths)	Aromatase inhibitor	Bone-loss Treatment (dose)	Intervention Groups
Rhee 2013	98	Korea	Randomized placebo-controlled double-blind	6 mth (24 wks)	Anastrozole or letrozole	Low dose alendronate + vitamin D3, All pts 500 mg calcium & 400 vitamin D, 24 weeks treatment	Alendronate and calcitrol Placebo
Van Poznak 2010 SABRE	234	US	Open-label high risk, randomized med risk, double-blind, phase III/IV	24	Anastrozole 1 mg/day (37% prior Tamoxifen)	Risedronate 35 mg/wk oral Calcium 1000 mg/day + vitamin D 400 IU/day	High risk – risedronate Med risk – risedronate Med risk – placebo Low risk– no bone tx
Ellis 2009	302	US + Canada (53 sites)	Randomized phase III open-label trial	24	Letrozole or Anastrozole (in 73%), Exemestane (in 11%)	Denosumab (subcutaneous 60 mg, 6 mths, 4 doses) Calcium + Vitamin D 400 IU/day	Denosumab Placebo
Rastelli 2011	60	US	Phase II, randomized, double-blind, placebo-controlled	6	Anastrozole (already on for 15-21 months)	Vitamin D2 high dose 50,000 IU every 8 or 16 weeks, 24 weeks treatment	High dose vitamin D2 Placebo
Martyn St James 2009	442	UK	Meta-analysis of RCTs	varied	Not applicable. Sedentary post-menopausal women.	Exercise protocol that included any running or jumping movements with or without resistance training	Exercise group Control

Stratified analyses were undertaken in many of the studies for:

- Prior chemotherapy (yes/no)
- Time since menopause
- BMD status: normal, osteopenia, osteoporosis (by T-score)
- Prior tamoxifen before aromatase inhibitor

Figures 7-10 present the results of the study findings for a % change in BMD lumbar spine and total hip. As shown in Figures 7 and 8, the treatment arms of upfront zoledronic acid, other bisphosphonates and denosumab consistently show positive % change in BMD measures while the placebo or other comparators show declines in BMD. Two exceptions were Safra and Hines where the placebo arms had positive change but were lower than the intervention arms in BMD lumbar spine. No clinical trials have directly compared oral versus intravenous bisphosphonates in this setting.

Although zoledronic acid studies dominated, collectively most studies with the various bone agents had between 2-6% in BMD lumbar spine and ~2% in total hip BMD. The % change tended to be higher with longer follow-up as indicated by the 60 month studies which showed linear increases at each yearly follow-up measurement (Brufsky, Harker et al. 2012, Llombart, Frassoldati et al. 2012). However, studies with shorter duration also showed similar % change as the 60 month studies and therefore no strong pattern emerged from these studies.

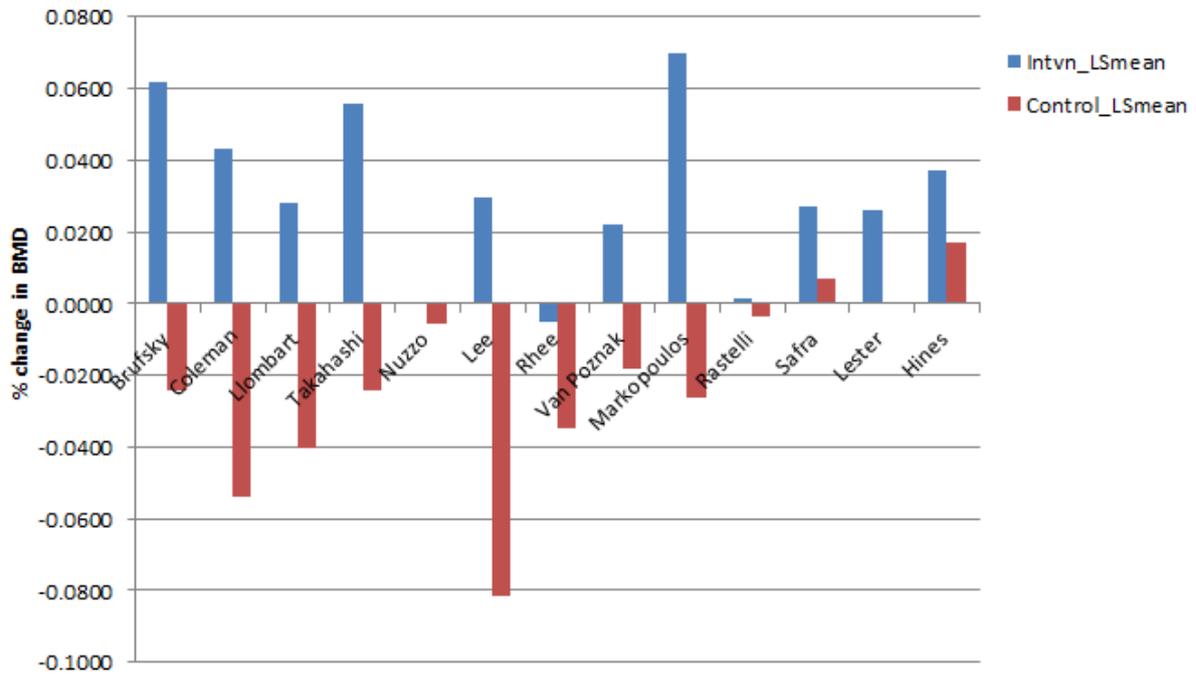
Studies that stratified their analyses and provided results by 'prior chemotherapy (yes/no)', prior tamoxifen (yes/no)' or by BMD status showed no significant differences in % change in BMD (Brufsky, Harker et al. 2012, Llombart, Frassoldati et al. 2012).

Rastelli *et al.* (2011) was the only vitamin D study and involved a short 6 month duration. The % change in BMD measures were positive, small, and significant in those taking vitamin D treatment compared with small declines in the placebo arm.

In the meta-analysis by Martyn St James (2009) of 15 exercise interventions for post-menopausal women, the authors found that impact protocols that included jogging mixed with walking and stair climbing, and protocols that incorporated impact exercise with high-magnitude loading (resistance exercises), were effective at lumbar spine (weighted mean difference (random effects) 0.025 g/cm<sup>2</sup> 95% CI (0.004 to 0.046) and 0.016 g/cm<sup>2</sup> 95% CI (0.005 to 0.027);  $p = 0.02$  and  $p = 0.005$  respectively). However, study heterogeneity was evident ( $I^2 = 88\%$  and  $I^2 = 73\%$ , where  $I^2$  measures the extent of inconsistency among the trials). Effects on femoral neck BMD following these types of protocols were also significant. High-impact only and odd-impact only protocols were ineffective in increasing BMD at any site.

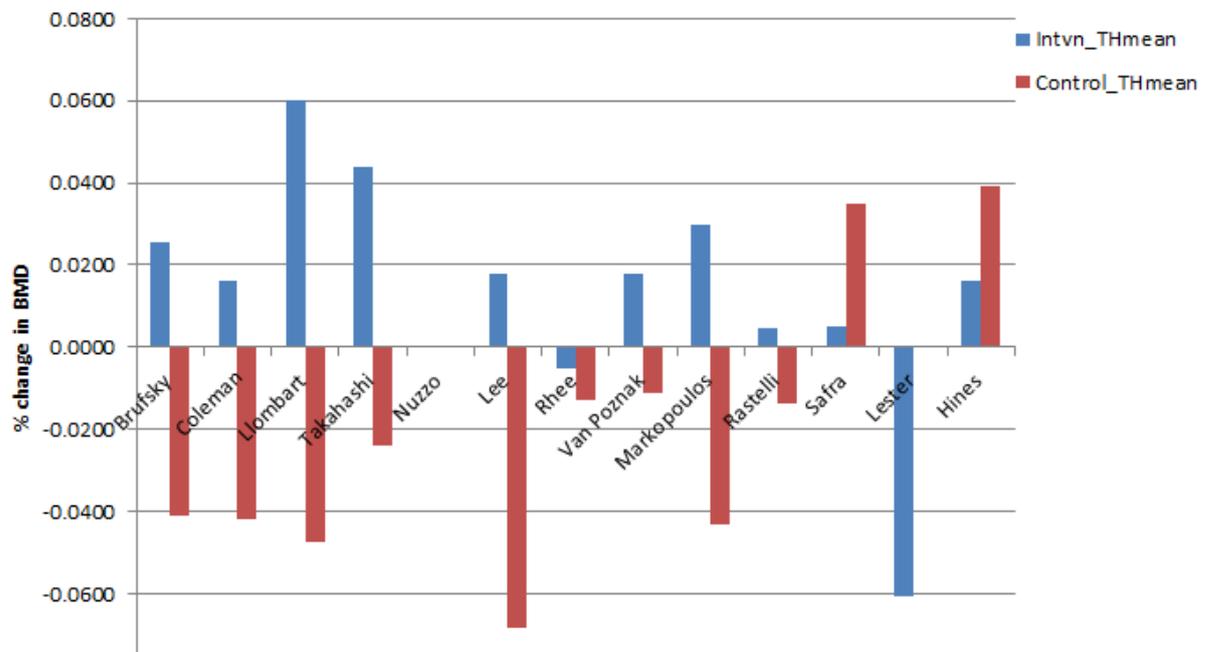
In the meta-analysis for BMD lumbar spine undertaken during this assessment (Figure 9), the standardised mean difference between the intervention and comparator arms were 1.46% (95%CI: 1.09%, 1.83%). However, study heterogeneity was problematic and high at 93.7%. Similarly, for BMD total hip (Figure 10), the mean difference was 1.48% (95%CI: 1.16%, 1.81%) with high study heterogeneity of 90.0%. No study dominated these results as they equally contributed to the final results (between 9-12%).

Figure 7: % change in BMD lumber spine of studies on treatments for AI-associated bone loss



NB: Control group for Bruksky, Coleman, Llombart, Hines and Takahashi is 'delayed zoledronic acid' not placebo.

Figure 8: % change in BMD total hip of studies on treatments for AI-associated bone loss



NB: Control group for Bruksky, Coleman, Llombart, Hines and Takahashi is 'delayed zoledronic acid' not placebo.

Figure 9: Funnel plot of standardized mean difference in %BMD (Lumbar spine)

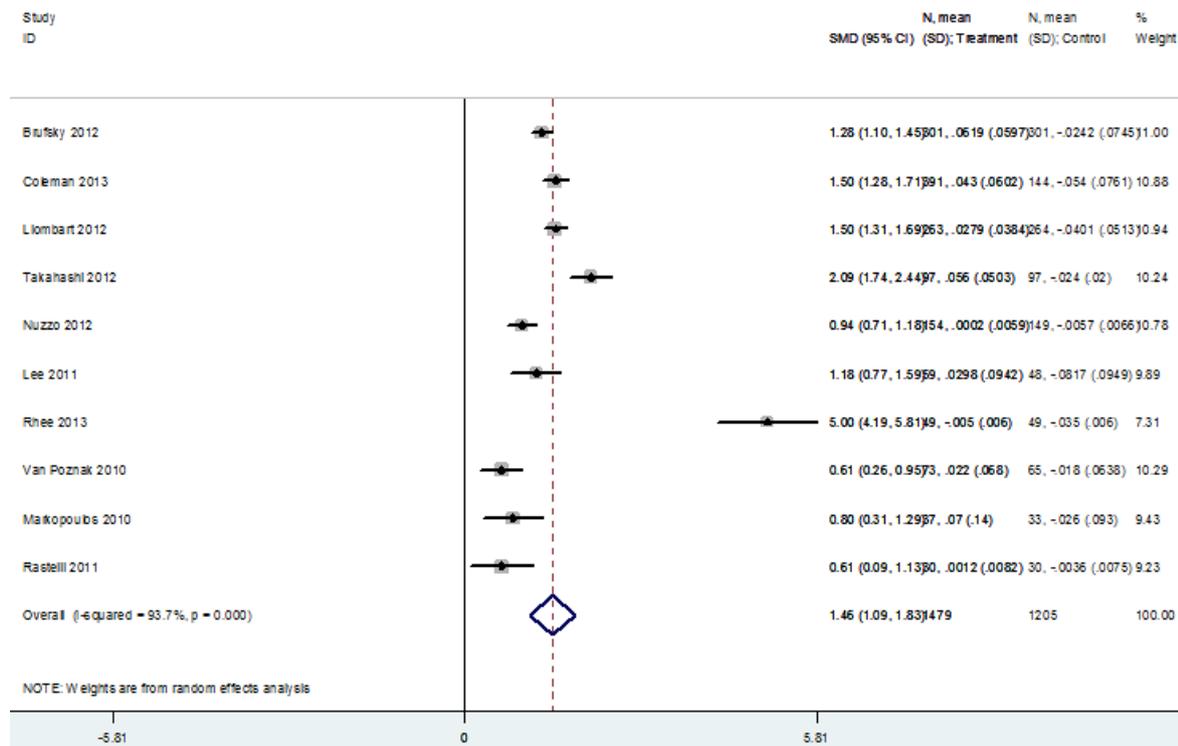
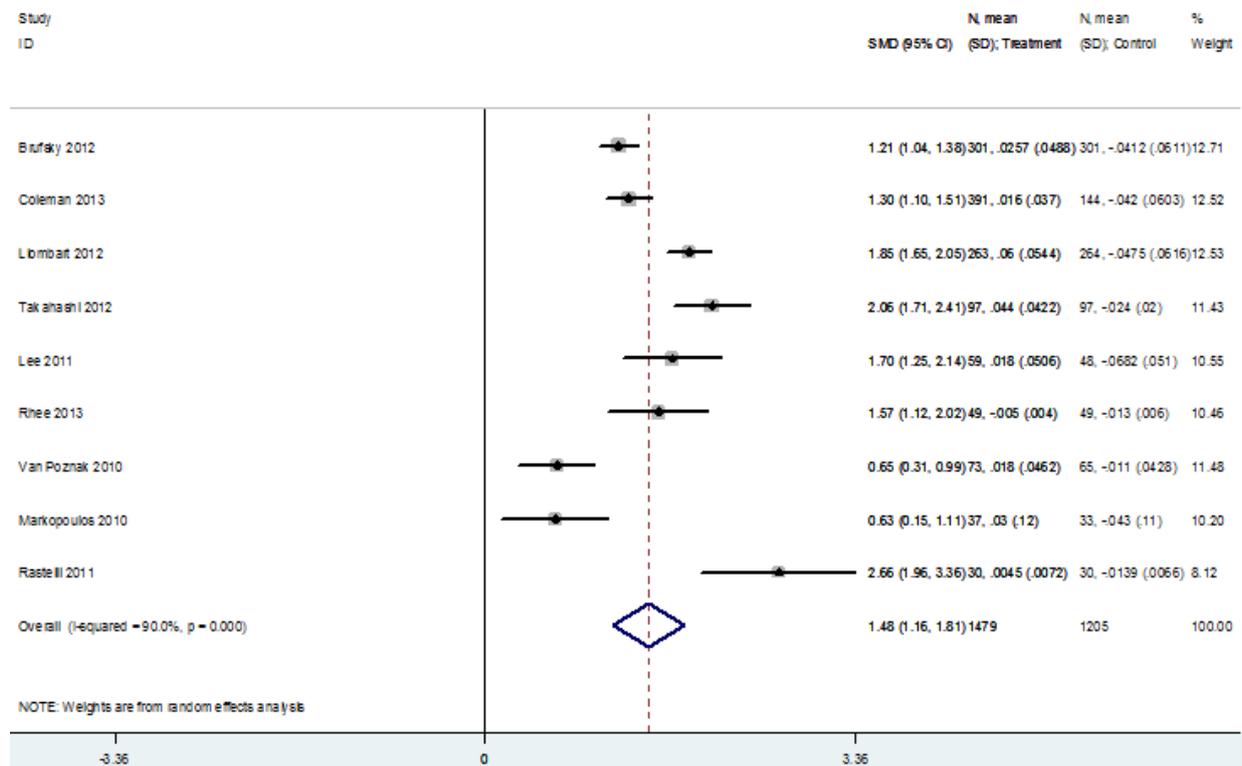


Figure 10: Funnel plot of standardized mean difference in %BMD (Total hip)



## Evidence for fracture prevention

Most studies in this assessment, including the large Z-FAST, ZO-FAST and E-ZO-FAST studies with 5-year follow-ups, were not powered to detect bone fractures as their endpoints. Nevertheless, many did report fracture rates and six studies reported no fractures in either treatment arms (Table 19).

Table 19: Summary of key results %change (95%CI or SD) and quality of studies<sup>1</sup>

Study	BMD -Total hip	BMD -Lumbar Spine	Fractures	Quality Assessment
Brufsky 2012	MD: +6.7, 2.6%±4.9 (upfront),-4.1% ±6.1 (delayed)	MD: +8.9% (7.4-8.0), 6.2%±5.97 (upfront),-2.4%±7.45 (delayed)	28 (9.3%) upfront 33 (11%) p=0.380	NHMRC Level II C1, P1, Q2 Medium
Coleman 2013	+1.6% ±3.7 (upfront) -4.2% ±6.0 (delayed)*	+4.3% ±6.0 (upfront) -5.4% ±7.6 (delayed)*	0.6% upfront, 1.5% delayed	NHMRC Level II C1, P1, Q2 Medium
Llombart 2012	+2.8% ±3.8 (upfront) -4.0% ±5.1 (delayed)*	+6.0% ±5.4 (upfront) -1.6% ±6.2 (delayed)*	At 3 yrs; 2.4% (upfront) 3.3% (delayed)	NHMRC Level II C1, P1, Q2 Medium
Takahashi 2012	Delay: -2.4% ±2.0% Upfront: 4.4%*± 5.5%	Delay: -2.4 ±2.0% Upfront: 5.6%*± 5.0%	1% (1.0%) (upfront) 4% (4.1%) (delayed)	NHMRC Level II C1, P1, Q2 Medium
Nuzzo 2012	NR	Letrozole: -0.57% (0.66) Letrozole + Zol 0.02% (0.59) MD 0.60% (0.46, 0.77)*	Nil	NHMRC Level II C1, P1, Q2 Medium
Safra 2011	NR	At 48 mths: Zol: +0.27% Pbo: 0.07%	Nil	NHMRC Level II C1, P1, Q2 Medium
Lee 2011	Zol: +1.8%* ± 5.1% Pbo: -6.82%* ± 5.1%	Zol: +2.98%* ± 9.4% Pbo: -8.17% (adjusted)* ± 9.5%	Nil	NHMRC Level II C1, P1, Q2 Medium
Hines 2009	Upfront: +1.2% Delayed: -3.3%*	Upfront: +4.96% Delayed: -2.3%*	Nil	NHMRC Level II C1, P1, Q2 Medium
Lester 2012	Osteoporosis:+2.72% (-4.0, +9.6) Osteopenic:-6.07% (-8.9, -3.7)	Osteoporosis:+9.65% (+4.9, +18.9) Osteopenic:+2.60% (-7.8, +18.4)	10 patients, 4 ibandronate, 3 placebo, 3 osteoporotic groups	NHMRC Level II C1, P1, Q2 Medium
Markopoulos 2010	Med rised 3.0% (SD 12) <sup>1</sup> Med pbo -4.3%* <sup>1</sup> (SD 11) High risk -2.5%* (SD 16)	Med rised 7.0%* <sup>1</sup> (SD 14) Med pbo -2.6% <sup>1</sup> (SD 9.3) High risk 8.0%*(SD 13)	Nil	NHMRC Level II C1, P1, Q2 Medium
Rhee 2013	Alendronate: -0.5 (±0.40) Pbo: -1.3 (±0.50)	Alendronate: -0.5 (±0.60) Pbo: -3.5 (±0.60)	NR	NHMRC Level II C1, P1, Q3 Poor
Van Poznak 2010	High risk: rised 2.0% (0.49, 3.44) Med risk: rised 1.8% (0.78, 2.86) Med risk: pbo -1.1% (-2.14, -0.10)* -0.4% (-2.10, -1.26)	High risk: rised 3.0% (1.4, 4.67)* Med risk: rised 2.2% (0.73, 3.76) Med risk: pbo -1.8% (-3.25, 0.25)* Low risk: -2.1% (-3.6, -0.53)*	(5 patients 2.1%)	NHMRC Level II C1, P1, Q2 Medium
Ellis 2009	MD: denosumab/pbo +4.5 (± 0.5%)*	MD: denosumab/pbo +7.5% (± 1.0%)*	NR	NHMRC Level II C1, P1, Q2 Medium
Rastelli 2011	High dose vitamin D2 BMD total hip - NR BMD fem neck: Vit D: +0.45 (±0.72), Placebo: -1.39 (±0.66)	Vit D: 0.12% (± 0.82) Placebo: -0.36 (±0.75)	Nil	NHMRC Level II C1, P1, Q2 Medium

1. Results extracted from publications, clinicaltrials.gov or emailed authors for additional information

\*p<0.05

AEs =Adverse events, BMD = bone mineral density; MD = mean difference; NHMRC = National Health and Medical Research Council; NR = not reported; pbo = placebo, pt = patients, Zol = zoledronic acid

### Quality of studies on treatments for aromatase-inhibitor-associated bone loss

Most studies were either phase II or open-label phase III studies. Several studies had open-label treatment for women with osteoporosis and double-blinded placebo controlled

randomisation for medium-risk (or osteopenic) women. All studies had relevant direct comparators for this assessment because in the placebo treatment arms, women received vitamin D and calcium supplements. Rastelli *et al.* (2011) was the exception where high-dose vitamin D was the intervention group and placebo (without vitamin D/calcium supplements) was used.

Most studies were assessed as 'medium' quality with some risk of bias or 'poor' quality where there was insufficient data to judge risk of bias.

Limitations of the studies included:

- Some studies did not report whether the BMD analyses were independent (blinded) to study investigators and study group allocation;
- Reports using 'mean difference' between treatment groups did not enable direct comparison across studies with absolute change within each group;
- Most studies did not state what they considered to be clinically meaningful change in BMD across time;
- High patient withdrawal in some studies were not fully explained;
- Compliance and adherence to bone resorptives or vitamin supplements was not reported; and
- The statistical precision of BMD change outcomes was not uniformly reported across studies. Studies by Ellis, Safra, Hines did not provide 95% confidence intervals or standard deviations/errors.

### **Safety of treatments for aromatase-inhibitor-associated bone loss**

A summary of the main adverse events for anti-resorptives and vitamin D is provided in Table 20. The reporting of adverse events was not uniform across the studies.

Osteonecrosis of the jaw (ONJ) is an area of exposed bone (not covered by gum) in the jaw region that does not heal within 8 weeks of identification. The cause of ONJ is unknown but use of high-dose zoledronic acid and people suffering cancer are among the risk factors. The symptoms are severe jaw pain, numbness, swelling, infection and loosening of teeth. ONJ was not a common adverse event across the studies, in most studies occurring in no patients, in 2/300 (0.67%) upfront patients in Z-FAST and 0.04% patients in the E-ZO-FAST study. In the ZO-FAST study, 7 patients were suspected of ONJ but 3 patients were confirmed with the condition. Patients with this event would have permanently discontinued from the study and the reports (in participant flow charts) did not document any patients who discontinued for this reason. Other studies did not report adverse events at all or in sufficient detail to be assessed (Lee 2011, Markopoulos 2010, Rhee 2013, Ellis 2009).

The common adverse events for women on anti-resorptive treatments were arthralgia, hot flushes, fatigue, myalgia, bone pain and fever. The proportions in Table 20 are for all severity levels of adverse events. Fever, hot flushes and fatigue are also symptoms common for AIs. There were no significant differences in the adverse event profiles for those in the treatment and no treatment arms. The exceptions were significantly higher fever experienced in participants of the Takahashi 2012 study and across most adverse events in Hines 2009.

Table 20: Common adverse events for women on BMD management (%) Intvn/Comparator

Study	Arthralgia	Hot flushes	Fatigue	Myalgia	Bone pain	Fever
Brufsky 2012	47.0/45.3	40.7/39.3	33.7/29.3	20.3/15.7	16.0/8.0	-
Coleman 2013	49.0/46.9	-	17.7/17.8	13.0/13.3	18.5/12.1	15.2/3.6
Llombart 2012	35.7/38.9	22.6/31.5	15.1/18.5	11.1/10.4	8.3/4.1	6.7/0.0
Takahashi 2012	51.6/48.5	13.7/9.3	-	6.4/6.2	-	23.0/3.1
Nuzzo 2012	13.0/3.0	28.0/32.0	10.0/11.0	-	13.0/5.0	18.0/0.0
Hines 2009	13.0/11.0	8.0/10.0	5.0/2.0	7.0/5.0	-	6.0/0.0
Safra 2011	26.0/21.0	4.0/21.0	17.0/8/0	-	-	34.0/0.0

pt = patients, AEs =Adverse events, BMD = bone mineral density

Bolded= significant at p<0.001

The remaining studies either did not report adverse events or reported them with little detail as follows:

- Lee 2011: Not reported
- Lester 2012: Nausea and indigestion reported in 4 (16%) of patients taking ibandronate
- Markopoulos 2010: 2 patients had arthralgia with medium risk
- Rhee 2013: 1 patient had epigastric pain, 1 had hemoptysis, 1 had bone pain and 1 patient had fever
- Van Poznak 2010: Total adverse events were not reported –AEs leading to discontinuation are reported in the paper.
- Ellis 2009: Authors stated ‘Arthralgia, pain in extremity, back pain and fatigue were most common adverse events.
- Rastelli 2011: 5 patients in the Vitamin D intervention group had hypercalcuria compared with 1 patient in the placebo group

## Summary of clinical evidence

A summary of the evidence for the effectiveness and safety of DXA and management of bone loss for women with breast cancer taking aromatase inhibitors is presented in Table 21.

Table 21: Summary of the clinical evidence of the main intervention

Intervention	Comparator	Comparative effectiveness outcomes			Safety
-	-	Minimal bone trauma fractures	Bone loss (BMD) lumbar spine	Bone loss (BMD) total hip	-
DXA and anti-resorptives	No DXA and lifestyle advice	No evidence	No evidence	No evidence	No evidence
DXA and anti-resorptives	Placebo	Superior <sup>1</sup>	Superior <sup>1</sup>	Superior <sup>1</sup>	Equivalent
No DXA and lifestyle advice	Placebo	No evidence	Insufficient evidence <sup>2</sup>	Insufficient evidence <sup>2</sup>	Insufficient evidence <sup>2</sup>

1. Based on large trials with zoledronic acid, bisphosphonates, denosumab

2. Based on one small pilot trial of high dose vitamin D

# Other relevant considerations

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## Expert opinion

HESP experts have advised that clinicians in Australia would not favour one fracture risk tool over another. They use various fracture risk tools and there is no standardization in terms of which tool is used. Two commonly used tools are the FRAX™ and the Garvan fracture risk calculator. Few BMD practices would quote a 5 or 10 year probability of fracture in their reports. Although clinical risk factors would be considered in routine practice, importance would be placed on BMD for early detection of low bone density for treatment. However, there is no standard uniformity in BMD reporting despite guidelines available by various organisations.

HESP experts further state that DXA densitometers are widely available in Australia and some States have mobile units serving remote towns. The densitometers may be under-utilised given that patients are still unassessed and untreated for minimal trauma fractures.

The older machines in Australia may be ageing but these are likely to remain accurate. Newer machines have faster acquisition and analysis times, and improved bone edge detection and display. The main issue is maintaining regular quality control with protocols in place to ensure system stability.

Oncologists would generally make the fracture risk assessment aided by the DXA report in situations where aromatase inhibitors are involved. Over the longer period, fracture risk assessment and DXA ordering may be continued by a general practitioner.

On the issue of the magnitude of change in BMD which is likely to be true change, the least significant change (LSC) value will depend on the precision or reproducibility of the BMD measurement. The LSCs are usually 0.05 g/cm<sup>2</sup> for spine total hip and radius and 0.07 g/cm<sup>2</sup> for the femoral neck. In group research, these values are less relevant than for individuals returning for repeat DXA measurement because smaller change is statistically significant with larger sample sizes.

Finally, on the issue of who should perform the BMD measurement, currently, a BMD is required to be personally performed by a specialist physician as per clause G12.1 in the MBS. This requirement is opposed by the ANZBMS, Osteoporosis Australia, Royal Australia and New Zealand College of Radiologists (RANZCR) and others. They believe that there should not be any issue with an appropriately certified BMD operator performing BMD measurement under the supervision of a specialist physician. However, the specialist physician needs to review and interpret the study and report the results. The test is relatively simple compared with other Category 2 tests (ECG, EEG, more complicated audiology tests, ophthalmology etc) and can be delegated without the need for personal onsite attendance of the specialist physician. It is argued, in addition, diagnostic imaging items in the MBS including radiology, nuclear medicine, MRI and ultrasound can all be performed under supervision by radiographers and nuclear medicine technologists. Many of these other tests which are able to be delegated to non-medical personnel to perform can be critical in helping to diagnose acute medical conditions requiring urgent medical intervention. Yet, BMD measurement used for the diagnosis of osteoporosis which is a chronic condition and where the treatment effect takes months require a

specialist physician to personally perform according to the MBS. In the opinion of the HESP advisor, this situation is illogical, counterintuitive and inefficient.

## **Consumer implications and other considerations**

On 8 November 2012, the Breast Cancer Network Australia (BCNA) provided feedback on MSAC application 1313. BCNA is a consumer advocacy group, representing the views of people affected by breast cancer. The BCNA welcomes and supports this application. They state:

BCNA supports the introduction of a Medicare rebate for women diagnosed with breast cancer who require a DXA test in conjunction with their aromatase inhibitor treatment. We are aware that these tests are an important adjunct for women being treated with aromatase inhibitors, and we are keen to see a Medicare rebate available in order to assist these women with the significant financial burden associated with their diagnosis, treatment and care.

BCNA is aware that the cost of DXA tests can be significant for women and, for many women, this cost can be ongoing. In May this year, BCNA surveyed women in our Review & Survey Group to investigate their experiences with DXA tests. Of the 114 women treated with an aromatase inhibitor who incurred a fee for their last test, we found that more than a third incurred a cost of more than \$100.

The survey results also highlighted that many women were required to have more than one test in conjunction with their aromatase inhibitor treatment, further contributing to the significant financial burden of their breast cancer diagnosis, treatment and care. Thirty per cent of women had a test every twelve months, and almost 30% every two years. Some women reported having up to six DXA tests in conjunction with their aromatase inhibitor treatment.

The full letter is available at: <https://www.bcna.org.au/about-bcna/advocacy/submissions-and-reviews/submission-dxa-scan-rebates>

# What are the economic considerations?

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## Economic research questions

The Protocol states the following economic research questions to be covered in this assessment:

1. What is the cost-effectiveness of DXA plus anti-resorptive therapies compared to no DXA and no anti-resorptive therapies?
2. What is the impact on cost-effectiveness of varied ages and eligibility criteria, as specified in the proposal?
3. What impact does treatment with aromatase inhibitors have on bone mineral density as a surrogate for minimal trauma fracture? This should include a consideration of the effect of other possible prognostic factors including age and previous treatment with tamoxifen.
4. What is the impact of different thresholds for therapy as advised by the available evidence?

On the basis of the evidence that showed 'DXA and anti-resorptives' were superior to placebo for reversing bone loss in women taking aromatase inhibitors, a cost-utility was performed. Although this does not represent a direct comparison with lifestyle advice/vitamin D/calcium, many women in the placebo arm of the anti-resorptive trials were provided with or allowed vitamin D/calcium supplements. An indirect comparison of the DXA and anti-resorptives and no DXA and lifestyle advice, using placebo as the common comparator, was not considered appropriate as the latter relied on one small trial with only 6-month duration.

## Existing economic studies

In order to inform the cost-utility analysis, Search 4 identified three studies considered relevant to this economic assessment; Ito 2012, Logman 2010, Mueller 2009. Studies by Logman and Ito specifically analysed interventions for women on aromatase inhibitors while Mueller et al. 2009 undertook a cost-utility analysis comparing clinical risk factor assessment with or without DXA in high-risk women for osteoporosis screening.

All studies undertook a Markov modelling technique and all were judged as having a high standard of reporting quality according to the CHEERS statement. Other features and key results of the models are listed in Table 22.

Table 22: Comparison of cost-effectiveness studies relevant to this assessment

-	Logman 2010	Ito 2012	Mueller 2009
Population	Early stage breast cancer on aromatase inhibitors	Stage I, II, IIIa breast cancer, post-menopausal, aromatase inhibitors	High risk women
Intervention (s)	Upfront zoledronic acid	Annual or one time DXA screening + oral bisphosphonates for either osteoporosis or osteopenia Universal bisphosphonates	Clinical risk factors + DXA (alendronate for osteoporosis)
Comparator	Delayed zoledronic acid	No intervention	Clinical risk factors alone
Model type	Markov	Markov	Markov
Model duration	Lifetime	Lifetime (until age 100)	Lifetime (until age 100)
Model cycles	1 year	1 year	1 year
Main clinical outcomes	Cumulative first fractures per 1000 women	Cumulative hip and all fractures per 100 women	Vertebral or hip fractures
Measure of benefit	QALY	QALY	QALY
Key results (ICERs)	£24,868 per QALY, 60 years, 2007 Upfront = -40 fractures per 1000	Annual + osteoporosis \$87,300 Annual + osteopenia \$129,300 Universal \$283,600 One time - dominated	€20,235 per QALY (60-70 years) 2006
Quality of reporting	High (CHEERS= 23/24)	High (CHEERS= 21/24)	High (CHEERS= 21/24)
Industry funded/sponsored	Yes	No	No

CHEERS = Consolidated Health Economic Evaluation Reporting Standards, DXA = dual x-ray absorptiometry, ICERs = incremental cost effectiveness ratios, QALY = quality adjusted life years

The study by Ito *et al.* (2012) was considered to be the most relevant and useful for this assessment. This is because they had a 'no intervention' comparator and included different frequencies of DXA scanning during AI treatment and different BMD thresholds for initiating treatment (osteoporosis or osteopenia). Their cohort model was also based on women aged 60 and oral bisphosphonates were used as the cheaper option compared with intravenous bisphosphonates (zoledronic acid).

The results by Ito *et al.* (2012) indicated that annual screening with DXA in this population was not found to be cost-effective while universal bisphosphonate treatment was also not cost-effective.

## Economic evaluation

An economic model was constructed in TreeAge Pro 2014. Table 23 lists the main structural components of the model.

Table 23: Structural components of the economic model

Component	Description
Population	Women with early stage breast cancer receiving aromatase inhibitors Starting age = 60 years
Intervention (s)	1. DXA and anti-resorptive therapy (women with osteoporosis) 2. DXA and anti-resorptive therapy (women with osteopenia and osteoporosis) 3. DXA and anti-resorptive therapy (all women in this population)
Comparator	No DXA and lifestyle advice only (all women in this population)
DXA testing	Annually
Model type	Markov state transition
Model duration	Lifetime
Model cycles	1 year
Main clinical outcome	Cumulative fractures per 1000 women
Main economic outcome	Incremental cost per QALY gained
Analyses performed	Expected value analysis Scenario analyses on different starting ages One-way sensitivity analyses Probabilistic sensitivity analysis (2000 simulations)

DXA = dual x-ray absorptiometry, QALY = quality adjusted life years

A Markov cohort model provides a structure for assessing the economic questions in this assessment. The starting age of the cohort of women is 60 years which is the average age of breast cancer diagnosis in Australia (AIHW 2012). The model duration is lifetime or a maximum of age 100 years.

Annual DXA scans were the frequency for the base case. Annual scans match the proposed MBS item description for the target population, align with current guidelines and appear to be current practice in Australia (see Consumer implications and other considerations). Two-yearly scans were tested in sensitivity analyses.

The model operates in one-yearly cycles and has four health states; anti-resorptive treatment, no treatment, second fracture and death. In each of the four comparison groups, the women face a risk of either hip, vertebral, other fracture or no fracture. As fractures are not very common, most women enter the no fracture arm each cycle. If women have a fracture, they face a risk of another fracture or they will stay well but will have anti-resorptive therapy for their initial osteoporotic fracture. The effectiveness of anti-resorptive therapy was based on the pooled evidence of several studies showing a protective effect against fractures. Evidence was available on the absolute fractures over 60 months in many trials of various bone therapies. In any group, once the women suffered a minimal trauma fracture, they were considered osteoporotic and remained on anti-resorptive therapy and annual DXA scans.

The risk of fractures increases sharply with age in both men and women (AIHW Osteoporosis 2012) and age is a component of all fracture risk factor assessment tools. Age-related fractures for Australian women (in 2006-07) were tabulated in the model showing fracture risk increases exponentially with age (2011 Osteoporosis Bulletin). Although the absolute number of fractures is increasing over time (4.4% per year in women over 55 years), the rate of fractures per 100,000 person-years has been decreasing in Australian women (Pasco *et al.* 2011). Fracture rates were derived from women in 2006-

07 for rates per 1000 women in 5-year age groups (AIHW Osteoporosis Bulletin 2011). For example, the table shows from a hip fracture rate of 24/1000 at age 55 and 1175/1000 at age 80. Rates were converted to probabilities.

To adjust the baseline age-related risk of fracture for women with breast cancer using AI therapy, the risk of fracture reported for this population in two meta-analyses was used (Amir, Seruga et al. 2011, Becker, Lipscombe et al. 2012).

Using Marshall *et al.* 1996 meta-analysis, fracture risk as a function of BMD decline was used to differentiate women who had normal BMD (RR 1.0), osteopenia (RR 1.5) and osteoporosis (RR 3.8). The latter fracture risk for osteoporosis was an assumption calculated by 2.5 standard deviations multiplied by the osteopenia risk. These risks were used in the model at the start to apply to the different intervention groups.

### Effectiveness of anti-resorptive therapy for fracture prevention

The baseline fracture risk for women taking AI therapies was adjusted for bone treatment using pooled values in the evidence (Table 24). High and low values of treatment effect were based on the rate ratios of Brufsky 2012 and Coleman 2013 studies, respectively. Therefore the use of ‘% change in BMD’ to link to fracture occurrence was not explicitly used in the model.

Table 24: Evidence for protective effect of bone therapy for women taking AIs

Study	Period	Fx site	% women on AI with fractures		% women on AI plus ARTx with fractures		RR
			% Fx	Av%/yr	% Fx	Av%/yr	
Neuner 2011	36 mths	Hip	1.7%	0.57%	-	-	-
		Non-vert	8.8%	2.93%	-	-	-
Goss 2013	4 years	Fragility	4.0%	1.0%	-	-	-
Becker 2012:					-	-	-
ATAC	100 mths	All	11.0%	1.32%	-	-	-
BIG-I-98	60 mths	All	9.3%	1.85%	-	-	-
ABCCSG/ARNO 95	28 mths	All	2.0%	0.86%	-	-	-
MA-17	30 mths	All	5.3%	2.12%	-	-	-
Brufsky 2012	60 mths	All	11.0%	2.2%	9.3%	1.86%	0.8455
Llombart 2012	36 mths	Spine	3.3%	1.1%	2.4%	0.80%	0.7273
Coleman 2013	36 mths	All	1.5%	0.5%	0.6%	0.20%	0.4000
-	-	-	Mean	1.44%	Mean	0.95%	0.6598

AI = aromatase inhibitors, ARTx = anti-resorptive therapies, Fx = fracture, RR = rate ratio, yr = year

### Cost inputs

In the model, it was assumed that all fractures resulted in hospitalisations (Borgstrom, Lekander et al. 2013). Further, all fractures were assumed to be minimal trauma fractures. The costs of fractures were derived from the latest AR-DRGs pertaining to the different fracture types; hip, vertebrae and ‘other’. These DRG codes were based on those reported in an AIHW 2011 Osteoporosis report (Australian Institute of Health and Welfare 2011). Fracture costs were tested at  $\pm 30\%$  of the mean costs in sensitivity analyses. The high cost may reflect the additional community nursing and home care that can often occur in older women following a fracture (Australian Institute of Health and Welfare 2011).

No costs or effects were included for AI treatment (or any other breast cancer therapy) as these were incurred in all women in the model at baseline and these would not affect the incremental outcomes. The annual cost of anti-resorptive therapy was assumed to be that of risedronate (oral bisphosphonate). Risedronate was assumed to be item 8974H, a pack containing 4 enteric coated tablets risedronate sodium 35 mg and 24 sachets containing granules of calcium carbonate 2.5 g (equivalent to 1 g calcium) with colecalciferol 22 micrograms. This aligns with the current trends in use of bisphosphonates in Australia (Figure 3). The higher cost of zoledronic acid was tested in a sensitivity analysis. Accompanying GP consultation costs were added to the overall bone therapy cost and 2 visits were assumed per year.

The cost of vitamin D tests were included only in the 'no DXA and lifestyle advice' strategy in the model and it was assumed that one test per year would be performed. Calcium and vitamin D tablets were assumed to be paid by the patient as over-the-counter purchases and no costs for these were included in the model.

### Utilities

Utility values in the model were for otherwise well women with early breast cancer on aromatase inhibitors, and those with hip, spine and 'other' fractures. Values were taken from Mansel *et al.* 2007 and were based on UK analyses of the ATAC trial (Mansel, Locker *et al.* 2007). Early stage breast cancer used the Australian base utility value from Viney *et al.* 2011 (0.895) (Viney, Norman *et al.* 2011) with, (from Mansel 2007) a disutility for 'disease free' (-0.011) and common adverse events for AEs with anastrozole (-0.027). These small decrements from background population utility were maintained for their remaining life to allow for ongoing health problems and anxiety during breast cancer survivorship. Further disutilities were applied to the baseline value (0.857) for all women in the model for hip (-0.131), spine (-0.095) and 'other' (-0.073) fractures, with the latter based on wrist fractures in Mansel *et al.* (2007).

Table 25 summarises the inputs used in the economic model with the values tested in sensitivity analyses.

Table 25: Model parameters, sensitivity values and sources

Description	Base	Low	High	Dist	Source
Starting Age (years)	60	45	70	-	AIHW 2012 Breast cancer in Aust.
Duration	lifetime	n/a	n/a	-	-
Cycle length	1 year	n/a	n/a	-	-
Discounting	5%	0%	7%	-	PBAC guidelines
Background mortality (adjusted for early stage breast cancer)	table	n/a	n/a	-	ABS life tables, AIHW 2012 Report to the nation (97% survival at 5 years)
<b>Probabilities and relative risks</b>	-	-	-	-	-
Prob of osteoporosis (55-64 yrs)	0.1495	0.0890	0.2100	beta	Henry 2011
Prob of osteopenia (55-64 yrs)	0.5390	0.5140	0.5640	beta	Henry 2011
RR fx in osteopenia (>1.0 SD drop in BMD)	1.50	1.40	1.60	-	Marshall 1996 vs normal BMD
RR fx in osteoporosis (>2.5 SD drop in BMD)	3.75	3.50	4.00	-	Assumption 2.5 x osteopenia
Weighted RR for osteopenia + osteoporosis	1.37	1.28	1.36	normal	Calculated from above
Weighted RR for osteopenia + normal BMD	1.32	1.23	1.41	normal	Calculated from above
Weighted RR for all women	1.68	1.57	1.80	normal	Calculated from above
Prob of hip fx	0.405			-	AIHW osteoporosis 2011 (table 2 p8)
Prob of spine fx	0.056			-	AIHW osteoporosis 2011 (table 2 p8)
Prob of other fx	0.539			-	AIHW osteoporosis 2011 (table 2 p8)
Age-related prob of fx in Aust women	table				2006-07 AIHW Bulletin
RR_fx+AI	1.47	1.34	1.61	-	Amir 2011 vs no AI therapy
RR of fx + AI with bone therapy)	0.6598	0.4000	0.8455	beta	Neuner 2011, Goss 2013, Becker 2012, Brufsky 2012, Llombart 2012, Coleman 2013
Prob of fx if osteoporotic, osteoporotic or osteopenic or all women, separated by hip, spine and other fx types, separated by treatment vs no treatment	table	-	-	-	Table created by different age groups fx with AI x RR osteopenia/porosis x tx or no tx
RR excess death 1 year after fx	2.87	2.52	3.27	normal	Haentjens P 2010 Fig 2 p27
RR excess death after 1 year after fx	2.25	1.74	2.92	normal	Haentjens P 2010 Fig 1 p26
Prob of 2 <sup>nd</sup> fx	73%	57%	92%	beta	Kanis 2004
<b>Costs (2014)</b>	-	-	-	-	-
Annual cost of hip fx	17512	12258	22766	gamma	AR DRG 2009-10
Annual cost of vertebral fx	11974	8381	15566	gamma	AR DRG 2009-10
Annual cost of other fx	2416	1691	3141	gamma	AR DRG 2009-10
Annual cost of bone treatment	619.80	n/a	1252	-	PBS item 8974H and MBS item 23 (risedronate)
Cost of single DXA scan	102.40	51.20	n/a	-	MBS proposed fee, low fee = biannual
Cost of vitamin D test	39.05	19.53	78.10	gamma	MBS item 66608
Annual cost of death/palliation care	8659	6061	11257	gamma	Seshamani & Gray 2005
<b>Utilities</b>	-	-	-	-	-
Background utility adjusted for AI therapy / brca	0.857	0.728	0.986	beta	Viney 2011, Mansel 2007
Disutility from a hip fx	-0.131	-0.111	-0.151	beta	Mansel 2007, ±15% assumed
Disutility from a vertebral fx	-0.095	-0.081	-0.109	beta	Mansel 2007, ±15% assumed
Disutility from an 'other' fx	-0.073	-0.062	-0.084	beta	Mansel 2007, ±15% assumed

RR = relative risk, fx = fracture, DXA = dual absorptiometry X-ray, AI = aromatase inhibitor, SD = standard deviation, BMD = bone mineral density

References: (Marshall, Johnell et al. 1996, Kanis, Johansson et al. 2004, Mansel, Locker et al. 2007, Haentjens, Magaziner et al. 2010, Australian Institute of Health and Welfare 2011, Henry, Pasco et al. 2011, Neuner, Yen et al. 2011, Viney, Norman et al. 2011, Becker, Lipscombe et al. 2012, Brufsky, Harker et al. 2012, Llombart, Frassoldati et al. 2012, Coleman, Boer et al. 2013, Goss, Ingle et al. 2013)

## Results of the economic evaluation

Table 26 provides the results of the economic evaluation. Incremental cost effectiveness ratios were produced for two outcomes; per QALY gain and per fracture avoided.

Table 26: Key results of economic evaluation (annual DXA scan, 60 year old cohort, 40 years)

Intervention	Mean Costs	Mean QALYs	Inc Costs	Inc QALYs	ICER QALYs	Fractures per 1000 women	ICER Fracture avoided
No DXA and lifestyle advice only (all women)	\$4056	11.657	ref	ref	ref	113	ref
DXA + ARtx (osteoporosis)	\$5331	11.956	\$1275	0.299	\$4,264	100	\$98,077
DXA + ARtx (osteoporosis + osteopenia)	\$10249	11.959	\$6193	0.302	\$20,507	80	\$187,667
DXA + ARtx (all women)	\$13131	11.960	\$9075	0.303	\$29,950	73	\$226,875

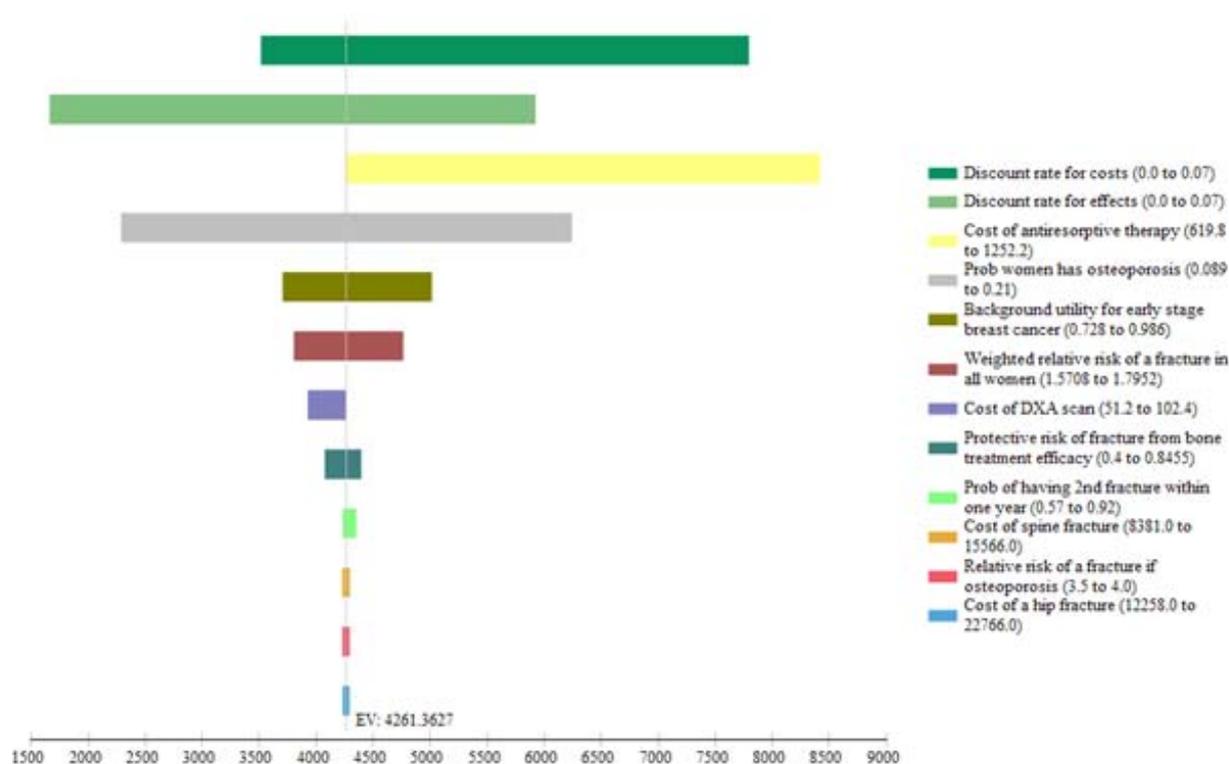
ARtx = Anti-resorptive therapy, DXA = dual absorptiometry X-ray, ICER = incremental cost effectiveness ratio, QALYs = quality adjusted life years

The model is mainly driven by costs rather than benefits. This is because the number of fractures is low over a 40 year period and similarly around 0.3 QALYs (4 months) of extra survival is predicted.

The model shows an ICER of \$4,264 per QALY gained for DXA and bone treatment for women with osteoporosis (BMD T-score <-2.5) compared with no DXA and lifestyle advice only. Similarly, for women with osteoporosis or osteopenia (BMD T-score <-1.0), DXA and bone treatment was also cost-effective, although less cost-effective than for osteoporotic women only. If incremental cost per fracture avoided was considered, no bone treatment strategy was cost-effective.

One-way sensitivity analyses were undertaken and the results are presented in Figure 11 for a selection of inputs which generated the most change in the base ICER per QALY.

Figure 11: One-way sensitivity results of ICER for DXA plus ARTx for osteoporosis vs no DXA and lifestyle



The results were most sensitive to the discount rates, the annual cost of bone therapy, the probability of having osteoporosis, and background utility for women with early breast cancer. However, all the sensitivity results showed that for DXA and bone treatment for osteoporosis, the ICERs were no higher than \$9,000 per QALY and therefore remain cost-effective per QALY gain.

Table 27 shows the results of the scenario analyses where cohorts of different ages were altered. This was undertaken to capture the range of women with early breast cancer in Australia; 76% of women with breast cancer are older than 50 years (Australian Institute of Health and Welfare & Cancer Australia 2012). A total of 83% of women aged 55 years and over would be considered to have established menopause.

**Table 27: Results of cost-utility analyses by different cohort starting ages**

Intervention	Mean Costs	Mean fx per 1000	Mean QALYs	Inc Costs	Inc QALYs	ICER
Age 50 years	-	-	-	-	-	-
No DXA and lifestyle advice only	\$2584	46	13.603	ref	ref	ref
DXA + ARtx (osteoporosis)	\$4134	41	13.727	\$1550	0.12	\$12,500
DXA + ARtx (osteoporosis + osteopenia)	\$9882	33	13.734	\$7298	0.13	\$55,710
DXA + ARtx (all women)	\$13461	30	13.734	\$10877	0.13	\$83,031
Base case: Age 60 years	-	-	-	-	-	-
No DXA and lifestyle advice only	\$4056	113	11.657	ref	ref	ref
DXA + ARtx (osteoporosis)	\$5331	100	11.956	\$1275	0.299	\$4,264
DXA + ARtx (osteoporosis + osteopenia)	\$10249	80	11.959	\$6193	0.302	\$20,507
DXA + ARtx (all women)	\$13131	73	11.960	\$9075	0.303	\$29,950
Base case: Age 65 years	-	-	-	-	-	-
No DXA and lifestyle advice only	\$5151	241	10.203	ref	ref	ref
DXA + ARtx (osteoporosis)	\$8349	215	10.738	\$3198	0.54	\$5,978
DXA + ARtx (osteoporosis + osteopenia)	\$10507	170	10.799	\$5356	0.60	\$8,987
DXA + ARtx (all women)	\$13256	155	10.797	\$8105	0.59	\$13,645

ARtx = Anti-resorptive therapy, DXA = dual absorptiometry X-ray, ICER = incremental cost effectiveness ratio, QALYs = quality adjusted life years

Table 27 shows that all strategies are more cost-effective in older age and less cost-effective in younger women compared with the base 60 year cohort. This is most likely due to the higher benefits of fracture prevention in older women where fracture rates over 65 begin to accelerate quickly. It will also be due to the relatively high bone therapy costs over a longer period of treatment in younger women.

Probabilistic sensitivity analyses were undertaken with 2000 iterations to provide a complete view of the uncertainty around the estimates used in the model. The results of these analyses are presented in Table 28.

**Table 28: Results of the probabilistic sensitivity analyses**

	Base ICER	PSA ICER	95% Credible Interval	% cost-effective at \$50000 per QALY
No DXA and lifestyle advice only	ref	ref	ref	ref
DXA + ARtx (osteoporosis)	\$4,264	\$4,209	(\$1,948, \$8,938)	100%
DXA + ARtx (osteoporosis + osteopenia)	\$20,507	\$20,334	(\$12,515, \$38,558)	99.5%
DXA + ARtx (all women)	\$29,950	\$29,857	(\$20,987, \$52,584)	96.5%

ARtx = Anti-resorptive therapy, DXA = dual absorptiometry X-ray, ICER = incremental cost effectiveness ratio, QALYs = quality adjusted life years

The results of these analyses clearly show that compared with no treatment and lifestyle advice, DXA plus bone treatment for women with osteoporosis or osteopenia would be cost-effective in the vast majority of these women. Similarly, bone treatment offered universally for all post-menopausal women taking aromatase inhibitors is also cost-effective when QALYs gained is the preferred outcome. These statements are subject to a willingness-to-pay threshold of \$50,000 per QALY gained.

## Financial estimates

### Approach

An epidemiological approach was taken to assess the financial implications of the proposed MBS listing of DXA scans for women with breast cancer taking AI therapy. The costings present the figures for the next five years taking into account repeat scans and ongoing treatment for bone density while on AI therapy. The estimates take into account the number of new cases of breast cancer each year. A summary of the estimates are presented in Table 29.

Table 29: Main parameters used in the financial estimates

Parameter	Value	Source / Rationale
Breast cancer	-	-
Incidence of breast cancer in Australia (women aged 50 to 69)	Year 1: 8108 Year 2: 8293 Year 3: 8479 Year 4: 8665 Year 5: 8851	AIHW 2014 ACIM books, Canberra: AIHW. Data available to 2010 (total new cases 14181). Figures were extrapolated to 2019. Below age 50, women will not have reached menopause or if they have can access item 12312 for hypogonadism. After age 70 women can access item 12323.
Proportion of 'early stage' breast cancer	90%	Estimated from Australian population based study by Hayes SC (2012).
Proportion of women with breast cancer receiving aromatase inhibitors	81%	Verry et al. 2012, Australian breast cancer study
% women treated with anti-resorptive therapy	-	-
Mean % women with osteoporosis	14.7%	Henry et al. 2011 Australian BMD T-score measurements on women from the Geelong Osteoporosis Study. Based on women aged 50-69 years.
Mean % women with osteopenia	49.1%	As above
Mean % women with normal BMD	36.3%	As above
DXA scans	-	-
Uptake in each year	100%	Scanners are widely available even in rural and remote areas in Australia (HESP advice). They are already widely used.
Frequency of scans	Annual	In line with proposed MBS description, clinical practice guidelines in breast cancer. Frequency every 2 years will be tested in sensitivity analyses.
Annual Costs	-	-
DXA scans	\$87.05	Proposed MBS fee at 85% - assume 15% patient co-payment
Vitamin D test	\$33.19	MBS item 66608 fee at 85% - assume 15% patient co-payment
Risedronate (oral tablet)	\$547.20	PBS item 8947H. This is one of the most used bisphosphonates in Australia. It is similar in price to Alendronate (oral tablet) PBS item 9351E (\$544.56).
Zoledronic acid (intravenous injection)	1179.66	PBS item 9288W – price was tested in sensitivity analysis
Osteoporotic bone fracture	\$9065.10	Weighted mean of Hip fracture AR-DRG (103B, 108A, 108B, 178A, 178B), vertebrae fractures AR-DRG (110A, 110B) and other fractures AR-DRG (177A, 177B, 161A, 161B). Similar codes were used in AIHW Osteoporosis snapshot. Proportion of fractures = 40.5% hip, 5.6% vertebrae, 53.9% other (AIHW Osteoporosis 2011)
GP visits	\$36.30	MBS item 23
Fracture rates	-	-
Incidence of bone fractures in women taking AIs for breast cancer	1.44%	Pooled estimate of several studies (see economic evaluation)
RR of bone tx efficacy	0.6598	Values in sensitivity 0.400, 0.8455. As above.

ACIM = Aust Cancer Incidence and Mortality, AIHW = Australian Institute of Health and Welfare, AI = aromatase inhibitor, AR-DRG = Australian Related Diagnosis Relative Group, DXA = dual x-ray absorptiometry, HESP = Health Expert Standing Panel, MBS = Medical Benefits Schedule, RR = relative risk, PBS = Pharmaceutical Benefits Schedule.

References: (Henry, Pasco et al. 2011, Hayes, Johansson et al. 2012, Verry, Lord et al. 2012)

The results of the financial estimates in the base case are presented in Table 30.

Table 30: Results of the financial estimates over next five years

	2015	2016	2017	2018	2019
Eligible population	-	-	-	-	-
Incidence of women with brca aged 50-69	8,108	8,293	8,479	8,665	8,851
Proportion with early stage	7297	7464	7631	7798	7966
Proportion taking aromatase inhibitors	5911	6046	6181	6317	6452
Total number of women each year	5911	11956	18138	24454	30906
Estimated uptake of DXA scans	-	-	-	-	-
Number of scans if annual	5911	11956	18138	24454	30906
Estimated women taking anti-resorptives	-	-	-	-	-
Proportion of women with osteoporosis	866	1752	2657	3583	4528
Total women treated	866	1752	2657	3583	4528
MBS Costs	-	-	-	-	-
DXA scans x uptake	\$514,510	\$1,040,770	\$1,578,913	\$2,128,721	\$2,690,367
Vitamin D tests	\$167,444	\$338,723	\$513,838	\$ 692,788	\$875,574
GP visits	\$183,120	\$370,434	\$561,943	\$757,647	\$957,546
PBS Costs of anti-resorptives	-	-	-	-	-
Annual cost of risedronate	\$473,815	\$958,484	\$1,454,006	\$1,960,382	\$2,477,611
Compliance rate of anti-resorptive	100%	95%	90%	85%	80%
Total cost of anti-resorptives	\$473,815	\$910,560	\$1,308,605	\$1,666,324	\$1,982,089
Hospital cost savings from fracture prevention	-	-	-	-	-
Expected incidence of fractures (all women on AI)	85	172	261	352	445
Number of women untreated	5045	10205	15481	20872	26379
Number of fractures in untreated women	73	147	223	301	380
Number of fractures in treated women	8	17	25	34	43
Fractures prevented	4	9	13	18	22
Cost of fractures avoided (weighted mean AR-DRG)	\$9,065	\$ 9,065	\$9,065	\$9,065	\$9,065
Total cost savings	-\$38,453	-\$77,787	-\$118,002	-\$159,098	-\$201,074
<b>TOTAL MBS COSTS</b>	<b>\$865,074</b>	<b>\$1,749,927</b>	<b>\$2,654,694</b>	<b>\$3,579,156</b>	<b>\$4,523,487</b>
<b>TOTAL PBS COSTS</b>	<b>\$473,815</b>	<b>\$910,560</b>	<b>\$1,308,605</b>	<b>\$1,666,324</b>	<b>\$1,982,089</b>
<b>TOTAL STATE GOVT COST SAVINGS</b>	<b>-\$38,453</b>	<b>-\$77,787</b>	<b>-\$118,002</b>	<b>-\$159,098</b>	<b>-\$201,074</b>
<b>TOTAL COSTS</b>	<b>\$1,300,436</b>	<b>\$2,582,699</b>	<b>\$3,845,297</b>	<b>\$5,086,383</b>	<b>\$6,304,502</b>

AI = aromatase inhibitor, AR-DRG = Australian Related Diagnosis Relative Group, brca = breast cancer, DXA = dual x-ray absorptiometry, MBS = Medical Benefits Schedule , PBS= Pharmaceutical Benefits Schedule.

The results in Table 30 indicate that the MBS would incur costs of \$13.372 million over the next five years. Total costs to the health system over the next 5 years are estimated at \$19.119 million.

Sensitivity analyses were performed on the frequency of DXA scans, the unit cost of scans and the proportion of women treated according to T-score thresholds (or BMD status), among others. The results of the sensitivity analyses are presented in Table 31. When DXA scans are offered to women every two years instead of annually, total MBS costs decrease from \$13.372 million to \$10.203 million.

Table 31: Sensitivity analyses of the financial estimates

	2015 \$	2016 \$	2017 \$	2018 \$	2019 \$
Base Case	-	-	-	-	-
Total MBS Costs	865,074	1,749,927	2,654,694	3,579,156	4,523,487
Total PBS Costs	473,815	910,560	1,308,605	1,666,324	1,982,089
Total OTHER cost savings	-38,453	-77,787	-118,002	-159,098	-201,074
Total Costs	1,300,436	2,582,699	3,845,297	5,086,383	6,304,502
95% with early stage breast cancer take AIs	-	-	-	-	-
Total MBS Costs	925,665	1,872,497	2,840,632	3,829,849	4,840,323
Total PBS Costs	555,709	1,067,940	1,534,784	1,954,331	2,324,672
Total OTHER cost savings	-45,099	-91,232	-138,397	-186,596	-235,828
Total Costs	1,436,275	2,849,206	4,237,018	5,597,584	6,929,167
DXA every 2 years	-	-	-	-	-
Total MBS Costs	865,074	1,235,462	2,128,390	2,526,635	3,447,375
Total PBS Costs	473,815	910,560	1,308,605	1,666,324	1,982,089
Total OTHER cost savings	-38,453	-77,787	-118,002	-159,098	-201,074
Total Costs	1,300,436	2,068,234	3,318,993	4,033,861	5,228,390
Women treated when BMD T-score <1.0	-	-	-	-	-
Total MBS Costs	663,402	1,341,964	2,035,821	2,744,752	3,468,933
Total PBS Costs	2,061,824	3,962,333	5,694,443	7,251,071	8,625,131
Total OTHER cost savings	167,330	-338,494	-513,490	-692,320	-874,982
Total Costs	2,557,895	4,965,803	7,216,774	9,303,503	11,219,082
All women on AI treated	-	-	-	-	-
Total MBS Costs	514,510	1,040,770	1,578,913	2,128,721	2,690,367
Total PBS Costs	3,234,233	6,215,424	8,932,460	11,374,229	13,529,617
Total OTHER cost savings	-262,479	-530,971	-805,475	-1,085,991	-1,372,521
Total Costs	3,486,264	6,725,223	9,705,898	12,416,958	14,847,463
Bone therapy cost = zol acid	-	-	-	-	-
Total MBS Costs	865,074	1,749,927	2,654,694	3,579,156	4,523,487
Total PBS Costs	1,021,456	1,962,995	2,821,106	3,592,281	4,273,010
Total OTHER cost savings	-38,453	-77,787	-118,002	-159,098	-201,074
Total Costs	1,848,077	3,635,135	5,357,799	7,012,340	8,595,423
RR fracture is lower = 0.40	-	-	-	-	-
Total MBS Costs	865,074	1,749,927	2,654,694	3,579,156	4,523,487
Total PBS Costs	473,815	910,560	1,308,605	1,666,324	1,982,089
Total OTHER cost savings	-67,819	-137,191	-208,116	-280,596	-354,628
Total Costs	1,271,070	2,523,296	3,755,183	4,964,885	6,150,948
RR fracture is higher = 0.8455	-	-	-	-	-
Total MBS Costs	865,074	1,749,927	2,654,694	3,579,156	4,523,487
Total PBS Costs	473,815	910,560	1,308,605	1,666,324	1,982,089
Total OTHER cost savings	-17,463	-35,327	-53,590	-72,253	-91,317
Total Costs	1,321,426	2,625,160	3,909,710	5,173,227	6,414,259

AI = aromatase inhibitor, AR-DRG = Australian Related Diagnosis Relative Group, BMD = bone mineral density, DXA = dual x-ray absorptiometry, MBS = Medical Benefits Schedule, RR =relative risk, PBS= Pharmaceutical Benefits Schedule.

When more women are treated with DXA and bone therapy, the PBS costs increased markedly but the MBS costs are fewer than in the base case because there is less vitamin D testing and GP visits undertaken in a large proportion of women. The relative risk of fractures only impacts on the State hospital budget and not the MBS or PBS costs. Similarly, PBS costs are implicated when zoledronic acid is used rather than oral risedronate and are significantly higher with zoledronic acid. When the proportion of women with early stage breast cancer taking AIs changes from the base case of 81% to 95%, all costs increase

### Costs to the patient

Over-the-counter vitamin D<sub>3</sub> supplements in tablet form are widely available in Australia. There are many suppliers and as mentioned in the Background, sales of vitamin D<sub>3</sub> products have increased 122% over the past 5 years. Vitamin D<sub>3</sub> tablets are available in different pack sizes, with or without calcium, and in hard or chewable tablet forms. They are sold from chemists, health food shops, supermarkets and online pharmacy outlets.

The unit costs of common brands of vitamin D<sub>3</sub> tablets from online companies are provided in Table 32. Based on an average cost per tablet of 1000IU of vitamin D<sub>3</sub> taken once per day for 12 months, the estimated costs of taking vitamin D<sub>3</sub> and calcium tablets in women on 'lifestyle advice' is \$57.63. This assumes online purchases where recommended retail prices are often discounted.

Table 32: Unit price of common brands of Vitamin D products in Australia

Brand	Product	Tablets per pack	Price
Ostelin	Vitamin D 500 IU and Calcium – chewable	60	\$10.69
Ostelin	Vitamin D <sub>3</sub> 1000IU and calcium	60	\$13.26
Ostelin	Vitamin D <sub>3</sub> 1000IU and calcium	250	\$36.99
Swisse	Vitamin D <sub>3</sub> 1000IU and calcium	250	\$27.99
Swisse	Ultraboost Vit D and Ca	90	\$14.99
Swisse	Vitamin D <sub>3</sub> 1000IU and calcium	150	\$10.98
Blackmores	Vitamin D	200	\$29.95
Blackmores	Vitamin D <sub>3</sub> 1000IU and calcium	100	\$17.95
Blackmores	Vitamin D <sub>3</sub> 1000IU and calcium	60	\$10.99

Source: Website search accessed on 11/4/14

If DXA scans in this population are funded, patients will face a small co-payment of \$15.36 for each DXA scan received during treatment. Currently women are spending \$300-\$500 on DXA scans in addition to their overall out-of-pocket expenses for breast cancer treatment.

# Discussion

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## Is it safe?

### DXA

DXA scans are regarded as safe, non-invasive and are widely available in Australia. The main concern for DXA scans is the emission of radiation and the accumulation of radiation from multiple scans over time.

HESP advice has indicated that DXA scans are safe and use very low radiation x-ray and the x-ray emitted is highly collimated or focused with little radiation scatter. There are pencil beam, narrow angle and broad angle fan beam DXA systems available. In general, the broader the x-ray beam the higher the radiation dose to the patient.

Although, there is little evidence on the radiation safety of DXA scans, one study on patients receiving 36 DXA scans over a longer period of time confirmed the negligible quantity of total radiation emitting from repeated DXA scans (Bandirali, Lanza et al. 2013). An earlier review has also confirmed the very small amount of radiation from various DXA scanners (Njeh, Fuerst et al. 1999).

Whether there are variations in safety risk pertaining to personnel with different qualifications, training or expertise when operating the DXA equipment is currently unknown. This would be difficult to measure as errors do not solely arise from the operator (such as patient positioning and study analysis) but also from machine factors (such as calibration drift and inherent system variability), and also patient factors (such as changes in the distribution of patient weight as well as fat and soft tissue which can affect the bone density measurement). HESP have advised that DXA is safe as only very low radiation doses are used, that is, the patient receives approximately 1/10<sup>th</sup> of the radiation dose from a standard chest x-ray. There is also minimal radiation scatter affecting the operator as the x-ray beam has low energies and is highly collimated. Nevertheless, requirement of a Radiation Use licence is appropriate to ensure appropriate radiation practice despite the low radiation doses. Site accreditation is also required to ensure sites maintain high standards of practice.

### Anti-resorptive therapies for fracture prevention

In the randomised controlled trial evidence in this assessment, the common adverse events for women on anti-resorptive treatments (i.e., arthralgia, hot flushes, fatigue, myalgia, bone pain and fever) were not significantly different across treatment arms. Whether all these events are considered to be attributed to anti-resorptive therapies is difficult because some symptoms (e.g., fever, hot flushes and fatigue) are also symptoms common for AIs, breast cancer and menopause in general. Osteonecrosis of the jaw was an infrequent adverse event with most studies reporting no cases. Areas of uncertainty for anti-resorptive treatments include their:

1. Optimal dose and schedule;
2. Dose relationship with osteonecrosis of the jaw; and
3. Effect on survival and cancer recurrence.

## Is it effective?

### DXA

The primary purpose of DXA scans is to predict low BMD and evidence suggests that DXA scans do this reasonably well, better than other modalities but they are not strong at predicting who will get fractures. This is partly due to there being many additional risk factors for fractures other than low BMD. So although poor BMD is a very strong risk factor for fractures, women with low BMD will not necessarily have a fracture. The relationship between low BMD and fracture incidence is also complicated due potential behavioural changes that occur when patients learn they have low BMD. For example, patients may change their health behaviours to avoid a fracture, by reducing their physical activity (to avoid falling) or they may boost their calcium intake.

Since the predictive performance of DXA for fractures is suboptimal, formal widespread osteoporosis screening is not recommended by leading health authorities. However, there are limited options for clinicians to accurately measure BMD and currently doctors place greater weight on a DXA report than a fracture risk factor assessment (HESP advice). In women with breast cancer, many international guidelines specifically advocate DXA. For example, the NICE recommendation is:

‘Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DXA) scan to assess bone mineral density if they are starting adjuvant aromatase inhibitor treatment’

Fracture risk increases between 1.5 to 2.0 fold for every one standard deviation of BMD T-score below normal. However, despite the consistently reported link between BMD and relative fracture risk, the absolute number of fractures is low even in a high-risk population like post-menopausal women taking aromatase inhibitors.

Low BMD may be considered an important health issue in its own right without the subsequent link to osteoporosis and fractures. Observations of background BMD levels as measured by DXA and using T-scores shows a large number of women are classified with osteopenia and osteoporosis in Australia. These women are expected to have worse BMD levels with aromatase inhibitors and subsequently higher risk of fractures.

One clear advantage of DXA for determining BMD is that BMD scoring is linked directly to the WHO osteoporosis definitions and reference ranges are available for Australia. However, there is presently non-uniform use of BMD reporting in Australia and quality control of densitometers and maintenance is very important.

### Anti-resorptive therapy for fracture prevention

In relation to the population of women taking aromatase inhibitors and bone fractures as a potential adverse event, the number needed to harm is high (46 women, pooled analysis by Amir et al. 2011). This challenges the clinical need of treating all women on aromatase inhibitors with anti-resorptive therapy when so few fractures are likely to be prevented.

Age remains a strong risk factor for fractures and women with early breast cancer are mostly under age 70 (75%). Nevertheless, osteopenia, the precursor of osteoporosis is very common in younger ages. Approximately 7% of major osteoporotic fractures occur in individuals aged between 35 and 49 years (Torpy, Brennan et al. 2012). This contributes to the high lifetime fracture risk in women and men after age 50 years. Furthermore, of all

women with breast cancer, 51% are between ages 50 and 70, and 1759 will be experiencing early menopause (age 50-54 years) and rapid bone loss (ACIM books 2014). Women who are over age 45 but undergo premature menopause will not be eligible for MBS item 12313 but bone loss may be particularly important in these women.

In Australia, a recent publication on the Geelong Osteoporosis Study has shown that the incidence of fractures is declining in women. Significant reductions in hip fracture rates were observed for women: 32% for ages 75 to 84 years and 29% for ages 85 years or older (Pasco, Brennan et al. 2011). This is most likely explained, according to their analyses, to trends over time of increased body weight and obesity rates across all age groups (Pasco, Brennan et al. 2011). They also state that the increased use of bone mineralisation treatments may also be contributing to the reduced incidence.

Anti-resorptive therapies in women taking aromatase inhibitors are effective according to the evidence base. The evidence for this statement is summarised in the matrix below.

**Table 33: Completed body of evidence assessment matrix**

Body of evidence (X axis) Component (Y axis)	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	-	-	-
Consistency	-	most studies consistent and inconsistency may be explained	-	-
Clinical impact	-	-	moderate	-
Generalizability	-	population/s studied in the body of evidence are similar to the target population	-	-
Applicability	-	applicable to Australian healthcare context with few caveats	-	-

Adapted from (NHMRC 2008)

Osteoporotic medications and particularly oral bisphosphonates have been linked with poor adherence and compliance (Silverman, Schousboe et al. 2011) outside of trial settings. The reasons for this are unclear but observations of poor compliance are common to other patients where medications for chronic diseases are taken in asymptomatic patients. Stomach complaints and other adverse events have been attributed to non-compliance of bisphosphonates but other possible explanations include; the perceived lack of fracture risk and benefit of taking the medication, scepticism of the effectiveness of the medication, forgetfulness, belief that nutritional interventions (vitamin D and calcium) may be better or cost barriers. Further Australian research on the extent and nature of non-compliance is important if the potential health benefits of the intervention (DXA and bone treatment) are to be fully realised.

Table 18 shows that the evidence for aromatase-inhibitor bone loss treatments involves study populations outside Australia with the largest studies in the UK and US. Based on the average age of women in the studies (~60 years), which is the same for women

diagnosed with breast cancer in Australia, the similar doses and duration of treatments for these women, the applicability of the findings to Australian women with breast cancer is likely to be reasonable. The consistency of the findings across different populations adds support to these results.

Issues that remain as sources of uncertainty relate to clinical practice in Australia and the expected role of clinicians in performing risk assessments, the non-uniform reporting requirements of BMD analyses in practice and the frequency of DXA scans needed. There are also controversies around whether a BMD test should be personally performed by the specialist physician or by a trained operator under supervision.

An additional study on vitamin D supplements provides supplementary evidence for this application. A 2014 systematic review on the effects of vitamin D supplements on bone mineral density showed an overall small benefit at the femoral neck (weighted mean difference 0.8% 95%CI 0.2-1.4%) with moderate trial heterogeneity ( $I^2=67%$   $p<0.01$ ) (Reid, Bolland et al. 2014). The authors have concluded that widespread use of vitamin D for osteoporosis prevention in adults without specific risk factors for vitamin D deficiency is inappropriate. Further they suggest that the effects of combination calcium and vitamin D on fracture risk are similar to those for calcium alone, suggesting the negligible effect of vitamin D. The implication of this systematic review is that vitamin D supplements may be inferior to bone resorptive agents. Following on from this, vitamin D testing will be unnecessary particularly if bone medications become routinely prescribed and combined with calcium and vitamin D<sub>3</sub>.

## What are the economic considerations?

Using the conventional economic outcome of incremental cost per QALY ratios, the results of the cost-utility analysis showed that DXA and bone treatment for women with osteoporosis was strongly cost-effective and relatively stable according to one-way and probabilistic sensitivity analyses. The ICERs were driven more by cost than by treatment effect with the modelling results showing small overall QALY gains (0.3) that were relatively inexpensive. However, when assessing cost-effectiveness using fractures avoided as the main clinical outcome, the ICERs would not be considered cost-effective. This presents a conflicting result but highlights the issue that the number of fractures avoided will be small; they are a tangible patient-relevant outcome and ultimately, the purpose of the nominated intervention.

The budgetary impact also shows the small cost-savings for expected fracture prevention to the MBS budget cost over the next 5 years. Annual DXA scans may be routine in women taking aromatase inhibitors and Clinical Practice Guidelines already support this frequency. However, this is not informed by the evidence *per se*. Clearly, the frequency of DXA scans will have a strong impact on the financial costs to MBS. DXA scans will affect 30,000 women by Year 5 as they continue to have annual DXA scans for 5 years. The total MBS costs are somewhat lower if DXA scans are offered every two years, from \$13.372 million to \$10.203 million.

Currently, women are spending \$300-\$500 on DXA scans in addition to their overall out-of-pocket expenses for breast cancer treatment. Two Australian studies on the out-of-pocket expenses faced by women are now outdated but report wide ranges in patient costs. One report observed direct expenses with an interquartile range from \$563 to \$6231 using cancer patients (mostly breast cancer) receiving treatment in Townsville (data from 2006-07) (Gordon, Ferguson et al. 2009). A second population-based Queensland study reported

direct and indirect costs of \$3855 in 2005 for women aged >50 years and lymph node negative breast cancer (Gordon, Scuffham et al. 2007). The additional expenses of DXA scans without MBS funding may be seen as excessive for many women already facing other substantial costs for their cancer treatment.

# Conclusions

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## Safety

DXA scans are a non-invasive and safe procedure with no serious patient safety issues. Despite emitting radiation, the levels emitted are negligible and are observed to be similar or lower than background radiation levels.

Women with breast cancer on aromatase inhibitors and taking anti-resorptive agents have reported some adverse events such as arthralgia, hot flushes, myalgia, bone pain and fever. Some of these symptoms are also reported for aromatase inhibitors alone. In trial evidence, there are no statistically significant differences in adverse events in the intervention and comparator arms. One serious side effect, osteonecrosis of the jaw, is an infrequent occurrence.

## Effectiveness

### Impact on patient management

There is clear evidence that the risk of fractures or reduction in bone density in women on aromatase inhibitors is higher than women not taking this treatment and otherwise healthy post-menopausal women. The combined use of clinical risk factor assessment and BMD analysis provides the best prediction of fracture risk. However, although the relative risk is higher among these women, the absolute fracture risk is low and fractures are a very rare event (NNH = 46). The higher fracture risk for aromatase inhibitor users remains regardless of:

- a. prior tamoxifen or
- b. the sequencing of aromatase inhibitor and tamoxifen or
- c. aromatase inhibitor compliance rates or
- d. the type of aromatase inhibitor.

Risk of fractures and declines in bone density subside when aromatase therapy stops but may not return to baseline pre-therapy levels. Risk of bone loss caused by aromatase inhibitor therapy is independent and additional to bone loss from ovarian failure secondary to chemotherapy which subsequently causes premature menopause

The evidence consistently shows that anti-resorptive treatment significantly improves BMD in women taking aromatase inhibitors. Studies with 60 month follow-ups showed linear increases in BMD in each successive year. Positive BMD occurred regardless of whether women were treated with prior chemotherapy or prior tamoxifen. Meta-analyses for BMD lumbar spine and total hip confirmed positive mean differences between the intervention and comparator arms but study heterogeneity was problematic.

### Impact on health outcomes

Fracture incidence was lower in anti-resorptive treatment arms but the trials included in this assessment were not of sufficient power or duration to detect differences in minimal trauma fractures across treatment and comparator arms. Clinical management with the proposed intervention is more effective than clinical management without it.

## **Economic considerations**

DXA scans offered annually to women taking aromatase inhibitors and anti-resorptive treatment for those with osteoporosis (BMD T-score  $>-2.5$ ) is highly cost-effective in terms of incremental cost per QALY gain.

### **Costing**

The expected uptake of DXA scans is estimated at 5911 procedures for 5911 patients in Year 1 rising to 30,906 DXA scans for 30,906 patients in Year 5.

The total cost to the Medical Benefits Scheme for the DXA plus anti-resorptives for osteoporotic women is estimated to be \$13.372 million over the next five years.

Total cost to the Australian healthcare system including MBS for DXA plus anti-resorptives for osteoporotic women is estimated to be \$19.119 million over the next five years.

# Appendix A Health Expert Standing Panel Members and Evaluators

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## Health Expert Standing Panel Members

Member	Nomination / Expertise or Affiliation
Joseph Wong FRACP	Physician, Nuclear Medicine and Bone Densitometry, Qscan Radiology Clinics
Michael Hooper	Endocrinologist

## Evaluators

Name	Organisation
Louisa Gordon	Griffith University
Martin Downes	Griffith University
Marcin Sowa	Griffith University

# Appendix B Search strategies

Search terms were:

## Search 1

### Ovid MEDLINE Search:

1. Aromatase inhibitors.mp.
2. exp Aromatase Inhibitors/
3. Aminoglutethimide.mp.
4. exp Aminoglutethimide/
5. Testolactone.mp.
6. exp Testolactone/
7. Anastrozole.mp.
8. Letrozole.mp.
9. Exemestane.mp.
10. Vorozole.mp.
11. Formestane.mp.
12. Fadrozole.mp.
13. exp Fadrozole/
14. Hydroxyandrostenedione.mp.
15. Androstatrien.mp.
16. exp Androstatrienes/
17. Androstene.mp.
18. exp Androstenes/
19. Arimidex.mp.
20. Femara.mp.
21. Aromasin.mp.
22. Rivizor.mp.
23. Formestane.mp.
24. Lentaron.mp.
25. Afema.mp.
26. Teslac.mp.
27. ATD.mp.
28. OXO-6.mp.
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. Breast cancer.mp.
31. exp Breast Neoplasms/
32. Breast neoplasm.mp.
33. Breast neoplasia.mp.
34. mammary gland neoplasia.mp.
35. mammary gland neoplasm.mp.
36. exp Neoplasms, Hormone-Dependent/
37. ER positive cancers.mp.
38. Oestrogen receptor positive cancers.mp.
39. estrogen receptor positive cancers.mp.
40. breast carcinoma.mp.
41. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. cancer treatment induced bone loss.mp.
43. CTIBL.mp.
44. Minimal trauma fracture.mp.
45. exp Fractures, Bone/
46. Aromatase inhibitor induced bone loss.mp.
47. AIBL.mp.
48. bone fracture.mp.
49. bone loss.mp.
50. skeletal fracture.mp.
51. exp Bone Resorption/
52. Bone Resorption.mp.
53. 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54. 29 and 41 and 53
55. limit 54 to (english language and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews))

### Cochrane Library

Search Name: Risk of MTF in brca taking AI  
 Last Saved: 18/02/2014 02:10:06.154

Description: Is the proposed population (women with brca taking AIs) at greater risk of minimal trauma fracture ?

- | ID  | Search   |
|-----|--|
| #1  | MeSH descriptor: [Aromatase Inhibitors] explode all trees  |
| #2  | MeSH descriptor: [Aminoglutethimide] explode all trees   |
| #3  | MeSH descriptor: [Testolactone] explode all trees  |
| #4  | MeSH descriptor: [Fadrozole] explode all trees   |
| #5  | MeSH descriptor: [Androstatrienes] explode all trees   |
| #6  | MeSH descriptor: [Androstenedione] explode all trees   |
| #7  | Aromatase inhibitors   |
| #8  | Aminoglutethimide  |
| #9  | Testolactone   |
| #10 | Anastrozole  |
| #11 | Letrozole  |
| #12 | Exemestane   |
| #13 | Vorozole   |
| #14 | Formestane   |
| #15 | Fadrozole  |
| #16 | Hydroxyandrostenedione   |
| #17 | Hydroxyandrostenedione   |
| #18 | Androstatrien  |
| #19 | Androstene   |
| #20 | Arimidex   |
| #21 | Femara   |
| #22 | Aromasin   |
| #23 | Rivizor  |
| #24 | Formestane   |
| #25 | Lentaron   |
| #26 | Afema  |
| #27 | Teslac   |
| #28 | ATD  |
| #29 | OXO-6  |
| #30 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 |
| #31 | Breast cancer  |
| #32 | Breast neoplasm  |
| #33 | Breast neoplasia   |
| #34 | mammary gland neoplasia  |
| #35 | mammary gland neoplasm   |
| #36 | Hormone Dependent Neoplasms  |
| #37 | ER positive cancers  |
| #38 | Oestrogen receptor positive cancers  |
| #39 | estrogen receptor positive cancers   |
| #40 | breast carcinoma   |
| #41 | MeSH descriptor: [Breast Neoplasms] explode all trees  |
| #42 | MeSH descriptor: [Neoplasms, Hormone-Dependent] explode all trees  |
| #43 | #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42   |
| #44 | cancer treatment induced bone loss   |
| #45 | CTIBL  |
| #46 | Minimal trauma fracture  |
| #47 | Aromatase inhibitor induced bone loss  |
| #48 | AIBL   |
| #49 | bone fracture  |
| #50 | bone loss  |
| #51 | skeletal fracture  |
| #52 | Bone Resorption  |
| #53 | MeSH descriptor: [Fractures, Bone] explode all trees   |
| #54 | MeSH descriptor: [Bone Resorption] explode all trees   |
| #55 | #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54  |
| #56 | #30 and #43 and #55  |

### CRD

- #### Risk of MTF in brca taking AI
- 1 (Aromatase inhibitors) IN DARE, NHSEED, HTA
  - 2 (Aminoglutethimide) IN DARE, NHSEED, HTA
  - 3 (Testolactone) IN DARE, NHSEED, HTA

4 (Anastrozole) IN DARE, NHSEED, HTA  
5 (Letrozole) IN DARE, NHSEED, HTA  
6 (Exemestane) IN DARE, NHSEED, HTA  
7 (Vorzole) IN DARE, NHSEED, HTA  
8 (Formestane) IN DARE, NHSEED, HTA  
9 (Fadrozole) IN DARE, NHSEED, HTA  
10 (Hydroxyandrostenedione) IN DARE, NHSEED, HTA  
11 (Androstatrien) IN DARE, NHSEED, HTA  
12 (Androstene) IN DARE, NHSEED, HTA  
13 (Arimidex) IN DARE, NHSEED, HTA  
14 (Femara) IN DARE, NHSEED, HTA  
15 (Aromasin) IN DARE, NHSEED, HTA  
16 (Rivizor) IN DARE, NHSEED, HTA  
17 (Formestane) IN DARE, NHSEED, HTA  
18 (Lentaron) IN DARE, NHSEED, HTA  
19 (Afema) IN DARE, NHSEED, HTA  
20 (Teslac) IN DARE, NHSEED, HTA  
21 (ATD) IN DARE, NHSEED, HTA  
22 (OXO-6) IN DARE, NHSEED, HTA  
23 MeSH DESCRIPTOR Aromatase Inhibitors EXPLODE  
ALL TREES  
24 MeSH DESCRIPTOR Aminoglutethimide EXPLODE  
ALL TREES  
25 MeSH DESCRIPTOR Testolactone EXPLODE ALL  
TREES  
26 MeSH DESCRIPTOR Fadrozole EXPLODE ALL TREES  
27 MeSH DESCRIPTOR Androstatrienes EXPLODE ALL  
TREES  
28 MeSH DESCRIPTOR Androstenes EXPLODE ALL  
TREES  
29 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8  
OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR  
#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23  
OR #24 OR #25 OR #26 OR #27 OR #28  
30 (Breast cancer) IN DARE, NHSEED, HTA  
31 (Breast neoplasm) IN DARE, NHSEED, HTA  
32 (Breast neoplasia) IN DARE, NHSEED, HTA  
33 (mammary gland neoplasia) IN DARE, NHSEED, HTA  
34 (mammary gland neoplasm) IN DARE, NHSEED, HTA  
35 (Hormone Dependent Neoplasms) IN DARE, NHSEED,  
HTA  
36 (ER positive cancers) IN DARE, NHSEED, HTA  
37 (Oestrogen receptor positive cancers) IN DARE, NHSEED,  
HTA  
38 (estrogen receptor positive cancers) IN DARE, NHSEED,  
HTA  
39 (breast carcinoma) IN DARE, NHSEED, HTA  
40 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL  
TREES  
41 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36  
OR #37 OR #38 OR #39 OR #40  
42 (cancer treatment induced bone loss) IN DARE, NHSEED,  
HTA  
43 (CTIBL) IN DARE, NHSEED, HTA  
44 (Minimal trauma fracture) IN DARE, NHSEED, HTA  
45 (Aromatase inhibitor induced bone loss) IN DARE,  
NHSEED, HTA  
46 (AIBL) IN DARE, NHSEED, HTA  
47 (bone fracture) IN DARE, NHSEED, HTA  
48 (bone loss) IN DARE, NHSEED, HTA  
49 (skeletal fracture) IN DARE, NHSEED, HTA  
50 (Bone Resorption) IN DARE, NHSEED, HTA  
51 MeSH DESCRIPTOR Bone Resorption EXPLODE ALL  
TREES  
52 #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48  
OR #49 OR #50 OR #51  
53 #29 AND #41 AND #52

## Search 2

### Ovid Medline:

1. FRAX.mp.
2. osteoporosis screening.mp.
3. QFracture.mp.
4. risk of fragility fracture.mp.

5. fracture risk assessment.mp.
6. clinical assessment.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Dual-energy X-ray absorptiometry.mp.
9. exp Absorptiometry, Photon/  
DXA.mp.
10. DEXA.mp.
11. DEXA.mp.
12. 8 or 9 or 10 or 11
13. 7 and 12
15. limit 13 to (english language and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews))

### Cochrane Library

Search Name: DXA vs Clinical assessment

Last Saved: 19/02/2014 23:44:26.451

### Description:

- |     |   |
|-----|---|
| ID  | Search  |
| #1  | Dual-energy X-ray absorptiometry                            |
| #2  | MeSH descriptor: [Absorptiometry, Photon] explode all trees |
| #3  | DXA.mp  |
| #4  | DEXA  |
| #5  | #1 or #2 or #3 or #4  |
| #6  | FRAX  |
| #7  | osteoporosis screening                                      |
| #8  | clinical assesment  |
| #9  | QFracture   |
| #10 | risk of fragility fracture                                  |
| #11 | fracture risk assessment                                    |
| #12 | #6 or #7 or #8 or #9 or #10 or #11                          |
| #13 | #5 and #12  |

### CRD

- 1 (Dual-energy X-ray absorptiometry )
- 2 MeSH DESCRIPTOR Absorptiometry, Photon EXPLODE  
ALL TREES
- 3 (DXA)
- 4 (DEXA)
- 5 #1 OR #2 OR #3 OR #4
- 6 (FRAX)
- 7 (osteoporosis screening)
- 8 (QFracture)
- 9 (risk of fragility fracture)
- 10 (clinical assessment)
- 11 #6 OR #7 OR #8 OR #9 OR #10
- 12 #5 AND #11

## Search 3

### Ovid Medline:

1. risedronate.mp.
2. ibandronate.mp.
3. zoledronic.mp.
4. exp Diphosphonates/  
Bisphosphonates.mp.
5. alendronate.mp.
6. Denosumab.mp.
7. strontium ranelate.mp.
8. exp Bone Density Conservation Agents/  
exp Raloxifene/  
Raloxifene.mp.
9. exp Teriparatide/  
Teriparatide.mp.
10. anti-resorptive.mp.
11. Fosamax.mp.
12. Actonel.mp.
13. Atelvia.mp.
14. disodium.mp.
15. Didronel.mp.
16. clodronate.mp.
17. BONEFOS.mp.
18. ibandronic acid.mp.
19. Bonviva.mp.
20. Zometa.mp.
21. Zomera.mp.
22. Aclasta.mp.

27.	Reclast.mp.	#6	Bisphosphonates
28.	selective estrogen receptor modulator.mp.	#7	alendronate
29.	SERM.mp.	#8	Denosumab
30.	Prolia.mp.	#9	strontium ranelate
31.	Xgeva.mp.	#10	MeSH descriptor: [Bone Density Conservation Agents]
32.	carbamazepine.mp.		explode all trees
33.	parathyroid hormone.mp.	#11	Raloxifene
34.	Protelos.mp.	#12	MeSH descriptor: [Raloxifene] explode all trees
35.	Protos.mp.	#13	Teriparatide
36.	calcitriol.mp.	#14	anti-resorptive
37.	exp Selective Estrogen Receptor Modulators/	#15	Fosamax
38.	exp Carbamazepine/	#16	Actonel
39.	exp Parathyroid Hormone/	#17	Atelvia
40.	exp Calcitriol/	#18	disodium
41.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	#19	Didronel
42.	Aromatase inhibitors.mp.	#20	clodronate
43.	exp Aromatase Inhibitors/	#21	MeSH descriptor: [Clodronic Acid] explode all trees
44.	Aminoglutethimide.mp.	#22	BONEFOS
45.	exp Aminoglutethimide/	#23	ibandronic acid
46.	Testolactone.mp.	#24	Bonviva
47.	exp Testolactone/	#25	Zometa
48.	Anastrozole.mp.	#26	Zomera
49.	Letrozole.mp.	#27	Aclasta
50.	Exemestane.mp.	#28	Reclast
51.	Vorozole.mp.	#29	selective estrogen receptor modulator
52.	Formestane.mp.	#30	MeSH descriptor: [Selective Estrogen Receptor Modulators]
53.	Fadrozole.mp.		explode all trees
54.	exp Fadrozole/	#31	SERM
55.	Hydroxyandrostenedione.mp.	#32	Prolia
56.	Androstatrien.mp.	#33	Xgeva
57.	exp Androstatrienes/	#34	carbamazepine
58.	Androstene.mp.	#35	MeSH descriptor: [Carbamazepine] explode all trees
59.	exp Androstenes/	#36	parathyroid hormone
60.	Arimidex.mp.	#37	MeSH descriptor: [Parathyroid Hormone] explode all trees
61.	Femara.mp.	#38	Protelos
62.	Aromasin.mp.	#39	Protos
63.	Rivizor.mp.	#40	calcitriol
64.	Formestane.mp.	#41	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or
65.	Lentaron.mp.	#42	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or
66.	Afema.mp.	#43	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or
67.	Teslac.mp.	#44	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or
68.	ATD.mp.	#45	#37 or #38 or #39 or #40
69.	OXO-6.mp.	#46	MeSH descriptor: [Aromatase Inhibitors] explode all trees
70.	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69	#47	MeSH descriptor: [Aminoglutethimide] explode all trees
71.	Breast cancer.mp.	#48	MeSH descriptor: [Testolactone] explode all trees
72.	exp Breast Neoplasms/	#49	MeSH descriptor: [Fadrozole] explode all trees
73.	Breast neoplasm.mp.	#50	MeSH descriptor: [Androstatrienes] explode all trees
74.	Breast neoplasia.mp.	#51	MeSH descriptor: [Androstenedione] explode all trees
75.	mammary gland neoplasia.mp.	#52	Aromatase inhibitors
76.	mammary gland neoplasm.mp.	#53	Aminoglutethimide
77.	exp Neoplasms, Hormone-Dependent/	#54	Testolactone
78.	ER positive cancers.mp.	#55	Anastrozole
79.	Oestrogen receptor positive cancers.mp.	#56	Letrozole
80.	estrogen receptor positive cancers.mp.	#57	Exemestane
81.	breast carcinoma.mp.	#58	Vorozole
82.	71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81	#59	Formestane
83.	41 and 70 and 82	#60	Fadrozole
84.	limit 83 to (english language and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews))	#61	Hydroxyandrostenedione
		#62	Hydroxyandrostenedione
		#63	Androstatrien
		#64	Androstene
		#65	Arimidex
		#66	Femara
		#67	Aromasin
		#68	Rivizor
		#69	Formestane
		#70	Lentaron
		#71	Afema
		#72	Teslac
		#73	ATD
			OXO-6
			#42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or
			#50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or
			#59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or
			#68 or #69 or #70
			#72 Breast cancer
			#73 Breast neoplasm

**Cochrane**

Search Name: Stage 2 search  
Last Saved: 20/02/2014 01:57:27.540  
Description:

ID	Search
#1	risedronate:ti,ab,kw (Word variations have been searched)
#2	ibandronate
#3	zoledronic
#4	Diphosphonates
#5	MeSH descriptor: [Diphosphonates] explode all trees

#74 Breast neoplasia  
 #75 mammary gland neoplasia  
 #76 mammary gland neoplasm  
 #77 Hormone Dependent Neoplasms  
 #78 ER positive cancers  
 #79 Oestrogen receptor positive cancers  
 #80 estrogen receptor positive cancers  
 #81 breast carcinoma  
 #82 MeSH descriptor: [Breast Neoplasms] explode all trees  
 #83 MeSH descriptor: [Neoplasms, Hormone-Dependent]  
 explode all trees  
 #84 #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or  
 #80 or #81 or #82 or #83  
 #85 #41 and #71 and #84

**CRD**

1 (Breast cancer)  
 2 (Breast neoplasm)  
 3 (Breast neoplasia)  
 4 (mammary gland neoplasia)  
 5 (mammary gland neoplasm)  
 6 (Hormone Dependent Neoplasms)  
 7 (ER positive cancers)  
 8 (Oestrogen receptor positive cancers)  
 9 (estrogen receptor positive cancers)  
 10 (breast carcinoma)  
 11 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL  
 TREES  
 12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8  
 OR #9 OR #10 OR #11  
 13 (risedronate)  
 14 (ibandronate)  
 15 (zoledronic)  
 16 MeSH DESCRIPTOR Diphosphonates EXPLODE ALL  
 TREES  
 17 (Diphosphonates)  
 18 (Bisphosphonates)  
 19 (alendronate)  
 20 (Denosumab)  
 21 (strontium ranelate)  
 22 MeSH DESCRIPTOR Bone Density Conservation Agents  
 EXPLODE ALL TREES  
 23 (Raloxifene)  
 24 MeSH DESCRIPTOR Raloxifene EXPLODE ALL TREES  
 25 (Teriparatide)  
 26 (anti-resorptive)  
 27 (Fosamax)  
 28 (Actonel)  
 29 (Atelvia)  
 30 (disodium)  
 31 (Didronel)  
 32 (clodronate)  
 33 (BONEFOS)  
 34 (ibandronic acid)  
 35 (Bonviva)  
 36 (Zometa)  
 37 (Aclasta)  
 38 (Reclast)  
 39 (selective estrogen receptor modulator)  
 40 MeSH DESCRIPTOR Selective Estrogen Receptor  
 Modulators EXPLODE ALL TREES  
 41 (SERM)

42 (Prolia)  
 43 (Xgeva)  
 44 (carbamazepine)  
 45 MeSH DESCRIPTOR Carbamazepine EXPLODE ALL  
 TREES  
 46 (parathyroid hormone)  
 47 MeSH DESCRIPTOR Parathyroid Hormone EXPLODE  
 ALL TREES  
 48 (Protelos)  
 49 (Protos)  
 50 (calcitrol)  
 51 (Zomera)  
 52 (Aromatase inhibitors)  
 53 (Aminoglutethimide)  
 54 (Testolactone)  
 55 (Anastrozole)  
 56 (Letrozole)  
 57 (Exemestane)  
 58 (Vorzole)  
 59 (Formestane)  
 60 (Fadrozole)  
 61 (Hydroxyandrostenedione)  
 62 (Androstatrien)  
 63 (Androstene)  
 64 (Arimidex)  
 65 (Femara)  
 66 (Aromasin)  
 67 (Rivizor)  
 68 (Formestane)  
 69 (Lentaron)  
 70 (Afema)  
 71 (Teslac)  
 72 (ATD)  
 73 (OXO-6)  
 74 MeSH DESCRIPTOR Aromatase Inhibitors EXPLODE  
 ALL TREES  
 75 MeSH DESCRIPTOR Aminoglutethimide EXPLODE ALL  
 TREES  
 76 MeSH DESCRIPTOR Testolactone EXPLODE ALL  
 TREES  
 77 MeSH DESCRIPTOR Fadrozole EXPLODE ALL TREES  
 78 MeSH DESCRIPTOR Androstatrienes EXPLODE ALL  
 TREES  
 79 MeSH DESCRIPTOR Androstenes EXPLODE ALL  
 TREES  
 80 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19  
 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR  
 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34  
 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR  
 #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49  
 OR #50 OR #51)  
 81 (#52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58  
 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR  
 #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73  
 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79)  
 82 #12 AND #80 AND #81

**Search 4**

1. Cost terms (title field)
  - a. cost\*
  - b. economic evaluation
2. Add all Search 3 terms above

# Appendix C Studies included in the review

## Study profiles of included studies on safety and effectiveness

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
Bell 2007 Australia	NHMRC Level III-3 POOR	Cross-study comparison, modelled the risk of anastrozole therapy	Healthy post-menopausal women, all women with breast cancer, women with breast cancer on anastrozole, women with breast cancer on tamoxifen Aged 64-69 (from ATAC)	All women with breast cancer Anastrozole Tamoxifen Healthy controls	None stated. Selected three large prospectively designed clinical studies: 1. NSABP-P 2. WHI 3. ATAC	RR of bone fracture RR of bone fracture for women taking anastrozole or tamoxifen were modelled/calibrated	5 years Treatment was 5 years duration
Goss 2013 Canada	NHMRC Level II MEDIUM	Phase III RCT open-label	7,576 women, median age 64 years, 4.1 years follow up	Exemestane vs anastrozole	Incl: HR+ breast cancer, postmeno, ECOG <=2, adequately excised Excl: metastatic, history of other cancer, prior tamoxifen	Event-free survival Osteoporosis Osteopenia (and others)	4.1 years median follow up
Kalder 2013 Germany	NHMRC Level III MEDIUM	Sub-study of RCT	63 women, 180 in RCT core study, matched pair analysis compliant vs non compliant, postmeno brca	Anastrozole compliant (≥80%) vs anastrozole non-compliant	Incl: HR+ breast cancer, postmeno, post surgery, radio or chemotherapy	% BMD Lumbar spine (baseline to 24 mths)	24 months
Neuner 2011 USA	NHMRC Level III MEDIUM	Population based prospective cohort of community dwelling women	2,748 women diagnosed with breast cancer in 2003, aged ≥65 yrs, 28% had initial tamoxifen therapy first, 28% initial AI (87% on anastrozole) Women at high risk of fractures	AI Tamoxifen No hormone therapy	Incl: incident breast cancer in 2003, in health maintenance org, Medicare claims database	Hip fractures Non-vertebrae fractures Time to event analyses	36 months
Eastell 2011 UK	NHMRC Level II MEDIUM	Phase III RCT – bone sub-study	60 Post-menopausal women with breast cancer who were participants of ATAC trial	Anastrozole Tamoxifen Combined	Incl: ATAC trial participants not with recurrence, not osteoporotic at 5 yrs, evaluable 5-yr bone scans. Excl: those taking bisphosphonates	Median % change in lumbar spine and total hip BMD from 5 to 7 years	7 years

## Study profiles of included systematic reviews

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intvn/ comparison	Conclusions/recommendation	Quality assessment
Amir 2011	Systematic review and meta-analysis of randomized trials that compared toxicity of aromatase inhibitors and tamoxifen as primary adjuvant hormone therapy in post-menopausal women with breast cancer	Search methods: Publications from 1996 to Apr 2010 were selected from MEDLINE, EMBASE and other electronic databases.  <i>Studies were included</i> if: they were randomized Phase III trials, early stage women with breast cancer, they had treatment duration of 5 years, post-menopausal women only	Mean age range years  Intervention/Comparator: Three cohorts: 1. 5 years Als vs 5 years tamoxifen 2. 2-3 years tamoxifen plus 2-3 years Als vs 5 years tamoxifen 3. 2-3 years tamoxifen plus 2-3 years Als vs 5 years Als  Statistics:	7 studies included enrolling 30,023 patients  Switching from tamoxifen to Als is the best balance between efficacy and toxicity.  There was no difference in the odds of cerebrovascular disease, other second cancer or death without breast cancer recurrence between strategies.	HIGH QUALITY Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? Yes Were the methods of the study appraisal reproducible? Yes Were sources of heterogeneity explored? No Was a summary of the main results clear and appropriate? Yes
<p>Meta-analysis pooled results: 7 Studies included: ATAC, BIG 1-98, ABCSG8/ARNO, IES, ITA, N-SAS BC03, TEAM</p> <p>Cardiovascular disease: Increased odds with longer use of Als OR 1.26 (95%CI: 1.1, 1.43) p&lt;0.001 NNH 132 Bone fractures: Increased odds with longer use of Als OR 1.47 (95%CI: 1.34, 1.61) p&lt;0.001 NNH 46 Venous thrombosis: Decreased odds with AI use OR 0.55 (95%CI: 0.46, 0.64) p&lt;0.001 NNH 79 Venous thrombosis: Decreased odds with AI use OR 0.34 (95%CI: 0.22, 0.53) p&lt;0.001 NNH 258</p> <p>Authors conclusions: Switching from tamoxifen to Als may be the best strategy to reduce toxicity and maximise effectiveness. Tamoxifen and Als have different toxicity profiles. Limitations: Studies had different duration of follow up, quality of AEs was variable in the studies included, data was not available on baseline host factors or use of concurrent medications – therefore potential confounding is an issue, AEs included all types not SAEs which may be more relevant</p>					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intvn/ comparison	Conclusions/recommendation	Quality assessment
Becker 2012	Systematic review of randomized trials that assessed adverse bone outcomes after aromatase inhibitors as primary adjuvant hormone therapy in post-menopausal women with breast cancer	<p>Search methods: Publications to Apr 2011 were selected from MEDLINE and EMBASE.</p> <p><i>Studies were included</i> if: they were randomized Phase III trials, early stage women with breast cancer - post-menopausal women only</p> <p><i>Outcomes:</i> bone fractures, bone turnover makers, BMD</p>	<p>Mean age range 59.9 to 65 years Median follow up: 24 to 100 months 11 Studies</p> <p><b>Intervention/Comparator:</b> Single therapy groups only- AIs for early stage breast cancer in post-menopausal women. AI vs Tamoxifen or Placebo</p>	<p>In the 4 bone sub-studies of large trials, there were statistically significant increases in:</p> <ol style="list-style-type: none"> <li>bone markers observed in AI arms of trials over 2 years.</li> <li>change in BMD % in spine and hip in AI groups.</li> </ol> <p>Fractures were significantly higher in women taking AIs but not statistically significant in NSAS BC-03, ATAC, IES. Statistically sign in ATAC, BIG I-98, ABCSG, IES. ATAC is largest: 9.3% letrozole vs 6.5% tamox p=0.002</p>	<p>HIGH QUALITY</p> <p>Was the research question specified? Yes</p> <p>Was the search strategy explicit and comprehensive? Yes</p> <p>Were the eligibility criteria explicit and appropriate? Yes</p> <p>Was a quality assessment of included studies undertaken? Yes</p> <p>Were the methods of the study appraisal reproducible? Yes</p> <p>Were sources of heterogeneity explored? No</p> <p>Was a summary of the main results clear and appropriate? Yes</p>
<p><b>Meta-analysis pooled results:</b> No pooled results. Fracture rates in trials were 1.5 times higher in women taking AI compared to not. Participants differed on baseline risk of fractures.</p> <p><b>Authors conclusions:</b> Bone markers, BMD and fractures are worse for women with early breast cancer treated with aromatase inhibitors compared with tamoxifen or placebo. The worse bone outcomes holds irrespective of treatment sequencing, follow-up time or type of AI.</p> <p><b>Limitations:</b> Studies had different duration of follow up, quality of AEs was variable in the studies included, data was not available on baseline risk factors for fractures – therefore potential confounding is an issue, AEs included all types not SAEs which may be more relevant. Little information on age on bone outcomes in studies – age is the strongest predictor of fractures.</p>					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intvn/ comparison	Conclusions/recommendation	Quality assessment
Edwards 2011	Systematic review of non-randomized trial evidence of adverse bone outcomes after cancer therapy in women with breast cancer	<p>Search methods: Publications 1998 to 2008 were selected from FDA's Adverse Event Reporting System, MEDLINE and PubMed.</p> <p><i>Studies were included</i> if: they were case reports, case series, adverse event databases</p> <p><i>Outcomes:</i> bone fractures, bone turnover makers, BMD</p>	<p>Intervention/Comparator:</p> <p>Statistics:</p>	<p>226 cases in FDA AERS of fractures associated with breast cancer therapy.</p> <p>77/228 (29%) were hip or femur fractures.</p> <p>AI were the most common therapy associated with fractures n=149 or 65%</p> <p>78 fractures were in younger women &lt;=64 years</p>	<p>POOR QUALITY</p> <p>Was the research question specified? Yes</p> <p>Was the search strategy explicit and comprehensive? Yes</p> <p>Were the eligibility criteria explicit and appropriate? No</p> <p>Was a quality assessment of included studies undertaken? No</p> <p>Were the methods of the study appraisal reproducible? Yes</p> <p>Were sources of heterogeneity explored? No</p> <p>Was a summary of the main results clear and appropriate? Yes</p>
<p>Meta-analysis pooled results:  No pooled results.  Fracture rates in trials were more common in women taking AI compared to other breast cancer therapies.</p> <p><b>Authors conclusions:</b> Fractures occur in women with early breast cancer treated with aromatase inhibitors compared to other treatments. Evidence outside of trial.</p> <p><b>Limitations:</b> Low data quality regarding reporting accuracy and completeness of reports.</p>					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Test comparison	Conclusions/recommendation	Quality assessment
Marshall 1996	To assess how well measures of BMD predict occurrence of osteoporotic fractures	<p>Search methods: Publications after 1985 were selected from Medline, EMBASE, SweMed, reference lists, known grey literature.</p> <p>Studies were included if BMD was by absorptiometry (single or dual energy, photon or x ray) QCT, QMRI or QUS, English language.</p> <p>Included: prospective cohort studies and case control studies (women with fractures to age-matched controls)</p>	<p>Mean age range: NS Women only, 90,000 person years, 2000 fractures</p> <p>Test: BMD measurements Comparator: None</p> <p>Follow-up duration: Range 1.8 to 24 years, weighted average 5.8 years ORs and RR were assumed equal.</p>	<p>BMD measurements predict fracture risk but not individuals who will have a fracture.</p> <p>Screening menopausal women for osteoporosis is not recommended</p>	<p>MEDIUM QUALITY</p> <p>Was the research question specified? Yes</p> <p>Was the search strategy explicit and comprehensive? Yes</p> <p>Were the eligibility criteria explicit and appropriate? No</p> <p>Was a quality assessment of included studies undertaken? Yes</p> <p>Were the methods of the study appraisal reproducible? No</p> <p>Were sources of heterogeneity explored? No</p> <p>Was a summary of the main results clear and appropriate? Yes</p>
<p>Meta-analysis pooled results:</p> <p>RR fractures all sites 1.5 (95%CI: 1.4, 1.6) except:</p> <p>RR spine fractures 2.3 (95%CI: 1.9, 2.8)</p> <p>RR hip fractures 2.6 (95%CI: 2.0, 3.5)</p> <p>No association between RR for dec BMD 1 sd and length of follow up.</p> <p>Sensitivity = 38% (at 1 SD) Specificity = 88%, PPV =36%</p> <p>Authors conclusions: BMD is a predictor of fracture risk irrespective of duration of follow up. No sub-group analysis or discussion on between BMD measurement methods.</p>					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Test comparison	Conclusions/recommendation	Quality assessment
Lim 2009	To assess evidence for the harms and benefits of osteoporosis screening.  Overview provided for clinical fracture risk tools, modalities of screening  American College of Preventive Medicine Position Statement	Search methods: PubMed, websites of leading health organisation, references, English language prior to Sept 2008	No RCTs exist for screening on fracture outcomes.  Clinical risk factor tools as detailed below.	Indirect evidence from prospective studies demonstrate that decreased BMD strongly predicts fractures.	POOR QUALITY Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? No Was a quality assessment of included studies undertaken? No Were the methods of the study appraisal reproducible? No Were sources of heterogeneity explored? No Was a summary of the main results clear and appropriate? Yes
<p><b>Unpooled results:</b>  Osteoporosis Self-assessment screening Tool (OST) Sensitivity = 88-92% Specificity = 37-52%, in women aged <math>\geq 45</math> years (better discriminative ability than ORAI or SCORE)  Osteoporosis risk assessment tool (ORAI) Sensitivity = 94.4% Specificity = 41.4%  Simple Calculated Osteoporosis Risk Estimation Score (SCORE) Sensitivity = 93.6% Specificity = 43.3%  Osteoporosis Index of Risk (OSIRIS) Sensitivity = 78.5% Specificity = 51.4%  WHO fracture-risk algorithm (FRAX)  WHI fracture risk calculator  Osteoporosis Society of Canada and the Canadian Association of Radiologists</p> <p><b>Authors conclusions:</b> DXA is the most widely used and accepted method of BMD measurement. Studies on the harms related to radiation exposure from repeated DXA scans are lacking. Screening for osteoporosis should be performed with DXA if available and not more frequently than every 2 years. Risk assessment tools may be useful supplements to BMD assessment because they provide the absolute fracture risk based on population cohort studies and they can be used when DXA is not available.</p>					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Test comparison	Conclusions/recommendation	Quality assessment
Kanis 2007	To assess the performance of clinical risk factors and BMD predict occurrence of osteoporotic fractures in men and women	<p>Search methods: Authors collated primary data from 9 population based studies and validated in 11 independent population cohorts</p> <p>Studies were included Primary cohorts: EVOS/EPOS, CaMos, Rochester, Rotterdam, DOES, Gothenburg II, Hiroshima, Sheffield, Gothenburg I.</p> <p>Validation cohorts: THIN, SOF, York, Geelong I, Geelong II, OPUS, PERF, EPIDOS, Miyama, SEMOF, WHI.</p>	<p>Mean age range: Primary cohort: 65 years Total n=46,340, 68% women, 850 hip &amp; 3318 other fractures</p> <p>Intvn: BMD + clinical risk factors Comparator: BMD alone or clinical risk factors alone</p> <p>Follow-up duration: 189,852 person years</p>	Use of clinical risk factors enhance BMD measurement by DXA in the prediction of hip and other osteoporotic fractures	<p>MEDIUM QUALITY</p> <p>Was the research question specified? Yes</p> <p>Was the search strategy explicit and comprehensive? n/a</p> <p>Were the eligibility criteria explicit and appropriate? n/a</p> <p>Was a quality assessment of included studies undertaken? Yes</p> <p>Were the methods of the study appraisal reproducible? Yes</p> <p>Were sources of heterogeneity explored? Yes</p> <p>Was a summary of the main results clear and appropriate? Yes</p>
<p><b>Meta-analysis pooled results:</b> Gradient of risk = increase in fracture risk per SD increase in risk score.</p> <p>Hip fracture (50 year old): BMD alone - GR 3.68 (95%CI: 2.61, 5.19) Clinical risk factors alone - GR 2.05 (95%CI: 1.58, 2.65) Both - GR 4.23 (95%CI: 3.12, 5.73)</p> <p>Other osteoporotic fractures (50 year old): BMD alone - GR 1.19 (95%CI: 1.05, 1.34) Clinical risk factors alone - GR 1.41 (95%CI: 1.28, 1.56) Both - GR 1.44 (95%CI: 1.30, 1.59)</p> <p><b>Authors conclusions:</b> Integrated BMD plus clinical risk factors better predicts fracture risk. Both are useful alone. Absolute fracture risk cannot be provided with data unless further calibration occurs.</p>					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Test comparison	Conclusions/recommendation	Quality assessment
Rud 2007	To assess the performance of the Osteoporosis Self-Assessment Tool versus DXA BMD measurements via systematic review	<p>Search methods: Publications up to 2005 were selected from PubMed, Web of Science, citation lists conference proceedings, EMBASE, SweMed, reference lists, known grey literature.</p> <p>Studies were included if they assessed performance of OST in peri or post-menopausal women (mean age <math>\geq</math> 45 years). BMD of any of : femoral neck, total hip, lumbar spine</p>	<p>36 studies, n =72315 women, median sample size 780.</p> <p>Test: OST Comparator: DXA</p> <p>Follow-up duration: Range 1.8 to 24 years, weighted average 5.8 years ORs and RR were assumed equal.</p>	<p>Clinical usefulness of OST is uncertain. It could be used to rule out femoral neck T-score <math>\leq</math> -2.5.</p> <p>Quality of studies according to QUADAS assessment was generally low.</p> <p>Heterogeneity between studies was high.</p>	<p>HIGH QUALITY</p> <p>Was the research question specified? Yes</p> <p>Was the search strategy explicit and comprehensive? Yes</p> <p>Were the eligibility criteria explicit and appropriate? Yes</p> <p>Was a quality assessment of included studies undertaken? Yes QUADAS used</p> <p>Were the methods of the study appraisal reproducible? Yes</p> <p>Were sources of heterogeneity explored? Yes</p> <p>Was a summary of the main results clear and appropriate? Yes</p>
<p><b>Meta-analysis pooled results:</b>  Range depending on BMD location:  White women: T score <math>\leq</math>-2.5 sensitivity 84-92% specificity 34-40%  Asian women: T score <math>\leq</math>-2.5 sensitivity 82-91% specificity 40-64%  White women: T score <math>\leq</math>-2.0 sensitivity 82-88% specificity 36-44%</p> <p>Likelihood Ratio of a Negative Test - White women: any region overall 0.37 (95%CI:0.27, 0.51) <math>I^2=88\%</math> Asian women: any region overall 0.29 (95%CI: 0.23, 0.37) <math>I^2=41\%</math></p> <p><b>Authors conclusions:</b> The evidence is of generally low quality to support the clinical usefulness of OST in ruling out low BMD indicating osteoporosis</p>					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, intervention comparison	Conclusions/recommendation	Quality assessment
Martyn St James & Carroll 2009	To assess the effects of differing impact exercise protocols on post-menopausal bone loss at the hip and spine.  Systematic review and meta-analysis. 15 trials were included, randomised allocation in 10 trials	Search methods: Publications up to Mar 2008 were selected from MEDLINE, EMBASE and other electronic databases. Additional references from 1986 to end March 2008 were searched for manually inselected peer-reviewed journals along with reference lists of other exercise reviews in the area reference lists of articles identified for inclusion and web searches  Studies were included if: they involved interventions of any exercise protocol that included any ground reaction force generating impact activity such as running or jumping-type movements where both feet leave contact with the ground.	Median years post menopause 5.2 years. Total n=442 exercise and n=250 non-exercise controls  Intervention: impact exercise protocols Comparator: Placebo  Outcomes: Total hip, femoral neck and lumbar spine BMD via DXA or other radiographic technique. (BMD g/cm <sup>2</sup> )  Caucasian women predominantly recruited and one Japanese study. Women did not take hormone replacement therapy in 7 trials	Mixed loading exercise programmes combining jogging with other low-impact loading activity and programmes mixing impact activity with high-magnitude exercise as resistance training appear effective in reducing post-menopausal bone loss at the hip and spine.	HIGH QUALITY Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? Yes Were the methods of the study appraisal reproducible? Yes Were sources of heterogeneity explored? Yes Was a summary of the main results clear and appropriate? Yes
<p>Meta-analysis pooled results:</p> <p>Impact protocols that included jogging mixed with walking and stair climbing, and protocols that incorporated impact exercise with high-magnitude loading (resistance exercises), were effective at lumbar spine (weighted mean difference (random effects) 0.025 g/cm(2) 95% CI (0.004 to 0.046) and 0.016 g/cm(2) 95% CI (0.005 to 0.027); p = 0.02 and p = 0.005 respectively), although heterogeneity was evident (I(2) = 88% and I(2) = 73%, where I(2) measures the extent of inconsistency among the trials).</p> <p>Effects on femoral neck BMD following these types of protocols were significant (weighted mean difference (fixed effect) 0.022 g/cm(2) 95% CI (0.014 to 0.030); p&lt;0.001 and 0.005 g/cm(2) 95% CI (0.001 to 0.010); p = 0.03 respectively). High-impact only and odd-impact only protocols were ineffective in increasing BMD at any site.</p> <p>Authors conclusions: Exercise in the form of jogging combined with other low impact activity such as walking or stair climbing and programs combining different impact (high/low) has a positive effect on preserving bone mineral density. Well designed and safe programs should be organised for post-menopausal women.</p>					

# Appendix D Assessment of economic evaluation studies

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) assessment of economic evaluations

No.	CHEERS criteria	Ito 2012	Logman 2010	Mueller 2009
1	Identifies the study as an economic evaluation in title and interventions described	✓ p.1468	✓ p.1529	✓ p.1106
2	Provides a structured summary of objectives, perspective, setting, methods (study design and inputs) results (base case and uncertainty analyses and conclusions.	✓ p.1468	✓ p.1529	✓ p.1106
3	Provides an explicit statement of the broader context of the study. Presents the study question and its relevance for health policy or practice decisions	✓ p.1468	✓ p.1529	✓ p.1106
4	Describes characteristics of the base case population and subgroups analysed and why they were chosen	✓ p.1469	✓ p.1530	✓ p.1107
5	States relevant aspects of the system in which the decision needs to be made	x	✓ p.1530	x
6	Describes the perspective of the study and relates this to the costs being evaluated	✓ p.1469	✓ p.1530	✓ p.1106-7
7	Describes the interventions or strategies being compared and state why they were chosen.	✓ p.1469	✓ p.1530	✓ p.1106-7
8	States the time horizon over which costs and consequences are being evaluated and says why appropriate	partial, p.1469	✓ p.1530	✓ p.1108
9	Reports the choice of discount rate(s) used for costs and outcomes and says why	partial, p.1469	✓ p.1531	partial, p.1108
10	Describes what outcomes were used as the measures of benefit and relevance for analysis	✓ p.1470	✓ p.1530	✓ p.1108
11	a) Single-study – describes fully the design features and why single study was sufficient for clinical effectiveness b) Synthesis-based – describes the methods used for identification of included studies and synthesis of clinical effectiveness data	n/a ✓ p.1469-70	n/a ✓ p.1530-31	n/a ✓ p.1108
12	If applicable, describes the population and methods used to elicit preferences for outcomes	✓ p.1470	Partial, p.1531	✓ p.1109
13	a) Single-study – describes fully the approaches to estimate resource use, valuation methods and any adjustments made b) Synthesis-based – describes the methods used for resource use associated with model health states, valuation and adjustments made	n/a ✓ p.1470	n/a ✓ p.1531	n/a
14	Reports the dates of the estimated resource quantities and unit costs, year reported for unit costs, methods for converting costs into a common currency base and exchange rate	✓ p.1470	✓ p.1531	✓ p.1108
15	Describes and gives reasons for the specific type of decision analytic model used. Illustration is highly recommended.	✓ p.1470, fig 1	✓ p.1531, fig 1	✓ p.1108, Fig 2
16	Describes all structural or other assumptions underpinning the decision-analytical model.	✓ p.1469-71	✓ p.1530-1532	✓ p.1108-10
17	Describes all analytical methods supporting the evaluation (methods dealing with skewed, missing or censored data, extrapolation methods, pooling data and any adjustments) and methods for handling population heterogeneity and uncertainty.	✓ p.1471	✓ p.1531-1532	✓ p.1108-10

No.	CHEERS criteria	Ito 2012	Logman 2010	Mueller 2009
18	Reports the values, ranges, references and if used probability distributions used for all parameters. Reports reasons or sources for distributions used to represent uncertainty. A table showing these is highly recommended	✓ p.1470 Table 1	✓ p.1531, Tables 2-4	✓ Tables 2-3 p.1111-12
19	Reports the mean values for each intervention, mean values for main categories of costs and outcomes as well as mean differences between comparator groups and incremental cost effectiveness ratio if relevant	✓ Tables 2-3, p. 1471	✓ Table 5	✓ p.1113
20	<p>a) Single study-based economic evaluation: Describes and effects of sampling uncertainty for the incremental cost and effectiveness estimates and impact of any assumptions</p> <p>b) Model-based economic evaluation: Describes the effects on the results of uncertainty for all input parameters, and related to structure of model and assumptions</p>	n/a  ✓ 1-way, Table 4, p.1472	n/a  ✓ p.1532, Fig 2	n/a  ✓ p.1113-15
21	If applicable, reports differences in costs, outcomes, input parameters that can be explained by variations between subgroups of patients with different baseline characteristics	n/a	n/a	✓ p.1113
22	Summarises key study findings and describes how they support the conclusions reached. Discussed limitations and generalisability of the findings and how they fit with current knowledge	✓ p.1472-3	✓ p.1533-1534	✓ p.1114-15
23	Source of funding and role of funder in study. Describes other non-monetary support	✓ p.1473 none	✓ Novartis	✓ p.1115 none
24.	Describes any potential for conflict of interest of study contributors in accordance with journal policy	✓ p.1473 none	✓ several	x

# Appendix E Existing Systematic Reviews and HTA reports

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Amir, E., B. Seruga, S. Niraula, L. Carlsson and A. Ocana (2011). "Toxicity of adjuvant endocrine therapy in post-menopausal breast cancer patients: a systematic review and meta-analysis." Journal of the National Cancer Institute **103**(17): 1299-1309.

Becker, T., L. Lipscombe, S. Narod, C. Simmons, G. M. Anderson and P. A. Rochon (2012). "Systematic review of bone health in older women treated with aromatase inhibitors for early-stage breast cancer." Journal of the American Geriatrics Society **60**(9): 1761-1767.

Hailey, D., L. Sampietro-Colom, D. Marshall, R. Rico, A. Granados and J. Asua (1998). "The effectiveness of bone density measurement and associated treatments for prevention of fractures. An international collaborative review." Int J Technol Assess Health Care. **14**(2): 237-254.

Homik, J. and D. Hailey (1999) "Selective testing with bone density measurement (Structured abstract)." Health Technology Assessment Database.

Kanis, J. A., A. Oden, O. Johnell, H. Johansson, C. De Laet, J. Brown, P. Burckhardt, C. Cooper, C. Christiansen, S. Cummings, J. A. Eisman, S. Fujiwara, C. Gluer, D. Goltzman, D. Hans, M. A. Krieg, A. La Croix, E. McCloskey, D. Mellstrom, L. J. Melton, 3rd, H. Pols, J. Reeve, K. Sanders, A. M. Schott, A. Silman, D. Torgerson, T. van Staa, N. B. Watts and N. Yoshimura (2007). "The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women." Osteoporos Int. **18**(8): 1033-1046. Epub 2007 Feb 1024.

Marshall, D., O. Johnell and H. Wedel (1996) "Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures (Structured abstract)." Bmj **312**, 1254-1259.

# Appendix F Excluded studies

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## Wrong publication type

1. Bertoldo F, Pancheri S, Zenari S, Boldini S. Emerging drugs for the management of cancer treatment induced bone loss. *Expert Opin Emerg Drugs*. 2010;15(2):323-42.
2. Hadji P, Aapro MS, Body JJ, Bundred NJ, Brufsky A, Coleman RE, et al. Management of aromatase inhibitor-associated bone loss in post-menopausal women with breast cancer: practical guidance for prevention and treatment. *Ann Oncol*. 2011;22(12):2546-55.
3. Screening for osteoporosis to prevent fractures (Structured abstract). Health Technology Assessment Database [Internet]. 1992; (1):[12 p.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-31995000029/frame.html>.
4. Brufsky A, Harker WG, Beck JT, Carroll R. Zoledronic acid (ZA) effectively inhibits cancer treatment-induced bone loss (CTIBL) in post-menopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (Let): 12 mos BMD results of the Z-FAST trial. *J Clin Oncol* [Internet]. 2005; 23(16 Suppl):[12s p.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/915/CN-00613915/frame.html>.
5. Ellis GK, Bone HG, Chlebowski RT, Paul D, Spadafora S, Smith J, et al. Subgroup analysis of a randomized, phase III study of the effect of denosumab in women with nonmetastatic breast cancer receiving aromatase inhibitor (AI) therapy [abstract no. 546]. *Journal of Clinical Oncology: ASCO annual meeting proceedings* [Internet]. 2008; 26:[17 p.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/346/CN-00776346/frame.html>.
6. Fox KR. Adding zoledronic acid to endocrine therapy in the adjuvant treatment of hormone-sensitive breast cancer in pre-menopausal women: a new care standard or a provocative idea? *Curr Oncol Rep*. 2010;12(1):1-3.
7. Frassoldati A, Brufsky A, Bundred N, Lambert-Falls R, Hadji P, Mena R, et al. The effect of zoledronic acid on aromatase inhibitor (AI) associated bone loss (AIBL) in post-menopausal women (PMW) with early breast cancer (EBC) receiving adjuvant letrozole: 24 months (MOS) integrated follow-up of the z-fast/zo-fast trials [Abstract No. 185PD]. *Ann Oncol* [Internet]. 2009; 19(Supplement 8):[78 p.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/399/CN-00784399/frame.html>.
8. Gnant M, Mlineritsch B, Schnippinger W, Luschin EG, Poestlberger S, Menzel C, et al. Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in pre-menopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12 [abstract no. LBA4]. *Journal of Clinical Oncology : ASCO annual meeting proceedings* [Internet]. 2008; 26:[6 p.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/747/CN-00652747/frame.html>.
9. Green AD, Colon-Emeric CS, Bastian L, Drake MT, Lyles KW. Does this woman have osteoporosis? (Structured abstract). *Jama* [Internet]. 2004; 292(23):[2890-900 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12005008071/frame.html>.

10. Hans DB, Kanis JA, Baim S, Bilezikian JP, Binkley N, Cauley JA, et al. Joint Official Positions of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(). Executive Summary of the 2010 Position Development Conference on Interpretation and use of FRAX in clinical practice. *J Clin Densitom.* 2011;14(3):171-80.
11. Johansson C, Johnell O, Jonson R, Lhunghall S, Marke LA, Marshall D, et al. Bone density measurement (Structured abstract). *Health Technology Assessment Database [Internet].* 1995; (1). Available from: <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-31996008270/frame.html>.
12. Lester J, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R, et al. Use of monthly oral ibandronate to prevent anastrozole-induced bone loss during adjuvant treatment for breast cancer: Two-year results from the ARIBON study [abstract no. 554]. *Journal of Clinical Oncology: ASCO annual meeting proceedings [Internet].* 2008; 26:[19 p.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/882/CN-00776882/frame.html>.
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# Glossary and abbreviations

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AI	aromatase inhibitors
AIHW	Australian Institute of Health and Welfare
ANZBMS	Australian and New Zealand Bone Mineral Society
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
ARTG	Australian Register of Therapeutic Goods
BCNA	Breast Cancer Network Australia
BMD	bone mineral density
BMI	body mass index
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CT	computerised tomography
Protocol	decision-analytic protocol
DXA	dual x-ray absorptiometry
ECOG	Eastern Cooperative Oncology Group
FRAX	Fracture Assessment
HESP	Health Expert Standing
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
MBS	Medical Benefits Schedule
MSAC	Medical Services Advisory Committee
MTF	minimal trauma fracture
NHMRC	National Health and Medical Research Council
NHS	National Health Service
OST	Osteoporosis Self-Assessment Tool
PASC	Protocol Assessment Sub-Committee
PBS	Pharmaceutical Benefits Schedule
QCT	Quantitative Computerised Tomography
QUS	Quantitative Ultrasound
RACGP	Royal Australian College of General Practitioners
RANKL	Receptor activator of nuclear factor kappa-B ligand
SERM	selective estrogen-receptor modulator
SMD	standardised mean difference
WHO	World Health Organisation

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