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Horizon Scanning Report

Quantitative ultrasound (QUS)

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Table of Contents

Tables

Figures

Executive Summary

Osteoporosis is a skeletal disorder that is characterised by compromised bone strength, which in turn may predispose an individual to an increased risk of bone fracture. Measurement of bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) is currently used to clinically diagnose osteoporosis. The World Health Organization defines osteoporosis on the basis of BMD using T-scores calculated from DXA measurements taken at the proximal femur and spine. BMD can be determined by peak bone mass and amount of bone loss. Factors which may contribute to the rate of bone loss include menopause in women, increasing age, low physical activity levels, some medications, certain medical conditions such as inflammatory bowel disease and coeliac disease, smoking and alcohol consumption. Osteoporosis is most commonly diagnosed after a fracture has occurred.

Although DXA is considered the gold standard for the diagnosis of osteoporosis it is not recommended to be used as a mass screening tool. The *sensitivity* of the T-score generated from BMD measurement by DXA at predicting fracture risk is low.

Quantitative ultrasound (QUS) is also intended to identify those individuals who may be at risk of experiencing a bone fracture. Once at-risk individuals have been identified, a DXA scan should be performed to establish a diagnosis of osteoporosis and to instigate appropriate treatment.

QUS uses high frequency soundwaves, which are transmitted through bone to measure the quality and strength of the bone. QUS devices may use several parameters to estimate BMD including speed of sound and broadband ultrasound attenuation. QUS measurements may be used to calculate a QUS T-score (patients with a T-score of $\leq$ -1 are considered to be at high risk of fracture), however this can not be compared to a T-score attained with DXA.

Heel QUS is currently offered by some pharmaceutical outlets with the cost of the test borne entirely by the consumer. QUS does not currently have a Medicare Benefits Schedule number.

None of the studies included in this assessment reported any adverse events associated with the use of quantitative ultrasound. QUS does not expose patients to ionising radiation and is therefore considered a safe technology.

QUS may be used to diagnose osteoporosis, or more correctly, to stratify patients according to their risk of fracture. However, results may vary according to the QUS parameter used, the type of device and the skeletal site tested.

A poor quality meta-analysis of nine studies found that QUS had a moderate sensitivity and a low specificity at predicting osteoporosis, according to the DXA reference standard. The sensitivity and specificity of QUS will vary depending on the cut-off level used.

A good quality meta-analysis of prospective cohort studies reported on the use of QUS to *predict* risk of fracture. It would appear that QUS measurements are

associated with fracture risk in older women and that QUS may be a valid alternative to DXA to assess fracture risk at non-spinal sites.

Studies included to assess the effectiveness of QUS at monitoring osteoporotic patients on medication highlighted inconsistencies associated with the use of QUS. QUS may offer the ability to monitor patients more frequently without exposure to ionising radiation, however a longer monitoring time period may be necessary before any effect of medication is noted.

A cost-effectiveness study was conducted describing the use of QUS as an alternative to DXA as a screening method for osteoporosis. QUS appears to be slightly more cost-effective than screening *all women* with DXA. However, DXA screening of all women is not recommended practice in Australia or New Zealand.

In summary, quantitative ultrasound devices suffer from a lack of standardisation. There is a lack of consensus regarding which of the diagnostic parameters should be used and there is variation in the skeletal site used in diagnosis. However, results from this assessment indicate that QUS may be a reasonable test for identifying osteoporosis. It may also be a valid alternative to DXA to assess fracture risk at non-spinal sites, especially in older women. There is conflicting evidence, however, that QUS could be used to guide therapy for osteoporotic patients.

It must be reiterated that all of studies included in this assessment used DXA as the reference standard for an osteoporotic diagnosis. However, DXA itself is an imperfect reference standard and has low sensitivity for predicting fracture risk. It is entirely possible that a false positive QUS test, according to DXA, could still in fact predict fracture risk.

The Australia and New Zealand Bone and Mineral Society and Osteoporosis Australia do not recommend the use of heel ultrasound as a routine screening tool to measure bone strength or to predict an individual's risk of fracture.

Reduction in bone mineral density occurs in osteoporosis. The current gold standard for measurement of bone mineral density and diagnosis of osteoporosis is Dual Energy

X-ray Absorptiometry (DXA). Mass screening by DXA is not recommended as the test has a low sensitivity for predicting fracture risk. Quantitative ultrasound measures attenuation of sound waves through bone to assess bone quality and density.

While quantitative ultrasound may be an alternative means of assessing risk of fracture at sites other than the spine, it is less sensitive than DXA at predicting osteoporosis and its reliability in monitoring therapy is unclear. Lack of standardisation of the devices, variation in parameters measured and assessment of different body parts means that results from quantitative ultrasound are unreliable. This may change with increased standardisation. It is a safe, relatively mobile technique and may prove useful in remote locations in assessing risk of fracture in an individual, however at present it has not proven robust. It is not useful to monitor bone status in an individual and is not recommended for general use in testing for bone density at this time.

Introduction

The National Horizon Scanning Unit, AHTA, School of Population Health and Clinical Practice, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of ultrasound for the assessment of bone fracture risk.

Several companies manufacture quantitative ultrasound bone absorptiometers for use amongst individuals deemed at risk of fracture. In Australia, heel quantitative ultrasound for the assessment of risk of fracture is currently offered in selected pharmaceutical outlets.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of the use of quantitative ultrasound to assess the risk of bone fracture, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with quantitative ultrasound for the assessment of bone fracture risk.

Background

Description of the technology

The procedure

Quantitative ultrasound (QUS) is considered a safe technology as it does not expose patients to ionising radiation, unlike the diagnostic modality considered to be the gold standard for osteoporosis testing, dual X-ray absorptiometry (DXA). In addition, the units tend to be small and portable, making testing for osteoporosis in community settings or rural and remote areas feasible (Figure 1) (Singer 2006).

Although an increasing body of literature has reported using the finger phalanges or the tibia as measurement sites, the most common site used in the diagnosis of osteoporosis with QUS is the calcaneus or heel (Homik & Hailey 1998).

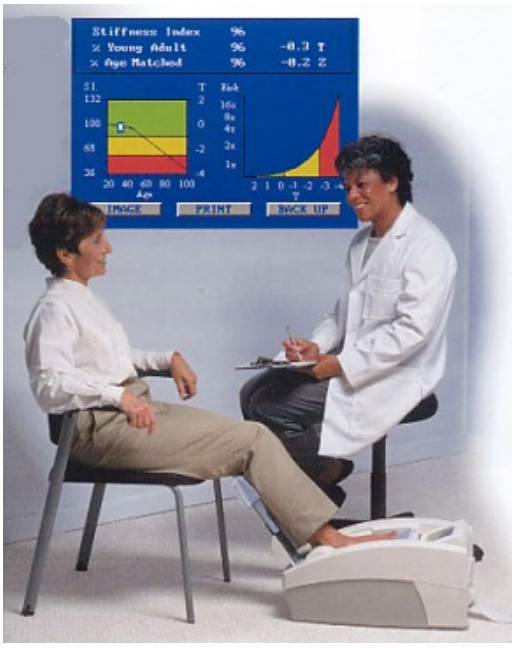


Figure 1 An example of a QUS unit (Medicus International 2006)

QUS uses high frequency soundwaves (between 0.1 and1.0 MHz[1]) that are produced and detected by piezoelectric transducers. The transducers must make good acoustical contact with the skin over the bone being tested. Different QUS devices use a variety of mechanisms to achieve this including wet methods, where the foot is immersed in a water bath, or dry methods, where there is direct contact of the transducers with the bone, with the use of coupling gel or pads to facilitate contact (Figure 2) (Homik & Hailey 1998; Lewiecki et al 2006).

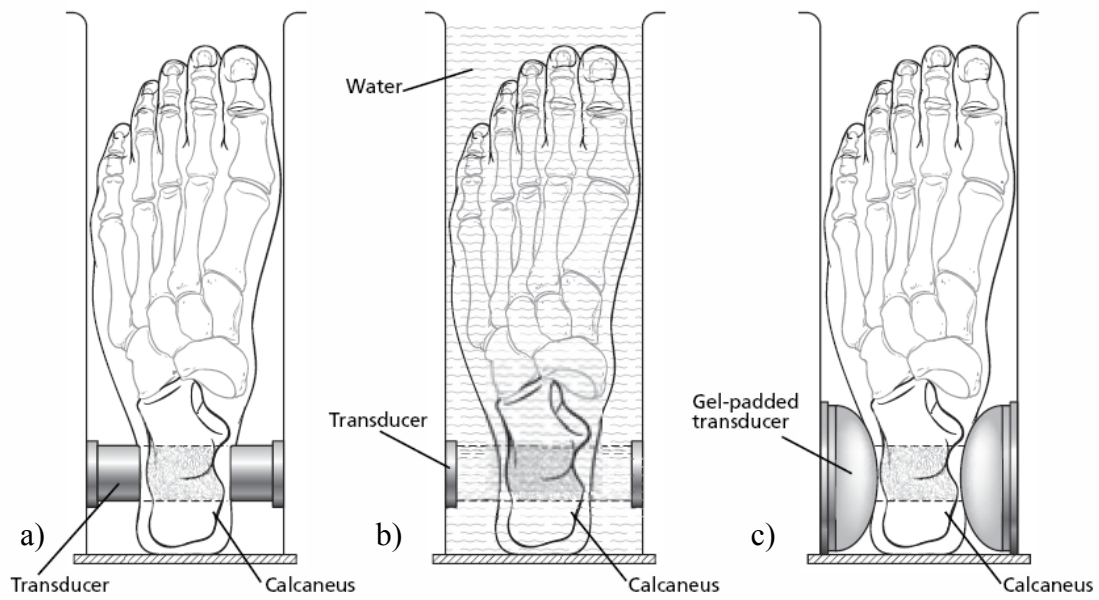


Figure 2 Quantitative ultrasound of the heel. Some devices bring the transducer into direct contact with the foot (a), others utilise a water bath to transmit sound waves (b) and others use gel-padded transducers (c) (Lewiecki et al 2006)

[1] MHz = megahertz

QUS uses the attenuation of sound waves, and the time taken for sound waves to transmit through bone as they pass through peripheral skeletal sites to measure bone characteristics. As described above, the transducers are placed close to a bone such as the heel, with little soft tissue overlying it. One of the transducers emits an ultrasound wave. During passage through the bone, the speed and amplitude of the ultrasound wave is attenuated with the changes detected by the second transducer (Boehm & Link 2004; Homik & Hailey 1998; Link & Majumdar 2003). Many commercial QUS devices measure the time taken for sound waves to travel between the two transducers, referred to as 'speed of sound' or SOS reported as m/second[2]. The rate of ultrasound attenuation, or loss of energy, over a given frequency range is referred to as the rate of 'broadband ultrasound attenuation' or BUA and is reported as decibels per megahertz (dB/MHz). The attenuation of sound waves is reduced when there is an increase in the number of attenuating elements, in this case the number of trabeculae in bone[3] (Lewiecki et al 2006; Link & Majumdar 2003). BUA therefore correlates with the physical density of the bone being measured (Homik & Hailey 1998). Studies have demonstrated that the speed of sound is reduced and broadband ultrasound attenuation is decreased with reductions in bone density and trabecular number, correlating to a diagnosis of osteopenia or osteoporosis (Link & Majumdar 2003).

The speed of sound and broadband ultrasound attenuation may be used to *estimate* bone mineral density (BMD) but can not be compared to a T-score attained with dual-energy x-ray absorptiometry (DXA) (see section on Treatment Alternatives) as these technologies are measuring different properties of bone (Lewiecki et al 2006). QUS measurements may be used to calculate a QUS T-score (which is different from the DXA T-score), which may vary with the QUS device used (Frost et al 2000). The risk of fracture utilising QUS T-scores is outlined in Table 1.

Table 1 Recommendations for DXA testing post-QUS (Lewiecki et al 2006)

QUS T-Score	Risk of fracture	Is DXA required?
≥ +1	Low	No, unless risk factors present
-1 < and > + 1	Intermediate	Yes
≤ -1.0	High	Yes

There are a number of differences between commercially available QUS machines which make comparison of data difficult. These differences include

[2] The speed of sound through bone ranges from 3,000-3,600 m/second in cortical bone and from 1,650-2,300 m/second in trabecular bone Lewiecki, E. M., Richmond, B. & Miller, P. D. (2006). 'Uses and misuses of quantitative ultrasonography in managing osteoporosis', *Cleveland Clinic Journal Of Medicine,* 73 (8), 742-+..

[3] The skeleton consists of two types of bone tissue: cortical and trabecular bone. Cortical bone is compact and forms the outer shell which covers the skeleton. Trabecular bone forms the inner part of the skeleton, and has more bone cells and is replaced faster than cortical bone. The percentage of cortical and trabecular bone varies depending on the bone in question. The centre of long bones consist of almost all cortical bone, whereas 75% of the vertebrae are trabecular bone SBU (2003). *Osteoporosis – Prevention, Diagnosis and Treatment: A Systematic Review,* The Swedish Council on Technology Assessment in Health Care, Stockholm, Sweden..

the use of different frequencies, different transducers as well as the measurement of different skeletal regions (Lewiecki et al 2006).

Intended purpose

Bones are constantly being constructed and reconstructed during the normal process of bone metabolism. This occurs through the activity balance of osteoclasts, cells which break down bone tissue, and osteoblasts, cells which build bone by mineralising tissue. This process is regulated by local endocrine factors and when the system is in balance the skeleton is maintained (SBU 2003). However, when there is an over-activity of osteoclasts or decreased activity of osteoblasts net bone loss occurs and structural damage results, as demonstrated in Figure 3 (Inzerillo & Zaidi 2002). With increasing age the production of oestrogen declines in women. In men and women, the production of bone constructive hormones and the formation of vitamin D in the kidneys both decrease with age. These factors combined with a decrease in physical activity with age which may lead to a loss of bone tissue in the elderly (SBU 2003).

Osteoporosis is a skeletal disorder that is characterised by compromised bone strength, which in turn may predispose an individual to an increased risk of bone fracture. In this context bone strength refers to a combination of both bone density and bone quality. Bone mineral density (BMD) is expressed as grams of mineral per area or volume (usually g/cm^2) and can be determined by peak bone mass and amount of bone loss. Bone quality refers to the architecture of the bone, biological bone turnover, cell viability, matrix composition and damage accumulation, such as micro-fractures. As BMD accounts for approximately 70 per cent of bone strength and can be more easily measured, bone strength and therefore osteoporosis is defined in terms of BMD (Boehm & Link 2004; Link & Majumdar 2003).

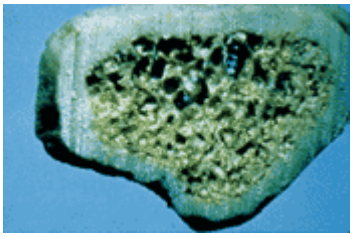
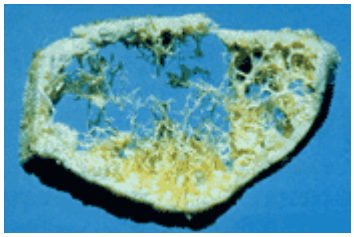
(a)  (b) 

Figure 3 **Cross section of normal (a) versus osteoporotic bone (b) (Osteoporosis Australia 2003)**

QUS is intended to identify those individuals who may be at risk of experiencing a bone fracture. Once at-risk individuals have been identified, a DXA scan should be performed to establish a diagnosis of osteoporosis and to instigate appropriate treatment. Depending on the individual risk profile, medication may be prescribed to prevent fracture. Pharmaceutical options include calcium or vitamin D supplements, bisphosphonates, selective oestrogen receptor modulators, oestrogen and calcitonin. To successfully prevent fractures therapy should be commenced at the earliest stage of disease and therefore early detection is of utmost importance (Boehm & Link 2004).

Clinical need and burden of disease

According to the Australian 2004-05 National Health Survey, approximately 585,785 people (3%) had a diagnosis of osteoporosis based on self-reported data, however these figures are likely to be an under-estimate of the true prevalence. Of these, an estimated 79 per cent were aged 55 years or over. There were four times as many women reporting a diagnosis of osteoporosis compared to men (AIHW 2007). Osteoporosis is most commonly diagnosed after a fracture has occurred. The cross-sectional Geelong Osteoporosis Study estimated that 90 out of every 1,000 females aged 50-54 years have a low bone mineral density (BMD) in the hip, spine or mid-forearm. This number increased to 380 per 1,000 females aged 60-64 years; 560 per 1,000 females aged 65-69 years and 870 per 1,000 females aged 80 years or older (AIHW 2005). Osteoporosis was reported as the main disabling condition in approximately 50,000 people aged 35 years or over in 2003 and it is one of the most common causes of disability in Australia (AIHW 2007).

Osteoporosis increases the risk of bone fractures. These occur with minimal trauma. Osteoporotic fractures are associated with a decreased quality of life and high health costs. Approximately 70 per cent of vertebral fractures are clinically undetected and many fractures of this type occur without symptoms. Conversely, non-vertebral fractures are painful. In particular, hip fractures cause a high degree of debilitation with 80 per cent of patients experiencing limitations to normal daily activities. In addition, 60 per cent of patients have difficulty with at least one essential activity of daily living, and approximately 40 per cent do not regain their former independence and have a permanent disability (AIHW 2005). A 2005 cross-sectional study of 3,071 patients from 105 Australian general practitioners reported 5.5 per cent (95% CI [4.2, 6.9]) had a current or previous osteoporotic fracture(s) (Britt et al 2007). A 24 per cent mortality rate within 12 months has been reported for hip fracture in Australia, which is approximately five times the mortality rate in an age-matched group without hip fracture (AIHW 2005).

The Geelong Osteoporosis Study group investigated the number of fractures that occur in a population of postmenopausal woman. This long running epidemiological study was conducted in the Geelong region which has a total urban and rural population of 220,000. During a two-year period 1,224 women aged ≥50 years experienced fracture at a rate of two per cent per annum. Eleven, 20, 33 and 36 per cent of these fractures occurred in women aged 50-59, 60-69, 70-79 and >80 years, respectively. Fractures of the hip were the most common (26%), followed by vertebral fractures (19%). Of those women with a fracture, only 56 per cent had a diagnosis of osteoporosis. The number of women with a fracture *and* osteoporosis was lowest in those aged 50-59 years and steadily increased with age 60-69 years (46%), 70-79 years (59%) and >80 years (69%) (Sanders et al 2006).

National data for the incidence of osteoporosis are unavailable. The Australian Institute of Health and Welfare (AIHW) suggests that there are approximately 51-73,000 new cases of osteoporotic fracture each year based on three prospective studies ascertaining osteoporotic fracture risk (AIHW 2005).

Osteoporosis is not a common principal diagnosis in regards to hospital separations. In 2003-04, osteoporosis accounted for 6,892 separations in

patients aged 55 years or older in Australian public and private hospitals. During this same period, there were 4,222 separations for fracture as a principal diagnosis, with osteoporosis as a secondary diagnosis, with an average length of stay of 13.9 days. The AIHW reported that approximately 64,000 hospital separations occur each year for bone fractures in people aged 55 years and over, with a large proportion due to osteoporosis (AIHW 2005).

In 2003, the age-standardised death rate for osteoporosis (listed as the underlying cause) was 3.9 per 1,000 persons and was listed as an additional cause for 1,303 deaths in patients aged 55 years and older. The death rate increased with age. Since 1999 there have been large increases in the age-specific death rates (32.9%) of osteoporosis in people aged 85 years and older (AIHW 2006).

The Medicare Benefits Schedule (MBS) lists several item numbers for bone densitometry testing, using either DXA or quantitative computerised tomography. In the year 2006 – 2007 there was a total of 178,118 of these services provided in the private sector, which may give an indication of the need for QUS.

The number of individuals who may benefit from screening with QUS in Australia, using age as a screening criteria, are summarised in Table 2 (ABS 2008).

Table 2 Estimated resident population of Australia in 2006 by age

Age in years	Females	Males	Total
55-59	634,836	636,723	1,271,559
60-64	491,775	496,072	987,847
65-69	393,943	385,226	779,169
70-74	326,360	302,778	629,138
75-79	299,330	252,158	551,488
80-84	239,328	166,000	405,328
85-89	138,933	75,405	214,338
90-94	61,649	24,167	85,816
95-99	15,091	4,305	19,396
>100	1,981	460	2,441

The 2002-03 New Zealand National Health Survey reported that one in 42 (2.4%) adults had a diagnosis of osteoporosis (2.9% females and 0.7% males) (MoH 2004). There are currently a lack of reliable incidence data for osteoporosis in New Zealand. In 1994, 2,276 women sustained a hip fracture and this number was predicted to rise to 3,500 in 2011 (Coney 2002). The risk of sustaining a fracture in the following year exceeded 0.5 per cent for women aged > 75 years in women and men aged> 80 years. This risk exceeds one per

cent from the age of 80 and 85 years in women and men, respectively (NZGG 2003). The lifetime risk of osteoporotic fracture in New Zealand has been estimated at 56 and 29 per cent for women and men aged 60 years and over, respectively (Davidson et al 2001).

Risk factors for osteoporosis

Bone mineral density (BMD) is affected by the peak bone density reached at adulthood and the rate of bone loss thereafter. Peak bone density is influenced by genetics, diet (in particular calcium, vitamin D and protein intake), and body mass index. Other factors which may contribute to the rate of bone loss include menopause in women, increasing age, low physical activity levels, some medications, certain medical conditions such as inflammatory bowel disease and coeliac disease, smoking and alcohol consumption (AIHW 2005; WHO Scientific Group on the Prevention and Management of Osteoporosis 2000).

Age is one of the major risk factors for osteoporosis. The Australian population is ageing, with the proportion of the population aged ≥65 years increasing. Based on 2004 figures, the Australian Bureau of Statistics predicts that the proportion of the population aged ≥65 years will increase by approximately 28 per cent by the year 2051. The number of people aged ≥65 years was approximately 2.6 million in 2004. This number is predicted to increase to 4.6 million by 2021, and 7-9 million by 2051. Additionally, life expectancy is predicted to continue increasing, although at a slower rate of increase than in previous years (Australian Bureau of Statistics 2006). Ageing of the population will increase the demand for osteoporosis screening and treatment.

Physical activity levels are relatively low in older Australians, with over a third of the population aged 55 years and older in 2001 reporting a sedentary lifestyle (AIHW 2005). Physical activity, particularly weight bearing activity, not only helps reduce bone loss but also improves balance and coordination, thereby reducing the risk of falling.

Although the reduction in oestrogen that occurs with menopause causes accelerated bone loss in women, the risks associated with oestrogen replacement therapy are now believed to outweigh the benefits and so it is not recommended as a preventive measure for osteoporosis (AIHW 2005).

Stage of development

Several quantitative ultrasound systems (bone absorptiometer) are listed on the Australian Register of Therapeutic Goods including: GE Healthcare Australia ARTG 98149, Hologic Sahara distributed by Insight Oceana Pty Ltd ARTG 114028 and McCue QUS distributed by Inderlec Medical Systems ARTG 117461

Heel QUS is currently offered by some pharmaceutical outlets with the cost of the test borne entirely by the consumer. QUS does not currently have a Medicare Benefits Schedule number. This may not be a deterrent to uptake as an Australian study has indicated that more than half of the women included in their study would be prepared to pay for screening using QUS (Naunton et al 2006).

The Australia and New Zealand Bone and Mineral Society and Osteoporosis Australia do not recommend the use of heel ultrasound as a routine screening tool to measure bone strength or to predict an individual's risk of fracture (ANZBMS 2008).

Treatment Alternatives

Existing comparators

Measurement of bone mineral density (BMD) is currently used to clinically diagnose osteoporosis. The World Health Organization defines osteoporosis on the basis of BMD using T-scores calculated from the non-invasive technique, dual energy x-ray absorptiometry (DXA) of the proximal femur and spine.

Two measures are taken from the projection image of the bone produced by the X-rays: (i) area bone density (g/cm^2); and (ii) bone mineral content (BMC) (g) (Kazakia & Majumdar 2006). BMD can be used to estimate the risk of fracture, with hip BMD being the best predictor of hip fracture risk, and hip and spine BMDs being equally useful for predicting vertebral fracture (Dunfield et al 2007).

The T-scores that are calculated are expressed in terms of standard deviations below that of a young, healthy female adult reference population. A BMD that is more than 2.5 standard deviations below that of a normal healthy population is defined as osteoporosis (Table 3) (AIHW 2005; Link & Majumdar 2003).

Table 3 World Health Organization definition of osteoporosis (Link & Majumdar 2003)

BMD T-Score (standard deviations)	Definition
>-1	Normal
<-1, >-2.5	Osteopenia
<-2.5	Osteoporosis
<-2.5 and osteoporotic fractures	Severe Osteoporosis

BMD = bone mineral density

The *sensitivity* of the T-score generated from BMD measurement by DXA at predicting fracture risk is low, as evidenced by the National Osteoporosis Risk Assessment longitudinal study of 140,000 women followed for 12 months. Although 2,259 new fractures were reported, only 6.4 per cent of these women had a reported baseline T-score of -2.5 standard deviations or less (Briot & Roux 2005). A 2003 systematic review reported that the accuracy estimates of DXA ranges from 3-9 per cent and precision estimates from 0.5-3 per cent (SBU 2003).

DXA can be applied at: (i) the lumbar spine; (ii) proximal femur; and (iii) peripheral sites such as the distal radius (wrist) and calcaneous (heel). The advantages and disadvantages of DXA for measuring BMD are summarised in Table 4 (Kazakia & Majumdar 2006).

Table 4 Advantages and disadvantages of DXA for measuring BMD

Advantages	Disadvantages
Low dose radiation	Does not distinguish between cortical and trabecular bone
Ease of use	Does not differentiate between changes due to bone geometry and bone density
Rapid measurement	Inaccuracies can occur due to variable soft tissue density and osteoarthritis of the spine
Many body parts	Limited accessibility

(Dunfield et al 2007; Kazakia & Majumdar 2006; SBU 2003)

Although DXA is considered the gold standard for the diagnosis of osteoporosis it is not used as a mass screening tool. DXA machines are large, require a dedicated room and a qualified radiology technician trained in reading DXA results (MacLaughlin et al 2005). Rural populations are unlikely to have access to DXA. Studies have shown that in the United States only 25 per cent of post-menopausal women have access to BMD testing and it has been postulated that this situation would be similar in Australia (Naunton et al 2006).

Another method used to assess BMD is quantitative computer tomography (QCT) which involves passing X-rays through the object to a detector. Rotation around the object produces a set of measurements that are used to generate a three-dimensional data set. Calibration measurements are applied to convert the data to mineral density, producing a volumetric BMD (g/cm^3). Measurements for clinical purposes are mainly taken from the lumbar spine. This technique enables assessment of bone density and geometry, unlike DXA and QUS, facilitating a greater understanding of the causes of any changes. QCT provides true density and can assess the difference between cortical and trabecular bone separately and the results of QCT are not affected by degenerative disease. However, QCT has a higher radiation dose than DXA, has a limited availability and is more expensive than DXA (Kazakia & Majumdar 2006). In addition there are major errors associated with the accuracy (range 5-15%) and precision (range 2-6%) of QCT (SBU 2003).

A large body of evidence describing the use of QUS as a potential diagnostic or prognostic tool exists in the published literature. However, the analysis of all of these studies is beyond the scope of this Horizon Scanning Report, therefore only limited evidence is presented in this non-comprehensive search of the literature.

Safety

None of the studies included in this assessment reported any adverse events associated with the use of quantitative ultrasound.

QUS does not utilise ionising radiation and is therefore considered to be a "safer" option than DXA, especially if a number of scans are required.

The number of false positives or false negatives obtained with testing with QUS is dependent on the cut-off value utilised. A lower cut-off value (<-1) will increase the number of false positives and may lead to a large number of individuals unnecessarily exposing themselves to ionising radiation from undergoing follow-up DXA testing. However, if higher QUS cut-off values are utilised (>-1), the number of false negatives will increase and may result in a large number of undiagnosed individuals at risk of fracture.

Effectiveness

QUS has a potential use in three distinct areas:

- as a *diagnostic* tool to identify individuals with or without osteoporosis, who may then be *triaged* to undergo confirmatory DXA testing; or
- as a *prognostic* tool to identify individuals at risk of fracture; or
- to *monitor* patients previously diagnosed as osteoporotic with DXA who are currently on medication.

Diagnosis of osteoporosis

A meta-analysis was conducted by Nayak et al (2006) to investigate the use of QUS to diagnose osteoporosis compared to the reference standard DXA (Table 5). Inclusion criteria required that all patients in the included studies be diagnosed by DXA with a T-score ≤ -2.5 and were therefore osteoporotic according to WHO guidelines. All participants underwent calcaneal QUS. Twenty-five studies were identified that satisfied the inclusion criteria. Included studies reported one or more of the following QUS parameters: broadband ultrasound attenuation, speed of sound, velocity of sound, quantitative ultrasound index or stiffness, which are all measures of bone characteristics (see Description of Technology). No study reported all parameters. Only the results of studies (n=11) that utilised the quantitative ultrasound index parameter were reported in this meta-analysis. These studies were heterogeneous in terms of study location (Europe (n=5), United States (n=4) and Asia (n=2), the number of study participants (range 110-772) and

mean age of participants (range 46-64 years), and thus population prevalence of osteoporosis as defined by WHO criteria (range 7-38%) (Nayak et al 2006).

All of the included studies recruited participants prospectively, as a cohort unclassified by disease state. Of the 25 studies, only seven reported the method of participant recruitment (consecutive or by random sampling). Each study included at least 30 participants with and 30 without, DXA-determined osteoporosis. These studies had participant completion rates of greater than 90 per cent. Most studies did not state the time which elapsed between DXA and QUS examinations or whether the results were interpreted independently (blinded) to each other (level III-2 diagnostic evidence)[4] (Nayak et al 2006).

Eleven studies used the Hologic Sahara QUS device and reported results in terms of the quantitative ultrasound index parameter. Of these 11 studies, nine reported results in terms of a T-score and were used to calculate test sensitivity and specificity. As previously discussed, patients with a T-score of ≤ -1 are considered to be at high risk of fracture (Lewiecki et al 2006). Using this cut-off level, QUS had a moderate sensitivity of 79 per cent and a low specificity of 58 per cent. The sensitivity of QUS improved markedly if a cut-off level of zero was used (93%), however the specificity decreased to 24 per cent with a wide confidence interval [10, 47]. A reduced specificity indicates that the test is poor at identifying individuals who *do not* have osteoporosis, and therefore the number of false positives would increase, which may result in more patients undergoing an unnecessary follow-up DXA (Nayak et al 2006).

Calculation of area under the curve (AUC) of the quantitative ultrasound index parameter indicated that QUS is a reasonable test for identifying osteoporosis (AUC = 0.76). This value was similar when the analysis was stratified according to the population studied, with an AUC of 0.76 for women only and 0.75 for post-menopausal women. Similar results were also obtained when ROC calculations were conducted using the other QUS parameters (see Table 5).

Using Bayes Theorum and previously obtained sensitivity and specificity data, the authors calculated the post-test probability of DXA-determined osteoporosis *after* testing with QUS. Given a QUS cut-off value of ≤ -1 (high fracture risk), the post-test probability of DXA-determined osteoporosis in a woman aged 70-79[5] years would be approximately 54 per cent, 95%CI [45, 62]. If the lower QUS T-score of – 1.5 was used for the same group of women, then the post-test probability of having DXA-determined osteoporosis would be approximately 22 per cent, demonstrating that when lower QUS cut-off values are used, the number of false negatives increase. If this patient had an intermediate or low QUS result (T-score > -1, see Table 1), then her post-test probability of having DXA-determined osteoporosis would be approximately 18 per cent, 95%CI [10, 24].

Similar results were reported by the authors for other QUS parameters, although these values were not presented in the meta-analysis.

[4] This evidence level reflects the highest level of studies contained within the meta-analysis.
[5] The prevalence, used in this study, of osteoporosis in this age group in women of the United States is approximately 39% (Table 5).

Table 5 Diagnosis of osteoporosis using QUS

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Nayak et al (2006)	III-2	Meta-analysis of 25 studies that met the inclusion criteria.	Adults with a DXA score of ≤-2.5 at the hip or spine.	**Quantitative ultrasound index (QUI)** **Diagnostic sensitivity and sensitivity** 11/25 (44%) studies utilsed the Hologic Sahara QUS device and reported results in terms of the broadband ultrasound index parameter. 9/11 (82%) of these studies reported T-scores Cut-off threshold QUI ≤ -1 Sensitivity (%) [95%CI] 79% [69, 86] Specificity (%) [95%CI] 58% [44, 70] Cut-off threshold QUI = 0 Sensitivity (%) [95%CI] 93% [87, 97] Specificity (%) [95%CI] 24% [10, 47] **AUC of all 11 studies** 0.76 95%CI [0.72, 0.79] AUC of women only 0.76 95%CI [0.70, 0.82] AUC of post-menopausal women 0.75 95%CI [0.66, 0.82] **Post-test probability of DXA-determined osteoporosis after testing with QUS in women** Cut-off threshold QUI ≤ -1 Age / Pretest prob (%) / +ve result [95%CI] % 50-59 / 15 / 25 [18, 30] 60-69 / 22 / 34 [26, 41] 70-79 / 39 / 54 [45, 62] >80 / 70 / 81 [76, 86] Cut-off threshold QUI > -1 Age / Pretest prob (%) / -ve result [95%CI] % 50-59 / 15 / 6 [3, 8] 60-69 / 22 / 10 [5, 12] 70-79 / 39 / 18 [10, 24] >80 / 70 / 46 [33, 56] **AUC of other QUS parameters** Broadband ultrasound attenuation 0.77 95%CI [0.73, 0.81] Speed of sound and Velocity of sound 0.74 95%CI [0.71, 0.77] Stiffness index 0.79 95%CI [0.71, 0.86]

DXA = dual energy x-ray absorptiometry, QUS = quantitative ultrasound, QUI = quantitative ultrasound index, AUC = area under the curve

QUS as triage

The use of QUS as a *diagnostic tool* to identify individuals with osteoporosis has been discussed previously (Table 5), however QUS may prove useful as a triage tool in determining those at risk individuals who should be referred on for screening with DXA (Table 6). DXA is not currently used as a mass screening tool and many communities do not have access to DXA, raising concerns about the under diagnosis of osteoporosis. The portability of QUS devices makes them an ideal tool for use in the community and may prove to be of particular benefit to rural and remote communities. It has been postulated that community pharmacist may provide a first stage osteoporosis "screening" or triage (Naunton et al 2006).

Few studies have reported on the use of QUS in a community setting. Naunton et al (2006) conducted a prospective community based study in Tasmania, Australia that enrolled 345 women at high-risk of osteoporosis (≥65 years). QUS measurements were taken and 201/345 (58.3%) women with results of QUS T-score ≤ -1 were referred onto their general practitioner, with 47 (32%) recommended for further testing. Of those referred on for further testing with DXA, 24/34 (71%) commenced medication to treat osteoporosis. This may indicate a correct diagnosis by QUS, however 120 of the original 345 high-risk women (34%) began medication (including calcium, vitamin D and anti-resorptive drugs) regardless of DXA status. This association may not necessarily be causal (level IV intervention evidence).

A similar community based study was conducted by MacLaughlin et al (2005). Women (n=97) considered to be at risk of osteoporosis underwent QUS testing in a community pharmacy. Although 54 (56%) had a QUS T-score of < -1 and were referred for a DXA scan, only 20 (37%) of these women completed the scan. There was a moderate correlation of DXA T-scores of the lumbar vertebrae and QUS (r=0.45, p=0.026) (level III-2 diagnostic evidence) (MacLaughlin et al 2005).

Both authors concluded that pharmacy-based QUS screening was a potentially useful method of identifying individuals at risk of fracture and/or osteoporosis and may be of particular use in rural areas.

The study by Nayak et al (2006) presented earlier in this report (Table 5) used the results of their meta-analysis to speculate on the utility of QUS as a pre-screening tool, used to identify individuals who may need further testing with DXA (level III-2 diagnostic evidence). Using these results, if a 1000 women aged 60-69 were screened with QUS, using a cut-off value of -1, then 500 women would return a positive result and therefore require further testing by DXA. Of these 500 "positive" women, 170 would have osteoporosis using the DXA criteria. Of the 500 negative women, 50 would be false negatives and would be positive using the DXA criteria. Results would be dependent on the pre-test probability, or prevalence of osteoporosis in the population and the choice of QUS cut-off value.

Several studies reported on the cost-effectiveness of using QUS as triage and these are reported in the cost analysis section.

Table 6 Using QUS as a triage tool

Study	Diagnostic level of evidence	Study design	Population	Outcomes
MacLaughlin et al (2005)	III-2	Cross-classification of women at risk of osteoporosis on DXA and QUS.	97 women >55 years with no current diagnosis of osteoporosis and had not undergone a DXA scan within the past 3 years. Mean age 66.2 ± 7.9 years. All women underwent QUS testing at a community pharmacy. Measurements were taken at the calcaneus utilising the Lunar Achilles Express Ultrasonometer (Wisconsin, USA).	54/97 (55.7%) QUS T-score < -1 and were referred for DXA. Of these: 45/54 (83.3%) were at moderate risk with T-score < -1 to > -2.5 9/54 (16.7%) at high risk with T-score ≤ -2.5 20/54 (37.0%) completed DXA scan 9/20 (45%) diagnosed with osteopenia 11/20 (55%) diagnosed with osteoporosis 5/97 (5.2%) had normal QUS result but were referred for DXA on clinical grounds. 4/5 (80%) diagnosed with osteopenia 1/5 (20%) diagnosed with osteoporosis 18/25 (72%) women who underwent DXA scan commenced medication **Pearson's Correlation between QUS and DXA (n=25)** Lumbar vertebrae 1-4 r= 0.45 p= 0.026
Study	**Intervention level of evidence**	**Study design**	**Population**	**Outcomes**
Naunton et al (2006)	IV	Post-test case series	345 women at high risk (>65 years) of osteoporosis. Median age 71 years (range 65-91 years). All women underwent QUS testing at a community pharmacy. Measurements were taken at the calcaneus utilising the Sahara Clinical Bone Sonometer (Hologic, Massachusetts, USA)	201/345 (58.3%) QUS T-score ≤ -1 and were referred to GP Of these: 147/201 (73.1%) visited GP Of these 47/147 (32%) recommended for further testing 34/47 (72.3%) completed follow-up testing and 24/34 (71%) were placed on medication

QUS = quantitative ultrasound, GP = general practitioner

Prognosis of fracture risk

A meta-analysis of 14 prospective cohort studies was conducted by Mańin et al (2006) reporting on the use of QUS to predict risk of fracture (Table 7). Inclusion criteria required that enrolled participants must have a baseline QUS value and that a fracture, the main outcome measure, occurred after this measurement had been taken. Fourteen studies were identified that satisfied the inclusion criteria, with a total population of 47,000 individuals and approximately 124,000 person-years of observation. Of these studies, 11 evaluated QUS at the heel, two took measurements at both the patella and phalanx and one study utilised the distal radius. All analyses were stratified by the type of parameter measured by QUS: bone ultrasound attenuation, speed of sound, quantitative ultrasound index or stiffness index. Four of the studies evaluated individuals who were < 60 years, however 57 per cent of the studies reported on individuals ≥ 70 years. Included studies were heterogeneous in terms of study location: Europe (n=7), United Kingdom (n=4) and United States (n=3). Only two of the included studies reported on the testing of a mixed male/female population, with only one of these stratifying results by sex. A meta-analysis could be undertaken of results for the female population alone. The size of the cohorts varied (range 130 to 14,824), however five studies evaluated cohorts of >5,000 individuals (36% of studies). Heterogeneity was assessed for all estimates and was not observed for the fractures outcome or for any of the QUS parameters analysed. Average length of follow-up ranged from one to 5.5 years (Marin et al 2006).

The relative risk for fractures for one standard deviation *decrease* in QUS parameters are summarised in Table 7. Of the 47,300 individuals enrolled in the 14 cohorts, there were a reported total of 2,350 fractures, including 653 fractures of the hip, 528 of the forearm or wrist and 386 fractures of the humerus. Lower values of the QUS parameters were associated with an increase of risk of fracture at any site. The age-adjusted relative risk for a fracture at any site ranged from 1.55 for QUS measured using broadband ultrasound attenuation, to 1.74 if the quantitative ultrasound index parameter was utilised. The relative risks for fracture at the hip were slightly higher for all QUS parameters, ranging from 1.71 to 1.94, however the relative risks were lower for fractures at the humerus (1.25-1.50) and the forearm/ wrist (1.34-1.44) regardless of the QUS parameter.

Five studies reported measurements made with QUS in addition to BMD measurements taken with DXA. The calculated relative risks for fracture using BMD were similar to those obtained using the QUS broadband ultrasound attenuation parameter (1.60 vs 1.50) (n= ~ 14,000). The speed of sound QUS parameter was utilised for a reduced number of individuals in these studies (n= ~7,000), however relative risk of fracture results were comparable to those obtained with DXA (1.77 vs 1.74).

The authors of this meta-analysis concluded that there is strong evidence that QUS measurements are associated with fracture risk in older women and that QUS should be considered a valid and cheaper alternative to DXA to assess fracture risk at non-spinal sites.

Table 7 Assessment of risk of fracture in women for each SD decrease in QUS parameters

Study	Prognostic level of evidence	Study design	Population	Outcomes
Mafin et al (2006)	I	Meta-analysis of 14 prospective cohort studies which met the inclusion criteria.	Adults with a fracture that had occurred after QUS measurement, mean age range: 58 ± 7.6 to 82.8 ± 5.9 years	**Fracture at any site** QUS parameter / Site measured / RR [95% CI] BUA / CAL / 1.55 [1.35, 1.78] SOS / all sites / 1.63 [1.37, 1.93] SOS / CAL / 1.59 [1.31, 1.95] QUI / CAL / 1.74 [1.39, 2.17] **Non-spinal fracture** QUS parameter / Site measured / RR [95% CI] BUA / CAL / 1.35 [1.20, 1.51] SOS / all sites / 1.34 [1.04, 1.74] QUI / CAL / 1.43 [1.22, 1.67] **Hip fracture** QUS parameter / Site measured / RR [95% CI] BUA / CAL / 1.75 [1.40, 2.20] SOS / all sites / 1.77 [1.24, 2.52] SOS / CAL / 1.71 [1.21, 2.42] QUI / CAL / 1.94 [1.46, 2.59] **Forearm/ wrist fracture** QUS parameter / Site measured / RR [95% CI] BUA / CAL / 1.44 [1.21, 1.72] SOS / all sites / 1.42 [1.09, 1.85] SOS / CAL / 1.34 [1.18, 1.53] QUI / CAL / 1.66 [1.47, 1.88] **Humerus fracture** QUS parameter / Site measured / RR [95% CI] BUA / CAL / 1.27 [1.05, 1.55] SOS / CAL / 1.25 [1.04, 1.49] QUI / CAL / 1.50 [1.23, 1.84] **Relationship between DXA & fracture** n= ~ 14,000 RR (BMD) = 1.60 [1.22, 2.05] vs RR (BUA) = 1.50 [1.26, 1.77] n= ~ 7,000 RR (BMD) = 1.74 [1.50, 2.02] vs RR (SOS) = 1.77 [1.17, 2.68]

SD = standard deviation, QUS = quantitative ultrasound, RR = relative risk (age adjusted), BUA = broadband ultrasound attenuation, SOS = speed of sound, QUI = quantitative ultrasound index, CAL = calcaneus, DXA = dual energy x-ray absorptiometry, BMD = bone mineral density

Monitoring osteoporotic patients with QUS

Three studies were included for assessment in this Horizon Scanning Report that investigated the use of QUS to monitor post-menopausal women on therapy (Table 8).

Drake et al (2002) compared the use of QUS and accuDXA (a small portable device which measures BMD utilising minimal ionising radiation) to the reference standard DXA to monitor women on the bisphosphonate drug, alendronate (level III-2 intervention evidence). Mean total hip BMD at baseline was 0.702 $g.cm^2 \pm 0.091$ and increased significantly by two ($p<0.05$) and 2.5 ($p<0.01$) per cent at six and 12 months, respectively. A similar trend was observed for BMD values obtained at the lumbar spine. The only significant changes in the QUS parameter speed of sound were a *decrease* detected at the radius at 12-months ($p=0.04$), and an *increase* at the tibia at 6-months ($p<0.01$), however there was no change between baseline and 12-months at the tibia. In addition, there was no significant baseline correlation observed between any of the QUS sites and total hip or lumbar spine DXA. It would appear from these results that QUS, unlike DXA, is not suitable for monitoring the response to alendronate therapy over time (Drake et al 2002).

Although the study by Sahota et al (2000) reported on the monitoring outcomes of several QUS parameters of women on hormone replacement therapy (HRT) compared to a control group of women, the actual values of the percent change from baseline were not reported (graphical presentation only). When the per cent change from baseline was evaluated with DXA (total hip and anteroposterior spine), BMD in the HRT group had a steady increase until reaching a plateau at 4-years ($p<0.01$). A slight but significant decline was observed in the BMD of individuals in the control group at 4-years ($p<0.01$). The mean per cent change from baseline of the QUS parameter speed of sound remained close to baseline and was not significant. For the majority of the follow-up period the QUS parameters broadband ultrasound attenuation and stiffness had a mean per cent change below that of baseline in the HRT group. The long-term standardised precision of DXA and QUS was calculated using the control group over the 4-year study.[6] The long-term standardised precision rate for QUS parameters were 2-3 times that of DXA of the anteroposterior spine. The authors concluded that QUS may have a potential role in the monitoring of patients on HRT, however the time period to follow patients is 2-3 times that of DXA (Sahota et al 2000).

These results were contradicted in the study by Gonnelli et al (2002) which reported on the use of *calcaneal* QUS to monitor post-menopausal women on alendronate therapy compared to a calcium supplement alone (level III-2 intervention evidence). In addition, this study reported on the monitoring outcomes of several QUS parameters, not just speed of sound. When the per cent change from baseline was evaluated with DXA, BMD in the alendronate group increased by 4.2 per cent at 12-months and continued to increase at 4-years to 7.6 per cent. A steady decline was observed in the BMD of

[6] These results were used to calculate the Standardised Precision = Precision divided by the annual rate of change in the control group. The treatment effect (defined as the percentage difference between the HRT and control groups at 2 and 4 years. The Treatment Response Index was calculated by dividing the 4-year treatment effect by the Standardised Precision.

individuals in the calcium supplement group (-0.9% at 12-months to -2.5% at 4-years). Similar trends were observed when the QUS parameters of broadband ultrasound attenuation and speed of sound were utilised, however the incremental changes were small in comparison. The QUS parameter stiffness appeared to be capable of monitoring the greatest treatment effect, with increases in the alendronate treatment group ranging from 3.2 per cent at 12-months to 9.0 per cent at 4-years. Stiffness was also superior in its accuracy (80%) compared to speed of sound (60%) and broadband ultrasound attenuation (25%). In addition, the monitoring time interval or the period of time required between scans to demonstrate a true change, was the shortest (2.2 years) for the stiffness parameter compared to 1.8 years for DXA-determined BMD. The authors concluded that although DXA-determined BMD remains the optimal method, calcaneal QUS measured via the stiffness parameter is a sensitive tool for monitoring patients on bisphosphonate treatment (Gonnelli et al 2002).

Although only three studies have been included for assessment of the effectiveness of monitoring with QUS in this Horizon Scanning Report, they highlight inconsistencies. QUS may offer the ability to monitor patients more frequently without exposure to ionising radiation, however a longer monitoring time period may be necessary before any effect of medication is noted. These studies also highlight the need to conduct further studies to ascertain the ideal site for QUS (consensus appears to favour the calcaneal) and, more importantly, the parameter used to interpret results. The response to treatment at particular skeletal sites may depend on the treatment given. Anti-resorptive drugs such as bisphosphonates act on high turn over trabecular bone. The calcaneus is made up almost entirely of trabecular bone, making it a more appropriate site than the phalanx for the QUS monitoring of patients on anti-resorptive medication (Gonnelli et al 2002) A more thorough investigation of the use of QUS for the monitoring of medication may be warranted.

Table 8 Monitoring the effect of medication on osteoporotic patients

Study	Intervention level of evidence	Study design	Population	Outcomes
Drake et al (2002)	III-2	Cross classification of post-menopausal women using BMD obtained with hip and spine DXA, phalangeal BMD obtained with accuDXA and speed of sound obtained with QUS. Measurements taken at baseline, 6 and 12 months.	81 women with post-menopausal osteoporosis with a DXA determined lumbar spine or total hip T-score of ≤ -2.5. Participants were randomised to receive either 80 or 160 mg alendronate. Data from the 2 groups were pooled. QUS at the radius, tibia, metatarsal and phalanx measured by the Sunlight Omnisense Ultrasound Bone Sonometer (Sunlight Medical, Rehovot, Israel)	**Mean difference using paired Wilcoxon test** **Total hip DXA (g/cm²)** Baseline T-score (SD) -1.86 (0.79) Mean change (SD) 0-6 months 2.0% (12.7) p<0.05 0-12 months 2.5% (2.3) p<0.01 **Lumbar spine DXA (g/cm²)** Baseline T-score (SD) -2.3 (0.91) Mean change (SD) 0-6 months 4.2% (11.7) p<0.01 0-12 months 6.1% (3.5) p<0.01 **accuDXA (g/cm²)** Baseline T-score (SD) -1.97 (1.15) Mean change (SD) 0-6 months 0.1% (4.5) NS 0-12 months 0.5% (4.6) p<0.05 **Radius SOS (m/s)** Baseline T-score (SD) -2.16 (1.43) Mean change (SD) 0-6 months -8.1 (104.4) NS 0-12 months -23.4 (145.1) p=0.04 **Tibia SOS (m/s)** Baseline T-score (SD) -1.3 (1.57) Mean change (SD) 0-6 months 57.4 (196.4) p<0.01 0-12 months 1.0 (122.3) NS **Metatarsal SOS (m/s)** Baseline T-score (SD) -0.5 (1.43) Mean change (SD) 0-6 months -24.6 (199.7) NS 0-12 months -28.5 (185.2) NS **Phalanx SOS (m/s)** Baseline T-score (SD) -2.34 (0.91) Mean change (SD) 0-6 months 12.2 (82) NS 0-12 months -5.5 (86.9) NS

				Baseline correlation between DXA and accuDXA and SOS **DXA** Hip / Spine accuDXA 0.27* / 0.22** Phalanx SOS -0.08 / 0.18 Radius SOS 0.16 / 0.05 Tibia SOS 0.05 / 0.17 Metatarsal SOS 0.10 / 0.15 * p<0.05 ** p=0.05 Remaining correlation coefficients NS
Gonnelli et al (2002)	III-2	Cross classification of post menopausal women using BMD obtained at the lumbar spine with DXA and parameters obtained with QUS (speed of sound, stiffness, broadband ultrasound attenuation). Measurements taken at baseline, 12, 24, 36 and 48 months.	150 post-menopausal women with a DXA determined lumbar spine T-score of ≤ -2.5. Women were randomly allocated to alendronate (n=74) or to calcium alone (n=76). Mean age 59.6 ± 5.3 years. QUS at the calcaneus measured by the Achillesplus (Lunar, Madison, Wisconsin, USA)	23/150 (15.3%) lost to follow-up The mean baseline values of BMD and QUS parameters were not significantly different between the alendronate and control groups. **Mean % changes from baseline** **BMD** Month / TRT / Control 12 / +4.2 / -0.9 24 / +5.0 / -1.7 36 / +6.2 / -2.1 48 / +7.6 / -2.5 **QUS parameters** **Broadband ultrasound attentuation** Month / TRT / Control 12 / +1.1 / -1.0 24 / +1.4 / -1.8 36 / +1.8 / -2.8 48 / +1.9 / -2.3 **SOS** Month / TRT / Control 12 / +0.4 / -0.1 24 / +0.7 / -0.2 36 / +0.9 / -0.2 48 / +1.2 / -0.3 **Stiffness** Month / TRT / Control 12 / +3.2 / -1.6 24 / +5.7 / -2.9 36 / +7.6 / -3.9 48 / +9.0 / -4.0 **Accuracy of QUS[a]** Stiffness 85% Speed of sound 60% BUA 25% **Monitoring time interval (years)[b]** BMD 1.8 Stiffness 2.2 Speed of sound 2.7 BUA 11.9

Sahota et al (2000)	III-2	Cross classification of post menopausal women using BMD obtained at the anteroposterior spine and total hip DXA and parameters obtained with QUS (speed of sound, stiffness, broadband ultrasound attenuation). Measurements taken at baseline, 12, 24, 36 and 48 months.	60 early post-menopausal women with a DXA determined T-score of > -2.5 at the anteroposterior spine (AP). Women allocated to HRT (n=30) or control (n=30) Age range 45-59 years. QUS at the calcaneus measured by the Achillesplus (Lunar, Madison, Wisconsin, USA	3/30 (10%) HRT lost to follow-up 1/30 (3.3%) control lost to follow-up **4-year standardised precision (SP)** **DXA** **SP** AP spine 1.1 Total hip 1.9 **QUS** BUA 2.1 SOS 3.5 Stiffness 2.5

BMD = bone mineral density, DXA = dual energy x-ray absorptiometry, accuDXA = small, portable device which emits negligible radiation and measures phalangeal BMD (manufactured by Shick Technologies, New York), HRT = hormone replacement therapy, SD = standard deviation, NS = not significant, BUA = broadband ultrasound attenuation, CV = coefficient of variation, AP spine = anteroposterior spine, SOS = speed of sound

[a] Accuracy of QUS parameters was obtained by dividing the total treatment effect by the long-term precision and then normalising to spinal BMD

[b] Monitoring time interval = the period between scans required to show a 'true' change

Marin et al (2004) examined the cost-effectiveness of QUS as an alternative to DXA as a screening method for osteoporosis in the Spanish National Health Service. Using data from previous studies, 267 post-menopausal women underwent QUS followed by DXA. Of the 27 women designated by QUS as non-osteoporotic, five (18.5%) were false negatives. Thirty-two women were designated as osteoporotic by QUS and four (12.5%) of these were false positives. An uncertain diagnosis was made in 208 women who were referred for DXA and of these, 114 (54.8%) were classified as osteoporotic by DXA. The number of true osteoporotic cases was 149 (55.8%) detected by DXA and 146 (54.6%) detected by QUS. The average health care cost for DXA and QUS was €13.31[7] and €1.66, respectively. The total cost of DXA in this study group was €3,554[8] with an average cost per true case detected of €23.85. The total cost of QUS was €3,211[9] with an average cost per true case detected of €22.00. The incremental cost-effectiveness was €114 per extra cost needed to generate each additional true positive result by DXA. QUS appears to be slightly more cost-effective than screening all women with DXA, however the QUS cut-off point used in this study was low (≤-2.5). This low cut-off value resulted in four (2.5%) false positives. The potential treatment of these women based on their QUS results was not taken into account in the cost-effectiveness analysis and may change the direction of the analysis substantially (Marin et al 2004).

A study conducted in the United Kingdom examined the cost of using QUS as a selective pre-screen to DXA (Sim et al 2005). QUS was performed on 115 women *after* they had undergone a DXA scan. DXA identified 53 (46%) women as osteoporotic. Calculation of area under the curve (AUC) of the QUS parameters broadband ultrasound attenuation (BUA) and velocity of sound (VOS) indicated that QUS is a reasonable test for identifying osteoporosis. As BUA had a superior AUC (0.90) compared to that of VOS (0.79), only BUA was used to calculate cost-effectiveness.

The unit costs for pencil-beam DXA, fan-beam DXA and QUS were £44, £32 and £16.40[10], respectively. The appropriate operating threshold for BUA was found to be 60 db/MHz, where the positive and negative predictive values were 86 and 85 per cent, respectively. The corresponding sensitivity and specificity values were 81 and 89 per cent, respectively. Although QUS identified 50/115 (43.5%) women as requiring DXA, only 43 of these (86%) were true positives. On the basis of these data, the maximum cost of screening all women with DXA was estimated to be £5,053. The total cost of using QUS as a pre-screen for DXA was £4,084[11], giving a difference of £969. However, QUS diagnosed 10 women as negative who were found to be positive by DXA, which represents a cost per additional woman with osteoporosis identified by DXA alone of £97. Choosing a higher BUA threshold would

[7] The current exchange rate is $1.69 = €1 on 9th April 2008
[8] (267 x 13.31)
[9] (267 x 1.66 plus 208 x 13.31)
[10] The current exchange rate is $2.14 = £1 on 8th April 2008
[11] (115 x £16.40 for QUS, plus 50 x £44 for follow-up DXA on QUS positive women)

increase the negative predictive value but would also have the effect of increasing the cost of using QUS as a pre-screen (a NPV of 96% increases the cost to £5,754, more than the cost of DXA).

The authors concluded that the use of the QUS parameter, BUA, is not cost-effective as a pre-screen for identifying women who should be referred on for further DXA scanning. Although this study used costs associated with providing the QUS scan in a hospital setting, the authors also thought it debatable whether or not costs would decrease if QUS was performed in a GP setting.

Harrison and Adams (2006) examined the cost of using QUS, peripheral DXA and several algorithms (based on risk factors) as a means of triaging post-menopausal women into high, moderate and low risk of osteoporosis. All women (mean age 61 years, ± 4) underwent a DXA scan to determine their osteoporosis status. Seventy women were diagnosed as osteoporotic and 137 as non-osteoporotic. All women regardless of initial diagnosis underwent testing with QUS and the risk-factor algorithms. Based on these results the women were classified as:
i) high-risk and given treatment for osteoporosis
ii) moderate-risk and referred for DXA
iii) low-risk requiring no further action.

Two types of QUS device, both measuring at the calcaneus, were used. Using the GE Lunar Achilles, 20 per cent of women were classified as high-risk, 40 per cent as moderate-risk and 31 per cent as low-risk. The CubaClinical QUS device classified 19, 57 and 24 per cent of women as high, moderate and low risk, respectively. Of the 137 women originally designated as non-osteoporotic based on DXA scans, approximately 10 per cent were misclassified as high-risk and given treatment. Conversely, 10 per cent of the true 70 osteoporotic women were classified as low-risk. The majority of the risk-factor algorithms performed poorly, misclassifying large numbers of osteoporotic patients into the low-risk category (10-31%). The use of risk-factor algorithms in conjunction with QUS did not affect the number of misclassifications by QUS alone.

The cost of performing a DXA scan on all women was £10,350[7] (£50 per scan). The cost of implementing the triage approach using QUS was approximately 260 per cent higher than that of scanning all women with DXA, which includes the high cost of treating non-osteoporotic women with unnecessary and expensive medication[12]. Costs are reduced if all women who fall into the high and moderate-risk categories are referred for DXA. Using this scenario, the cost of using QUS was 85-92 per cent (£8806 to £9506) of scanning all women for DXA. Although the second method is more cost effective than using DXA for all women, it is more expensive than the £3,500 required to DXA scan only those women who were truly osteoporotic (Harrison & Adams 2006).

It must be reiterated that all of these studies used DXA as the reference standard for an osteoporotic diagnosis. However, DXA itself is an imperfect reference standard and has low sensitivity for predicting fracture risk (see

[12] Treatment costs calculated for five years

Treatment Alternatives). It is entirely possible that a false positive QUS test, according to DXA, could still in fact predict fracture risk.

The Sahara Ultrasound BMD unit is typical of the many quantitative ultrasound units on the market. Manufactured by Hologic Inc it is distributed in Australia and New Zealand (Australian Register of Therapeutic Goods number is 114028). The basic cost of these units is $18-20,000 (personal communication Insight Oceana, Australian distributor). The cost of a QUS screen in 2005 was approximately $50-60, however non-profit organisations such as Osteoporosis WA offered the service at a reduced cost of $30 (Arthritis Foundation of WA 2005).

It is also worth noting the results of an Australian study investigating the cost-effectiveness of targeted drug therapy for patients with osteoporosis (Sanders et al 2006). Data on all fractures over a 2-year period in women over 50 years were collected by the Geelong Osteoporosis Study group. BMD data were available for 587 women with incident fractures and 817 controls. Only 56 per cent of women with a fracture had osteoporosis, and only 59 per cent of women with the 'classic osteoporotic' fracture (hip, Colles and vertebral) had osteoporosis. If all Australian women over the age of 50 years were treated with anti-resorptive drugs, the average cost of averting one fracture would be $111,000 annually, but only 18,000 (36%) of the 50,000 fractures would be averted (total cost of treatment $2000 million annually). If only women with osteoporosis were treated 13,800 (27%) fractures would be averted at an annual cost of $459 million. However, these women would need to be identified by a mass screening programme, adding $114 million to the total cost (screening women 50+ years every 2-years). Screening using a BMD cut-off T-score of -2.5 misses 80, 54, 41 and 31 per cent of fractures in those aged 50-59, 60-69, 70-70 and 80+, respectively. Treating women in the 50-59 age group with osteoporosis would cost $156,400 per averted fracture, compared to $28,500 for women in the 80+ age group. If osteoporosis and age (>60 years) were used as criteria for treatment the population burden of fractures would only be reduced by 28 per cent. This leaves a remaining 72 per cent of fractures in this defined population, which would need to be prevented by other means.

Informed Consent

Practitioners have an ethical obligation to inform patients of the effectiveness of scanning with the QUS device, and to tailor that information to the patients' circumstances. Individuals should be appraised of the potential for false negatives and positives using the QUS technology. In addition, individuals should be given a basic understanding of what a QUS test result represents in terms of their risk of fracture or risk of osteoporosis. Individuals need to be made aware of the repercussions of a "positive" QUS result in terms of further confirmatory testing by DXA and treatment with anti-resorptive medication.

Ethical considerations

QUS has the potential to be used as a diagnostic tool for those individuals deemed at risk of fracture or osteoporosis, or as a mass screening tool.

The use of QUS as a diagnostic screening tool (including its use as a screening tool to triage for further assessment) raises ethical issues that are typical of many screening programs. All screening tests have consequences besides the early identification and treatment of disease. The balance between the benefits arising from early detection and the harms resulting from these other consequences is therefore crucial, and it is this issue of balance that is a stake for the use of QUS as a screening tool.

As a diagnostic screening tool, the use of QUS is likely to result in people who have a false positive result receiving unnecessary medication, worrying unnecessarily about their health and/or changing activities of daily living to accommodate a false diagnosis. As a tool to triage people for further assessment, the use of QUS may lead to people receiving DXA unnecessarily. In both cases, there will be unnecessary costs to the Australian health system as well. Taken together, these consequences suggest that the adverse effects of screening using QUS are significant enough to warrant caution in the use of the technology as a screening tool.

Against this view, one needs to consider what the alternatives might be to the use of QUS. For people in urban areas, the use of DXA, while more dangerous in terms of ionising radiation, is less likely than QUS to give rise to the harms associated with inappropriate diagnosis or treatment. People in rural and remote areas, however, do not necessarily have access to DXA. For them, the choice may be between an inaccurate screening tool for osteoporosis and no screening at all. In this situation, the harms associated with the use of QUS (whether as a diagnostic test alone or as a pre-screen for referral) may be outweighed by the benefits of having a diagnostic tool for osteoporosis, albeit an imperfect tool.

If one accepts that it may be ethically appropriate to use QUS as a substitute for DXA (or as the first stage in referral to DXA) in rural and remote areas, the next ethical problem is the issue of access to the service. At the moment people in urban areas have ready access to DXA (which is available on the MBS).

People living in rural and remote areas can use QUS, if it is available in local pharmacies, but they need to pay the full cost of this service. Whether the cost of the service is a deterrent to uptake is unclear. Naughton's study found that more than half of the women included in their study would be prepared to pay for screening using QUS (Naunton et al 2006), which also implies that almost half the women would not be willing to pay. Regardless of willingness to pay, for provision to be fair and just, QUS would need to be available to people in rural and remote regions at the same cost and level of availability as DXA is in urban areas.

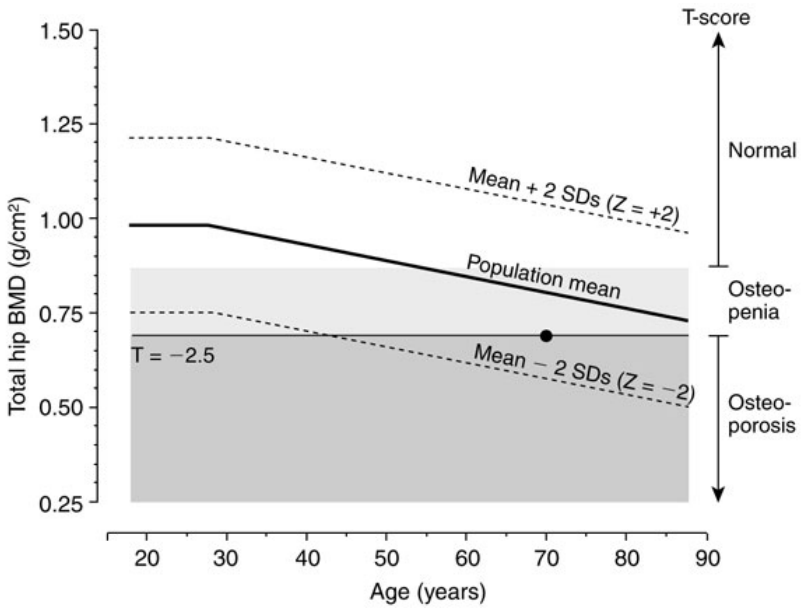
This would, of course, create other difficulties. There would considerable pressure to make QUS available to all people, regardless of place of residence. Should this happen, we would have exactly the outcome we had not wanted in the first place: a widely available, but inaccurate, screening tool for which the balance of benefits over harms for the community is questionable.

Training

Minimal training would be required for the use of a QUS device, however practitioners would require a good understanding of the interpretation of results in order to explain them to the person being tested and to determine follow-up care.

Clinical Guidelines

In 2002, Osteoporosis Australia and the National Prescribing Service developed guidelines for the prevention of osteoporosis (Sambrook et al 2002). These guidelines support those developed by the World Health Organization in that the current "gold standard" for the diagnosis of osteoporosis is bone mineral density determined by DXA. Osteoporosis is defined in terms of DXA T-scores, which represents the number of standard deviations away from the mean BMD of a young normal population (Figure 4).



● Indicates a woman aged 70 years with a BMD Z-score of -1, which is within the reference range for age. However, this Z-score means the woman has double the risk of fracture compared with a 70 year old woman with average BMD for her age. Further her T-score is -2.5 indicating her BMD is at the threshold for osteoporosis.

Figure 4 **T- and Z-scores with WHO thresholds (Sambrook et al 2002)**
Relationship between hip BMD and age in women showing the difference between: (i) Z-score (number of SDs from population mean for age). Z= -2.0 to +2.0 is the reference range; and (ii) T-score (number of SDs from the mean for a young, healthy population). A T-score of -2.5 is defined as the threshold for osteoporosis.

These guidelines do not recommend the use of DXA as a population screening tool. The recommend that BMD measurement should only be used if a treatment decision is based on the result of the test, and DXA is not justified as a screening tool in a healthy population. The working group go on to say that

the usefulness of population screening will depend on the prevalence of disease and the cost of the screening test. They conclude "Screening of unselected populations (eg, using ultrasound in pharmacies) is not recommended by any authoritative group in the field of bone biology." (Sambrook et al 2002, pg S6)

The Australia and New Zealand Bone and Mineral Society and Osteoporosis Australia also do not recommend the use of heel ultrasound as a routine screening tool to measure bone strength or to predict an individual's risk of fracture. (ANZBMS 2008).

Osteoporosis New Zealand's recommendations for the management of osteoporosis suggest the use of DXA for the determination of BMD in situations where the result will impact on patient care decision making ie in post-menopausal women, women aged over 60 years and men aged over 70 years or patients prescribed glucocorticoids. Osteoporosis New Zealand acknowledges that QUS may be an attractive option for screening due to its low cost and portability, however a lack of precision precludes it as a tool for monitoring osteoporosis. They also state that as QUS is not sufficiently predictive of DXA that it should not be used in routine osteoporosis assessment (Osteoporosis New Zealand 2005).

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of the use of ultrasound for the assessment of bone fracture risk, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Availability and Level of Evidence

Seven peer reviewed studies were included for assessment in this Horizon Scanning Report. See Appendix B for profiles of these studies.

One study reported on the diagnostic accuracy of quantitative ultrasound compared to DXA for the assessment of risk of fracture or osteoporosis. Nayak et al (2006) conducted a meta-analysis of 25 poor quality studies -studies did not state whether of not patients were recruited consecutively or if researchers were blinded to the results of DXA diagnosis. However, only the results of 11 studies have been presented as these studies all used the same QUS device and reported results in terms of the same QUS parameter (level III-2 diagnostic evidence).

Two studies were included that reported results in terms of triaging patients based on the results of QUS. The study by MacLaughlin et al (2005) reported both the diagnostic accuracy of QUS compared to DXA as well as the outcomes of women referred for further testing on the basis of their QUS results (level III-2 diagnostic evidence). The remaining study by Naunton et al (2006) reported on the management outcomes of women scanned by QUS followed by a DXA scan (level IV intervention evidence).

One high level study was included which assessed the risk of fracture in women. The meta-analysis by Mańin et al (2006) reported the outcomes of 14 prospective cohort studies that followed an estimated 47,000 individuals for approximately 124,000 person-years (level I prognostic evidence).

Three studies reported the outcomes of women on osteoporotic medication who were scanned with DXA and QUS at regular intervals (level III-2 intervention evidence).

Search Strategy used for the Report

The medical literature (Table 10) was searched utilising the search terms outlined in Table 9 to identify relevant studies and reviews, until January 2008. In addition, major international health assessment databases were searched.

Table 9 Search terms utilised

Search terms
MeSH
Bone and Bones/ultrasonography; Calcaneus/ultrasonography; Fractures, Bone/ultrasonography; Osteoporosis/ultrasonography;
Text words
Quantitative AND ultrasound; Quantitative AND ultrasonography; osteoporosis AND ultrasound; osteoporosis AND ultrasonography, QUS
Limits
Human, English

Table 10 Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au/default.aspx
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html
Websites of Specialty Organisations	
Australian and New Zealand Bone and Mineral Society	http://www.anzbms.org.au/resources/DXA/index.cfm
Osteoporosis Australia	http://www.osteoporosis.org.au/
National Osteoporosis Foundation	http://search.atomz.com/search/?sp-q=guidelines&x=0&y=0&sp-a=00011ce7-sp00000001

Sources of Further Information

A number of trials are currently using QUS as a means of assessing the effect of various interventions on enrolled patients. Only one of the registered trials is investigating QUS as a means of screening individuals for osteoporosis. The Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta are conducting the OsteoPharm Study: A randomised trial of a community pharmacist-initiated screening and intervention program for osteoporosis. Participants are required to be at risk of osteoporosis (early menopause, family history of osteoporosis, previous fracture, systemic steroid use) and aged over 50 years. Individuals randomised to the intervention group would undergo screening by a community pharmacist, receive quantitative ultrasound (QUS) measurements and referral to the primary care physician. The control group would receive usual care, defined as provision of generic pamphlet on osteoporosis. Enrolment commenced in 2005, with a target of 250 individuals and the study was expected to be finalised late 2007 (CCT 2007). Publication is therefore likely within the next two years.

Conclusions

Osteoporosis is a skeletal disorder that is characterised by compromised bone strength, which in turn may predispose an individual to an increased risk of bone fracture. The cross-sectional Geelong Osteoporosis Study estimated that 90 out of every 1,000 females aged 50-54 years have a low BMD in the hip, spine or mid-forearm. This number increased to 380 per 1,000 females aged 60-64 years; 560 per 1,000 females aged 65-69 years and 870 per 1,000 females aged 80 years or older.

Measurement of bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) is currently used to clinically diagnose osteoporosis. The World Health Organization defines osteoporosis on the basis of BMD using T-scores calculated from DXA measurements taken at the proximal femur and spine. BMD can be determined by peak bone mass and amount of bone loss. Factors which may contribute to the rate of bone loss include menopause in women, increasing age, low physical activity levels, some medications, certain medical conditions such as inflammatory bowel disease and coeliac disease, smoking and alcohol consumption. Osteoporosis is most commonly diagnosed after a fracture has occurred.

The *sensitivity* of the T-score generated from BMD measurement by DXA at predicting fracture risk is low, as reported by the National Osteoporosis Risk Assessment longitudinal study of 140,000 women followed for 12 months. Although 2,259 new fractures were reported, only 6.4 per cent of these women had a reported baseline T-score indicating a diagnosis of osteoporosis. Accuracy and precision estimates of DXA range from 3-9 and 0.5-3 per cent, respectively.

Thus, although DXA is considered the gold standard for the diagnosis of osteoporosis it is not recommended as a mass screening tool.

Quantitative ultrasound (QUS) is intended to identify those individuals who may be at risk of experiencing a bone fracture. Once at-risk individuals have been identified, a DXA scan should be performed to establish a diagnosis of osteoporosis and to instigate appropriate treatment.

QUS uses high frequency soundwaves, which are transmitted through bone to measure the quality and strength of the bone. The most common measurement site is the calcaneus, or heel. QUS devices may use several parameters to estimate BMD including speed of sound and broadband ultrasound attenuation. QUS measurements may be used to calculate a QUS T-score (patients with a T-score of $\leq$ -1 are considered to be at high risk of fracture), however this can not be compared to a T-score attained with DXA.

Heel QUS is currently offered by some pharmaceutical outlets with the cost of the test borne entirely by the consumer. QUS does not currently have a Medicare Benefits Schedule number.

None of the studies included in this assessment reported any adverse events associated with the use of quantitative ultrasound. QUS does not expose patients to ionising radiation and is therefore considered a safe technology. However, patient safety issues regarding the number of false positives and

false negatives remain a concern. The number of false positives or false negatives obtained with testing with QUS is dependent on the cut-off value used. A lower cut-off value (<-1) will increase the number of false positives and may lead to a large number of individuals unnecessarily exposing themselves to ionising radiation from undergoing follow-up DXA testing. However, if higher QUS cut-off values are used (>-1), the number of false negatives will increase and may result in a large number of undiagnosed individuals at risk of fracture.

QUS may be used to diagnose osteoporosis, or more correctly, to stratify patients according to their risk of fracture. However, results may vary according to the QUS parameter used, the type of device and the skeletal site tested. The 2006 meta-analysis conducted by Nayak et al described the results of 11 prospective studies that reported QUS results obtained by the same device type at the calcaneus (heel) and in terms of the quantitative ultrasound index parameter. Results were compared to the reference standard DXA.

Nine studies reported results in terms of a T-score and were used to calculate test sensitivity and specificity. Using the QUS T-score cut-off of -1, QUS had a moderate sensitivity of 79 per cent and a low specificity of 58 per cent. The sensitivity of QUS improved markedly if a cut-off level of zero was used (93%), however the specificity decreased to 24 per cent with a wide confidence interval [10, 47]. A reduced specificity indicates that the test is poor at identifying individuals who *do not* have osteoporosis, and therefore the number of false positives would increase, which would result in more patients undergoing an unnecessary follow-up DXA. Calculation of area under the curve (AUC) of the quantitative ultrasound index parameter indicated that QUS is a reasonable test for identifying osteoporosis (AUC = 0.76).

Two studies reported on the use of QUS as a triage tool in community settings (pharmacies). Women with QUS results below the T-score cut-off value of -1 were referred on to their general practitioners or for further DXA testing. Compliance with referral was 37 and 73 per cent in the respective studies. It is unclear from these studies whether commencement of bone prophylaxis was related to QUS, a follow-up DXA, or other risk factors. The role of QUS in changing management of at-risk patients is therefore unknown.

A good quality meta-analysis of prospective cohort studies reported on the use of QUS to *predict* risk of fracture. All analyses were stratified by the type of parameter measured by QUS. The age-adjusted relative risk for a fracture at any site ranged from 1.55 for QUS measured using broadband ultrasound attenuation, to 1.74 if the quantitative ultrasound index parameter was utilised. The relative risks for fracture at the hip were slightly higher for all QUS parameters, ranging from 1.71 to 1.94, however the relative risks were lower for fractures at the humerus (1.25-1.50) and the forearm/ wrist (1.34-1.44) regardless of the QUS parameter. Five studies reported measurements made with QUS in addition to BMD measurements taken with DXA. The calculated relative risks for fracture using BMD were similar to those obtained using the QUS bone ultrasound attenuation parameter (1.60 vs 1.50) (n= ~ 14,000). The speed of sound QUS parameter was used for a reduced number of individuals in these studies (n= ~7,000), however the relative risk of fracture was comparable to those obtained with DXA (1.77 vs 1.74). It would appear from

this evidence that QUS measurements are associated with fracture risk in older women and that QUS may be a valid alternative to DXA to assess fracture risk at non-spinal sites.

Three studies assessed the effectiveness of QUS at monitoring osteoporotic patients on medication. However, these studies highlight inconsistencies associated with the use of QUS. QUS may offer the ability to monitor patients more frequently without exposure to ionising radiation, however a longer monitoring time period may be necessary before any effect of medication is noted. These studies also highlight the need to conduct further studies to ascertain the ideal skeletal site for QUS (consensus appears to favour the calcaneal) and, more importantly, the parameter used to interpret results.

A typical QUS device costs approximately $20,000 and the cost of an individual scan may be in the region of $50-60.

A cost-effectiveness study was conducted describing the use of QUS as an alternative to DXA as a screening method for osteoporosis in the Spanish National Health Service. Post-menopausal women underwent QUS followed by DXA. The total cost of DXA in this study group was €3,554 with an average cost per true case detected of €23.85. The total cost of QUS was €3,211 with an average cost per true case detected of €22.00. The incremental cost-effectiveness indicated an increased cost of €114 to generate each additional true positive result by DXA. QUS appears to be slightly more cost-effective than screening all women with DXA, however the QUS cut-off point used in this study was low (≤-2.5). This low cut-off value resulted in four (2.5%) false positives. The potential treatment of these women based on their QUS results was not taken into account in the cost-effectiveness analysis and could have changed the direction of the analysis

In summary, quantitative ultrasound devices suffer from a lack of standardisation, there is a lack of consensus regarding which of the diagnostic parameters should be used, and there is variation with regard to the skeletal site used in diagnosis. Results from this assessment indicate that QUS may be a reasonable test for identifying osteoporosis. In addition, it may be a valid alternative to DXA to assess fracture risk at non-spinal sites, especially in older women. There is, however, conflicting evidence regarding the role of QUS to guide therapy for osteoporotic patients.

It must be reiterated that all of studies included in this assessment used DXA as the reference standard for an osteoporotic diagnosis. However, DXA itself is an imperfect reference standard and has low sensitivity for predicting fracture risk. It is entirely possible that a false positive QUS test, according to DXA, could still in fact predict fracture risk.

The Australia and New Zealand Bone and Mineral Society and Osteoporosis Australia do not recommend the use of heel ultrasound as a routine screening tool to measure bone strength or to predict an individual’s risk of fracture.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis [**]	Prognosis	Aetiology [†††]	Screening
I [*]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among consecutive patients with a defined clinical presentation [††]	A prospective cohort study [***]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among non-consecutive patients with a defined clinical presentation[††]	All or none [§§§]	All or none [§§§]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study [‡] Interrupted time series without a parallel control group	Diagnostic case-control study [††]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [‡‡]	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

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

‡ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

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

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

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

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

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

Appendix B: Profiles of Studies

Study	Location	Study design	Study population	Study details	Outcomes assessed
Drake, W.M. Brown, J.P. Banville, C. Kendler, D.L. (2002)	Vancouver, Canada	Diagnostic evidence level III-2	81 women with post-menopausal osteoporosis with a DXA determined lumbar spine or total hip T-score of ≤ -2.5. Mean age 70.2 ± 4.6 years	Women were stratified according to baseline lumbar spine T-score (≥ -3 or < -3), presence or absence of baseline vertebral fracture, duration of previous treatment with levormeloxifene or placebo (≥ 6 months or < 6 months) and then randomised to receive either 80 or 160 mg alendronate sodium once weekly.	The clinical utility of multi-site QUS speed of sound measurements (radius, phalanx, tibia, metatarsal) and phalangeal BMD measurements in the monitoring of response to alendronate therapy. Measurements taken at baseline, 6 and 12 months.
Gonnelli, S. Cepollaro, C. Montagnani, A. Martini, S. Gennari, L. Mangeri, M. Gennari, C. (2002)	Siena, Italy	Diagnostic evidence level III-2	150 post-menopausal women with a DXA determined lumbar spine T-score of ≤ -2.5. Mean age 59.6 ± 5.3 years.	Women were randomly allocated to treatment with alendronate (10mg/day) plus calcium supplement (n=74) or to calcium alone (n=76).	The clinical utility of calcaneal QUS measurements in the monitoring of response to alendronate therapy. Measurements taken at baseline, 12, 24, 36 and 48 months.
MacLaughlin, E.J. MacLaughlin, A.A. Snella, K.A. Winston, T.S. Fike, D.S. Raehl, C.R. (2005)	Texas, USA	Intervention evidence level IV	97 women >55 years with no current diagnosis of osteoporosis and had not undergone a DXA scan within the past 3 years. Mean age 66.2 ± 7.9 years.	All women underwent calcaneal QUS at a community pharmacy. Women with T-score < -1 were referred to their general practitioner.	Number referred for DXA scan.

Mañin, F. Gonzalez-Macias, J. Diez-Perez, A. Palma, S. Delgado-Rodriguez, M. (2006)	United Kingdom	Prognostic evidence level I	Adults with a fracture that had occurred after QUS measurement. Mean age range: 58 ± 7.6 to 82.8 ± 5.9 years	Meta-analysis of 14 prospective cohort studies. Inclusion criteria: studies must include a baseline measurement of QUS, main outcome reported was fracture which must have occurred after QUS measurement and results must be reported as relative risk. Two researchers independently extracted results.	Relative risk for fracture.
Nayak, S. Olkin, I. Liu, H. Grabe, M. Gould, M.K. Allen, I.E. Owens, D.K. Bravata, D.M. (2006)	Stanford, USA	Diagnostic evidence level III-2	Adults with a DXA determined T-score of ≤-2.5 at the hip or spine.	Meta-analysis of 25 studies. Inclusion criteria: studies must use DXA as reference standard, studies must test at least 30 patients with and 30 patients without DXA-determined osteoporosis. Two researchers independently extracted results.	Sensitivity and specificity of calcaneal QUS in diagnosing osteoporosis compared to the reference standard DXA. Studies reported one or more of the following: broadband ultrasound attenuation, speed of sound, velocity of sound, quantitative ultrasound index or stiffness parameters. Regression analysis to predict sensitivity and specificity changes as a function of threshold, calculation of area under the curve as a measure of test accuracy.

Naunton, M. Peterson, G.M. Jones, G. (2006)	Tasmania, Australia	Intervention evidence level IV	345 women at high risk (>65 years) of osteoporosis, with no current diagnosis of osteoporosis, not being treated with osteoporotic medication and had not undergone a DXA scan within the past 2 years. Median age 71 years (range 65-91 years).	All women underwent calcaneal QUS at a community pharmacy. Women with T-score ≤ -1 were referred to their general practitioner.	Number referred for further testing and number taking medication.
Sahota, O. San, P. Cawte, A. Pearson, D. Hosking, D.J. (2000)	Nottingham, United Kingdom	Diagnostic evidence level III-2	60 early post-menopausal women with a DXA determined T-score of > -2.5 at the anteroposterior spine. Age range 45-59 years.	30 women were allocated to treatment with hormone replacement therapy (HRT) and 30 women matched for body mass index and BMD were selected as controls.	The clinical utility of calcaneal QUS measurements in the monitoring of response to HRT therapy. Measurements taken at baseline then annually over a 4-year period.

DXA = dual energy x-ray absorptiometry, QUS = quantitative ultrasound, HRT = hormone replacement therapy

Appendix C: Glossary

DEXA or DXA	dual energy x-ray absorptiometry
QUS	quantitative ultrasound
BMD	bone mineral density
T score	standardised BMD as compared to sex-matched young adults
Z score	standardised BMD as compared to age and sex-matched individuals
HRT	hormone replacement therapy
BUA	broadband ultrasound attenuation
QCT	quantitative computed tomography
SOS	speed of sound
SI	stiffness index calculated from the SOS and BUA
Sensitivity	is the ability of a test to correctly identify those individuals with the disease.
Specificity	is the ability of a test to correctly identify those individuals who do not have the disease.

Appendix D: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.mihsr.monash.org/cce/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

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

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?accueil

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Agency for Drugs and Technology in Health (CADTH)
  http://www.cadth.ca/index.php/en/

- Canadian Health Services Research Foundation (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI)
  http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES)
  http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

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

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM) http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp

- Catalan Agency for Health Technology Assessment (CAHTA) http://www.gencat.net/salut/depsan/units/aatrm/html/en/Du8/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment http://www.cmt.liu.se/

SWITZERLAND

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

UNITED KINGDOM

- NHS Quality Improvement Scotland http://www.nhshealthquality.org/nhsqis/qis_display_home.jsp?pContentID=43&p_applic=CCC&pElementID=140&pMenuID=140&p_service=Content.show&

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/

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

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

UNITED STATES

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

- Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC) http://www.bcbs.com/tec/index.html

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