Australian Government
Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network
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Horizon Scanning Technology Prioritising Summary

Ultrasound for assessment of risk of fracture

October 2007

AHTA
Adelaide Health Technology Assessment

ISBN
Publications Approval Number:

Electronic copies can be obtained from http://www.horizonscanning.gov.au

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PRIORITISING SUMMARY

REGISTER ID: **000343 (REFERRAL)**

NAME OF TECHNOLOGY: **ULTRASOUND FOR ASSESSMENT OF RISK OF FRACTURE**

PURPOSE AND TARGET GROUP: **OSTEOPOROSIS DIAGNOSIS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☐ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☒ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☒ Yes — ARTG number 98149
- ☐ No
- ☐ Not applicable

There are likely to be other ultrasound devices capable of bone density measurements approved by the TGA, however, these could not be identified from the TGA database.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
USA		✓	
Europe		✓	
Japan		✓	
Australia		✓	

IMPACT SUMMARY:

This prioritising summary investigates the effectiveness of quantitative ultrasound (QUS) in predicting and diagnosing osteoporosis related fractures

BACKGROUND

Quantitative ultrasound (QUS) can be used to measure several parameters of bone structure, such as surrogate bone mineral density. Additionally it may also provide information on bone microstructure. It is generally agreed that QUS does not directly assess bone mineral density (BMD) but rather the combination of bone structure with bone density give QUS values that are *strongly correlated* with BMD, and thus, importantly, fracture risk.

Ultrasound is a mechanical wave and, as such, is affected by the mechanical properties of the substrates it passes through. QUS uses transmission of ultrasound through the assessed bone, in contrast to other ultrasound applications, such as foetal ultrasound, which uses pulse-echo methods.

QUS offers many advantages over conventional measures to assess bone health, including being safe, radiation free, portable, and inexpensive when compared to the gold standard, DXA. Additionally, as QUS is affected by more than just bone density, it may give more information about bone health than DXA, such as the structure of the targeted bone.

QUS delivers two directly measured values: broadband ultrasound attenuation (BUA) and speed of sound. QUS assessment is generally performed on the calcaneal (heel) bone. This is becoming an accepted method of measuring bone strength and predicting osteoporetic fracture (Malavolta et al 2004).

Clinical Need and Burden of Disease

Osteoporosis is a major cause of disability and mortality in Australia. From self-reported information, 586,000 Australians have osteoporosis, which constitutes approximately three per cent of the total population. In 2003, an estimate of the proportion of Australians with a disability due to osteoporosis was 50,000 people over the age of 35 years. Osteoporosis is associated with 12,000 disabilities occurring in Australians of working age. Osteoporosis causes major restrictions on lives of those affected with 40 per cent requiring assistance with mobility outside their homes, and 45 per cent reporting profound or severe restrictions on activities such as self-care or mobility (AIHW 2007). Each year in Australia 64,000 hospital separations occur due to bone fractures in the age group 55 and above, many of these fractures may be attributed to osteoporosis. Australia has an ageing population and hence the incidence and prevalence of osteoporosis is expected to increase in coming years. The need for accurate diagnosis is critical as early intervention can facilitate patient improvements and even the prevention of symptoms and disabilities (AIHW 2007).

Diffusion

No direct evidence was found to indicate the diffusion of this technology into general use in Australia, although it seems likely that QUS is being used to some extent given the Australian research published on QUS and the maturity of the technology.

Comparators

Dual-energy X-ray absorptiometry (DXA) has become the gold-standard for measuring bone mineral density and there are well defined international standards for interpreting DXA data for osteoporosis. DXA can be used to measure axial and appendicular sites, although it is generally used to measure density at either the lumbar spine or at the hip. Density as measured by DXA is a real density and is given in units of kg/cm^2. A T-score is derived from this value by comparing it to values derived from sex-matched young adults from the general population. If the T-score is greater than 2.5 standard deviations (SD) less than the mean young adult population value, the patient tested is categorised as having osteoporosis (Table 1).

Table 1 Diagnostic criteria for osteoporosis in specific populations

Population	Diagnostic Criteria for Osteoporosis
Postmenopausal women	T-score of -2.5 or less (based on female reference values)
Men aged >65 years	T-score of -2.5 or less (based on male reference values)
Men aged 50-65 years	T-score of -2.5 or less along with other risk factors for fracture

Adapted from (Singer 2006)

This system is not effective for all members of the population as reported in a 2004 study by Siris et al (2004). This study investigated the ability of T-scores derived from peripheral BMD (either BMD derived from QUS or peripheral DXA) to predict fractures in 149,254 white women aged from 50-104 years (mean 64.5 years). In the twelve months after BMD determination 2,259 fractures, including 393 hip fractures, occurred. Only 6.4 per cent of the women with fractures were in the range of BMD that would classify them as osteoporotic (Siris et al 2004). This highlights the poor sensitivity of the current system of T-scores and classifications (Singer 2006).

Another newly emerging approach to diagnosis osteoporosis is the detection of specific biomarkers for bone turnover. Although, as yet, there is little evidence that these can accurately determine BMD or diagnose osteoporosis (Singer 2006).

SAFETY AND EFFECTIVENESS ISSUES

QUS has many advantages over DXA, such as cost, safety, ease of use and portability and availability, yet despite this there are many unresolved issues which prevent QUS from becoming the standard technique for the diagnosis of osteoporosis. These issues range from the lack of appropriate standards, incompatibility with existing diagnostic criteria designed around DXA, variability in results due to the variation in manufacturers' approaches to US measurements, and user-to-user variability. There is much debate over the exact role that QUS should fill (Malavolta et al 2004).

Much of the current controversy over the role of QUS is due to the complicated interaction of the existing BMD system centred around DXA, and the newer but potentially effective QUS system. This is evidenced by the fact that several studies have shown that prospectively QUS has the ability to predict fractures due to osteoporosis independently of BMD (Bauer et al 1997; Hans et al 1996).

In a longitudinal study[1] on 14,824 men and women who were followed for a mean period of 2 years, the ability of calcaneum BUA to quantitate the risk of fracture was

[1] The European Prospective Investigation into Cancer (EPIC-Norfolk)

assessed (Khaw et al 2004) (prognostic evidence level II). Subjects were recruited from general practice clinics in nine countries. No reference standard was used in this study. Those with the lowest ten per cent BUA values had a relative risk of 4.44 for fracture over a two-year period compared to the subjects with the highest thirty per cent of BUA values. A one-SD drop in BUA paralleled an increased relative risk of fracture of 1.95. Given all the advantages of QUS, this value compares favourably with the relative risk of 2.6 associated with a one-SD fall in a DXA based study (Cummings et al 1993). This study counted all fractures, not just specific osteoporetic fractures. Despite this the relative risk of a hip fracture was 2.2 for a one-SD fall in BUA. There were differences in the relative risk of fracture for men and women, however this was accounted for by the differences in BUA between the sexes (Khaw et al 2004). This major study demonstrated that QUS could be used in both men and women to assess the risk of fracture

A 10 year prospective study involving 3,883 women investigated the ability of DXA and QUS to identify women who are at an increased risk of fracture. DXA was performed on the neck and spine, and QUS was performed on the calcaneus. When considering all fractures suffered by the women, all techniques performed similarly, with a drop of one-SD in the measured values conferring a similar risk of fracture. The hazard ratio (HR) for any fracture per one-SD reduction in spine BMD was 1.61 (95% CI[1.42, 1.83]) and the neck of the femur was 1.54 (95% CI [1.34, 1.75]). The area under the curve (AUC) for a ROC[2] analysis showed spine (AUC= 0.62) and femoral neck (AUC = 0.59) BMD to be significant predictors for all incident fractures (p <0.001). The HR for a one-SD reduction in BUA was 1.53 (95% CI [1.19, 1.96]) and 1.44 (95% CI [1.12, 1.86]) when adjusted for neck BMD. The AUC for BUA was 0.62. There was no significant difference between any of the AUCs (spine, neck of femur and BUA).

When looking at just women who suffered fractures classically attributed to osteoporosis, again all three techniques performed similarly. When neck BMD was accounted for, QUS on the calcaneus was the most accurate at predicting fracture in the population (HR 2.25, [1.51, 3.34], AUC = 0.72). QUS did not, however, perform significantly better than the other two diagnostic modes. The authors conclude that both DXA and QUS are predictive of fracture, however in the case of QUS, this is independent of BMD measurements and therefore may be a better predictor (Stewart et al 2006)(prognostic evidence level II).

A major issue in the field of QUS bone assessment is the lack of standardisation among ultrasound instruments. The variability of results from QUS measurements can be attributed to manufacturer-to-manufacturer approaches to QUS analysis, and the fact that correct and reproducible positioning of US probes are necessary to obtain

[2] ROC = receiver operator characteristic analysis

consistent results. Despite this, QUS has been shown in many studies to be at least as accurate as DXA in identifying women at risk of fracture (Malavolta et al 2004).

COST IMPACT

Kraemer et al (2006) conducted an economic analysis of QUS and DXA utilising a decision analysis model with a hypothetical cohort of 1,000 post-menopausal women. Data on BMD using DXA, QUS values and the incidence of hip fractures were obtained from the Study of Osteoporotic Fractures cohort. Sequential QUS followed by DXA (for those with low QUS values) identified fewer women for treatment than DXA alone. Both approaches prevented nearly three hip fractures per 1,000 women. When using lower QUS cut off values, fewer hip fractures were prevented. Costs and numbers needed to treat were lower at all QUS cut off points and decreased further at lower QUS cut off points. Cost savings were inversely related to fractures prevented. So although a very low QUS cut off value (50 dB/MHz) saved US$355 per women, this was at the expense of an additional 1.42 fractures per 1,000 women. For QUS alone, the number of women identified for treatment, and therefore total costs, increased with an increase in the QUS cut off value. This was also true of the number of hip fractures prevented and the number needed to treat to prevent a hip fracture. QUS alone, at cut off values greater than 65 dB/MHz, prevented more hip fractures than DXA alone, however the number of women identified for treatment and therefore total costs were much higher. At all QUS cut off points above 50 dB/MHz , the number of women needed to treat to prevent one hip fracture was higher for QUS alone than for DXA alone. The authors concluded that sequential QUS followed by DXA on the women who were positive by QUS gave the greatest saving in the number of treatments at the lowest total cost (Kraemer et al 2006).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

There is a large body of literature on QUS, which could not be covered within the scope of this prioritising summary. The largest, most relevant and recent studies were chosen to represent the spectrum of evidence on the subject. A more thorough review would be beneficial as all published data could be assessed.

SUMMARY OF FINDINGS

From the literature reviewed it is apparent that QUS is a safe and effective technique and may also provide both greater access and lower costs compared to DXA. The main issue is the interaction between the emerging technology of QUS and the system in place for the current standard, DXA. A concerted effort is needed to delineate the exact role of QUS, be that as a sole screening tool or as an adjunct to DXA. In addition, issues such as which population QUS is best suited to be used on and at what age still need to be addressed. A set of manufacturing standards for ultrasound instruments used for QUS and for clinicians wishing to utilise QUS may remove much of the confusion from the field.

HEALTHPACT ACTION:

There is a substantial body of literature published on this topic and given the potential benefits, HealthPACT have recommended that a Horizon Scanning report be conducted.

NUMBER OF INCLUDED STUDIES

Prognostic evidence level II	2

REFERENCES:

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Siris, E. S., Chen, Y. T. et al (2004). 'Bone mineral density thresholds for pharmacological intervention to prevent fractures', *Arch Intern Med*, 164 (10), 1108-1112.

Stewart, A., Kumar, V. & Reid, D. M. (2006). 'Long-term fracture prediction by DXA and QUS: a 10-year prospective study', *J Bone Miner Res*, 21 (3), 413-418.

SEARCH CRITERIA TO BE USED:

Bone Density

Bone and Bones/ ultrasonography
Osteoporosis/diagnosis/therapy/ultrasonography
Ultrasonography/history/instrumentation/methods
Densitometry, X-Ray