

# An Update on Dual-Energy X-Ray Absorptiometry

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Dual-energy x-ray absorptiometry (DXA) scans to measure bone mineral density at the spine and hip have an important role in the evaluation of individuals at risk of osteoporosis, and in helping clinicians advise patients about the appropriate use of antifracture treatment. Compared with alternative bone densitometry techniques, hip and spine DXA examinations have several advantages that include a consensus that bone mineral density results should be interpreted using the World Health Organization T score definition of osteoporosis, a proven ability to predict fracture risk, proven effectiveness at targeting antifracture therapies, and the ability to monitor response to treatment. This review discusses the evidence for these and other clinical aspects of DXA scanning. Particular attention is directed at the new World Health Organization Fracture Risk Assessment Tool (FRAX) algorithm, which uses clinical risk factors in addition to a hip DXA scan to predict a patient's 10-year probability of suffering an osteoporotic fracture. We also discuss the recently published clinical guidelines that incorporate the FRAX fracture risk assessment in decisions about patient treatment.

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Osteoporosis is widely recognized as an important public health problem because of the significant morbidity, mortality, and costs associated with its complications, namely, fractures of the hip, spine, forearm, and other skeletal sites.<sup>1</sup> The incidence of fragility fractures is highest among elderly white women, with 1 in every 2 women suffering an osteoporosis-related fracture in their lifetime.<sup>2</sup> Each year in the United States an estimated 2 million people suffer a fragility fracture, with hip fractures alone causing hospitalization, disability, and loss of independence for 300,000 individuals.<sup>3</sup> Hip fractures are often the focus of attention because 20% of patients die in the first year after a fracture, and they also incur the greatest morbidity and medical costs.<sup>4</sup> However, fractures at other sites also cause significant morbidity and costs,<sup>5</sup> and vertebral fractures as well as hip fractures are associated with an increased risk of death.<sup>6,7</sup> In the year 2005, osteoporotic fractures in the United States were responsible for estimated costs of \$19 billion.<sup>3</sup> Due to the aging population the annual number of fractures as a result of osteoporosis is expected to increase to more than 3 million by 2025.<sup>3</sup>

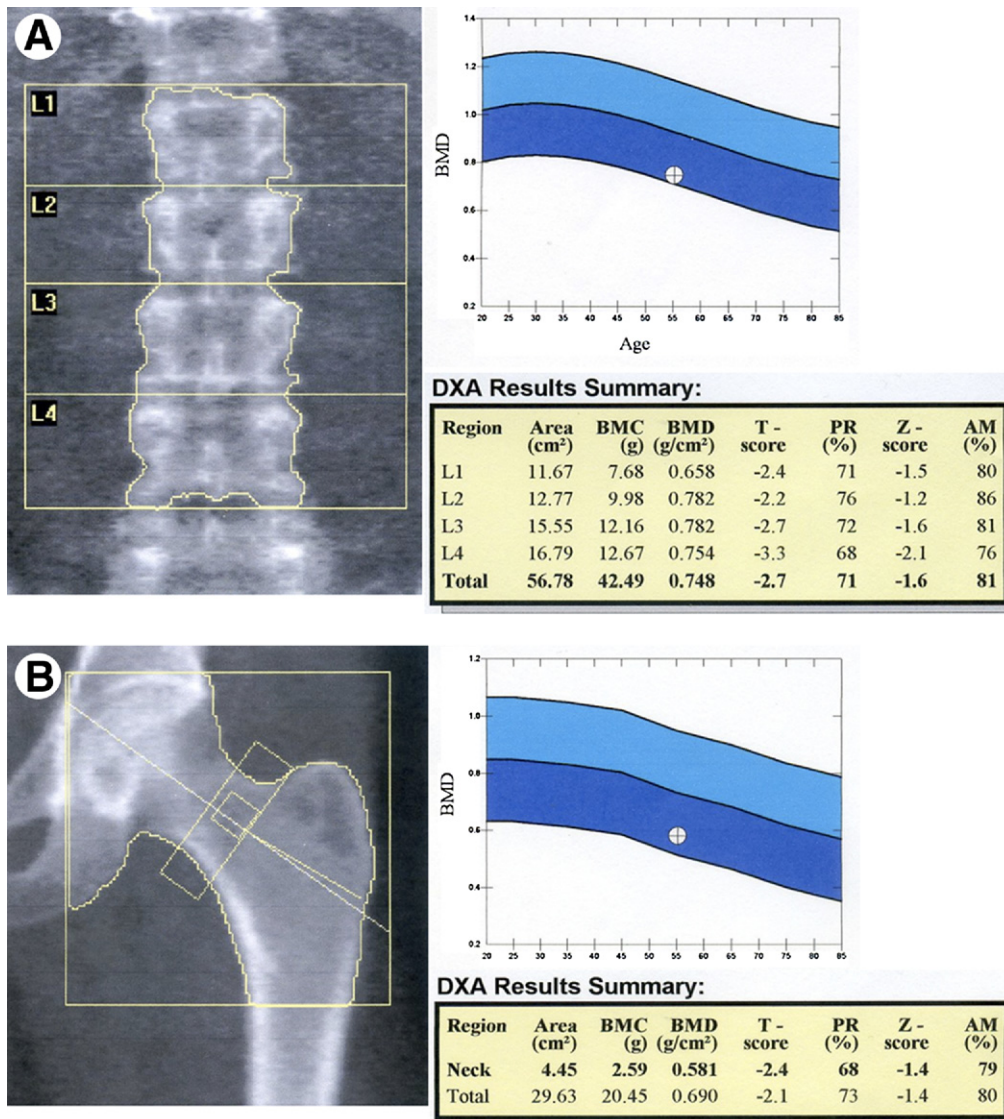
Although for many years there was an awareness of the morbidity and mortality associated with fragility fractures, actual progress only came with the ability to diagnose osteo-

porosis before fractures occur and the development of effective treatments. Measurements of bone mineral density (BMD) played a crucial role in both these developments. Until the mid-1980s, bone-density measurements were used mainly for research, and it was only with the introduction of dual-energy x-ray absorptiometry (DXA) scanners in 1987 that they entered routine clinical practice.<sup>8</sup> Further milestones included the first publication showing that bisphosphonate treatment prevents bone loss,<sup>9</sup> the publication of the World Health Organisation (WHO) report defining osteoporosis in postmenopausal white women as a BMD T score at the spine, hip, or forearm of  $\leq -2.5$ ,<sup>10,11</sup> and the Fracture Intervention Trial confirming that bisphosphonate treatment can prevent fractures.<sup>12</sup> Since then, several large trials have provided evidence of the effectiveness of bisphosphonates,<sup>13-17</sup> selective estrogen receptor modulators,<sup>18</sup> recombinant human parathyroid hormone,<sup>19</sup> and strontium ranelate<sup>20-22</sup> in the prevention of fragility fractures. The most significant recent development is the Fracture Risk Assessment Tool (FRAX) initiative, which enables physicians to use information about a patient's clinical risk factors in combination with a hip DXA scan to assess the 10-year probability of fracture for individual patients.<sup>23</sup>

## The Clinical Role of Bone Density Measurements

Today, BMD measurements have an important role in the evaluation of patients at risk of osteoporosis and in the ap-

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**Figure 1** (A) Scan printout of a spine dual-energy x-ray absorptiometry (DXA) examination. The printout shows (left) scan image of the lumbar spine; (top right) patient's age and bone mineral density (BMD) plotted with respect to the manufacturer's reference range; (bottom right) BMD figures for individual vertebrae and total spine (L1-L4), together with the interpretation in terms of T and Z scores. (B) Scan printout of a hip DXA examination. The printout shows (left) scan image of the hip; (top right) patient's age and total hip BMD plotted with respect to the National Health and Nutrition Examination Survey (NHANES III) reference range<sup>28</sup>; (bottom right) BMD figures for the femoral neck and total hip regions of interest, together with the interpretation in terms of T and Z scores using the NHANES III reference range. (Color version of figure is available online.)

appropriate use of antifracture treatment.<sup>24-27</sup> In general, the preferred method of testing is to use DXA scans to measure BMD of the lumbar spine and hip (Fig. 1).<sup>28</sup> DXA examinations have 3 major roles, namely, the diagnosis of osteoporosis, the assessment of patients' risk of fracture, and monitoring response to treatment. The reasons for using DXA include the fact that hip BMD is the most reliable measurement for predicting hip fracture risk,<sup>29-31</sup> the use of spine BMD for monitoring treatment,<sup>32,33</sup> and the consensus that in postmenopausal white women and older men spine and hip DXA scans should be interpreted using the WHO T score definition of osteoporosis (Table 1).<sup>11,25,34</sup> Other important advantages of DXA include the short scan times, easy set up of

patients for scanning, low radiation dose, and good measurement precision (Table 2).

Patients' DXA results are usually presented as T and Z scores (Fig. 1). T scores are calculated by taking the difference between a patient's measured BMD and the mean BMD in healthy young adults, matched for gender and ethnic group, and expressing the difference relative to the young adult population standard deviation (SD):

$$T \text{ score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young adult population SD}} \quad (1)$$

**Table 1** The WHO Definitions of Osteoporosis and Osteopenia Used to Interpret Spine, Hip, and Forearm DXA Scan Results in Postmenopausal White Women<sup>10,11</sup>

Terminology	T Score Definition
Normal	$T \geq 1.0$
Osteopenia	$-2.5 < T < -1.0$
Osteoporosis	$T \leq -2.5$
Established osteoporosis	$T \leq -2.5$ in the presence of one or more fragility fractures

Z scores are similar to T scores except that instead of comparing the patient's BMD with the young adult mean, it is compared with the mean BMD expected for the patient's peers (eg, for a healthy subject matched for age, gender, and ethnic group):

$$Z \text{ score} = \frac{\text{Measured BMD} - \text{Age matched mean BMD}}{\text{Age matched population SD}} \quad (2)$$

Spine and hip DXA scan results in postmenopausal women and men over the age of 50 years are interpreted using T scores in accordance with the WHO definition of osteoporosis (Table 1). The International Society for Clinical Densitometry recommends using the lowest T score figure between the lumbar spine, femoral neck, and total hip sites.<sup>34</sup> T scores for black and Asian patients should be calculated using the white Caucasian reference range.<sup>34</sup> Before reporting DXA results it is always important to carefully scrutinize the scan image to ensure the scan is correctly analyzed and there are no artifacts over the bone or soft tissue that might affect the interpretation. In elderly patients, the spine T score is frequently elevated due to osteophytes and other signs of degenerative disease. Vertebrae that on visual inspection are obviously affected by such changes should be excluded from the spine analysis. For a spine scan to be regarded as a diagnostic, there should be at least 2 evaluable vertebrae.<sup>34</sup>

DXA results in children and adults under the age of 50 years should be interpreted using Z scores.<sup>34</sup> In children, in particular, BMD results reflect bone size as well as skeletal status, and the results should not be interpreted using T scores.<sup>34,35</sup> DXA examinations in children are best performed at specialist centers with experience in scan interpretation. Numerous approaches to reporting pediatric DXA scans have been published that make allowance for the child's age, height, and sexual maturity.<sup>35,36</sup>

## The Physical Principles of DXA Scans

DXA scanners evaluate BMD by measuring the transmission of x-rays through the body at 2 different photon energies.<sup>37</sup> The mathematical theory of DXA, referred to as basis set decomposition, states that across a broad range of photon energies, the x-ray transmission through any physical object can be decomposed into the equivalent areal densities ( $\text{g}/\text{cm}^2$ ) of any 2 chosen reference materials.<sup>38</sup> The 2 materials for DXA scanning are bone mineral (hydroxyapatite,

$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ) and soft tissue. Provided that the object under study is composed solely of the 2 reference materials, the computed areal densities will accurately reflect the true densities.

As a measurement technique, DXA has 2 important limitations. First, because the scan is a two-dimensional (2D) projection image, the measurements of areal density are affected by bone size as well as the true 3D volumetric density of the bone tissue.<sup>35</sup> This is the basic difficulty with the interpretation of pediatric DXA scans discussed above. However, to a certain extent it affects adult scans as well, causing differences between men and women, black people, and white people, as well as less obvious effects due to different bone sizes in different individuals.

The second limitation of the DXA technique is that for the purpose of x-ray transmission the human body is composed of 3 basic types of tissue, bone, lean, and fat.<sup>39-42</sup> The limitation of only being able to distinguish 2 types of tissue arises from the fact that there are only 2 x-ray attenuation processes involved—Compton scattering and the photoelectric effect.<sup>38</sup> Because these 2 processes have different dependencies on photon energy and atomic number, DXA measurements can distinguish bone from soft tissue because of the higher atomic number of the calcium ( $Z = 20$ ) and phosphorous ( $Z = 15$ ) atoms in bone compared with the carbon, nitrogen, and oxygen atoms in the soft tissue ( $Z = 6, 7, 8$ ). Fat is largely composed of repeated methylene units ( $(\text{CH}_2)_n$ ), whereas the x-ray attenuation of lean tissue is similar to water ( $\text{H}_2\text{O}$ ). The difference in x-ray attenuation between fat and lean tissue is therefore equivalent to the atomic number difference between carbon and oxygen. If the composition of the soft tissue overlying the bone region of interest (ROI) is not known, then this will cause an error in the BMD measurement.<sup>39,42</sup> The size of these accuracy errors is discussed further below.

## DXA Precision Errors

Clinicians who report DXA scans will be aware that BMD measurements are affected by precision<sup>43,44</sup> and accuracy errors.<sup>40-42</sup> Precision errors measure the reproducibility of BMD

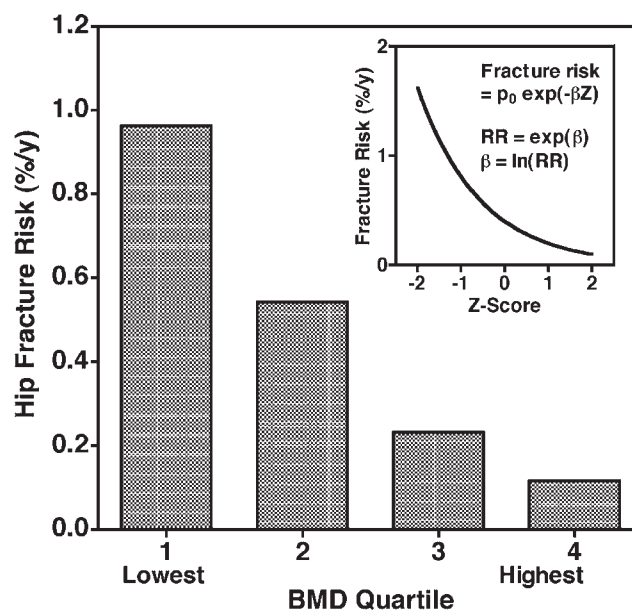
**Table 2** Advantages of Central DXA

- Consensus that BMD results can be interpreted using WHO T scores
- Proven ability to predict fracture risk
- Used in WHO FRAX algorithm for predicting 10-year risk of fracture
- Proven for effective targeting of antifracture treatments
- Good precision
- Effective at monitoring response to treatment
- Stable calibration
- Effective instrument quality control procedures
- Short scan times
- Rapid patient set up
- Low radiation dose
- Availability of reliable reference ranges

results in individual patients and can be demonstrated by performing repeated scans on a representative group of subjects.<sup>34</sup> Precision is usually expressed in terms of the coefficient of variation (CV) and is typically approximately 1%-1.5% for spine and total hip BMD and 2%-2.5% for femoral neck BMD.<sup>45</sup> DXA scanners have excellent long-term precision because their calibration is very stable, and there are effective instrument quality control procedures provided by manufacturers to detect any long-term drifts should they occur. An understanding of precision errors is important for the interpretation of follow-up DXA scans. The BMD changes observed on follow-up scans are interpreted in terms of the least significant change (LSC) equal to approximately 3 times the CV, and only changes greater than the LSC are regarded as clinically significant.<sup>43</sup> The International Society for Clinical Densitometry recommends that each DXA center should determine its own figure for LSC by performing duplicate scans in 30 subjects.<sup>34</sup> However, centers that follow this recommendation should be aware that it has 2 important limitations: (1) precision studies are often performed under optimal conditions that produce an unrealistically optimistic view of what is likely to be achieved in routine practice; (2) a precision study based on performing duplicate scans in as few as 30 subjects results in large statistical errors with a 95% confidence interval of about  $\pm 30\%$  of the measured figure.<sup>44</sup> Thus, a true CV of 1.5% might result in measured values anywhere between 1.0% and 2.0%. To achieve good quality follow-up DXA studies, the most important principles are that (1) technologists should be dedicated and well-trained; (2) careful attention should be focused to the daily instrument quality control procedures as recommended by the manufacturer.

**DXA Accuracy Errors:** The clinical interpretation of DXA scans is also affected by accuracy errors in BMD measurements caused by one of the fundamental limitations of DXA measurements discussed above, namely, that the human body is composed of 3 types of tissue rather than 2.<sup>39-42</sup> Accuracy errors are caused by the inhomogeneous distribution of adipose tissue in the human body and involve both bone marrow and soft tissue that is external to the bone in the path of x-ray beam.<sup>42</sup> They are subtler than precision errors and their clinical effect less easily appreciated, not least because the conditions necessary for a carefully conducted precision study also ensure that any scan-to-scan variation in the soft tissue accuracy error is minimized.

Because of the large thickness of tissue in the abdomen, the areal density of soft tissue for a spine DXA scan is considerably greater than that of bone mineral (range 15-25 g/cm<sup>2</sup> compared with a typical BMD figure of 1 g/cm<sup>2</sup>), and therefore even small differences in x-ray attenuation between lean and adipose tissue discussed above can generate clinically significant measurement errors in the BMD results. In practice, the accuracy error is minimized by comparing measurements over the bone ROI with those in an adjacent soft tissue reference area (Fig. 1). However, errors still arise due to differences in the percentage of adipose tissue between the bone and soft tissue ROI's,<sup>40,46</sup> and to variations in the composition of bone marrow.<sup>47</sup> Accuracy errors are important because



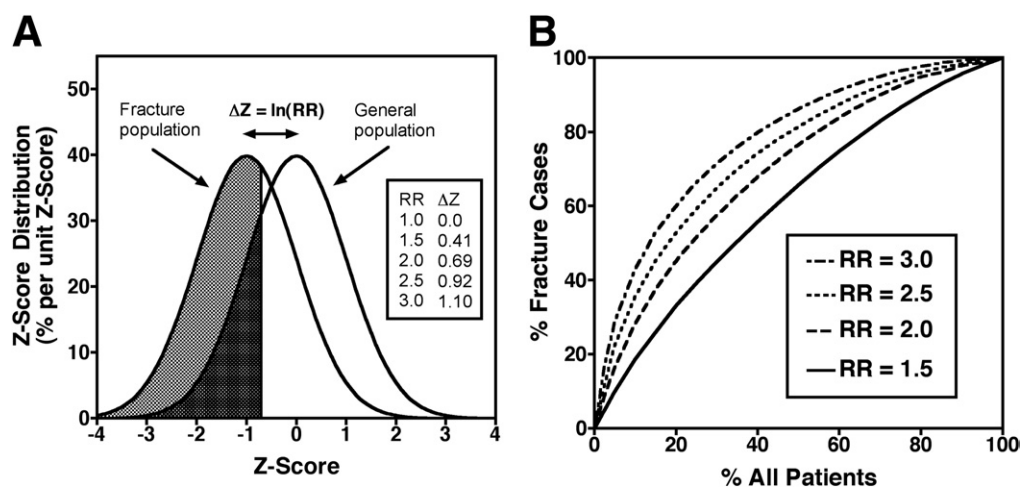
**Figure 2** Incidence of hip fracture risk by bone mineral density (BMD) quartile for femoral neck BMD. Data are taken from the 2-year follow-up of the Study of Osteoporotic Fractures.<sup>62</sup> Inset diagram: data from fractures studies are fitted using a gradient-of-risk model, in which the fracture risk varies exponentially with Z score with gradient  $\beta$ . Results are expressed in terms of the relative risk (RR), which is the increased risk of fracture for each unit decrease in Z score. The value of RR is found from  $\beta$ , using the relationship  $RR = \exp(\beta)$ . Alternatively,  $\beta$  is found by taking the natural logarithm of RR ( $\beta = \ln(RR)$ ).

they may cause the apparent T score value to misrepresent the patient's true bone status.<sup>42</sup>

Although there are simple methods for determining the precision error,<sup>34</sup> the only reliable way of quantifying the soft-tissue accuracy errors is either through cadaver studies,<sup>40,41,48-52</sup> or computed tomography or magnetic resonance imaging studies that image the distribution of adipose tissue and allow the errors to be estimated from theoretic calculations.<sup>46,53,54</sup> Cadaver studies always involve small numbers of individuals (typically 10-20 subjects), and the statistical errors are therefore large. Studies of spine and hip DXA suggest that the patient-to-patient variation in the accuracy error is about 5%-7%, resulting in T score errors ( $\pm 1$  SD) of approximately  $\pm 0.5$ .<sup>42</sup>

## Which Type of Measurement Is Best?

In addition to DXA systems for measuring the spine and hip, a variety of other types of bone densitometry equipment is also available.<sup>8,55</sup> These include quantitative computed tomography (QCT) measurements of the spine and hip,<sup>56,57</sup> peripheral DXA (pDXA) systems for measuring the forearm, heel, or hand,<sup>58</sup> and quantitative ultrasound (QUS) devices for measurements of the heel and other peripheral sites.<sup>59</sup> In principle, pDXA and QUS devices offer a rapid, inexpensive, and convenient method of evaluating skeletal status that



**Figure 3** (A) Distribution of Z score values in a fracture population compared with the age-matched general population. The curve for the general population is a bell-shaped curve symmetrically distributed around its peak at  $Z = 0$ . The corresponding curve for the population of patients who will suffer an osteoporotic fracture is a similar bell-shaped curve that is offset from the general population by a Z score difference of  $\Delta Z = \ln(RR)$ , where  $RR =$  relative risk. The inset table lists values of  $RR$  and  $\Delta Z$ . (B) Plot of the receiver operating characteristic (ROC) curves was obtained by evaluating the areas under the 2 bell-shaped curves shown in (A) up to an arbitrarily chosen Z score threshold and plotting the 2 areas against each other for different values of the relative risk ( $RR$ ). The ROC curve shows the percentage of fracture cases who fall below the BMD threshold (shaded area under the fracture population curve in [A]) plotted against the percentage of subjects in the general population who fall below the same threshold (shaded area under the general population curve in [A]). It therefore shows the true-positive fraction (patients who sustain a fracture and were correctly identified as being at risk) against the false-positive fraction (patients who were identified as being at risk but who never actually had a fracture). The larger the value of  $RR$  the wider the separation of the 2 curves in (A) and the more effective BMD measurements are at discriminating the patients who will have a fracture.

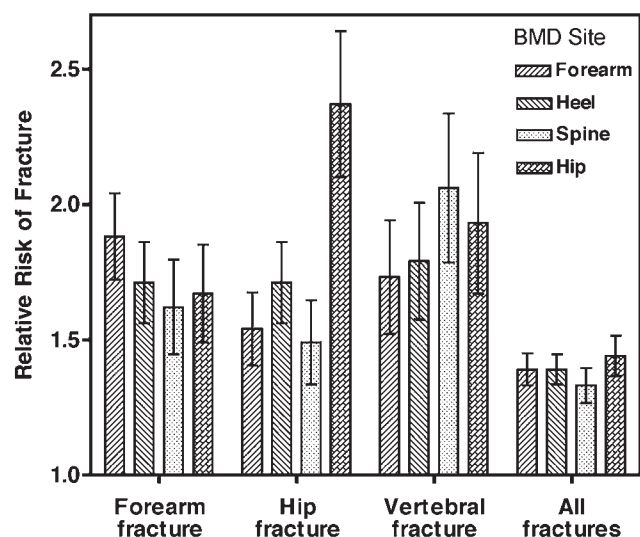
makes them attractive for wider use. In practice, however, these alternative types of measurement correlate poorly with central DXA of the spine and hip, with correlation coefficients in the range  $r = 0.5-0.65$ <sup>60</sup> and consequent random differences in T and Z scores of  $\pm 1.0$ . Thus far, the lack of agreement with central DXA has proved a barrier to reaching a consensus on the use of these other methods.<sup>60,61</sup>

Given the choice of all these different types of measurement, how do we decide which is the most effective one? Fundamental to the clinical application of BMD measurements is their ability to identify patients at risk of fracture, and therefore the most important way of evaluating and comparing different techniques is through prospective studies of incident fractures.<sup>29</sup> Figure 2 shows how data from a fracture study can be analyzed to quantify the relationship between BMD and fracture risk.<sup>62</sup> When patients are divided into quartiles on the basis of their BMD, an inverse relationship is found between fracture incidence and BMD. To describe this relationship, the data are fitted with a gradient-of-risk model in which the fracture probability increases exponentially with decreasing Z score with gradient  $\beta$  (Fig. 2, inset). Results are usually expressed in terms of the relative risk ( $RR$ ), which is defined as the increased risk of fracture for each unit decrease in Z score.

The larger the value of  $RR$  (or equivalently, the steeper the gradient-of-risk), the more effective a technique is at discriminating between patients who will suffer a future fracture and those who will not. To understand the reason for this, con-

sider a large group of subjects chosen randomly from the general population. For such a group, the distribution of Z score values approximates to a Gaussian curve (Fig. 3A). The distribution of Z score values for the group of patients who will at some future date experience an osteoporotic fracture is found by multiplying the Gaussian curve representing the general population by the exponential gradient-of-risk curve. When this is done the distribution of Z score values for the fracture population is found to be a second Gaussian curve with the same SD as the first but with its peak offset to the left by an amount  $\Delta Z$  equal to the gradient-of-risk  $\beta$  (or equivalently to the natural logarithm of the  $RR$ ) ( $\Delta Z = \beta = \ln(RR)$ ) (Fig. 3A).<sup>63</sup>

To understand the importance of selecting a technique with a high  $RR$  value, consider choosing some arbitrary Z score value in Figure 3A as the threshold for making decisions about patients' treatment (eg, this might be the Z score value equivalent to a T score of  $-2.5$ ). The areas under the 2 curves can be evaluated to find the percentages of patients in the fracture population and the general population with Z score results below the chosen threshold. As the threshold is varied and the 2 percentages plotted against each other we obtain a receiver operating characteristic (ROC) curve (Fig. 3B) in which the percentage of true positives (patients who will suffer a fracture in the future and were correctly identified to be at risk) is plotted against the percentage of false positives (patients who are identified to be at risk but who never have a fracture). Figure 3B is fundamental for under-



**Figure 4** Values of the relative risk (RR) (defined as the increased risk of fracture for a 1 SD decrease in BMD) for fractures at different skeletal sites (wrist, hip, spine, and any fracture) for BMD measurements made at 4 different sites (forearm, heel, spine, and femoral neck). The errors bars show the 95% confidence intervals. Data are taken from the 10-year follow-up of the Study of Osteoporotic Fractures (SOF) study population.<sup>30</sup> In the SOF data, the largest value of RR is for the prediction of hip fracture risk from a hip BMD measurement (RR = 2.4). From the ROC curves shown in Figure 3B this means that the clinically most effective DXA scan measurement is to use hip BMD to predict hip fracture risk.

standing the clinical value of any type of BMD measurement used to identify and treat patients at risk of fracture. It shows that the larger the RR value of the measurement technique the more effective it will be at identifying patients with the greatest probability of fracture.

## Results From Fracture Studies

One of the clinical advantages of DXA scans is that their ability to identify patients at risk of fracture has been assessed and proven in a large number of epidemiologic studies.<sup>29</sup> One of the most informative of these is the Study of Osteoporotic Fractures (SOF), a study of 9704 white US women aged 65 years and over who had baseline measurements of hip, spine, forearm, and heel BMD when the study commenced in the late 1980s.<sup>30</sup> The SOF 10-year follow-up data have confirmed the association between BMD and fracture risk with high statistical reliability for many types of fracture and confirm that the prediction of hip-fracture risk from a hip BMD measurement has the largest RR value and is the most effective type of DXA examination (Fig. 4).<sup>30</sup> Another recent study of the relationship between hip fracture and hip BMD based on a meta-analysis of 12 different fracture studies from Canada, Europe, Japan, and Australia found similar RR values to the SOF study in both men and women, but with an age dependence with individuals aged 50-60 years having a larger RR value than subjects aged 80-85 years.<sup>31</sup>

One of the strengths of the SOF study is the large number of fracture cases. To make meaningful comparisons between

different techniques, it is essential to have large studies with several hundred fracture cases to achieve adequate statistical power. As the SOF study has progressed, the results have consistently confirmed the ability of hip BMD measurements to predict hip fracture risk with an RR value of approximately 2.5, with the statistical errors becoming smaller as the number of fractures has increased.<sup>30,62,64</sup>

## Appropriate Targeting of Anti-Fracture Treatments

Another advantage of spine and hip DXA (Table 2) is the proven ability to identify patients who will respond successfully to pharmaceutical treatments for preventing osteoporotic fractures. Table 3 lists the principal clinical trials of the agents proven to prevent vertebral and/or nonvertebral fractures.<sup>12-21</sup> It is notable that all the trials listed enrolled patients on the basis of entry criteria that included a hip or spine T score demonstrating either osteoporosis or severe osteopenia. In some of these trials, the data analysis showed that the treatment was effective only in subjects with a hip or spine T score of  $-2.5$  or less.<sup>13,15,16,21</sup> These findings have created some uncertainty about selecting patients for treatment based on criteria other than a spine or hip T score because of the poor correlation between different techniques and the lack of evidence that individuals chosen using other criteria will respond to treatment.<sup>65</sup>

## Choice of Reference Ranges

Over the last 15 years the interpretation of DXA scans has been guided by the WHO T score definition of osteoporosis (Table 1). However, care is necessary in the choice of reference data for the calculation of T score values if scan results are to be interpreted reliably. For consistency, most guidelines on patient treatment recommend the use of the Third National Health and Nutrition Examination Survey (NHANES III) reference database for T score derivation in the hip.<sup>28</sup> This recommendation resulted from a study that compared the spine and hip T score results calculated using the manufacturers' reference ranges for the 2 most widely used brands of DXA scanner manufactured by GE-Lunar and Hologic, respectively.<sup>66</sup> Although good agreement was found for spine T scores measured on the 2 manufacturers' systems, a systematic difference of almost 1 T score unit was found between the femoral neck T scores. This discrepancy was reconciled by both manufacturers agreeing to adopt the hip reference range derived from the NHANES III study,<sup>67</sup> which was based on measurements of over 14,000 randomly selected men and women from across the whole of the United States. Because there was insufficient time in the NHANES III study to measure spine BMD as well as the hip, spine DXA results are usually interpreted using the manufacturers' reference data.

**Table 3** Fracture Prevention Studies That Have Selected Patients Using Central DXA

Class of Agent	Name of Drug	Study Name	T Score Thresholds for Patient Enrollment <sup>a</sup>
Bisphosphonate	Alendronate	FIT 1 <sup>12</sup>	Femoral neck T score < -1.5 <sup>b</sup>
		FIT 2 <sup>13</sup>	Femoral neck T score < -1.5
	Risedronate	VERT NA <sup>14</sup>	Spine T score < -2 <sup>b</sup>
		HIP <sup>15</sup>	Femoral neck T score < -3.2 <sup>c</sup>
Selective estrogen receptor modulator	Ibandronate	BONE <sup>16</sup>	Spine T score in range -2 to -5 <sup>b</sup>
	Zoledronate	HORIZON <sup>17</sup>	Femoral neck T score < -2.5 <sup>b</sup>
Parathyroid hormone	Raloxifene	MORE <sup>18</sup>	Spine or femoral neck T score < -1.8 <sup>b</sup>
Strontium	PTH (1-34)	Neer's study <sup>19</sup>	Spine or femoral neck T score < -1 <sup>b</sup>
	Strontium ranelate	SOTI <sup>20</sup>	Spine T score < -1.9 <sup>b</sup>
		TROPOS <sup>21</sup>	Femoral neck T score < -2.2

FIT, Fracture Intervention Trial; VERT NA, Vertebral Efficacy With Risedronate Therapy (North America) study; HIP, Risedronate Hip study; BONE, Oral Ibandronate Osteoporosis vertebral fracture trial in North America and Europe; HORIZON, HORIZON Pivotal Fracture trial; MORE, Multiple Outcomes of Raloxifene Evaluation; SOTI, Spinal Osteoporosis Therapeutic Intervention; TROPOS, Treatment of Peripheral Osteoporosis.

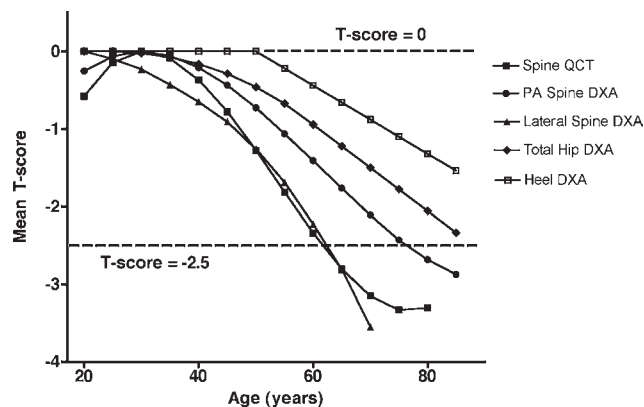
<sup>a</sup>T score thresholds are those calculated using the NHANES III reference range for the hip and the Hologic reference range for spine BMD.<sup>28</sup>

<sup>b</sup>Study entry criteria also included prevalent vertebral fractures.

<sup>c</sup>Study entry criteria also included clinical risk factors.

## Interpretation of T Scores Using the WHO Criteria

As explained above, there is widespread consensus that spine, hip, and forearm DXA measurements should be interpreted using the WHO T score definition of osteoporosis. However, the WHO definition should not be used to interpret QCT or QUS measurements, or pDXA results at sites other than the 33% radius.<sup>34</sup> The reason for this rule can be understood from Figure 5. When the reference ranges for different types of bone density measurement are plotted as graphs of mean T score against age, the curves obtained are found to be different for the different techniques used. For example, the curves for spine QCT and lateral spine DXA



**Figure 5** Age-related decline in mean T scores at different BMD sites for healthy white female subjects. The hip DXA data are taken from the NHANES study.<sup>28,67</sup> The DXA normative data for the PA and lateral spine regions were obtained from the Hologic reference ranges. Heel data are for the GE-Lunar PIXI pDXA device. Spinal QCT is that used by the Image Analysis reference system. Filled circles: PA spine, Filled diamonds: total hip, Triangles: lateral spine, Filled squares: QCT spine, Open squares: heel.

decrease relatively rapidly with age and cross the WHO threshold of  $T = -2.5$  at age 60 (Fig. 5). This means that if we were to interpret QCT and lateral DXA measurements using the WHO criteria we would find that 50% of 60-year-old women had osteoporosis. In contrast, for some types of heel pDXA and QUS devices the curve decreases relatively slowly with age such that patients would need to reach age 100 before 50% of them were found to have osteoporosis. For DXA measurements of the spine, femoral neck, and 33% radius, the 3 curves decrease in a similar manner with age crossing the  $T = -2.5$  threshold at age 75. It is clear that if care is not taken in applying the WHO criteria appropriately then cases of osteoporosis may be either under- or overdiagnosed depending on the measurement technique used. In the analysis of the SOF study data, it was shown that an uncritical application of the WHO definition can lead to the apparent incidence of osteoporosis varying between 3% and 60%.<sup>60</sup> In principle, bone densitometry techniques other than central DXA can be used with appropriate device-specific thresholds to identify a group of patients with high results who are unlikely to have osteoporosis, and a second group with low results who can be treated without further testing.<sup>68</sup> Patients with intermediate results can be referred for a central DXA examination for a definitive decision. However, the clinical application of this triage algorithm requires the availability of adequate information about the device-specific thresholds.

## The WHO FRAX Fracture Risk Algorithm

Views on the best way of using information from DXA scans to advise patients about the use of anti-fracture treatment continue to evolve.<sup>2,24,69,70</sup> As emphasized above, the real clinical value of BMD examinations lies in the information they provide about fracture risk. An important limitation of the WHO T score approach to making decisions about treat-

**FRAX<sup>®</sup> WHO Fracture Risk Assessment Tool**

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### Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country : **US (Caucasian)** Name / ID :  About the risk factors

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth  
Age:  Y:  M:  D:

2. Sex  Male  Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture  No  Yes

6. Parent fractured hip  No  Yes

7. Current smoking  No  Yes

8. Glucocorticoids  No  Yes

9. Rheumatoid arthritis  No  Yes

10. Secondary osteoporosis  No  Yes

11. Alcohol 3 or more units per day  No  Yes

12. Femoral neck BMD (g/cm<sup>2</sup>)  
Hologic  T-score: **-2.2**

**BMI 21.3**  
The ten year probability of fracture (%)  
with BMD

Major osteoporotic	<b>26</b>
Hip fracture	<b>3.3</b>

**Weight Conversion:**  
pound:    
120 pound = 54.43 kg

**Height Conversion:**  
inch:    
63 inch = 160.02 cm

**Figure 6** Calculation of the 10-year probabilities of hip fracture or a major osteoporotic fracture (humerus, forearm, hip, or clinical vertebral fracture) using the WHO Fracture Risk Assessment Tool (FRAX).<sup>23</sup> (Color version of figure is available online.)

ment is that age as well as BMD is an important factor in determining the likelihood of a patient having a fracture within the next 5 or 10 years.<sup>2,24,71</sup> For any hip T score figure, fracture risk in men and women between the ages of 50 and 90 years varies greatly according to age.<sup>2,71</sup> The FRAX initiative is a new approach to the use of BMD scans that seeks to improve decisions about treatment by basing them on the 10-year probability of the patient sustaining an osteoporotic fracture (Fig. 6).<sup>23</sup> This has a number of advantages, including the targeting of osteoporosis treatment according to the patient's risk of fracture,<sup>2</sup> the incorporation of additional clinical risk factors (Table 4), such as a history of previous fracture to refine the algorithm for estimating fracture probability,<sup>24</sup> and the use of health economic criteria to set thresh-

**Table 4** Clinical Risk Factors Included in FRAX Algorithm<sup>23</sup>

- Country or geographic region
- Ethnic origin (US only)
- Age
- Gender
- Weight and height (BMI)
- Previous history of fracture (after age 50)
- Parental history of hip fracture
- Current smoking habit
- Current or past use of corticosteroids
- Rheumatoid arthritis
- Secondary osteoporosis
- Alcohol intake  $\geq 3$  units daily
- Hip BMD

olds for intervention based on the costs of treatment, savings to health services, and the contribution of fracture prevention to patients' quality of life.<sup>69</sup>

The value of using information from additional risk factors that give independent information about fracture probability over and above that provided by age and BMD can be explained by reference to the ROC curve shown in Figure 3B. With all types of bone densitometry measurement, the fracture and nonfracture patients have overlapping BMD distributions (Fig. 3A), leading to ROC curves (Fig. 3B) in which at any given T score threshold, only a certain percentage of future fracture cases are identified for treatment at the cost of also treating a large number of patients who are not going to have a fracture. As explained above, the best that can be done with bone densitometry alone is to choose the BMD measurement site with the highest RR value that will optimize the ROC curve. However, by combining BMD data with age and other appropriately chosen risk factors (Table 4), the ROC curve can be further improved so that treatments are better targeted on the patients at the highest risk.<sup>72</sup>

The new WHO FRAX algorithm is based on a series of meta-analyses of data from 12 independent fracture studies from North America, Europe, Asia, and Australia.<sup>73-78</sup> These enrolled a total of 60,000 men and women with more than 250,000 person-years of follow-up, and included more than 1100 cases of hip fracture and 3300 osteoporotic fractures.<sup>73</sup> After the fracture risk algorithm had been constructed using these studies as the primary data, a validation study was performed using data from 11 independent population-



based cohorts that were not used in the development of the original model.<sup>72</sup> These latter involved a total of 230,000 subjects with more than 1.2 million person-years of follow-up. By reason of its large numbers, its international character, and the care taken in its construction and implementation the FRAX algorithm has unique authority.

Because of the need to build the correct parameters into the model, including the interdependence of the various risk factors, there is a specific requirement that the BMD information is obtained from a hip DXA scan. Although femoral neck BMD was used in the development of the FRAX algorithm, the website states that total hip BMD may be used instead.<sup>23</sup> The reliance on BMD measurements from a single skeletal site raises the question of whether fracture risk prediction might be improved by combining BMD data from more than one site. Interestingly, and perhaps contrary to intuition, a meta-analysis of the spine and femoral neck BMD data showed that addition of the spine site does not improve the ROC curve.<sup>79</sup> Although this finding may seem surprising, a mathematical analysis supplies the reason: although hip and spine BMD measurements are quite poorly correlated ( $r = 0.5-0.65$ ), even this degree of correlation is too high for a second BMD site to provide worthwhile additional information about fracture risk.<sup>80</sup> However, it is important to ask the question what information is lost by relying on just a single BMD site. The FRAX website provides information on the 10-year risks of hip fracture and any major osteoporotic fracture (defined as a hip, wrist, humerus, or clinical vertebral fracture).<sup>23</sup> Hip BMD is the best predictor of hip fracture risk, and all DXA sites are more or less equally effective at predicting a fragility fracture at any site. However, if one wished to specifically predict the probability of a vertebral fracture, then there is evidence that a spine BMD measurement is more effective for this purpose than hip BMD.<sup>29,81</sup>

The FRAX website may also be used to evaluate 10-year fracture risk using clinical risk factors alone without BMD information.<sup>23,27</sup> This enables it to be used in a triage approach to select patients for DXA examination for whom the BMD information is most likely to make a significant contribution to their management.<sup>27,82</sup> A website provided by the United Kingdom National Osteoporosis Guidelines Group (NOGG) uses a “traffic light” scheme to divide patients into a red zone (those who justify fracture prevention treatment on the basis of clinical risk factors alone), a green zone (those who can be reassured that they are at low risk and a DXA scan is unlikely to change this), and an orange zone (those who should go for a DXA scan before deciding on any treatment).<sup>83</sup>

Another advantage of the new FRAX approach is that it enables fracture risk thresholds for intervention to be established based on economic criteria that can be adjusted for practice in different countries.<sup>84,85</sup> A series of health economic analyses have examined the rationale for fracture prevention and the cost-effectiveness of different osteoporosis treatments.<sup>86-90</sup> These analyses show that, taking account of all types of fracture, the cost-effective intervention thresholds correspond to T score values between  $-2$  and  $-3$  over an age range of 50-80 years.<sup>24,69</sup>

**Table 5 Treatment Criteria from the National Osteoporosis Foundation 2008 Guidelines<sup>25</sup>**

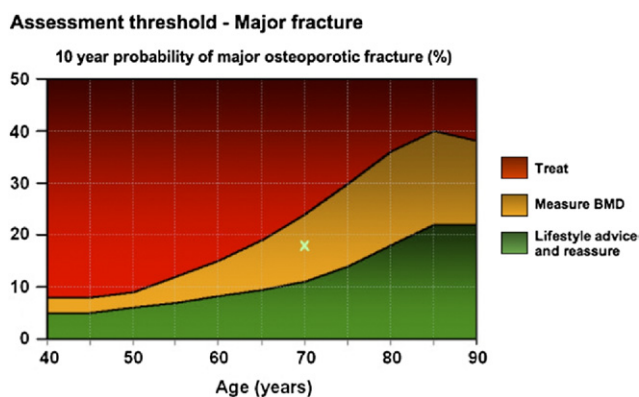
<p><b>Postmenopausal women and men age 50 and older regardless of ethnicity who meet one or more of the following criteria:</b></p> <p><b>A previous hip or vertebral fracture</b></p> <p><b>T score <math>-2.5</math> or less at the femoral neck, total hip, or spine</b></p> <p><b>T score between <math>-1.0</math> and <math>-2.5</math> at the femoral neck, total hip, or spine and one or more of the following:</b></p> <p><b>a. Other previous fractures</b></p> <p><b>b. A secondary cause of osteoporosis associated with a high risk of fracture</b></p> <p><b>c. 10-year fracture risk as assessed by FRAX of 3% or more at the hip or 20% for a major osteoporosis-related fracture (humerus, forearm, hip, or clinical vertebral fracture)</b></p>
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## New Treatment Guidelines Incorporating FRAX

The launch of the FRAX website in 2008 was followed by the publication of new guidelines with recommendations on how estimates of 10-year fracture probability should be incorporated into decisions about patient treatment.<sup>25,27</sup> Most commentators have noted that treating patients solely according to their fracture risk results in fewer younger individuals receiving treatment because, although they might have a low T score, their short-term risk of fracture is small. Instead, treatment is directed toward elderly patients who, even if they do not meet the T score definition of osteoporosis, are at high risk because of their age.

The first of these new guidelines was published by the US National Osteoporosis Foundation.<sup>25</sup> This is directed at the treatment of postmenopausal women and men age 50 and older who, regardless of ethnicity, meet one of the following criteria (Table 5): a previous hip or vertebral fracture, a hip or spine T score of  $-2.5$  or less, or (among several supplementary criteria) those with a 10-year fracture risk as assessed by FRAX of 3% or more at the hip and 20% or more for a major osteoporosis-related fracture. Compared with the previous National Osteoporosis Foundation guidelines, the new recommendations mean that greater numbers of elderly patients will receive treatment at the expense of some younger patients who met the less restrictive criterion used previously of a hip T score of  $-2.0$  or less.

In the United Kingdom, a different treatment algorithm was issued by the NOGG group.<sup>27,83</sup> Users of the FRAX website who select the United Kingdom as the country of origin are given the option of viewing the 10-year fracture probability plotted on a graph with a traffic light color scheme (Fig. 7).<sup>23</sup> On the basis of clinical risk factors alone, this can be used to triage patients and determine whether they should be sent for a DXA scan. After the BMD result is known the data can be re-entered at the FRAX website and a definitive treatment recommendation obtained. Notably, the NOGG algorithm has a fracture threshold for treatment that varies with



**Figure 7** Output from the UK National Osteoporosis Guidelines Group website.<sup>83</sup> The traffic light color scheme shows the patient's 10-year probability of a major osteoporotic fracture plotted against age. If the result lies in the orange zone, the patient should be sent for a DXA examination and the clinical risk factors re-evaluated together with the hip BMD result for a definitive decision on treatment. If the result lies in the red or green zones then either treatment should be considered or the patient reassured that they are a low risk. (Color version of figure is available online.)

age. This is because the threshold for recommending treatment is based on the patient having a 10-year fracture risk equivalent to that of an individual who has just experienced their first osteoporotic fracture.<sup>27</sup> This choice serves to partly reverse the bias in FRAX toward the treatment of older patients.

## Monitoring Response to Treatment

Verifying response to treatment using follow-up DXA scans is widely believed to have a beneficial role in encouraging patients to continue taking their medication, and also in identifying nonresponders who may benefit from a different treatment regimen. Central DXA has a number of advantages as a technique for monitoring patients' response, of which one of the most important is the good precision of BMD measurements (see discussion of precision errors above). A second requirement for effective patient monitoring is a measurement site that shows a large response to treatment. The best BMD site for follow-up measurements is the spine because the treatment changes are usually the largest and the precision error is as good or better than that at most other sites.<sup>91,92</sup> Nevertheless, the limited sensitivity means that the use of DXA scanning for patient monitoring is more controversial than its use for the diagnosis of osteoporosis and prescription of treatment. If used for this purpose, follow-up scans should not be performed more frequently than every 1-2 years. When comparing BMD changes on follow-up scans with the LSC figure it is important to bear in mind that in some subjects who are seriously overweight or experience large weight changes precision might be significantly poorer than usual.<sup>45</sup>

## Postscript

The evolution of ideas about the clinical role of bone densitometry has some way to go before they can be regarded as well grounded in science. One important question is the scientific rationale for the continued use of T scores.<sup>93</sup> The FRAX assessment tool makes it abundantly clear that a low BMD result is best regarded as just another clinical risk factor for fracture (Table 4). Given the magnitude of the soft-tissue accuracy errors ( $\pm 0.5$  T score units) and the discordant T scores between different skeletal sites ( $\pm 1$  T score unit), it does not seem plausible that BMD measurements should continue to be regarded as a uniquely special indicator of skeletal status. An important merit of the FRAX scheme is that it directs attention to the primary importance of achieving the best ROC curve possible.<sup>72</sup> In contrast, developments based around T scores can all too easily ignore the fact that the central clinical requirement of bone densitometry is effective discrimination between high- and low-risk individuals. Although the T score paradigm has been beneficial and an important factor behind the large expansion in the clinical application of bone densitometry over the past 15 years, it has also proved a poor guide to the best avenues for further development of the field, and has led to much effort being directed at irrelevant issues.<sup>93</sup> From a scientific perspective T scores are an unnecessary imposition between a BMD measurement and the evaluation of the patient's risk of fracture.

Arriving at a well-founded appreciation of the strengths and limitations of DXA requires that more attention is paid to some important technical issues, such as the soft-tissue accuracy errors that affect spine and hip measurements, the limitations of relying on 2D projection images that fail to allow for bone size, and the discordant evaluations of skeletal status obtained from different BMD sites. This review has emphasized these issues because too often their significance for the clinical applications of DXA is overlooked or ignored. We have argued elsewhere that the central limitation to the clinical utility of bone densitometry is the large overlap of the fracture and nonfracture populations shown diagrammatically in Figure 3A, and that although the BMD accuracy errors might seem large, in the end, they are not that important because they do not significantly degrade the ROC curve.<sup>42</sup> The problem of discordant findings from different BMD sites is an issue that should not be ignored. In principle, all types of bone densitometry measurements are of equal value. However, given the problem of discordant T scores, it is unavoidable that different types of measurement will select different sets of individuals from the entire group of patients who will sustain a future fracture. In the end, the only thing that really matters is that we decide to use that measurement or a combination of measurements that provides the optimum ROC curve.

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