

## CLINICAL PRACTICE

## Screening for Osteoporosis

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**At her annual visit, a 60-year-old woman asks her physician whether she should have a bone-density test to screen for osteoporosis. The patient went through menopause at age 52 and received postmenopausal hormone therapy for four years. She takes 500 mg of calcium twice daily and exercises regularly. She has no personal history of fractures, but her mother had a hip fracture at the age of 82. Her height is 63 in. and her weight is 120 lb. What should her physician advise?**

## THE CLINICAL PROBLEM

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Fractures due to osteoporosis are a principal cause of disability and death.<sup>1,2</sup> Approximately 1.5 million fragility fractures (fractures occurring after trauma no greater than a fall from a standing height) occur annually in the United States, and this number will increase as the “baby boomers” reach their 70s. Fewer than one third of patients who have had fragility fractures are appropriately evaluated and treated for osteoporosis,<sup>3-5</sup> despite a high risk of future fractures. The rates of diagnosis are even lower among those who have not yet had a fracture. Practitioners should routinely recommend that patients have an adequate total intake of calcium (1200 mg per day for postmenopausal women) and of vitamin D (400 to 800 IU per day) and participate in weight-bearing exercise — interventions that are safe and inexpensive. However, the incidence of fractures among patients in high-risk control groups who have received calcium and vitamin D in clinical trials is still high.<sup>6</sup> A discussion of pharmacotherapy is beyond the scope of this review, but certain drugs can substantially reduce the risk of fracture in women at high risk for osteoporosis on the basis of bone mineral density and other factors.<sup>7,8</sup> Thus, it is important to identify these patients by appropriate screening.

Current data indicate that too few bone-mineral-density measurements are obtained among patients in high-risk groups.<sup>3</sup> On the other hand, there is a clinical impression that there may be too many measurements obtained among early postmenopausal or premenopausal women, who are at low risk for fracture.

## STRATEGIES AND EVIDENCE

Measurement of bone mineral density at the lumbar spine and proximal femur by dual-energy x-ray absorptiometry is a reliable and safe way to assess the risk of fracture in postmenopausal women.<sup>9,10</sup> However, many other factors (which are reviewed below) influence fracture risk and should be considered in making recommendations regarding bone densitometry and therapy.<sup>11,12</sup>

Screening for osteoporosis should ideally provide an estimate of the absolute risk of any fragility fracture during the subsequent 5 or 10 years.<sup>5</sup> More work is needed to refine such predictions, but some estimates are available. For example, the absolute

10-year risk of a fragility fracture in a postmenopausal woman with a T score indicating low bone mineral density—which is defined as a value 2.5 SD or more below the mean for a young adult (T score,  $-2.5$  or less)—and no other risk factors is less than 5 percent at the age of 50 but more than 20 percent at the age of 65. Absolute risk increases further with additional risk factors, particularly a previous fragility fracture.<sup>13</sup>

Estimates of relative risk associated with various factors differ among studies, but there is general consensus regarding the importance of several key factors in risk assessment. In postmenopausal white women, the relative risk of fracture is increased by a factor of 1.5 to 3 for each decrease of 1.0 in the T score, depending on the site measured.<sup>6,9,14,15</sup> The relative risk increases by a factor of 2 to 3 per decade after the age of 50.<sup>16,17</sup> The risk increases by a factor of 1.2 to 2 for patients who have a family history of fracture in a first-degree relative, who weigh less than 126 lb (57 kg), who have recently lost 10 lb or more of weight, who had a delayed menarche (e.g., at an age of more than 15 years), or who currently smoke.<sup>18-21</sup> These factors are also associated with a greater likelihood of low bone mineral density.

The most important risk factor for fracture, independent of bone mineral density, is a previous fragility fracture. This history increases the risk of future fractures by as much as a factor of 8; the risk is highest in the first year or two after the initial episode.<sup>6,22</sup> Silent vertebral fractures (identified radiologically) also increase the risk and should be looked for in patients who have lost more than 2 cm of height.<sup>23</sup> There is also an association between traumatic fractures and osteoporosis,<sup>24</sup> and thus any fracture in a postmenopausal woman should prompt consideration of bone-density measurement.

Falls are another important predictor, particularly for hip fracture in the elderly. Hence, factors that increase the risk of falling—such as impaired vision, neuromuscular deficits, or medications that affect balance—should also be assessed.<sup>25</sup> Several other risk factors should be assessed, although their relationship to bone density and fractures is less clear-cut. Low intake of alcohol (one to two drinks per day) is associated with increased bone mineral density, but higher intakes are associated with low bone mass and an increased risk of fracture, perhaps related to falls.<sup>26</sup> Low 25-hydroxyvitamin D levels (less than 20 ng per milliliter) in-

crease the risk of fragility fractures; this is attributed not only to lower bone mineral density but also to a direct neuromuscular effect of vitamin D that may reduce the frequency of falls.<sup>27,28</sup>

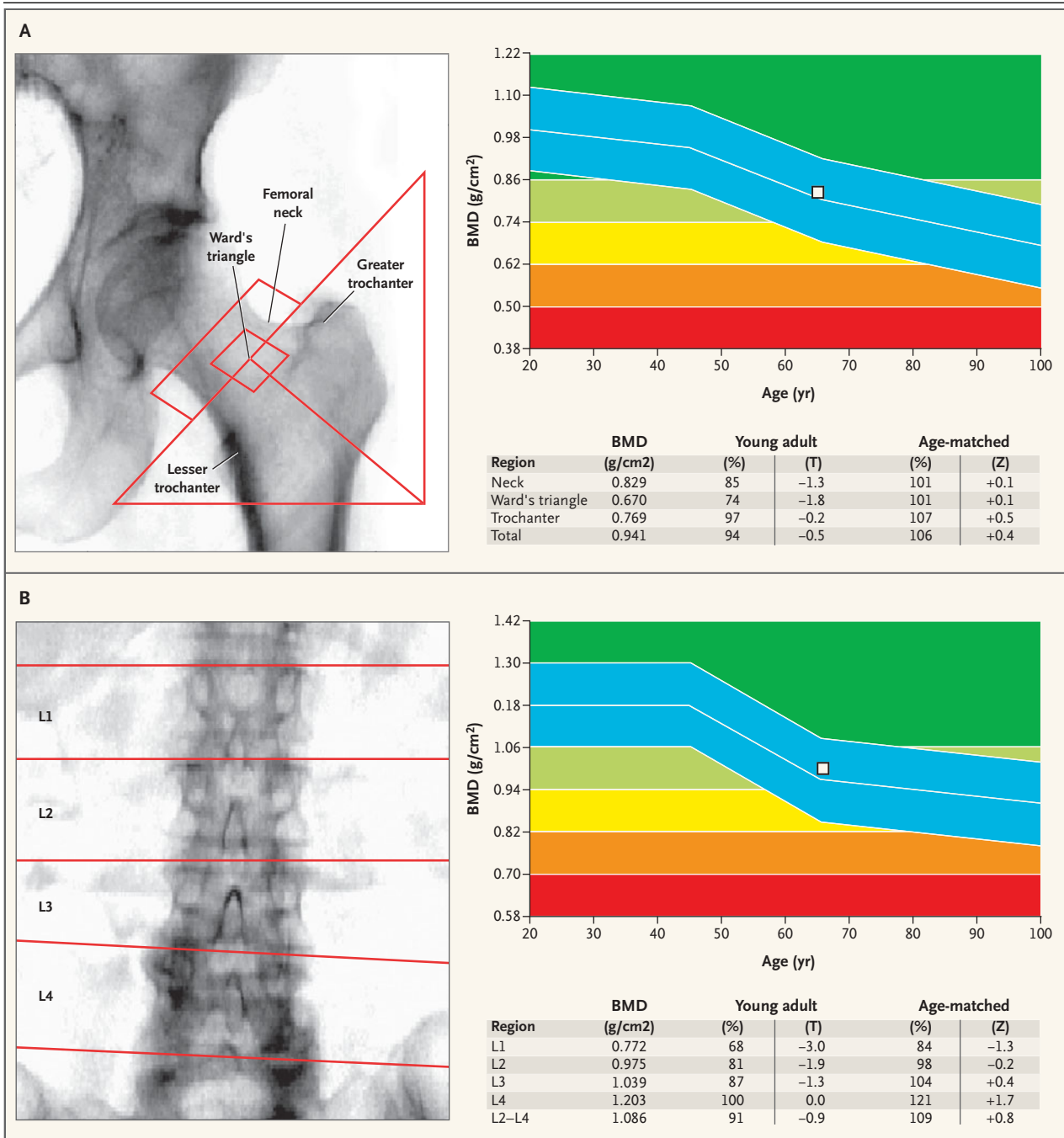
Patients with inflammatory disorders involving the musculoskeletal, gastrointestinal, or pulmonary system and patients who have chronic renal disease or have undergone organ transplantation are also at increased risk for low bone mineral density and fracture.<sup>29,30</sup> Medications, particularly glucocorticoids, may be an aggravating factor. Discontinuation of postmenopausal estrogen therapy may result in accelerated bone loss. Other at-risk populations include patients with hypogonadism due to drugs such as luteinizing hormone-releasing hormone agonists and aromatase inhibitors, with anorexia nervosa, or with the “athletic triad” of low body weight, loss of menses, and low bone mineral density.<sup>31-35</sup> Neurologic diseases can cause bone loss due to immobilization and to the adverse effects of antiepileptic drugs on vitamin D homeostasis.<sup>36,37</sup> Less common causes include congenital abnormalities such as osteogenesis imperfecta and homocystinuria, cancer involving the skeleton (particularly myeloma), and hyperplastic anemia.<sup>30,38</sup>

#### BONE DENSITOMETRY

##### *Dual-Energy X-Ray Absorptiometry*

In 1991, a consensus panel defined osteoporosis as “a loss of bone mass and microarchitectural deterioration of the skeleton leading to increased risk of fracture.”<sup>39</sup> Since microarchitectural deterioration cannot be directly measured, a panel of the World Health Organization (WHO) recommended that the diagnosis of osteoporosis be made when the T score on bone-mineral-density measurement by dual-energy x-ray absorptiometry is  $-2.5$  or lower.<sup>40</sup> They also suggested that the term “osteopenia,” or “low bone mass,” be applied when T scores are from  $-1.0$  to  $-2.5$ . Because there are many more persons with osteopenia than persons with osteoporosis, approximately half of fragility fractures occur in the osteopenic group, although the relative risk of fracture is higher in the osteoporotic population.<sup>14</sup>

The current practice is to perform dual-energy x-ray absorptiometry of the lumbar vertebrae (L1 to L4); the hip, including the femoral neck, Ward’s triangle, the greater trochanter, and the total hip (which includes all these measures)<sup>41</sup>; or both (Fig. 1). The results are presented visually, includ-



**Figure 1.** Dual-Energy X-Ray Absorptiometry of the Spine and Hip of a 66-Year-Old Postmenopausal Woman.

A diagnosis of osteoporosis can be made in this patient on the basis of the bone mineral density (BMD) of the hip (Panel A) and the spine (Panel B). The density of lumbar vertebrae 1 through 4 (L1 through L4), both as a percentage of the mean value for a young adult and as a T score, does not indicate osteoporosis, because of the high values for L3 and L4. Since the latter probably reflect osteoarthritic changes in the spine, the use of the two lowest values is recommended for diagnosis.<sup>41</sup> Note that in this patient the T scores at the hip are relatively high, as compared with the spine. The density of the total hip includes the lesser trochanter and adjacent cortical bone and thus has a higher value. The red lines on the left side of each panel indicate the specific area being measured, and the blue areas on the right side indicate the expected age-related means ( $\pm 1$  SD) for white women. Bone-mineral-density measurement results in less than 10 mrem of radiation exposure, as compared with 30 to 60 mrem for a chest radiograph. The color stripes in each panel indicate the degree of concern related to bone density; red denotes high concern and green low concern.

ing both T scores and Z scores (the bone density in the patient as compared with other people of the same age and size expressed as the number of SDs above or below the mean). Of the hip measures, the femoral neck and total hip, in particular, are the most useful in predicting fracture, whereas measurements of Ward's triangle show great variation and are of little clinical value. Although it has been suggested that the WHO definition of osteoporosis should be reserved for patients with low T scores for the total hip, low T scores at other sites are also considered diagnostic of osteoporosis. Spinal measurements may be particularly important in younger postmenopausal women, since they may show osteoporotic values earlier than the hip.

A problem with spinal measurements in older women, however, is that sclerotic changes that occur with age, largely owing to osteoarthritis, may result in an artifactual increase in measured bone mineral density. A careful examination of the actual dual-energy x-ray absorptiometry printout may help resolve this issue. Measurement of mineral density in forearm bone is not used routinely but is recommended for patients with primary hyperparathyroidism, since this site may show the greatest bone loss.<sup>42</sup> Z scores are more informative than T scores in young persons, since the scoring allows comparison of bone density with persons of similar age, height, and weight. More generally, a Z score of  $-2.0$  or lower is considered an indication of the need for more intensive evaluation of possible secondary causes of bone loss,<sup>30,43</sup> although such causes should be considered in all cases.

#### *Quantitative Computed Tomography*

Bone density can also be measured by quantitative computed tomography (CT).<sup>44</sup> This technique can analyze trabecular and cortical bone separately and is a sensitive measure of early bone loss in the vertebrae. However, the application of T scores to predict the risk of fracture with the use of quantitative CT has not been validated, and this technique is usually more costly and results in greater exposure to radiation than does dual-energy x-ray absorptiometry.

#### **PERIPHERAL MEASUREMENTS**

Because of the limited availability, lack of portability, and relatively high cost of dual-energy x-ray absorptiometry, screening with the use of peripheral densitometry has been developed. These techniques include peripheral dual-energy x-ray absorp-

tiometry, x-ray absorptiometry, and ultrasonography of the radius, heel, and hands. The finding of decreased bone mineral density with these techniques predicts an elevated risk of fracture. However, the interpretation of T scores may not correspond to that of central dual-energy x-ray absorptiometric measurements.<sup>45</sup> Peripheral measurements can be used to assess whether dual-energy x-ray absorptiometry is indicated. To ensure that few patients with low bone mineral density are missed, the use of a conservative cutoff value (for example, a peripheral T score of  $-1.0$  or lower) is prudent. Peripheral measurements should not be used for decision making in regard to diagnosis and management.

#### **SELECTING PATIENTS FOR BONE DENSITOMETRY**

A number of recommendations for decision making in regard to bone-mineral-density screening have been developed, but all of these strategies have limitations.<sup>46</sup> The Osteoporosis Self-Assessment Tool, which uses a formula based only on age and body weight, results in a recommendation for testing in 90 percent of women who have osteoporosis but also in as many as 60 percent of women who do not. More complex formulas using other risk factors have not been shown to enhance sensitivity and specificity by very much. Current guidelines (which are summarized below) recommend that all women have a measurement of bone mineral density at the age of 65 years (in selected women, earlier). If these guidelines are used, recommendations in regard to decision making would be needed only for younger women and men, for whom the sensitivity and specificity of the recommendations have not been evaluated.

Strong indicators of the risk of future fracture are considered to be a basis for the recommendation of bone-mineral-density testing before the age of 65 years. A prior fragility fracture warrants bone mineral density testing not only among postmenopausal women but also among men and premenopausal women. A family history of fracture, low body weight, and a loss of either weight (5 percent of baseline weight or more) or height are additional indications,<sup>23,47</sup> as are conditions or drugs known to be associated with bone loss, including primary hyperparathyroidism, hyperthyroidism, hypogonadism (due to disease or drugs), Cushing's syndrome, and long-term glucocorticoid therapy (for example, prednisone at 5 mg or more daily for six months or more<sup>31</sup>). Although there is less evidence on which to base a decision in regard to the

need for bone densitometry in men and in nonwhite postmenopausal and premenopausal women, low bone mineral density also increases the risk of fracture in these groups.<sup>17,48</sup> Hence, pending further information, it is logical to consider a history of fragility fracture, height loss, and the presence of secondary causes of osteoporosis to be indications for bone mineral density measurement.

#### LABORATORY ASSESSMENT

Laboratory assessment is not used to screen for the presence of osteoporosis but is routinely indicated in patients with low Z scores (for example,  $-2.0$  SDs or below) and may be useful in other patients with low bone density, with the goal of identifying secondary causes (such as elevated serum calcium levels suggesting hyperparathyroidism) or factors that can aggravate bone fragility (such as a low level of 25-hydroxyvitamin D) that can be treated. Clinical or laboratory evidence of disorders such as hyperthyroidism, glucocorticoid excess, gonadal dysfunction, gastrointestinal or renal disease, and cancer warrants appropriate testing. Patients with low bone mineral density and weight loss should be screened for celiac disease, even if they do not have gastrointestinal symptoms.<sup>49</sup>

Biochemical markers of increased bone resorption (collagen cross-links in serum or urine) or increased bone formation (bone-specific alkaline phosphatase and osteocalcin) are associated with an increase in fracture risk.<sup>12</sup> However, these markers show substantial variability, and there are insufficient data to support their use in deciding for or against bone densitometry or pharmacotherapy.<sup>50</sup>

sorptiometry systems, which can measure vertebral-body shape and size and detect such “silent” fractures, is uncertain.<sup>51</sup>

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#### GUIDELINES FROM PROFESSIONAL SOCIETIES

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The U.S. Preventive Services Task Force (USPSTF), the National Osteoporosis Foundation (NOF), and the American Association of Clinical Endocrinologists (AACE) have recommended that all women should have a measurement of bone mineral density at the age of 65 years.<sup>52-54</sup> This recommendation is based on the sharp increase in the incidence of fracture that occurs in association with low bone mineral density after the age of 65, as well as clinical trials showing a reduction in the risk of fracture when these women are treated. The USPSTF recommends that women who are 60 to 65 years old and have multiple risk factors undergo bone-mineral-density testing, whereas NOF and AACE suggest that any postmenopausal woman with multiple risk factors should be tested; however, the guidelines do not specify how risk factors should be assessed or weighted. The International Society for Clinical Densitometry and AACE have provided additional guidelines for testing in men, premenopausal women, and children.<sup>41</sup> These guidelines recommend bone-mineral-density testing in patients who have diseases or are receiving drugs that are likely to cause secondary osteoporosis (including glucocorticoids, antiepileptic drugs, luteinizing hormone-releasing hormone agonists, and aromatase inhibitors) and in all patients with fragility fractures.

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#### AREAS OF UNCERTAINTY

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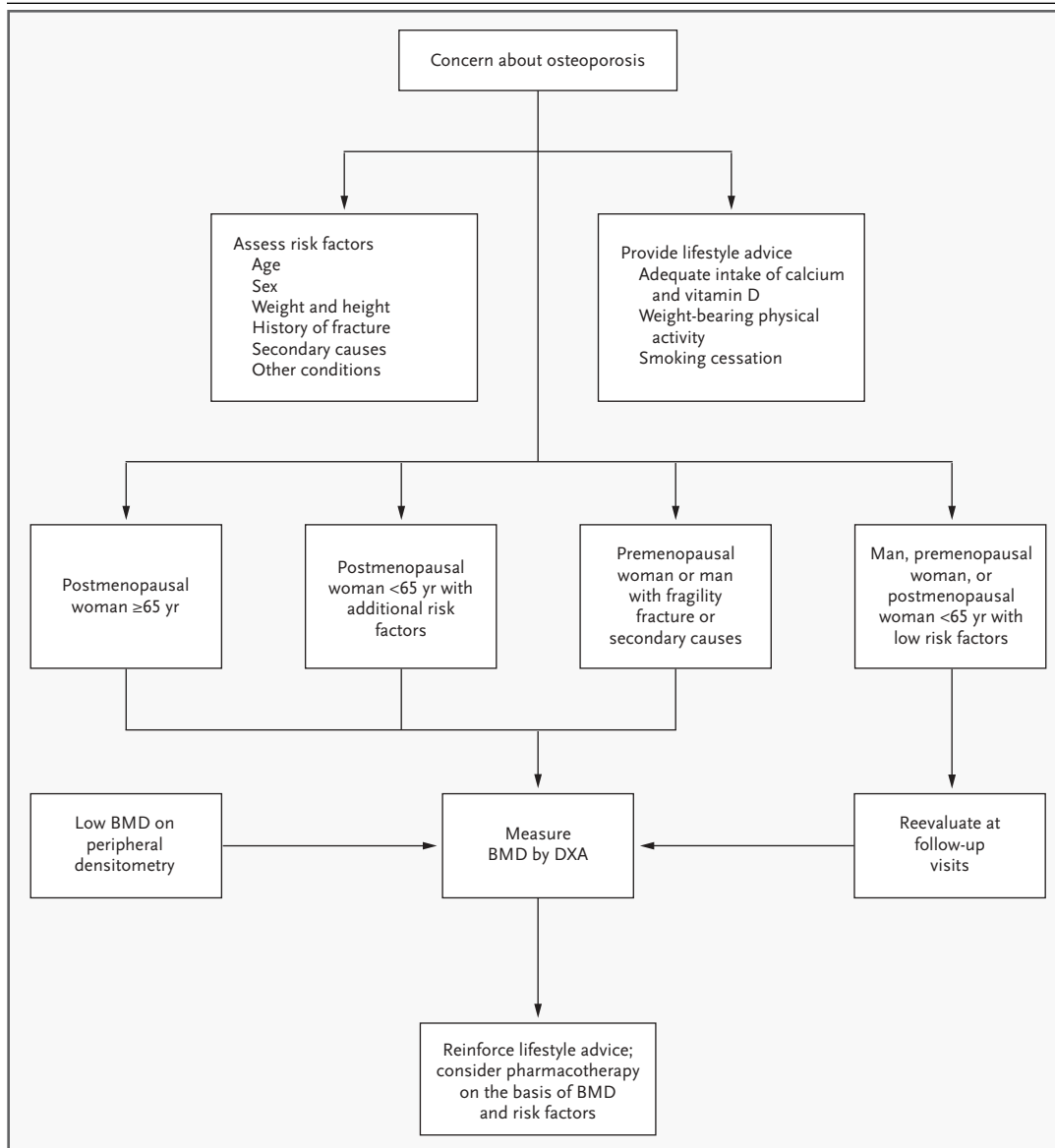
Data are limited on the relationship between measured bone density and the risk of fracture in premenopausal women, men, and nonwhite persons. There is little information on the effectiveness of screening in enhancing prevention and treatment programs. Data are lacking to guide the frequency of repeated measurements when the initial screening shows normal bone mineral density. Standards are needed for quality control and interpretation of bone-mineral-density tests.<sup>41</sup> Although it is clear that “silent” vertebral compression fractures are associated with an increased risk of fracture,<sup>17</sup> the effect on screening of newer dual-energy x-ray ab-

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#### SUMMARY AND RECOMMENDATIONS

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Bone-mineral-density measurements should be obtained routinely in all women over the age of 65 years and in men and younger women who have had a fragility fracture. Compliance with this recommendation alone would be a great advance in comparison with current practice. As is outlined in Figure 2, all patients should be asked about risk factors and secondary causes of osteoporosis and should be advised about the recommended intake of calcium and vitamin D (1200 mg and 400 to 800 IU daily, respectively, for postmenopausal women), weight-bearing physical activity, and the dan-



**Figure 2. Flow Chart for Recommendations Regarding Selection of Patients for Dual-Energy X-Ray Absorptiometry (DXA).**

For peripheral densitometry, each system will have different levels of T-score cutoff. In most cases, dual-energy x-ray absorptiometry will be recommended for patients with T scores of  $-1.0$  or lower. It is important to identify diseases or drugs that are likely to cause skeletal fragility or to increase the risk of falls. Risk factors that routinely warrant bone-mineral-density testing include an age of more than 65 years, a personal history of fracture (particularly fragility fracture) or height loss of more than 2 cm, a family history of fracture in a first-degree relative, low body weight (less than 126 lb), and recent weight loss (more than 5 percent). Other risk factors include female sex, late menarche, early menopause, low calcium intake, vitamin D insufficiency, smoking, excess alcohol intake, physical inactivity and muscle weakness, and impaired vision or balance. Secondary causes of osteoporosis include hyperparathyroidism, hyperthyroidism, Cushing's syndrome, glucocorticoid therapy, inflammatory disorders (including arthritis, bowel disease, and pulmonary disease), hypogonadism (including treatment with luteinizing hormone-releasing hormone agonists and aromatase inhibitors), cancer (especially hematologic conditions), congenital disorders (including osteogenesis imperfecta and homocystinuria), and neurologic disorders (including immobilization and treatment with antiepileptic drugs). BMD denotes bone mineral density.

gers of smoking. The decision to measure bone mineral density in postmenopausal women under the age of 65 should be made on the basis of the presence of risk factors that increase the likelihood of detecting osteoporosis or osteopenia. For example, in the patient described in the vignette, obtaining a dual-energy x-ray absorptiometric scan would be justified on the basis of the patient's family history of fracture, her low weight, and the likelihood that a finding of low bone mineral density would influence her treatment.

Although data to guide the frequency of re-screening are lacking, it would be appropriate to

repeat bone mineral density measurement in two years in patients with osteopenia and in three to five years in patients with normal bone density. Many of these patients will not lose bone if they have an adequate intake of calcium and vitamin D and exercise regularly. Risk factors should be reassessed and lifestyle advice reinforced at every visit with the patient. This approach is consistent with the recent Surgeon General's Report on Bone Health and Osteoporosis ([www.surgeongeneral.gov](http://www.surgeongeneral.gov)).

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