Clinical Practice Guideline

Adult Osteoporosis


June 2016
Table of Contents

Introduction........................................................................................................................................... 5

Establishing the Diagnosis of Osteoporosis and Risk of Fracture(s).............................................. 5
  Fracture Risk Assessment ................................................................................................................ 5
  Indications for Baseline Bone Mineral Density Testing \cite{4,8-11} ..................................................... 7
  Indications for a Vertebral Fracture Assessment \cite{5,8,9,12} ......................................................... 8

Technique for Performing a Bone Mineral Density Scan.............................................................. 9
  Personnel and Facility Requirements \cite{4,14} ............................................................................. 9
  Documentation ............................................................................................................................... 10

Monitoring Bone Mineral Density ................................................................................................. 12

Secondary Causes of Osteoporosis or Metabolic Bone Disease ................................................. 12

Treatment of Osteoporosis\cite{5,8,10,16-18} ...................................................................................... 13
  Universal Recommendations ....................................................................................................... 13
  Pharmacologic Treatment ............................................................................................................. 14
  Recommendations for Patients Receiving Glucocorticoids ...................................................... 15

Special Considerations in the Management of Osteoporosis ...................................................... 17
  Drug Holiday ............................................................................................................................... 17
  Calcium and Cardiovascular Risk .............................................................................................. 18
  Proton Pump Inhibitors and Osteoporosis .................................................................................. 18
  Osteonecrosis of the Jaw and Potent Anti-resorptives .............................................................. 19
  Potent Antiresorptives and Atypical Femur Fractures ............................................................... 19

Glossary .............................................................................................................................................. 22

Appendix A ....................................................................................................................................... 24
  Essential Elements from Osteoporosis Clinical Guidelines ..................................................... 24

References ......................................................................................................................................... 26

Document Updates ......................................................................................................................... 30
List of Tables

Table 1. Recommended monitoring intervals for BMD studies using DXA ............................................... 12
Table 2. Recommended pharmacologic treatments for patients with osteoporosis ............................... 15
Table 3. Management of postmenopausal women and men over the age of 50 years
    starting or receiving glucocorticoids based on FRAX ................................................................. 16
Table 4. Management of premenopausal women and men under the age of 50 years
    with a prevalent fragility fracture starting or receiving glucocorticoids .................................... 17
Table 5. The 2014 ASBMR definition of AFF ......................................................................................... 20
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFF</td>
<td>Atypical femur fracture</td>
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<tr>
<td>ASBMR</td>
<td>American Society for Bone and Mineral Research</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Bisphosphonate</td>
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<tr>
<td>CBC</td>
<td>Complete blood count</td>
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<tr>
<td>CBDT</td>
<td>Certified Bone Densitometry Technologist</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DXA</td>
<td>Dual energy X-ray absorptiometry</td>
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<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FRAX®</td>
<td>World Health Organization Fracture Risk Assessment Tool</td>
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<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td>ICSI</td>
<td>Institute for Clinical Systems Improvement</td>
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<td>IOF</td>
<td>International Osteoporosis Foundation</td>
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<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>ISCD</td>
<td>International Society for Clinical Densitometry</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LSC</td>
<td>Least significant change</td>
</tr>
<tr>
<td>MBD</td>
<td>Metabolic bone disease</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NOF</td>
<td>National Osteoporosis Foundation</td>
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<tr>
<td>ONJ</td>
<td>Osteonecrosis of the jaw</td>
</tr>
<tr>
<td>OPE</td>
<td>Oral procedure and event</td>
</tr>
<tr>
<td>PA</td>
<td>Posterior-anterior (e.g., view in a DXA scan)</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>SDs</td>
<td>Standard deviations</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VFA</td>
<td>Vertebral fracture assessment</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
Introduction

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.\textsuperscript{1} It is often asymptomatic, under-recognized and undertreated. Fractures, which are a complication of osteoporosis, pose an enormous healthcare burden, with significant morbidity and mortality, and contribute to rising healthcare costs.\textsuperscript{2} In 2002 alone, the annual cost of treating osteoporosis and associated fractures in the Medicare population was estimated to be approximately $16 billion.\textsuperscript{3}

There is considerable confusion about the appropriate diagnosis, monitoring, and treatment of individuals with low bone mass/osteopenia or osteoporosis. Rheumatologists and other specialists are frequently called upon to diagnose and treat this disease. They routinely see patients at increased risk for osteoporosis including postmenopausal women, older men and women, and individuals on glucocorticoids.

Establishing the Diagnosis of Osteoporosis and Risk of Fracture(s)

Osteoporosis can be defined based on measurement of a T-score ≤-2.5 in the lumbar spine, total hip, or femoral neck on a central dual energy X-ray absorptiometry (DXA) study in post-menopausal women and men aged 50 years and older. The diagnosis of osteoporosis can also be made in younger individuals with known secondary causes of metabolic bone disease ([MBD]; e.g., glucocorticoid use). In certain circumstances, the 33% radius (also called distal 1/3\textsuperscript{rd} radius) may be utilized. Other hip regions of interest, which include Ward’s triangle and the greater trochanter should not be used.\textsuperscript{4} In contrast to T-scores, which compare the patient’s bone mineral density (BMD) to young normal controls, Z-scores compare the patient’s BMD to age-matched controls. A diagnosis of osteoporosis is not to be made in younger individuals without secondary causes of MBD. Instead, they might be labeled as having “low bone mass for age” if their Z-score was <-2.0.

There is also a clinical definition of osteoporosis based on a history of a low trauma/fragility fracture in an adult.\textsuperscript{5} Thus a patient with densitometric evidence of low bone mass/osteopenia with a low trauma vertebral fracture is said to have osteoporosis. The International Society for Clinical Densitometry (ISCD) position is that any low trauma fracture, defined as a fracture occurring in the context of a fall from standing height or lesser trauma, is sufficient to establish a diagnosis of osteoporosis, regardless of BMD.\textsuperscript{4}

Fracture Risk Assessment

In the last decade, fracture risk assessment tools have been developed and used with increasing frequency. These have allowed the healthcare provider to calculate a quantitative rather than qualitative risk of future fracture and thus more appropriately guide treatment decisions. The Fracture
Risk Assessment Tool FRAX®, developed at the University of Sheffield for the World Health Organization (WHO), is the most well-known and widely utilized tool.

The value of fracture risk assessment tools is based on several important observations. First, more low trauma fractures occur in individuals who do not meet the densitometric definition of osteoporosis than occur in those who do. Second, the single best predictor of future fracture is a prior fracture. According to the Institute for Clinical Systems Improvement (ICSI), more than half of women over the age of 50 years will develop a fracture sometime during their lifetime. Approximately one fourth of women over the age 50 years will have an osteoporotic fracture of the spine and, by the age of 75 years, more than one third of all women will have had a least one vertebral fracture. All adults with a history of vertebral, hip, proximal humeral, ankle, pelvis, or distal forearm fracture are felt to have a higher-than-average risk for a future fracture. Finally, factors in addition to BMD and fracture history such as age, body mass index (BMI), frailty, alcohol and cigarette use, family history of osteoporotic fracture, steroid use, and rheumatoid arthritis (RA) are known to influence the risk of future fracture.

FRAX integrates clinical risk factors and BMD at the femoral neck to calculate the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). The models used to develop the FRAX diagnostic tool were derived from studying patient populations in North America, Europe, Latin America, Asia, and Australia. FRAX has been used globally to guide treatment decisions. In the United States (US), the National Osteoporosis Foundation (NOF) Clinician’s Guide to Prevention and Treatment of Osteoporosis provides a framework that prioritizes using FRAX in those individuals not yet receiving Food and Drug Administration (FDA)-approved drug therapy, who have not had prior fragility fractures and who have low bone mass/osteopenia.

It is recognized that all risk assessment tools have limitations and clinical judgment remains important. At the 2010 FRAX Position Development Conference, the ISCD and the International Osteoporosis Foundation (IOF) collaboratively agreed on several limitations to FRAX, including the following:

- Falls are a risk factor for fracture but are not included in the current FRAX model. Fracture probability may be increased in individuals with frequent falls, but that risk cannot be quantified at the present time.
- The model underestimates fracture risk in individuals with multiple prior fractures.
- FRAX identifies only parental history of hip fracture but no other fragility fractures that may be a risk factor for fracture.
- The model underestimates fracture probability in patients on prednisone doses exceeding 7.5 mg/day.
  - High-dose inhaled glucocorticoids may be a risk factor for fracture and are not accounted for.
  - In individuals with adrenal insufficiency, appropriate glucocorticoid replacement has not been shown to increase fracture risk, and use of steroids in this setting should not be included in FRAX calculations.
FRAX may underestimate or overestimate major osteoporotic fracture risk when the lumbar spine T-score is much lower or higher (>1 standard deviation [SD]) than the femoral neck T-score.

FRAX with BMD predicts fracture risk better than clinical risk factors or BMD alone.
- Use of FRAX without BMD is appropriate when BMD is not readily available or to identify individuals who may benefit from a BMD measurement.

Additional potential tools for the assessment of fracture risk such as the trabecular bone score, markers of bone turnover (serum C-telopeptide, urine N-telopeptide) and hip axis length are available. Of these, the trabecular bone score has the greatest ability to further quantitate fracture risk and can now be incorporated into the FRAX calculation on the Sheffield website (https://www.shef.ac.uk/FRAX/tool.jsp).

**Indications for Baseline Bone Mineral Density Testing**[^1][^4][^8][^11]

United Rheumatology requires the use of DXA for the evaluation of patients referred for BMD testing.

Patients who meet one or more of the following indications should be referred for a *baseline BMD (DXA) study*:

- Women aged ≥65 years and men aged ≥70 years
- Postmenopausal women aged ≤65 years who are menopausal and men aged <70 years if they have a risk factor for low bone mass or osteoporosis, including but not limited to:
  - Low body weight (BMI ≤20 kg/m²) with no other risk for a fracture
  - Prior fracture as an adult
  - Use of high-risk medication, including but not limited to:
    - Glucocorticoids
    - Aromatase inhibitors
    - Androgen deprivation therapy
    - Anticonvulsants such as phenytoin or phenobarbital
    - Chronic heparin
  - Known diseases associated with bone loss or low bone mass
  - Current smoking
- Adults with a low trauma/fragility fracture
- Adults with a disease-associated bone loss or low bone mass
- Adults taking medications associated with bone loss or low bone mass including but not limited to:
  - Glucocorticoids
  - Aromatase inhibitors
  - Androgen deprivation therapy
  - Chemotherapy
  - Anticonvulsants such as phenytoin or phenobarbital
• Women with a fracture risk equal to that of a 65-year-old postmenopausal female (BMI=25) with no other risk factors
  o A FRAX analysis without BMD is indicated if the 10-year major osteoporotic fracture risk is >9.3%.

**Indications for a Vertebral Fracture Assessment**

A vertebral fracture assessment (VFA) is an important part of fracture risk assessment because up to 20% of individuals with low bone mass/osteopenia will be found to have previously undiagnosed vertebral body compression fractures. The recognition of these morphometric fractures changes the diagnosis to osteoporosis and could alter decisions regarding the initiation of drug therapy for osteoporosis. Additionally, increasing numbers and higher grades of vertebral-body fractures have been found to correlate with increasing fracture risk. Lateral views of the thoracic and lumbar spine can be performed, using either plain films or DXA equipment if VFA imaging is available.

**United Rheumatology encourages the use of DXA equipment for VFA, because it is associated with lower cost and lower radiation exposure than plain films.**

A VFA should be performed if a patient has a T-score in the lumbar spine, total hip, or femoral neck of < -1.0 and meets one of the following parameters:

- Women aged ≥70 years or men aged ≥80 years
- Self-reported but undocumented prior vertebral fracture
- Prospective height loss of 1.5 inches (4 cm) or more, defined as the difference between the current height and peak height at age 20
- Prospective height loss of 0.8 inches (2 cm) or more, defined as the difference between the current height and a previously documented height measurement
- Glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for at least 3 months

The ability to measure the precise current height of a patient is essential for evaluating the potential loss of height and identifying patients at risk for vertebral fracture. Therefore, all rheumatologists should have a wall-mounted stadiometer.
Technique for Performing a Bone Mineral Density Scan

The best imaging modality for BMD is a DXA study. It is the only modality accepted by United Rheumatology.

The DXA examination should include the following:

1. Posterior-anterior (PA) view of the lumbar spine and one or both hips. Bone mass density of the spine and hip should be measured in all patients.

2. If the evaluation of the lumbar spine or hip is compromised by extensive degenerative disease or heavy vascular calcifications, fractures, scoliosis, or metal implants; then images of the non-dominant forearm should be obtained.

3. When evaluating the lumbar spine, it is preferable to use all 4 vertebrae (L1-L4); however, a minimum of 2 adjacent vertebrae must be used to calculate the T-score. Bone mass density should not be measured in a single vertebra. Vertebrae with a difference in T-score ≥ 1.0 compared to an adjacent vertebra may be excluded from the calculation. In addition, vertebrae with evidence of fractures, prior surgery, metal plates or screws, overlying tubing, or marked degenerative changes should also be excluded from the calculation.

4. In a patient with known hyperparathyroidism, a PA of the non-dominant forearm should be obtained.

5. Bone mass density of the hip may be measured on either or both side(s) and should include the lowest value obtained of the femoral neck or total hip.

Personnel and Facility Requirements

1. Facility accreditation by ISCD is encouraged but not required

2. All providers interpreting DXA scans must have passed the ISCD certification examination at least one time

3. All technologists performing this examination must maintain current certification in bone densitometry from the American Registry of Radiologic Technologists (AART) or a qualification as a Certified Bone Densitometry Technologist (CBDT) from the ISCD.

4. Each facility must have a quality control (QC) program which should be designed in consultation with a qualified medical physicist.

5. All facilities must have a supervising physician who is responsible for the QC program.

6. All facilities must have a supervising technologist who is responsible for QC procedures.

   These procedures should be performed at least 3 times per week prior to the first clinical examination. A permanent record of the QC tests must be available on site. The supervising technologist is also responsible for determining the precision error and the least significant change (LSC) which should represent pooled data from all technologists.

7. Any new technologist must perform a precision study and if acceptable, the results must be pooled with the data from all the technologists at the facility.
8. Cross calibration according to the recommendations of the ISCD should be performed when changing any hardware including changing out the entire system.

**Documentation**

The information in this section is based on the ISCD 2015 Official Positions. Additional sources are provided where appropriate.

A permanent record must be maintained according to appropriate state law for retention of records and imaging; including patient history forms (written or electronic), requests or referrals for the examination, printouts or the electronic equivalent of images (including regions of interest, if provided), and the BMD values. All images must include:

- Patient demographics
- Date of examination
- Image orientation
- Facility name
- Unit manufacturer and model

**Minimum DXA report requirements are:**

1. Patient demographics including but not limited to:
   a. Name
   b. Unique medical-record number
   c. Date of birth
   d. Gender
2. Name of referring provider
3. Indications for the test
4. Name of the manufacturer and model number of the equipment used
5. Risk factors, including fragility or low trauma fractures
6. Assessment of technical quality of the study, and the reason for exclusion of a specific site, if appropriate
7. Skeletal sites scanned
8. BMD in g/cm² for each site
9. T-score and Z-score, where appropriate for each site
10. Classification according to the WHO criteria
11. General recommendation for evaluation of secondary causes of low BMD, if the scan demonstrates osteoporosis and the work-up has not been done recently
12. Recommendations for the necessity and timing of a follow-up DXA scan
Optional items in a DXA report:
1. Specific recommendations for evaluation of secondary causes of MBD
2. Recommendations for pharmacological and non-pharmacological interventions
3. Recommendations for further non-BMD testing such as X-ray, magnetic resonance imaging (MRI), computed tomography (CT), etc.

DXA-report items that should not be included:
1. A statement that there has been bone loss without knowledge of previous bone density study
2. Mention of ‘mild’, ‘moderate’, or ‘marked’ low bone mass/osteopenia or osteoporosis
3. Separate diagnoses for different regions of interest (e.g., low bone mass/osteopenia at the hip and osteoporosis at the lumbar spine)

Minimum VFA Report Items:
1. Patient demographics including but not limited to:
   a. Name
   b. Unique medical record number
   c. Date of birth
   d. Gender
2. Name of referring provider
3. Indications for the test
4. Type of examination (radiographs or absorptiometry)
5. Risk factors, including low trauma/fragility fractures
6. Assessment of technical quality of the study, including vertebrae that cannot be evaluated
7. Vertebral deformities, and whether or not deformities are consistent with vertebral fracture
8. Location and grade of each vertebral body compression fracture
   The Genant visual semi-quantitative method is the current clinical technique of choice for diagnosing vertebral fractures.
9. If the study is a follow-up, it should compare the prior studies and comment on the significance of changes, if any.
Monitoring Bone Mineral Density

Follow-up BMD studies should be conducted at the same facility using the same equipment as the prior study, whenever possible. The recommended intervals for follow-up BMD studies are indicated in Table 1.

Table 1. Recommended monitoring intervals for BMD studies using DXA

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Intervals for Follow-up Studies</th>
</tr>
</thead>
</table>
| Treatment with calcium and vitamin D only OR If results would lead to initiation of drug therapy | • Every 2 years, if approaching intervention threshold based on T-score or FRAX  
• Every 3 to 5 years, if BMD is borderline low and there are some clinical risks  
• Not more frequently than once every 5 years, if the patient is comfortably above the intervention threshold |
| Treatment with an FDA-approved drug for osteoporosis | • Initial follow up at 1 to 2 years, to exclude progression of disease, defined as significant decline in BMD based on LSC.  
• Every 2 years, until BMD plateaus.  
• Not less than every 2 years or more than every 5 years after BMD has stabilized. |
| Completed FDA-approved drug therapy for osteoporosis (Drug holiday) | • Every 2 years, until a significant decline in BMD is identified. |

BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; FDA, Food and Drug Administration; FRAX, World Health Organization Fracture Risk Assessment Tool; LSC, least significant change

Secondary Causes of Osteoporosis or Metabolic Bone Disease

An evaluation for secondary causes of MBD should be performed in all individuals with osteoporosis based on a DXA study, prior fragility fracture, or a 10-year fracture risk meeting or exceeding NOF thresholds for initiation of drug therapy.

The following laboratory studies should be requested, if not performed since the diagnosis was established:8, 16, 17

- Complete blood count (CBC) and chemistry profile (including serum calcium, creatinine, alkaline phosphatase, and phosphorus)
- Thyroid stimulating hormone (TSH), if the patient is receiving thyroid hormone supplementation
- 25-hydroxy vitamin D level
- Parathyroid hormone (PTH) level
- 24-hour urine calcium
Other laboratory tests that may be helpful in the work-up for secondary causes of MBD, if the history or exam are suggestive, include: \(^8,^16\)

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- 24-hour urine free cortisol
- Total and free testosterone in men
- Serum and urine protein electrophoresis, immunofixation/immuno-electrophoresis
- Anti-endomysial and anti-gliadin antibodies

Common secondary causes of MBD include but are not limited to: \(^8,^16,^18\)

- Hyperthyroidism
- Primary hyperparathyroidism
- RA
- Renal insufficiency or renal failure
- Inflammatory bowel disease (IBD)
- Celiac disease
- Hypogonadism
- Human immunodeficiency virus (HIV) infection
- Alcoholism
- Chronic liver disease
- Organ transplantation
- Cushing’s disease
- Insulin-dependent diabetes mellitus

**Treatment of Osteoporosis** \(^5,^8,^{10-18}\)

**Universal Recommendations**

- Counsel on the risk of osteoporosis and related fractures.
- Advise on a diet that includes adequate amounts of total calcium intake (1000 mg per day for men aged 50 to 70 years; 1200 mg per day for women aged >50 years and men aged >70 years), incorporating dietary supplements if diet is insufficient.
- Advise on vitamin D intake including supplements, if necessary, for individuals aged 50 years and older to maintain a 25-hydroxy vitamin D level ≥32.
• Recommend regular weight-bearing and muscle strengthening exercises to improve agility, strength, posture, and balance; maintain or improve bone strength; and reduce the risk of falls and fractures.

• Assess risk factors for falls, and offer appropriate modifications (e.g., home safety assessment, balance exercises, correction of vitamin D insufficiency, avoidance of central nervous system (CNS) depressant medications, careful monitoring of antihypertensive medication, and visual correction when needed).

• Advise on smoking cessation and avoidance of excessive alcohol.

Pharmacologic Treatment

FDA-approved pharmacologic treatment (Table 2) should be initiated in the following settings:

- Recent low trauma/fragility fractures, except those in fingers and toes
- T-scores of ≤-2.5 at the femoral neck, total hip, or lumbar spine by DXA
- Postmenopausal women and men aged ≥50 years with T-scores between -1 and -2.5 (low bone mass/osteopenia) at the femoral neck, total hip, or lumbar spine by DXA AND
- A 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability of ≥20% based on FRAX

An oral bisphosphonate can be the initial choice for those patients requiring drug therapy, unless the patient is at high risk for fracture based on multiple prior fractures or a very low T-score ≤-3.0 (see below). Oral bisphosphonates are contraindicated in those with significant gastroesophageal reflux disease (GERD), esophageal motility disorders, or renal insufficiency with an estimated glomerular filtration rate (GFR) of ≤35 mL/minute. Generic oral bisphosphonates such as alendronate, ibandronate, and risedronate are significantly cheaper than their respective brand-name products (Fosamax®, Boniva®, and Actonel®). If the response to a generic bisphosphonate is not adequate based on a significant decline in bone density on repeat DXA study at 2-year follow-up, other therapy should be considered. A decline in BMD in a patient treated with a generic bisphosphonate may be seen, as some recent studies have demonstrated variability in rates of disintegration and absorption among individual generic bisphosphonates which can affect tolerability, adherence, and possibly efficacy of generic bisphosphonates when compared to their brand-name equivalents.20,21

Raloxifene is an appropriate alternative in younger women with a low risk of hip fracture, particularly in those at increased risk for breast cancer and/or those with significant GERD that makes oral bisphosphonates problematic. Raloxifene is contraindicated in men.

Parenterally administered medications currently available include zoledronic acid (Reclast®), denosumab (Prolia®), and teriparatide (Forteo®). The FDA recommends using teriparatide and denosumab in individuals at high risk for fracture. High-risk individuals are those with a history of osteoporotic fracture
or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapies. Denosumab is often used in individuals who are unable to take either an oral or parenteral bisphosphonate because of renal insufficiency. Teriparatide is the only anabolic drug currently available and therefore is often the initial choice in individuals presenting with multiple fragility fractures or very low T-scores ≤-3.0.

Zoledronate can be used to treat osteoporosis and is also an attractive alternative in individuals with low bone mass / osteopenia who might only need 1 infusion every 2 to 3 years. Like denosumab, it is often used in individuals with significant gastrointestinal intolerance to oral bisphosphonates or in those with significant declines in BMD while on oral bisphosphonate therapy. Zoledronate is contraindicated in patients with estimated GFRs ≤35 mL/minute.

There are no data to support the use of nasal or injectable calcitonin for the treatment of osteoporosis or increased fracture risk in postmenopausal women. Similarly, there are no fracture data to support the use of combination therapy (e.g., bisphosphonate + teriparatide; denosumab + teriparatide; raloxifene + bisphosphonate).

**Table 2. Recommended pharmacologic treatments for patients with osteoporosis**

<table>
<thead>
<tr>
<th>Drug Classification</th>
<th>Generic Name</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>Bisphosphonates</td>
<td>alendronate</td>
<td>Fosamax®</td>
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<tr>
<td></td>
<td>ibandronate</td>
<td>Boniva®</td>
</tr>
<tr>
<td></td>
<td>risedronate</td>
<td>Actonel®, Atelvia®</td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>Reclast®, Zometa®, Aclasta®, Aredia®</td>
</tr>
<tr>
<td></td>
<td>pamidronate</td>
<td></td>
</tr>
<tr>
<td>Estrogen agonist/antagonist</td>
<td>raloxifene*</td>
<td>Evista®</td>
</tr>
<tr>
<td>RANK ligand inhibitor</td>
<td>denosumab</td>
<td>Prolia®</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>teriparatide</td>
<td>Forteo®</td>
</tr>
</tbody>
</table>

*Contraindicated in men

FDA, Food and Drug Administration; RANK, receptor activator of nuclear factor Kappa-B

**Recommendations for Patients Receiving Glucocorticoids**

The use of glucocorticoids is frequently necessary in the treatment of inflammatory conditions but is fraught with multiple comorbidities and potential mortality. Osteoporotic fractures are of significant concern in these patients. At any given BMD T-score, the incidence of new vertebral fractures in postmenopausal women receiving glucocorticoids is increased when compared with nonusers. Fractures appear to occur at higher bone density than that seen in postmenopausal osteoporosis, perhaps due to the effect of glucocorticoids on the osteocyte. Importantly, a rapid decline in BMD can begin within the first 3 months of glucocorticoid therapy and peak at 6 months, followed by a slower but steady loss of BMD with persistent steroid use.
The management of a patient receiving glucocorticoid therapy should follow the American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. According to these guidelines, fractures in patients on glucocorticoid therapy may occur without a decline in BMD. A FRAX risk assessment should be performed in all postmenopausal women and men over the age of 50 years who are treated with glucocorticoids. FRAX assigns a low risk, medium risk, and high risk to patients based on the calculated 10-year major osteoporotic fracture risk. Low risk is defined as <10%; medium risk between 10% and 20%; and high risk as >20%. All high-risk patients should be treated.

The management of postmenopausal women and men over the age of 50 years who will be given glucocorticoids or are already taking them is shown in Table 3. The management of premenopausal women and men aged 50 years or younger who will be given glucocorticoids or are taken them is outlined in Table 4. At this time, there are no definitive published guidelines concerning the duration of treatment.

**Table 3. Management of postmenopausal women and men over the age of 50 years starting or receiving glucocorticoids based on FRAX**

<table>
<thead>
<tr>
<th>Glucocorticoid Dose</th>
<th>Low FRAX Risk</th>
<th>Medium FRAX Risk</th>
<th>High FRAX Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.5 mg/day for ≥3 months</td>
<td>No treatment</td>
<td>alendronate or risedronate</td>
<td></td>
</tr>
<tr>
<td>≥7.5 mg/day for ≥3 months</td>
<td>alendronate or risedronate or zoledronate</td>
<td>alendronate or risedronate or zoledronate</td>
<td></td>
</tr>
<tr>
<td>≤5 mg/day for ≤1 month</td>
<td></td>
<td>alendronate or risedronate or zoledronate</td>
<td></td>
</tr>
<tr>
<td>≥5 mg/day for ≤1 month OR</td>
<td>teriparatide is preferred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any dose used for &gt;1 month</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Management of premenopausal women and men under the age of 50 years with a prevalent fragility fracture starting or receiving glucocorticoids

<table>
<thead>
<tr>
<th>Glucocorticoid Dose</th>
<th>Women (No Childbearing Potential)</th>
<th>Women (Childbearing Potential)</th>
<th>Men &lt;50 Years Of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 mg/day for 1 to 3 months</td>
<td>alendronate or risedronate</td>
<td>No consensus</td>
<td>alendronate or risedronate</td>
</tr>
<tr>
<td>&gt;7.5 mg/day for 1 to 3 months</td>
<td>zoledronate</td>
<td>No consensus</td>
<td>zoledronate</td>
</tr>
<tr>
<td>Any dose for &gt;3 months</td>
<td>alendronate or risedronate or zoledronate or teriparatide</td>
<td>No consensus</td>
<td>zoledronate or risedronate or zoledronate or teriparatide</td>
</tr>
<tr>
<td>&gt;7.5 mg/day for &gt;3 months</td>
<td>alendronate or risedronate or teriparatide</td>
<td>No consensus</td>
<td></td>
</tr>
<tr>
<td>≤7.5 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Special Considerations in the Management of Osteoporosis

Special considerations in the treatment of osteoporosis pertain to the application of a drug holiday, the potential correlation of calcium and cardiovascular risk, the use of proton pump inhibitors (PPIs) in patients with osteoporosis, and osteonecrosis of the jaw (ONJ) or atypical femur fractures (AFFs) with the use of potent antiresorptives.

Drug Holiday

In the last decade, concerns about the potential of ONJ and AFFs associated with long-term bisphosphonate and denosumab use have led to the recommendation that patients treated for osteoporosis stop drug therapy after a pre-specified period of time. This is based on the concern that the risk of long-term therapy might be greater than the potential benefit of fracture reduction. Both the NOF and the ICSI suggest that patients be considered for a bisphosphonate ‘drug holiday’ after 5 years of treatment.

The American Society for Bone and Mineral Research (ASBMR) Task Force recently published their recommendations for managing patients on long-term bisphosphonate therapy. In long-term studies of alendronate (FLEX trial) and zoledronate (HORIZON trial), patients who remained on drug for 10 years (alendronate) and 6 years (zoledronate) had lower rates of vertebral fracture than corresponding groups that switched to placebo at 5 and 3 years, respectively. Hip T-scores of between -2.0 and -2.5 in the FLEX trial and below -2.5 in the HORIZON trial predicted a beneficial response to continued therapy. Therefore, the Task Force recommended that after 3 years of intravenous bisphosphonate (IV BP)
therapy or 5 years of oral bisphosphonate (oral BP) therapy, fracture risk be reassessed. For those at higher risk, continued treatment for at least 6 years (IV BP) or 10 years (oral BP) was recommended.

It is important to realize that bisphosphonates have different binding affinities to bone and only alendronate and zoledronate remain avidly bound to bone for several years or longer once the drug has been withdrawn. As such, the concept of a drug holiday, where a drug is withdrawn and the benefit (fracture reduction) persists while risk is reduced, is really only applicable to alendronate and zoledronate. Several authors have provided more in-depth analyses of how to determine the need for a drug holiday as opposed to continued treatment.

Calcium and Cardiovascular Risk

There have been conflicting reports about calcium supplements and increased risk of cardiovascular events. Several meta-analyses and a subgroup analyses of the Women’s Health Initiative raised the issue of a possible increased risk of cardiovascular disease (CVD) associated with calcium supplements. However, others such as the Nurses’ Health Study, a prospective cohort study with 74,245 women who were followed for 24 years, did not find that calcium supplements increased the risk of CVD. In addition, another review of studies and meta-analyses of calcium supplements did not find an increased risk of CVD. In fact, some studies have suggested a cardioprotective effect of calcium plus vitamin D. Vitamin D itself has been demonstrated to be cardioprotective.

Further study in this area is needed to clarify this controversy. Current Institute of Medicine (IOM) recommendations advocate calcium supplements to promote bone health in patients who do not obtain the recommended calcium intake through dietary sources.

Proton Pump Inhibitors and Osteoporosis

The relationship between proton pump inhibitor (PPI) usage and a potential increase in osteoporotic fracture remains unclear. The Canadian Multicentre Osteoporosis Study showed that, while PPI users had lower BMD at baseline than nonusers, PPI use over 10 years did not appear to be associated with accelerated BMD loss. The association between PPIs and osteoporosis-related fractures had been suggested in several retrospective analyses, and the strength of the relationship varied from study to study. To date, no prospective analyses have been published, and no mechanism of action has been proposed by which PPI usage could increase the risk for fracture. Prior studies that have analyzed the association between PPI use and BMD have produced conflicting data, so that the actual relationship between PPI use and BMD is poorly characterized.

Multiple meta-analyses assessing the risk of PPI use and fractures were published in 2011. The majority of these studies showed that the risk of hip (relative risk [RR], 1.2 to 1.30) and spine (RR, 1.6) fractures increased moderately among PPI users. These studies were limited by heterogeneity, and when the studies were adjusted for other risk factors for fracture, PPIs were no longer causal. Histamine H2 receptor antagonists were not associated with an increased risk for fracture. Based on these data, low BMD may be a marker for other comorbidities that predispose patients for PPI use rather than a
direct effect of PPI therapy. One study published in 2011 calculated a ‘refractory GERD score’; which determined that higher use of PPIs was associated with female gender, higher comorbidities, and greater overall costs. Further study is suggested, but currently no change in the prescribing habits for PPIs is required.

**Osteonecrosis of the Jaw and Potent Anti-resorptives**

Patients are diagnosed with ONJ if they have the following 3 findings:

- Currently or previously treated with either anti-resorptive or anti-angiogenic agents
- Exposed bone or bone that can be probed through an intra- or extra-oral fistula in the maxillofacial region that has been present for more than 8 weeks
- No history of radiation therapy to the area in question or no obvious metastatic disease in the area in question

The risk for ONJ associated with oral bisphosphonate therapy in postmenopausal osteoporosis is felt to be low, with estimates ranging from 1:10 000 to <1:100 000 patient treatment years. Osteonecrosis of the jaw has also been reported in patients receiving parenteral bisphosphonates and denosumab. There are no data to suggest that serum C-telopeptide can predict ONJ risk. Invasive oral procedures and events (OPEs) have been studied in the FREEDOM trial, which compared the safety of subcutaneous denosumab 60 mg every 6 months with placebo over 3 years. In the extension trial, patients who had received placebo were also switched to denosumab, and both groups were followed for an additional 5 years. Forty-two percent of women reported an invasive OPE during the 5-year extension trial, with ONJ seen in 0.4% of patients reporting an OPE and in 0.05% of women who did not have an invasive OPE. The exposure-adjusted incidence rate of ONJ was 4.2 per 10 000 patient years.

Although the risk of ONJ is low, a common-sense approach to using potent antiresorptives such as bisphosphonates and denosumab might be to follow recommendations in the ‘Warnings and Precautions’ section for Prolia: “A routine oral exam should be performed by the prescriber prior to initiation of treatment. A dental examination with appropriate preventative dentistry is recommended prior to treatment in patients with risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene and comorbid disorders (e.g., periodontal and/or pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment.” (Section 5.4, Page 7).

**Potent Antiresorptives and Atypical Femur Fractures**

The recognition of potential AFF in postmenopausal women treated with long-term oral and parenteral bisphosphonates and with denosumab has had a significant impact, not only on the prescribing patterns of physicians but also the willingness of patients to take these drugs. The increasing use of a drug holiday is a direct result of these concerns. Although the absolute risk is low, ranging from 3.2 to 50 cases per 100 000 patient years, the risk does increase with long-term use. Two studies suggest a risk
of >100 cases per 100 000 patient years with 5 to 9 years of bisphosphonate use. The fact that this risk is still quite low compared to the risk of common postmenopausal and age-related osteoporotic fractures has not helped to diminish patient anxiety.

A task force established by the ASBMR published definitions of AFFs, their epidemiology, risk factors, and management in 2010, with an update in 2014. The revised case definition is helpful for distinguishing these fractures from the more common osteoporotic fragility fractures, which occur in the femur (Table 5).

**Table 5. The 2014 ASBMR definition of AFF**

<table>
<thead>
<tr>
<th>Major Features</th>
<th>Minor Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture is associated with minimal or no trauma, as in a fall from a standing height or less.</td>
<td>Generalized increase in cortical thickness of the femoral diaphyses.</td>
</tr>
<tr>
<td>Fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur.</td>
<td>Unilateral or bilateral prodromal symptoms such as dull or arching pain in the groin or thigh.</td>
</tr>
<tr>
<td>Completed fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.</td>
<td>Bilateral incomplete or complete femoral diaphysis fractures.</td>
</tr>
<tr>
<td>The fracture is non-comminuted or minimally comminuted.</td>
<td>Delayed fracture healing.</td>
</tr>
<tr>
<td>Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ('breaking' or 'flaring').</td>
<td></td>
</tr>
</tbody>
</table>

**AFF**, atypical femoral fracture; **ASBMR**, American Society for Bone and Mineral Research
To lower the likelihood of an AFF, United Rheumatology provides the following recommendations based on expert consensus:

- AFFs appear to occur most commonly in younger more active women, perhaps due to microfractures and stress reactions that fail to heal and then propagate. In these women, a shorter-duration therapy of 3 to 5 years with a subsequent drug holiday until BMD declines significantly again or the use of IV zoledronate every 2 to 3 years seems prudent.

- Although the mechanism of action of denosumab is different from bisphosphonates, it is also a potent antiresorptive. Accordingly, switching to denosumab after bisphosphonate therapy may not lower the risk of AFFs.

- Query patients at each visit whether they are experiencing groin or thigh pain. If examination fails to identify a clear cause of their pain (e.g., trochanteric bursitis, hip osteoarthritis), obtain a radiograph of the femur and look for signs of early stress reactions such as cortical beaking.

- Promptly withdraw bisphosphonate or denosumab therapy in those found to have AFF and image the contralateral femur for signs of fracture (X-ray, bone scan, MRI) as bilaterality is not uncommon.

Recommendations for management of incomplete AFF are provided in the 2010 and 2014 ASBMR Task Force Recommendations. Prophylactic reconstruction nail fixation is recommended for painful incomplete AFF. For minimal pain, conservative therapy with limited weight-bearing activity and possible use of teriparatide is suggested based on positive outcomes in some reported cases, although placebo-controlled trials are not available.

Appendix A lists all the essential elements that the provider should collect at each clinical visit for osteoporosis screening.
# Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3rd radius or 33% radius</td>
<td>Bone mineral density measured in the distal third of the radius in the non-dominant arm.</td>
</tr>
<tr>
<td>Atypical femoral fracture (AFF)</td>
<td>Low trauma fracture of the femur, potentially associated with long-term use of bisphosphonates or denosumab. The earliest symptoms may be groin or thigh pain. X-rays may demonstrate findings suggestive of a stress fracture in the lateral cortex of the femoral shaft.</td>
</tr>
<tr>
<td>Bone mineral density (BMD)</td>
<td>Describes the amount of calcium and other mineral content in bone. The greater the calcium and mineral content, the higher the bone density. BMD is measured by DXA, which measures mineral content in g/cm³ but is often reported as a ‘T-score’ (see below) in adults.⁴</td>
</tr>
<tr>
<td>Dual energy X-ray absorptiometry (DXA)</td>
<td>A technology using very low-dose X-rays to determine BMD. It is the preferred method for evaluating patients for osteoporosis of the lumbar spine and hip. Imaging of the lumbar spine and hip (axial skeleton or central DXA) is the best method to diagnose osteoporosis, monitor results of drug therapy, and predict the risk of fracture(s). The appendicular skeleton (wrist, radius, or forearm) is sometimes used to supplement central imaging, when the evaluation of the lumbar spine or hip is compromised.⁵, ⁸</td>
</tr>
<tr>
<td>FRAX®</td>
<td>The WHO Fracture Risk Assessment Tool, developed by the WHO in cooperation with other medical societies, to identify individuals at increased risk for a fracture. This computer-based algorithm is available online (<a href="https://www.shef.ac.uk/FRAX/tool.jsp">https://www.shef.ac.uk/FRAX/tool.jsp</a>) and determines the 10-year probability of any major osteoporotic fracture and the 10-year probability of a hip fracture.¹⁹</td>
</tr>
<tr>
<td>Genant semi-quantitative method</td>
<td>A technique recommended to assess for vertebral fracture whether using VFA or plain radiographs. The reader first visually scans all vertebrae for presence of deformity using loss of height as well as lack of parallelism of the end plates, cortical buckling, end-plate deformities, and loss of vertical continuity of vertebral morphology.¹⁴ Vertebrae are then assigned a grade of 1 (mild), 2 (moderate) or 3 (severe), based on the degree of height loss between anterior–posterior dimensions (wedge), anterior-middle dimensions (biconcave) or posterior-anterior dimensions (crush).</td>
</tr>
<tr>
<td>Low trauma/fragility fracture</td>
<td>A fracture that occurs either spontaneously or as the result of a fall from a standing height or less. It also includes fractures that result from coughing, sneezing, or any quick movement such as opening a window.⁸</td>
</tr>
</tbody>
</table>
**Low bone mass/osteopenia**  
The term low bone mass is preferred by both the NOF and the ISCD over osteopenia. Low bone mass describes a bone density measurement that is between -1.0 and -2.5 SDs below the mean BMD of a young adult reference population.

**Osteoporosis**  
There are two definitions of osteoporosis:  
1) A densitometric definition based on a T-score of -2.5 or lower.  
2) A clinical definition based on a history of a low trauma/fragility fracture in an adult.

**T-score**  
A calculation used to report the results of BMD or bone densitometry tests. The T-score describes the number of SDs above or below the mean BMD of a young adult reference population.
## Appendix A

### Essential Elements from Osteoporosis Clinical Guidelines

| Demographics | • Gender, age, race, height/weight/BMI |
| Social and Personal History | • Alcohol use of more than 2 units per day  
  • Current cigarette use  
  • Dietary calcium intake |
| Medications (to include current vs prior, and start/stop dates) | • Steroids for more than 3 months  
  • Current thyroid hormone supplement, neuroleptics, aromatase inhibitors, androgen deprivation, estrogens, bisphosphonates (type), raloxifene, teriparatide, calcitonin, denosumab, vitamin D supplement, or calcium supplement |
| Past Medical History | • Maximum adult height (for historical height loss)  
  • RA, systemic lupus erythematosus (SLE), IBD, renal calculi, celiac disease, gastric bypass, anorexia, alcoholism, hypogonadism, insulin-dependent diabetes mellitus, multiple myeloma, hyperparathyroidism  
  • Skeletal radiation, GERD, arterial/venous thrombotic events  
  • ONJ, atypical femoral fractures  
  • Low trauma fracture as an adult  
    o Type of fracture and date (excluding fingers, toes, and skull)  
    o Vertebral fractures: number and grade |
| Review of Systems | • Acute/sub-acute back pain  
  • Dental health  
  • Frequent falls, frailty  
  • Significant dysphagia |
| Family History | • Hip fracture in either parent  
  • Diagnosis of osteoporosis in other family members  
  • Renal calculi |
| Physical Examination | • Height: current  
  o vs past height (for “measured height loss”)  
  o vs maximal height (for “historical height loss”)  
  • Kyphosis  
  • Ability to stand on either leg for >6 seconds  
  • Oral health/dental evaluation |
| **DEXA Data**  
<table>
<thead>
<tr>
<th>(if have the study is performed in the rheumatology office)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Machine type</td>
</tr>
<tr>
<td>- Least significant change for L spine and hip</td>
</tr>
<tr>
<td>- Lowest T-score</td>
</tr>
<tr>
<td>- BMD (gm/cm²) in femoral neck (to calculate FRAX)</td>
</tr>
<tr>
<td>o Lowest of 2 values if both hips present</td>
</tr>
<tr>
<td>- FRAX result</td>
</tr>
<tr>
<td>- Vertebral morphometry if height loss or back pain; VFA (if available) lateral T and L spine radiographs if not</td>
</tr>
<tr>
<td>- Trabecular bone score (if available)</td>
</tr>
</tbody>
</table>
References


## Document Updates

<table>
<thead>
<tr>
<th>Document Version</th>
<th>Description of Changes</th>
<th>Approval Date</th>
</tr>
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<tbody>
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<td>1.1.2016</td>
<td>Creation of first version</td>
<td>29 Jun 2016</td>
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