AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Postmenopausal Osteoporosis

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A Major Public Health Problem

- Osteoporosis is a major public health problem. More than 10 million Americans have osteoporosis, and an additional 43 million have low bone mass, according to data from the U.S. National Health and Nutrition Examination Survey.
- More than 2 million osteoporosis-related fractures occur each year in the United States, and more than 70% of these occur in women.
- More than 20% of postmenopausal women have prevalent vertebral fractures. As the most common osteoporotic fracture, vertebral fractures are a hallmark of the disease and indicate a high risk for future fractures. They are also associated with impaired pulmonary function and increased mortality risk, especially respiratory deaths. However, the majority of vertebral fractures (2/3) are asymptomatic.

Camacho PM, Petak SM, Binkley N et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016 Update. *Endocr Pract.* 2016;22(Suppl 4):1-42.
Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29:2520-2526.
Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22:465-475.
Puisto V et al. Vertebral fracture and cause-specific mortality: a prospective population study of 3,210 men and 3,730 women with 30 years of follow-up. *Eur Spine J* 2011; 20:2181–2186.

Prevalence of Osteoporosis Increases With Age

- Age is an independent risk factor for osteoporotic fractures. The risk increases progressively with age, doubling every 5 to 10 years. Nearly one-quarter (24.8%) of women 65 and older have osteoporosis. For women 80 and older, that figure rises to more than one-third (35.6%), according to a report from the CDC.
- In addition, more than half (52.3%) of women 65 and older have low bone mass (osteopenia). Although fracture risk is highest in women with osteoporosis, most women who experience a fracture have osteopenia, because there are many more women in this category.

The Centers for Disease Control and Prevention. "Percentage of Adults Aged 65 and Over With Osteoporosis or Low Bone Mass at the Femur Neck or Lumbar Spine: United States, 2005–2010." https://www.cdc.gov/nchs/data/hestat/osteoporsis/osteoporosis2005_2010.htm. Accessed August 2, 2018.
Ross PD. "Risk Factors for Osteoporotic Fracture." *New England Journal of Medicine* 1998; 27: 289-301.

Most Women with Osteoporosis Are Not Treated

- Postmenopausal osteoporosis is preventable and treatable, but only a small proportion of women at increased risk for fracture are evaluated and treated.
- Even among women with fractures, lack of treatment is common. Fewer than 1 in 4 women age 67 or older with an osteoporosis-related fracture undergoes bone density measurement or begins osteoporosis treatment.

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Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res*. 1994;9:1137-1141.

Diagnosing Osteoporosis

- Postmenopausal osteoporosis can be diagnosed based on the World Health Organization (WHO) definition: a bone mineral density (BMD) T-score of -2.5 or below in the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius.

World Health Organization Criteria for Classification of Osteopenia and Osteoporosis

Category	T-score
Normal	–1.0 or above
Low bone mass (osteopenia)[a]	Between –1.0 and –2.5
Osteoporosis	–2.5 or below

[a] Fracture rates within this category vary widely. The category of "osteopenia" is useful for epidemiology studies and clinical research but is problematic when applied to individual patients and must be combined with clinical information to make treatment decisions.

Note: this is table 4 from the AACE Guidelines.

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Additional Diagnostic Criteria

- In addition to the WHO bone mineral density criteria, these may also be used to diagnose osteoporosis:
  - Low-trauma spine or hip fracture, *regardless* of BMD
  - Osteopenia or low bone mass (T-score between –1 and –2.5) with a fragility fracture of proximal humerus, pelvis, or possibly distal forearm
  - Low bone mass or osteopenia and high FRAX® (Fracture Risk Assessment Tool) fracture probability based on country-specific thresholds

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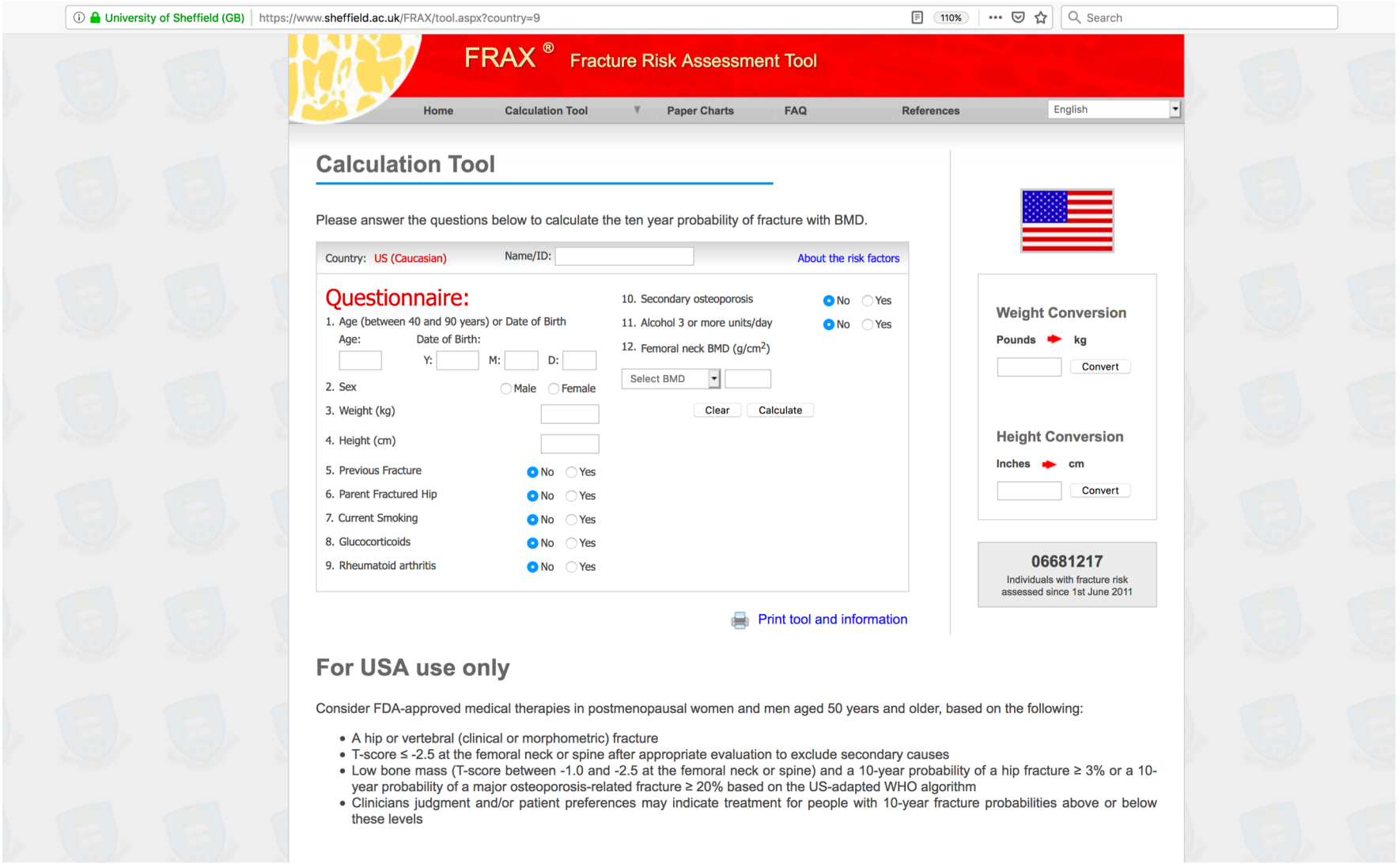
The Fracture Risk Assessment Calculator

- The FRAX calculator is [available online] from the University of Sheffield, UK



Screening for Postmenopausal Osteoporosis

- All postmenopausal women age 50 or older should undergo clinical assessment for osteoporosis and fracture risk, including a detailed history and physical examination. Tools such as FRAX should be used when available.
- BMD testing is the gold standard in diagnosing osteoporosis. However, this test is not always available. The decision to measure BMD should be based on an individual's clinical fracture risk profile and skeletal health assessment.

Camacho PM, Petak SM, Binkley N et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016 Update. *Endocr Pract*. 2016;22(Suppl 4):1-42.

Screening Recommendations

- Both the AACE and the U.S. Preventive Services Task Force recommend BMD testing for all women aged 65 and older as well as younger postmenopausal women at increased risk for bone loss and fracture based on fracture risk analysis.
- BMD measurement is not recommended in children, adolescents, healthy young men, or premenopausal women, unless there is a significant fracture history or there are specific risk factors for bone loss.

Nelson HD, Haney EM, Dana T, Bougatsos C, Chou R. Screening for osteoporosis: an update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2010;153: 99-111.

Camacho PM, Petak SM, Binkley N et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016 Update. *Endocr Pract*. 2016;22(Suppl 4):1-42.

Clinical Presentation

- Fracture is the single most important manifestation of postmenopausal osteoporosis. Osteoporotic fractures are usually caused by low-energy injuries such as a fall from standing height.
- Vertebral fractures, however, may occur during routine daily activities, without a specific fall or injury. In clinical practice, it may be difficult or impossible to reconstruct the mechanical force applied to bone in a particular fall.

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Clinical Presentation

- Osteoporosis-related fractures can lead to pain, disability, and deformity. They reduce quality and quantity of life.
- Hip fractures are the most serious consequence of postmenopausal osteoporosis. Women with hip fracture have an increased mortality of 12% to 20% during the subsequent two years. More than 50% of hip fracture survivors are unable to return to independent living. Many survivors require long-term nursing home care
- Other low-trauma, osteoporosis-related fractures include those of the proximal humerus, pelvis, and in some cases the distal forearm.

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Black DM and Rosen CJ. Postmenopausal Osteoporosis. *The New England Journal of Medicine* 2016; 374:254-262.

Treatment

- To identify coexisting medical conditions that cause or contribute to bone loss, an appropriate medical evaluation is indicated for all women with postmenopausal osteoporosis. Some causes of secondary osteoporosis include the following.

Endocrine or metabolic causes	Nutritional/GI conditions	Drugs	Disorders of collagen metabolism	Other
Acromegaly	Alcoholism	Antiepileptic drugsa	Ehlers-Danlos syndrome	AIDS/HIVa
Diabetes mellitusType 1Type 2	Anorexia nervosa	Aromatase inhibitors	Homocystinuria due to cystathionine deficiency	Ankylosing spondylitis
Growth hormone deficiency	Calcium deficiency	Chemotherapy/ immunosuppressants	Marfan syndrome	Chronic obstructive pulmonary disease
Hypercortisolism	Chronic liver disease	Depo-Provera	Osteogenesis imperfecta	Gaucher disease
Hyperparathyroidism	Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn's disease, and gastric resection or bypass)	Glucocorticoids		Hemophilia
Hyperthyroidism	Total parenteral nutrition	Gonadotropin-releasing hormone agents		Hypercalciuria
Hypogonadism	Vitamin D deficiency	Heparin		Immobilization
Hypophosphatasia		Lithium		Major depression
Porphyria		Proton pump inhibitors		Myeloma and some cancers
Pregnancy		Selective serotonin reuptake inhibitors		Organ transplantation
		Thiazolidinediones		Renal insufficiency/ failure
		Thyroid hormone (in supraphysiologic doses)		Renal tubular acidosis
				Rheumatoid arthritis
				Systemic mastocytosis
				Thalassemia

Note: This is table 11 from the AACE guidelines.

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Treatment

- Because causes of secondary osteoporosis are common even in apparently healthy, postmenopausal women, laboratory testing should be considered for all women with osteoporosis. Laboratory evaluation could include:
  - Complete blood cell count (CBC)
  - Comprehensive metabolic panel (includes calcium, albumin, and creatinine tests)
  - Serum 25-hydroxyvitamin D
  - Phosphate
  - 24-hour urine collection for calcium, sodium, and creatinine.

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Treatment

- If medical history, physical findings, or laboratory test results suggest causes of secondary osteoporosis, additional laboratory evaluation is warranted and may include, but is not limited to, the following.
  - Serum intact parathyroid hormone (PTH) concentration for possible primary or secondary hyperparathyroidism
  - Serum thyrotropin
  - Tissue transglutaminase antibodies for suspected celiac disease
  - Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma
  - Urinary free cortisol or other tests for suspected adrenal hypersecretion
  - Serum tryptase, urine N-methylhistidine, or other tests for mastocytosis
  - Bone marrow aspiration and biopsy to look for marrow-based diseases
  - Undecalcified iliac crest bone biopsy with double tetracycline labeling (recommended for patients with bone disease and renal failure to establish the correct diagnosis and direct management)
  - Genetic testing for unusual features that suggest rare metabolic bone diseases

Note: This is taken from table 12 in the AACE guidelines.

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Treatment

- Lifestyle modifications may improve musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures. These include:
- An adequate intake of calcium and vitamin D
  - Daily supplementation with vitamin D_3 at a dose of 1,000 to 2,000 IU is typically needed to maintain an optimal serum 25(OH)D level.
  - For adults age 50 and older, the recommended calcium intake (dietary plus supplements if necessary) is 1,200 mg/day.
- Lifelong participation in regular, weight-bearing, resistance exercise
- Balance-improving exercises to minimize falls
- Avoiding tobacco and excessive use of alcohol
- Eliminating potential risk factors for falling.

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Black DM and Rosen CJ. Postmenopausal Osteoporosis. *The New England Journal of Medicine* 2016; 374:254-262.

Treatment

- The AACE strongly recommends pharmacologic therapy for the following patients:
  - Those with osteopenia or low bone mass and a history of fragility fracture of the hip or spine.
  - Those with a T-score of –2.5 or lower in the spine, femoral neck, total hip, or 33% radius.
  - Those with a T-score between –1.0 and –2.5 in the spine, femoral neck, total hip, or 33% radius, if the FRAX® 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% (in the U.S.) or above the country-specific threshold in other countries or regions.

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Treatment

- A number of agents are approved by the U.S. Food and Drug Administration for prevention and/or treatment of postmenopausal osteoporosis. Full prescribing information should be reviewed before recommending any specific agent.

Drug	Prevention	Treatment
Alendronate (Fosamax)	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weeklyb 70 mg + Dc
Calcitonin (Miacalcin, Fortical)	—	200 IU intranasally once daily, or 100 IU SQ qod
Denosumab (Prolia)	—	60 mg SQ every 6 mo
Estrogen (multiple formulations)	Multiple regimens	—
Ibandronate (Boniva, generic form)	2.5 mg PO daily 150 mg PO monthly	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 mo
Raloxifene (Evista)	60 mg PO daily	60 mg PO daily
Risedronate (Actonel, Atelvia, generic form)a	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 150 mg PO monthly
Abaloparatide (Tymlos)	—	80 mcg subcutaneously daily
Teriparatide (Forteo)	—	20 µg SQ daily
Zoledronic acid (Reclast, generic infusion form)	5 mg IV every 2nd y	5 mg IV once yearly

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Treatment

- There are no-head-to-head trials comparing the efficacy of approved drugs. However, four agents (alendronate, risedronate, zoledronic acid, and denosumab) have evidence for broad anti-fracture efficacy (spine, hip, and non-vertebral fracture risk reduction). These should be considered as initial options for most patients who are candidates for pharmacologic therapy.

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Treatment

- Patients who have lower or moderate fracture risk can be started on oral agents.
- Injectable agents such as teriparatide, abaloparatide, denosumab, or zoledronic acid can be considered as initial therapy for those who have the highest fracture risk.

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Treatment

- For patients at high risk of spine fracture but not at risk for hip or non-vertebral fractures, ibandronate and raloxifene may be appropriate. Raloxifene has the additional benefit of reducing breast cancer risk.
- Denosumab is the agent of choice for patients with renal insufficiency. The AACE cautions against using in dialysis patients and those with stage 5 kidney disease due to risk of hypocalcemia.

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Sequential Therapy: Follow Anabolic Therapy with Antiresorptive Agents

- Treatment with anabolic agents (teriparatide, abaloparatide) should always be followed by antiresorptive therapy to prevent bone density decline and loss of fracture efficacy. The rationale for using an antiresorptive agent after anabolic therapy is based on both the limited period that anabolic therapy is used and on data showing that bone mineral density declines if antiresorptive therapy is not initiated.

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Leder BZ. Optimizing sequential and combined anabolic and antiresprptive osteoporosis therapy. *Journal of Bone and Mineral Research* 2018; 2:62-68.

Combination Therapy: Under Investigation

- Combination therapies for osteoporosis are being evaluated, but there are as yet no studies showing that treatment with two or more osteoporosis drugs has a greater effect on fracture reduction than treatment with a single agent.
- Studies of bisphosphonate/PTH analog combinations suggest they do not provide substantial clinical benefit compared with monotherapy. The most promising combination studied to date is teriparatide and denosumab. The DATA study showed that bone mineral density at the spine and hip increased significantly more in postmenopausal women on this combination compared to either drug alone.

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Leder BZ. Optimizing sequential and combined anabolic and antiresprptive osteoporosis therapy. *Journal of Bone and Mineral Research* 2018; 2:62-68.
Leder BZ et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab* 2014; 99:1694–700.
Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* 2013;382:50–56.

Combination Therapy: AACE Recommendation

- Combination therapy substantially raises the cost and probably increases the potential for side effects. Until the effect of combination therapy on fracture risk is better understood, the AACE does not recommend combination therapy for prevention or treatment of postmenopausal osteoporosis.
- However, in certain situations when the patient needs a stronger agent because fracture risk is especially high or there is demonstrated suboptimal effect from raloxifene or hormone replacement therapy (i.e., recurrent fractures, high bone resorption markers, or progression of BMD loss), yet the patient has specific non-bone reasons to continue with these agents, another antiresorptive agent or anabolic therapy could be added to the therapy.

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Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* 2013;382:50–56.

Discontinuation of Denosumab: Clinical Considerations

- Denosumab is a fast-acting and potent antiresorptive agent. However, its effects are rapidly reversible. When denosumab is discontinued, bone turnover rates increase to levels above pretreatment baseline.
- Clinicians should be aware that this post-denosumab "rebound" has been linked to an increased risk of compound vertebral fractures. In addition, evidence suggests that switching from denosumab to teriparatide in particular can lead to bone loss in postmenopausal women.

Leder BZ. Optimizing sequential and combined anabolic and antiresprptive osteoporosis therapy. *Journal of Bone and Mineral Research* 2018; 2:62-68.
Leder BZ et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet* 2015; 386:1147–1155.
Anastasilakis AD et al. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res* 2017; 32:1291–1296.

Treatment

- The AACE has developed the following treatment algorithm as part of its 2016 clinical practice guidelines.
- The full guidelines are available at https://www.aace.com/files/postmenopausal-guidelines.pdf.