ICSI Institute for Clinical Systems Improvement

Health Care Guideline

Diagnosis and Treatment of Osteoporosis

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Health Care Guideline:
Diagnosis and Treatment of Osteoporosis

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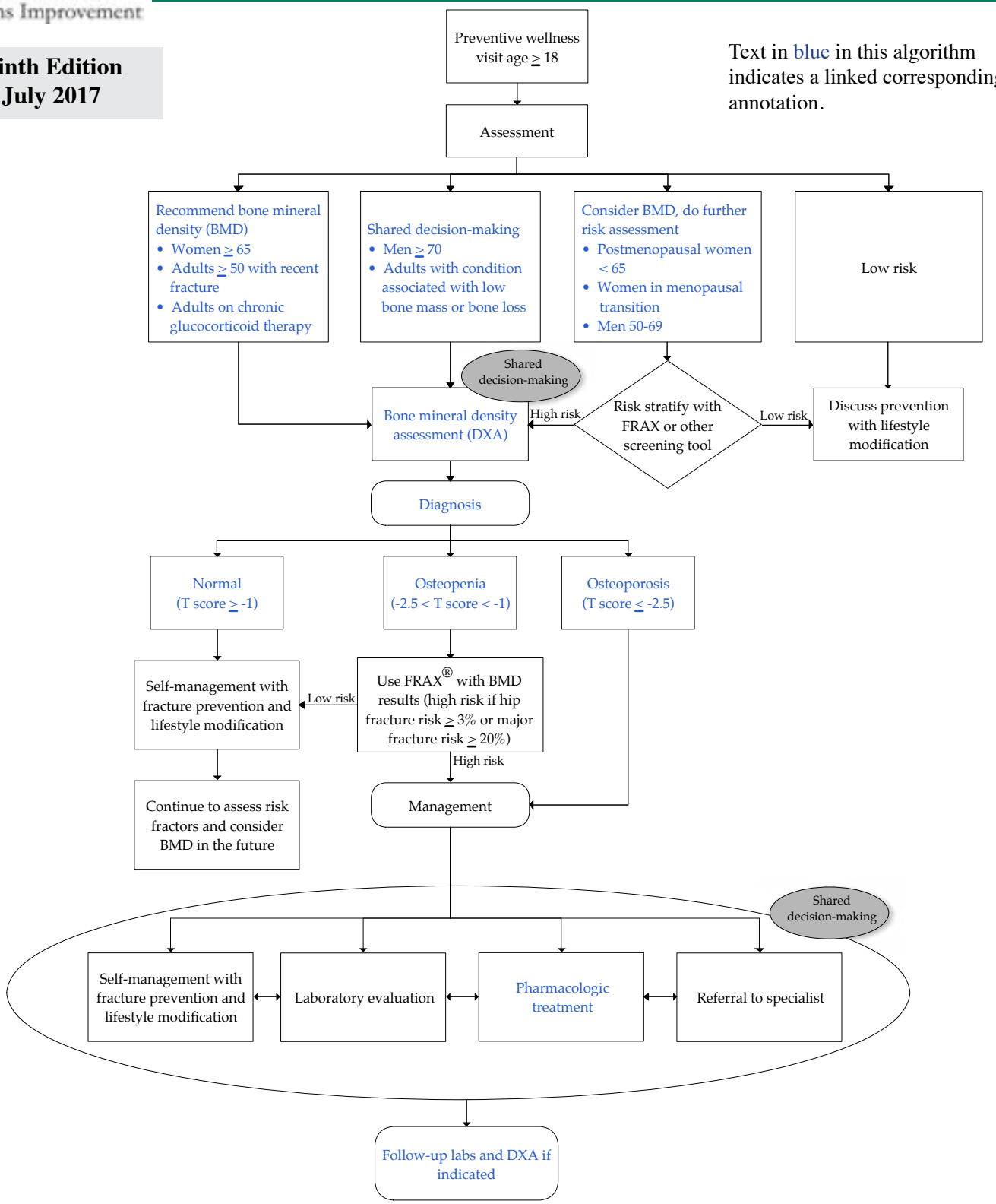

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Work Group Leader
Ann Kearns, MD, PhD
Endocrinology, Mayo Clinic

Work Group Members
Fairview Health Services
Mary Homan, MD
Family Medicine

HealthPartners Medical Group and Regions Hospital
Alison Forney-Gorman, MD, MPH
Family Medicine

Mayo Clinic
Anne Kramlinger, MD
Family Medicine

North Memorial Health Care
Mary Sauer, PharmD, BCACP
Family Medicine

University of Minnesota Physicians
Sharon Allen, MD, PhD
Family Medicine

ICSI
Jodie Dvorkin, MD, MPH
Project Manager/Health Care Consultant

Evidence Grading

Literature Search

A consistent and defined literature search process is used in the development and revision of ICSI guidelines. A formal literature search was conducted in PubMed. It included systematic reviews, meta-analyses, randomized controlled trials and observational studies, and was limited to adults over 18 years of age. The search was from January 1, 2010 – September 1, 2016, and included the following terms related to osteoporosis: fracture risk assessment (FRAX), trabecular bone score (TBS), screening, low-impact fracture, fragility fracture, calcium supplementation and cardiovascular risk, calcium supplementation and stroke risk, frequency of bone density screening, primary prevention, diet, exercise, bone mineral density assessment, screening laboratory profile, bisphosphonates, glucocorticoids and bone mineral density, steroids and bone mineral density, transplantation and bone mineral density, body habitus, body mass index, cigarette smoking, calcium intake, vitamin D intake, alcohol, estrogen, zoledronic acid, calcitonin, raloxifene, denosumab, ligand inhibitor, teriparatide, calcitriol, combination therapy and abaloparatide.

In addition to the literature searches, articles were obtained by work group members and ICSI staff. Those vetted by the work group were included in the guideline when appropriate.

ICSI utilizes the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology system. GRADE involves systematically evaluating the quality of evidence (high, moderate, low, very low) and developing a strength of recommendation (strong, weak). For more detailed information on GRADE, please visit http://www.gradeworkinggroup.org/.

In addition, when GRADE methadology could not be applied, the expert work group developed consensus recommendations.

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Recommendation Table

The following table is a list of evidence-based recommendations for the Diagnosis and Treatment of Osteoporosis.

Topic	Recommendation	Relevant Resources
Assessment	**ICSI Work Group Consensus Recommendation** 1. Recommend bone mineral density ▪ Women ≥ 65 years of age ▪ Adults over age 50 with recent fracture ▪ Adults on chronic glucocorticoid therapy ≥ 3 months 2. Shared-decision making: ▪ Men ≥ 70 years of age ▪ Adults with a known condition associated with low bone mass or bone loss 3. Consider bone mineral density and do further risk assessment ▪ Postmenopausal women younger than 65 years of age and women in the menopausal transition ▪ Men 50-69 years of age	*International Society for Clinical Densitometry, 2015; Cosman, 2014; U.S. Preventive Services Task Force, 2011*
Counseling on Lifestyle Modification	**ICSI Work Group GRADE Recommendation** Primary prevention and treatment for low bone density should include counseling on lifestyle modification regarding nutrition, physical activity, smoking, and alcohol. (Strength of Recommendation: Strong, Quality of Evidence: Low)	*Hannan, 2000; Huopio, 2000; Hoidrup, 1999; Ulrich, 1999*
Bone Mineral Density Assessment	**ICSI Work Group GRADE Recommendation** When available, central dual-energy x-ray absorptiometry (DXA) is the preferred method for assessing bone mineral density. (Strength of Recommendation: Strong, Quality of Evidence: Low)	*Hailey, 1998*
Diagnosis	**ICSI Work Group Consensus Recommendation** Referral to a specialist should be considered for the following patients: ▪ Abnormal labs for osteopenia/osteoporosis evaluation ▪ Patient is not doing well on initial therapy ▪ Patient with multiple fractures ▪ Patients with multiple comorbidities ▪ Premenopausal women Poor renal function (estimated creatine clearance ≤ 35 ml/min)	
Pharmacologic Treatment	**ICSI Work Group GRADE Recommendation** Bisphosphonates should be considered (unless contraindicated) for reduction of fracture risk (both vertebral and non-vertebral) in: • Postmenopausal women with osteoporosis (Strength of Recommendation: Strong, Quality of Evidence: High) • Men with osteoporosis (Strength of Recommendation: Strong, Quality of Evidence: Moderate)	Postmenopausal women with osteoporosis: *Miller, 2012; Eisman, 2008; Black, 2007; Chestnut, 2005; Chestnut, 2004; McClung, 2001; Black, 2000; Fogelman, 2000; Harris, 1999* Men with osteoporosis: *Chen, 2015*
Pharmacologic Treatment	**ICSI Work Group Consensus Recommendation** Bisphosphonates should be considered in postmenopausal women and men with osteopenia and increased fracture risk as well as patients with glucocorticoid-induced osteoporosis. This increased risk can be determined using the FRAX® tool post-BMD.	*Cohen, 1999; Saag, 1998*

Foreword

Introduction

Osteoporosis is a generalized skeletal disorder characterized by compromised bone strength and deterioration of bone quality, often leading to fragility (low trauma) fractures. The impact of this disorder is substantial in terms of cost, morbidity and mortality. According to data from the National Health and Nutrition Examination Survey (2005-2008), 9% of adults age 50 and older had osteoporosis at the femur neck or lumbar spine. About 47% had low bone mass at either site *(Looker, 2012)*. The impact of this disorder is significant in terms of cost, morbidity and mortality.

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Scope and Target Population

This guideline addresses the prevention, diagnosis and management of bone loss in adults age 18 and older, including lifestyle modification, evaluation and drug treatment. It does not address the pediatric population.

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Aim

1. Increase the percentage of adults appropriately screened for osteoporosis.

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Related ICSI Scientific Documents

Guidelines

- Healthy Lifestyles

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Definition

Clinician – All health care professionals whose practice is based on interaction with and/or treatment of a patient.

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Algorithm Annotations

Screening

Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved peak bone mass, or both. We recommend maintaining peak bone mass for all patients. To achieve and maintain maximum bone density, patients should have medical history and risks for osteoporosis reviewed when they present to their clinician's office.

There is broad consensus that mass population screening of all individuals is neither cost effective nor appropriate. Many professional organizations have published their own guidelines describing whom to select for bone densitometry.

Below is a table summarizing recommendations from the United States Preventive Services Task Force (2011), the National Osteoporosis Foundation (2014) and the International Society for Clinical Densitometry (2015). Taking these recommendations into consideration, the ICSI Diagnosis and Treatment of Osteoporosis work group, by expert consensus, developed the following categories:

1) Recommend bone mineral density assessment
2) Use shared-decision making
3) Consider bone mineral density assessment and do further risk assessment

ICSI Work Group Consensus	Population	U.S. Preventive Services Task Force (2011)	National Osteoporosis Foundation (2014)	International Society for Clinical Densitometry (2015)
Recommend bone mineral density assessment	Women ≥ age 65	Recommend	Recommend	Recommend
	Adults > age 50 with recent fracture	Not addressed	Recommend, specifies adults who have had a fracture at ≥ age 50	Recommend, specifies adults with fragility fracture
	Adults on chronic glucocorticoid therapy for ≥ 3 months	Not addressed	Recommend	Recommend, specifies adults taking medications associated with low bone mass or bone loss
Shared decision-making	Men ≥ age 70	Insufficient evidence	Recommend	Recommend
	Adults with a known condition associated with low bone mass or bone loss	Not addressed	Recommend	Recommend
Consider bone mineral density, do further risk assessment	Postmenopausal women < age 65 and women in the menopausal transition	Recommend BMD* if risk for fracture for woman ≥ age 65 with no additional risk factors (equivalent to FRAX score 9.3% 10-year risk)	Recommend BMD if additional risk factors	Recommend if additional risk factors
	Men ages 50-69	Insufficient evidence	Recommend BMD if additional risk factors	Recommend BMD if additional risk factors

BMD: bone mineral density

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Recommend Bone Mineral Density Assessment

Women age 65 and older

There is general consensus across organizations that women age 65 and older should undergo bone mineral density (BMD) assessment to screen for osteoporosis *(International Society for Clinical Densitometry, 2015; Cosman, 2014; U.S. Preventive Services Task Force, 2011)*.

Adults age 50 and over with recent fracture

For the purpose of this guideline, a low-impact (fragility) fracture is defined as a fracture occurring spontaneously or from a fall at a height no greater than the patient's standing height. This includes fractures from activities such as a coughing, sneezing or abrupt movement (e.g., opening a window), and patients who have prevalent low-impact vertebral compression fracture documentation on radiographs regardless of their degree of symptoms. All men and postmenopausal women with low-impact (fragility) fracture should be considered for BMD assessment. Adults with a history of vertebral fracture, hip fracture, proximal humerus, ankle, pelvis or distal forearm fracture are at higher than average risk for a future fracture.

The presence of a vertebral compression fracture (VCF) increases the risk for subsequent fracture beyond the risk indicated by bone density alone *(National Osteoporosis Foundation, 2010; Kanis, 1997)*.

Non-vertebral fractures can also be indicators of increased risk for subsequent fracture. Schroeder, et al. reviewed 256 second hip fractures in 3,898 adults. Ninety-two percent were contralateral, and half the repeat fractures occurred in less than three years after the index fracture. Although the risk of the first hip fracture was 1.6 per 1,000 men and 3.6 per 1,000 women, the risk for a second hip fracture was 15 per 1,000 men and 22 per 1,000 women *(Schrøder, 1993)*.

Women with prior fracture and low bone density appear to be the most responsive to antiresorptive therapy, and pharmaceutical trials suggest that women with prior fracture can reduce their risk for subsequent fractures by 30-50%. This has been shown for FDA-approved osteoporosis therapies. The largest therapy-induced BMD increase is observed in patients with the lowest BMD and vertebral fractures, the population at highest risk *(Ettinger, 1999; Hochberg, 1999)*.

Adults on chronic glucocorticoid therapy

Osteoporosis prevention and treatment measures and BMD testing should be considered for anyone who is started on, has been taking or has a history of taking exogenous glucocorticoid therapy (at a dose of more than 5 mg prednisone or equivalent per day for three or more months).

Bone mineral density loss and fractures associated with oral glucocorticoid use

Oral glucocorticoids cause biphasic loss of bone, with up to 15% bone loss during the initial phase lasting a few months. This is characterized by an increase in bone resorption and a decrease in bone formation, and many other factors that adversely affect bone strength.

After the initial phase, bone loss is slower, characterized by lower rates of bone resorption and formation. The degree of bone loss is correlated with both the average daily and total cumulative dose of glucocorticoids used, regardless if glucocorticoids are used daily or on alternate days. Retrospective cohort studies have shown a significant increased rate of fracture in these patients.

Bone mineral density loss associated with inhaled glucocorticoids

Although not as profound as with oral glucocorticoids, inhaled high-potency glucocorticoids used to treat asthma and chronic obstructive airways disease have been shown to cause bone loss when used over an extended time period. A cross-sectional study showed that cumulative exposure to 5,000 mg of beclomethasone (2,000 mcg/day for seven years) was associated with enough loss of BMD to double

fracture risk. One three-year longitudinal study of inhaled triamcinolone therapy in chronic obstructive pulmonary disease showed significant bone loss compared to those treated with a placebo inhaler. No studies documenting or suggesting increased rates of fracture attributable to inhaled or nasal glucocorticoids have been done *(Lung Health Study Research Group, The, 2000; Wong, 2000; Lipworth, 1999)*.

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Shared Decision-Making

Men age 70 years and older

Routine screening of men is not widespread. Screening men for osteoporosis is still an area of controversy with differing recommendations among guidelines. According to the U.S. Preventive Services Task Force (2011), current evidence in insufficient to assess the balance of benefit and harms of screening for osteoporosis in men. However, the National Osteoporosis Foundation (2014) and the International Society for Clinical Densitometry (2015) recommend screening of osteoporosis in men over the age of 70. It is the expert opinion of this work group that clinicians use shared decision-making with this group of patients and discuss the benefits and harms of screening. We recommend BMD assessment in men older than 70 who have additional risk factors for osteoporosis.

Adults with a known condition associated with low bone mass or bone loss

Please see Appendix A, "Secondary Causes of Osteoporosis," for conditions associated with osteoporosis. Clinicians should consider screening for osteoporosis in these patients. The decision to screen and when to screen should be based on the patient's entire clinical picture.

Organ transplantation

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation *(Ebeling, 2007; Maalouf, 2005)*.

Consider all patients for a baseline BMD test at acceptance into transplantation program and follow-up BMD testing be performed yearly prior to transplantation. If patients are taking high-dose steroid medication before transplantation, BMD testing should be performed every 6-12 months.

After solid organ or allogenic bone marrow transplantation, consider BMD testing once a year to detect any ongoing bone loss.

Pretransplantation bone loss

Patients accepted for solid organ or allogenic bone marrow transplantation may develop significantly decreased BMD before transplantation. The decrease in BMD before transplantation is multifactorial, with contributing factors including systemic effects of end-organ disease, hypogonadism, chronic steroid therapy, chronic anticoagulation, effects of other medications and relative immobilization *(Hamdy, 2007)*.

Post-transplantation bone loss

Solid organ and allogeneic bone marrow transplantation are associated with a rapid decrease in BMD at all skeletal sites during the first year after transplantation. Most patients lose in the range of 8-10% of their pretransplant bone density in the first year after transplant, often worse at the hip than the lumbar spine, if therapy to prevent this is not initiated at the time of transplant *(Tauchmanová, 2007)*. The rapid decrease is caused by multiple factors, but predominantly due to high-dose steroid therapy in the first six months to one year after transplantation. Other factors include the effects of other immunosuppressive drugs, particularly cyclosporine and tacrolimus, persistent hypogonadism, and immobilization early after transplantation. BMD

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typically stabilizes during the second year after transplantation and then begins to recover to some degree toward baseline during the third year after transplantation. Atraumatic or mildly traumatic fractures occur fairly frequently in patients after transplantation, especially in the first few months to years after receiving a graft *(Fleischer, 2008; Stein, 2007; Tauchmanová, 2007)*.

Consider Bone Mineral Density Assessment, Do Further Risk Assessment

Women less than age 65 and men ages 50-69

Women who are younger than age 65 years and men ages 50-69 may benefit from a detailed assessment of clinical risk factors to help decide whether a BMD assessment is needed. See "Risk Assessment" section for more information.

Significant height loss

Height loss or acquired kyphosis should prompt consideration for lateral vertebral fracture assessment with dual energy x-ray absorptiometry (DXA) or plain radiographs of the thoracic and lumbar spine.

A study in 2011 determined the association between the degree of height loss and risk of a vertebral fracture in 231 men and women over age 65. Height loss and vertebral fracture were significantly associated. The magnitude of the association is translated to an increase of odds of 19% for 1/2 inch of height loss and 177% for 3 inches of height loss. They concluded that height loss is an indicator for the presence of vertebral fractures *(Xu, 2011)*.

It is recommended to perform densitometric VFA (vertebral fracture assessment) or lateral spine films in adults with a T-score of < -1.0 and a historical height loss of > 1.5 inches. Note that the radiation exposure of spinal x-rays is markedly higher than that of vertebral assessment, but the latter is less accessible to clinicians *(International Society for Clinical Densitometry, 2015; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001)*.

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Risk Assessment

For patients who do not fit into a high-risk category, an assessment of risk factors should take place to determine if BMD testing is warranted. This may be done by a thorough history or by using a risk assessment tool.

FRAX® is one example of a risk assessment tool that may aid in identifying patients who would benefit from a BMD assessment. FRAX® is an algorithm for fracture risk assessment developed by the WHO (World Health Organization) in cooperation with other organizations and societies. This tool uses easily obtainable clinical information, with or without BMD measurements, to estimate the 10-year risk for hip fracture and major osteoporotic fracture.

FRAX® is not meant for premenopausal women, if the patient is on osteoporosis treatment or if the patient has recently been on osteoporosis treatment (within the last two years).

The FRAX® calculation can be found on the Web at http://www.shef.ac.uk/FRAX.

Factors in FRAX® include:

- Country/race
- Age (40-90)
- Sex
- Weight
- Height
- Previous fracture

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- Parent fractured hip
- Current smoking
- Glucocorticoids
- Rheumatoid arthritis
- Secondary osteoporosis
- Alcohol (three or more units a day)
- Bone mineral density (femoral neck)

The U.S. Preventive Services Task Force recommends screening of women younger than age 65 if their risk for fracture is equal to or greater than a 65-year-old woman with no additional risk factors. Using FRAX®, a 65-year-old woman with no additional risk factors has a 9.3% 10-year risk for osteoporotic fracture. Thus, FRAX can be used without BMD to estimate a woman's risk with a threshold of 9.3% to go on to assess BMD *(U.S. Preventive Services Task Force, 2011)*.

There are recognized limitations to FRAX. Because answers are limited to "yes" and "no" responses, dose effects are not considered.

FRAX® does not include many risk factors that may influence the screening and treatment decision (e.g., falling, medications other than steroids, family history of spinal fractures, functional status and the number and severity of prior fractures). FRAX® also does not factor in severity of prior spinal vertebral fracture *(Hans, 2011)*. History of conditions associated with bone loss, other than rheumatoid arthritis, is also not included.

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Counseling on Lifestyle Modification

Recommendation	Quality of Evidence and Strength of Recommendation
Primary prevention and treatment for low bone density should include counseling on lifestyle modification regarding nutrition, physical activity, smoking and alcohol.	**Quality of Evidence:** Low **Strength of Recommendation:** Strong
Benefit: Lifestyle modifications can improve bone mineral density. They also have positive implications for many other health conditions. **Harm:** There is no harm in counseling patients on self-management of lifestyle factors. One consideration from a resource perspective is time needed for clinicians to have these conversations. However, because nutrition, physical activity, smoking and alcohol affect health in many ways, this time is well spent as a prevention tool. **Benefit-Harms Assessment:** The benefits of discussing lifestyle factors with patients far exceed any negligible harms related to time and resources.	
Relevant Resources: *Hannan, 2000; Huopio, 2000; Høidrup, 1999; Ulrich, 1999*	

While assessing the patient for risk factors for fracture, clinicians should also use this opportunity to provide counseling on any relevant risk factors that would benefit from lifestyle modification. Please see the ICSI Healthy Lifestyles guideline for detailed information about diet, physical activity, tobacco and alcohol.

Physical Activity

Sedentary lifestyle is a risk factor for osteoporosis. The type of physical activity and optimal age for greatest benefit is still unclear. Lack of continued physical activity may lead to bone loss.

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Meta-analysis of several studies indicates that athletes have a 25% greater BMD than simply active people, and that active people have a 30% higher BMD compared to inactive people. An inactive person needs to be made aware of the increased risk to bone health. Some studies suggest that increased physical activity is modestly protective against fracture, independent of BMD *(Bemben, 1999; Branca, 1999)*.

Exercise is well known for its many benefits, both short term and long term. Weight-bearing and muscle-strengthening exercises have been shown to be an integral part of osteoporosis prevention, as well as a part of the treatment process.

Regular physical exercise has numerous benefits for individuals of all ages. There is evidence that physical activity early in life contributes to higher peak bone mass. Physical activity during early age was more strongly associated with higher BMD at all sites than was physical activity in the past two years. Lifetime weight bearing is more strongly associated with higher BMD of the total and peripheral skeleton than is non-weight-bearing exercise. Exercise during the later years in the presence of adequate calcium and vitamin D probably has a modest effect on slowing the decline in BMD.

Physical activity, particularly weight-bearing exercise, is thought to provide the mechanical stimuli, or "loading," important for the maintenance and improvement of bone health. Resistance training may have more profound site-specific effect than aerobic exercise. High-intensity resistance training may have added benefits for decreasing fracture risks by improving strength and balance, and increasing muscle mass *(Layne, 1999)*. High-impact exercise and weight training stimulate accrual of bone mineral content in the skeleton.

Randomized clinical trials have shown exercise to decrease the risk of falls by approximately 25%. Stronger back extensor muscles have been shown to decrease the risk of vertebral fractures independent of pharmacotherapy. Those who exercise may fall differently and decrease their fracture risk as a result. However, it is important to avoid over-stressing the spine and cause new injury. Spinal flexion exercises have demonstrated an increased risk of vertebral fractures *(Sinaki, 2005; Sinaki, 2002; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001)*. Exercise should focus on strengthening back extension and may include weighted and unweighted prone position, extension exercises, isometric contraction of the paraspinal muscles and careful loading of the upper extremities *(Sinaki, 2005; Sinaki, 2002)*.

All three components of an exercise program are needed for strong bone health: impact exercise such as jogging, brisk walking, stair climbing; strengthening exercise with weights; and balance training, such as Tai Chi or dancing. Patients should be encouraged and offered assistance in developing a lifetime program of exercise that they will continue to do and enjoy. As a result, as they age they will be stronger and more flexible, and have improved balance and quality of life.

Adequate Calcium Intake

A balanced diet of calcium-rich products and appropriate nutrition should be discussed with patients *(Hannan, 2000; Heaney, 2000)*.

Comprehensive reviews of the relationship of calcium intake and bone health reported that sufficient amounts of calcium slows age-related bone loss and may reduce osteoporotic fracture risk. Both dietary sources and calcium supplements are related to promoting bone health *(Heaney, 2000; Riggs, 1998; Cumming, 1997; Recker, 1996; Chapuy, 1992; Dawson-Hughes, 1990)*. When food sources do not provide enough calcium, supplements can be used to meet this goal. Bioavailability of calcium in food sources and supplements is a factor in achieving daily calcium recommendations. See the USDA table for foods rich in calcium (http://www.nal.usda.gov/fnic/foodcomp/search). The goal is to achieve adequate calcium with diet alone if possible.

Bioavailability from calcium supplements is affected by meals, dose size and tablet disintegration. Calcium absorption efficiency decreases at doses greater than 600 mg; therefore, supplements should be taken in divided doses. Taking calcium carbonate supplements on an empty stomach may increase the risk of kidney stones and may not be well absorbed, therefore, calcium carbonate is best taken with meals. Absorption of

calcium carbonate may be decreased in the environment of achlorhydira (PPIs, histamine receptor blockers), high-dose proton-pump inhibitor use or histamine receptor blockers when calcium supplement is taken on an empty stomach. Calcium citrate is better absorbed by patients with medication-induced achlorhydria *(O'Connell, 2005; Ross, 2000; Heller, 1999; Institute of Medicine, 1997)*.

Both low fractional calcium absorption and low dietary calcium intake have been associated with increased fracture risk. Since fractional calcium absorption is affected by multiple factors and decreases with age, adequate lifetime dietary calcium is an important recommendation for bone health *(NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001; Weaver, 2000)*.

The effect of calcium supplementation on cardiac risk has been questioned. A recent expert panel convened by the National Osteoporosis Foundation and American Society for Preventive Cardiology adopted the position that calcium intake from dietary sources or supplements has no relationship to the risk for cardiovascular or cerebrovascular disease or all-cause mortality in generally healthy adults. This includes calcium with and without vitamin D. The panel notes that in light of current evidence, calcium intake from food or supplements is safe from a cardiovascular standpoint, up to 2,000 to 2,500 mg/day *(Kopecky, 2016)*.

Over supplementation may be associated with an increased risk of kidney stones and vascular calcification *(Bolland, 2008; Reid, 2002)*.

Adequate Vitamin D

Vitamin D is essential for calcium absorption and bone metabolism. Aging is associated with decreasing 25-OH vitamin D levels, progressive renal insufficiency, reduced sun exposure and reduced skin capacity for vitamin D production. Vitamin D insufficiency and overt deficiency can cause secondary hyperparathyroidism, which in turn leads to increased bone turnover. Studies of combined calcium and vitamin D supplementation have demonstrated reductions in bone loss and reductions in hip and non-vertebral fractures. This supplement-induced benefit on bone mass can be lost when the calcium and vitamin D are discontinued *(LeBoff, 1999; Dawson-Hughes, 1997)*.

Studies concerning vitamin D and bone health demonstrate daily vitamin D supplementation in the range of 700-800 international units can decrease hip fracture risk in the elderly by 26% and any non-vertebral fracture by 23% *(Bischoff-Ferrari, 2005)*.

Normal BMI

Primary prevention should include counseling patients on achievement and maintenance of a normal BMI of 20-25 *(Hannan, 2000)*. Low body mass index (BMI) (less than 20) is a strong independent risk factor for osteoporosis and fracture. A weight less than 127 pounds, associated with small bones, is a risk factor for osteoporosis *(Ravn, 1999)*.

Smoking Cessation

Cigarette smoking is a modifiable risk factor for osteoporosis. Smokers do not absorb dietary or supplemental calcium as efficiently as non-smokers. Smokers have reduced gonadal steroids and earlier menopause, and there is an increase in bone remodeling markers in heavy smokers. There is an increase in bone resorption. Both the increased risk among current smokers and the decline in risk 10 years after smoking cessation are in part accounted for by the difference in BMI *(Huopio, 2000; Cornuz, 1999)*.

Smoking cessation counseling should be done at every visit *(Huopio, 2000)*. Discussion can include helpful strategies such as nicotine replacement therapy with patches and gum, bupropion, varenicline and smoking cessation classes may also be discussed.

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Limit Alcohol Intake

A high level of alcohol intake is associated with decreased BMD. Studies have reported an association between alcohol intake greater than one ounce of hard liquor or one drink per day (28-30 g) and decreased BMD both at the trochanter site and in total BMD. In a four-year longitudinal evaluation by the Framingham Osteoporosis Study, this association was found in women, but not in men. An association between high levels of alcohol use by both men and women, and hip fracture was found in a large prospective Danish study. In the Nurses' Health Study cohort (age 35-64), alcohol intake (more than 25 g or one drink per day) was associated with increased risk of hip fracture and forearm fracture when compared with non-drinkers *(Hannan, 2000; Høidrup, 1999)*.

There are conflicting data about the effects of moderate alcohol use on BMD. Alcohol use has been demonstrated to affect bone formation, even at moderate levels of no more than one drink per day for women and no more than two drinks per day for men. Alcohol has a direct, antiproliferative effect on osteoblasts. It also has a dose-dependent suppressive effect on osteocalcin levels. Some studies have reviewed the potential effect of alcohol on levels of parathyroid hormone, calcitonin and vitamin D metabolites, but no clear mechanism was identified *(Klein, 1997)*.

Limit alcohol use to no more than one drink per day for women and no more than two drinks per day for men. One drink equals 12 ounces of beer, 5 ounces of wine or 1.5 ounces of 80-proof distilled spirits. This limit will help to protect bone health and reduce the risk of falls.

Prevention of Falls

Falls are common in people over the age of 65. Falls increase the risk of fracture. Counseling patients on recognizing and avoiding hazards inside and outside the home is recommended. It can also be helpful to counsel patients on improving balance and other strategies to avoid falls.

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Bone Mineral Density (BMD) Assessment

Recommendation	Quality of Evidence and Strength of Recommendation
When available, central dual-energy x-ray absorptiometry (DXA) is the preferred method for assessing bone mineral density.	**Quality of Evidence:** Low **Strength of Recommendation:** Strong
Benefit: DXA is widely available, non-invasive, and has low radiation exposure. Most of the trials on pharmacologic therapy utilized DXA as the diagnostic tool for osteoporosis. **Harm:** There is radiation exposure for DXA, which although small, is still present. **Benefit-Harms Assessment:** The benefits of DXA as a diagnostic tool outweigh the small risk of radiation that is involved.	
Relevant Resources: *Hailey, 1998*	

Measurements of BMD with central (hip or spine) dual-energy x-ray absorptiometry (DXA) predict fracture risk and allow for the identification of people who are at increased risk of fracture. Reviews of prospective cohort studies and case control studies have documented a direct relationship between decreasing BMD and increasing fracture risk *(Chandler, 2000; Cummings, 1995)*. Additionally, there is evidence that stabilization or increases in BMD with therapy for osteoporosis are associated with substantial reductions in fracture incidence. Therefore, densitometry offers an objective measurement of a patient's response to treatment over time *(Miller, 1999; Hailey, 1998)*. At this time there are no cost-effectiveness data for monitoring response to treatment. DXA is ideally performed by a technologist certified by the International Society for Clinical Densitometry (ISCD) or the American Registry of Radiologic Technologists (ARRT).

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An individual's BMD is compared to a reference-normal young adult population and described as a T-score, the number of standard deviations (SD) above or below the mean of the reference population. A T-score is calculated from the following equation:

[(measured BMD - young adult population mean BMD)/young adult population SD]

A Z-score is the number of standard deviations above or below the mean for gender, ethnicity and age-matched healthy population. A Z-score is calculated from the following equation:

[(measured BMD - age-matched population mean BMD)/age-matched population SD]

Normal, low bone density (osteopenia) and osteoporosis are defined by the lowest T-score of lumbar spine (at least two evaluable vertebrae required), femoral neck and total hip. The one-third radius site may be used if either the lumbar spine or femur is non-evaluable.

The following classifications apply to women postmenopausal and men age 50 and older:

Normal	T-score ≥ -1
Low bone density (osteopenia*)	T-score between -1 and -2.5
Osteoporosis	T-score ≤ -2.5
Severe osteoporosis	Reserved for patients with a fragility fracture(s) *and* a T-score less than or equal to -2.5

* Following a Position Development Conference on bone densitometry in 2005, the International Society of Clinical Densitometry recommends that the term "osteopenia" be retained, but "low bone mass" or "low bone density" are the preferred terms *(Baim, 2008; Binkley, 2006)*.

(International Society for Clinical Densitometry, The, 2007)

In women premenopausal and men under age 50, the Z-scores should be used rather than the T-scores in identifying those with low bone density. The World Health Organization classifications should not be used. According to the International Society for Clinical Densitometry, a Z-score of -2.0 or lower is defined as "below the expected range for age," and a Z-score above -2.0 is "within the expected range for age" *(International Society for Clinical Densitometry, The, 2007)*.

Techniques Other than Central DXA

There are numerous techniques currently available to assess BMD in addition to central DXA; they include the following:

Peripheral DXA (pDXA)

pDXA measure areal bone density of the forearm, finger or heel. Measurement by validated pDXA devices can be used to assess vertebral and overall fracture risk in postmenopausal women. There is lack of sufficient evidence for fracture prediction in men. pDXA is associated with exposure to trivial amounts of radiation. pDXA is not appropriate for monitoring BMD after treatment at this time.

CT-based absorptiometry

Quantitative computed tomography (QCT) measures volumetric trabecular and cortical bone density at the spine and hip, whereas peripheral QCT (pQCT) measures the same at the forearm or tibia. In postmenopausal women, QCT measurement of spine trabecular BMD can predict vertebral fractures, whereas pQCT of the forearm at the ultra distal radius predicts hip but not spine fractures. There is a lack of sufficient evidence for fracture prediction in men. QCT and pQCT are associated with greater amounts of radiation exposure than central DXA of the spine and hip or pDXA, respectively.

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In addition, abdominal CT scans performed for reasons other than BMD measurements can be analyzed and volumetric BMD reported as an additional assessment.

Quantitative ultrasound densitometry (QUS)

Quantitative ultrasound densitometry (QUS) does not measure BMD directly but rather speed of sound (SOS) and/or broadband ultrasound attenuation (BUA) at the heel, tibia, patella and other peripheral skeletal sites. A composite parameter using SOS and BUA may be used clinically. Validated heel QUS devices predict fractures in postmenopausal women (vertebral, hip and overall fracture risk) and in men age 65 and older (hip and non-vertebral fractures). QUS is not associated with any radiation exposure *(Baim, 2008)*.

Additional DXA Assessments

Additional features are now available with central DXA machines and associated software.

Vertebral fracture assessment

Vertebral fracture assessment (VFA) is broadly indicated when there is a reasonable pretest probability that a prevalent vertebral fracture will be found on the study that would influence management of that patient. Lateral spine images are obtained, and vertebral body shape is analyzed. This allows for detection of vertebral deformity that can indicate a compression fracture. Previously unrecognized vertebral compressions can provide additional information to fracture risk assessment (see FRAX). If there is doubt, dedicated spines x-rays may be indicated to further evaluate. The advantages of VFA versus standard spine x-rays are convenience, lower cost and markedly lower radiation exposure.

According to ISCD (2015), lateral spine imaging with standard radiography or densitometric VFA is indicated when T-score < -1.0 and one or more of the following are present:

- Women age 70 and older or men age 80 and older with T-score < -1.0
- Historical height loss > 4 cm (>1.5 inches)
- Self-reported but undocumented prior vertebral fracture
- Recent or ongoing glucocorticoid therapy equivalent to ≥ 5 mg of prednisone or equivalent per day for ≥ 3 months

According to NOF (2014), vertebral imaging should be considered in:

- Women age 70 and older or men age 80 and older with T-score at the spine, total hip or femoral neck ≤ -1.0
- Women age 65-69 and men age 70-79 with T-score at the spine, total hip or femoral neck ≤ -1.5
- Postmenopausal women and men age 50 and older with the following risk factors
  - Low-trauma fracture during adulthood (age 50 and older)
  - Historical height loss ≥ 1.5 in (4 cm)
  - Prospective height loss of 0.8 in. (2 cm)or more
  - Recent or ongoing long-term glucocorticoid therapy

Trabecular bone score

A large portion of bone strength is explained by BMD, but there is growing interest in other factors often referred to as "bone quality." The analysis of vertebral bone quality from DXA images can be performed with additional software. The trabecular bone score (TBS) is a measure of bone texture that correlates with

bone microarchitecture. It is used alongside DXA BMD in FRAX calculation to adjust fracture risk prediction. Individuals with low bone quality (low TBS) have increased fracture risk compared to individuals with equivalent areal BMD and high TBS.

Single energy femur exam

Some DXA machines have additional capability to assess the femur for features that may indicate the development of atypical femur fractures. High-resolution imaging of the femur is performed on the DXA machine with relatively low radiation exposure and little need to reposition the patient. Findings suggestive of developing atypical femur fracture need additional imaging to further characterize. This feature may be useful in patients on long-term anti-resorptive agents.

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Diagnosis

Diagnosis of osteoporosis is obtained by DXA measurement of bone density at the hip and the lumbar spine, preferably performed by trained technologists on properly maintained and calibrated instruments. The resulting T-scores measure the number of standard deviations from the mean level for a young adult population. T-scores are an accurate evaluation of bone density variability in women postmenopausal and men age 50 and older. In premenopausal women, men less than age 50 years, the International Society for Clinical Densitometry (ISCD) recommends the diagnosis of osteoporosis be made based on ethnic or race- adjusted Z-scores.

The diagnosis and decision to treat is further clarified by calculation of the FRAX score.

Normal (T-score ≥ -1)

Normal bone density is defined as a T-score ≥ -1 for women postmenopausal and men age 50 and older or for premenopausal women, men less than age 50 with a Z-score above –2.0.

Patients in this category at initial screen should not automatically be assumed to remain at low risk of future fracture over their remaining lifetime years. Patients should be assessed periodically by reviewing risk factors for osteoporosis, evaluating current primary prevention efforts, and reviewing the clinical history for osteoporotic fractures subsequent to the initial bone density evaluation. Clinical judgment must be used in determining the appropriate intervals between repeated measurements of BMD over time. Whenever repeating the measurement occurs, it is ideal to use the same densitometer. In some patients, such as those expected to have high bone turnover and rapid bone loss due to early postmenopausal status, initiation or continuation of steroid therapy, organ transplantation or other causes, it may be appropriate to re-measure bone density as soon as 6-12 months after the initial measurement. In those patients not expected to have high turnover or rapid loss, it is appropriate to re-measure BMD at an appropriate interval, such as 2 to 10 years after the initial assessment depending on baseline BMD, in order to detect patients who lose significant bone density over time. The FRAX® analysis can guide the frequency of the repeat DXAs.

Osteopenia (T-score between -1 and -2.5)

Osteopenia, or low bone mass, is defined as a T-score between -1 and -2.5.

Use FRAX® to determine if treatment of osteopenia is indicated. Fracture risk prediction is improved when clinical risk factors are combined with BMD. FRAX® is most accurate in women postmenopausal and men age 50 and older.

Based on this model, postmenopausal women and men age 50 and older with osteopenia by DXA and a FRAX® hip fracture risk ≥ 3% or major osteoporotic fracture risk ≤ 20% score ≥ 3 % or a 10-year hip fracture probability of ≥ 20 % would be good candidates for pharmacological prevention of osteoporosis *(Cosman, 2014)*.

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Applying the FRAX® analysis retrospectively to prior fracture studies have yielded conflicting correlation with the FRAX® risk and medication efficacy. More studies in this area are needed *(Donaldson, 2012; Hans, 2011)*.

The work group did not find specific evidence regarding osteopenia and secondary workup. It is the work group consensus that additional labs for patients with osteopenia should be left to clinician judgment, depending on patient history and characteristics.

Osteoporosis (T-score ≤ -2.5)

Osteoporosis is defined as a T-score of ≤ -2.5 on BMD. For certain patients where the burden of obtaining a DXA is significant, it may be reasonable to make a presumptive diagnosis of osteoporosis and start treatment despite the absence of a BMD assessment.

Once a diagnosis of osteoporosis is confirmed by BMD, it is important to evaluate for certain diseases that are commonly associated with bone loss. These diseases are listed in Appendix A, "Secondary Causes of Osteoporosis." In broad categories, these include chronic inflammatory autoimmune conditions, endocrinopathies, malignancies and malabsorptive states.

While there are no standard agreements or recommendations regarding initial laboratory for patients with osteoporosis, the work group recommends clinicians consider first the labs that may be needed prior to initiating a medication, and second, additional labs needed for diagnostic workup.

Evaluation prior to starting pharmacologic treatment

- 25 hydroxy (OH) vitamin D level:
  - Optimal level is greater than or equal to 30 ng/mL in most patients.
  - It is also important to ensure adequate vitamin D stores prior to initiation of advanced pharmacologic osteoporosis therapies.
- Serum calcium:
  - To rule out hypocalcemia (in malabsorption/vitamin D deficiency) or hypercalcemia (in hyperparathyroidism).
  - It is important to correct hypocalcemia prior to initiation of advanced pharmacologic osteoporosis therapies.
- Serum creatinine:
  - This should be drawn in order to screen for renal dysfunction and to assure safety of advanced pharmacologic osteoporosis therapies.
- TSH:
  - Should be drawn in patients on thyroid hormone supplementation.
  - Consider for other patients as clinically indicated.

Additional evaluation

The following more extensive evaluation for secondary causes of osteoporosis may be considered on an individual basis. Severity of disease should be considered when making this determination.

- 24-hour urine calcium excretion:
  - This is low in a malabsorptive state (such as in celiac sprue or after gastric bypass), in vitamin D deficiency or in patients on thiazide diuretics.

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  - This is high in idiopathic hypercalciuria (which is a correctable cause of bone loss) in primary hyperparathyroidism and commonly in patients with excessive calcium intake.

- A biochemical profile that provides information on:
  - Alkaline phosphatase: elevated in Paget's disease, prolonged immobilization, acute fractures, osteomalacia and other bone disease.
  - Phosphorus: decreased in osteomalacia.
  - Parathyroid hormone level even if serum calcium is normal.
- A complete blood count may suggest bone marrow malignancy or infiltrative process (anemia, low white blood cells or low platelets) or malabsorption (anemia, microcytosis or macrocytosis).
- An elevated sedimentation rate or C-reactive protein may indicate an inflammatory process or monoclonal gammopathy.
- Testosterone (total and free) in men and estradiol (total and bioavailable) in women; LH and FSH and prolactin if evidence of hypogonadotropic hypogonadism.
- Tissue transglutaminase if clinical suspicion for gluten enteropathy or low 25-OH vitamin D.
- Serum and urine protein electrophoresis, with a conditional immunoelectrophoresis.

The labs above are not an exhaustive list of the laboratory evaluation. Because many clinical conditions are associated with bone loss (refer to Appendix A, "Secondary Causes of Osteoporosis"), the patient's clinical picture is essential to determining what evaluation is needed. A referral to a specialist should be considered when a more extensive evaluation is needed.

Referral

While referral to a specialist can be made at any time, it is the consensus of this work group that a specialist be considered for the following patients:

- Abnormal labs for osteopenia/osteoporosis evaluation
- Patient is not doing well on initial therapy
- Patient with multiple fractures
- Patients with multiple comorbidities
- Premenopausal women
- Poor renal function (estimated creatine clearance ≤ 35 ml/min)

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Pharmacologic Treatment

Recommendation	Quality of Evidence and Strength of Recommendation
Bisphosphonates should be considered (unless contraindicated) for reduction of fracture risk (both vertebral and non-vertebral) in: • **Postmenopausal women with osteoporosis** • **Men with osteoporosis**	**Quality of Evidence:** Postmenopausal women with osteoporosis (High) Men with osteoporosis (Moderate) **Strength of Recommendation:** Strong
Benefit: Bisphosphonates have been shown to improve bone mineral density and reduce the incidence of fracture. **Harm:** As with any medication, bisphosphonates may be associated with side effects. While rare, osteonecrosis of the jaw is a serious adverse effect of bisphosphonates, as are atypical femur fractures. **Benefit-Harms Assessment:** For most patients with osteoporosis, the benefits of the medication outweigh the risks. However, the benefit-harm assessment should be done for each individual patient to evaluate whether this medication is appropriate.	
Relevant Resources: **Postmenopausal women with osteoporosis:** *Eriksen, 2014; Miller, 2012; Eisman, 2008; Black, 2007; Chestnut, 2005; Chestnut, 2004; McClung, 2001; Black, 2000; Fogelman, 2000, Harris, 1999* **Men with osteoporosis:** *Chen, 2015*	

In addition to treatment for the patient groups above, it is the consensus of this work group that bisphosphonates be considered in postmenopausal women, and men with osteopenia and increased fracture risk as well as patients with glucocorticoid-induced osteoporosis. This increased risk can be determined using the FRAX® tool post-BMD.

Anti-Resorptive Agents (Bisphosphonates)

Summary

Alendronate (in both daily and weekly preparations) has been shown to increase BMD and reduce the incidence of vertebral, hip and non-vertebral fractures in postmenopausal women having existing vertebral fractures, and those with low BMD (approximately 2.1 SD below peak) compared to placebo (calcium and vitamin D). In the Fracture Intervention Trial (FIT), which evaluated 3658 women with osteoporosis, treatment with alendronate produced a 48% lower risk of new radiographic vertebral fractures and a reduction of hip fractures by 53% versus placebo. For all clinical fractures the reduction in risk was 30% *(Black, 2000)*.

Risedronate, also available in daily and weekly preparations, has shown a 41% risk reduction in the number of new vertebral fractures after three years compared to placebo in the VERT trial. In the first year, a 65% risk reduction was seen. The trial also showed 39% fewer non-vertebral fractures in the risedronate group over three years *(Fogelman, 2000; Harris, 1999)*. McClung, et al. showed that risedronate reduced the risk of hip fractures in women ages 70-79 with documented osteoporosis but not women greater than age 80 who entered the trial on the basis of risk fractures alone *(McClung, 2001)*.

Daily and intermittent dosing of ibandronate has been shown to improve BMD and reduce vertebral fractures in 2,946 postmenopausal women with osteoporosis and vertebral fractures, compared with calcium and vitamin D alone. New vertebral fractures were reduced 60% with daily dosing and 54% with intermittent dosing. Non-vertebral fractures were reduced only in a subpopulation with BMD T-scores < -3.0. A non-inferiority trial indicated equivalency of effect using surrogate markers of BMD and biomarkers for a monthly 150 mg dose *(Chesnut, 2005; Miller, 2005; Chesnut, 2004)*.

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The DIVA trial comparing intravenous ibandronate 3 mg every three months with daily ibandronate showed superiority in surrogate markers of BMD and biomarkers of bone turnover. This offers an injectable bisphosphonate alternative in patients who are unable to use oral bisphosphonates *(Delmas, 2006)*.

Excellent clinical trial data based on BMD and biomarkers supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal low bone density (osteopenia) or osteoporosis. The best clinical trials have been done with alendronate, risedronate and ibandronate. In 2012, a meta-analysis of 116 studies reviewed the comparative effectiveness of drug treatments to prevent fragility fractures. There were 139,647 patients, and 86% of the patients were females. The median follow-up was 24 months. Alendronate, risedronate and zoledronic acid showed a 42-65% reduction in vertebral fractures and a 50-55% reduction in hip fractures. Ibandronate showed the lowest reduction in overall fracture risk, but differences were not statistically significant.

Zoledronic acid 5 mg IV infusion annually is FDA approved for the treatment of osteoporosis in postmenopausal women and for fracture prevention after a hip fracture as well as once every two years for prevention of first fracture. This agent improved BMD and decreased bone turnover markers for three years in the pivotal fracture trial *(Black, 2007)*. In this trial of zoledronic acid versus placebo (calcium + vitamin D) in postmenopausal women with low bone mass with and without fracture, there was a 70% relative risk reduction (RR) in vertebral fractures, a 41% RR in hip fractures and a 25% RR in non-vertebral fractures. There was a 33% RR in clinical fractures and a 77% RR in clinical vertebral fractures. In a post-hip fracture trial, there was a 35% RR in clinical fractures and a significant 28% RR in all-cause mortality in the zoledronic acid group versus placebo *(Lyles, 2007)*. Clinically, zoledronic acid is generally reserved for patients who cannot tolerate or have contraindication to oral bisphosphonates, or when adherence is a major issue.

Treatment of osteoporosis in men

Meta-analysis of nine RCTs evaluated the efficacy of bisphosphonates as a class for treatment of osteoporosis in men (N=2464) and showed a 36% relative risk reduction vertebral fracture and 52% relative risk reduction in non-vertebral fractures *(Chen, 2015)*.

Clinical trial data supports the use of alendronate for preventing bone loss in men diagnosed with osteoporosis. Alendronate has been shown to increase BMD at the spine, hip and total body, and to prevent vertebral fractures and height loss in men with osteoporosis *(Orwoll, 2000)*.

Men who received risedronate 35 mg once a week for four years had a significant increase in lumbar spine BMD and decrease in bone turnover markers. These effects were similar to the effects in women with a similar safety profile *(Boonen, 2012)*.

In men with low bone density, yearly zoledronic acid 5 mg was as efficacious at increasing BMD and lowering bone turnover markers as once-weekly alendronate 70 mg *(Orwoll, 2010)*. Furthermore, once-yearly intravenous zoledronic acid has been shown to increase bone mass at the hip and femoral neck within 90 days of repair of low trauma hip fracture *(Boonen, 2011)*. Treatment in men with zoledronic acid resulted in a 67% risk reduction of new vertebral fractures, as well as an increase in BMD and decrease in bone turnover markers *(Boonen, 2011)*.

Bisphosphonates, particularly zoledronic acid, should be given to men undergoing androgen deprivation therapy for prostate cancer with pre-existing bone loss and should be considered to prevent bone loss in those without osteoporosis *(Serpa Neto, 2012)*.

Delayed release risedronate (Atelvia) and ibandronate are not approved for use in men.

Treatment and prevention of glucocorticoid-induced osteoporosis

Alendronate increases lumbar spine, femoral neck, trochanter and total body BMD in patients who require long-term (at least one year) glucocorticoid therapy at dosages of at least 7.5 mg daily *(Saag, 1998)*.

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Risedronate has also been shown to increase BMD in patients receiving glucocorticoid therapy. Treatment with risedronate 5 mg a day did have a trend of reduced fracture incidence *(Cohen, 1999)*. Zoledronic acid is also approved for glucocorticoid-induced osteoporosis.

Clinical trial data supports the use of oral bisphosphonates for reducing bone loss in men and women diagnosed with glucocorticoid-induced bone loss. The delayed release risedronate (Atelvia) and ibandronate are not approved for glucocorticoid-induced osteoporosis.

Post-transplantation

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation.

Several studies have shown that intravenous pamidronate *(Aris, 2000)* and zoledronic acid *(Yao, 2008; Crawford, 2006)* may prevent bone loss after organ transplantation. A few small studies have evaluated oral bisphosphonate therapy in post-transplant patients *(Trabulus, 2008; Torregrosa, 2007; Yong, 2007; Maalouf, 2005; Shane, 2004)*.

Duration of Treatment

After five years of continuous use of a bisphosphonate, patients should be assessed for candidacy for a "drug holiday." The rationale for a "drug holiday" is to avoid the ongoing use of a bisphosphonate when anti-fracture efficacy persists once treatment has been discontinued. A secondary rationale is to potentially decrease the risk of atypical femur fractures and of osteonecrosis of the jaw, both of which may be associated with prolonged use of bisphosphonates. The appropriateness of a "drug holiday" is most firmly established for alendronate by the FLEX® trial. After five years of alendronate, FIT participants were randomized to five years of placebo or additional five years of alendronate. This trial *(Black, 2006)* revealed no significant cumulative risk of non-vertebral fractures after five years between those continuing and those discontinuing alendronate. However, further analyses indicated that participants with hip BMD T-score in the osteoporosis range benefited, i.e., had fewer fractures during the second five years if they received alendronate compared to those receiving placebo. Recent trials have evaluated the treatment duration of zoledronic acid and found that after six annual infusions with the drug, the benefits are maintained for at least three years *(Black, 2015)*. Therefore after three years of therapy, those at higher risk (bone density in the osteoporosis range, prevalent fracture, etc.) may benefit from an additional three years of zoledronic acid.

Therefore, patients with an increased or stable bone density on bisphosphonates and no history of prevalent fragility fracture(s) should be considered for an interruption in therapy. Those with a perceived high fracture risk (e.g., persistently low bone density [T-scores < -2.5] or a history of fragility fracture[s]) may not be considered for such a hiatus in therapy. Bone density should be monitored during the "drug holiday" every two years, preferably on the same machine at a center with adequate quality controls. A decrease in bone density or an intercurrent fracture would trigger considering reinstitution of osteoporosis therapy. The duration and potential discontinuation of treatment should be personalized for individual patients based on their response to treatment, fracture risk and comorbidities. The FDA recommends reassessment of continuation of bisphosphonates after three to five years.

Contraindications/Risks

Bisphosphonates and the risk of osteonecrosis of the jaw

There is circumstantial evidence establishing an association between IV bisphosphonates and bisphosphonate-related osteonecrosis of the jaw (BRONJ) in malignancy with the following observed: 1) a positive correlation between bisphosphonate potency and risk of BRONJ, 2) a negative correlation between bisphosphonate potency and duration of bisphosphonate exposure before development of BRONJ, and 3) a positive correlation between the duration of bisphosphonate exposure and developing BRONJ. Causation has not been

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established. The American Dental Association recommends that all patients on antiresportive medications for osteoporosis should receive routine dental care. Clinicians should not modify routine dental care solely because of use of oral antiresorptive agents. Discontinuing bisphosphonates just before dental procedures may not lower the risk but may have negative effects on low bone mass treatment outcomes *(Hellstein, 2011)*.

American Association of Oral Maxillofacial Surgeons (AAOMS) in its 2009 position paper defines BRONJ as exposed bone in the maxillofacial region that has persisted more than eight weeks with current or previous treatment with a bisphosphonate and no history of radiation treatment to the jaw *(Ruggiero, 2009)*. Case series, case control studies and cohort studies in cancer patients estimate the cumulative incidence of BRONJ ranging from 0.8 to 12%. In oral bisphosphonate used for osteoporosis, the incidence studies of BRONJ vary widely from 0.01 to 0.06% *(Ruggiero, 2009)*.

AAOMS has refined the risk factors in its 2009 position paper to include drug-related risk factors, such as the bisphosphonate potency and duration of treatment, dental alveolar surgery concomitant oral disease, periodontal disease and genetic factors (in multiple myeloma). Preventive factors include modifications of IV bisphosphonate dosing schedule and undergoing preventive dental interventions before initiating IV bisphosphonate treatment.

AAOMS notes discontinuing IV bisphosphonate offers no short-term therapeutic benefits, but if systemic conditions permit, long-term discontinuation might stabilize established sites and reduce risks of new sites and clinical symptoms. This is a treatment team decision. Discontinuing oral bisphosphonate therapy in patients with BRONJ is associated with gradual improvement *(Ruggiero, 2009)*.

Bisphosphonates and risk of atrial fibrillation

Studies have suggested that at least some postmenopausal women taking oral or intravenous bisphosphonates for osteoporosis may be at increased risk of atrial fibrillation. The HORIZON Trial *(Black, 2007)* demonstrated an unexpected mildly increased risk of serious atrial fibrillation. This was not seen in a subsequent trial of postmenopausal women following hip fracture that showed that zoledronic acid reduced fractures and mortality but did not show an increased incidence of atrial fibrillation in this older population at higher risk of atrial fibrillation *(Lyles, 2007)*. Reanalysis of the Fracture Intervention Trial with alendronate and a retrospective review of risedronate data did not show an increased risk of atrial fibrillation *(Cummings, 2007; Black, 1996)*. Conflicting data is reported from two separate population-based case control studies from Seattle, WA, *(Heckbert, 2008)* and Denmark *(Sørenson, 2008)*. In light of the conflicting results from these studies, it is premature to stop oral or intravenous bisphosphonates in patients with postmenopausal osteoporosis due to concerns about atrial fibrillation.

The most recent systematic review that includes evaluation of randomized control trials and meta-analyses concludes that there is discordance among the data due to serious weaknesses in the studies and that more information is needed to determine if bisphosphonates increase risk of atrial fibrillation, and that if there is an increased risk, the magnitude of the risk is small *(Howard, 2010)*.

Bisphosphonates and risk of atypical femur fracture

Atypical femur fractures have short oblique or transverse fracture lines in the subtrochanteric or diaphyseal location with evidence of cortical thickening on radiography. There is concern that bisphosphonate use is associated with an increased risk of atypical femur fracture. A large observational study showed increased rates of atypical femur fractures in people taking alendronate; however, larger cumulative doses were not associated with higher rates of atypical femoral fractures compared to smaller cumulative doses, suggesting fractures maybe associated with osteoporosis rather than bisphosphonate use *(Abrahamsen, 2010)*. There was also a trend toward increased atypical fracture rates with longer duration of alendronate use. Thus, there is controversy as to whether the total cumulative dose of alendronate effect the risk of typical femur fractures. Importantly, larger cumulative doses have been shown to significantly decrease hip and vertebral

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fractures, which are much more common than atypical femur fractures, so there is a net reduction in fracture with bisphosphonate use *(Schilcher, 2011)*.

RANK Ligand (RANKL) Inhibitor/Human Monoclonal Antibody (Denosumab)

Summary

Denosumab is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor approved by the FDA for treatment of postmenopausal osteoporosis with a high risk of fracture. Denosumab inhibits the formation, function and survival of osteoclasts by binding to RANK, resulting in decreased bone resorption and increased bone mass and strength. Denosumab was initially approved in 2010 for the treatment of osteoporosis in postmenopausal women at high risk for fracture. In 2011 the indication was extended to men treated with androgen deprivation therapy and women receiving adjuvant aromatase inhibitor therapy for breast cancer and at high risk for fracture. In 2012 it was approved for use in men with osteoporosis.

In a study of 7,868 women between ages 60 and 90 with diagnosed osteoporosis (T-score of less than -2.5 but no less than -4.0 at the lumber spine or total hip), denosumab was found to reduce the cumulative incidence of new vertebral fractures in comparison to placebo ($p<0.001$). This resulted in a relative decrease of 68%. Incidence of hip and non-vertebral was also lower in the denosumab group, with relative risk reductions of 40% and 20%, respectively *(Cummings, 2009)*.

A pre-planned analysis of results from the three-year, placebo-controlled FREEDOM trial were evaluated for the effect of denosumab administration on fracture-healing. Six hundred sixty seven postmenopausal female subjects ages 61 to 90 who received either 60 mg of denosumab or placebo subcutaneously every six months for three years and experienced non-vertebral fractures during this period were included in the results analysis. It was concluded denosumab 60 mg every six months does not appear to delay fracture healing or contribute to other complications even with administration near the time of the fracture *(Adami, 2012)*.

The FREEDOM extension study *(Papapoulus, 2015)* likewise demonstrated sustained reduction in bone turnover markers with continued gains in bone mineral density at five (lumbosacral spine LSP 13.1%, hip 6%) and eight years (LSP 18.4 % , hip 8.3 %). The incidence of adverse effects did not increase over time.

Duration of treatment

Denosumab is administered subcutaneously every six months by a health professional. No dose adjustments are needed for hepatic or renal impairment. The reduced frequency and supervised administration of denosumab may help improve patient adherence. In addition, denosumab's lack of accumulation in bone and reversibility of antiresorptive effects over time may prove safer for prolonged use.

Pre-existing hypocalcemia and vitamin D deficiency must be corrected prior to initiating therapy. Adequate calcium and vitamin D need to be consumed during therapy.

There is no persistence of effect after discontinuation of denosumab. Bone loss does occur, and there have been reports of increased risk of vertebral fractures after discontinuation *(Anastasilakis, 2017; McClung, 2017)*.

Contraindications/risks

The most serious risk is hypocalcemia occurring in about 2% of patients receiving denosumab. The incidence is increased with renal impairment. As with bisphosphonates, denosumab has been associated with atypical femoral fracture and osteonecrosis of the jaw.

RANKL inhibition of non skeletal cells may cause immune suppression, although the extent of this risk remains unclear. While the initial FREEDOM data showed increased incidence of endocarditis (3% vs. 0% placebo) and severe skin infection (0.4 % vs. < 0.1 % placebo), in the FREEDOM extension trial rates were similar to placebo *(Papapoulus, 2015; Cummings, 2009)*.

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Anabolic Agents (Parathyroid hormone 1-34, Teriparatide)

Summary

Daily subcutaneous injection of teriparatide, a recombinant form of the N terminal 34 amino acids of parathyroid hormone, has been studied in both men and women, in combination with other agents and alone, and in glucocorticoid-induced osteoporosis and postmenopausal osteoporosis. Although teriparatide stimulates both bone formation and bone resorption, its net effect is felt to be anabolic. Demonstrated anti-fracture efficacy and BMD increases have resulted in FDA approval for treatment of osteoporosis in men, postmenopausal women and glucocorticoid-induced osteoporosis *(Finkelstein, 2003; Neer, 2001)*.

In spring 2017, a second anabolic agent, abaloparatide (Tymlos), was approved for treatment of postmenopausal osteoporosis with a high risk of fracture. Abaloparatide is an analog of human parathyroid hormone related peptide, PTHrP (1-34), which acts as an agonist at the parathyroid hormone-1 receptor. It is given as a daily subcutaneous injection. The efficacy of abaloparatide for the treatment of postmenopausal osteoporosis was evaluated in an 18-month, randomized, multicenter, double-blind, placebo-controlled clinical trial in postmenopausal women; it demonstrated an absolute risk reduction in new vertebral fractures of 3.6% at 18 months and a relative risk reduction of 86% compared to placebo. The relative risk reduction in non-vertebral fractures for abaloparatide compared to placebo was 43%, and the absolute risk reduction was 2.0% *(Miller, 2016)*.

The cost and burden of daily injections limit the use of these agents to those individuals with severe osteoporosis (very low BMD, multiple fractures) or those who have not done well with other therapies or those with significant glucocorticoid-induced osteoporosis (teriparatide).

Two comparative studies suggest that teriparatide may be superior to oral bisphosphonates in treating glucocorticoid-induced osteoporosis *(Glüer, 2013; Saag, 2007)*. Further research is needed is this area. Comparative study of abaloparatide and teriparatide, and placebo demonstrated both anabolic agents superior to placebo in reducing the risk of new vertebral fractures (primary endpoint) and no difference from each other in the secondary endpoint of reducing nonvertebral fractures *(Miller, 2016)*.

Duration of treatment

For both anabolic agents, teriparatide and abaloparatide, use is approved for only two years. Cumulative use of abaloparatide and parathyroid hormone analogs (e.g., teriparatide) for more than two years during a patient's lifetime is not recommended. A gradual decrease in bone mass has been noted after discontinuation of teriparatide therapy; however, immediate follow-up therapy with an antiresorptive agents been shown to preserve the benefits *(Sambrook, 2007; Hodsman, 2005)*. Additional treatment courses are not recommended.

Contraindications/risks

Both teriparatide and abaloparatide carry a black box warning about possible risk for osteosarcoma based on a rodent model. It is generally not used in individuals with a baseline increased risk of osteosarcoma (including Paget disease, prior radiation, unexplained elevation of alkaline phosphatase, prior external beam or implant radiation therapy involving the skeleton, or in patients with open epiphyses). Post marketing surveillance has not demonstrated an increase incidence of osteosarcoma in humans with teriparatide use *(Andrews, 2012)*. Teriparatide is also not used in patients with bone metastases, a history of skeletal metastases, hyperparathyroidism, or preexisting hypercalcemia, or active malignancy.

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Medications for Select Patient Populations

Selective estrogen receptor modulator (SERM)

The first SERM approved for the prevention and treatment of postmenopausal osteoporosis was raloxifene.

The MORE trial was a large three-year randomized placebo-controlled study in postmenopausal women with osteoporosis. Raloxifene showed an increase in BMD and reduced the risk of vertebral fractures. The risk of non-vertebral fractures did not differ between placebo and raloxifene. Raloxifene was associated with a lower incidence of breast cancer but an increased risk of venous thromboembolism compared with placebo (RR 3.1, 95% CI 1.5-6.2) *(Ettinger, 1999)*.

The CORE four-year trial extension of 4,011 women continuing from MORE (7,705) showed no difference in overall mortality, cardiovascular events, cancer or non-vertebral fracture rates *(Ensrud, 2006; Siris, 2005)*. In the STAR trial *(Vogel, 2006)*, raloxifene was found comparable to tamoxifen for the prevention of invasive breast cancer. Thus, raloxifene appears to be the drug of choice for women with osteoporosis if the main risk is of vertebral fracture and there is an elevated risk of breast cancer.

In 2015, conjugated estrogen/bazedoxifine (CE/BZA) was approved for the treatment of moderate to severe vasomotor symptoms associated with menopause and the treatment of postmenopausal osteoporosis. It exerts estrogenic activity on bone but anti-estrogenic activity on the uterus and breast. SMART 1 was a two year randomized phase 3 trial that evaluated the effects of CE/BZA compared with raloxifene and placebo on endometrial tissue and bone mineral density. Women randomized to CE/BZA had statistically significant increased BMD compared to those in the raloxifene and placebo groups. Adverse events including venous thromboembolism and cardiovascular events were similar between the CE/BZA and placebo groups *(Pickar, 2009)*.

Gonadal hormone therapy

Female gonadal hormone therapy

Estrogen is not currently recommended as a first-line agent in the management or prevention of osteoporosis. It should be used for prevention of postmenopausal osteoporosis only in women at significant risk who cannot take non-estrogen therapies. It is unknown if conclusions of the Women's Health Initiative can be applied to younger (under age 50) postmenopausal women taking estrogen in other doses, formulations or modes of administration.

The use of supplemental estrogen in immediate postmenopause has been well accepted in preventing the rapid loss of bone that occurs in this interval *(Komulainen, 1997; Prince, 1991)*.

The Women's Health Initiative study showed that premarin significantly reduced the risk of both vertebral, hip fractures and all fractures *(Women's Health Initiative, The, 2004)*. The other available data come mainly from observational and epidemiological trials. Meta- and decision analysis estimates have suggested a relative risk of hip fracture in estrogen-treated women of 0.46-0.75. A long-term controlled trial of 10 years demonstrated a 75% reduction in radiologic vertebral fracture in oophorectomized women compared to controls. A shorter trial of one-year duration revealed a 60% reduction in the risk of vertebral fracture in women with osteoporosis using a 0.1 mg estradiol patch and medroxyprogesterone compared to controls *(Writing Group for the Women's Health Initiative Investigators, 2002; Torgerson, 2001)*.

Male gonadal hormone therapy

The bone loss associated with male hypogonadism is reversed by testosterone therapy at least partly via aromatization to estrogen. Testosterone therapy, although not FDA approved for osteoporosis, is an option for men symptomatic with hypogonadism who do not have contraindications to the use of testosterone therapy *(Behre, 1997; Katznelson, 1996)*. Due to potential serious side effects including increased risk for venous thromboembolic events and concerns regarding cardiovascular safety in 2015,

the FDA clarified that testosterone should be administered only for hypogonadism caused by disorders of the testicles, pituitary gland or brain in adult males and not for the treatment of low testosterone due to aging. See the following link for more information from the FDA: http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm.

Testosterone replacement improves BMD in male hypogonadism, as illustrated in a study of 72 such men receiving testosterone replacement therapy *(Behre, 1997)*.

The increase in BMD averaged 39% in the first year of testosterone replacement and eventually reached and was maintained in the normal range. The response was greatest in the first year in previously untreated patients and was most pronounced in those with lowest bone density measurements at baseline.

Medications No Longer Used to Treat Osteoporosis or Not Approved in the United States

Calcitonin

Although calcitonin may be effective to reduce the risk of vertebral fractures in osteoporosis *(Chesnut, 2000)*, it is less efficacious than bisphosphonates. This along with concerns about increased risk of cancer with prolonged use led the FDA to conclude that the benefits may not outweigh the risks. Therefore, calcitonin use as a treatment for osteoporosis is limited to those individuals for whom alternatives are not possible *(Food and Drug Administration, 2015)*.

A meta-analysis has shown the efficacy of calcitonin (nasal or parenteral) as a short-term treatment of acute pain from a compression fracture. Patients with compression fractures and acute (< 1 week) pain were compared to those with chronic (> 3 months) pain. Benefits in pain reduction with calcitonin treatment were observed in those with acute pain at 1, 2, 3 and 4 weeks. No benefit was found in those with chronic pain. The underlying mechanism of pain relief is not understood *(Knopp-Sihota, 2012)*.

Strontium ranelate (not available in the U.S.)

Strontium ranelateis is a novel agent for treatment of osteoporosis in Europe. The mechanism of action is unclear, but effects on markers of bone turnover suggest an anti-resorptive effect. Post-marketing surveillance indicated an association of use with an increased risk of myocardial infarction, venous thromboembolism and severe skin reactions. This has resulted in restrictions on its use in Europe. The use of over-the-counter formulations is not advised.

Calcitriol (1, 25-OH vitamin D)

Studies of the efficacy of calcitriol in postmenopausal osteoporosis have yielded mixed results, and it is not recommended for use. There may be some benefit in post-transplant and glucocorticoid-induced osteoporosis, but use in those settings is not routinely recommended.

Alternative and Complementary Agents

There is conflicting data on a number of non-FDA approved substances for possible use in prevention and treatment of osteoporosis. These include phytoestrogens, natural progesterone, magnesium, vitamin K and horsetail. There is very limited data from randomized controlled trials of these agents for prevention or treatment of osteoporosis.

Routine supplementation with the following agents has either not been well studied or not shown benefit for treatment or prevention of osteoporosis.

Phytoestrogens

Phytoestrogens are naturally occurring compounds contained in foods derived from plants and having some estrogen-like activity. Phytoestrogens derived from soy include the isoflavones daidzein and genistein. Other plants containing phytoestrogens include black cohosh, dong quai, red clover,

alfalfa and licorice root. Several studies have suggested that soy protein or soy extract containing 75-90 mg of isoflavones may increase BMD or slow BMD loss, and improve biochemical markers of bone turnover in peri- and postmenopausal women *(Shenoy, 2013; Setchel, 2003; Ho, 2001; Alekel, 2000; Horiuchi, 2000; Potter, 1998)*. Lower doses did not seem to find similar results except for two studies that specifically looked at Japanese and Chinese women between the ages of 30 and 40, who consumed on average 50 mg of isoflavones daily from dietary soy *(Ho, 2001; Somekawa, 2001)*. There are conflicting studies that suggested soy protein did not significantly improve BMD in peri- and postmenopausal women *(Tai, 2012; Liu, 2009; Gallagher, 2004; Kreijkamp-Kaspers, 2004)*.

Ipriflavone is a synthetic isoflavone derivative, currently available as a dietary supplement. A multicenter, randomized trial of ipriflavone showed no significant effect on bone density or risk of vertebral fractures *(Alexandersen, 2001)*. It is not recommended for osteoporosis prevention or treatment *(Alexandersen, 2001)*.

Natural progesterone

In 1999, a one-year, randomized placebo-controlled trial by Leonetti showed no protective effect of transdermal progesterone on bone density. The study included 102 postmenopausal women *(Leonetti, 1999)*. In a separate study, using topical progesterone for two years suggested the progesterone was as effective as soy milk in preventing bone loss in postmenopausal women with osteoporosis. However, the study also suggested that the combination of soy milk and progesterone resulted in greater bone loss *(Lydeking-Olsen, 2004)*.

Magnesium

The Women's Health Initiative (WHI) observed 73,684 postmenopausal women and the total daily magnesium intake in these women through questionnaires. The magnesium was obtained either through food or supplementation. BMD was recorded for 4,778 women in this observational study. Whole-body BMD was 2% higher ($P < 0.001$) and baseline hip BMD was 3% higher ($P < 0.001$) in women who consumed more than 422.5 mg daily of magnesium. The study also found women who consumed the highest magnesium intake were also more physically active and were therefore at an increased risk of falls. Overall, the study suggested that lower magnesium intake was associated with lower BMD but not increased risk of fractures *(Orchard, 2014)*. In 2016, a meta-analysis of 12 studies suggested high magnesium supplementation was not significantly associated with increased risk of total hip or lumbar spine fractures *(Farsinejad-Marj, 2016)*.

Vitamin K

The effects of vitamin K on BMD and fracture risk are conflicting. A systematic review and meta-analysis of randomized controlled trials found 13 trials with data on bone loss and seven Japanese trials that reported fracture data. All but one study suggested an advantage of using oral phytonadione and menquinone to help reduce bone loss. Data from the seven Japanese trials was pooled finding an odds ratio (OR) of 0.40 (95% CI, 0.25-0.65) for vertebral fractures, an OR of 0.23 (95% CI, 0.12-0.47) for hip fractures and an OR of 0.19 (95% CI, 0.11-0.35) for all non-vertebral fractures with the use of menaquinone *(Cockayne, 2006)*. However, a randomized, double-blind placebo-controlled trial looked at 334 healthy Norwegian women between the ages of 50 and 60 to understand the effects vitamin K2 and bone loss rate. Women were randomized to take 360 mcg of vitamin K2 or placebo. After 12 months there were no statistical differences in bone loss rate between the groups *(Emaus, 2010)*. A prospective analysis of the Nurses' Health Study found that women in the lowest group, based on vitamin K consumption, had the highest risk of hip fractures during the 10-year follow-up *(Shiraki, 2000)*.

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Medication Adherence

Adherence is a major problem with medications for bone loss. A large meta-analysis of six large observational trials involving 106,961 patients concluded that one-third to one-half of patients did not take their medications for osteoporosis as directed. The vast majority of the poor adherence was in the first three to six months of treatment *(Kothawala, 2007)*. The literature suggests that 45-50% of patients on one of these agents have stopped them within one year *(Cramer, 2005)*. Adherence to therapy was associated with significantly fewer fractures at 24 months *(Siris, 2006)*. The use of follow-up bone densitometry and bone markers have not been shown to improve adherence. Follow-up phone calls or visits have shown improvement in adherence *(Cramer, 2006)*. Several studies support weekly bisphosphonate dosing versus daily, and/or monthly dosing versus weekly to improve compliance *(Cooper, 2006; Emkey, 2005; Recker, 2005)*. It is important to include the patient in discussions related to their treatment options, including rationale, risks and benefits. Shared decision-making (SDM) is a model that facilitates these discussions. Please see Appendix C for more information on this model.

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Treatment Failure

There is no consensus as to what constitutes a true treatment failure for patients on pharmacologic treatment for bone loss. It is unclear if an intercurrent fracture once on a medication for at least a year is a treatment failure, but generally it is considered as such, assuming there is no other cause for lack of efficacy. A significant decrease in BMD on treatment is generally considered a treatment failure but is quite unusual. Other more common causes of such a decrease must first be ruled out: patient not taking the medication or not taking it as scheduled or properly (bisphosphonate), malabsorption, calcium or vitamin D deficiency or an unrecognized secondary cause of bone loss. In case of treatment failure, an alternative agent or combination therapy should be considered.

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Follow-Up Testing

Every attempt should be made to perform the follow-up DXA test at the same testing center as the original to improve the accuracy of the follow-up data. Lumbar spine and the total proximal femur have the highest reproducibility and are the preferred sites for monitoring therapy *(Bonnick, 1998)*. Changes in BMD should be reported as significant only if they exceed the "least significant change" for the DXA center *(Faulkner, 1999; Miller, 1999; Bonnick, 1998)*. Stability or increase in BMD indicates successful therapy. A significant decline in BMD may require further investigation.

On Treatment for Osteoporosis

Monitoring patients on drug therapy for the treatment of osteopenia or osteoporosis can be considered one to two years after initiating medical therapy for osteoporosis and every two years thereafter *(Miller, 1999)*. No study has been done as to whether follow-up BMD testing on therapy enhances fracture risk reduction, but it may affect patient adherence to therapy *(Eastell, 2003)*. Therapy should not be withheld if follow-up bone density testing is not available.

More frequent BMD testing may be warranted in certain clinical situations, such as every 6-12 months in the case of glucocorticoid-treated patients or those on suppressive doses of thyroid hormone. Other patients at risk for accelerated bone loss include women at early menopause or those who have discontinued estrogen and are not on another bone protective agent.

Incorporating FRAX scoring into the follow-up interval decision may be helpful as it identifies those patients at highest risk; however, The FRAX® tool has not been validated in patients currently or previously treated

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with pharmacotherapy for osteoporosis. Patients not on medication for two to three years might be considered untreated for FRAX purposes.

In addition, biochemical markers such as the bone formation marker PINP and the bone resorption marker C-terminal cross-linked telopeptides of type I collagen (CTx) can be drawn to determine if treatment is producing the expected effect. However, these markers exhibit significant within-subject and between-subject variability so it is difficult to know which is the best bone marker for measuring the response. The interval between repeat BMD screenings may be longer for patients without major risk factors and who have an initial T-score in the normal or upper low bone mass range but an elevated FRAX score.

On "Holiday" from Bisphosphonates

If on holiday from bisphosphonates, monitoring should include clinical assessment for fractures, falling, any interval chronic disease occurrence and consideration of serial BMD testing, use of biochemical markers, and vertebral imaging in some patients *(Cosman, 2014)*. There is no data to guide the reinstitution of medication. Expert opinion suggests that it may be reasonable to continue to monitor without medication if BMD is stable, and to reinitiate therapy if the T-score worsens to less than -2.5 or additional risk such as fracture arise *(Adler, 2016)*.

Discontinued Treatment of Other Agents

Discontinuing treatment of osteoporosis with other agents may result in rapid bone loss and does not carry the antifracture effect seen in treatment with bisphosphonates. References to these effects can be found in the individual medication sections. Therefore, in the situation where treatment is discontinued with agents other than bisphosphonates, consider selecting an alternative medication or pursuing closer follow-up testing with DXA and FRAX.

Lack of Response on Treatment

A significant decrease in BMD on therapy may be due to a variety of factors, including medication issues, like adherence, improper administration or absorption, missed secondary cause of osteoporosis, or inadequate calcium or vitamin D intake/supplementation. Rarely there is true treatment failure of the drug itself. Screening interval may need to be decreased to encourage compliance, and workup for secondary causes should be reassessed.

Re-Screening for Patients Not Treated

The recommendations for re-screening are less clear. In a large, good-quality, prospective cohort study of 4,124 women 65 years or older, repeated BMD measurement up to eight years after an initial measurement did not result in statistically significant differences in risk ratio estimates for non-vertebral, hip or vertebral fractures *(Nelson, 2010)*.

Another observational study suggested that the current follow up screening interval is far too frequent. These recommendations come from an assessment of the Study on Osteoporotic Fractures (SOF) data where 4,957 women with normal BMD or osteopenia were followed for 15 years for the development of osteoporosis. The results suggested that osteoporosis would develop in less than 10% of older, postmenopausal women during screening intervals that are set at approximately 15 years for women with normal BMD or mild osteopenia (T-score, greater than -1.50) at the initial assessment, five years for women with moderate osteopenia (T-score, -1.50 to -1.99), and one year for women with advanced osteopenia (T-score, -2.00 to -2.49). The limitations of the study were the inclusion of women on estrogen, the lack of attention to the spine bone density, the lack of attention to other risk factors and not applying the FRAX tool *(Gourlay, 2012)*.

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The Aims and Measures section is intended to provide protocol users with a menu of measures for multiple purposes that may include the following:

- population health improvement measures,
- quality improvement measures for delivery systems,
- measures from regulatory organizations such as The Joint Commission,
- measures that are currently required for public reporting,
- measures that are part of Center for Medicare Services Physician Quality Reporting initiative, and
- other measures from local and national organizations aimed at measuring population health and improvement of care delivery.

This section provides resources, strategies and measurement for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Aims and Measures
- Implementation Recommendations
- Implementation Tools and Resources
- Implementation Tools and Resources Table

Aims and Measures

1. Increase the percentage of adults appropriately screened for osteoporosis.

   Measures for accomplishing this aim:

   a. Percentage of women age 65 and older who are evaluated for osteoporosis with the bone mineral density assessment.

   b. Percentage of patients age 50 and older with a history of low-impact (fragility) fracture who were evaluated for osteoporosis with bone mineral density assessment.

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Measurement Specifications

Measurement #1a

Percentage of women age 65 and older who are evaluated for osteoporosis with the bone mineral density assessment.

Population Definition

Women age 65 and older.

Data of Interest

$$\frac{\text{\# of female patients age 65 and older who are evaluated for osteoporosis with the bone mineral density assessment}}{\text{\# female patients age 65 and older with an annual preventive visit}}$$

Numerator and Denominator Definitions

Numerator: Number of female patients age 65 and older who are evaluated for osteoporosis with the bone mineral density assessment.

Denominator: Number of female patients age 65 and older with a preventive visit in the last 12 months.

Method/Source of Data Collection

Query electronic medical records for the total number of patients who meet criteria in the denominator. From that, determine the number that meets the numerator criteria.

Time Frame Pertaining to Data Collection

Select a time frame that best aligns with your clinic's quality improvement activities.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #1b

Percentage of patients age 50 and older with a history of low-impact (fragility) fracture who were evaluated for osteoporosis with bone mineral density assessment.

Population Definition

Patients age 50 and older.

Data of Interest

$$\frac{\text{\# of patients age 50 and older who were evaluated for osteoporosis with bone mineral density assessment}}{\text{\# of patients age 50 and older with a history of low-impact (fragility) fracture}}$$

Numerator and Denominator Definitions

Numerator: Number of patients age 50 and older who were evaluated for osteoporosis with bone mineral density assessment.

Denominator: Number of patients age 50 and older with a history of low-impact (fragility) fracture.

Method/Source of Data Collection

Query electronic medical records for the total number of patients who meet criteria in the denominator. From that, determine the number that meets the numerator criteria.

Time Frame Pertaining to Data Collection

Select a time frame that best aligns with your clinic's quality improvement activities.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Implementation Tools and Resources

Criteria for Selecting Resources

The following tools and resources specific to the topic of the guideline were selected by the work group. Each item was reviewed thoroughly by at least one work group member. It is expected that users of these tools will establish the proper copyright prior to their use. The types of criteria the work group used are:

- The content supports the clinical and the implementation recommendations.
- Where possible, the content is supported by evidence-based research.
- The author, source and revision dates for the content are included where possible.
- The content is clear about potential biases and conflicts of interests and/or disclaimers are noted where appropriate.

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Implementation Tools and Resources Table

Author/Organization	Title/Description	Audience	Web sites/Order Information
Fracture Risk Assessment Tool (FRAX®)	Information on the FRAX® tool.	Health Care Professionals and Patients	https://www.shef.ac.uk/FRAX/
International Society of Clinical Densitometry	Professional organization site.	Health Care Professionals	http://www.iscd.org
Mayo Health Oasis Women's Health Resource	Women's health information.	Patients	http://www.mayoclinic.org/diseases-conditions/osteoporosis/home/ovc-20207808
National Osteoporosis Foundation	Web site has general information about osteoporosis prevention and treatment.	Health Care Professionals and Patients	http://www.nof.org
NIH – Osteoporosis and Related Bone Diseases Resources Center	Current information about osteoporosis and research.	Health Care Professionals and Patients	http://www.niams.nih.gov/health_info/bone/
United States Department of Agriculture	USDA Nutrient Database.	Professionals and Public	https://ndb.nal.usda.gov/ndb/
United States Preventive Services Task Force	Recommendations for clinical preventive services.	Health Care Professionals and Patients	https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/osteoporosis-screening?ds=1&s=osteoporosis

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The subdivisions of this section are:

- References
- Appendices

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Links are provided for those new references added to this edition (author name is highlighted in blue).

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Appendix A – Secondary Causes of Osteoporosis

The chronic conditions most commonly seen in clinical practice have been printed in **bold** type.

* This list was not reviewed during the 2017 revision.

Secondary Causes of Osteoporosis

I. Endocrine disorders
- **Cushing's syndrome**
- **Male or female hypogonadism**
  - Hyperprolactinemia
  - Klinefelter's syndrome
  - Surgical removal of ovaries or testes
  - Turner's syndrome
  - Other causes of hypogonadism
- **Hyperthyroidism**
- **Primary hyperparathyroidism**
- Acromegaly
- Addison's disease
- Growth hormone deficiency
- Type 1 diabetes mellitus

II. Rheumatologic disorders
- **Ankylosing spondylitis**
- **Juvenile polyarticular arthritis**
- **Rheumatoid arthritis**
- **Systemic lupus erythematosus**

III. Malignancy
- Leukemia
- Multiple myeloma
- Systemic mastocytosis

IV. Pharmacotherapy
- **Anticonvulsants (phenytoin or phenobarbital)**
- **Glucocorticoid excess**
- Intravenous heparin

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- **L-thyroxine overreplacement**
- Long-term warfarin use
- Chronic lithium therapy
- Chronic phosphate binding (aluminum-containing) antacids
- Drugs causing hypogonadism
  - Aromatase inhibitors
  - Chemotherapy (methotrexate or other antimetabolites)
  - Depo-medroxy progesterone acetate (Depo-provera®)
  - Gonadotropin-releasing hormone (GnRH) agonists (buserelin, leuprolide, nafarelin)
  - Thiazolidines
  - Selective serotonin reuptake inhibitors
- Extended tetracycline use, diuretics causing hypercalciuria, phenothiazine derivatives, cyclosporin A, or tacrolimus (FK506) may be associated with decreased bone density in humans and are known to be toxic to bone in animals or to induce calciuria and/or calcium malabsorption in humans
- Proton pump inhibitor use

V. Chronic obstructive liver disease

- **Primary biliary cirrhosis**

VI. Gastrointestinal disease

- **Celiac disease**
- **Inflammatory bowel disease (Crohn's disease in particular)**
- Gastrectomy, intestinal bypass surgery or small/large bowel resection
- Pernicious anemia

VII. Renal insufficiency or failure

VIII. Miscellaneous causes

- **Vitamin D deficiency**
- **Alcohol abuse**
- **Anorexia nervosa or bulemia**
- **Movement disorders (Parkinson's disease)**
- Amyloidosis
- Chronic obstructive pulmonary disease
- Treatment for endometriosis
- Epidermolysis bullosa
- Hemophilia

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- Hemochromatosis
- Idiopathic scoliosis
- Lacto-vegetarian dieting
- Lactose intolerance
- Pregnancy and lactation (reversible)
- Prolonged parenteral nutrition
- Sarcoidosis

IX. Immobilization

- Prolonged bed rest or wheelchair-bound from any cause
- Space flight
- Spinal cord syndromes

X. Genetic diseases

- Congenital porphyria
- Ehlers-Danlos syndrome
- Gaucher's disease and other glycogen storage diseases
- Homocystinuria
- Hypophosphatasia
- Marfan's syndrome
- Menkes' syndrome
- Mitochondrial myopathies
- Multiple dystrophy
- Multiple sclerosis
- Osteogenesis imperfecta
- Riley-Day syndrome (familial dysautonomia)
- Sickle cell anemia
- Thalassemia

XI. Idiopathic causes

- Idiopathic osteoporosis of young adults
- Juvenile osteoporosis
- Regional osteoporosis: reflex sympathetic dystrophy, transient osteoporosis of the hip, or regional migratory osteoporosis

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Appendix B – Medication Summary Table

Generic (Brand)	Indications[6]	Adverse Drug Reactions[6]	Contraindications[6]	Number Needed to Treat (NNT) 1,2,3,4, 8,9,10 *NNT for vertebral and hip fractures over three years calculated from the results of randomized, double-blinded, pivotal phase 3 trials vs placebo
Bisphosphonates				
Alendronate (Fosamax) **Alendronate with vitamin D (Fosamax Plus D)** **Alendronate effervescent tablet (Binosto)**	**TREATMENT** • Postmenopausal osteoporosis • Increased bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women **PREVENTION** • Postmenopausal osteoporosis	• Common: abdominal pain, flatulence, indigestion, diarrhea, headache, fever • Serious: Osteonecrosis of the jaw (ONJ), gastric ulcer, esophageal erosion, esophagitis, dysphagia, atypical fractures	• Abnormalities of the esophagus that delay esophageal emptying • Inability to stand or sit upright for at least 30 minutes • Hypersensitivity to alendronate or any of its excipients • Hypocalcemia prior to beginning therapy • Not recommended for patients with CrCl ≤ 35 ml/min	Hip fracture: 91 Vertebral fracture: 14
Risedronate (Actonel) **Risedronate delayed release (Atelvia)** *approved only for prevention and treatment of postmenopausal osteoporosis*	**TREATMENT** • Postmenopausal osteoporosis • Increased bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women **PREVENTION** • Postmenopausal osteoporosis	• Common: rash, abdominal pain, constipation, nausea, indigestion, diarrhea • Serious: arthralgia, osteonecrosis of the jaw (ONJ), peripheral edema, myalgia, benign prostatic hyperplasia, esophageal erosion, esophagitis, atypical fractures	• Abnormalities of the esophagus that delay esophageal emptying • Inability to stand or sit upright for at least 30 minutes • Hypersensitivity to risedronate or any of its excipients • Hypocalcemia prior to beginning therapy • Not recommended for patients with CrCl ≤ 30 ml/min	Hip fracture: 91 Vertebral fracture: 20
Ibandronate (Boniva)	**TREATMENT** • Postmenopausal osteoporosis **PREVENTION** • Postmenopausal osteoporosis	• Common: hypertension, abdominal pain, diarrhea, indigestion, nausea, backache, pain in limb, headache, bronchitis, upper respiratory infection • Serious: arthralgia, osteonecrosis of the jaw (ONJ), peripheral edema, myalgia, benign prostatic hyperplasia gastric ulcer, esophageal erosion, esophagitis, dysphagia, atypical fractures	• Abnormalities of the esophagus that delay esophageal emptying • Inability to stand or sit upright for at least 30 minutes • Hypersensitivity to ibandronate or any of its excipients • Hypocalcemia prior to beginning therapy • Not recommended for patients with CrCl ≤ 30 ml/min	Hip fracture: No effect demonstrated Vertebral fracture: 21
Zoledronic acid (Reclast)	**TREATMENT** • Postmenopausal osteoporosis • Increased bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women **PREVENTION** • Postmenopausal osteoporosis	• Common: peripheral edema, fatigue, fever, asthenia, headache, dizziness, backache, pain in limb • Serious: atrial fibrillation, cardiac dysrhythmiua, Stevens-Johnson syndrome, hypocalcemia, Aseptic necrosis of bone of jaw, myalgia	• Hypersensitivity to zoledronic acid or any of its excipients • Hypocalcemia prior to beginning therapy • Not recommended in patients with a creatinine clearance less than 35 mL/min	Hip fracture: 91 Vertebral fracture: 14
RANKL Inhibitor				
Denosumab (Prolia)	**TREATMENT** • Postmenopausal osteoporosis • Increase bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women	• Common: hypercholesterolemia, vomiting, anemia, arthralgia, backache, pain in limb, asthenia, cystitis, nasopharyngitis, upper respiratory infection, fatigue • Serious: endocarditis, cellulitis, dermatitis, hypocalcemia, anaphylaxis, hypersensitivity reaction, aseptic necrosis of bone of jaw, atypical fracture of femur and vertebral column, cancer	• Hypersensitivity to any component of the product • Hypocalcemia prior to beginning therapy • Pregnancy	Hip fracture: 200 Vertebral fracture: 21

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Appendix B – Medication Summary Table

Generic (Brand)	Indications[6]	Adverse Drug Reactions[6]	Contraindications[6]	Number Needed to Treat (NNT) 1,2,3,4, 8,9,10 *NNT for vertebral and hip fractures over three years calculated from the results of randomized, double-blinded, pivotal phase 3 trials vs placebo
Recombinant Parathyroid Hormone				
Teriparatide (Forteo)	**TREATMENT** • Postmenopausal osteoporosis with high risk for fracture (history of osteoporotic fracture, multiple risk factors, failed/intolerant of previous therapy) • Glucocorticoid-induced osteoporosis with high risk of fractures • Increased bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture (history of osteoporotic fracture, multiple risk factors, failed/intolerant of previous therapy)	**BLACK BOX WARNING:** shown to cause an increase in the incidence of osteosarcoma in male and female rats, dependent on dose and duration of treatment. • Common: hypotension, syncope, rash, sweating symptom, hyperuricemia, constipation, diarrhea, indigestion, nausea, vomiting, arthralgia, spasm, asthenia, dizziness, rhinitis, increasing frequency of cough, pharyngitis • Serious: angina pectoris	Paget's disease • Any prior therapeutic radiation involving the skeleton • Bone metastases or history of skeletal malignancies • Metabolic bone disease (other than osteoporosis) • Hypercalcemia • Pregnant and nursing women • Unexplained elevated alkaline phosphatase • Hypersensitivity, pediatric populations or young adults with open epiphyses	Hip fracture: 200 over 19 months Vertebral fracture: 11 over 19 months
Estrogen Agonists/Antagonist				
Raloxifen (Evista)	**TREATMENT** • Postmenopausal osteoporosis • Breast cancer in postmenopausal women with osteoporosis **PREVENTION** • Postmenopausal osteoporosis	**BLACK BOX WARNING**: risk of deep vein thrombosis and pulmonary embolism. • Common: hot sweats, leg cramp • Serious: VTE, cerebrovascular accident	Pregnancy • History of venous thromboembolism • Women who are pregnant or may become pregnant • Nursing women	Hip fracture: No effect demonstrated Vertebral fracture: 29
Conjugated Estrogens/Bazedoxifene acetate (Duavee)	**PREVENTION** • Postmenopausal osteoporosis	**BLACK BOX WARNING**: endometrial cancer, cardiovascular disorders and probable dementia • Common: diarrhea, indigestion, nausea, upper abdominal pain, neck pain, spasm, dizziness, pain in throat • Serious: VTE, cerebrovascular accident, retinal vascular disorder, primary malignant neoplasm of endometrium	• Use not recommended in women older than 75 years • History of venous thromboembolism • Estrogen-dependent neoplasia • Pregnancy, nursing women • Uterine bleeding • Active or history of breast cancer, stroke or myocardial infarction	Its effects on vertebral, hip or overall fracture rate are not known

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Appendix C – ICSI Shared Decision-Making Model

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The Collaborative Conversation™ Shared Decision-Making and the Translation of Evidence into Practice

A consistent finding from clinical and health services research is the failure to translate research into practice. The translation of evidence into practice can be advanced through the use of shared decision-making since shared decision-making results in evidence being incorporated into patient and clinician consultations.

Shared decision-making (SDM) is a process in which patient and clinicians collaborate to clarify all acceptable options, ensure that the patient is well-informed and chose a course of care consistent with patient values and preferences and the best available medical evidence. (Minnesota Shared Decision-Making Collaborative [MSDMC], 2011).

Evidence-based guidelines may recommend the use of shared decision-making for decisions in instances where the evidence is equivocal, when patient action or inaction (such as medication adherence or lifestyle changes) can impact the potential outcome, or when the evidence does not indicate a single best recommendation.

SDM is a patient-centered approach that involves a conversation between the patient and the clinician. It is ideal to involve caregivers and family members in these conversations as well. Family members and caregivers can participate in discussions, ask questions, hear content the patient may miss and provide invaluable support in decision follow-through. Although only patients and clinicians are specifically mentioned throughout this document for brevity purposes, this does not diminish the importance of caregivers and families in patient-centered care.

Both the patient and the clinician bring expertise to the shared decision-making conversation. Clinicians' expertise includes disease etiology, prognosis, options for treatment including the burden and benefit to the patient, and outcome probabilities. Patients' expertise lies in their knowledge of their risk tolerance, body, priorities, family and financial issues, as well as their daily experience with the condition (adapted from Making Shared Decision-Making a Reality. No decision about me, without me. Coulter, A., Collins, A., The King's Fund 2011).

Treatment options vary in their burden on a patient. SDM offers an opportunity to help the patient select a treatment to which they can adhere. When conversations discussing options occurs, patients and clinicians are actively engaged while considering the attributes and issues of the available options. This empathic approach results in the clinician and patient co-creating a decision and a plan of care (adapted from Montori, V., the Mayo Clinic KER UNIT, April 2015). Decision aids can be supportive of this conversation when they communicate the best available evidence to inform the patient and clinician discussion.

Without a conversation, clinicians may make assumptions about what the patient prefers. This creates the potential for discrepancies between what clinicians assume and what patients want, resulting in a "preference misdiagnosis" (adapted from Health Policy Publishing, LLC, May 2013).

Difficulty in initiating a conversation is cited by patients and clinicians as one of the barriers to shared decision-making. To address this impediment, ICSI worked with patients, practicing clinicians, and other stakeholders to develop the Collaborative Conversation™ model for use across the care continuum.

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Collaborative Conversation™

A collaborative approach towards decision-making is a fundamental tenet of Shared Decision-Making (SDM). The Collaborative Conversation™ is an interprofessional approach that nurtures relationships; enhances patients' knowledge, skills and confidence as vital participants in their health; and encourages them to manage their health care. Within a Collaborative Conversation™ , the perspective is that the patient, rather than the clinician, knows which course of action is most consistent with the patient's values and preferences.

Use of Collaborative Conversation™ elements and tools is even more necessary to support patient, care clinician and team relationships when patients and families are dealing with high stakes or highly charged issues. A diagnosis of a life-limiting illness is one example of such a circumstance.

The overall objective for the Collaborative Conversation™ approach is to create an environment in which the patient, family and care team work collaboratively to reach and carry out a decision that is consistent with the patient's values and preferences, along with the best available evidence. A rote script, completed form or checklist does not constitute this approach. Rather it is a set of skills employed appropriately for the specific situation. These skills need to be used artfully to address all aspects of the person involved in making a decision: cognitive, affective, social and spiritual.

Key communication skills help build the collaborative conversation approach. These skills include (Adapted from O'Connor, Jacobsen Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting their Health [2007], and Bunn H, O'Connor AM, Jacobsen MJ Analyzing decision support and related communication [1998, 2003])

1. **Listening skills**

   Encourage patient to talk by providing prompts to continue such as ***go on, and then? and uh huh*** or by repeating the last thing a person said, ***It's confusing***.

   Paraphrase content of messages shared by patient to promote exploration, clarify content and to communicate that the person's unique perspective has been heard. The clinician should use their own words rather than just parroting what they heard.

   Reflection of feelings usually can be done effectively once trust has been established. Until the clinician feels that trust has been established, short reflections at the same level of intensity expressed by the patient without omitting any of the message's meaning are appropriate. Reflection in this manner communicates that the clinician understands the patient's feelings and may work as a catalyst for further problem solving. For example, the clinician identifies what the person is feeling and responds back in his or her own words like this: "***So, you're unsure which choice is the best for you.***"

   Summarize the person's key comments and reflect them back to the patient. The clinician should condense several key comments made by the patient and provide a summary of the situation. This assists the patient in gaining a broader understanding of the situation rather than getting mired down in the details. The most effective times to do this are midway through and at the end of the conversation. An example of this is "***You and your family have read the information together, discussed the pros and cons, but are having a hard time making a decision because of the risks.***"

   Perception checks ensure that the clinician accurately understands a patient or family member perspective, and may be used as a summary or reflection. They are used to verify that the clinician is interpreting the message correctly. The clinician can say, "***So you are saying that you're not ready to make a decision at this time. Am I understanding you correctly?***"

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2. **Questioning Skills**

   Open and closed questions are both used, with the emphasis on open questions. Open questions ask for clarification or elaboration and cannot have a yes or no answer. An example would be, "***What else would influence you to choose this?***" Closed questions are appropriate if specific information is required, such as "***Does your daughter support your decision?***"

   Other skills such as summarizing, paraphrasing, and reflection of feeling can be used in the questioning process so that the patient doesn't feel pressured by questions.

   Verbal tracking, referring back to a topic the patient mentioned earlier, is an important foundational skill (Ivey & Bradford-Ivey). An example of this is the clinician saying, "***You mentioned earlier…***"

3. **Information-Giving Skills**

   Providing information and **providing feedback** are two methods of information giving. The distinction between providing information and giving advice is important. Information giving allows a clinician to supplement his or her knowledge and helps to keep the conversation patient centered. Giving advice, on the other hand, takes the attention away from the patient's unique goals and values, and places it on those of the clinician.

   Providing information can be sharing facts or responding to questions. An example is "***If we look at the evidence, the risk is…***" **Providing feedback** gives the patient the clinician's view of the patient's reaction. For instance, the clinician can say, "***You seem to understand the facts and value your daughter's advice.***"

When to Initiate a Collaborative Conversation™

Certain seminal events occur along the care continuum, creating especially opportune times for collaborative conversations. More than one of these opportunities may present at a time, and they will occur in no specific order.

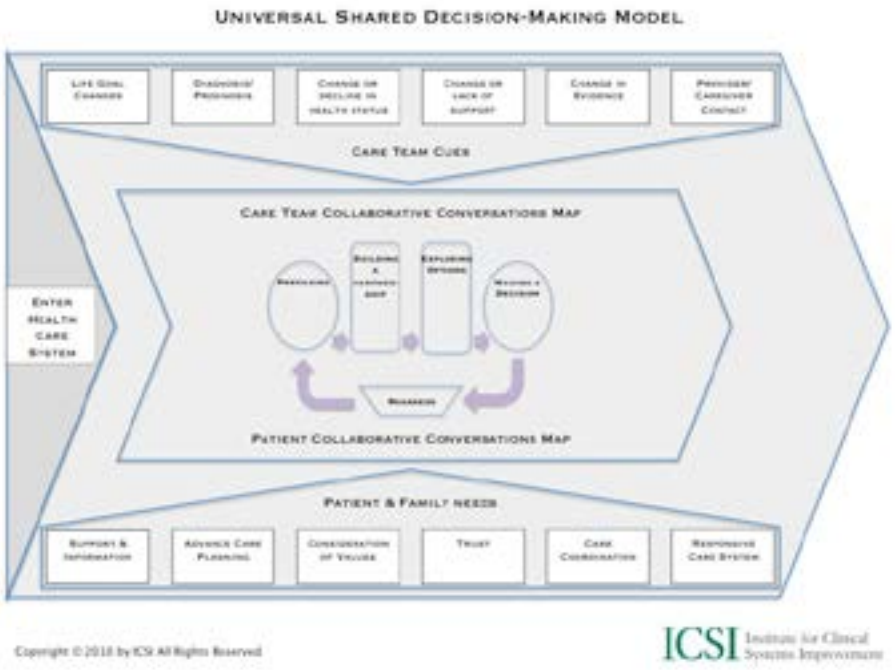

Table 1

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Cues for the Care Team to Initiate a Collaborative Conversation™:

- Life goal changes: *Patient's priorities change related to things the patient values such as activities, relationships, possessions, goals and hopes, or things that contribute to the patient's emotional and spiritual well-being.*
- Diagnosis/prognosis changes: *Additional diagnoses, improved or worsening prognosis.*
- Change or decline in health status: *Improving or worsening symptoms, change in performance status or psychological distress.*
- Change or lack of support: *Increase or decrease in caregiver support, change in caregiver, change in caregiver status, change in financial standing, difference between patient and family wishes.*
- Disease progression: *Change in physical or psychological status as a result of the disease progression.*
- Clinician/caregiver contact: *Each contact between the clinician/ caregiver presents an opportunity to reaffirm with the patient that the care plan and the care he or she is receiving are consistent with his or her values.*

Patient and Family Needs within a Collaborative Conversation™

- Request for support and information: *Decisional conflict is indicated by, among other things, the patient verbalizing uncertainty or concern about undesired outcomes, expressing concern about choice consistency with personal values, or exhibiting behavior such as wavering, delay, preoccupation, distress or tension. Support resources may include health care professionals, family, friends, support groups, clergy and social workers. When patient expresses a need for information regarding options and their potential outcomes, the patient should understand the key facts about the options, risks and benefits, and have realistic expectations. The method and pace with which this information is provided to the patient should be appropriate for the patient's capacity at that moment.*
- Advance Care Planning: *With the diagnosis of a life-limiting illness, conversations around advance care planning open up. This is an opportune time to expand the scope of the conversation to other types of decisions that will need to be made as a consequence of the diagnosis of a life-limiting illness.*
- Consideration of Values: *The personal importance a patient assigns potential outcomes must be respected. If the patient is unclear how to prioritize his or her preferences, value clarification can be achieved through the use of decision aids, detailing the benefits and harms of potential outcomes in terms of how they will directly affect the patient, and through collaborative conversations with the clinician.*
- Trust: *The patient must feel confident that his or her preferences will be communicated to and respected by all caregivers.*
- Care Coordination: *Should the patient require care coordination, this is an opportune time to discuss the other types of care-related decisions that need to be made. These decisions will most likely need to be revisited often. Further, the care delivery system must be capable of delivering coordinated care throughout the continuum of care.*
- Responsive Care System: *The care system needs to support the components of patient- and family-centered care so the patient's values and preferences are incorporated into the care he or she receives throughout the care continuum.*

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The Collaborative Conversation™ Map is the heart of this process. The Collaborative Conversation Map™ can be used as a stand-alone tool that is equally applicable to clinicians and patients, as shown in Table 2. Clinicians use the map as a clinical workflow. It helps get the shared decision-making process initiated and provides navigation for the process. Care teams can use the Collaborative Conversation™ to document team best practices and to formalize a common lexicon. Organizations can build fields from the Collaborative Conversation™ Map in electronic medical records to encourage process normalization. Patients use the map to prepare for decision-making, to help guide them through the process and to share critical information with their loved ones.

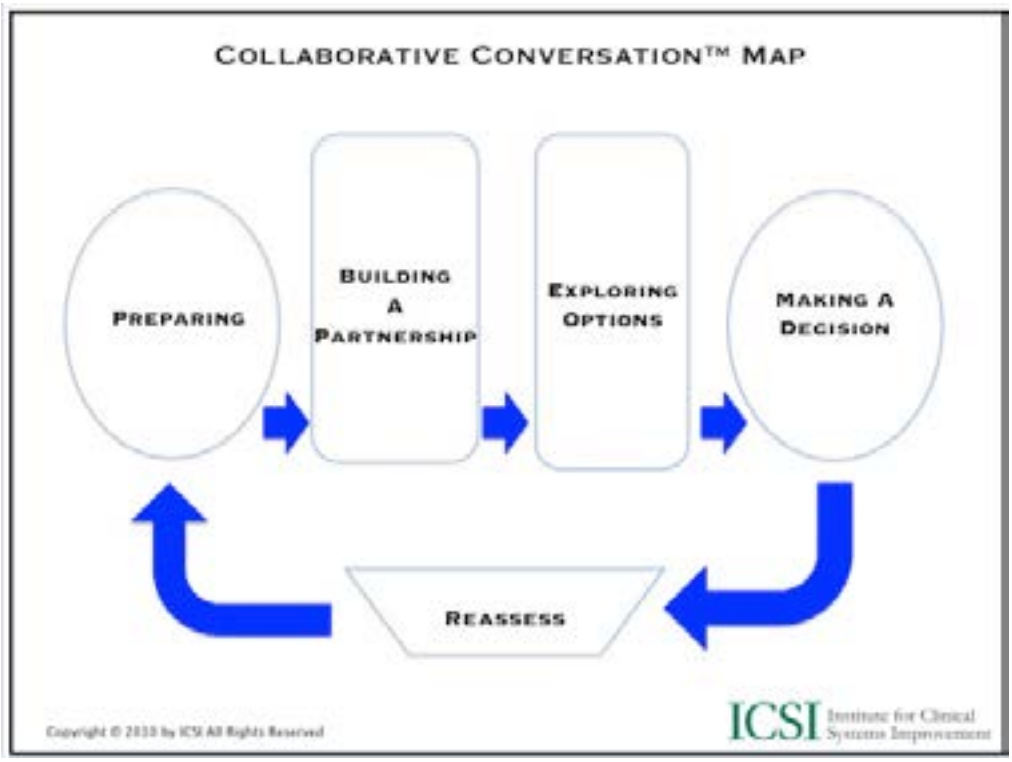

Table 2

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Evaluating Shared Decision-Making

It has proven challenging to assess shared decision-making. Measuring shared decision-making remains important for continued adoption of shared decision-making as a mechanism for translating evidence into practice; promoting patient-centered care; and understanding the impact of shared decision-making on patient experience, outcomes and revenues. Many assessments exist, but they are often proxy measures.

Two suggested methods for measuring shared decision-making are the CollaboRATE tool and the SURE Test. These two tools measure different aspects of shared decision-making, as described below.

The CollaboRATE tool measures the level of shared decision-making in the clinical encounter from the patient's perspective. It is a brief patient-reported measure of shared decision-making. The tools and guidance on their use can be found at http://www.collaboratescore.org/.

The SURE Test is a brief screening questionnaire the patient uses to access his or her readiness and capacity to make a decision or to determine whether he or she is comfortable with the choice that was made. In other words, it provides information on how likely a patient may be experiencing decisional conflict. If the SURE Test indicates decisional conflict may exist, the Decisional Conflict Scale should be completed in order to assess clinically significant decisional conflict.

Shared decision-making is a useful mechanism for translating evidence into practice. While research on the impacts of shared decision-making continues to grow, there is mounting evidence that both patients and clinicians benefit from SDM. Shared decision-making offers the opportunity to bring evidence and the patient's values into the patient/clinician discussion of health choices.

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8009 34th Avenue South, Suite 1200 • Bloomington, MN 55425 • Phone: 952-814-7060 • www.icsi.org

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ICSI has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report, Clinical Practice Guidelines We Can Trust (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI policy regarding Conflicts of Interest is available at http://bit.ly/ICSICOI.

Funding Source

The Institute for Clinical Systems Improvement provided the funding for this guideline revision. ICSI is a not-for-profit, quality improvement organization based in Bloomington, Minnesota. ICSI's work is funded by the annual dues of the member medical groups and three sponsoring health plans in Minnesota. Individuals on the work group are not paid by ICSI but are supported by their medical group for this work.

ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups and sponsoring health plans review and provide feedback but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

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Disclosure of Potential Conflicts of Interest

Sharon Allen, MD, PhD (Work Group Member)
Professor of Family Medicine, Family Medicine and Community Health, University of Minnesota Physicians
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: None
Research Grants: National Institute on Drug Abuse (NIDA) for smoking cessation studies in women.
Financial/Non-Financial Conflicts of Interest: None

Alison Forney-Gorman, MD, MPH (Work Group Member)
Family Medicine Physician Hospitalist, Family Practice; HealthPartners Medical Group and Clinics, North Suburban Family Physicians - Roseville
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Mary Homan, MD (Work Group Member)
Family Medicine; Fairview Health Services
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Ann Kearns, MD, PhD (Work Group Leader)
Consultant, Endocrinology; Mayo Clinic
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Anne Kramlinger, MD (Work Group Member)
Family Medicine Consultant Physician; Mayo Clinic
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Mary Sauer, PharmD, BCACP (Work Group Member)
Medication Management (MTM) Practitioner, MTM Pharmacy – Family Medicine; North Memorial Health Care
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
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ICSI seeks review from members and the public during the revision process.

Member Review

All ICSI documents are available for member review at two points in the ICSI revision process. The ICSI Response Report is sent to members at the beginning of a document revision. The goal of this report is to solicit feedback about the guideline, including but not limited to the algorithm, content, recommendations and implementation. Members are also welcome to participate in the public comment period (see below).

The work group would like to thank the following organizations for participating in the Diagnosis and Treatment of Osteoporosis pre-revision review:

- *CentraCare*
- *Hudson Physicians*

Public Comment

ICSI makes a draft of the guideline available to the public on the ICSI website. The public is invited to comment in an effort to get feedback prior to its finalization. All comments will be reviewed by the ICSI facilitator and work group members when needed. ICSI work group may or may not make changes to the guideline based on public comment responses.

The work group would like to thank all those who took time to thoughtfully and thoroughly review our draft and submitted comments for the Diagnosis and Treatment of Osteoporosis.

Invited Reviews

For some guidelines, ICSI will invite experts in the community to comment on a guideline draft prior to finalization. This is done during the public comment period.

No invited review was done for the Diagnosis and Treatment of Osteoporosis guideline.

ICSI Patient Advisory Council (PAC)

The ICSI Patient Advisory Council responds to any guideline review requests put forth by ICSI facilitators and work groups. The PAC members may be involved at the beginning, middle and/or end of the revision process. Patient advisors who serve on the council consistently share their experiences and perspectives in either a comprehensive or partial review of a document.

The ICSI Patient Advisory Council did not review the Diagnosis and Treatment of Osteoporosis guideline.

ICSI would like to acknowledge the contributions of Erin Monahan, PA-C, to this guideline. Ms. Monahan was initially a member of the work group but due to changes in employment during the revision, could no longer participate as a work group member. She had no conflict of interest disclosures.

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Document History

- Refer to the Evidence Grading section for information about the GRADE system that was adopted in 2011.
- This document was initially approved by the Committee for Evidence-Based Practice (CEBP) in April 2017. Following the review, the guideline was updated to include information on abaloparatide. The updated guideline was renewed by CEBP in July 2017 and approved.

The next revision will be no later than July 2022.

Original Work Group Members

Dana Battles, MD
Internal Medicine
Aspen Medical Group

Bart Clarke, MD
Endocrinology
Mayo Clinic

Renee Compo, RN, CNP
Nursing
HealthPartners Medical Group

Dianne Eggen, MPH
Health Education
HealthPartners Health Plan

Jane Flad, MD
Family Practice
Family HealthServices Minnesota

J. Michael Gonzalez-Campoy, MD, PhD
Endocrinology
Aspen Medical Group

Beth Green, MBA, RRT
Measurement/Implementation Advisor
ICSI

Richard Kopher, MD
Gynecology
HealthPartners Medical Group

Michelle Kotten, PharmD
Pharmacy
HealthPartners Medical Group

Jenelle Meyer, RN
Facilitator
ICSI

John Schousboe, MD
Rheumatology
Park Nicollet Health Services

Christine Simonelli, MD
Internal Medicine, Work Group Leader
HealthEast Clinics

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Contact ICSI at:
8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)
Online at http://www.ICSI.org

ICSI Document Development and Revision Process

Overview

Since 1993, the Institute for Clinical Systems Improvement (ICSI) has developed more than 60 evidence-based health care documents that support best practices for the prevention, diagnosis, treatment or management of a given symptom, disease or condition for patients.

Audience and Intended Use

The information contained in this ICSI health care guideline is intended primarily for health professionals and other expert audiences.

This ICSI health care guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients and families are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI health care guideline and applying it in their individual case.

This ICSI health care guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition.

Document Development and Revision Process

The development process is based on a number of long-proven approaches and is continually being revised based on changing community standards. The ICSI staff, in consultation with the work group and a medical librarian, conduct a literature search to identify systematic reviews, randomized clinical trials, meta-analysis, other guidelines, regulatory statements and other pertinent literature. This literature is evaluated based on the GRADE methodology by work group members. When needed, an outside methodologist is consulted.

The work group uses this information to develop or revise clinical flows and algorithms, write recommendations, and identify gaps in the literature. The work group gives consideration to the importance of many issues as they develop the guideline. These considerations include the systems of care in our community and how resources vary, the balance between benefits and harms of interventions, patient and community values, the autonomy of clinicians and patients and more. All decisions made by the work group are done using a consensus process.

ICSI's medical group members and sponsors review each guideline as part of the revision process. They provide comment on the scientific content, recommendations and implementation strategies. This feedback is used by and responded to by the work group as part of their revision work. Final review and approval of the guideline is done by ICSI's Committee on Evidence-Based Practice. This committee is made up of practicing clinicians and nurses, drawn from ICSI member medical groups.

Implementation Recommendations and Measures

These are provided to assist medical groups and others to implement the recommendations in the guidelines. Where possible, implementation strategies are included that have been formally evaluated and tested. Measures are included that may be used for quality improvement as well as for outcome reporting. When available, regulatory or publicly reported measures are included.

Document Revision Cycle

Scientific documents are revised as indicated by changes in clinical practice and literature. ICSI staff monitors major peer-reviewed journals for any pertinent evidence that would affect a particular guideline and recommendation.

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