ICSI Institute for Clinical Systems Improvement

Health Care Guideline

Diagnosis and Treatment of Osteoporosis

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ICSI
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Health Care Guideline:

Diagnosis and Treatment of Osteoporosis

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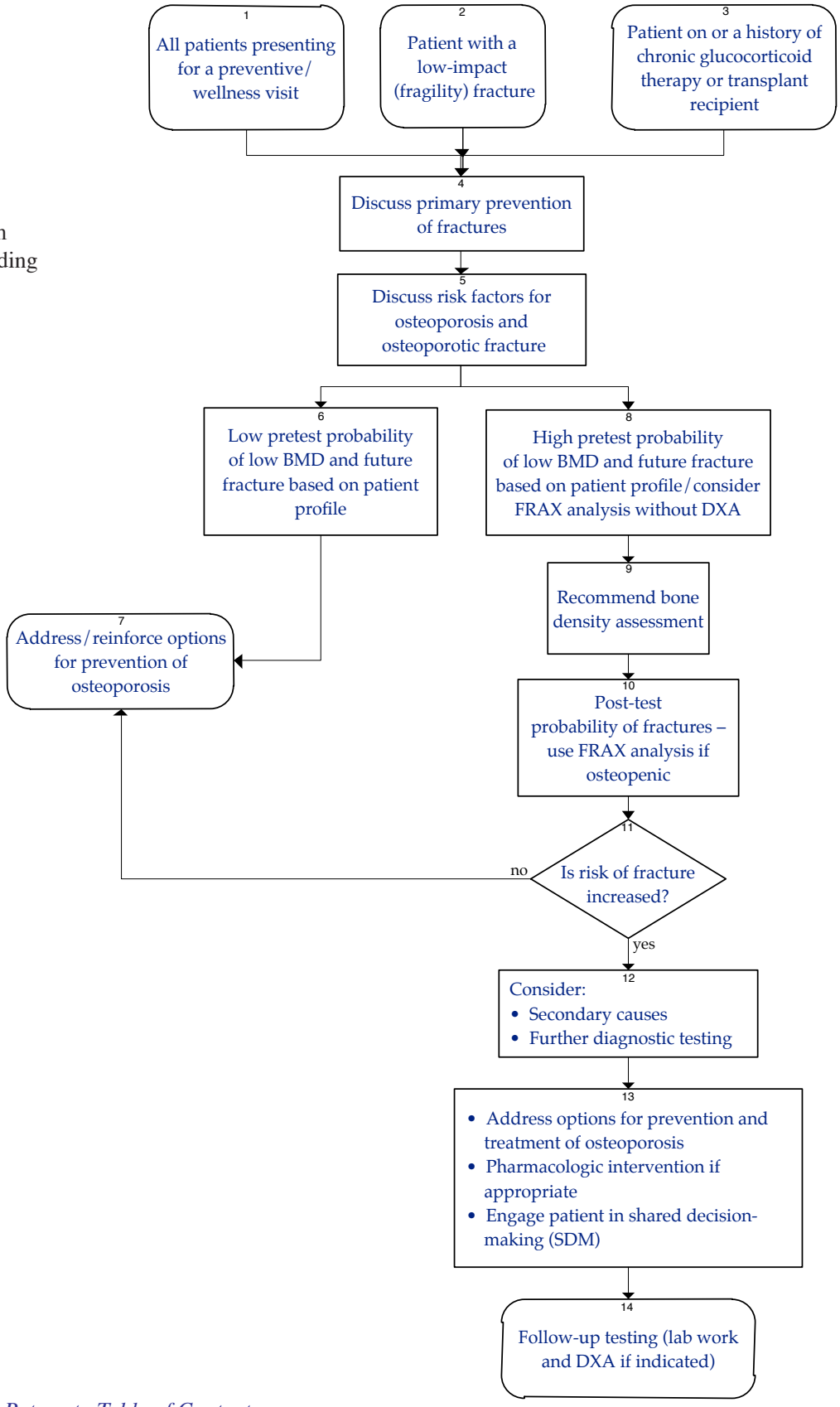

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Evidence Grading

Literature Search

A consistent and defined process is used for literature search and review for the development and revision of ICSI guidelines. The literature search was divided into two stages to identify systematic reviews, (stage I) and randomized controlled trials. Literature search terms used for this revision include frequency of DXA, primary and secondary workups, fracture risk assessment (FRAX®), calcium as it pertains to cardiovascular risk, osteoporosis in men, vitamin D and prolia (denosumab) from January 2010 through January 2013.

GRADE Methodology

Following a review of several evidence rating and recommendation writing systems, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

GRADE has advantages over other systems including the current system used by ICSI. Advantages include:

- developed by a widely representative group of international guideline developers;
- explicit and comprehensive criteria for downgrading and upgrading quality of evidence ratings;
- clear separation between quality of evidence and strength of recommendations that includes a transparent process of moving from evidence evaluation to recommendations;
- clear, pragmatic interpretations of strong versus weak recommendations for clinicians, patients and policy-makers;
- explicit acknowledgement of values and preferences; and
- explicit evaluation of the importance of outcomes of alternative management strategies.

In the GRADE process, evidence is gathered related to a specific question. Systematic reviews are utilized first. Further literature is incorporated with randomized control trials or observational studies. The evidence addresses the same population, intervention, comparisons and outcomes. The overall body of evidence for each topic is then given a quality rating.

Once the quality of the evidence has been determined, recommendations are formulated to reflect their strength. The strength of a recommendation is either strong or weak. Low quality evidence rarely has a strong recommendation. Only outcomes that are critical are considered the primary factors influencing a recommendation and are used to determine the overall strength of this recommendation. Each recommendation answers a focused health care question.

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Crosswalk between ICSI Evidence Grading System and GRADE

Category	Quality Definitions	Strong Recommendation	Weak Recommendation
High Quality Evidence	Further research is very unlikely to change our confidence in the estimate of effect.	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients.	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risks but recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is a recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefits, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

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Recommendations Table

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

Note: Other recommendation language may appear throughout the document as a result of work group consensus but is not included in this evidence-based recommendations table.

Topic	Quality of Evidence	Recommendations	Strength of Recommendation	Annotation Number	Relevant Resources
All patients presenting for a preventive/ wellness visit	Moderate	Clinicians should screen for osteoporosis in women aged 65 years and older and in younger women whose fracture risk is equal or greater than 9.3% from FRAX analysis or are considered to be at fracture risk.	Strong	1	*U.S. Preventive Services Task Force, 2011*
Patient on or a history of chronic glucocorticoid therapy or transplant recipient	Moderate	Osteoporosis prevention and treatment measures, and bone mineral density testing should be considered for anyone who is started on or has been on glucocorticoid therapy (at a dose of more than 5 mg prednisone or equivalent per day for three or more months).	Strong	3	*Grossman, 2010*
Discuss primary prevention of fractures	Low	Primary prevention should include counseling patients on achievement and maintenance of a normal BMI (20-25).	Strong	4	*Hannan, 2000; Hoidrup, 1999b*
	Low	A balanced diet including adequate dairy products and appropriate nutrition should be discussed with patients.	Strong		*Hannan, 2000; Hoidrup, 1999b*
	Low	Patients should be encouraged and offered assistance in developing a lifetime program of exercise that they will continue to do and enjoy.	Strong		*Ulrich, 1999*
	Moderate	Smoking cessation counseling should be done at every visit.	Strong		*Huopio, 2000*
High pretest probability of low BMD and future fracture based on patient profile	Moderate	Risk stratify patients to determine the appropriateness of bone density testing.	Strong	8	*National Osteoporosis Foundation, 2011*
Recommended bone density assessment	Moderate	Utilize bone mineral density measurement with central DXA as it is the single best imaging predictor of fracture risk as well as the best monitor of patient response to treatment.	Strong	9	*Hailey, 1998*

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Topic	Quality of Evidence	Recommendations	Strength of Recommendation	Annotation Number	Relevant Resources
Is risk of fracture increased?	High	In cases of osteopenia, the femoral neck T-score should be used in combination with clinical risk factors to predict a given patient's fracture risk in the FRAX® model.	Strong	11	*Hans, 2011*
Consider secondary causes/further diagnostic testing	Low	An initial screening laboratory profile should be considered in all patients with osteoporosis.	Strong	12	*Barzel, 2003; Tannenbaum, 2002*
Address options for prevention and treatment of osteoporosis	Moderate	Lifestyle adjustments are universally recommended for bone health.	Strong	13	*National Osteoporosis Foundation, 2010*
	Moderate	Adequate calcium and vitamin D intake as well as regular exercise should be discussed with patients for the prevention of osteoporosis.	Strong		*Moyer, 2013; Heany, 2011; Holick, 2008; Ulrich, 1999*
	Moderate	Bisphosphonates are indicated for reduction of fracture risk (both vertebral and non-vertebral), including postmenopausal women, men and in the setting of glucocorticoid use.	Strong		*Serpa Neto, 2005*
	High	Once-yearly intravenous zoledronic acid may be given to men undergoing androgen deprivation therapy for prostate cancer with osteoporosis and should be considered to prevent bone loss in those without osteoporosis.	Strong		*Boonen, 2011*
	Moderate	Bisphosphonates, particularly zoledronic acid, should be given to men undergoing androgen deprivation therapy for prostate cancer with osteoporosis and should be considered to prevent bone loss in those without osteoporosis.			*Serpa Neto, 2010*
	High	Anabolic therapy with parathyroid hormone is indicated for patients with particularly high risk for future fracture, and data shows reduction in vertebral and non-vertebral fracture.	Strong		*Neer, 2011*

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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 World Health Organization defines osteoporosis as a bone density of 2.5 standard deviations or more below a reference group of young Caucasian females *(World Health Organization, 2004 [Reference])*. A low bone mass is frequently found, but not required, for the diagnosis. (A fragility fracture, regardless of the bone mass, necessitates the diagnosis.) Osteoporosis is by far the most common bone disease *(World Health Organization, 2004 [Reference])*. Osteoporosis can be a primary disorder or can be caused by a host of other factors, (e.g., diseases, lifestyle, medications, etc.) The impact of this disorder is massive in terms of cost, morbidity and mortality. An estimated 1.5 million individuals suffer a fragility fracture annually *(Riggs, 1998 [Reference])*. An estimated 40% of women and 25-33% of men during their lifetime will suffer a hip, spine or wrist fracture in their lifetime *(Binkley, 2006 [Reference])*. Projections indicate a two- to threefold increase in osteoporosis by 2040 *(U.S. Preventive Services Task Force, 2012 [Reference])*.

Of the types of fractures, the most devastating effects are from hip fractures. Most of these occur after a fall, which are more frequent with aging. The one-year mortality rate of a hip fracture is approximately 28% in women and 35% in men *(U.S. Department of Health and Human Services, 2004 [Reference])*. Some, but not all, of these deaths would be avoided with preventive interventions. Twenty-five percent of these patients will become disabled, and many will require long-term nursing home placement *(Ray, 1997 [Reference])*. Given the aging population, the frequency, cost and burden of fractures will continue to increase.

Annual direct care expenditures for osteoporotic fractures ranged from $12.2 billion to $17.9 billion in 1999. This constitutes 7% of total health care costs for women over the age of 45 *(Hoerger, 1999 [Reference])*.

Although the fracture risk is highest in cases of osteoporosis, the actual number of fractures is highest in the large group of subjects with milder bone loss (osteopenia) *(Siris, 2004 [Reference])*. This group has often been both over- and undertreated. The development of the FRAX® model of risk assessment in 2010 has furthered the field immensely due to a much more accurate fracture risk assessment, leading to more appropriate treatment decisions *(Kanis, 2010 [Reference])*.

The U.S. Preventive Services Task Force (USPSTF) advises bone densitometry for all women age 65 and over and younger if risk is equal to 65 year olds without other risk factors (9.3%). However, in 2004, no more than 45% of these women actually were tested *(Surgeon General's Report, 2004 [Reference])*. The vast majority of the utility of bone densitometry is from the initial scan. The role of follow-up scanning is controversial but generally performed.

Several effective bone agents have been developed since the advent of bisphosphonates in 1994. Most of these are "anti-resorptive" agents, and one is an anabolic (bone forming) drug. These medications generally decrease fracture risk by 50% in patients who adhere to the medication treatment.

Non-adherence is a major problem with medications for bone loss. Non-adherence leads to an increase in fracture risk *(Siris, 2006 [Reference])*. Far too little focus and research is being spent on this critical problem. There has been concern over the last five years of possible unforeseen consequences of medications that suppress bone turnover. These include osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). The former is extremely rare and the latter is unusual but have lead to the concept of limiting the use of bisphosphonates to three to five years in those without a marked fracture risk *(Siris, 2006 [Reference])*.

These highly publicized, rare associations have further increased patient reluctance to start therapy and have exacerbated non-adherence.

Novel agents, taking advantage of recently discovered pathways, and new delivery systems of parathyroid hormone are on the horizon. However, the high cost of these agents may hamper application.

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The major challenges facing this field currently include low rates of initial screening with Dual-energy X-ray absorptiometry (DXA), lack of initial treatment in cases with a high fracture risk, and poor adherence with prescribed treatment.

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Scope and Target Population

This guideline addresses the prevention, diagnosis and management of bone loss in adults, including lifestyle modification, evaluation and drug treatment. It does not address the pediatric population in which a low bone mass leading to fracture is very rare and pharmacologic intervention is only occasionally indicated. Pediatric bone specialists most commonly manage unusual fractures in children.

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Aims

1. Increase the percentage of female patients age 18 years and older who are evaluated for osteoporosis risk factors during a preventive visit. *(Annotation #1)*
2. Increase the percentage of female and male patients age 50 years and older and diagnosed with osteoporosis who receive treatment for osteoporosis. *(Annotation #13)*
3. Improve diagnostic and therapeutic follow-up for osteoporosis of adults presenting with a history of low-impact (fragility) fracture for men and women age 50 or older. *(Annotation #2)*

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Clinical Highlights

- Discuss risk factors for osteoporosis and primary prevention with all patients presenting for preventive/wellness health visits. (*Annotations #4, 5; Aim #1*)
- Address pharmacologic options for prevention and treatment of osteoporosis with appropriate preventive/wellness at risk for or who currently have signs and symptoms of osteoporosis. (*Annotation #13; Aims #2, 3)*

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Related ICSI Scientific Documents

Guidelines

- Healthy Lifestyles
- Prevention and Management of Obesity for Adults
- Preventive Services for Adults

Protocols

- Prevention of Falls Protocol

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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

1. All Patients Presenting for a Preventive/Wellness Visit

Recommendation:

- Clinicians should screen for osteoporosis in women aged 65 years of age and older and in younger women whose fracture risk is equal to or greater than 9.3% from FRAX® analysis or are considered to be at fracture risk *(Strong Recommendation, Moderate Quality Evidence) (U.S. Preventive Services Task Force, 2011).*

Consider the following:

- Review risks of osteoporosis with patients during preventive/wellness vists and discuss the importance of maintaining strong bones.
- Record accurate serial heights and observe for acquired kyphosis.
- Screening for osteoporosis in men over age 70 and men aged 50-69 years of age based on risk factor profile.

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 risks for osteoporosis reviewed when they present to their clinician's office. In women aged 65 years of age and older and in younger women whose fracture risk is equal to or greater than 9.3% from FRAX® analysis or are considered to be at fracture risk, there is at least moderate benefit in treating DXA-detected osteoporosis *(U.S. Preventive Services Task Force, 2011[Reference]).* Routine screening of men is not widespread. The National Osteoporosis Foundation (NOF) recommends screening of osteoporosis in men over the age of 70 and men ages 50-69 based on risk factor profile. However, current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men *(U.S. Preventive Services Task Force, 2011[Reference]).* In addition to reviewing historical risk factors (discussed in Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture"), it is important to record accurate serial height measurements with a stadiometer and observe posture for acquired kyphosis. Patients with significant acquired kyphosis and/or an historical height loss greater than 4 cm (1.6 inches) or measured height loss greater than 2 cm (0.8 inches) should have lateral vertebral assessment with DXA or thoracic and lumbar spine radiographs and bone density testing. 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, 2007 [Reference]; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001 [Reference]).*

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2. Patient with a Low-Impact (Fragility) Fracture

Consider the Following:

- Consider all adults with a history of vertebral fracture, hip fracture, proximal humerus, ankle, pelvis or distal forearm fracture at higher than average risk for a future fracture.
- Review lifestyle risk factors for osteoporosis.
  - Discuss adequacy of total calcium and vitamin D intake.
  - Address home safety, fall prevention and specific exercises for muscle strength.

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- Consider bone density testing in patients with fractures who are willing to accept treatment.
- Consider all men* and postmenopausal women with low-impact (fragility) fracture as potential candidates for pharmacologic intervention, and women and men over age 70 with prior fragility fracture as candidates for osteoporosis therapy even without bone density testing.

* Although we have the best data on postmenopausal women, there may be a similar risk in men, and we are including men in this guideline recommendation *(Melton, 1998 [Reference])*.

Discuss osteoporosis risk with any adult who has a history of a low-impact (fragility) fracture that may be related to osteoporosis. For the purpose of this guideline, a low-impact fracture will be 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 cough, sneeze 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. Many adults do not realize that having one fracture in their adult lifetime indicates an increased risk of future fractures, especially in the first few years following the fracture, and may be an indication for bone density testing. This historical risk factor provides information that may be additive to bone mineral density information. There may be mechanical influences caused by having had one fracture that increase subsequent risk by altering balance and increasing fall risk *(Johnell, 2004 [Reference])*.

It is estimated that 50% of women over age 50 will develop a fracture in their remaining lifetime and the annualized risk increases with age. Twenty-five percent of women over age 50 will experience an osteoporotic vertebral fracture, so that by age 75 more than one in three women has sustained at least one vertebral 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 [Guideline]; Kanis, 1997 [Reference])*.

Black, et al. examined data from the Study of Osteoporotic Fractures, a prospective study of 9,704 postmenopausal women over age 65. After a mean of 3.7 years, patients with a prevalent vertebral fracture had an increase in subsequent radiographically documented vertebral fracture, hip fractures and all non-vertebral fractures combined. After adjusting for age, there was not a statistically significant increase in wrist fractures *(Black, 1999 [Reference])*. Other studies support this observation *(Huopio, 2000 [Reference]; Davis, 1999 [Reference])*.

Relative Risk of Fracture at Various Sites in the Presence of a Radiographic Vertebral Compression Deformity

Site of Subsequent Fracture	Relative Risk (95% CI)
Vertebral	5.4 (4.4, 6.6)
Hip	2.8 (2.3, 3.4)
Any non-vertebral site	1.9 (1.7, 2.1)

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 [Reference])*.

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Fractures of the wrist (Colles' fractures) can also be indicators of significant risk for osteoporosis or future fractures *(Schousboe, 2005b [Reference])*. The prospective study by Earnshaw, et al. reported bone densities in men and women with a history of Colles' fracture. In patients less than 65 years, BMD was lower in the hip and non-fractured distal radius than age-matched controls *(Earnshaw, 1998 [Reference])*. A retrospective case-control study of patients in Sweden who sustained non-osteoporotic fractures early in life was reported *(Karlsson, 1993 [Reference])*. They reported an odds ratio of subsequently developing an osteoporotic fracture after ankle fracture of 1.8 (range 1.3-2.7) over 14 years. The overall increase in risk from any non-osteoporotic fracture for men was 2.3 (range 1.4-3.6) and for women 1.6 (range 1.04-2.3). Gunnes reported similar results from a population-based, retrospective study of 29,802 postmenopausal women. Again an odds ratio for hip fracture after ankle fracture was 1.6 (95% CI 1.1-2.3) and 3.0 (95% CI 2.4-5.0) for a previous humerus fracture *(Gunnes, 1998 [Reference])*.

The presence of previous fractures noted by clinical or x-ray assessment is an independent risk factor for future fracture risk.

Women with prior fracture and low bone density are 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 [Reference]; Hochberg, 1999 [Reference])*.

Risk of Subsequent Hip Fracture

Klotzbuecher performed a statistical synthesis of studies with reported relative risk and confidence intervals to derive a summary estimate of the relative risk of future hip fracture *(Klotzbuecher, 2000 [Reference])*.

Overall, prior fracture at any site is a clear risk factor for the development of a future hip fracture (RR=1.8: 95% CI: 1.5, 2.2).

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3. Patient on or a History of Chronic Glucocorticoid Therapy or Transplant Recipient

Recommendation:

- Osteoporosis prevention and treatment measures and bone mineral density testing should be considered for anyone who is started on or has been on glucocorticoid therapy at a dose of more than 5 mg prednisone or equivalent per day for three continuous or more months *(Strong Recommendation, Moderate Quality Evidence) (Grossman, 2010)*.

Consider the Following:

- Consider all patients for a baseline bone mineral density test at acceptance into a transplantation program, and that follow-up bone mineral density testing be performed yearly prior to transplantation.

Glucocorticoid Therapy

Osteoporosis prevention and treatment measures and bone mineral density testing should be considered for anyone who is started on or 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). Osteoporosis prevention measures should also be considered for those who have been or can be expected to be on a daily high-dose inhaled glucocorticoid for several years. While it is never too late in the course of glucocorticoid therapy to prevent or treat osteoporosis, it is preferable to start preventive measures against bone loss when

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glucocorticoid therapy is started, for two reasons. First, the greatest amount of bone is lost during the first several months of glucocorticoid use. Second, the risk of fracture at any given level of bone mineral density is greater in those on chronic glucocorticoid therapy than in those who are not on a glucocorticoid. That is, fracture risk is disproportionately increased in those with glucocorticoid-induced low bone density relative to those with low bone density associated with the aging process and/or the postmenopausal state. The loss of bone density on steroids generally totally or nearly totally recovers over a period of months after the steroids have been stopped *(Kanis, 2004 [Reference])*.

Bone Mineral Density Loss and Fractures Associated with Oral Glucocorticoid Use

Oral glucocorticoids cause a 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 that 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. In three studies, 11% percent of asthma patients suffered a fracture after one year of corticosteroids, 30% of patients with giant cell arteritis after two years of treatment, and 34% of women with rheumatoid arthritis after five years of treatment.

Oral glucocorticoids have also been shown to be associated with reduced bone mass and vertebral fracture in children with asthma or juvenile rheumatoid arthritis *(Sinigaglia, 2000 [Reference]; Lane, 1998 [Reference]; Varanos, 1987 [Reference]; Rüegsegger, 1983 [Reference])*.

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 bone mineral density 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 [Reference]; Wong, 2000 [Reference]; Lipworth, 1999 [Reference])*.

Mechanisms of Bone Loss

Glucocorticoids reduce the activity of osteoblasts (cells responsible for new bone formation), resulting in reduction of bone collagen synthesis. Up to 30% less bone is formed during the bone remodeling cycle, and osteoblasts undergo earlier programmed cell death (apoptosis). Osteoclasts (cells that resorb bone) are more active during the early phase of glucocorticoid therapy, but the mechanisms of this are controversial. Osteocyte apoptosis is also increased by glucocorticoids, which may impair repair of microfractures and damage. Most investigators have found that glucocorticoids decrease intestinal absorption of calcium and increase urinary calcium loss. Glucocorticoids may reduce testosterone levels in men and estrogen levels in women by decreasing pituitary secretion of the gonadotropins FSH and LH, and adrenal androgens in postmenopausal women (*Weinstein, 1998 [Reference])*.

The microanatomy and histomorphometry of glucocorticoid-induced osteoporosis differs from that of postmenopausal osteoporosis in many respects. While a similar loss of trabecular bone occurs with both, glucocorticoid-induced osteoporosis is associated with a greater degree of trabecular thinning and less trabecular rupture than postmenopausal osteoporosis, and greater decreases of indices of bone formation *(Aaron, 1989 [Reference])*.

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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 [Reference]; Maalouf, 2005 [Reference])*.

Pretransplantation Bone Loss

Patients accepted for solid organ or allogenic bone marrow transplantation may develop significantly decreased bone mineral density before transplantation. The decrease in bone mineral density 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. Atraumatic or minimally traumatic fractures may occur in patients waiting for transplantation *(Hamdy, 2007 [Reference])*.

Posttransplantation Bone Loss

Solid organ and allogeneic bone marrow transplantation are associated with a rapid decrease in bone mineral density at all skeletal sites during the first year after transplantation. 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. Bone mineral density 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 [Reference]; Stein, 2007 [Reference]; Tauchmanová, 2007 [Reference])*.

On the basis of these observations, it is recommended that all patients have a baseline bone mineral density test at acceptance into a transplantation program, and that follow-up bone mineral density testing be performed yearly prior to transplantation. If patients are taking high-dose steroid medication before transplantation, bone mineral density testing should be performed every 6-12 months.

After solid organ or allogenic bone marrow transplantation, all patients should have bone density testing once a year to detect ongoing bone loss, if it is present. 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 [Reference])*.

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4. Discuss Primary Prevention of Fractures

Recommendations:

- Primary prevention should include counseling patients on achievement and maintenance of a normal BMI of 20-25 *(Strong Recommendation, Low Quality Evidence) (Hannan, 2000; Hoidrup, 1999b)*.
- A balanced diet including dairy products and appropriate nutrition should be discussed with patients *(Strong Recommendation, Low Quality Evidence) (Hannan, 2000; Hoidrup, 1999b)*.
- Patients should be encouraged and offered assistance in developing a lifetime program of exercise that they will continue to do and enjoy *(Strong Recommendation, Low Quality Evidence) (Ulrich, 1999)*.

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- Smoking cessation counseling should be done at every visit *(Strong Recommendation, Low Quality Evidence) (Huopio, 2000)*.
- Assess risk factors for osteoporosis and osteoporotic fracture *(Strong Recommendation, High Quality Evidence) (National Osteoporosis Foundation, 2010)*.

Consider the Following:

- Women who are prematurely hypogonadal and hypogonadal men should be considered for hormonal replacement therapy to help maintain bone health.

Body Habitus

Low body mass index (BMI) (less than 20) is a strong independent risk factor for osteoporosis and fracture. Weight less than 127 pounds, associated with small bones, is a risk factor for osteoporosis *(Ravn, 1999 [Reference])*. Primary prevention should include counseling patients on achievement and maintenance of a healthy body weight (BMI between 20 and 25). See also the ICSI Prevention and Management of Obesity for Adults guideline. A balanced diet including dairy products and appropriate nutrition should be discussed with patients *(Hannan, 2000 [Reference]; Hoidrup, 1999b [Reference])*.

Gonadal Hormonal Status

Women who are prematurely hypogonadal and hypogonadal men who are at increased risk for fracture should be considered for hormonal replacement therapy. For further information, please see Annotation #12, "Consider Secondary Causes/Further Diagnostic Testing," as well as Annotation #13, "Address Options for Prevention and Treatment of Osteoporosis/Pharmacologic Intervention if Appropriate/Engage Patient in Shared Decision-Making (SDM)."

Exercise

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.

It is clear that exercise late in life, even beyond 90, can increase muscle mass and strength twofold or more in frail individuals. It will also improve function, delay in loss of independence, and contribute to improved quality of life *(Ulrich, 1999 [Reference])*.

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 osteoporosis risks by improving strength and balance, and increasing muscle mass *(Layne, 1999 [Reference])*.

High-impact exercise and weight training stimulate accrual of bone mineral content in the skeleton. Lower-impact exercises, such as walking, have beneficial effects on other aspects of health and function, although their effects on BMD have been minimal.

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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 risks as a result. However, spinal flexion exercises have demonstrated an increased risk of vertebral fractures *(Sinaki, 2005 [Reference]; Sinaki, 2002 [Reference]; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001 [Reference])*.

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.

Cigarette Smoking/Smoking Cessation

Cigarette smoking is a risk factor for osteoporosis. The rates of bone loss are approximately one and one-half to two times greater for current smokers than for non-smokers. 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, suggesting decreased calcium absorption. There is also 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. Smoking is a modifiable risk factor *(Huopio, 2000 [Moderate Quality Evidence]; Cornuz, 1999 [Reference])*.

Smoking cessation counseling should be done at every visit. Discussion can include helpful strategies such as nicotine replacement therapy with patches, gum, etc. Bupropion, verenicline and available smoking cessation classes may also be discussed. For more information on smoking cessation, please consult the ICSI Healthy Lifestyles guideline.

Alcohol Restriction

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. See Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture."

Calcium

Adequate calcium intake from food sources and supplements promotes bone health. 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 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.

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Calcium Dietary and Supplement Recommendations *(Institute of Medicine, 2011)* – General Population Recommendations

Men and women ages 19-50	1,000 mg/day
Men ages 51-70	1,000 mg/day
Women aged 51 and older	1,200 mg/day
Men aged 71 and older	1,200 mg/day
Pregnant women and breast feeding aged 18 and older	1,300 mg/day

(Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine, Dietary Reference Intakes for Calcium and Vitamin D, Washington, DC; National Academy Press; 2011, Accessed at http://www.nap.edu/catalog.php?record id=13050 on 31 May 2012.)

Calcium and Vitamin D – Dietary and Supplement Recommendations (National Osteoporosis Foundation, www.nof.org) Recommendations for Those at Risk for Bone Loss

	Calcium	**Vitamin D**
Adults under age 50	1,000 mg/day	400 IU/day to 800 IU/day
Adults age 50 and older	1,200 mg/day	800 IU/day to 1,000 IU/day

http://www.nof.org

The role of vitamin D in fall prevention remains unclear. The data available for vitamin D supplementation is inconsistent.

Calcium supplementation has been shown to increase the ratio of HDL cholesterol to LDL cholesterol by almost 20% in healthy postmenopausal women by binding to fatty acids in the gut. The effect of calcium supplementation on cardiac risk is unclear at this time. Oversupplementation may be associated with an increased risk of kidney stones and vascular calcification *(Bolland, 2008 [Reference]; Reid, 2002 [Reference])*.

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 [Reference]; Weaver, 2000 [Reference])*.

Calcium absorption is compromised when oxalic acid is present in foods such as dark, green, leafy vegetables. An exception is soybeans. A variety of foods with calcium is recommended.

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 with meals and in divided doses. Taking calcium carbonate supplements on an empty stomach may increase the risk of kidney stones and may not be well absorbed. Absorption of calcium carbonate may be decreased in the environment of achlorhydira, 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 (PPIs, histamine receptor blockers) *(O'Connell, 2005 [Reference]; Ross, 2000 [Reference]; Heller, 1999 [Reference]; Institute of Medicine, 1997 [Reference])*.

Calcium slows age-related bone loss.

Calcium may reduce osteoporosis fracture risk.

A meta-analysis by Heaney, et al. 2012, looked at eight randomized control trials of calcium supplementation and CVD and eight observational studies with calcium and CVD as primary end points. They applied the Bradford Hill Criteria for causal inference regarding association between exposure and disease outcome.

They concluded that Relative Risk was marginally statistically significant, results have been mixed at best, there is not a dose response association and absorptive calcemia is unlikely to be great enough to promote calcification of tissue. Therefore, a causal inference is not currently warranted between consumption of calcium from diet or supplements and increased risk of cardiovascular events.

Vitamin D

Adequate vitamin D intake supports calcium absorption and bone metabolism. Since sunlight exposure cannot be assumed to produce needed vitamin D, dietary and supplement sources are essential. Many adults are deficient in vitamin D, and supplements are often needed to meet daily requirements.

Vitamin D requirements vary with age.

Recommendations of Adequate Intake of Vitamin D from the Institite of Medicine, 2011

Men/women 18-70	600 IU/day
Men/women 71 and older	800 IU/day

(Institute of Medicine, 2011 [Reference])

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 [Meta-analysis])*.

The effects of optimal vitamin D levels include:

- maximum suppression of circulating parathyroid hormone (PTH)
- increased calcium absorption
- decreased rates of bone loss
- improved lower extremity functioning

(Bischoff-Ferrari, 2005 [Meta-analysis]; Dawson-Hughes, 2005 [Reference])

The high-risk group, i.e., the elderly, long-term care residents and those with no sunlight exposure, would be expected to receive the greatest benefit from vitamin D supplementation *(Dawson-Hughes, 2005 [Reference])*.

Target levels for optimum 25-OH vitamin D are 30 ng/mL and often require oral supplementation of 800-1,000 international units. This recommendation is based on the level of vitamin D at which secondary hyperparathyroidism no longer occurs in most people. However, most multivitamins contain 200 to 400 international units. Routine monitoring of vitamin D levels after reaching target levels is not necessary *(National Osteoporosis Foundation, 2010 [Moderate Quality Evidence]; Dawson-Hughes, 2005 [Reference])*.

There is some controversy over whether vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) is more effective. The vast majority of vitamin D supplements over-the-counter are currently vitamin D_3. In one study, when vitamin D_2 or D_3 was given at 1,000 IU daily, they were equally effective at maintaining vitamin D levels *(Holick, 2008 [Reference])*. In other studies, however, when they were given at a dose of 50,000 IU as a single dose *(Armas, 2004 [Reference])* or weekly for 12 weeks *(Heaney, 2011 [Reference])*, vitamin D_3 was two to three times more potent at raising and maintaining vitamin D levels than vitamin D_2.

Although milk is the only dairy source of vitamin D, studies have demonstrated highly variable levels of vitamin D fortification in milk in both the U.S. and Canada. Other food sources of vitamin D are affected by the time of year they are harvested *(Institute of Medicine, 1997 [Reference])*.

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Prevention of Falls/Increased Likelihood of Falling

Many factors increase the likelihood of falling, and most hip and wrist fractures occur after a fall. Included in these factors are impaired eyesight, certain medications that affect balance, poor health, frailty, low physical function (such as slow gait and speed and decreased quadriceps strength), dementia and history of past falls. Age-related muscle loss (sarcopenia) may also predispose to fall risk *(Ensrud, 1997 [Reference])*. Preventing falls reduces fractures. Modifying environmental and personal risk factors can be effective in reducing falls. Home visits have been shown to help with this. Also, in some studies, soft or hard hip protector pads have been shown to reduce hip fractures in frail, elderly, adults in community based health care centers. However, adherence in wearing them limits their use and efficacy *(Sinaki, 2005 [Reference]; Kannus, 2000 [Reference]; NHS Centre for Reviews and Dissemination, 1996 [Reference])*.

Please see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture."

Also see ICSI Prevention of Falls protocol.

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5. Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture

The following are risk factors for osteoporosis and osteoporotic fracture:

- A prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- The use of oral corticosteroids for greater than three continuous months
- Rheumatoid arthritis
- Secondary causes of osteoporosis*
- Daily alcohol use of three or more units daily
- Advanced age (greater than 65)
- Body habitus (weight less than 127 pounds or BMI less than or equal to 20)
- Caucasian or Asian race
- Hypogonadism
- Sedentary lifestyle
- Diet deficient in calcium or vitamin D without adequate supplementation
- Increased likelihood of falling

(Baim, 2008 [Reference])

* For a list of secondary causes of osteoporosis, please see Appendix A, "Secondary Causes of Osteoporosis," and Annotation #3, "Patient on or a History of Chronic Glucocorticoid Therapy or Transplant Recipient."

African-American women have a decreased risk, partly because they begin menopause with a higher bone mineral density (BMD) and have a lower rates of bone loss after menopause. Besides these, age and prior fracture are also predictors of fracture independent of bone mineral density *(Bohannon, 1999 [Reference]; Melton, 1999 [Reference]*).

Body Habitus

See Annotation #4, "Discuss Primary Prevention of Fractures."

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Family History of Osteoporosis

Family studies have shown a genetic component to BMD. Family history is an independent predictor of peak BMD, and a family history of osteoporosis in a first-degree relative is related to decreased peak BMD. Maternal fractures are associated with lower BMD and have been shown to be a site-specific predisposition to fracture. There is some evidence that parental history of hip fracture, before age 70, is a risk factor for future fracture independent of bone mineral density *(National Osteoporosis Foundation, 2010 [Moderate Quality Evidence]; Omland, 2000 [Reference]).*

Cigarette Smoking

See Annotation #4, "Discuss Primary Prevention of Fractures."

Sedentary Lifestyle

Sedentary lifestyle is a risk factor for osteoporosis. The type of physical activity and optimal age for greatest benefit is still unclear. Studies do show that physical activity in youth was more strongly associated with higher BMD at all sites. Lack of continued physical activity may lead to bone loss.

Wolff's law states that stress or mechanical loading applied to the bone via the muscle and tendons had direct effect on bone formation and remodeling. 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 bone mineral density *(Bemben, 1999 [Reference]; Branca, 1999 [Reference]).*

Alcohol Intake

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 [Reference]).*

A high level of alcohol intake is associated with decreased bone mineral density. There are conflicting data about the effects of moderate alcohol use on bone mineral density. Studies have reported an association between alcohol intakes greater than one ounce of hard liquor or one drink per day (28-30 g) and decreased bone mineral density 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 years), 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. Other studies have not shown the fracture risk from alcohol to be independent of bone mineral density *(Hannan, 2000 [Reference]; Hoidrup, 1999a [Reference]).*

Low Calcium Intake

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 dairy sources and calcium supplements are related to promoting bone health. Calcium enhances therapy with antiresorptive medication, such as estrogen *(Heaney, 2000 [Reference]; Riggs, 1998 [Reference]; Cumming, 1997 [Reference]; Recker, 1996 [Reference]; Chapuy, 1992 [Reference]; Dawson-Hughes, 1990 [Reference]).*

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Inadequate 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 [Reference]; Dawson-Hughes, 1997 [Reference])*. See also Annotation #4, "Discuss Primary Prevention of Fractures."

Increased Likelihood of Falling

See Annotation #4, "Discuss Primary Prevention of Fractures."

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6. Low Pretest Probability of Low BMD and Future Fracture Based on Patient Profile

Bone density testing in general is not recommended for the following individuals who are at low risk of low bone density and future fracture:

- Premenopausal women who have not had a fracture with minor trauma, are not on chronic glucocorticoid therapy or other medications that could decrease bone density, do not have secondary amenorrhea, and do not have a chronic disease associated with bone loss.
- Eugonadal men less than age 70 who have not had a fracture with minor trauma, are not on glucocorticoid therapy or androgen deprivation therapy, and do not have any significant additional risk factors associated for bone loss.
- Postmenopausal women under age 65 who do not have any significant additional risk factors. See Annotation #8, "High Pretest Probability of Low BMD and Future Fracture Based on Patient Profile/Consider FRAX® Analysis without DXA."

(National Osteoporosis Foundation, 2010 [Moderate Quality Evidence])

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7. Address/Reinforce Options for Prevention of Osteoporosis

Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved peak bone mass, or both. Because of this, clinicians are encouraged to periodically review historical risk factors (see Annotation #4, "Discuss Primary Prevention of Fractures") and primary prevention strategies (see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture") with their patients. Preventive health maintenance exams provide an excellent opportunity for this review.

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8. High Pretest Probability of Low BMD and Future Fracture Based on Patient Profile/Consider FRAX® Analysis without DXA

Consider the Following:

- Risk stratify patients to determine the appropriateness of bone density testing.

The following individuals are at sufficiently high risk for low bone mass and future fracture that a bone mineral density test is justified to further define that risk. This assumes that the individual being tested is willing to consider pharmacologic treatment for low bone mass documented on a bone density test.

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- Prior fracture with minor trauma (fall from standing height or less).
- Those who have been, or are anticipated to be, on glucocorticoid therapy for three or more months at a dose equivalent to or greater than 5 mg prednisone per day.
- Radiographic osteopenia, or vertebral deformity consistent with fracture.
- All women 65 years of age or older.
- Postmenopausal women less than 65:
  - Surgical or natural menopause before age 45
  - Additional risk factors
- Men over the age of 70 and men aged 50-69 years of age based on risk factor profile.
- The FRAX® tool can be used to estimate the 10-year fracture risk based on individual risk factors, in persons who have not had bone density testing. Factors such as low body weight, current smoking, and family history of fragility fracture are included in this calculation.

It is the current recommendation of the National Osteoporosis Foundation and U.S. Preventive Services Task Force that screening be considered in postmenopausal women below age 65 if their 10-year fracture risk is 9.3% or greater based on FRAX® tool (calculated without BMD). This is equal to the 10-year fracture risk of a 65-year-old woman without additional risk factors *(National Osteoporosis Foundation, 2011 [Moderate Quality Evidence]; U.S. Preventive Services Task Force, 2011 [Recommendation Statement])*. See Annotation #11, "Is Risk of Fracture Increased?" for discussion on FRAX®.

In the ICSI algorithm, individuals are judged to be at high or low risk for bone loss based on their personal and family history, and medical evaluation. This implies that those in the high-risk group will be offered a bone density test.

Defining a group of individuals at "high risk" for osteoporosis is in fact daunting, because clinical risk factors in the absence of bone densitometry have poor sensitivity and specificity for osteoporosis. The use of the FRAX® fracture risk calculation should aid in stratifying fracture risk more accurately. There is, nonetheless, broad consensus that assessment of clinical risk factors should be done to determine who should have a bone density test. Similarly, there is broad consensus that mass population screening of all individuals or even of all postmenopausal women is neither cost effective nor appropriate. Many professional organizations, including the United States Preventive Services Task Force, National Osteoporosis Foundation, the North American Menopause Society, the Endocrine Society, National Institutes of Health, American College of Physicians, American Association of Clinical Endocrinologists Endocrinologists and the American College of Rheumatology have published their own guidelines describing whom to select for bone densitometry.

The National Osteoporosis Foundation (NOF) conducted a cost-effectiveness analysis *(Eddy, 1998 [Reference])* regarding the prevention, detection and treatment of osteoporosis. They concluded that bone densitometry was reasonable for all women over age 65, and for postmenopausal women under age 65 with one of the following risk factors: thin body habitus, family history of fracture and current cigarette smoking. In the guideline that NOF published based on this study, estrogen deficiency, lifelong low calcium intake, alcoholism, impaired eyesight, recurrent falls, inadequate physical activity, and poor health or frailty are also listed as reasons to get a bone density test for a postmenopausal woman under age 65.

Individuals who have had a prior low-trauma fracture, are beginning or have been on chronic glucocorticoid therapy, or have had organ transplantation are at highest risk for future fracture. Height loss or acquired kyphosis per se are not indications for a bone density test but should prompt lateral vertebral fracture assessment with DXA or plain radiographs of the thoracic and lumbar spine. These are now Medicare approved indications for DXA. (Note that the radiation exposure of spinal x-rays are markedly higher than lateral vertebral assessment, but the latter is less accessible to clinicians.)

Any vertebral deformity consistent with a fragility fracture found radiographically indicates a higher risk of future fracture. We have not included risk of falls or poor eyesight, since these are not risk factors for low bone density per se, and because the majority of these individuals will be over age 65. Inadequate physical activity and lifelong low calcium intake are not included, since in other studies these have not added much predictive value for low bone mass to other groups of risk factors *(Cadarette, 2000 [Reference]; Lydick, 1998 [Reference]; Bauer, 1993 [Reference])*. Severe loss of mobility (prolonged immobilization), however, is a risk factor for osteoporosis and is included.

Chronic diseases such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, prolonged hyperthyroidism, and hyperparathyroidism are associated with bone loss, and for many individuals with these diseases a bone density test is indicated. Heavy alcohol intake is also an indication for a bone density test.

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9. Recommend Bone Density Assessment

Recommendation:

- Utilize bone mineral density measurement with DXA as it is the single best imaging predictor of fracture risk as well as the best monitor of patient response to treatment *(Strong Recommendation, Moderate Quality Evidence) (U.S. Preventive Services Task Force, 2011)*.

Measurements of BMD with DXA can 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 bone fracture risk. 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 *(Hailey, 1998 [Moderate Quality Evidence]; Miller, 1999a [Reference])*. 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).

Current practice is to describe an individual's bone mineral density as compared to a reference-normal population. In this sense, a T-score is the number of standard deviations above or below the mean for a gender and ethnicity-matched young adult healthy 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 of lumbar spine (at least two evaluable vertebrae required), femoral neck, and total femur T-score according to the World Health Organization. The one-third radius site may be used if either the lumbar spine or femur is non-evaluable.

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

- Normal: A T-score greater than or equal to -1.
- Low bone density (osteopenia): A T-score between -1 and -2.5*.
- Osteoporosis: A T-score less than or equal to -2.5.

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- The term "severe osteoporosis" is 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 [Reference]; Binkley, 2006 [Reference])*.

(International Society for Clinical Densitometry, The, 2007 [Reference])

For patients who decline bone density studies, reinforce osteoporosis prevention.

In premenopausal women, men under age 50 and children, the Z-scores should be used rather than the T scores in identifying those with low bone density. The WHO 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 [Reference])

The Bone Mass Measurement Act of 1998 *(Department of Health and Human Services, 1998 [Reference])* broadened the selective screening by mandating Medicare coverage for densitometry services for individuals at risk of osteoporosis as defined by the following criteria:

- An estrogen-deficient woman at clinical risk for osteoporosis
- An individual with vertebral abnormalities
- An individual receiving or planning to receive long-term glucocorticoid therapy greater than or equal to 5.0 mg prednisone/day or an equivalent dose for greater than or equal to three months
- An individual with primary hyperparathyroidism
- An individual being monitored to assess the response to or the efficacy of an FDA-approved drug for osteoporosis therapy

The National Osteoporosis Foundation (http://www.NOF.org) also recommends bone density testing in the following:

- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Younger postmenopausal women and men age 50 to 69 about whom you have concern based on their clinical risk factor profile
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk such as low body weight, prior low-trauma fracture, or high-risk medication
- Adults who have a fragility fracture after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose greater than or equal to 5 mg prednisone or equivalent for three months or longer) associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy for osteoporosis
- Anyone being treated for osteoporosis, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment.
- Postmenopausal women discontinuing estrogen should be considered for bone density testing

(National Osteoporosis Foundation, 2010 [Moderate Quality Evidence])

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10. Post-Test Probability of Fractures – Use FRAX® Analysis if Osteopenic

Recommendation:

- In cases of osteopenia, the femoral neck T-score should be used in combination with clinical risk factors to predict a given patient's fracture risk in the FRAX® model *(Strong Recommendation, High Quality Evidence) (Hans, 2011)*.

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 [Reference]; Hans, 2011 [High Quality Evidence])*.

Fracture risk in an individual patient is defined as the likelihood of sustaining an osteoporotic fracture over an interval of time. Current fracture risk is defined as the likelihood of an osteoporotic fracture in the patient's remaining lifetime years.

Current fracture risk can be expressed in terms of absolute risk, relative risk or incidence (annual) risk. Absolute fracture risk is the actual risk of fracture for a given patient. Relative risk of fracture is the ratio of the absolute risk of fracture for the patient compared to the absolute risk of fracture for a young adult-, gender-, and ethnicity-matched reference population. Relative risk of fracture is increased by 1.5-3.0 times for each 1.0 standard deviation decrease in bone density below the mean for young adults of the same gender and ethnicity. Fracture risk data in elderly postmenopausal women suggest that fracture prediction is nearly equal regardless of the skeletal site assessed or the type of technology used, with the exception that hip fracture risk is best predicted by proximal femoral bone mineral density measurement (*Melton, 1993 [Reference]*). Similar data are being accumulated for men, although the numbers of studies published so far are much smaller *(Kanis, 2008 [Reference]; Melton, 1998 [Reference])*.

See also Annotation #11, "Is Risk of Fracture Increased?"

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11. Is Risk of Fracture Increased?

Low fracture risk is clinically defined by a bone mineral density T-score above -1.0 (normal bone density by the WHO definition).

Osteoporosis is defined by a BMD T-score of less than or equal to -2.5, and low bone density (osteopenia) is defined as a T-score of -1 to -2.5.

The World Health Organization (WHO) has developed a FRAX® WHO Fracture Risk Assessment Tool that is based on absolute fracture risk. This allows prediction of the 10-year absolute fracture risk for hip fracture and all osteoporotic fractures based on femoral neck bone density. In the absence of femoral neck BMD, total hip BMD may be substituted; however, use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated. The FRAX® calculation can be found on the Web at http://www.shef.ac.uk/FRAX.

For the U.S. population, treatment continues to be recommended for adults with prior hip or vertebral fragility fracture and adults with osteoporosis by T-score. Treatment is cost effective when the 10-year probability of hip fracture is greater than or equal to 3%, or 10-year probability of any osteoporotic fracture is greater than or equal to 20%. This is a basic tool that should be used in the clinical context of the patient.

Limitations of FRAX® patients with significantly lower BMD of the spine than the femur may have risk for vertebral fracture not captured in the model, and clinical judgment should be used regarding the need for treatment despite a lower fracture risk from the FRAX® calculation. Since FRAX® was designed to be a simple tool (yes-no answers), "dose effects" are not considered (e.g., four prevalent fractures is weighted the

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same as one). The number of cigarettes per day is not weighted nor is the steroid dose or duration, amount of alcohol, etc.). FRAX® does not include many risk factors that may influence the treatment decision (e.g., falling, medications other than steroids, family history of spinal fractures, functional status and the severity of prior fractures). FRAX® also does not factor in severity of prior spinal vertebral fracture *(Hans, 2011 [High Quality Evidence])*. FRAX® applies to patients ages 40-90 whom have either never been treated or have not been treated with a bisphosphonate for at least two years or a non-bisphosphonate for at least one year *(Kanis, 2008 [Reference])*.

Previous osteoporotic fractures sustained by the patient, history of osteoporotic fractures sustained by the patient's family members, increased rate of bone turnover, the patient's risk of falling, and the use of medications that predispose to falling also help predict future fracture risk *(Riis, 1996 [Reference])*.

Bone mineral density is the single best predictor of future fracture. About 80% of the variance in bone strength and resistance to fracture in animal models is explained by bone mineral density, and numerous studies have demonstrated that fracture risk is predicted by bone mineral density *(Chandler, 2000 [Reference]; Cummings, 1995 [Reference])*.

Patients found to have low risk of future fracture by bone mineral density testing should not automatically be assumed to remain at low risk of future fracture over their remaining lifetime years. Patients should be periodically reassessed by reviewing risk factors for osteoporosis, evaluating current primary prevention efforts, reviewing the clinical history for osteoporotic fractures subsequent to the initial bone density evaluation, and measuring bone mineral density. Clinical judgment must be used in determining the appropriate intervals between repeated measurements of bone mineral density over time. Whenever remeasurement 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 remeasure 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 remeasure bone density at an appropriate interval, such as 2 to 10 years after the initial assessment depending on baseline bone density, in order to detect patients who lose significant bone density over time. The FRAX® analysis can guide the frequency of the repeat DXAs.

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12. Consider Secondary Causes/Further Diagnostic Testing

Recommendation:

- An initial screening laboratory profile should be considered in all patients with osteoporosis *(Strong Recommendation, Low Quality Evidence) (Barzel, 2003; Tannenbaum, 2002)*.

Certain diseases 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.

Recommended initial laboratory evaluation for all patients with osteoporosis without prior workup:

- 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).

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- It is important to correct hypocalcemia prior to initiation of advanced pharmacologic osteoporosis therapies.

- 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.
  - 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.
- Serum creatinine:
  - This should be drawn in order to screen for renal dysfunction and in order 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.

Two studies were done to evaluate for a cost-effective testing strategy for secondary causes of osteoporosis. They found that these above items, along with a PTH, were enough to diagnose most secondary causes in women who appeared healthy *(Barzel, 2003 [Reference]; Tannenbaum, 2002 [Reference])*. We counter that a PTH may not initially be needed because the serum calcium and vitamin D levels, if abnormal, would catch most cases of secondary hyperparathyroidism.

However, there is a phenotype of primary hyperparathyroidism known as normocalcemic primary hyperparathyroidism. In this phenotype, parathyroid hormone is elevated and serum calcium is normal. Other causes for the elevation in PTH must be ruled out, such as renal insufficiency, hypercalciuria, gastrointestinal malabsorption, vitamin D deficiency, and thiazide diuretic or lithium use. In a study by Lowe, et al. it was found that many patients with normocalcemic hyperparathyroidism were symptomatic, with bone loss and other complications typically characteristic of primary hyperparathyroidism. Currently, these patients would be treated similarly to other patients with osteoporosis, but they should be monitored for the emergence of hypercalcemia.

The following more extensive evaluation for secondary causes of osteoporosis could be considered, on an individual basis, as indicated:

- A biochemical profile that provides information on:
  - Alkaline phosphatase
    - elevated in Paget's disease, prolonged immobilization, acute fractures, oseomalacia and other bone diseases
  - 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.

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- 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.
- 24-hour urinary free cortisol or overnight dexamethasone suppression test if clinical suspicion of glucocorticoid excess.
- Serum and urine protein electrophoresis, with a conditional immunoelectrophoresis.

At this time there is no consensus about the routine use of serum and/or urine markers of bone turnover in the evaluation of patients with osteoporosis.

Refer to Appendix A, "Secondary Causes of Osteoporosis," for a table with the common causes of secondary osteoporosis.

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13. Address Options for Prevention and Treatment of Osteoporosis/ Pharmacologic Intervention if Appropriate/Engage Patient in Shared Decision-Making (SDM)

Recommendations:

- Lifestyle adjustments are universally recommended for bone health *(Strong Recommendation, Moderate Quality Evidence) (National Osteoporosis Foundation, 2010)*.
- Adequate calcium and vitamin D intake as well as regular exercise should be discussed with patients for the prevention of osteoporosis *(Strong Recommendation, Moderate Quality Evidence) (Moyer, 2013; Heaney, 2000; Ulrich, 1999)*.
- Bisphosphonates are indicated for reduction of fracture risk (both vertebral and non-vertebral), including postmenopausal women, men and in the setting of glucocorticoid use *(Strong Recommendation, Moderate Quality Evidence) (Serpa Neto, 2010)*.
- Once-yearly intravenous zoledronic acid may be given to men and women within 90 days of a hip fracture *(Strong Recommendation, Moderate Quality Evidence) (Boonen, 2011)*.
- Bisphosphonates, particularly zoledronic acid, should be given to men undergoing androgen deprivation therapy for prostate cancer with osteoporosis and should be considered to prevent bone loss in those without osteoporosis *(Strong Recommendation, Moderate Quality Evidence) (Serpa Neto, 2010)*.
- Anabolic therapy with parathyroid hormone is indicated for patients with particularly high risk for future fracture, and data shows reduction in vertebral and non-vertebral fracture *(Strong Recommendation, High Quality Evidence) (Neer, 2011)*.

Consider the Following:

- Nasal calcitonin is now considered a third-line treatment for osteoporosis but may be useful in some populations for short-term therapy.
- SERM treatment with raloxifene in postmenopausal women has been shown to reduce vertebral fracture risk and is FDA approved for the prevention of breast cancer.

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- RANKL inhibitor, denosumab, has been shown to reduce the cumulative incidence of new vertebral and hip fractures in postmenopausal osteoporosis.
- Means to improve medication adherence, as poor adherence with osteoporosis medications is a large problem. Adherence is associated with significantly fewer fractures.

Please see the medication tables in Appendix C, "Recommended Pharmacologic Agents," for specific information on pharmacologic agents for treatment and prevention of osteoporosis.

Osteoporosis Prevention (also see Annotation #4, "Discuss Primary Prevention of Fractures") for Patients at High Risk

Estrogen

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 50 years of age) postmenopausal women taking estrogen in other doses, formulations or modes of administration.

Calcium and Vitamin D (See Annotation #4, "Discuss Primary Prevention of Fractures")

Bisphosphonates

Bisphosphonates are approved for prevention of postmenopausal women and glucocorticoid-induced osteoporosis. Bisphosphonates and calcitriol therapy may also be effective at preventing bone density loss after transplantation *(El-Agroudy, 2005 [Reference])*. Studies indicate that pharmocologic vitamin D preparations or intravenous bisphosphonates (pamidronate, zoledronic, etc.) or oral bisphosphonates (alendronate, risendronate, etc.) are more likely to prevent bone loss after transplantation than calcium and vitamin D with or without calcitonin. Bone mineral density testing should be performed every six months to one year until bone mineral density is shown to be stable or improving on therapies for osteoporosis (see Annotation #3, "Patient on or a History of Chronic Glucocorticoid Therapy or Transplant Recipient"). Bisphosphonate therapy should also be considered in men undergoing androgen deprivation therapy for the treatment of prostate cancer to prevent osteoporosis *(Serpa Neto, 2005 [Moderate Quality Evidence])*.

Raloxifene

Raloxifene is FDA-approved for the prevention of osteoporosis and prevention of breast cancer in postmenopausal women.

Posttransplantation Bone Loss

Antiresorptive therapy and calcitriol may be effective at preventing bone density loss after transplantation *(El-Agroudy, 2005 [Reference])*. Considering the rates of bone loss after transplantation described in Annotation #3, "Patient on or a History of Chronic Glucocorticoid Therapy or Transplant Recipient," bone mineral density testing should be performed every six months to one year until bone mineral density is shown to be stable or improving on therapies for osteoporosis. Studies demonstrate that standard calcium and vitamin D supplementation, with or without calcitonin, is not able to prevent bone loss after transplantation. Other studies indicate that pharmacologic vitamin D preparations or intravenous bisphosphonates, such as pamidronate, or zoledronic acid, or oral bisphosphonates, such as alendronate or risedronate, are more likely to prevent bone loss after transplantation.

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Osteoporosis Treatment

Bisphosphonates have the strongest data showing risk reductions in both vertebral, hip and other non-vertebral fractures. Other treatments include raloxifene (see SERM in this annotation) and calcitonin.

Parathyroid hormone 1-34 (teriparatide) (PTH) is used for patients at highest risk for fracture. It could be first-line therapy for those patients.

In addition to calcium, vitamin D, exercise, physical therapy, surgical repair and radiologic intervention as appropriate, the therapies listed below may be used. Clinicians should be aware that patient adherence to osteoporosis therapy has been historically poor.

Gonadal Hormone Therapy

Female gonadal hormone therapy

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

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 [Reference])*. 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 [Reference]; Torgerson, 2001 [Reference])*.

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, seems a reasonable first therapeutic intervention in men symptomatic with hypogonadism who do not have contra-indications to the use of testosterone therapy *(Behre, 1997 [Reference]; Katznelson, 1996 [Reference])*.

Bisphosphonates

Treatment and prevention of osteoporosis in postmenopausal women

Alendronate has been shown to increase bone mineral density and reduce the incidence of vertebral, hip and non-vertebral fractures in postmenopausal women having existing vertebral fractures, and those with low bone mineral density (approximately 2.1 SD below peak) compared to placebo (calcium and vitamin D). In the Fracture Intervention Trial (FIT) treatment with alendronate produced a 47% lower risk of new radiographic vertebral fractures ($p < 0.001$). Hip fracture relative hazard for alendronate versus placebo was 0.49 (0.23-0.99), and for the wrist it was 0.52 (0.31-0.87) *(Black, 1996 [Reference])*.

Risedronate 5 mg 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 [Reference]; Harris, 1999 [Reference])*.

Risedronate (enteric coated) is an enteric-coated version of risedronate combined with EDTA. It is FDA approved for the treatment of postmenopausal women with osteoporosis. The main advantage of the enteric-coated version is that fasting is not required. This feature may improve adherence. It is to be given in a 35 mg dose once weekly after breakfast. Calcium and PPIs should not be taken in close proximity to its use.

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Its pivotal BMD trial showed that it was "non-inferior" to risedronate immediate release 5 mg daily. The anti-fracture efficacy is thus assumed to be comparable to risedronate immediate release. The side effect profile and black box warnings are comparable to risedronate immediate release.

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 [Reference])*.

Daily and intermittent ibandronate has been shown to improve bone density 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 and 54% with intermittent dosing. Non-vertebral fractures were reduced only in a subpopulation with bone density 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 [Reference]; Miller, 2005 [Reference]; Chesnut, 2004 [Reference])*.

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

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. *(*See Appendix C, "Recommended Pharmacologic Agents.")

Zoledronate 5 mg IV infusion annually is FDA approved for the treatment of osteoporosis in postmenopausal women and for fracture prevention after a hip fracture. This agent improved BMD and decreased bone turnover markers for three years in the pivotal fracture trial *(Black, 2007 [Reference])*. In this trial of zoledronate 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-spinal 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 zoledronate group versus placebo *(Lyles, 2007 [Reference])*. Clinically, zoledronate is generally reserved for patients who cannot tolerate or have contraindication to oral bisphosphonates or if adherence is a major issue.

Duration of treatment

After five years of continuous use of a bisphosphonate, patients should be assessed for candidacy for a five-year "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 stopped. A secondary rationale is to decrease the rare occurrence of atypical fractures of the femoral shaft and the exceedingly rare occurrence of osteonecrosis of the jaw, both of which may be associated with prolonged use of bisphosphonates. The appropriateness of a "drug holiday" is more firmly established for alendronate per the FLEX trial, but had not been studied with other bisphosphonates. Some experts would consider it such a hiatus in therapy with other bisphosphonates. There is no expert agreement or data to support the theory as to if such a gap in therapy is appropriate, and, if so, in which patients. The FLEX trial *(Black, 2006 [Reference])* revealed no difference in non-vertebral or prevalent fractures for five years after stopping alendronate after five years vs. daily alendronate for 10 years. The incidence of clinical vertebral fractures was doubled to 5.5% in the placebo group; however, a patient with an increased or stable bone density on bisphosphonates and no history of prevalent fragility fracture(s) should certainly be considered for such an interruption in therapy. Those with a perceived high fracture risk (e.g., very low bone density or a history of fragility fracture[s], or other significant risk factors) would likely not be considered for such a hiatus in therapy. Bone density should be monitored during the

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"drug holiday" every two years if bone density can be done on the same machine at a center with adequate quality controls. A decrease in bone density or an intercurrent fracture would necessitate reinstitution of therapy. The FDA recommends reassessment of continuation of bisphosphonates after three to five years.

Treatment of osteoporosis in men

Currently approved therapies for the treatment of osteoporosis in men are alendronate, denosumab, risedronate, zoledronic acid and teriparatide.

Alendronate has been shown to increase bone mineral density at the spine, hip and total body and prevents vertebral fractures and in height loss in men with osteoporosis *(Orwoll, 2000 [Reference])*.

Clinical trial data support the use of alendronate for preventing bone loss in men diagnosed with osteoporosis.

Men who received risedronate 35 mg once a week for four years had a significant increase in lumbar spine bone mineral density and decrease in bone turnover markers. These effects were similar to the effects in women with a similar safety profile *(Boonen, 2012 [Moderate Quality Evidence])*. Once-yearly zoledronic acid 5 mg was as efficacious at increasing bone mineral density and lowering bone turnover markers as once-weekly alendronate 70 mg in men with low bone density. Both medications were similarly tolerated, though zoledornic acid was preferred *(Orwoll, 2010 [Reference])*.

Once-yearly intravenous zoledronic acid may be given to men and women within 90 days of a hip fracture *(Boonen, 2011 [Moderate Quality Evidence])*.

Treatment in men with zoledronic acid resulted in a 67% risk reduction of new vertebral fractures, as well as an increase in bone density and decrease in bone turnover markers *(Boonen, 2011 [Moderate Quality Evidence])*.

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, 2010 [Moderate Quality Evidence])*.

Denosumab has been shown to be efficacious in men undergoing androgen deprivation therapy for non-metastatic prostate cancer. It was associated with increased bone mineral density as well as a decrease in new vertebral fractures *(Smith, 2009 [Reference])*.

Treatment and prevention of glucocorticoid-induced osteoporosis

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

Risedronate has also been shown to increase bone mineral density in patients receiving glucocorticoid therapy. Treatment with risedronate 5 mg a day did have a trend of reduced fracture incidence *(Cohen, 1999 [Reference])*.

Clinical trial data supports the use of oral bisphosphonates for reducing bone loss in men and women diagnosed with glucocorticoid-induced bone loss.

Teriparatide is approved only for duration of two years. A gradual decrease in bone mass has been noted after discontinuation of teriparatide therapy; however, immediate follow-up therapy with a bisphosphonate has been shown to preserve the benefits *(Sambrook, 2007 [Reference]; Hodsman, 2005 [Reference])*.

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Posttransplantation

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 [Reference])* and zoledronate *(Yao, 2008 [Reference]; Crawford, 2006 [Reference])* may prevent bone loss after organ transplantation. A few small studies have evaluated oral bisphosphonate therapy in posttransplant patients *(Trabulus, 2008 [Reference]; Torregrosa, 2007 [Reference]; Yong, 2007 [Reference]; Maalouf, 2005 [Reference]; Shane, 2004 [Reference])*.

Bisphosphonates – Risks Associated with Use

Bisphosphonates and the risk of osteonecrosis of the jaw

Bisphosphonates are used and are effective in the treatment/management of cancer related conditions, including:

- Hypercalcemia of malignancy
- Skeletal related events associated with bone metastasis from breast, prostate and lung cancer
- Management of lytic lesions in multiple myeloma

There is circumstantial evidence establishing an association between IV bisphosphonates and bisphosphonate-related osteonecrosis of the jaw (BRONJ) in malignancy with the following observations:

- A positive correlation between bisphosonate potency and risk of BRONJ
- A negative correlation between bisphosphonate potency and duration of bisphosphonate exposure before development of BRONJ
- A positive correlation between the duration of bisphosphonate exposure and developing BRONJ

Causation has not been 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 [Reference])*.

American Association of Oral Maxillofacial Surgeons in the 2009 position paper has developed a working case definition of BRONJ that includes:

- Current or previous treatment with a bisphosphonate
- Exposed bone in the maxillofacial region that has persisted more than eight weeks
- No history of radiation treatment to the jaw

They note other conditions may be confused with BRONJ.

The risk of BRONJ is not clearly defined. IV bisphosphonate remains the major risk factor. 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%.

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AAOMS has refined the risk factors in their 2009 position paper, including:

- Drug-related risk factors
  - Bisphosonate potency
  - Duration of bisphosonate treatment
- Local risk factors
  - Dental alveolar surgery
  - Concomitant oral disease
  - Peridontal disease
- Demographic and systemic factors
- Genetic factors (in multiple myeloma)
- Preventive factors
  - IV bisphosonate dosing schedules may reduce incidence
  - Preventive dental interventions completed before initiating IV bisphosonate treatment

Treatment goals, staging and strategies for BRONJ are also noted in this source.

AAOMS notes discontinuing IV bisphosonate 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 bisphosonate therapy in patients with BRONJ is associated with gradual improvement. Again, if systemic conditions permit, decision-making is with consultation of the full treatment team.

Primary source: American Association of Oral and Maxillofacial Surgeon (AAOMS) Position Paper on Bisphosonate Related Osteonecrosis of the Jaw 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 [Reference])* 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 [Reference])*. Reanalysis of the Fracture Intervention Trial with alendronate and a retrospective review of risedronate data did not show an increased risk of atrial fibrillation *(Black 1996 [Reference]; Cummings, 2007 [Reference])*. Conflicting data is reported from two separate population-based case control studies from Seattle, WA *(Heckbert, 2008 [Reference])* and Denmark *(Sorenson, 2008 [Reference])*. 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. Patients who are currently on bisphosphonates are advised to continue their medication as prescribed and to direct any questions they have about their medication to their health care clinician.

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 [Reference])*.

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Bisphosphonates and risk of subtrochanteric fracture

Atypical femoral 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 femoral fracture. A large observational study showed increased rates of atypical femoral 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 [Reference])*. There was also a trend toward increased atypical fracture rates with longer duration of lendronate use. Thus, there is controversy as to whether the total culmulative dose of alendronate effect the risk of typical femoral fractures. Importantly, larger cumulative doses have been shown to significantly decrease hip and vertebral fractures, which are much more common than atypical femoral fractures, so there is a net reduction in fracture with bisphosphonate use *(Schilcher, 2011 [Reference])*.

Selective Estrogen Receptor Modulator (SERM)

The only SERM approved for the prevention and treatment of postmenopausal osteoporosis is 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. There was an increased risk of venous thromboembolism compared with placebo (RR 3.1, 95% CI 1.5-6.2) *(Ettinger, 1999 [Reference])*.

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 [Reference]; Siris, 2005 [Reference])*.

In the STAR trial *(Vogel, 2006 [Reference])*, 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 spinal fracture and there is an elevated risk of breast cancer.

Calcitonin

Treatment of osteoporosis in postmenopausal women

Nasal salmon-calcitonin 200 international units daily has shown a 33% risk reduction in new vertebral fractures compared with placebo (RR 0.67, 95% CI 0.47-0.97, p = 0.03). This occurred without significant effects on BMD. BMD measurements were not blinded to investigators, and 59% (744) of participants withdrew from the study early. Also, a dose response was not observed with respect to risk reduction of vertebral fractures *(Chesnut, 2000 [Reference])*. Other more efficacious agents have largely replaced the use of this agent except in rare clinical cases.

Posttransplantation

Several studies have shown that nasal spray calcitonin has little effect on prevention of bone loss after organ or bone marrow transplantation *(Välimäki, 1999a [Reference]; Välimäki, 1999b [Reference])*.

Anabolic Agents

Parathyroid hormone 1-34 (teriparatide)

Daily subcutaneous injections of recombinant human PTH 1-34 has been studied in both men and women, in combination with other agents and alone, and in glucocorticoid-induced osteoporosis and postmenopausal osteoporosis. It is universally effective at building bone and decreasing fractures, and its metabolic effects seem to continue even after discontinuation of the drug. PTH has been approved by the FDA for treatment of osteoporosis, but carries a black box warning about possible risk for osteosarcoma based on a rodent model *(Neer, 2001 [Reference])*.

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In a study of 83 men with osteoporosis, bone density was increased significantly more with teriparatide alone than with either teriparatide and alendronate or alendronate alone ($p<0.001$). Femoral neck bone density was also significantly greater using teriparatide than alendronate ($p<0.001$) or combination therapy ($p<0.01$) *(Finkelstein, 2003 [Reference])*.

Ongoing studies determining the cost effectiveness of teriparatide will be evaluated in the future.

RANK Ligand (RANKL) Inhibitor/Human Monoclonal Antibody

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 is administered SUBQ every six months by a health professional. In addition calcium 1,000 mg and at minimum 400 IU of vitamin D must be taken daily. The reduced frequency and supervised administration of denosumab may help improve patient adherence.

Pre-existing hypocalcemia and vitamin D deficiency must be corrected prior to initiating therapy.

In a study of 7,868 women between 60 and 90 years of age 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 were also lower in the denosumab group, with relative risk reductions of 40% and 20%, respectively *(Cummings, 2009 [Reference])*.

A preplanned analysis of results from the three-year, placebo-controlled Freedom trial were evaluated for the effect of denosumab administration on fracture-healing. Six hundred and sixty-seven postmenopausal female subjects aged 61 to 90 years of age 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 [Reference])*.

In a multicenter, double blind controlled trial, postmenopausal women were randomly assigned to either a subcutaneous every six month denosumab injection or a placebo for three years. The incidence of infections was similar in both groups. However, the incidence of serious adverse events of infections including skin (mainly cellulitis, erysipelas), gastrointestinal, renal, urinary, ear and endocarditis were numerically higher in the denosumab treated group, but the number of events were small. The infections in the denosumab group were not related to time or duration of exposure to denosumab, suggesting that the RANKL inhibition with denosumab does not influence infection risk. Clinicians should advise patients treated with denosumab about possible increased risk of infections *(Watts, 2012 [High Quality Evidence])*.

Strontium Ranelate (not currently available in the U.S.)

Strontium ranelate, a divalent cation-like calcium, is a novel anabolic agent for treatment of osteoporosis. The mechanism of action is felt to be a stimulation of bone formation related to an increase in osteoprogenitor cell replication and inhibition of bone resorption. The exact mechanism is unknown. Results of animal and human studies indicate this may be a useful, safe agent for osteoporosis. A double-blind, placebo-controlled trial in postmenopausal women with at least one vertebral fracture showed that 2 g of strontium ranelate daily for three years reduced new vertebral fractures 49% in the first year and 41% in three years (RR .59 [.48-.73]). Bone density increased 14.4% at the lumbar spine and 8.3% at the femur at three years *(Meunier, 2004 [Reference]; Rubin, 2003 [Reference]; Meunier, 2002 [Reference])*. All non-vertebral fractures were reduced 16% and hip fractures were reduced in women with a T-score of less than or equal to -2.4 *(Reginster,*

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2005 [Reference]). Another formulation of Strontium may be available in the U.S. but not in an adequate strength to be effective. The use of this product over-the-counter is not advised.

Calcitriol (1, 25-OH vitamin D)

Posttransplantation

Stempfle et al. randomized 132 patients (111 men, 21 women) with a mean age of 51 years ± 25 months after cardiac transplantation to receive elemental calcium 1,000 mg daily, hormone therapy (if hypogonadal), and calcitriol 0.25 mg daily, or calcium, hormone therapy, and placebo for 36 months.

They found that lumbar spine bone mineral density increased by 5.7% ± 4.4% in the calcitriol group and by 6.1% ± 7.8% in the placebo group over 36 months, without a statistical difference between the groups. Two percent of patients had incident fractures in the first year, 3.4% during the second year, and none the third year of the trial *(Stempfle, 1999 [Reference])*.

Combination Therapy

Estrogen and bisphosphonates

To date there have been no combination therapy studies that have shown a fracture benefit over and above a single-agent therapy versus single agent therapy. Therefore, it is unknown at this time whether combination therapy reduces the incidence of fractures *(Harris, 2001 [Reference]; Bone, 2000 [Reference]; Lindsay, 1999 [Reference])*. Combination therapy should be considered in cases of significant bone loss on a single antiresorptive agent once other causes of such bone loss have been eliminated or if the pretreatment fracture risk is quite high *(Johnell, 2002 [Reference])*.

Comparative Trials

Alendronate versus intranasal calcitonin

Alendronate 10 mg daily has been shown to significantly increase bone mineral density at the lumbar spine ($p<0.001$), femoral neck ($p<0.001$), and trochanter ($p<0.001$) compared with intranasal calcitonin 200 international units daily *(Downs, 2000 [Reference])*.

Alendronate versus risedronate

The FACT trial *(Rosen, 2005 [Reference])* is a two-year trial that randomized 1,053 postmenopausal women with low bone mass to either alendronate 70 mg/week or risedronate 35 mg/week with BMD change and changes in biochemical markers of bone turnover as the primary endpoints. The published data showed a significantly greater gain in BMD with alendronate than risendronate. Although both agents decreased bone turnover into the premenopausal range, alendronate decreased bone turnover significantly greater than risendronate. The GI tolerability was comparable, including a subgroup of patients with preexisting GI disorders. The clinical significance of this trial for fracture reduction differences between alendronate and risedronate is not known since it was not powered to measure fracture reduction differences between the two drugs *(Bonnick, 2006 [Reference])*.

Alendronate versus teriparatide

A 18-month study of anabolic therapy in patients receiving long-term glucocorticoids at high risk for fracture compared daily teriparatide 20 mcg injections to oral alendronate in 428 men and women. At study conclusion, teriparatide therapy was found to increase lumbar spine and total hip bone mineral density significantly more than alendronate ($P<0.001$). The study was not statistically powered to assess a reduction in the risk of vertebral fractures. However, there was a notable reduction in new vertebral fractures in those taking teriparatide versus alendronate (6.1% versus 0.6%). In patients with high risk of fracture secondary to long-term glucocorticoid therapy, teriparatide may be considered a therapeutic option *(Saag, 2007 [Reference])*.

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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, synthetic isoflavones such as ipriflavone, natural progesterone cream, magnesium, vitamin K and eicosopentanoic acid. There are very limited data from randomized controlled trials of these agents for prevention or treatment of osteoporosis. A multicenter, randomized trial of ipriflavone showed no significant effect on bone density or risk of vertebral fractures *(Alexandersen, 2001 [Reference])*.

Routine supplementation with the following agents has either not been 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. A small number of short-term trials in postmenopausal women treated with soy protein extracts have conflicting results *(Alekel, 2000 [Reference]; Horiuchi, 2000 [Reference]; Potter, 1998 [Reference])*.

Ipriflavone

Ipriflavone is a synthetic isoflavone derivative, currently available as a dietary supplement. It is not recommended for osteoporosis prevention or treatment *(Alexandersen, 2001 [Reference])*.

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 [Reference])*.

Magnesium

Some epidemiologic studies have correlated increasing levels of dietary magnesium with higher bone density. There are very few data available on the effects of magnesium supplementation in osteoporosis *(Stendig-Lindberg, 1993 [Reference])*.

Vitamin K

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 [Reference])*.

Eicosapentaenoic and gamma-linolenic acid supplementation

EPA (eicosapentaenoic acid) and GLA (gamma-linolenic acid) have beneficial effects on calcium absorption and bone mineralization in animal models *(Kruger, 1998 [Reference])*.

Kampo formulae

In China and Japan, kampo formulae (derived from plants) are used for the treatment of osteoporosis. Studies are underway to isolate their active components and characterize their biologic activity *(Li, 1998 [Reference])*.

Adherence to medications for bone loss

Adherence (compliance + persistence) 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 [Reference])*. The literature suggests

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that 45-50% of patients on one of these agents have stopped them within one year *(Cramer, 2005 [Reference])*. Adherence to therapy was associated with significantly fewer fractures at 24 months *(Siris, 2006 [Reference])*. 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 [Reference])*. Although not studied, a close relationship with a primary care clinician who thoroughly discusses the rationale, risks and benefits of treatment most likely improves adherence significantly, especially if followed up by a phone call or visit. Several studies support weekly bisphosphonate dosing versus daily, and/or monthly dosing versus weekly to improve compliance *(Cooper, 2006 [Reference]; Emkey, 2005 [Reference]; Recker, 2005 [Reference])*. It is important to include the patient in discussions related to their treatment options. Shared Decision-Making (SDM) is a model that facilitates these discussions. Please see Appendix D for more information on this model.

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 bone density 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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14. Follow-Up Testing (Lab Work and DXA if Indicated)

Sequential bone density testing using central DXA may be useful and is generally suggested in monitoring drug therapy for the treatment of osteopenia or osteoporosis *(Miller, 1999a [Reference])*. The utility follow-up bone densitometry depends on the quality control of the DXA center. There is a lack of evidence supporting the value of frequent repeat densitometry. It remains a controversial topic. At this point the work group suggests that such testing be considered no more than every 12-24 months. A frequency as often as every 6-12 months may be indicated 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*. The lumbar spine and the total proximal femur have the highest reproducibility and are the preferred sites for monitoring therapy *(Bonnick, 1998 [Reference])*. Changes in BMD should only be reported as significant if they exceed the "least significant change" for the DXA center *(Faulkner, 1999 [Reference]; Miller, 1999a [Reference]; Bonnick, 1998 [Reference])*. Stability or increase in BMD indicates successful therapy. A significant decline in BMD may require further investigation.

*Medicare provides coverage for bone densitometry with central DXA every two years to monitor osteoporosis therapy. http://www.medicare.com/services-and-procedures/preventative-screening/bone-mass-measurement.html.

An observational retrospective analysis of the Study of Osteoportic Fractures (SOP) *(Gourlay, 2012 [Reference])* suggested that in women over the age of 67, the currently accepted follow-up interval is far too frequent. Using age, femoral neck and total hip T score alone, it was calculated that the time for each increment of T score for 10% of the subjects to reach a T score of -2.5 (osteoporosis) would take 17 years (normal BMD to T score of -1.49); five years (T scores -1.5 to -1.99) and one year (T score -2 to -2.49). On average the older the woman, the shorter the duration to achieve a T score of <-2.5. 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®. The FRAX® score is probably a better indicator to determine the timing interval of bone density testing. In conclusion, it appears that the currently recommended follow-up bone density interval is too frequent, but that the intervals suggested in this trial may

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be too infrequent and the FRAX® score, if available, should be factored into the follow-up decision. The frequency should depend upon the anticipated rate of change.

A significant decrease in BMD on therapy may be due to:

- Poor drug adherence
- Improper medication administration technique in the case of bisphosphonates
- A missed secondary cause of osteoporosis (e.g., hyperparathyroidism, malabsorption)
- Inadequate calcium intake
- Untreated vitamin D deficiency
- A true treatment failure due to the drug itself
- Malabsorption of orally administered drugs

Further follow-up BMD testing after stability or improvement over three to four years has been demonstrated is recommended by most experts. 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 [Reference])*. Therapy should not be withheld if follow-up bone density testing is not available.

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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 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 female patients age 18 years and older who are evaluated for osteoporosis risk factors during an annual preventive visit.

   Measures for accomplishing this aim:

   a. Percentage of patients who were assessed for risk factors for osteoporosis during an annual preventive visit.

   b. Percentage of patients who were found to be at risk for bone loss or fractures who had bone densitometry.

   c. Percentage of patients with whom adequacy of vitamin D and calcium dietary supplementation were addressed.

2. Increase the percentage of female and male patients age 50 years and older and diagnosed with osteoporosis, who receive treatment for osteoporosis.

   Measure for accomplishing this aim:

   a. Percentage of patients diagnosed with osteoporosis who are on pharmacologic therapy.

3. Improve diagnostic and therapeutic follow-up for osteoporosis of adults presenting with a history of low-impact (fragility) fracture for men and women age 50 or older.

   Measures for accomplishing this aim:

   a. Percentage of patients with a history of low-impact (fragility) fracture who were assessed for osteoporosis.

   b. Percentage of patients with a history of low-impact (fragility) fracture assessed for secondary causes of osteoporosis.

   c. Percentage of patients with a history of low-impact (fragility) fracture and diagnosed with osteoporosis due to secondary causes offered treatment.

   d. Percentage of patients with a low-impact (fragility) fracture who are taking calcium and vitamin D dietary supplementation.

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Measurement Specifications

Measurement #1a

Percentage of patients who were assessed for risk factors for osteoporosis during an annual preventive visit.

Population Definition

Female patients age 18 years and older.

Data of Interest

$$\frac{\text{\# of patients assessed for risk factors for osteoporosis during an annual preventive visit}}{\text{\# patients with an annual preventive visit}}$$

Numerator and Denominator Definitions

Numerator: Number of patients age 18 years and older who were assessed for risk factors for osteoporosis during an annual preventive visit.

Denominator: Number of patients age 18 years 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 age 18 years and older who had a preventive care visit in the last 12 months. Determine the number of patients who were assessed for risk factors for osteoporosis during preventive care visit.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 who were found to be at risk for bone loss or fractures who had bone densitometry.

Population Definition

Female patients age 18 years and older.

Data of Interest

$$\frac{\text{\# of patients who had bone densitometry}}{\text{\# of patients with an annual preventive visit who were found to be at risk for bone loss or fractures}}$$

Numerator and Denominator Definitions

Numerator: Number of patients age 18 years and older who had bone densitometry done.

Denominator: Number of patients age 18 years and older with a preventive visit in the last 12 months and found to be at risk for bone loss or fractures.

Method/Source of Data Collection

Query electronic medical records for the total number of patients age 18 years and older who had a preventive care visit in the last 12 months. Determine the number of patients who were assessed for risk factors for osteoporosis during preventive care visit and were found to be at risk for bone loss or fractures. Determine the number of patients who had bone densitometry done in the same time period.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 #1c

Percentage of patients with whom adequacy of vitamin D and calcium dietary supplementation were addressed.

Population Definition

Female patients age 18 years and older.

Data of Interest

$$\frac{\text{\# of patients with whom adequacy of vitamin D and calcium dietary supplementation were addressed}}{\text{\# of patients with an annual preventive visit}}$$

Numerator and Denominator Definitions

Numerator: Number of patients with whom adequacy of vitamin D and calcium dietary supplementation were addressed.

Denominator: Number of patients age 18 years 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 age 18 years and older who had a preventive care visit in the last 12 months. Determine the number of patients with whom adequacy of vitamin D and calcium dietary supplementation were addressed.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 #2a

Percentage of patients diagnosed with osteoporosis who are on pharmacologic therapy.

Population Definition

Patients age 50 years and older with a diagnosis of osteoporosis.

Data of Interest

$$\frac{\text{\# of patients who are on pharmacologic therapy}}{\text{\# of patients with a diagnosis of osteoporosis}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who are on pharmacologic therapy.

Denominator: Number of patients age 50 years and older with a diagnosis of osteoporosis.

Method/Source of Data Collection

Query electronic medical records for the total number of patients age 50 years and older who have a diagnosis of osteoporosis. Determine the number of patients who are on pharmacologic therapy.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 #3a

Percentage of patients with a history of low-impact (fragility) fracture who were assessed for osteoporosis.

Population Definition

Patients age 50 years and older.

Data of Interest

$$\frac{\text{\# of patients who were assessed for osteoporosis}}{\text{\# of patients with a history of low-impact (fragility) fracture}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who were assessed for osteoporosis.

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

Method/Source of Data Collection

Query electronic medical records for the total number of patients age 50 years and older who have a history of low-impact (fragility) fracture Determine the number of patients who were assessed for osteoporosis.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 #3b

Percentage of patients with a history of low-impact (fragility) fracture assessed for secondary causes of osteoporosis.

Population Definition

Patients age 50 years and older.

Data of Interest

$$\frac{\text{\# of patients assessed for secondary causes of osteoporosis}}{\text{\# of patients with a history of low-impact (fragility) fracture}}$$

Numerator and Denominator Definitions

Numerator: Number of patients assessed for secondary causes of osteoporosis.

Denominator: Number of patients age 50 years 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 age 50 years and older who have a history of low-impact (fragility) fracture. Determine the number of patients who were assessed for secondary causes of osteoporosis.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 #3c

Percentage of patients with a history of low-impact (fragility) fracture and diagnosed with osteoporosis due to secondary causes offered treatment.

Population Definition

Patients age 50 years and older.

Data of Interest

$$\frac{\text{\# of patients diagnosed with osteoporosis due to secondary causes offered treatment}}{\text{\# of patients with a history of low-impact (fragility) fracture}}$$

Numerator and Denominator Definitions

Numerator: Number of patients diagnosed with osteoporosis due to secondary causes offered treatment.

Denominator: Number of patients age 50 years 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 age 50 years and older who have a history of low-impact (fragility) fracture. Determine the number of patients who were diagnosed with osteoporosis due to secondary causes offered treatment.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 #3d

Percentage of patients with a low-impact (fragility) fracture who are taking calcium and vitamin D dietary supplementation.

Population Definition

Patients age 50 years and older.

Data of Interest

$$\frac{\text{\# of patients who are taking calcium and vitamin D dietary supplementation}}{\text{\# of patients with a low-impact (fragility) fracture}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who are taking calcium and vitamin D dietary supplementation.

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

Method/Source of Data Collection

Query electronic medical records for the total number of patients age 50 years and older who have a low-impact (fragility) fracture. Determine the number of patients who are taking calcium and vitamin D dietary supplementation.

Time Frame Pertaining to Data Collection

Monthly, quarterly, semi-annually or annually. 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 when appropriate 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
Agency for Healthcare Research and Quality	Osteoporosis decision support tools for patients.	Public and professionals	http://www.effectivehealthcare.ahrq.gov/ehc/desicionaids/osteoporosis/
American Academy of Orthopedic Surgeons	Professional organization site; osteoporosis informed.	Professionals and public	http://www.aaos.org
American College of Rheumatology	Professional organization site; patient education material.	Professionals	http://www.rheumatology.org/practice/clinical/patients/diseases_and_conditions/osteoporosis.asp
Bonnick, Sydney, MD	Osteoporosis Handbook (2000); book on prevention and treatment of osteoporosis.	Public	Taylor Publishing
Foundation for Osteoporosis Research and Education	Current information about osteoporosis and research.	Public and professionals	http://www.fore.org
International Osteoporosis Foundation	International organization site.	Public and professionals	http://www.osteofound.org
International Society of Clinical Densitometry	Professional organization site.	Public and professionals	http://www.iscd.org
Lane, Nancy E., MD	The Osteoporosis Book (1999); book on prevention and treatment of osteoporosis.	Public and professionals	Oxford University Press
Mayo Clinic Health Solution, Rochester, MN	Mayo Clinic Guide to Preventing & Treating Osteoporosis (2008); book covering topics related to osteoporosis.	Public and Professionals	http://www.bookstore.mayoclinic.com
Mayo Health Oasis Women's Health Resource	Women's health information.	Public	http://www.mayoclinic.com
National Osteoporosis Foundation	Web site has general information about osteoporosis prevention and treatment By calling organization this educational information can be ordered: - Be BoneWise™ Exercise; Video on weight-bearing and strength-training exercises -Boning Up on Osteoporosis -The Male Frame: A practical guide to men's bone health	Public and professionals	http://www.nof.org Phone: 202/223-2226

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Implementation Tools and Resources Table

Author/Organization	Title/Description	Audience	Web sites/Order Information
NIH – Osteoporosis and Related Bone Diseases Resources Center	Current information about osteoporosis and research.	Public and professionals	http://www.osteo.org or http://www.niams.nih.gov/Health_info/bone/
North American Menopause Society	Professional organization site with menopause-related topics.	Public and professionals	http://www.menopause.org
North American Menopause Society	Professional journal.	Professionals	http://www.menopausejournal.com
United States Department of Agriculture	USDA Table of Nutrient Retention Factors (Release 6); table with list of foods and nutrient breakdown.	Professionals and public	http://www.ars.usda.gov/nutrientdata
United States Department of Human Services	Surgeon General's report on Bone Health and Osteoporosis (2004).	Professionals and public	http://www.surgeongeneral.gov/library/reports/bonehealth/ (click on full report)

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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.

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
- **L-thyroxine overreplacement**

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- 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
- Hemochromatosis

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- 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 – Densitometry

Universal bone densitometry screening of women age 65 and older and men age 70 and older is now recommended by nearly all specialty societies that have constructed guidelines for the diagnosis and management of osteoporosis, including the United States Preventive Services Task Force *(National Osteoporosis Foundation, 2011 [Moderate Quality Evidence]; U.S. Preventive Services Task Force, 2002 [Reference])*. Moreover, universal screening with bone densitometry followed by treatment of those diagnosed with osteoporosis was found in one study to be cost effective for women age 65. It becomes more cost effective as women age into their 80s and 90s *(Schousboe, 2005a [Reference])*.

There are numerous techniques currently available to assess BMD in addition to densitometry with 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 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.
- **Quantitative ultrasound densitometry (QUS) –** 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 65 and older (hip and non-vertebral fractures). QUS is not associated with any radiation exposure.

(Baim, 2008 [Reference])

The International Society of Clinical Densitometry (ISCD) was formed in 1993 to ensure uniformity in the interpretation of bone mineral density tests. ISCD certification has become the standard of care for physicians interpreting bone mineral density tests and technologists performing the exam. Bone densitometry should not be performed by individuals without ISCD and American Registry of Radiologic Technologists (ARRT) certification. Uniformity in interpretation of densitometry results will improve patient care. The Web address for ISCD is http://www.iscd.org.

Limitations of Densitometry

BMD represents a continuous variable. There is overlap in BMD values between individuals with and without fragility fractures. DXA BMD measures areal bone density. This introduces potential size artifacts, whereby smaller individuals will have a lower areal bone density value than larger individuals. Thus, fracture risk is multifactorial and not solely defined by areal BMD. Computerized tomography (CT) is the only measure of volumetric bone density.

A calculated volumetric BMD, bone mineral apparent density (BMAD), can be done on DXA scans of adults with particularly short stature (less than five feet tall) using the bone mineral content and bone area. A calculation tool can be found at http://courses.washington.edu/bonephys/opBMAD.html.

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The three manufacturers of dual x-ray absorptiometry (DXA) densitometers have published equations to convert manufacturer-specific units to standardized, non-manufacturer specific units. Formulas are available for both spine BMD and femur BMD. Using these formulas, standardized BMD (sBMD) values obtained by scanning a patient on any one of these instruments should fall within 2-5% (spine) or 3-6% (total femur) of each other. sBMD use and incorporation of NHANES III BMD data into all machines will help decrease the limitations of T-score use *(Steiger, 2000 [Reference]; Hanson, 1997 [Reference]; Looker, 1997 [Reference])*.

Vertebral Fracture Assessment (VFA)

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 (see the ISCD position statement when available in 2013). The following are reasonable indications for a VFA at the time a bone density test is done:

Postmenopausal women with low bone mass by BMD criteria, PLUS any one of the following:

- Age 70 years or more
- Historical height loss (current height compared to recalled height as young adult) greater than 4 cm (1.6 inches)
- Prospective height loss (current height compared to a previous measured height) greater than 2 cm (0.8 inches)
- Self-reported prior vertebral fracture (not previously documented)
- Two or more of the following:
  - Age 60 to 69
  - Historical height loss of 2 to 4 cm
  - Self-reported prior non-vertebral fracture
  - Chronic disease associated with increased risk of vertebral fracture (COPD, rheumatoid arthritis, Crohn's disease)

Men with low bone mass by BMD criteria PLUS any one of the following:

- Age 80 years or more
- Historical height loss (current height compared to recalled height as young adult) greater than 6 cm (2.4 inches)
- Prospective height loss (current height compared to a previous measured height) greater than 3 cm (1.2 inches)
- Self-reported prior vertebral fracture (not previously documented)
- Two or more of the following:
  - Age 70 to 79
  - Historical height loss of 3 to 6 cm
  - Self-reported prior non-vertebral fracture
  - Chronic disease independently associated with vertebral fracture

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- On androgen deprivation therapy or status postorchiectomy

Men or postmenopausal women with osteoporosis by BMD criteria for whom documentation of one or more prevalent vertebral fractures would alter clinical management

Women or men with chronic systemic glucocorticoid therapy (prednisone 5.0 mg or more per day for three or more months, or equivalent)

(International Society for Clinical Densitometry, 2007 [Reference])

The advantages of VFA versus standard spine x-rays are convenience, lower cost and markedly lower radiation exposure.

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Appendix C – Recommended Pharmacologic Agents

Medication	Indications	Reduction in Fracture Risk[2]	Adverse Drug Reactions[1]	Contraindications
Bisphosphonates				
Alendronate	**TREATMENT** • Postmenopausal osteoporosis • Increase bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women **PREVENTION** • Postmenopausal osteoporosis	Vertebral: +++ Non-vertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia, flu-like symptoms (rare postmarket experience) • Atypical fracture of the thigh	• Abnormalities of the esophagus that delay esophageal emptying • Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with CrCl ≤ 35 ml/min
Ibandronate	**TREATMENT** • Postmenopausal osteoporosis **PREVENTION** • Postmenopausal osteoporosis	Vertebral: +++ Non-vertebral: + Hip: -	• Esophagitis, abdominal pain, diarrhea • Influenza-like illness, jaw osteonecrosis (rare) musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia • Atypical fracture of the thigh	• Uncorrected hypocalcemia • Inability to stand or sit upright at least 60 minutes • Hypersensitivity • Not recommended for patients with CrCl ≤ 30 ml/min
Risedronate	**TREATMENT** • Postmenopausal osteoporosis • Glucocorticoid-induced osteoporosis • Increase bone mass in men with osteoporosis **PREVENTION** • Postmenopausal osteoporosis • Glucocorticoid-induced osteoporosis	Vertebral: +++ Non-vertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia • Atypical fracture of the thigh	• Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with CrCl ≤ 30 ml/min
Risedronate delayed release	**TREATMENT** • Postmenopausal osteoporosis	Vertebral: +++ Non-vertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia • Atypical fracture of the thigh	• Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with CrCl ≤ 30 ml/min
Zoledronic acid	**TREATMENT** • Postmenopausal osteoporosis • Paget's disease	Vertebral: +++ Non-vertebral: ++ Hip: ++	• Acute phase reaction: fever, flu-like symptoms, HA, arthralgia/myalgia • Jaw osteonecrosis (rare), transient increase in creatinine, atrial fibrillation, hypocalcemia • Atypical fracture of the thigh	• Hypersensitivity to zoledronic acid or any of its excipients • Uncorrected hypocalcemia • Not recommended in patients with a creatinine clearance less than 35 mL/min

1. Based on patient specific data
2. +++ >50% reduction; ++ 40-50% reduction; + <40% reduction; - Unable to show reduced risk; N/A No data available from RCT

Note: This data comes from pharmaceutical-sponsored trials and are not head-to-head comparisons.

* Approved for breast cancer prevention in postmenopausal women with osteoporosis

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Appendix C – Recommended Pharmacologic Agents

Medication	Indications	Reduction in Fracture Risk[2]	Adverse Drug Reactions[1]	Contraindications
Selective Estrogen Receptor Modulator (SERM)				
Raloxifene (Evista®)*	**TREATMENT** • Postmenopausal osteoporosis **PREVENTION** • Postmenopausal osteoporosis • Breast cancer	Vertebral: +++ women without fx ++ women with fx Non-vertebral: - Hip: -	• Hot flashes • Leg cramps • Increased risk of venous thromboembolic events	• Pregnancy • History of venous thromboembolism • Hypersensitivity • Nursing women
Parathyroid Hormone (PTH)				
Teriparatide	**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 • Increase 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)	Vertebral: +++ Non-vertebral: +++ Hip: N/A	**BLACK BOX WARNING:** shown to cause an increase in the incidence of osteosarcoma in male and female rats, dependant on dose and duration of treatment. • Orthostatic hypotension • Increase in serum calcium • Increase in urinary calcium • Increase in serum uric acid	• 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
Calcitonin				
Calcitonin-salmon (Miacalcin® and Fortical® nasal spray)	**TREATMENT** • Postmenopausal osteoporosis in women with at least five years postmenopause with low bone masss relative to healthy premenopausal females	Vertebral: + Non-vertebral: - Hip: -	• Nausea • Flushing • Rhinitis with nasal spray	• Hypersensitivity

1. Based on patient specific data
2. +++ >50% reduction; ++ 40-50% reduction; + <40% reduction; - Unable to show reduced risk; N/A No data available from RCT

Note: This data comes from pharmaceutical-sponsored trials and are not head-to-head comparisons.

* Approved for breast cancer prevention in postmenopausal women with osteoporosis

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Appendix C – Recommended Pharmacologic Agents

Medication	Indications	Reduction in Fracture Risk[2]	Adverse Drug Reactions[1]	Contraindications
Estrogens				
Estrogens	**PREVENTION** • Postmenopausal osteoporosis	Vertebral: +++ Non-vertebral: ++ Hip: +++	• Bloating • Breast tenderness • Uterine bleeding • Those with an intact uterus must also take a progestin to prevent endometrial cancer • Breast cancer • Increased risk of myocardial infarction, stroke, venous thrombosis or pulmonary embolism • Comments: Dementia, gall bladder disease, hypercalcemia, visual abnormalities hypertension are also mentioned	• Pregnancy • History of thromboembolic disorders • Breast cancer (except appropriately selected patients treated for metastatic disease) • Estrogen dependent neoplasia • Undiagnosed abnormal vaginal bleeding • Hypersensitivity • Liver dysfunction or disease, active or recent (within one year) • Stroke or MI
RANK ligand (RANKL) inhibitor				
Denosumab	**TREATMENT** • Postmenopausal osteoporosis with high risk of fracture	Vertebral: +++ Non-vertebral: + Hip: ++	• Pain (back, extremity and musculoskeletal) • Hypertriglyceridemia • Cystitis • Infectious disease • Rash • Hypocalcemia • Aseptic necrosis of jaw (rare) • Atypical femoral fracture	• Uncorrected pre-existing hypocalcemia

1. Based on patient specific data
2. +++ >50% reduction; ++ 40-50% reduction; + <40% reduction; - Unable to show reduced risk; N/A No data available from RCT

Note: This data comes from pharmaceutical-sponsored trials and are not head-to-head comparisons.

* Approved for breast cancer prevention in postmenopausal women with osteoporosis

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Pharmacologic Bone Active Agents Non-FDA Approved for Osteoporosis

Medication	Comments
Bisphosphonates	
Etidronate	Low oral absorption. Inconvenient dosing cycle but is the least expensive bisphosphonate.
Pamidronate	Available only as an intravenous dosage form*.
Zoledronic acid	A potent bisphosphonate indicated for hypercalcemia of malignancy*.
Others	
Calcitriol	Insufficient data. Most often used in renal failure and renal osteodystrophy.
Cholecalciferol	Insufficient data to assess effectiveness as monotherapy.
Ergocalciferol	Insufficient data to assess effectiveness as monotherapy.
Nandrolene deconoate	Insufficient data. Adverse effects would limit use.
Sodium fluoride	Mixed results from clinical trials. Monotherapy may cause osteomalacia or other bone abnormalities.
Tamoxifen	Insufficient data. Increases bone mineral density. Adverse effects would limit use in general population.
Testosterone (various products available)	To treat underlying condition of hypogonadism in men.
Tibolone	A synthetic agent with progestogenic, estrogenic and androgenic activity. Not yet an FDA-approved product.
Strontium ranelate	Increases BMD and reduces fractures. Not yet available in U.S. in appropriate strength.

* Intravenous bisphosphonates have been associated with osteonecrosis of the jaw following dental extraction. Most reported cases have been in cancer patients *(Woo, 2006 [M])*.

Appendix D – ICSI Shared Decision-Making

ICSI Institute for Clinical Systems Improvement

The technical aspects of Shared Decision-Making are widely discussed and understood.

- **Decisional conflict** occurs when a patient is presented with options where no single option satisfies all the patient's objectives, where there is an inherent difficulty in making a decision, or where external influencers act to make the choice more difficult.
- **Decision support** clarifies the decision that needs to be made, clarifies the patient's values and preferences, provides facts and probabilities, guides the deliberation and communication and monitors the progress.
- **Decision aids** are evidence-based tools that outline the benefits, harms, probabilities and scientific uncertainties of specific health care options available to the patient.

However, before decision support and decision aids can be most advantageously utilized, a Collaborative Conversation™ should be undertaken between the provider and the patient to provide a supportive framework for Shared Decision-Making.

Collaborative Conversation™

A collaborative approach toward decision-making is a fundamental tenet of Shared Decision-Making (SDM). The Collaborative Conversation™ is an inter-professional 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 both the patient and the provider play key roles in the decision-making process. The patient knows which course of action is most consistent with his/her values and preferences, and the provider contributes knowledge of medical evidence and best practices. Use of Collaborative Conversation™ elements and tools is even more necessary to support patient, care provider and team relationships when patients and families are dealing with high stakes or highly charged issues, such as diagnosis of a life-limiting illness.

The overall framework 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. A rote script or a 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 involved in making a decision: cognitive, affective, social and spiritual.

Key communication skills help build the Collaborative Conversation™ approach. These skills include many elements, but in this appendix only the questioning skills will be described. (For complete instruction, see 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?, uh huh,"* or by repeating the last thing a person said, "*It's confusing*."

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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 provider should use his/her own words rather than just parroting what he/she heard.

Reflection of feelings usually can be done effectively once trust has been established. Until the provider 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 provider understands the patient's feelings and may work as a catalyst for further problem solving. For example, the provider identifies what the person is feeling and responds back in his/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 provider 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 situations 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 provider accurately understands a patient or family member, and may be used as a summary or reflection. They are used to verify that the provider is interpreting the message correctly. The provider can say *"So you are saying that you're not ready to make a decision at this time. Am I understanding you correctly?"*

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 provider 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 provider to supplement the patient's 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 provider.

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 provider's view of the patient's reaction. For instance, the provider can say, *"You seem to understand the facts and value your daughter's advice."*

Additional Communication Components

Other elements that can impact the effectiveness of a Collaborative Conversation™ include:

- Eye contact
- Body language consistent with message
- Respect

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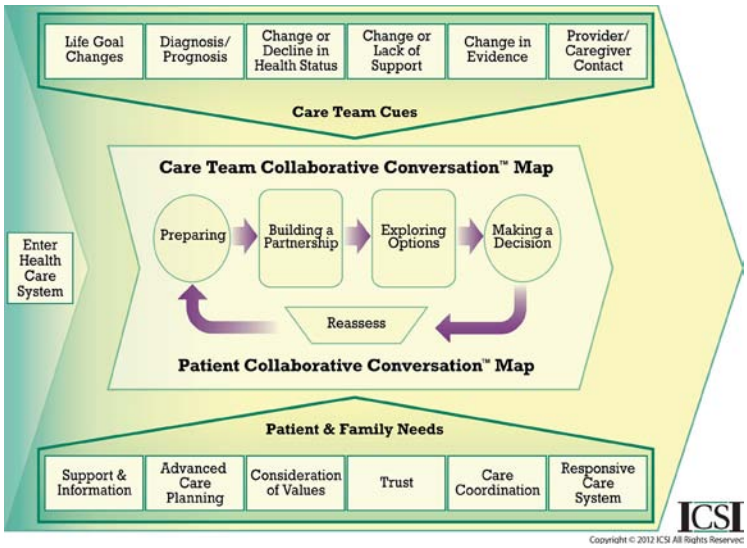
- Empathy
- Partnerships

Self-examination by the provider involved in the Collaborative Conversation™ can be instructive. Some questions to ask oneself include:

- Do I have a clear understanding of the likely outcomes?
- Do I fully understand the patient's values?
- Have I framed the options in comprehensible ways?
- Have I helped the decision-makers recognize that preferences may change over time?
- Am I willing and able to assist the patient in reaching a decision based on his/her values, even when his/her values and ultimate decision may differ from my values and decisions in similar circumstances?

When to Initiate a Collaborative Conversation™

A Collaborative Conversation™ can support decisions that vary widely in complexity. It can range from a straightforward discussion concerning routine immunizations to the morass of navigating care for a life-limiting illness. Table 1 represents one health care event. This event can be simple like a 12 year-old coming to the clinic for routine immunizations, or something much more complex like an individual receiving a diagnosis of congestive heart failure. In either case, the event is the catalyst that starts the process represented in this table. There are cues for providers and patient needs that exert influence on this process. They are described below. The heart of the process is the Collaborative Conversation™. The time the patient spends within this health care event will vary according to the decision complexity and the patient's readiness to make a decision.



Regardless of the decision complexity there are cues applicable to all situations that indicate an opportune time for a Collaborative Conversation™. These cues can occur singularly or in conjunction with other cues.

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, or caregiver status, change in financial standing, difference between patient and family wishes.
- **Change in medical evidence or interpretation of medical evidence:** Providers can clarify the change and help the patient understand its impact.
- **Provider/caregiver contact:** Each contact between the provider/caregiver and the patient presents an opportunity to reaffirm with the patient that his/her care plan and the care the patient is receiving are consistent with his/her values.

Patients and families have a role to play as decision-making partners, as well. The needs and influencers brought to the process by patients and families impact the decision-making process. These are described below.

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 and/or exhibiting behavior such as wavering, delay, preoccupation, distress or tension. Generational and cultural influencers may act to inhibit the patient from actively participating in care discussions, often patients need to be given "permission" to participate as partners in making decisions about his/her care.

  Support resources may include health care professionals, family, friends, support groups, clergy and social workers. When the patient expresses a need for information regarding options and his/her potential outcomes, the patient should understand the key facts about 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.
- **Consideration of Values:** The personal importance a patient assigns potential outcomes must be respected. If the patient is unclear how to prioritize the preferences, value clarification can be achieved through a Collaborative Conversation™ and by the use of decision aids that detail the benefits and harms of potential outcomes in terms the patient can understand.
- **Trust:** The patient must feel confident that his/her preferences will be communicated 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. Furthermore, the care delivery system must be able to provide 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/she receives throughout the care continuum.

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 providers and patients as shown in Table 2.

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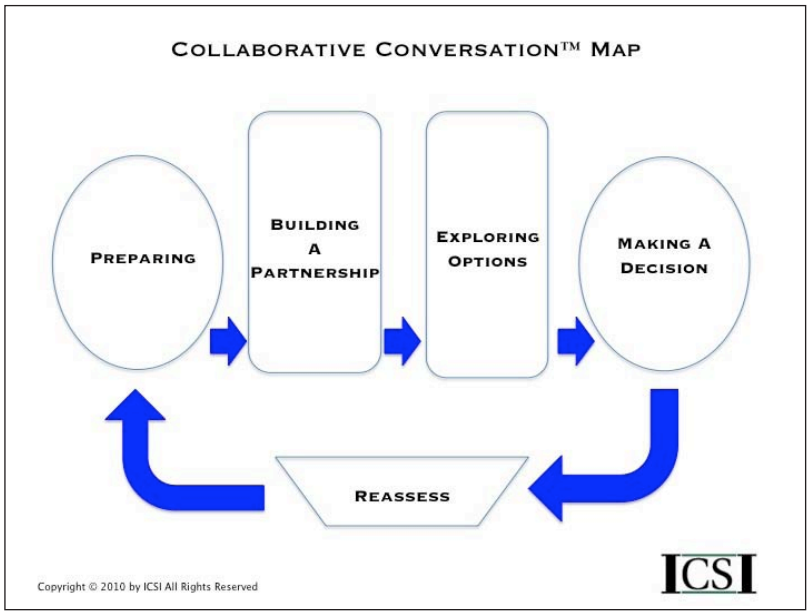
Providers use the map as a clinical workflow. It helps get the Shared Decision-Making process initiated and provides navigation for the process. Care teams can used the Collaborative Conversation™ to document team best practices and to formalize a common lexicon. Organizations can build fields from the 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.



Evaluating the Decision Quality

Adapted from O'Connor, Jacobsen "Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting Their Health" [2007].

When the patient and family understand the key facts about the condition and his/her options, a good decision can be made. Additionally, the patient should have realistic expectations about the probable benefits and harms. A good indicator of the decision quality is whether or not the patient follows through with his/her chosen option. There may be implications of the decision on patient's emotional state such as regret or blame, and there may be utilization consequences.

Decision quality can be determined by the extent to which the patient's chosen option best matches his/her values and preferences as revealed through the Collaborative Conversation™ process.

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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 five sponsoring health plans in Minnesota and Wisconsin. 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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All ICSI documents are available for review during the revision process by member medical groups and sponsors. In addition, all members commit to reviewing specific documents each year. This comprehensive review provides information to the work group for such issues as content update, improving clarity of recommendations, implementation suggestions and more. The specific reviewer comments and the work group responses are available to ICSI members at http://Osteoporosis.

The ICSI Patient Advisory Council meets regularly to respond to any scientific document review requests put forth by ICSI facilitators and work groups. Patient advisors who serve on the council consistently share their experiences and perspectives in either a comprehensive or partial review of a document, and engaging in discussion and answering questions. In alignment with the Institute of Medicine's triple aims, ICSI and its member groups are committed to improving the patient experience when developing health care recommendations.

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Acknowledgements

ICSI Patient Advisory Council

The work group would like to acknowledge the work done by the ICSI Patient Advisory Council in reviewing the Diagnosis and Treatment of Osteoporosis and thank them for their suggestion(s) to improve the language and add content for Shared Decision-Making.

Invited Reviewers

During this revision, the following groups reviewed this document. The work group would like to thank them for their comments and feedback.

HealthPartners Health Plan, Bloomington, MN
Mayo Clinic, Rochester, MN
North Clinic, Robbinsdale, MN

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Document History

- Refer to the Evidence Grading section for information about the GRADE system that was adopted in 2011.

Released in July 2013 for Eighth Edition.
The next scheduled revision will occur within 24 months.

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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, implementation strategies and barriers to implementation. 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 every 12-24 months as indicated by changes in clinical practice and literature. ICSI staff monitors major peer-reviewed journals every month for the guidelines for which they are responsible. Work group members are also asked to provide any pertinent literature through check-ins with the work group midcycle and annually to determine if there have been changes in the evidence significant enough to warrant document revision earlier than scheduled. This process complements the exhaustive literature search that is done on the subject prior to development of the first version of a guideline.

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