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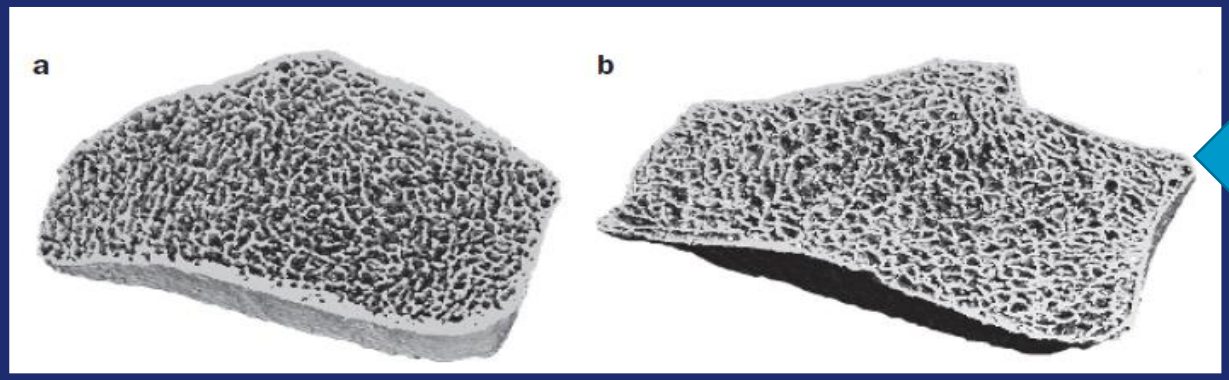
# Osteoporosis

# Outline

- Definition and demographics
- Risk factors
- Diagnosis
- Treatment options

# Definition of Osteoporosis

- Osteoporosis is:
  - A systemic skeletal disease
  - Defined by low bone mass and structural damage to bone tissue
  - Leads to increased bone fragility and high fracture risk
  - Three most common sites for fragility fractures are the hip, spine and wrist




Osteoporotic bone

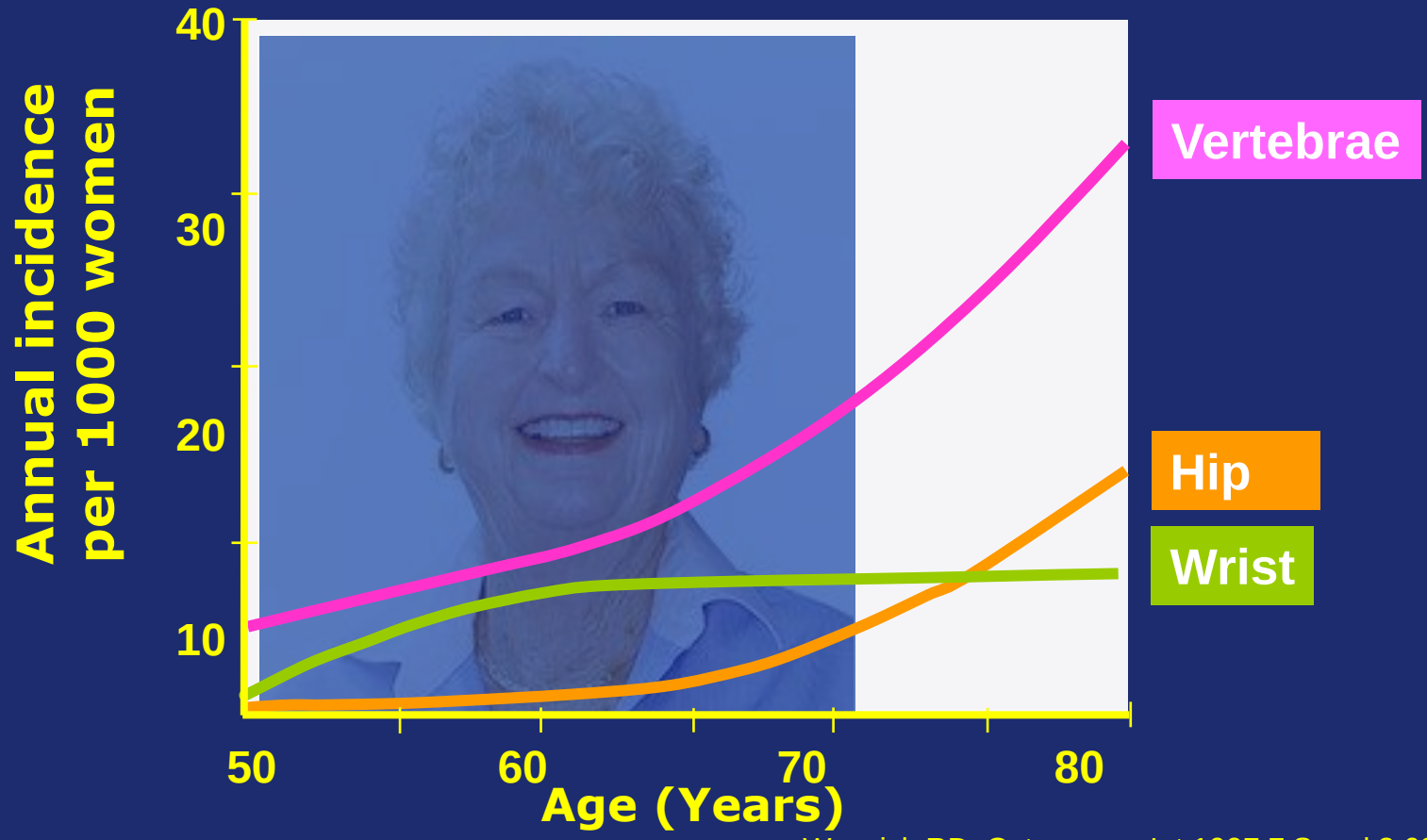
*Walsh, 2014*

*Ignatius, Anita, and Jan Tuckermann. "New horizons for osteoanabolic treatment?." **Nature Reviews Endocrinology14.9 (2018**): 508.*

# Definition of Osteoporosis

- Diagnosed on basis of either a health outcome (low-impact or fragility fracture) or an intermediate outcome (low bone mineral density—BMD)
- Low-impact fracture: one that occurs after a fall from standing height or less
- Fragility fracture: occurs spontaneously or with no trauma (cough, sneeze, sudden movement)

# Incidence of Osteoporotic Fractures in Women




Wasnich RD, Osteoporos Int 1997;7 Suppl 3:68-72

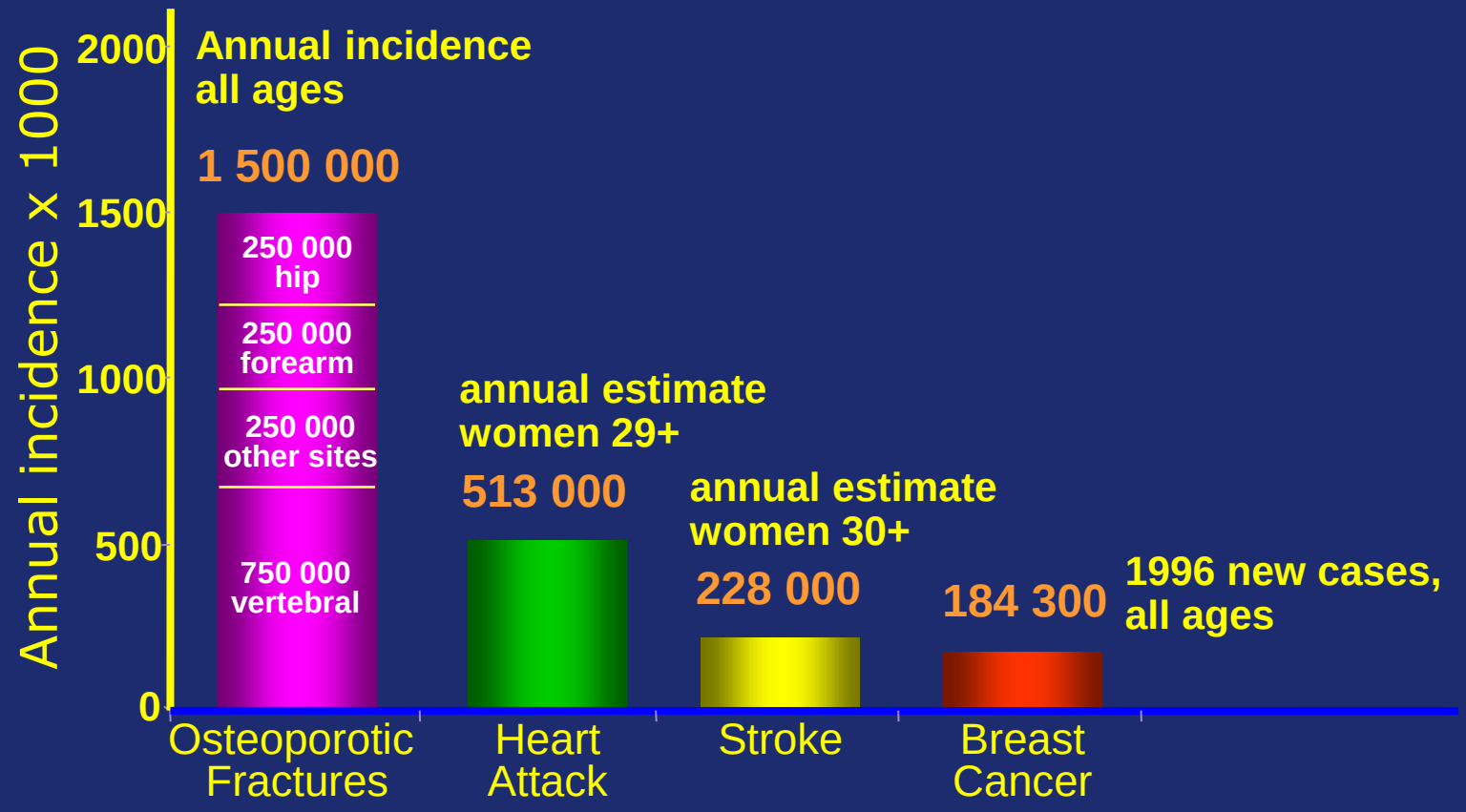
# Incidence of Osteoporosis

- Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds.

- Osteoporosis (diagnosed and undiagnosed) is estimated to affect 200 million women worldwide, approximately:
  - One-tenth of women aged 60
  - One-fifth of women aged 70
  - Two-fifths of women aged 80
  - Two-thirds of women aged 90

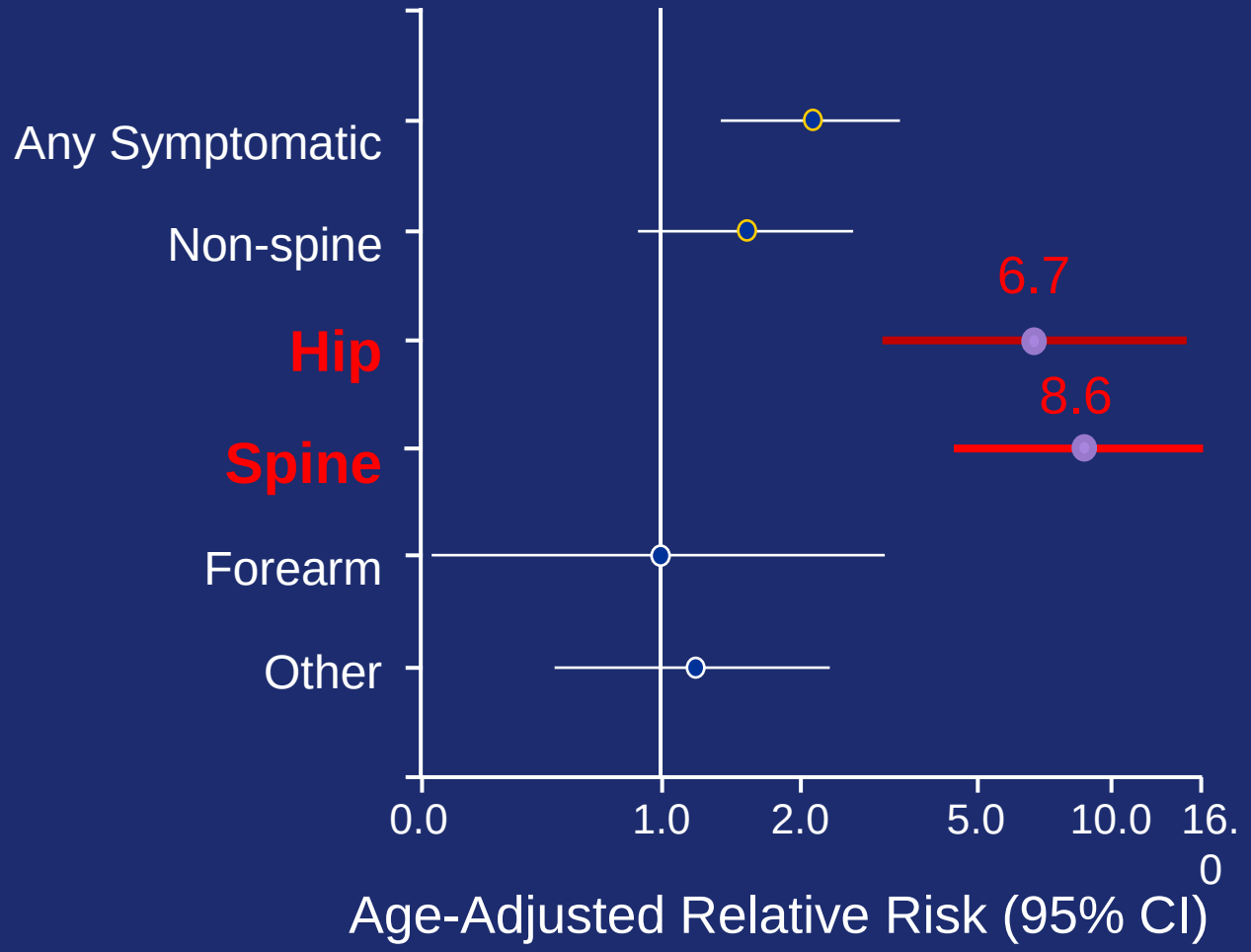
***Larijani B**, Tehrani MM, Hamidi Z, Soltani A, Pajouhi M. Osteoporosis, global and Iranian aspects. Iranian Journal of Public Health. 2004:1-7.*

# Osteoporotic Fractures: Comparison with Other Diseases




American Heart Association,1996
American Cancer Society,1996
Riggs BL & Melton LJ 3rd, Bone, 1995;17(5 suppl):505S-511S

# Mortality Following Clinical Fractures Fracture Intervention Trial




Cauley JA, et al. *Osteoporos Int*. 2000;11:556-561

*6459 postmenopausal women ages 55-81 years,followed for an average of 3.8 years

# Risk Factors for Osteoporosis and Related Fractures

## Major Risk Factors

- **Personal history of fracture as an adult**
- **History of fragility fracture in first degree relative**
- **Low body weight (<127 lbs)**
- **Current history of smoking**
- **Use of oral corticosteroids for more than 3 months**

**Additional Risk Factors**

- **Impaired vision**
- **Estrogen deficiency**
- **Poor health/ fragility**
- **Recent falls**
- **Low calcium intake (lifelong)**
- **Low physical activity**
- **Excessive use of alcohol (more than 2 drinks/ day)**

National Osteoporosis Foundation. Available at http://www.nof.org/physguide.

# Osteoporosis Guideline Recommendations for Screening

## AACE Guidelines[1]

- Evaluate all postmenopausal women aged ≥50 yr for osteoporosis risk
- Obtain a detailed history, physical exam, and clinical fracture risk assessment with FRAX® or other tool
- Consider BMD testing based on clinical fracture risk profile
- When BMD is measured, axial DXA measurement of the lumbar spine and hip should be used, with **1/3 radius**

## IOF-ESCEO Guidelines[2]

- **Use country-specific FRAX® in postmenopausal women at risk for fracture**
- **In intermediate-risk individuals, include DXA BMD measurement if available in FRAX® calculation**
- **Trabecular bone score may be used as an adjunct to BMD and FRAX®**
- Vertebral fracture assessment should be considered if ≥4 cm height loss, kyphosis, recent or current long-term oral steroid therapy, or BMD T-score ≤-2.5

## NAMS Guidelines[3]

- Measure bone density in postmenopausal women with risk factors for low bone density
  - Women ≥65 yr
  - Women ≥50 yr with additional risk factors
  - History of fracture since menopause
  - Known medical causes of bone loss or fracture

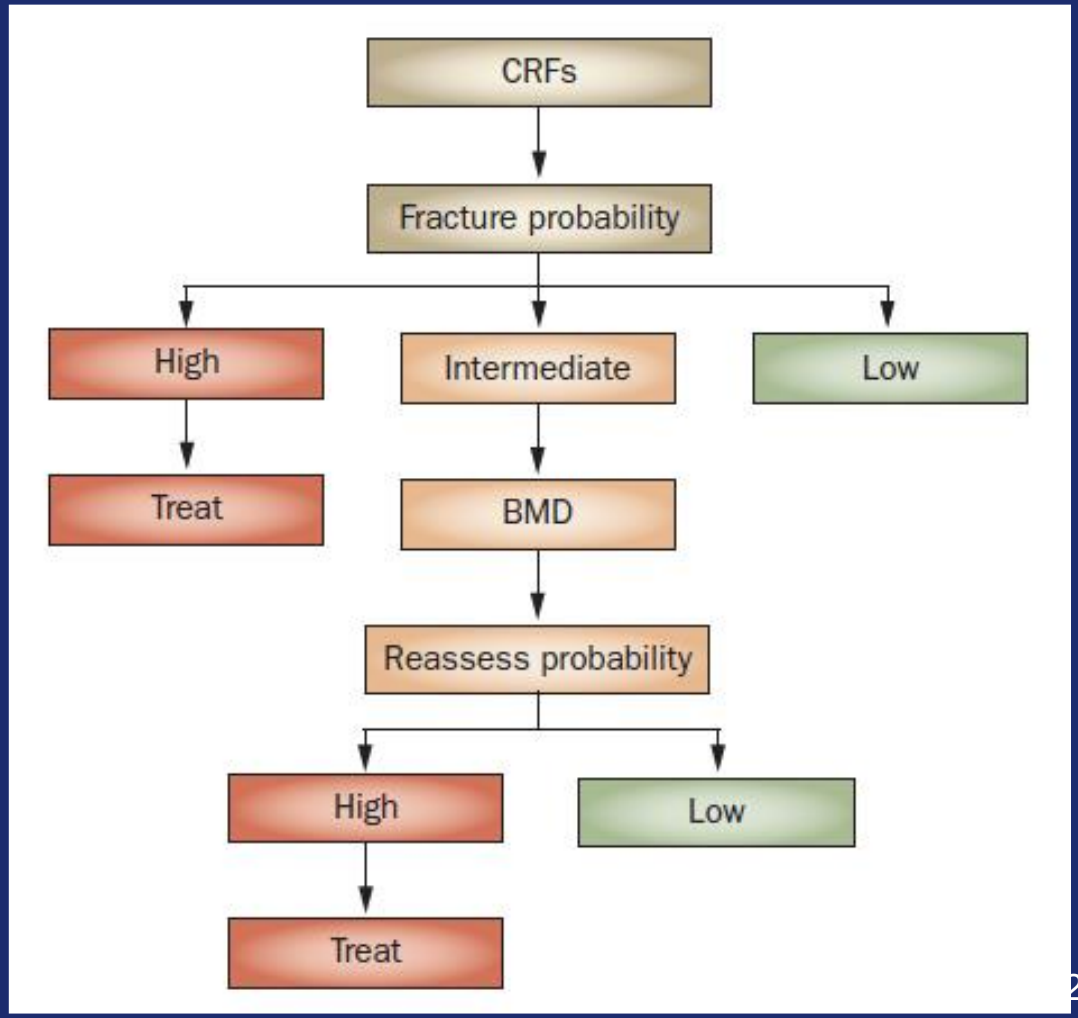
# Screening Strategies and fx-risk estimation

- Several models have been developed for calculation of fracture risk
- FRAX® algorithm is a model developed to obtain an estimate of the patient's absolute risk of fracture over the next 10 years based on BMD score and clinical risk factors (CRF)
- This model is developed as a case-finding strategy for men and women at high risk of fracture, determining fracture risk at which BMD testing (or intervention) should be conducted

*Curry, Susan J., et al. "Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement." **Jama 319.24 (2018):** 2521-2531.*

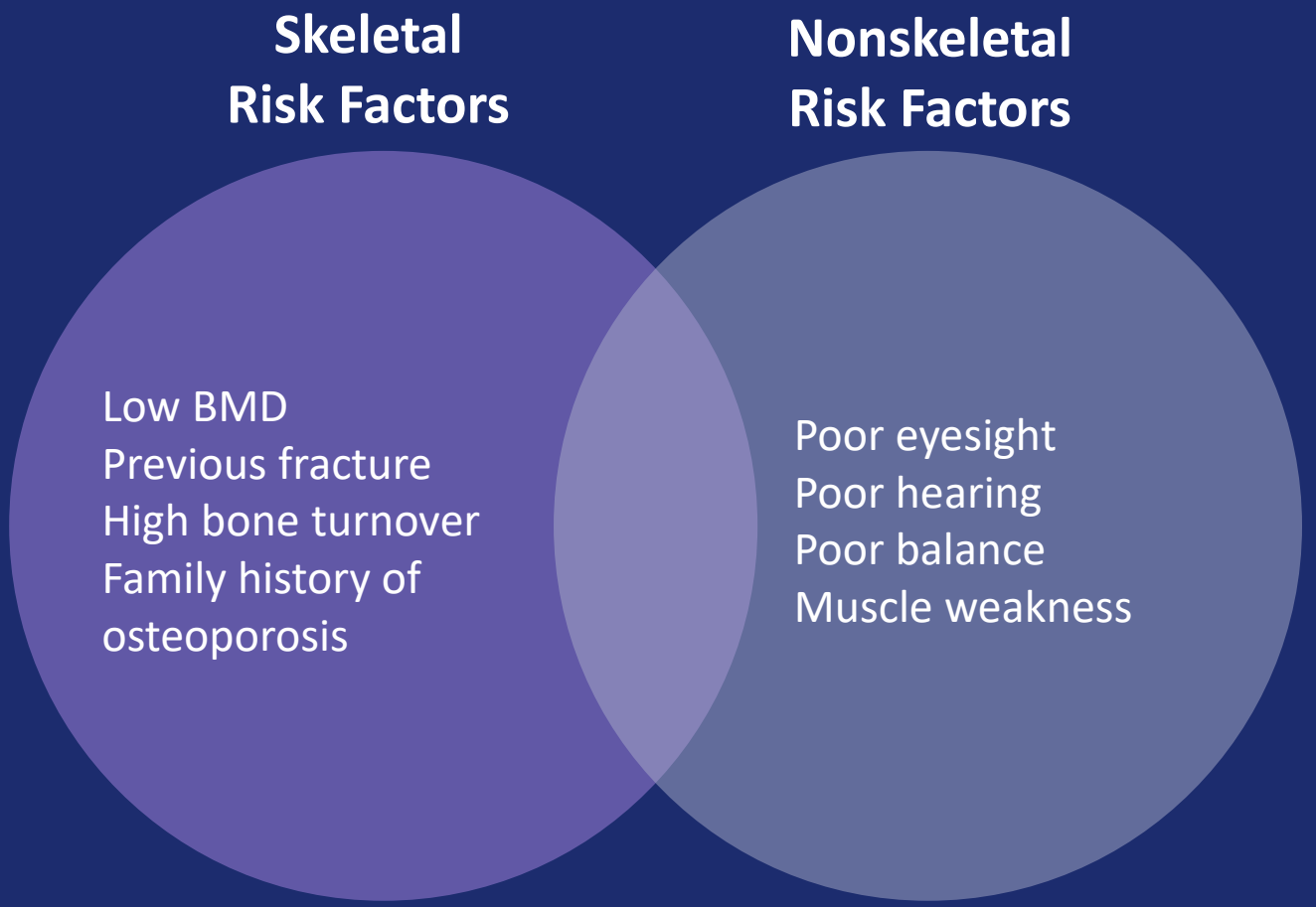
# FRAX-based Osteoporosis Management

- Possibility of osteoporosis and high fracture risk is calculated based on:
  - Clinical risk factors (CRF)
  - BMD values
- Treatment is also recommended for any woman with a previous fragility fracture without need for measuring BMD



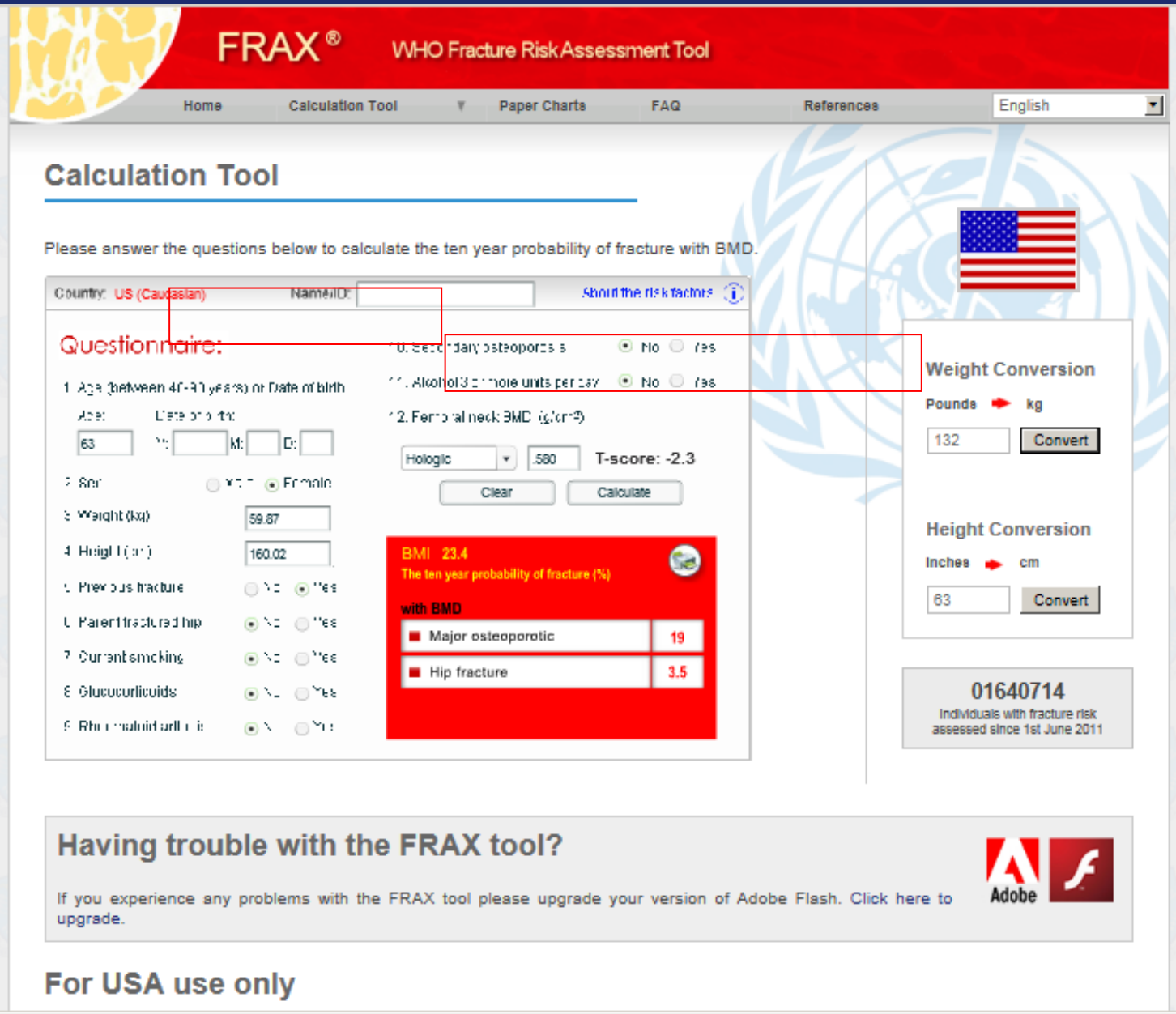

*Compston, J., et al. "UK clinical guideline for the prevention and treatment of osteoporosis."* ***Archives of osteoporosis 12.1 (2017):*** *43.*

# Components of Fracture Risk



# WHO Absolute Fracture Risk Model  FRAX

- Estimates absolute fracture risk using  epidemiology of osteoporosis, risk factors and therapeutic data.
- By basing treatment  decisions on fracture probability, therapy can be targeted to those who would receive the greatest benefit.
- Calculation tool is online and calculates the 10 year risk for hip fractures and any osteoporosis related fracture.
- Using a series of clinical questions, BMD data, weight and height the tool calculates these risks for individual patients.
- Treatment is recommended for a 10 year hip fracture risk over 3% and a 10 year osteoporotic fracture risk over 20%.




http://www.shef.ac.uk/FRAX/. Accessed August 2014.

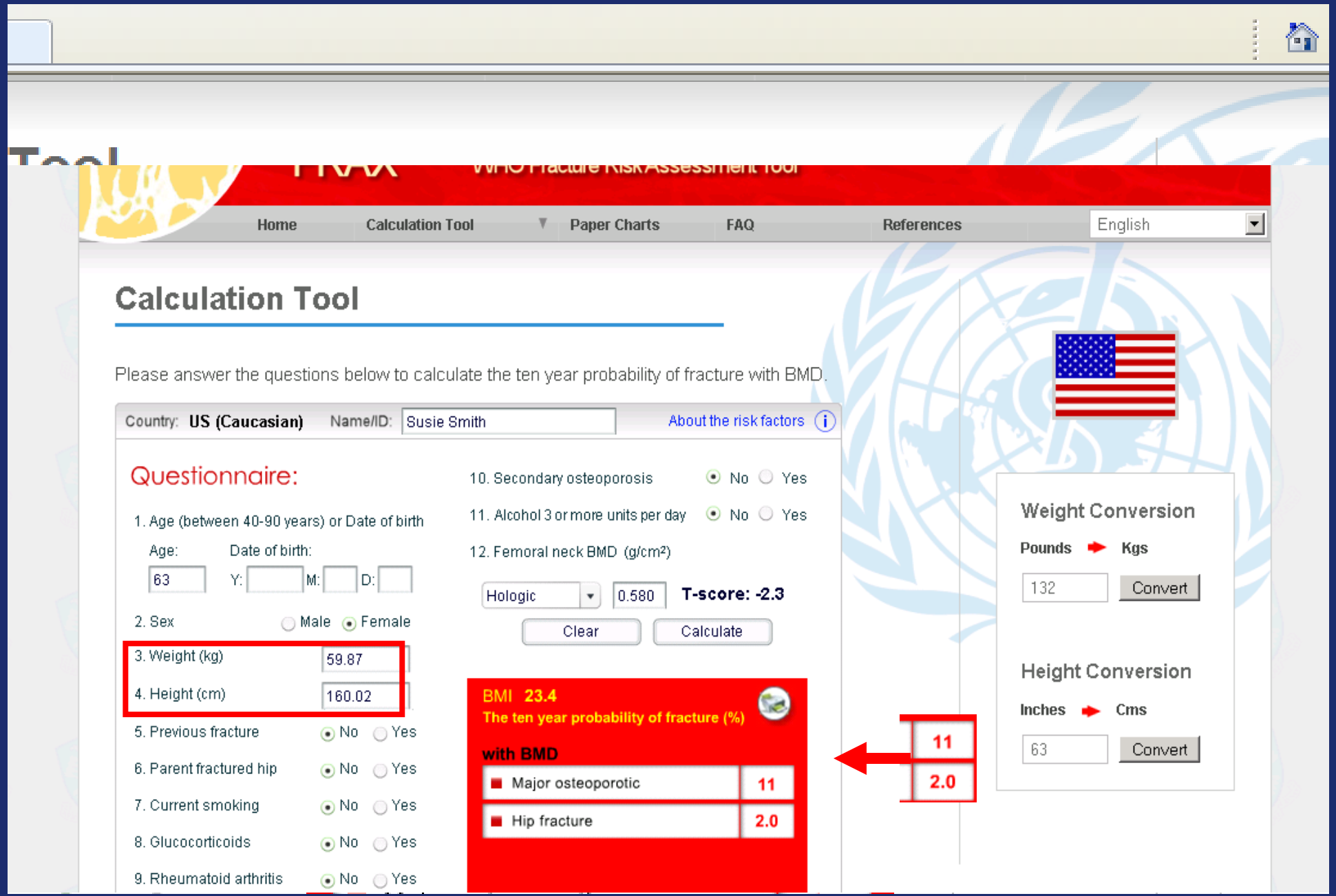
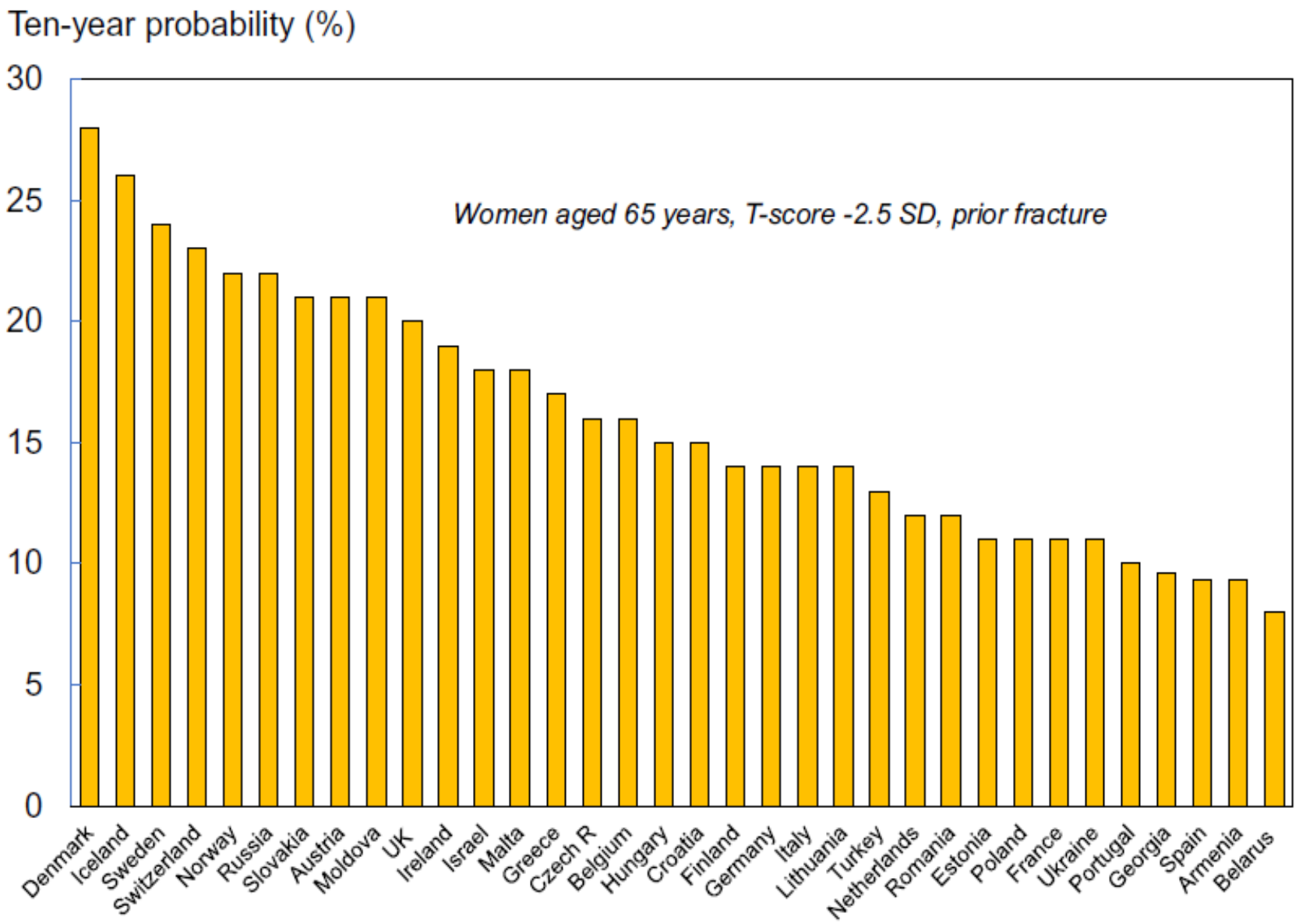

Home
Calculation Tool
Paper Charts
FAQ
References
English
Calculation Tool
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: US (Caucasian)
Name/ID: Susie Smith
About the risk factors
Questionnaire:
1. Age (between 40-90 years) or Date of birth
Age:
Date of birth:
63
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
59.87
4. Height (cm)
160.02
5. Previous fracture
6. Parent fractured hip
7. Current smoking
8. Glucocorticoids
9. Rheumatoid arthritis
10. Secondary osteoporosis
11. Alcohol 3 or more units per day
12. Femoral neck BMD (g/cm²)
Hologic
0.580
T-score: -2.3
Clear
Calculate
BMI 23.4
The ten year probability of fracture (%)
with BMD
Major osteoporotic
11
Hip fracture
2.0
11
2.0
Weight Conversion
Pounds
Kgs
132
Convert
Height Conversion
Inches
Cms
63
Convert

Fig. 3 Ten-year probability (%) of a major osteoporotic fracture in women from different European countries. BMI set to 25 kg/m$^2$. Data from http://www.shef.ac.uk/FRAX



# Benefits of FRAX

| |
|---|
| Derives 10-year probability of clinical event from measurable parameters |
| Internationally recognized and validated |
| Based on data from multiple cohorts |
| Easily accessible on the Internet or DXA software |
| Helps identify patients who need treatment |
| Can be used to reassure low-risk patients |

Watts NB, et al. *J Bone Miner Res* 2009;24:975-979.

# Limitations of FRAX

| |
|---|
| Not valid to monitor patients on treatment |
| Only femoral neck BMD is considered |
| Risk is “yes/no” – there is no consideration of “dose” (e.g., fractures, glucocorticoids, smoking, alcohol) |
| Not all risk factors are included (eg, risk of falling) |
| Clinical judgment is required |
| Do patients with high FRAX scores benefit from medication? (Unknown) |

- Rheumatoid arthritis may be entered into the FRAX® algorithm as a surrogate for fracture risk associated with type 2 diabetes mellitus

# Type 2 diabetes

- Type 2 diabetes is associated with an increase in fracture risk that is independent of FRAX probability.
- Adjustments :

use of the rheumatoid arthritis input to FRAX

use of the TBS adjustment,

reduction of the FN-BMD T-score input by 0·5 SD,

increasing the age input to FRAX by 10 years

# *Adjustment of FRAX-derived fracture probability according to dose of glucocorticoids*

**Table 1** Adjustment of FRAX-derived fracture probability according to dose of glucocorticoids. Data from ref. [40]

| Daily dose of prednisolone (mg) | Average adjustment for major osteoporotic fracture probability | Average adjustment for hip fracture probability |
|---|---|---|
| <2.5 | −20% | −35% |
| 2.5–7.5 | None | None |
| ≥7.5[a] | +15% | +20[a] |

[a]For high doses of prednisolone, greater upward adjustment of fracture risk may be appropriate

Juliet Compston, Glucocorticoid-induced osteoporosis: an update. Endocrine, 22 March 2018

- Lumbar spine BMD
- Increase/decrease FRAX estimate for a major fracture by one tenth for each rounded T-score difference between LS and FN

Consider individual with a femoral neck T-score of −1.7 and a major osteoporotic FRAX probability of 18%. If the lumbar spine T-score is −3.5 then this indicates an offset of −1.8 (−3.5 minus −1.7). This is rounded to the nearest whole number (−2). One tenth of the FRAX estimate based upon the femoral neck is 1.8%, which is multiplied by the rounded offset value (giving 3.6%). This is then added (because lumbar spine T-score is worse than femoral neck T-score) to the original FRAX estimate (18%) giving a final (rounded) probability of 22% (18%+3.6%).

# Thresholds for intervention

- FRAX is first used without BMD to estimate fracture risk; individuals with sufficiently high fracture risk are considered for treatment, whereas those with a very low fracture risk are managed without medication, and an intermediate group undergoes BMD testing for refinement of their fracture risk

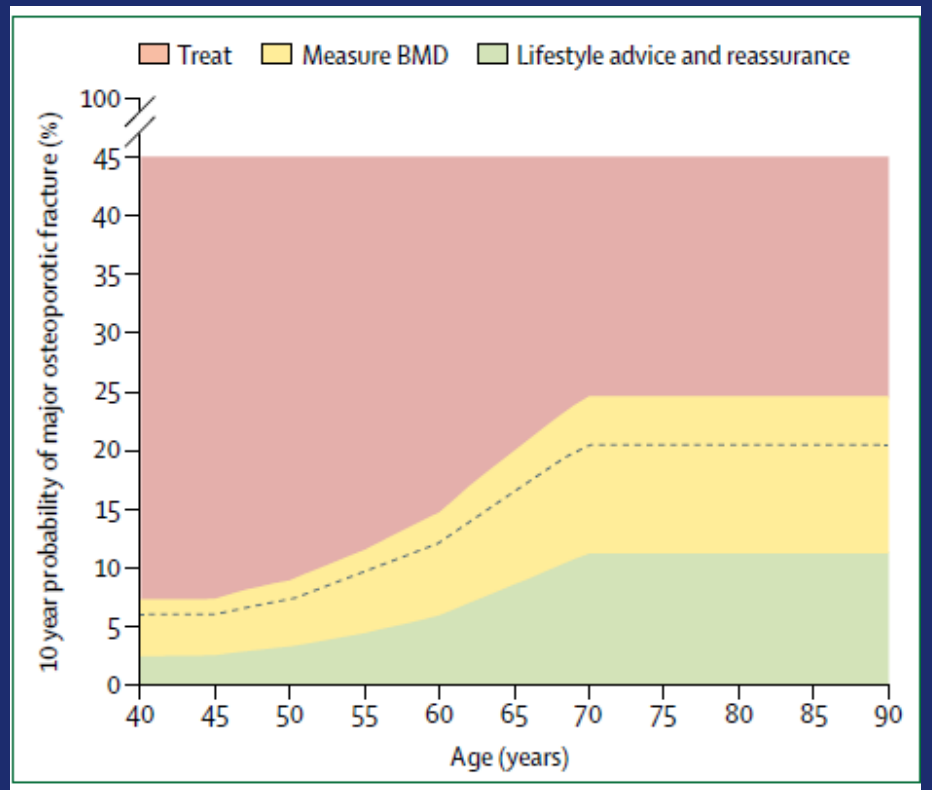



*Figure 2:* UK National Osteoporosis Guidelines Group assessment and treatment thresholds


- Compston J, Bowring C, Cooper A, Cooper C, Davies C, FrancisR, Kanis JA, Marsh D, McCloskey EV, Reid DM, Selby P(2013) Diagnosis and management of osteoporosis in postmenopausalwomen and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas

# Bone Densitometry

- Non-invasive test for measurement of BMD
- Major technologies
  - Dual-energy X-ray Absorptiometry (DXA)
  - Quantitative Ultrasound (QUS)
  - Quantitative Computerized Tomography (QCT)
- Many manufacturers
- Numerous devices
- Different skeletal sites

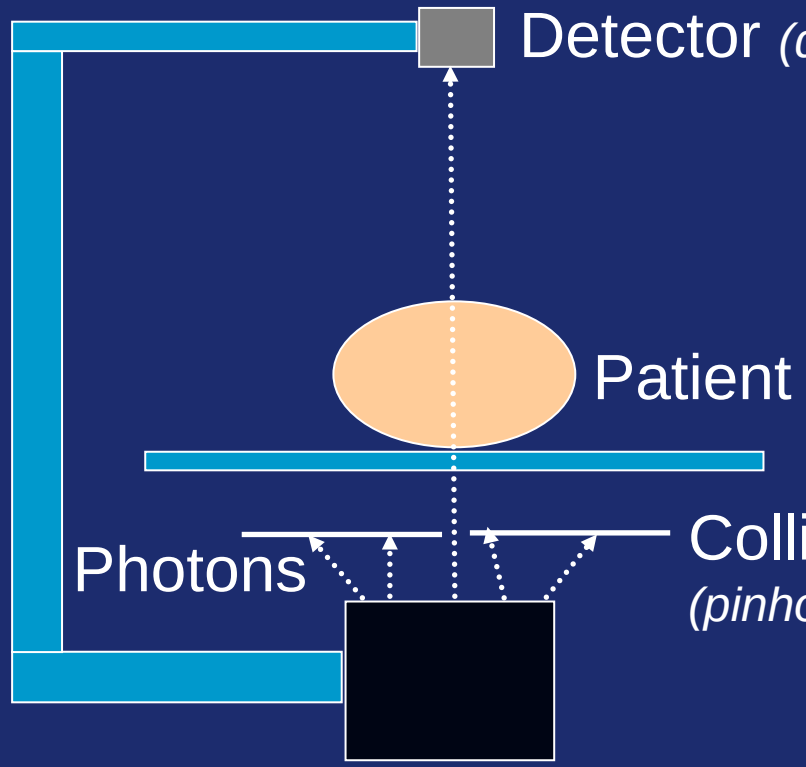
# Dual-energy X-ray absorptiometry

- DXA measures the attenuation (or loss of energy) of X-rays of two different energies when passed through the body, and digitally calculates the bone mineral content (BMC, in g) and BMD (bone mineral content per projected area, in g/cm2) for any region of interest

- Measurements of BMD by DXA have a prominent role in international osteoporosis guidelines and a low BMD is a well-established risk factor for fracture

*Larijani B, Tehrani MR, Hamidi Z, Soltani A, Pajouhi M. Osteoporosis, prevention, diagnosis and treatment. Journal of Reproduction & Infertility. 2005;6(1):5-24.*

# DXA Technology

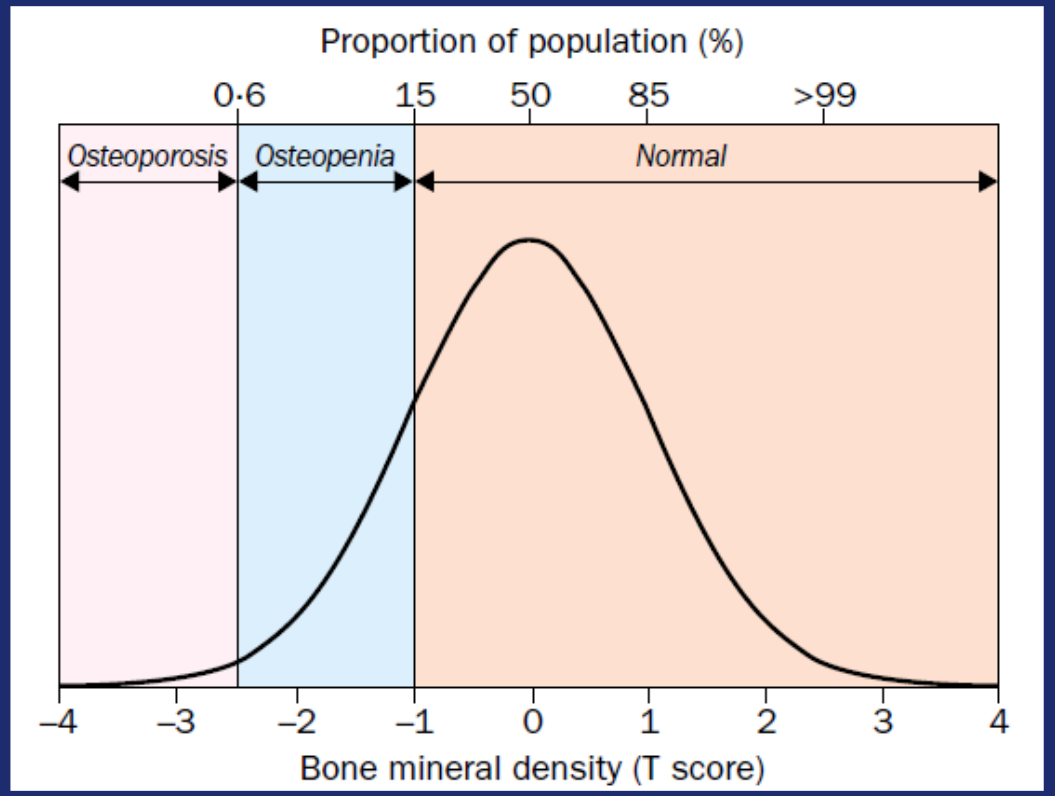



Very low radiation to patient.

Very little scatter radiation to technologist

# Strengths & Limitations of DXA

- Strengths include:
  - Low radiation exposure
  - Excellent precision
  - Low cost
  - Ease of use
  - Short measurement times
- Limitations are:
  - Two-dimensional measurement
  - It has great limitations for assessment fracture risk and monitoring responses to therapy.
  - Artifacts (such as those caused by degenerative changes, presence of osteophytes and aortic calcification) are a nuisance




Bouxsein, 2008

*Kim, Tiffany Y., and Anne L. Schafer. "Variability in DXA reporting and other challenges in osteoporosis evaluation." JAMA internal medicine 176.3 (2016): 393-395.*

# What DXA Really Measures: Bone Mineral Content (BMC) In Grams and Area In $cm^2$

- "Areal" BMD is calculated in $g/cm^2$
- "T-score" compares the patient's BMD with the young-normal mean BMD and expresses the difference as a standard deviation (SD) score

# Bone Density Testing Is Done For Three Reasons

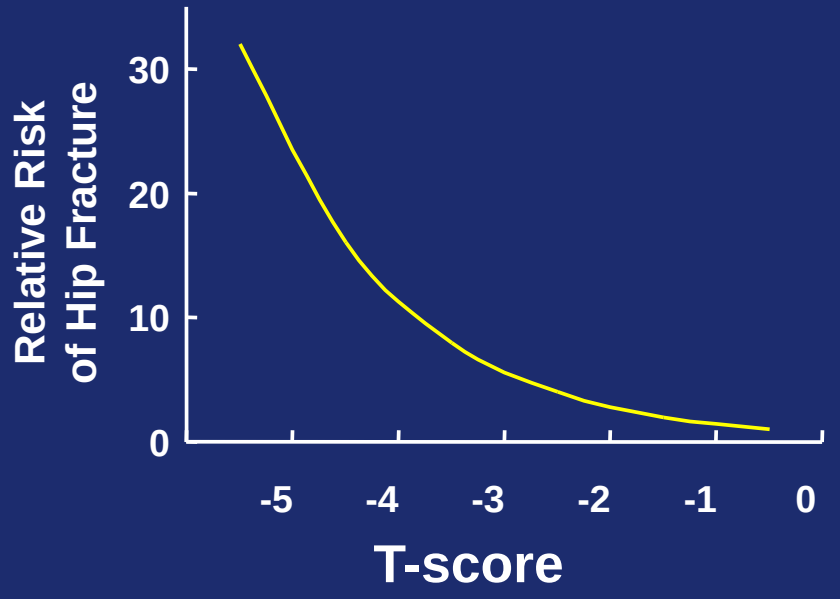
- To diagnose osteoporosis
- To predict fracture risk
- To monitor therapy

## RR of Fx for 1 SD decrease in BMD (age-matched)

| Site | Hip Fx | vertebral Fx |
|---|---|---|
| Distal radius | 1.8 | 1.7 |
| Proximal radius | 2.1 | 2.2 |
| Calcaneous | 2.0 | 2.4 |
| Spine | 1.6 | 2.3 |
| Femoral neck | 2.6 | 1.8 |

(marshall D,et al,BMJ. 1996:,312:1254)

# Strong Relationship Between Bone Density and Bone Strength




- Bone density accounts for 60% to 80% of bone strength in untreated patients[1]
- Best early predictor of fracture risk[2]
- Permits diagnosis before fractures


1. Kushida K. *Clin Calcium.* 2004;14:11-17.
2. Fogelman J, Blake GM. *J Nucl Med*. 2000;41:2015-2025.

# Which Skeletal Sites Should Be Measured?

Every Patient

- Spine
  - L1-L4
- Hip
  - Total Hip
  - Femoral Neck

Some Patients

- Forearm (33% radius, 1/3 radius)
  - If hip or spine cannot be measured
  - Hyperparathyroidism
  - Very obese

*Use lowest T-score of these skeletal sites*

# T-score

$$\frac{\text{Patient's BMD} - \text{Young-Adult Mean BMD}}{\text{1 SD of Young-Adult Mean BMD}}$$

Example:

$$\text{T-score} = \frac{0.7\ \text{g/cm}^2 - 1.0\ \text{g/cm}^2}{0.1\ \text{g/cm}^2} = -3.0$$

# Z-score

$$\frac{\text{Patient's BMD} - \text{Age-Matched Mean BMD}}{\text{1 SD of Age-Matched Mean BMD}}$$

Low Z-score (less than -2.0) has been suggested by some to increase likelihood of secondary osteoporosis, however . . .

- This is not validated in clinical trials
- High index of suspicion for secondary causes of osteoporosis is recommended for all patients

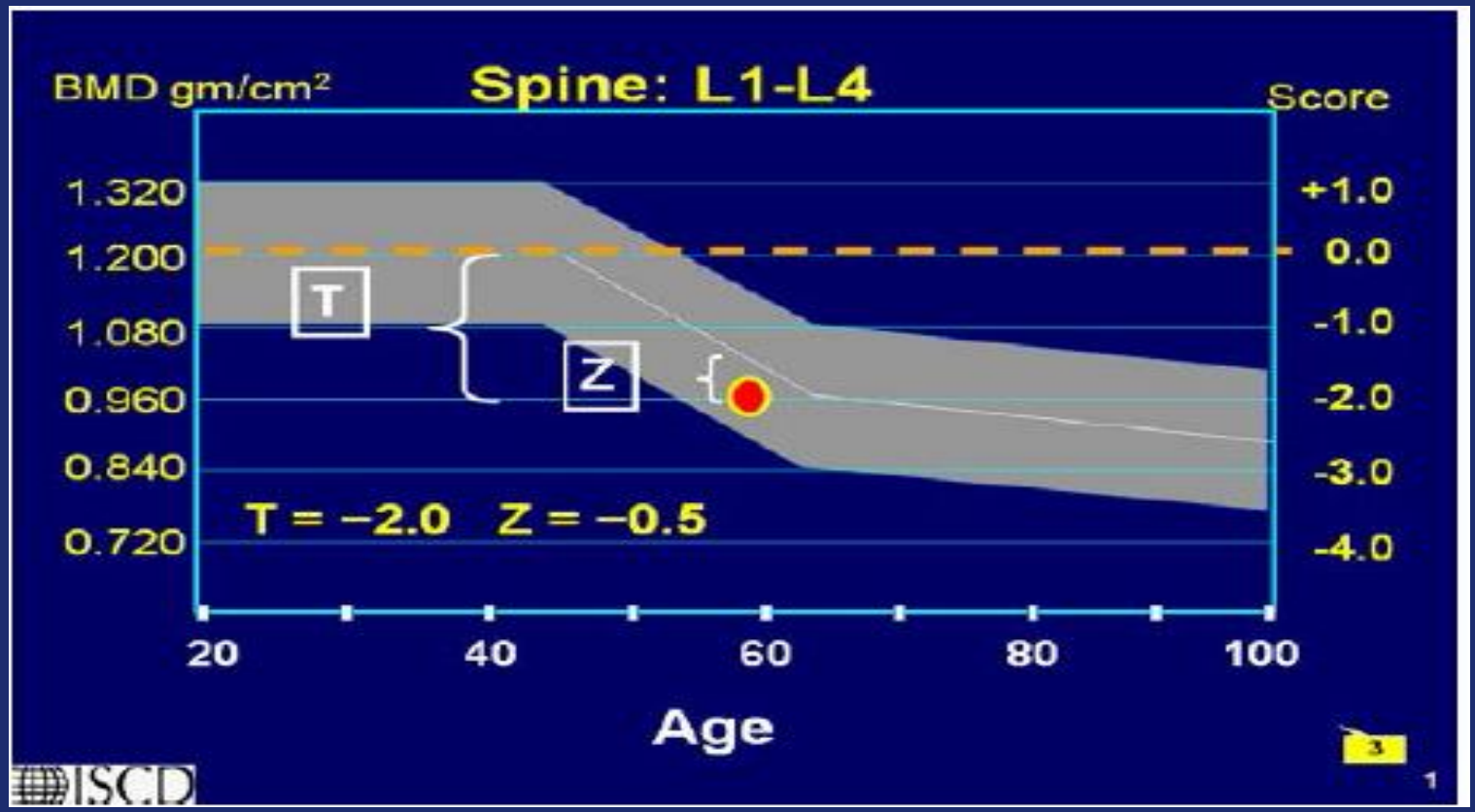
# T Scores and Z Scores

**T Scores**

- Number of standard deviations (SDs) from the mean bone density values in normal sex-matched young adults.
- Used to make the diagnosis of osteopenia and osteoporosis.

**Z score**

- Number of SDs from the normal mean bone density value for age- and sex-matched controls.
- If lower than -2.0 may suggest presence of a secondary cause of osteoporosis.
- Used to assess bone loss in premenopausal females.


BMD gm/cm²
Spine: L1-L4
Score
1.320
1.200
1.080
0.960
0.840
0.720
+1.0
0.0
-1.0
-2.0
-3.0
-4.0
T
Z
T = −2.0 Z = −0.5
20
40
60
80
100
Age
ISCD

- the fracture risk varies markedly in different countries, but the T-score varies only by a small amount
- . significance of any given T-score to fracture risk in women from any one country depends on age

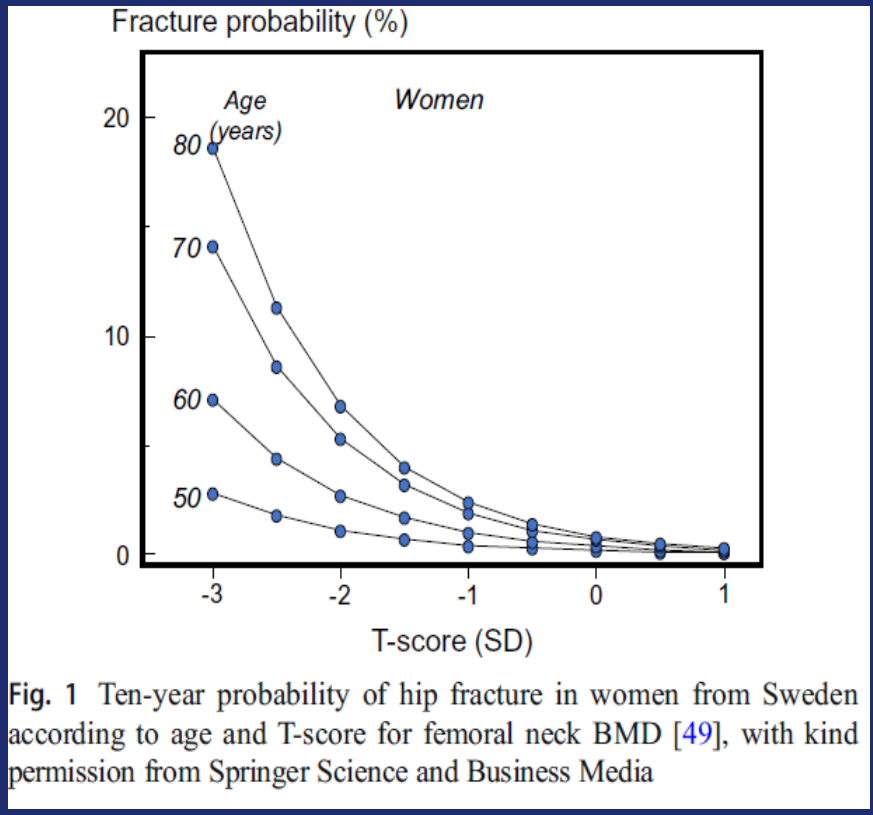



Fig. 1 Ten-year probability of hip fracture in women from Sweden according to age and T-score for femoral neck BMD [49], with kind permission from Springer Science and Business Media

Since the T-score for BMD decreases with age, a T-score of, say, − 2.5 SD becomes less significant as a risk indicator with age [118–120]. Thus, with advancing age, the difference in the probability of fracture between the general population and those with a T-score of − 2.5 SD diminishes and indeed, from the age of 78 years in the USA and 81 years onwards in Kuwait, the fracture probability becomes progressively lower than that of the age and sex-matched individuals (Fig. 5).

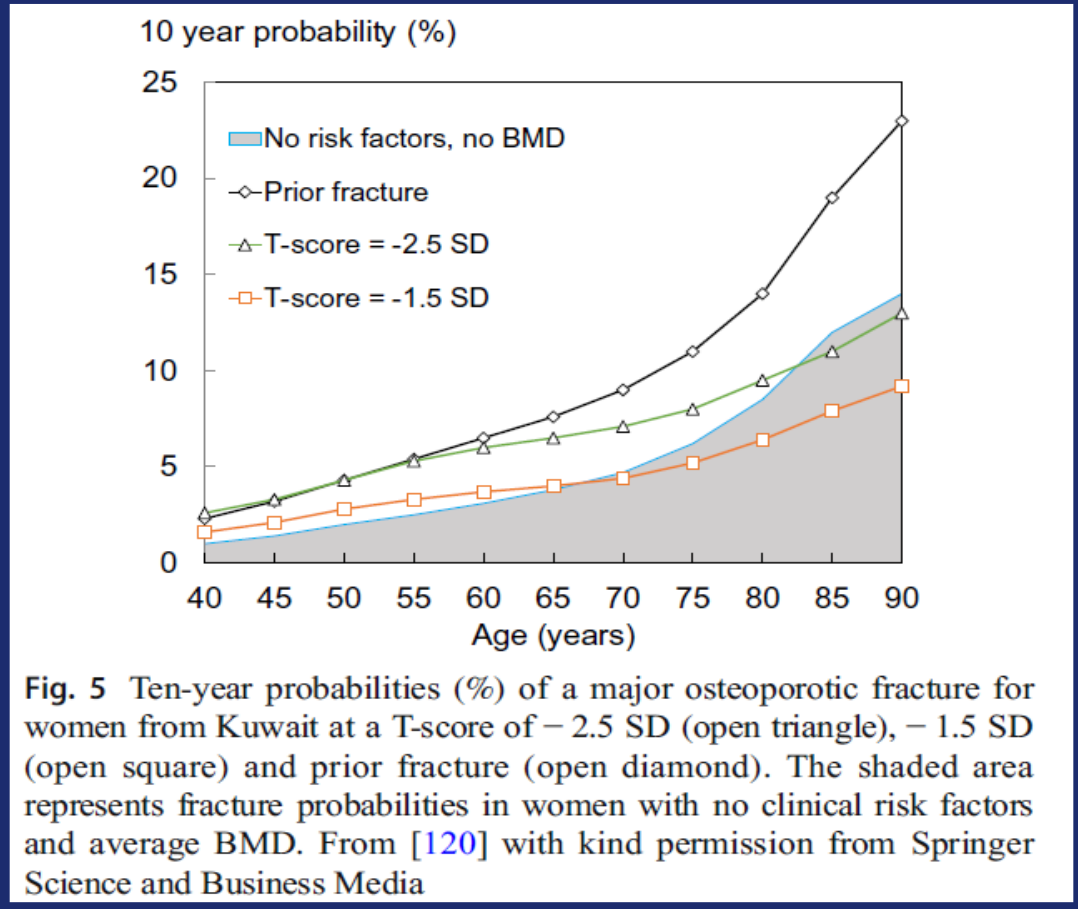
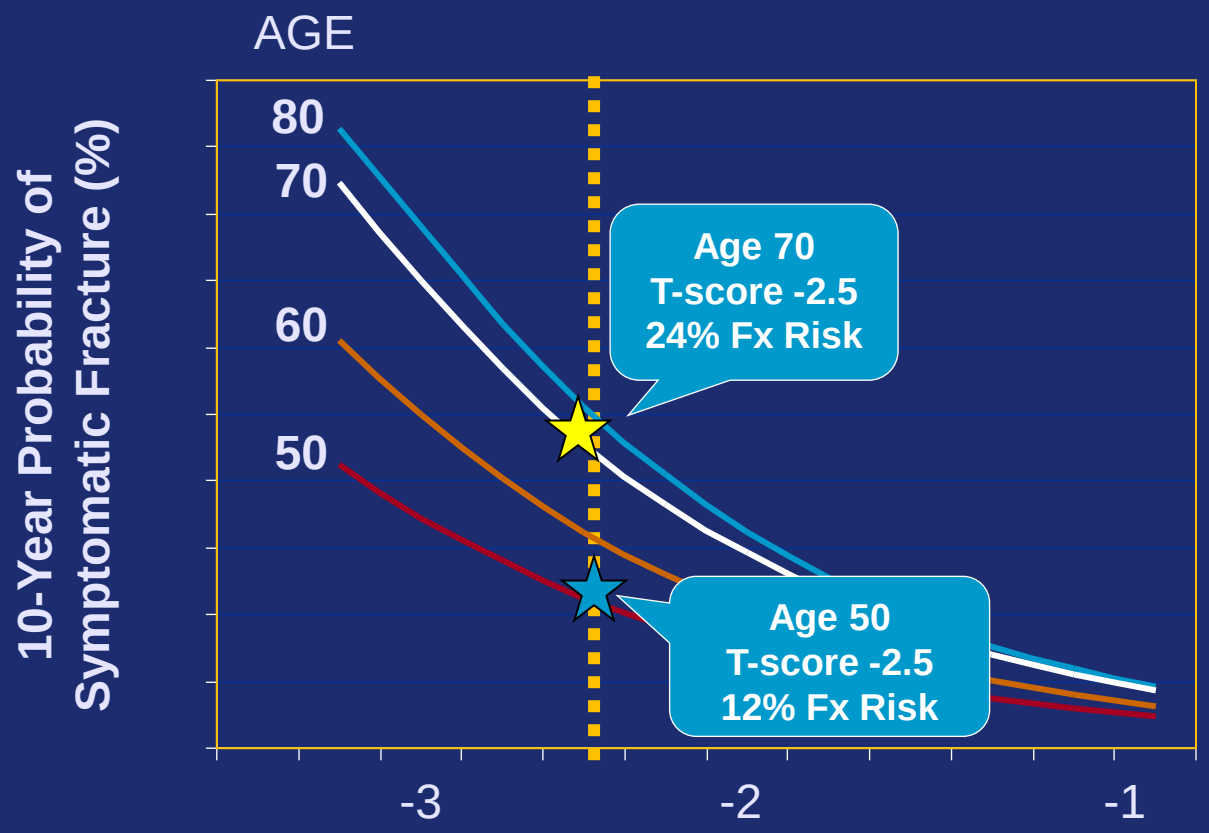



**Fig. 5** Ten-year probabilities (%) of a major osteoporotic fracture for women from Kuwait at a T-score of − 2.5 SD (open triangle), − 1.5 SD (open square) and prior fracture (open diamond). The shaded area represents fracture probabilities in women with no clinical risk factors and average BMD. From [120] with kind permission from Springer Science and Business Media

# Age Is a Major Risk Factor for Fracture




With kind permission from Springer Science+Business Media: Kanis JA ,et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int.*2001;12:989-995. Adapted from Fig. 3. © 2001 International Osteoporosis Foundation and National Osteoporosis Foundation.

# BMD by DXA Measures the T-Score

| Category | T-Score |
|---|---|
| Normal | -1.0 and above |
| Low bone mass (osteopenia) | Between -1.0 and -2.5 |
| Osteoporosis | -2.5 and below |
| Sever Osteoporosis | Osteoporosis + fracture |

# Why -2.5 for WHO Diagnosis?

Professor John Kanis says:

“Such a cutoff value identifies approximately 30% of postmenopausal women as having osteoporosis using measurements made at the spine, hip or forearm. This is approximately equivalent to the lifetime risk of fracture at these sites.”

Kanis JA et al. J Bone Miner Res. 1994;9:1137.

# AACE Guidelines: Clinical Diagnosis of Osteoporosis

I. Presence of fragility fractures (regardless of BMD)

II. T-score -2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius

III. T-score between −1.0 and −2.5 **and** a fragility fracture of proximal humerus, pelvis, or distal forearm

IV. T-score between -1.0 and -2.5 **and** increased fracture risk per FRAX

❖ Initial diagnosis of osteoporosis persists even when subsequent DXA measurement shows a T-score better than -2.5

Camacho. Endocr Pract. 2020;26(suppl 1):1.

# AACE Guidelines Indications for Bone Mineral Density Testing

All women 65 years of age or older

All postmenopausal women

- With a history of fracture(s) without major trauma
- With osteopenia identified radiographically
- Starting or taking long-term systemic glucocorticoid therapy (≥3 months)

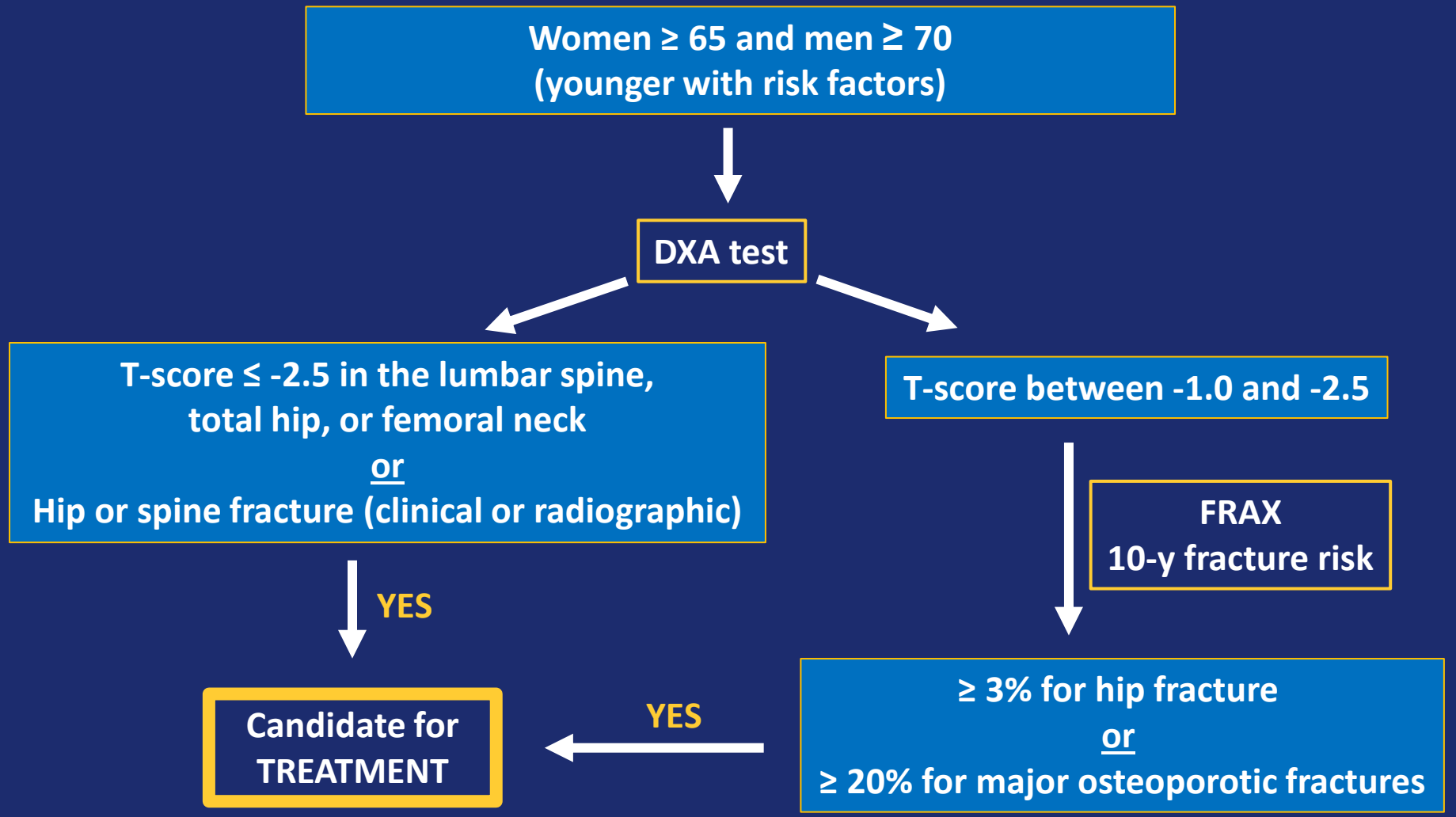
Other perimenopausal or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions

- Low body weight (<127 lb or body mass index <20 kg/m2)
- Long-term systemic glucocorticoid therapy (≥3 months)
- Family history of osteoporotic fracture
- Early menopause
- Current smoking
- Excessive consumption of alcohol

Secondary osteoporosis

Camacho. Endocr Pract. 2020;26(suppl 1):1.

# Whom to Treat: NOF Guidelines 2014




nof.org/hcp/resources/913. Accessed August 2014.

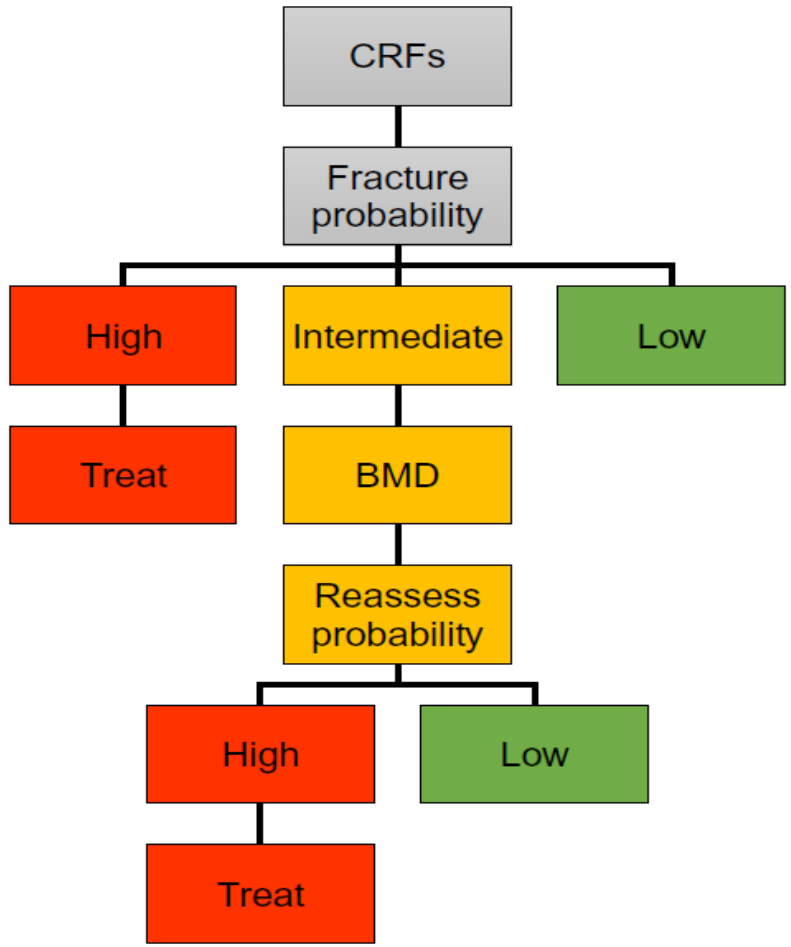



**Fig. 4** Management algorithm for the assessment of individuals at risk of fracture [114], with kind permission from Springer Science and Business Media

# BMTs and their Clinical Applications

- Bone turnover markers (BTMs) have great applications in bone remodeling.

- BTMs that predict Bone Loss
  - Bone Formation Markers: P1NP, BALP, OC
  - Bone Resorption Markers: DPD, NTX
- BTMs that predict Fracture
  - Bone Formation Markers: BALP, P1CP, P1NP, OC
  - Bone Resorption Markers: TRAP, CTX, NTX

A marker of bone formation (serum PINP) and a marker of bone resorption (serum CTX-I) should be used as reference analytes in a clinical setting

Serum procollagen type I amino-terminal propeptide (s-PINP)

serum carboxy-terminal cross-linking telopeptide of type I collagen (s-βCTX)

Early changes in BTMs are associated with long-term BMD changes in women taking antiresorptive or anabolic

Clinicians might use the results of BTMs obtained after 3 to 6 months of oral bisphosphonate therapy to counsel patients that the therapy is effective and to maintain their compliance, rather than waiting 2 years for a DXA result

More of the fracture reductions associated with antiresorptive therapy than do increases in BMD

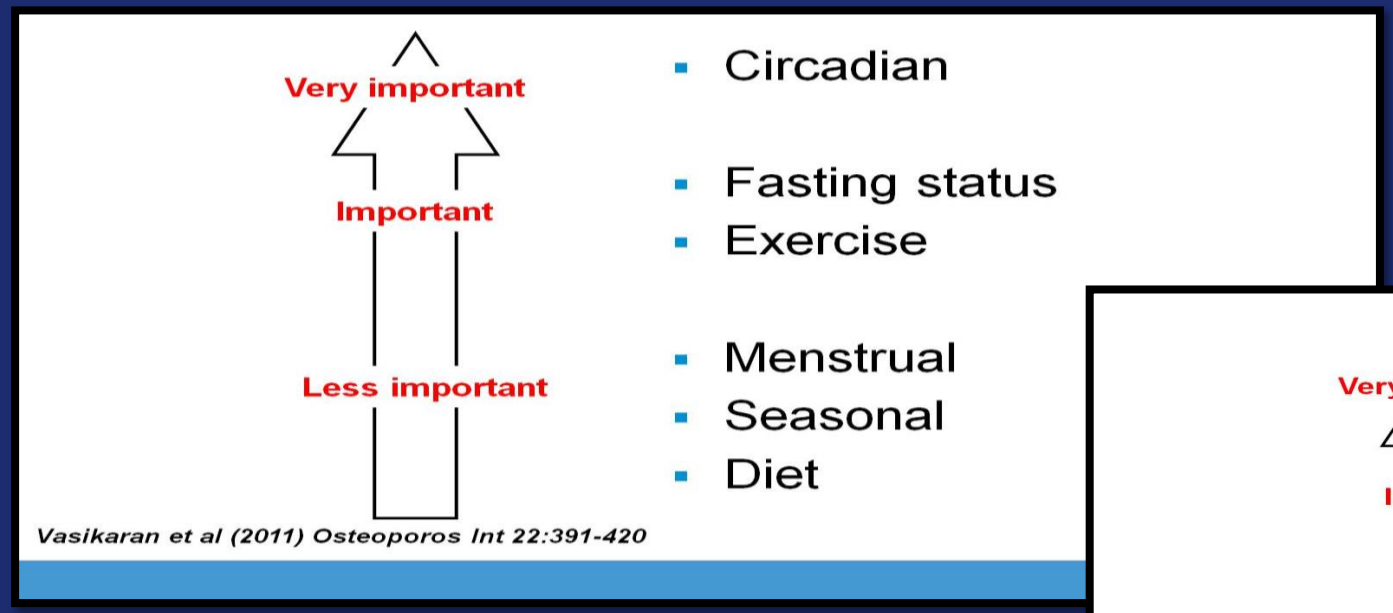
In the setting of renal insufficiency or if there are insurance issues, then bone-specific alkaline phosphatase may be used

Recent fracture will transiently raise BTMs

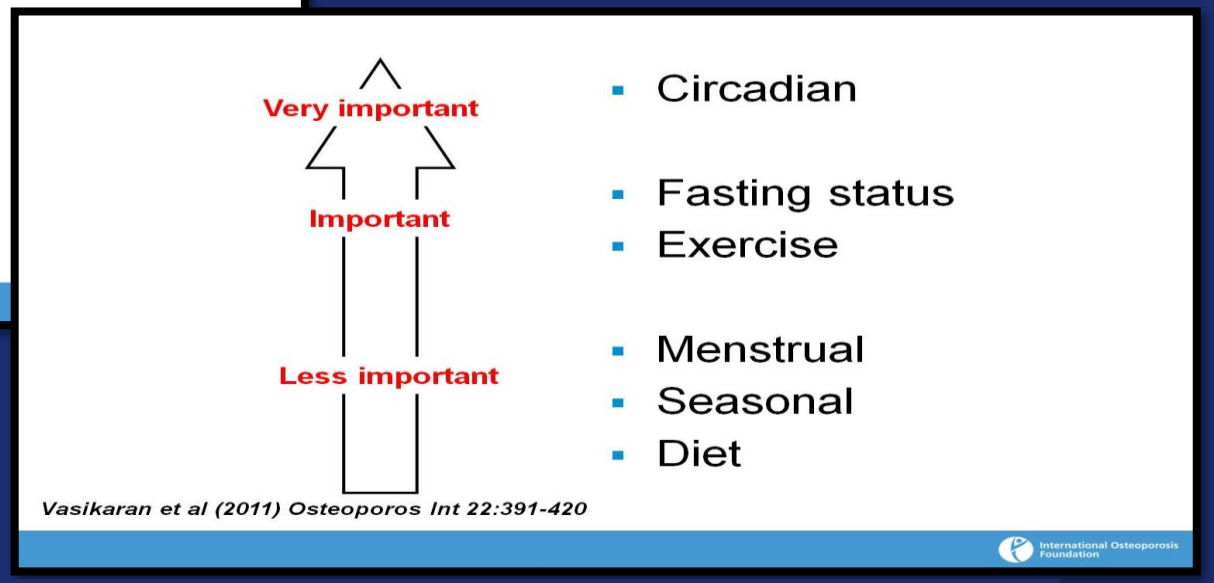
loss of BMD in the face of well-suppressed BTMs (greater than the least significant change [LSC] of the BTMs) and stable body weight might raise concern for factors that may confound DXA interpretation and prompt further scrutiny of DXA images

Potential use of BTMs in the setting of a bisphosphonate drug holiday, where highly suppressed bone turnover (as compared with a baseline value) indicates continued antiresorptive effect and, theoretically, continued antifracture benefit

# Factors which Can Influence BMT Measurement




Factors influencing BMT in **different populations**




Factors influencing BMT concentrations in different situations in **individual patients**

*Vasikaran, Samuel, et al. "Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards." Osteoporosis International 22.2 (2011):*

# Advantages

- Evidence-based clinical practice guidelines have included BTMs as a method for monitoring the effects of therapy*
- Measurement of BTMs is potentially useful in assessing the offset of effect after discontinuation of therapy and may provide insight on restarting therapy after a drug holiday**

*Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. *Int J Clin Pract*. 2009;63(1): 19–26

**J Bone Miner Res*. 2012;27(5):963–974.

# BTMs to Screen Bisphosphonates Adherence

- IOF working group recommends measuring PINP and CTX at baseline and 3 months after starting therapy to check for a decrease above the least significant change (decrease of >38% for PINP and 56% for CTX).

- Detection rate for PINP is 84%, for CTX 87% and, if variation in at least one is considered when measuring both, the level of detection is 94.5%.

*Diez-Perez, Adolfo, et al. "International osteoporosis foundation and european calcified tissue society working group. Recommendations for the screening of adherence to oral bisphosphonates. " **Osteoporosis International 28.3 (2017)**: 767-774.*

# Practical point

- Serum C- telopeptide of type I collagen (βCTX) and serum procollagen I N-propeptide (PINP) are considered as reference markers
- Under clinical conditions, a precision error of approximately 10 % is estimated for both analytes
- LSC estimates for serum βCTX and PINP are approximately 25 %

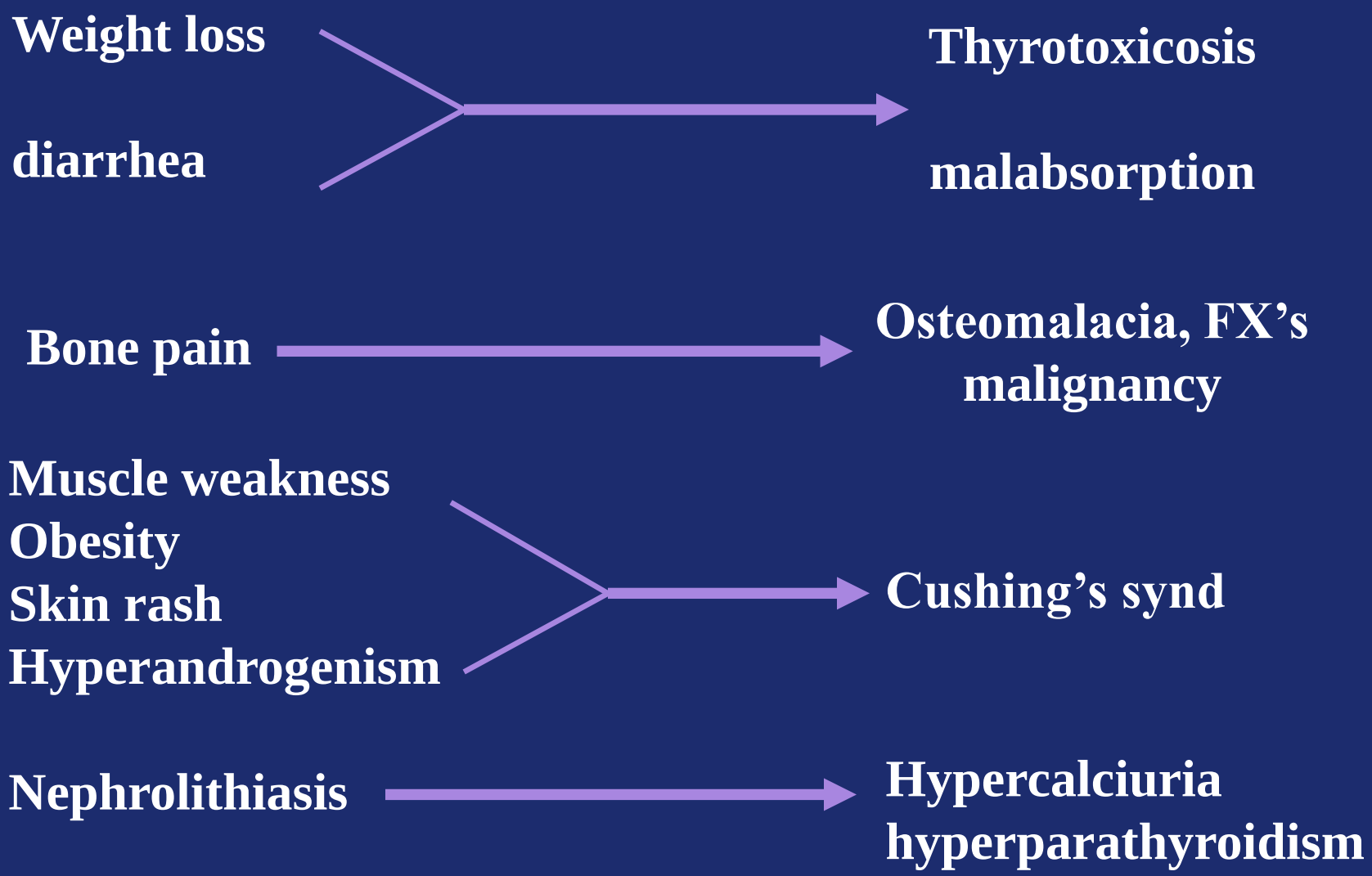
Treatment failure in osteoporosis. Osteoporos Int,2012, 23:2769–74

# Routine Procedures Proposed in the Investigation of Osteoporosis

- **Routine**
  - History and physical examination
  - Blood cell count, sedimentation rate, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
  - Lateral radiograph of lumbar and thoracic spine
  - Bone densitometry (DXA)
- **Other procedures**
  - X-Ray – vertebral fracture assessment
  - Markers of bone turnover, when available


J.Kanis et al. Osteoporos Int. 2008;epub

# History & Physical Examination



# Causes for Secondary Osteoporosis in Adults

| | |
|---|---|
| Endocrine Disorders | Hyperthyroidism, hypogonadism, Cushing's syndrome, type 1 DM, hyperparathyroidism |
| Nutritional Conditions | Malabsorption syndromes and malnutrition, chronic liver disease, gastric operations, Vit D deficiency, calcium deficiency, alcoholism |
| Drugs | Glucocorticoids, anticonvulsants, gonadotropin-releasing hormone agonists, excessive T4, lithium |
| Disorders of collagen metabolism | Osteogenesis imperfecta, Homocystinuria, Ehlers-Danlos syndrome, Marfans syndrome |
| Other | Rheumatoid arthritis, COPD, renal tubular acidosis, hypercalciuria, smoking, organ transplantion, immobilization, mastocytosis |

**Table 13**
**Laboratory Tests to Consider in Detecting Secondary Osteoporosis**

Complete blood cell count
Serum chemistry, including calcium, phosphate, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, and electrolytes
24-hour collection for calcium, sodium, and creatinine excretion (to identify calcium malabsorption or hypercalciuria)
Serum 25-hydroxyvitamin D

Additional tests if clinically indicated might include (but not limited to):

- Serum intact parathyroid hormone concentration for possible primary or secondary hyperparathyroidism
- Serum thyrotropin
- Tissue transglutaminase antibodies for suspected celiac disease
- Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma
- Urinary free cortisol or other tests for suspected adrenal hypersecretion
- Serum tryptase, urine N-methylhistidine, or other tests for mastocytosis
- Bone marrow aspiration and biopsy to look for marrow-based diseases
- Undecalcified iliac crest bone biopsy with double tetracycline labeling

    Recommended for patients with bone disease and renal failure to establish the correct diagnosis and direct management
    May be helpful in the assessment of patients with the following:
        Suspected osteomalacia or mastocytosis when laboratory test results are inconclusive
        Fracture without major trauma despite normal or high bone density
        Vitamin D–resistant osteomalacia and similar disorders to assess response to treatment

Genetic testing for unusual features that suggest rare metabolic bone diseases


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# Osteoporosis Pharmacotherapy

# Pharmacological therapy

**Pharmacological therapy is recommended:**

- For postmenopausal women with **hip or vertebral fractures**
- Those with T-scores of **-2.5 or less** in the femoral neck, total hip, or lumbar spine
- Those with T-scores of **-1 to -2.5** and a 10-year probability of **≥20%** for major osteoporotic fractures or **≥3%** for hip fractures based on the FRAX tool

# Guidance From NOF 2014 and AACE 2020: Whom to Treat

- After exclusion of secondary cause, treat postmenopausal women and men age ≥50 yr who have:

## Osteoporosis

**Clinical**

- Hip or spine fracture

*OR*

**BMD by DXA**

- T-score ≤-2.5 in spine, femoral neck, total hip, or 1/3 radius

## Osteopenia/Low Bone Mass

**BMD by DXA**

- T-score between -1.0 and -2.5

*AND*

**FRAX 10-Yr Fracture Risk**

- ≥3% for hip
- ≥20% for major osteoporotic-related fracture

Treatment is also recommended for any woman with a previous fragility fracture without need for measuring BMD

Cosman. Osteoporosis Int. 2014;25:2359. Camacho. Endocr Pract. 2020;26(suppl 1):1.

# Vitamin D Supplementation

## Goal

- Adequate 25-hydroxyvitamin D level: ≥30 ng/mL[1-3]
- Desirable range: 30-50 ng/mL[2,3]
  - Toxicity unlikely with levels up to 100 ng/mL[4]

## Supplements

- Most patients require vitamin D3 at 1000-2000 IU/day to achieve this[2]
- Supplements are available (eg, 1000 IU, 2000 IU, 50,000 IU)
- "Safe upper limit" is 4000 IU/day[1]

1. Cosman. Osteoporosis Int. 2014;25:2359. 2. Camacho. Endocr Pract. 2020;26(suppl 1):1.
3. Ross. J Clin Endocrinol Metab. 2011;96:53. 4. Dudenkov. Mayo Clin Proc. 2015;90:577.

# Patient Education to Reduce Risk

- Exercise including weight bearing, balance, and resistance
- Avoid unhealthy habits (eg, smoking)
- Prevent falls in homes
  - Refer for physical therapy if appropriate

Camacho. Endocr Pract. 2020;26(suppl 1):1.

# FDA-Approved
# Osteoporosis Medications

## Antiresorptives

- Estrogen/HRT*
- Bisphosphonates
  - Alendronate (Fosamax)*
  - Risedronate (Actonel)*
  - Ibandronate (Boniva)
  - Zoledronic Acid (Reclast)*
- SERMS:
  - Raloxifene (Evista)
  - Bazedoxifene (Duavee)
- Calcitonin (Miacalcin)
- Denosumab(Prolia)*

## Anabolics

- Parathyroid Hormone (Teriparatide, Forteo)
- PTHrP Analogue (Abalopartide, Tymlos)*
- Romosozumab(Evenity)

*reduces non vertebral fracture

# Pharmacologic Treatment Options

## Antiresorptive Agents

- Bisphosphonates
  - Alendronate
  - Ibandronate
  - Risedronate
  - Zoledronate
- Anti-RANKL Ab
  - Denosumab
- Hormone related
  - Raloxifene

## Dual Action

- Anti-sclerostin Ab
  - Romosozumab

## Anabolic Agents

- PTH/PTHrP related
  - Abaloparatide
  - Teriparatide

# Indications for Prevention and Treatment

| Medication | | | | Postmenopausal Osteoporosis | | Glucocorticoid-Induced Osteoporosis | | Osteoporosis in Men |
|---|---|---|---|---|---|---|---|---|
| Generic Name | Brand Name | Dosing Method | Dosing Interval | Prevention | Treatment | Prevention | Treatment | Treatment |
| Estrogen | Many | Various | Various | ✓ | | | | |
| Alendronate | Fosamax | PO | Q1D,W | ✓ | ✓ | | ✓ | ✓ |
| Risedronate | Actonel | PO | Q1W,M | ✓ | ✓ | ✓ | ✓ | ✓ |
| Risedronate | Atelvia | PO | Q1W | | ✓ | | | |
| Ibandronate | Boniva | PO | Monthly | ✓ | ✓ | | | |
| Ibandronate | Boniva | IV | Q3M | | ✓ | | | |
| Zoledronate | Reclast | IV | Q12M | ✓ | ✓ | ✓ | ✓ | ✓ |
| Raloxifene | Evista | PO | Q1D | ✓ | ✓ | | | |
| Calcitonin | Miacalcin, Fortical | IN | Q1D | | ✓ | | | |
| Denosumab | Prolia | SC | Q6M | | ✓ | | ✓ | ✓ |
| Estrogen + BAZ | Duavee | PO | Q1D | ✓ | | | | |
| Teriparatide | Forteo | SC | Q1D x 24+ mo | | ✓ | | ✓ | ✓ |
| Abaloparatide | Tymlos | SC | Q1D x 24 mo | | ✓ | | | |
| Romosozumab | Evenity | SC | Q1M x 12 | | ✓ | | | |

www.endocrine.org/patient-engagement/endocrine-library/osteoporosis-treatment. Alendronate sodium PI. Risedronate sodium IR PI. Risedronate sodium DR PI. Oral ibandronate sodium PI. Ibandronate sodium IV PI. Zoledronic acid PI. Raloxifene PI. Calcitonin salmon PI. Denosumab PI. Bazedoxifene and conjugated estrogens PI. Teriparatide PI. Abaloparatide PI. Romosozumab PI.

# FDA-Approved Medications: Evidence for Fracture Reduction in Postmenopausal Women

| Class | Drug | Vertebral | Nonvertebral | Hip |
|---|---|---|---|---|
| Calcitonin | Calcitonin | ✓ | No | No |
| Hormone related | Raloxifene | ✓ | No | No |
| Bisphosphonate | Ibandronate | ✓ | No | No |
| Bisphosphonate | Alendronate | ✓ | * | ✓ |
| Bisphosphonate | Risedronate | ✓ | ✓ | * |
| Bisphosphonate | Zoledronate | ✓ | ✓ | ✓ |
| Anti-RANKL Ab | Denosumab | ✓ | ✓ | ✓ |
| PTH | Teriparatide | ✓ | ✓ | No data |
| PTH-related protein | Abaloparatide | ✓ | ✓ | No data |
| Anti-sclerostin Ab | Romosozumab | ✓ | No data | No data |

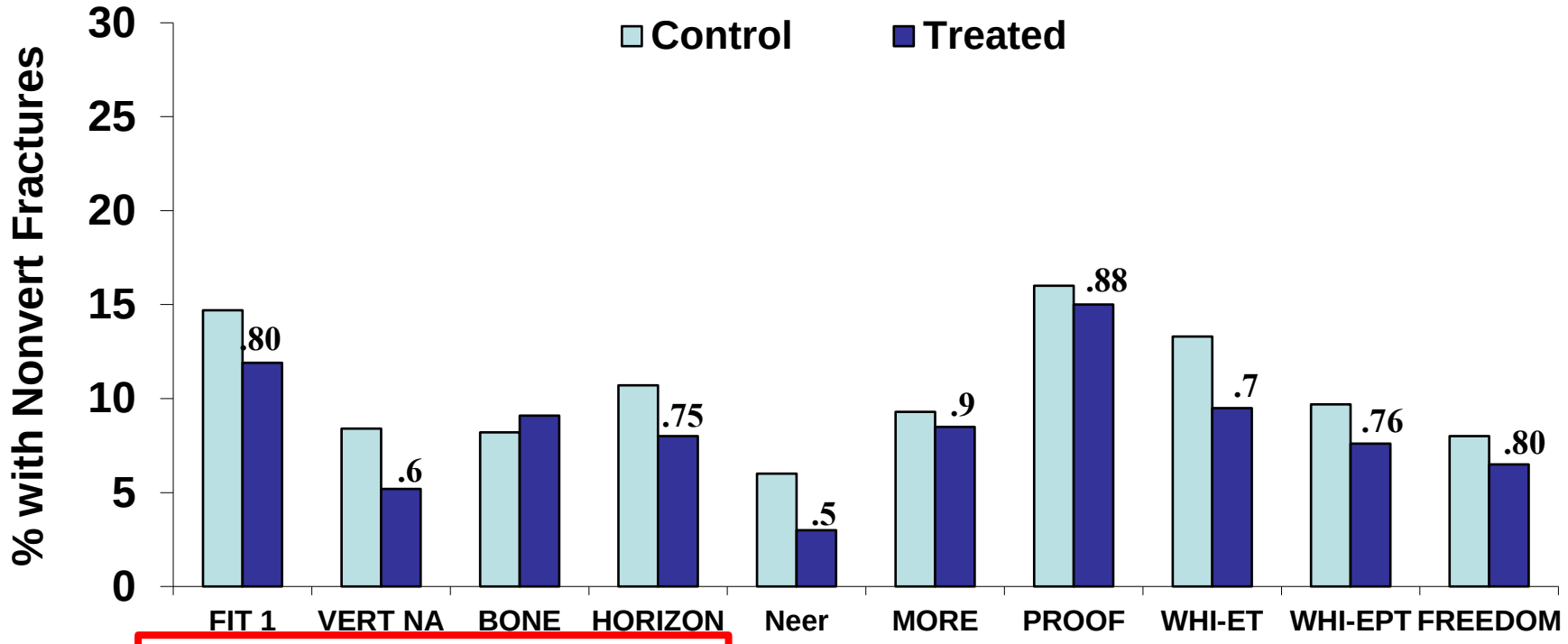
*Evidence for effect but not FDA-approved indication.

# BMD Response to therapy

| Drug (Trial) | Increase in spine BMD | Decrease in vertebral Fx |
|---|---|---|
| Alendronate (FIT ll) | %8.3 | %44 |
| Alendronate (FIT l) | %7.9 | %47 |
| Residronate (RVE) | %7.1 | %49 |
| Residronate (RVN | %5.4 | %41 |
| Raloxifen (MORE) | %2.6 | %40 |
| Calcitonin(PROOF) | %1.2 | %36 |

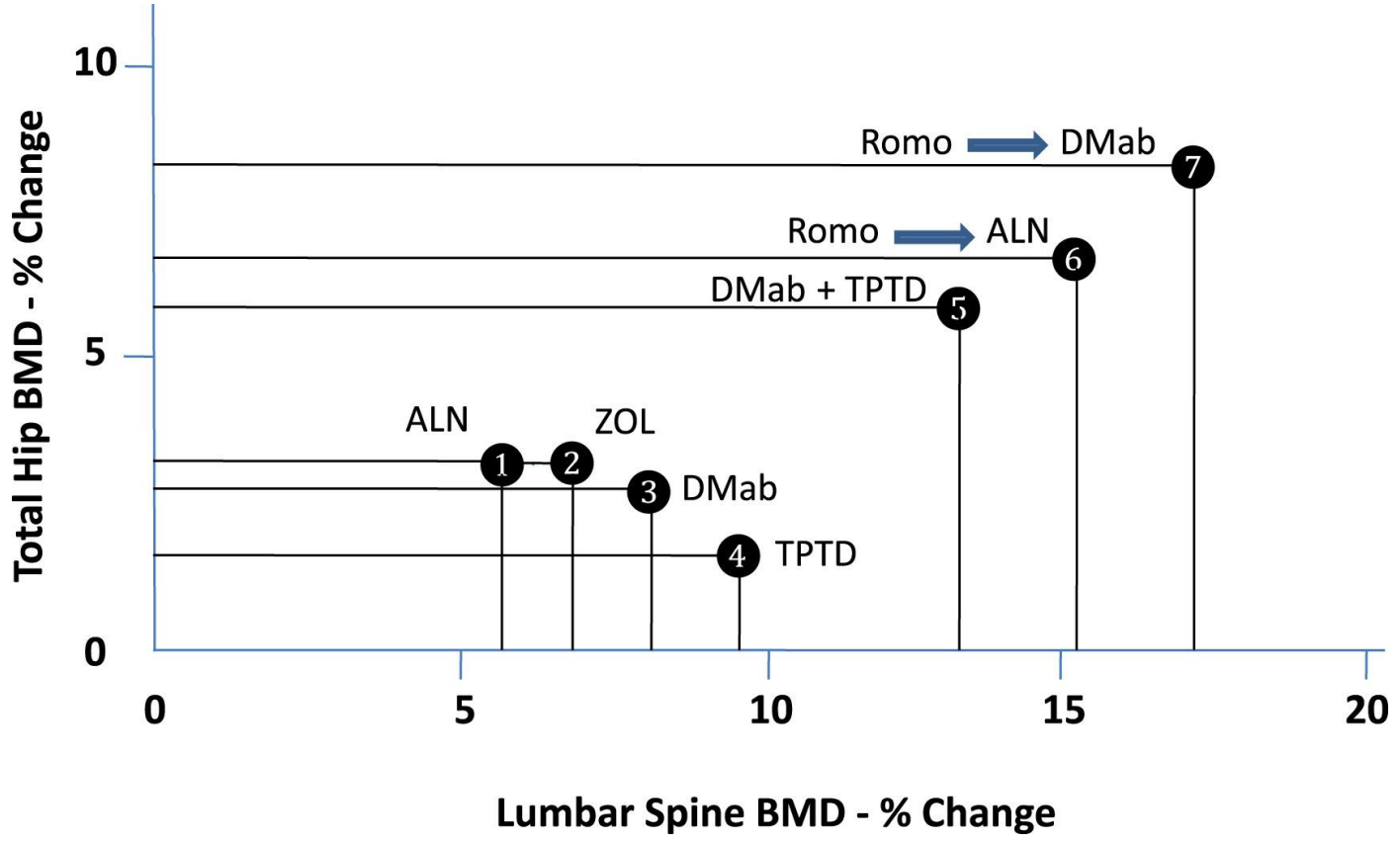
other interventions may increase BMD but less than LSC

# Nonvertebral Fracture Risk in RCTs of Osteoporosis Treatments




| D | ALN | RIS | IBN | ZOL | TPT | RLX | CTN | ET | EPT | DMAB |
|---|---|---|---|---|---|---|---|---|---|---|
| RR ⬇ | 20% | 40% | - | 25% | 50% | 10% | 12% | 30% | 24% | 20% |
| AR ⬇ | 2.8% | 3.2% | - | 2.7% | 3% | 0.8% | 1% | 3.8% | 2.1% | 1.5% |

# Change in BMD at **24 months** in Spine and Total Hip with Various Regimens






McClung Osteo Sarc 2018

# Risk Stratification and Implications

| Level of Risk | Examples | Treatment |
|---|---|---|
| Low<br>(ES, AACE) | T-score >-1.0, and no hip or vertebral fracture, and<br>FRAX MOF/HF <20%/3% | Nonpharmacologic |
| Moderate<br>(ES) | T-score >-2.5, and no hip or vertebral fracture, and<br>FRAX MOF/HF <20%/3% | Nonpharmacologic or bisphosphonate |
| High<br>(ES, AACE) | T-score ≤-2.5, or prior hip or vertebral fracture, or FRAX MOF/HF ≥20%/3% | Bisphosphonate<br>Denosumab<br>SERM |
| **Very High (ES)** | T-score ≤-2.5 and fractures, or multiple vertebral fractures, or severe vertebral fracture (>40% vertebral height loss) | Anabolic<br>Bisphosphonate<br>Denosumab |
| **Very High (AACE)** | T-score <-3.0, fracture in past 12 mo, fracture on treatment, fracture on harmful drugs, multiple fractures, high fall risk, FRAX MOF/HF >30%/4.5% | Anabolic<br>Bisphosphonate<br>Denosumab |

Sho

# Identifying Very High Fracture Risk

## AACE Guidelines[1]

- Fracture within 12 mo
- Fractures while on osteoporosis therapy
- Multiple fractures
- Fractures while on medications causing skeletal harm
- T-score <-3.0
- High risk for or history of injurious falls
- FRAX® major osteoporotic fracture >30%, hip fracture >4.5%

## ENDO Guidelines[2]

- Multiple spine fractures AND
- Hip or spine T-score ≤-2.5

## NAMS Guidelines[3]

- Prior and recent fractures
- T-score <-3.0
- Fractures or BMD loss while taking antiremodeling therapy

1. Camacho. Endocr Pract. 2020;26(suppl 1):1. 2. Shoback. J Clin Endocrinol Metab. 2020;105:587. 3. NAMS. Menopause. 2021;28:937.

# AACE Guidelines for Management of Osteoporosis: High Fracture Risk

| Patient Criteria | Risk | Initial Rx | Reassess | Comments |
|---|---|---|---|---|
| • T-score between -1.0 and -2.5 and history of fracture<br>• T-score ≤-2.5 in lumbar spine, femoral neck, total hip, or 1/3 radius<br>• FRAX major osteoporotic fracture ≥20%, hip fracture ≥3% | **HIGH RISK** | Antiresorptive | Every 1-2 yr by DXA | Clinical management depends on BMD and facture risk category |

**Injectable agents are recommended as initial therapy for patients who are at very high fracture risk or unable to use oral therapy**

# AACE Guidelines for Management of Osteoporosis: Very High Fracture Risk

| Patient Criteria | Risk | Initial Rx | Reassess | Comments |
|---|---|---|---|---|
| • Fracture within 12 mo<br>• Fractures while receiving osteoporosis therapy<br>• Multiple fractures<br>• Fractures while receiving medications causing skeletal harm<br>• T-score <-3.0<br>• High risk for or history of injurious falls<br>• FRAX major osteoporotic fracture >30%, hip fracture >4.5% | **VERY HIGH RISK** | • Anabolic agent<br>• Injectable antiresorptive | Every 1-2 yr by DXA | Antiresorptive therapy should follow anabolic therapy |

**Injectable agents are recommended as initial therapy for patients who are at very high fracture risk or unable to use oral therapy**

# AACE Recommendations for Initial Treatment

| High Risk | Very High Risk | Spine-Specific Efficacy |
|---|---|---|
| ▪ Alendronate | ▪ Abaloparatide | ▪ Ibandronate |
| ▪ Denosumab | ▪ Denosumab | ▪ Raloxifene |
| ▪ Risedronate | ▪ Romosozumab | |
| ▪ Zoledronate | ▪ Teriparatide | |
| | ▪ Zoledronate | |

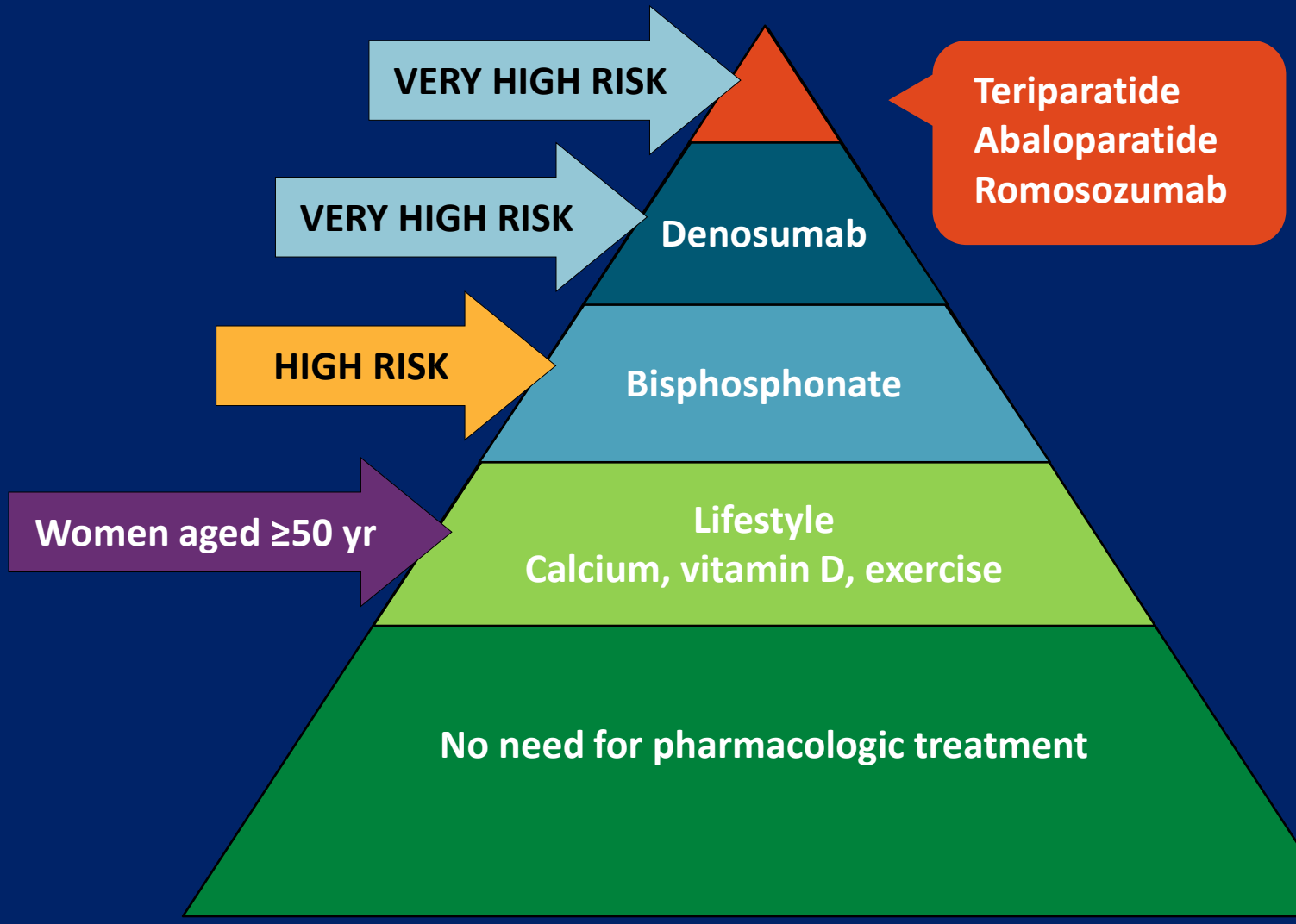
**Consider alternative therapy or reassessment for secondary osteoporosis for recurrent fractures or significant bone loss while receiving treatment**

# AACE Recommendations for Initial Treatment

| High Risk | Very High Risk | Spine-Specific Efficacy |
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| ▪ Denosumab | ▪ Denosumab | ▪ Raloxifene |
| ▪ Risedronate | ▪ Romosozumab | |
| ▪ Zoledronate | ▪ Teriparatide | |
| | ▪ Zoledronate | |

**Consider alternative therapy or reassessment for secondary osteoporosis for recurrent fractures or significant bone loss while receiving treatment**

# Spectrum of Fracture Risk



# AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

## High risk/no prior fractures

Alendronate, denosumab, risedronate, zoledronate*** • **Alternate therapy:** Ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

Assess compliance • Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

Switch to injectable antiresorptive if on oral agent • Switch to abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture

## Very high risk/prior fractures

Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate*** • Alternate therapy: Alendronate, risedronate

Reassess yearly for response to therapy and fracture risk

| Denosumab | Romosozumab for 1 year | Abaloparatide or teriparatide for up to 2 years | Zoledronate |
|---|---|---|---|
| Continue therapy until the patient is no longer high risk and ensure transition with another antiresorptive agent | Sequential therapy with oral or injectable antiresorptive agent | Sequential therapy with oral or injectable antiresorptive agent | If stable, continue therapy for 6 years**** • If progression of bone loss or recurrent fractures, consider switching to abalopa-ratide, teriparatide or romosozumab |

BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

osteoporotic fracture risk ≥ 20% or hip fracture ris
regions may have different thresholds.
** Indicators of very high fracture risk in patients with low bone den
advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.
*** Medications are listed alphabetically.
**** Consider a drug holiday after 6 years of IV zoledronate.
During the holiday, an anabolic agent or a weaker antiresorptive such as raloxifene could be used.

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# Pharmacological therapy

**Pharmacological therapy is recommended:**

- For postmenopausal women with **hip or vertebral fractures**
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- Those with T-scores of **-1 to -2.5** and a 10-year probability of **≥20%** for major osteoporotic fractures or **≥3%** for hip fractures based on the FRAX tool