Boning Up on Osteoporosis: It's Not Just About the T-score

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Disclosure

I have no financial interests or relationships to disclose.

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Learning Objectives

- Identify patients at high risk of osteoporosis and osteoporotic fracture and select evidence-based screening and diagnostic modalities
- Recognize the efficacy, risks, and benefits of new and emerging treatments for osteoporosis
- Understand the latest guidelines for the prevention and treatment of osteoporosis

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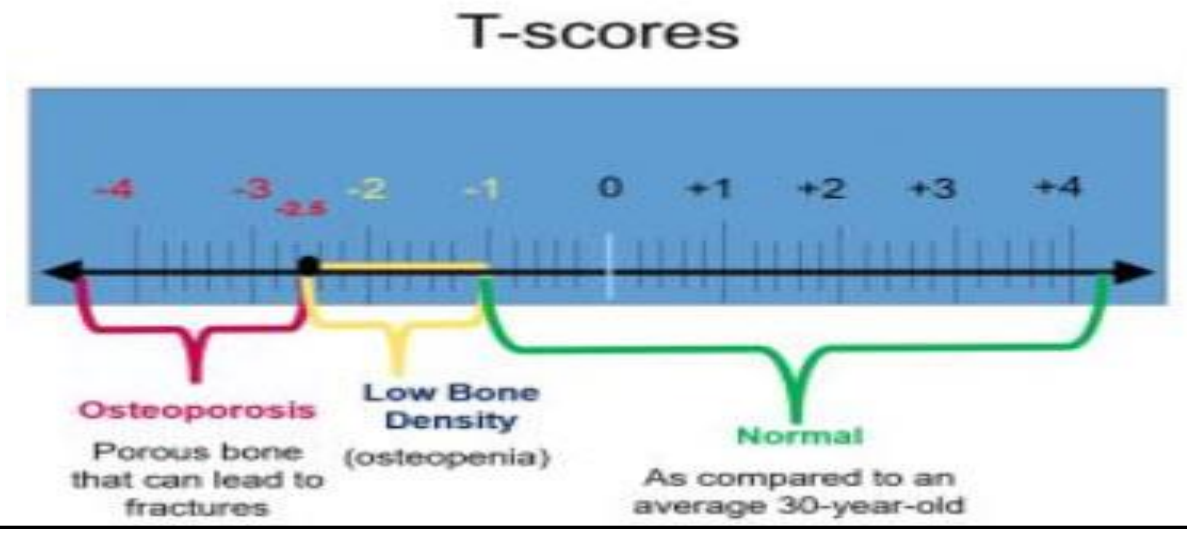
W.H.O.'s Definition of Low Bone Mass and Osteoporosis

World Health Organization Definition-Criteria:

CLASSIFICATION	T-score
NORMAL BMD (Bone Mineral Density)	> -1.0
Low Bone Mass (Osteopenia)	-1.0 -- -2.49
Osteoporosis	≤ -2.50

4

World Health Organization Definition-Criteria:



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W.H.O's Definition of Osteoporosis

"A T score of -2.5 or worse, meaning 2.5 standard deviations below the mean for a normative population of young healthy women".

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Definition of Osteoporosis

Osteoporosis: bone loss which leads to a decrease in bone strength which leads to an increased risk of fracture.

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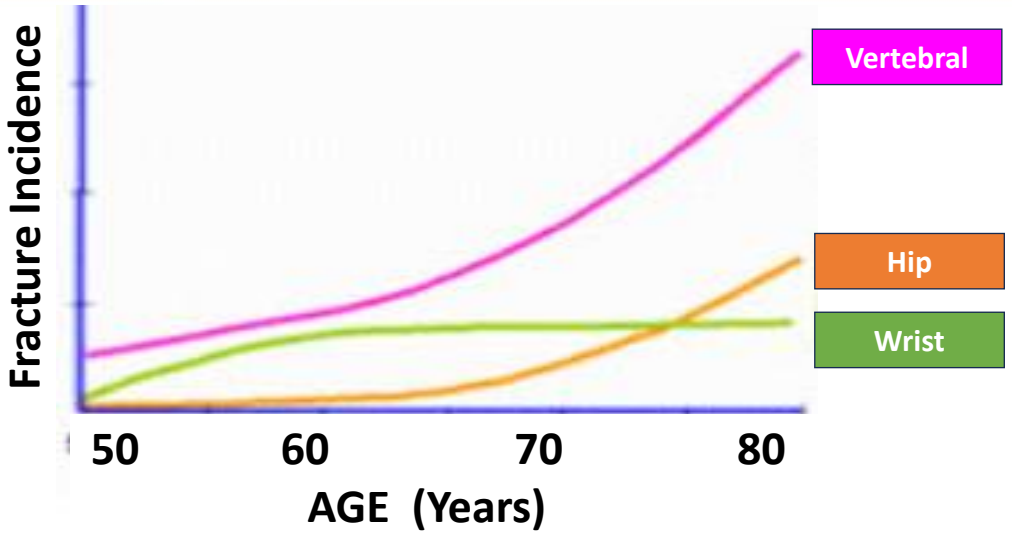
One More Definition: Severe Osteoporosis AKA "Very High Risk of Fracture" (Disparate Definitions)

- **1. A T-score of ≤ -3.0**
- **2. A history of multiple fragility fractures**
- **3. One who experienced a fragility fracture while on Rx**
- **4. Woman taking ≥7.5 mg prednisolone daily (long-term Rx)**

8

Incidence of Osteoporotic Fractures by Site



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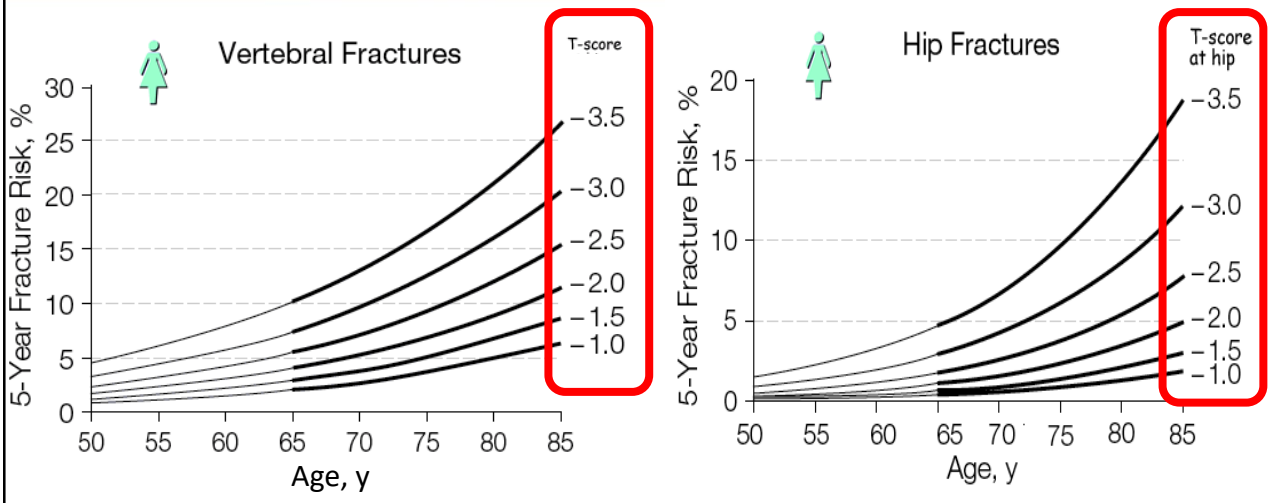
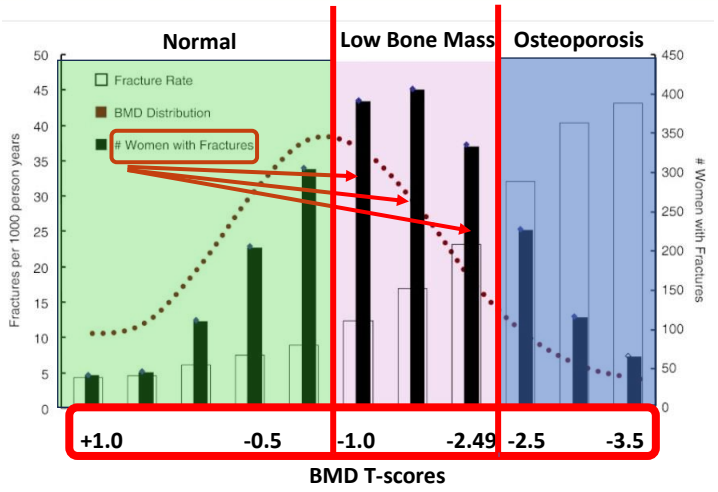
We've Been Taught to Think Like This



10

Your Patient's Absolute Risk of a Fracture (Black Bars)



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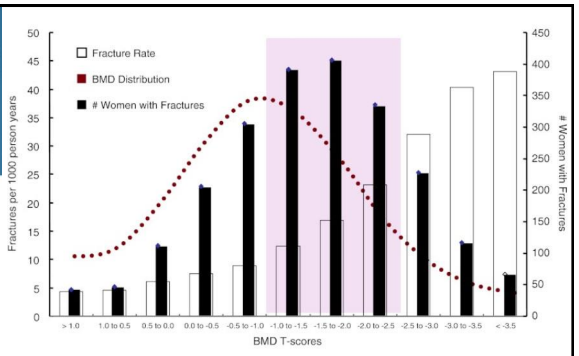

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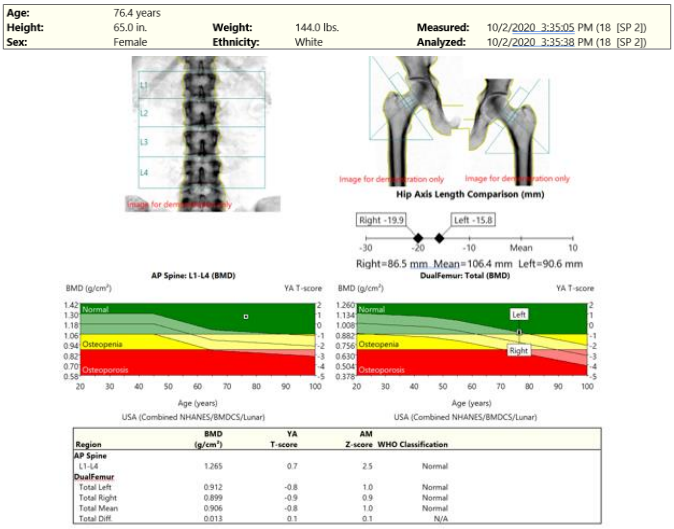
What We Forget ALL TOO OFTEN

- The definition of osteoporosis is NOT just a T score of ≤ -2.5



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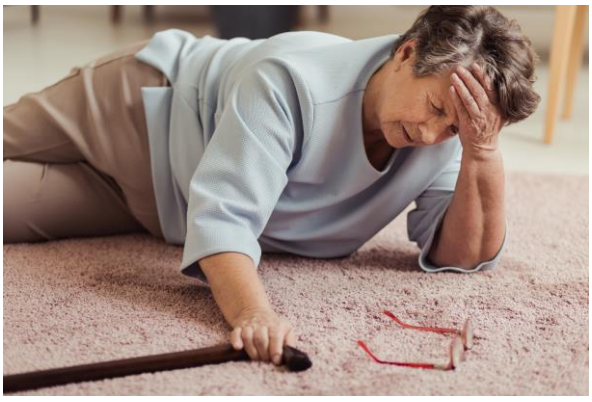
Osteoporosis Can Also Be Defined by A FALL

- A fall from standing height that results in…
  - a fragility fracture of the spine or hip qualifies as defining osteoporosis, irrespective of her T-score

    AND
  - a fragility frx of the proximal humerus or distal forearm/wrist, IF her T-score is any value < -1.0



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We've Been Exposed to a LOT of MYTH-information

- **It is all too easy to focus on T-scores … and to forget why we are measuring BMD**
- **Our goal is NOT to achieve improved T-scores**
- **Our goal IS TO PREVENT the FRACTURES and falls that directly result from osteoporosis- called fragility fractures**

BMD = bone mineral density

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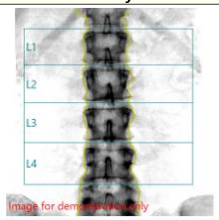
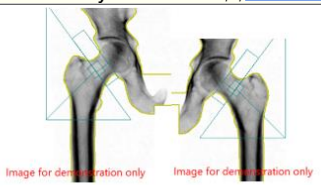
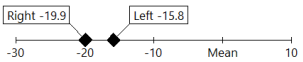
Age:	76.4 years				
Height:	65.0 in.	**Weight:**	144.0 lbs.	**Measured:**	10/2/2020 3:35:05 PM (18 [SP 2])
Sex:	Female	**Ethnicity:**	White	**Analyzed:**	10/2/2020 3:35:38 PM (18 [SP 2])



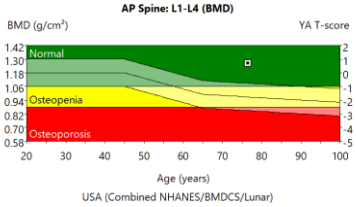


Hip Axis Length Comparison (mm)



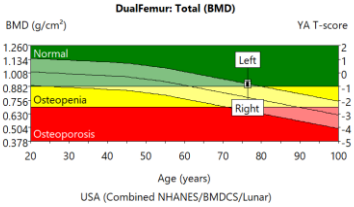
Right=86.5 mm Mean=106.4 mm Left=90.6 mm

AP Spine: L1-L4 (BMD)



USA (Combined NHANES/BMDCS/Lunar)

DualFemur: Total (BMD)



USA (Combined NHANES/BMDCS/Lunar)

Region	BMD (g/cm²)	YA T-score	AM Z-score	WHO Classification
AP Spine				
L1-L4	1.265	0.7	2.5	Normal
DualFemur				
Total Left	0.912	-0.8	1.0	Normal
Total Right	0.899	-0.9	0.9	Normal
Total Mean	0.906	-0.8	1.0	Normal
Total Diff.	0.013	0.1	0.1	N/A

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Peripheral DXA of Distal Radius (or Heel)

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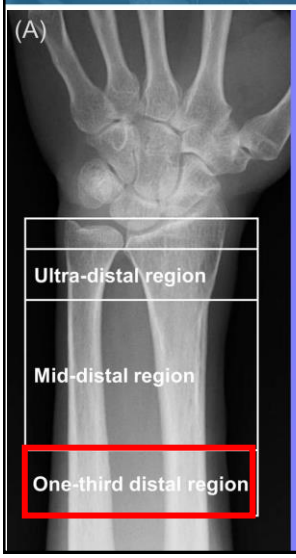
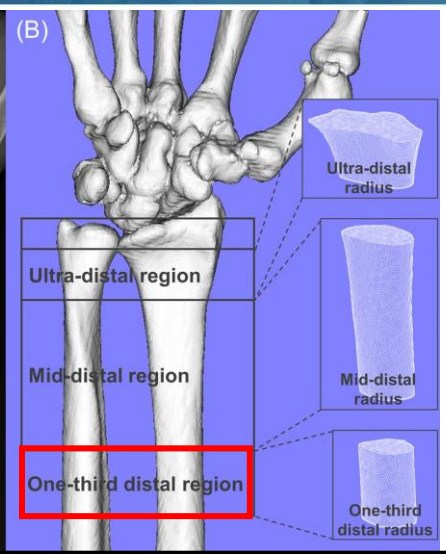
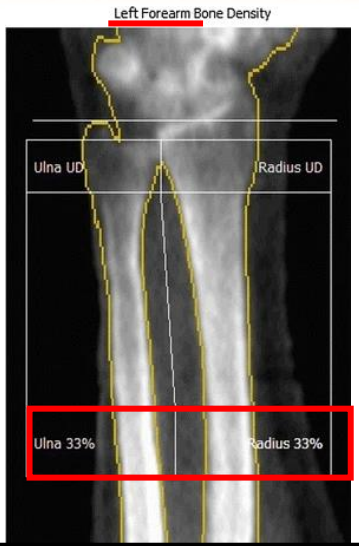
"1/3 Distal Radius" AKA "the 33% Radius" in the NON-DOMINANT Forearm







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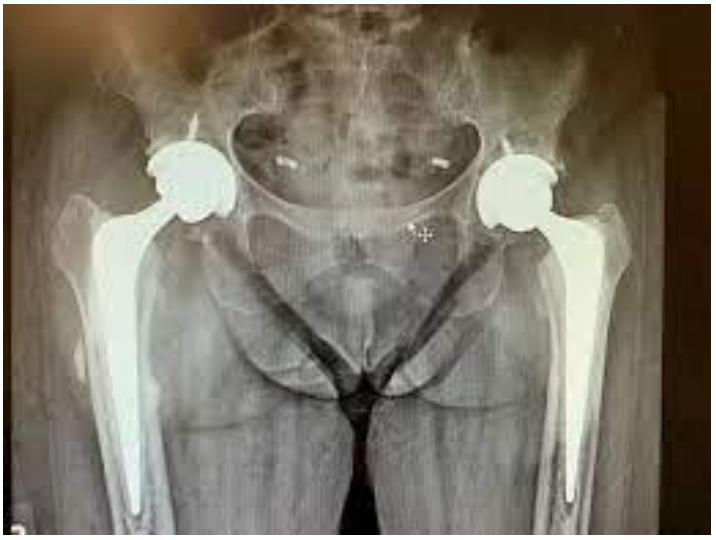
Peripheral DXA of 1/3 Distal Radius for Patients with Prior Surgery



19

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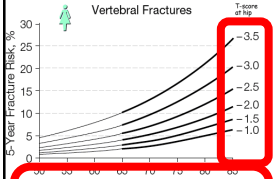
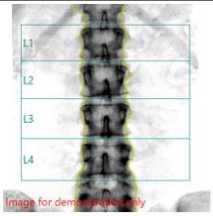
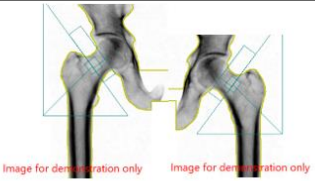


RELATIVE fracture risk





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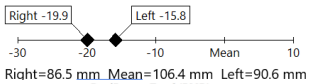

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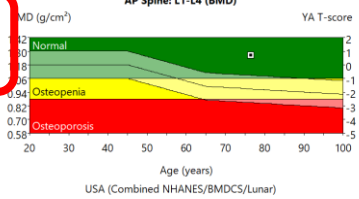

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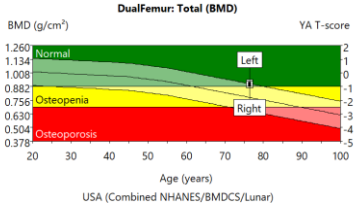

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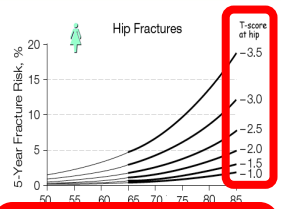

RELATIVE fracture risk

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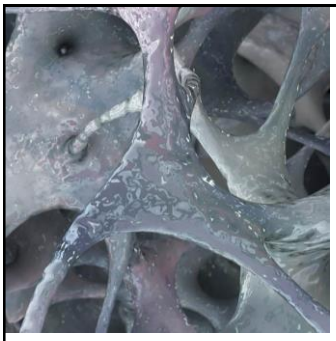
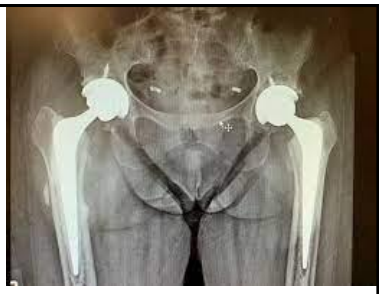


How Might We Do a Better Job Predicting…



ACTUAL FRACTURE RISK ?
(Absolute Risk, Not Relative Risk)

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The Optimal Fracture Prediction Profile - 2024

Combination:

- **BMD (central DXA**; peripheral DXA is satisfactory if central DXA testing is not available/reliable)
- **FRAX®**
- +/- Trabecular Bone Score (TBS)

DXA = bone density scanning / dual-energy x-ray absorptiometry

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How Familiar Are YOU with the FRAX Tool?

A. I've never heard of it
B. I've heard of it, but never (or rarely) use it clinically
C. I use it sometimes, but not routinely
D. I use it routinely

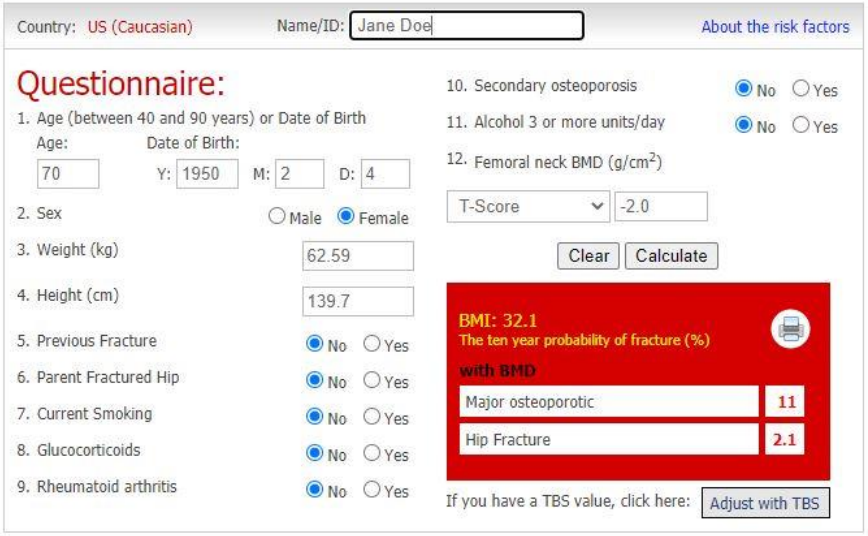
FRAX® Risk Assessment
ACTUAL (Not Relative) Fracture Risk

This patient has a 10-year hip fracture risk of ____%; and a 10-year major osteoporotic fracture risk of ____%

Based upon…

- Age, gender, ethnicity
- **Y N** Hx of fragility fracture, >50 y/o
- **Y N** Rheumatoid arthritis
- **Y N** Family Hx of a hip fracture - parent
- **Y N** Low BMI / body weight
- **Y N** Ever-Hx of steroid Rx ≥ 5mg/d x ≥ 3 mos
- **Y N** Alcohol - ≥ 3 units / day
- **Y N** Current smoking
- +/- BMD @ femoral neck

Lewiecki EM. JBMR. 2007; 22: 1832-41.



https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9

Thresholds for High Risk: ≥20% major; ≥3% hip

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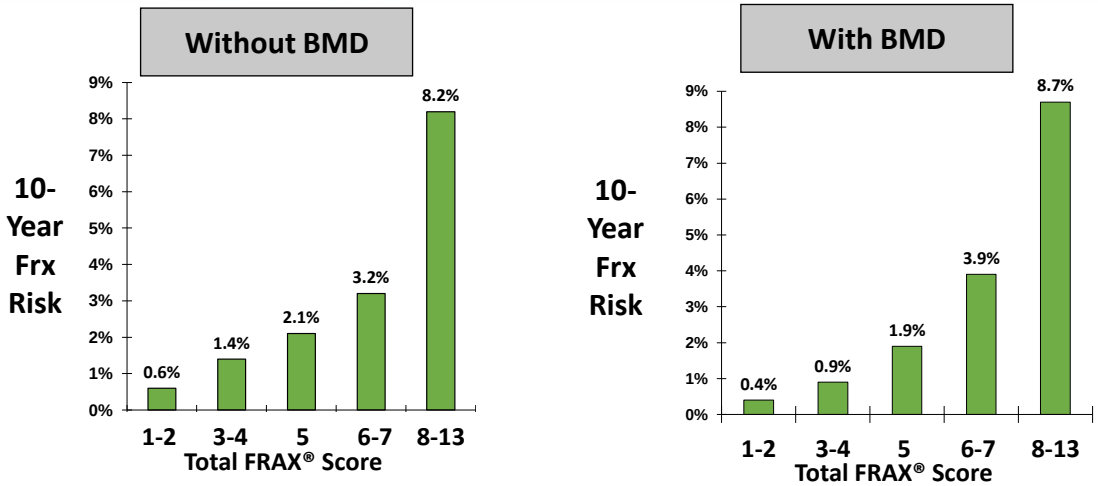
Ten-Year Risk of Hip Fracture



Quintiles Fracture Index

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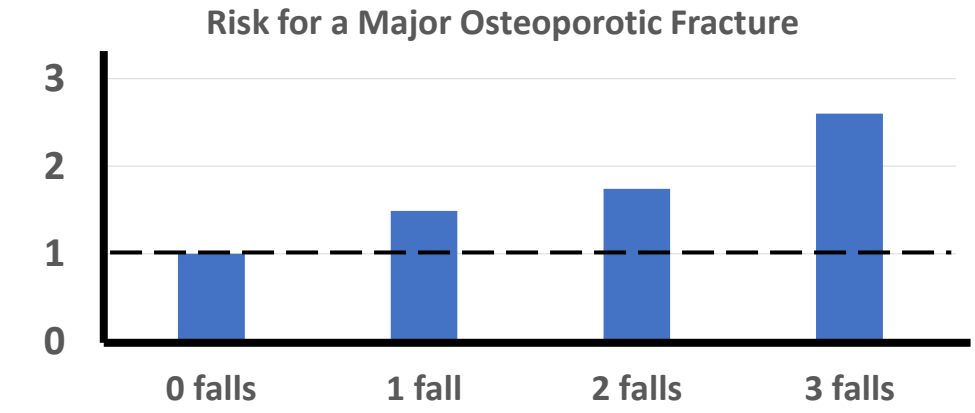
One Powerful Screening Question in Addition to FRAX®

"Have you fallen in the past year ?"



Leslie WD. Osteopor Int. 2019. Aug 2. doi: 10.1007/s00198-01905106-3

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Limitations of FRAX

- **Valid only given specific conditions:**
- Postmenopausal women > 40 y/o
- Not on Rx
  - Cannot follow-up/repeat FRAX after beginning Rx
- No prior hip or vertebral fracture
- Categorical dichotomous variables
  - Does not allow for degrees of risk-exposure

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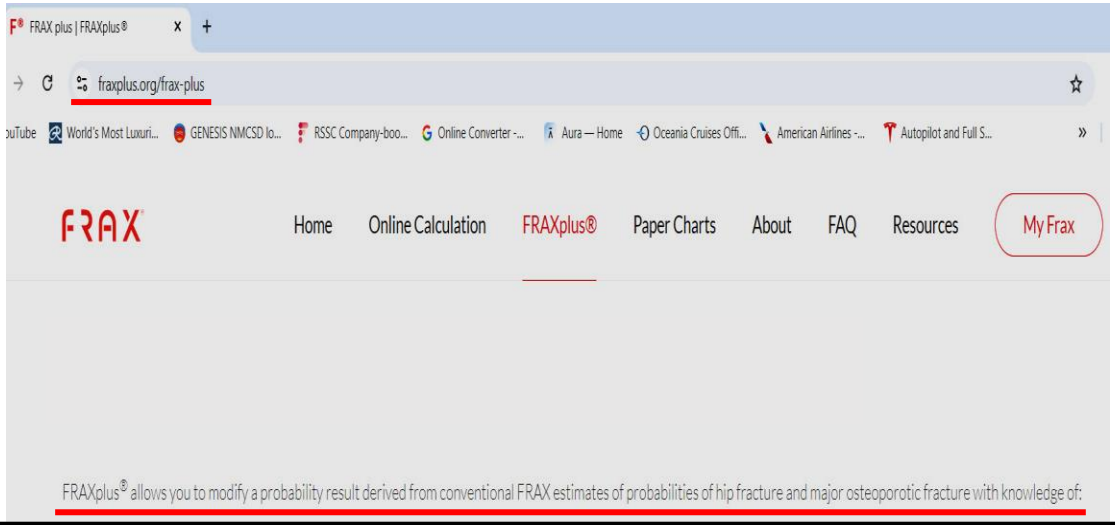
FRAXplus® Risk Assessment



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FRAXplus® Risk Assessment

Select the SINGLE most dominant factor – most likely to impact the actual risk score. (FRAXplus® provides guidance to clinicians for this)

- Recency of a previous osteoporotic (fragility) fracture
- HIGH-dose glucocorticoids
- Type-2 diabetes
- Concurrent lumbar spine BMD
- Details of falls history – 0, 1, 2, or 3 over the past 12 months
- Trabecular bone score
- Hip axis length

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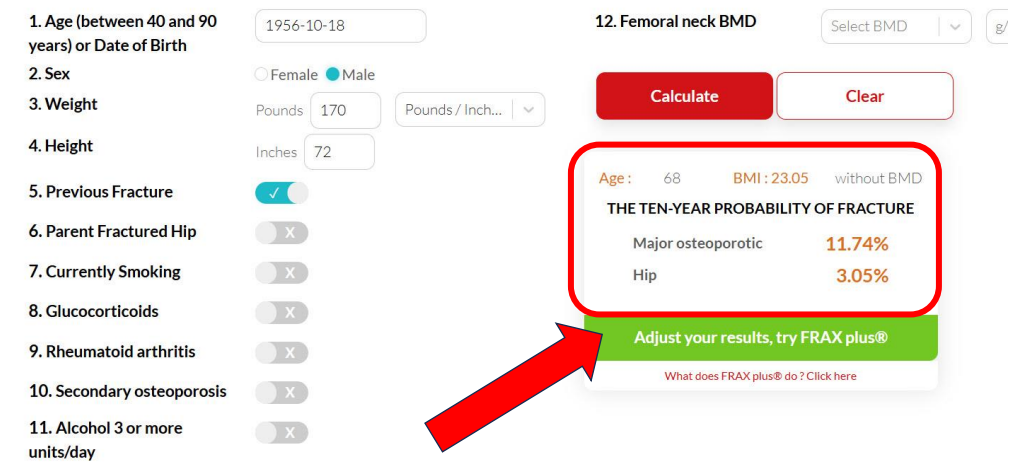
How to Use FRAXplus® - Step 1



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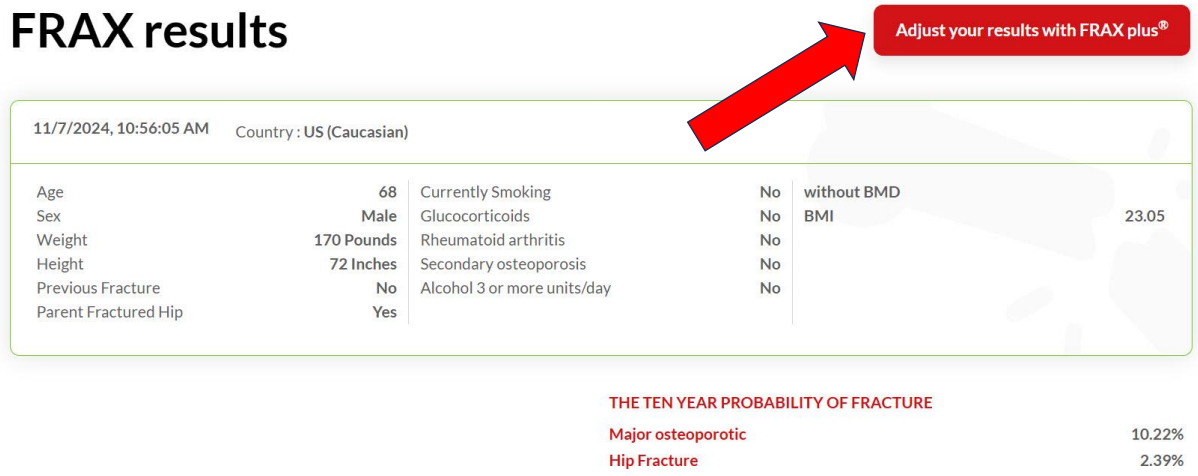
How to Use FRAXplus® - Step 2



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How to Use FRAXplus® - Step 3

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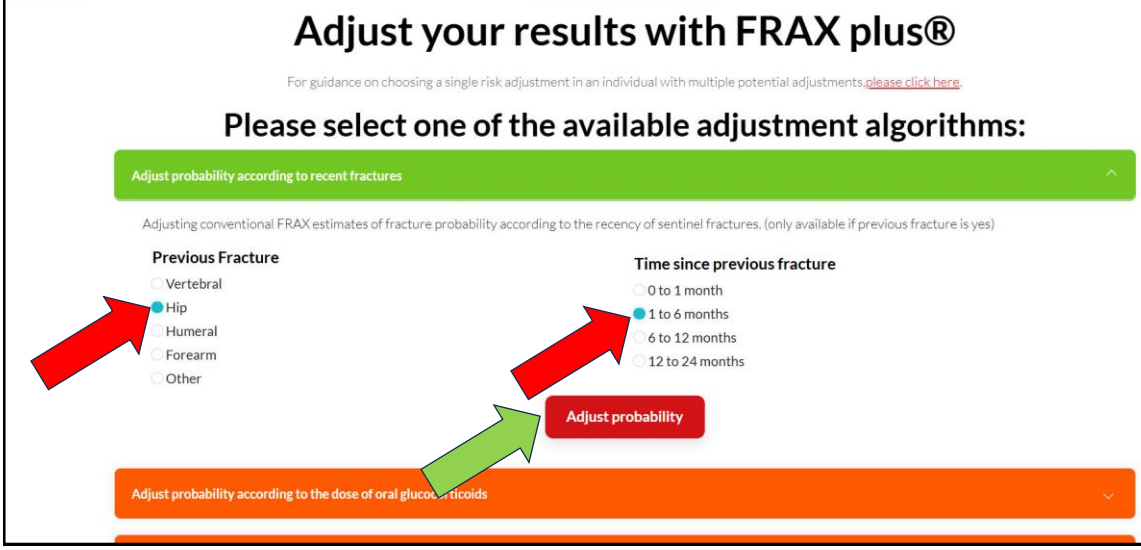
How to Use FRAXplus® - Step 4



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How to Use FRAXplus® - Step 5

Age	68	Currently Smoking	No	without BMD	
Sex	Male	Glucocorticoids	No	BMI	23.05
Weight	170 Pounds	Rheumatoid arthritis	No		
Height	72 Inches	Secondary osteoporosis	No		
Previous Fracture	Yes	Alcohol 3 or more units/day	No		
Parent Fractured Hip	No				

THE TEN-YEAR PROBABILITY OF FRACTURE

Major osteoporotic	UNadjusted	11.74%
Hip Fracture		3.05%

PROBABILITY ADJUSTED ACCORDING TO RECENT FRACTURE

Previous Fracture		Hip
Time since previous fracture		1 to 6 months
Adjusted Major osteoporotic	ADJUSTED	18%
Adjusted Hip Fracture		9.16%

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FRAXplus® - Results

THE TEN-YEAR PROBABILITY OF FRACTURE

Major osteoporotic	FRAX	11.74%
Hip Fracture		3.05%

PROBABILITY ADJUSTED ACCORDING TO RECENT FRACTURE

Previous Fracture		Hip
Time since previous fracture		1 to 6 months
Adjusted Major osteoporotic	FRAXplus®	18%
Adjusted Hip Fracture		9.16%

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They DO Charge to Use FRAXplus®

	FRAX	FRAX plus
Web	Free	Credits*
Desktop	Licence	Licence + Credits*
Mobile	Licence	Licence + Credits*
Embedded	Licence	Licence
Web Service	Licence	Licence

* 5 free credits when creating new account
* 50% discount for low and lower-middle income economies according to the World Bank Country Classification

Buy Credits
(1 credit = 1 FRAXplus® adjustment)
Click below

50	~~100 EUR~~ 50 EUR*
100	~~200 EUR~~ 100 EUR*
200	~~400 EUR~~ 200 EUR*

*50% special discount for the launch of the new FRAX website
If you need to purchase more credits, please contact us.

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U.S. Preventive Services Task Force (USPSTF) and AACE Recommendations

- Screen all (women and men) >50 with a history and a FRAX® or other fracture risk calculator (e.g. Garvan, CAROC); repeat q 5 years
- Screen all women ≥ 65 years old with BMD testing
- Also do BMD testing for women < 65 who are at increased risk for osteoporosis based upon formal risk assessment tools (e.g. FRAX®)
  - e.g. a FRAX® **score of ≥ 8.2-9.8%** risk for a major osteoporotic fracture (score for a weight-matched 65 y/o without any risk factors)

AACE = American Association of Clinical Endocrinologists

Curry SJ. USPSTF Recommendations JAMA. 2018;319: 2521-31. Guirguis-Blake J. USPSTF Evidence Report. JAMA. 2018; 319(16): 1705-16.
AACE Guidelines for Clinical Practice Guidelines for PMO. Endocrine Practice 2020; 6 (Suppl)

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Which Women to do DXA Before 65 Years Old (But Not Premenopausal Women)

- FRAX®: >8.2—9.8% 10-yr risk of a major osteoporotic fracture
- PMHx fragility fracture
- Radiographically-identified low BMD
- Starting or taking ≥ 3 months of glucocorticoid therapy (esp. if >7.5 mg prednisolone/day)
  - Or aromatase inhibitors long-term
- Any ONE of these risk factors, IF she would be willing to consider Rx:
  - Low body weight (<58Kg (127 lbs) or BMI <20 kg/m^2)
    - Low body weight is the single best predictor of low BMD
  - Early menopause
  - Current smoker
  - Excessive ethanol intake (>2 units/day)

PMHx = patient medical history

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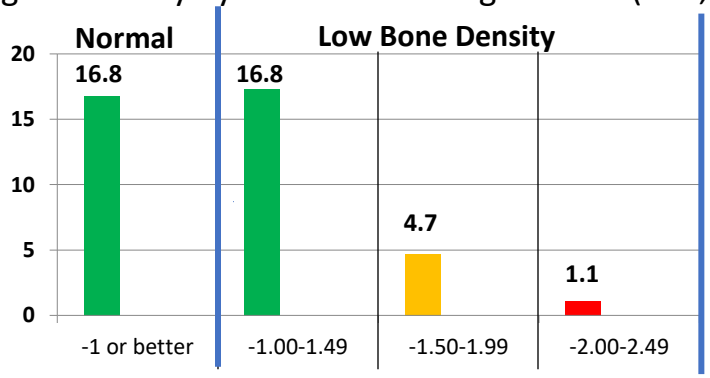
When to Repeat DXA?

- Medicare allows q 24 months
- Gourlay's data suggest: stratify by initial value at age 65--67 (n=4,957)

# of years for <u>10%</u> of women to develop osteoporosis



Gourlay M. NEJM. 2012; 366: 225-33.
Gourlay ML. Am J Med. 2017;130: 862.e15-862.e23

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Conclusions from a Composite Literature Review (Including Gourlay's Data)

- If Normal BMD (>-1.0) → re-screen in 10--15 years
- If T-score -1.0 to -1.4 → re-screen in 5—10 years
- If T-score -1.5 to -1.99 → re-screen in 3--5 years
- If T-score -2.0 to -2.49 → re-screen in 2 years
- If T-score < -2.50 → Recommend treatment

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Most Recent Recommendations

American College of OB/GYN:

Repeat DEXA every 1--3 years during Rx, until findings are stable (MODERATE-QUALITY Evidence)

American Association of Clinical Endocrinologists:

Monitor therapy every 1-2 years, or less frequently, as clinically indicated

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Laboratory Testing in Osteoporosis

ALL Patients

- CBC
- CMP (Calcium, renal function, phosphorus, magnesium)
- 25-hydroxyvitamin D level
- PTH
- 24-hour urine for calcium, creatinine

Selective - As Indicated

- TSH
- Serum/urine protein electrophoresis
- tTG antibodies
- Cortisol
- 24-hour urine cortisol

CBC = complete blood count; CMP = complete metabolic panel; PTH = parathyroid hormone; TSH = thyroid-stimulating hormone; tTG = tissue transglutaminase

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Summary: Predicting Fracture Risk

It's NOT just a DXA T-score

- FRAX® Risk Score and +/- Trabecular Bone Score (TBS)
- Recent falls (esp. in past 12 months)
- Loss of height since age 25 (abnl > 1.6")
  - Morphometric evidence of prior vertebral fracture (even if asymptomatic)
- Impaired visual acuity (over age 65)
- Ability to rise from a chair without use of arms

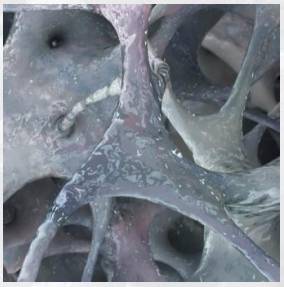
44

Chair Rise Test: SUCCESSFUL

45

Chair Rise Test: UNSUCCESSFUL

46



Diagnosis

Treatment

47

To Prevent Fractures (esp. Hip Fractures)

48

Simple First Steps to Reduce Fall & Fracture Risks

- Assess postural blood pressure and pulse
- If poor eyesight – ophthalmologic/optometry referral
- If poor balance/abnormal gait – define the etiology
  - Consider physical therapy referral
  - Consider Tai Chi for balance
- Minimize sedative/sleep meds
- Exercise
  - Weight-bearing & muscle-strengthening x 30 min 3x/wk minimum
- Household evaluation
  - Lighting, rugs, rails, cords, pet or grandchild toys

Grossman JM. Curr Opin Rheum. 2011; 23: 203-210.

49

Calcium & Vitamin D - Dietary Sources Are Preferred AACE Guidelines 2020; ACOG 2022

- Advise adequate dietary Ca++
  - Supplement as needed – to total (dietary + supplement) 1200 mg/d after age 50 (vs. 1000 mg/d ages 19-49)
  - Not to exceed >2,000 mg/day
- Vitamin D3 supplementation (if needed)
  - Goal: maintain @ 30-50 ng/mL (equivalent to 75-125 mmol/L)
  - Supplement with 600 IU/d up to age 70; 800-2000 IU/day after age 70
- Encourage discontinuation of smoking
- Avoid excessive ETOH (> 2 units/day)

ETOH = ethanol

50

NAM Recommendations for Calcium & Vit D

AGE	9--18	19--49	50--70	>70
Calcium (mg / day)	1300	1000	1200	1200
Vitamin D (IU / day)	600	600	600	800

AACE: 1000-2000 IU/day

51

How Can We Prevent the Most Fractures…

Based Upon the Best Available Evidence And for the Best Value $$

52

Who to Treat – 2024 Guidelines

- Strongly recommend Rx for patients with a T-score of -2.5 or lower
- Strongly recommend Rx for patients who've had a fragility (low-trauma) fracture of the hip or spine
- Strongly recommend Rx for patients with a T-score between -1.0 and -2.5 if…
  - If they've had fragility (low-trauma) fracture of the pelvis, proximal humerus, or distal forearm
  - If their FRAX® score is high (10-year risk is >3% @ hip and/or >20% in general)
- (Some experts strongly recommend Rx for patients whose FRAX® score is high (10-year risk is >3% @ hip and/or >20% in general)

Grade A; Evidence Level 1

53

How Can FRAX® Guide Management? AACE Guidelines 2021

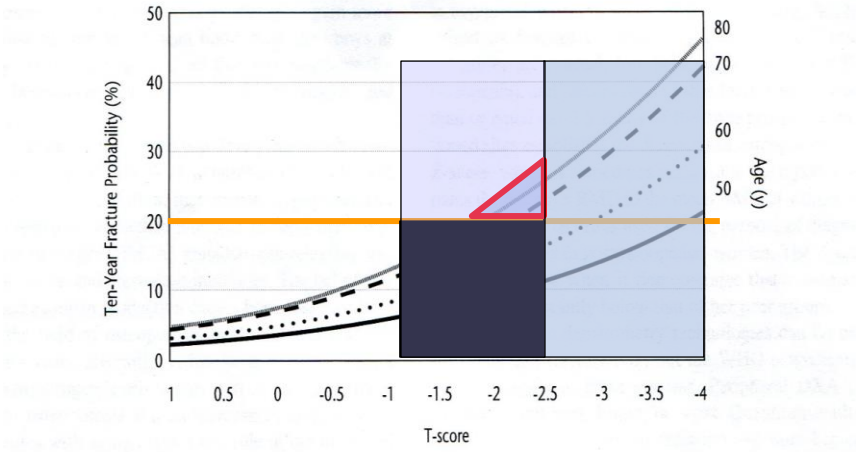
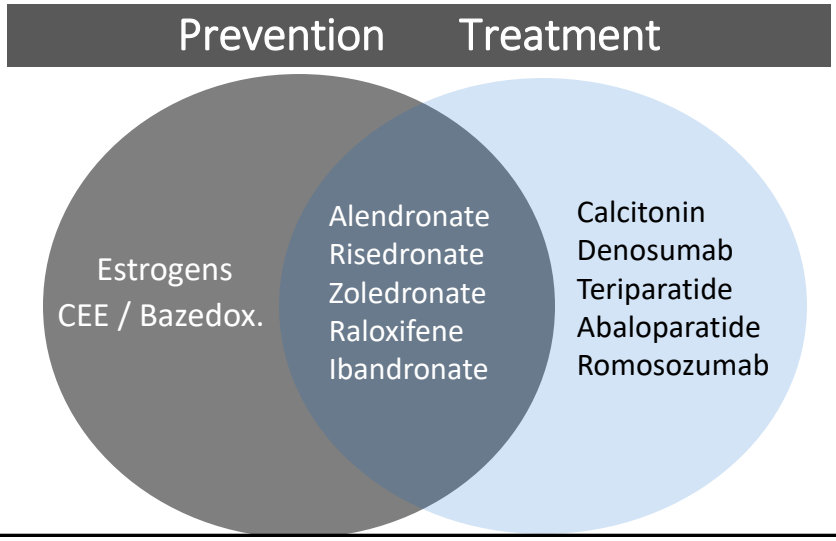


Fig. Kanis et al, Osteopor Int. 2001; 12(12): 989-95.

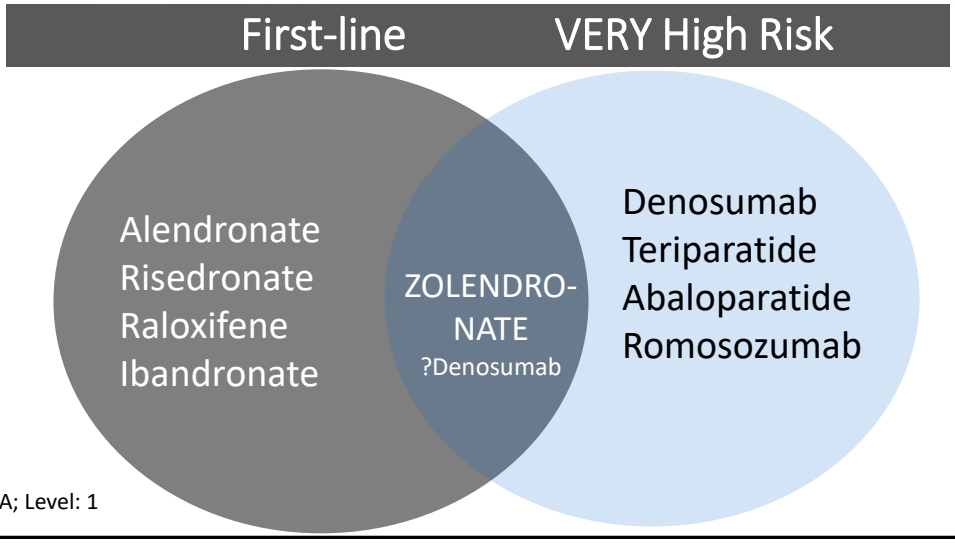
54

Postmenopausal Osteoporosis per the FDA



55

Treatment of Osteoporosis per AACE Guidelines 2020; ACOG 2022; ACP 2024



Grade: A; Level: 1

56

ACP 2024 Guidelines

ACP Journals ACP GUIDELINES FOR TX/PREV'N OF PRIMARY OSTEO IN WOMEN (&MEN) 2023 – UPDATED May, 2024.

Free access

Clinical Guidelines

3 January 2023

Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians

57

ACP Recommendations May, 2024

- Use bisphosphonates for first-line pharmacologic treatment for postmenopausal women with primary osteoporosis in order to reduce the risk of fractures (HIGH QUALITY EVIDENCE)
  - Males (LOW QUALITY EVIDENCE)
- Use denosumab for 2nd –line* pharmacologic treatment for postmenopausal women with primary osteoporosis in order to reduce the risk of fractures (MODERATE QUALITY EVIDENCE)
  - Males (LOW QUALITY EVIDENCE)
  - *due to (1) cost, and (2) results are not much better than with bisphosphonates

58

NAMS- Position Statement

- For women at very high risk for fracture (disparate definitions)
  - Begin with an osteoanabolic agent
    - More effective than antiresorptive agents (AKA “anti-remodeling agents”)
- No agent “cures” osteoporosis
  - Drug holidays are acceptable/recommended (only for bisphosphonates)
    - McClung M. Jnl N Amer Menopause Soc. 2021; 28(9): 973-97

59

F.A.C.T. Head-to-Head

Fosamax-**A**ctonel **C**omparison **T**rial

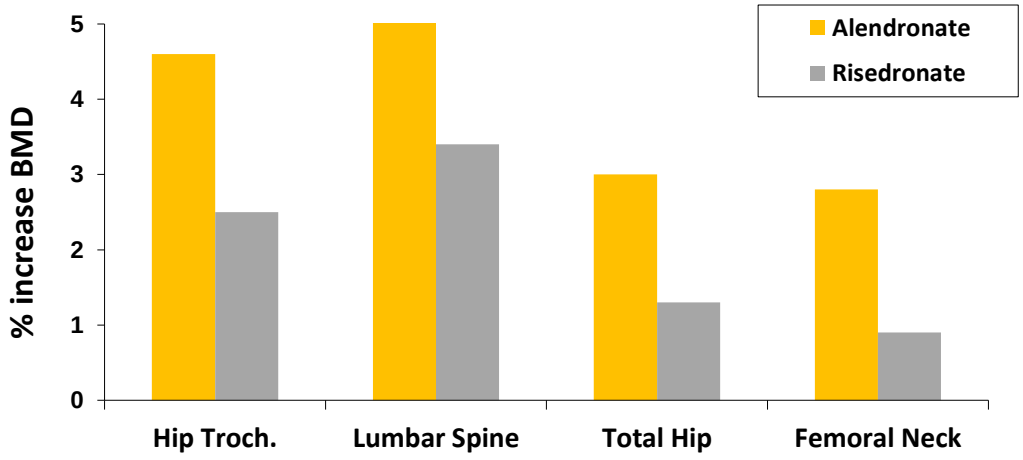
Fosamax 70 mg q wk vs. Actonel 35 mg q wk

- DBDDummyCRT (each pt took two pills – one active and one look-alike dummy to the other)
- N=1,053 women with postmenopausal osteoporosis (T < -2.5)
- All women were also given Ca++/Vit D
- F/U DXA BMD at 12 and 24 months

Rosen CJ. JBMR 2005; 20(1): 141-51.

60

Increases in BMD with Alendronate vs. Risedronate at 24 Months in F.A.C.T.



Reid D. Int J Clin Pract 2008; 62: 575-84.

61

F.A.C.T Clinical Adverse Events Over 24 Months

Number (%) of Patients	Alendronate 70 mg/wk (N=411) n (%)	Risedronate 35 mg/wk (N=414) n (%)
With 1 or more AE	358 (87.1)	356 (86.0)
With serious AE	51 (12.4)	56 (13.5)
With 1 or more UGI AE	102 (24.8)	95 (22.9)
With serious UGI AE	4 (1.0)	6 (1.4)
Death due to serious UGI AE	0 (0.0)	1 (0.2)
Clinical Fractures	**34 (8.3)**	**34 (8.2)**

Reid D. Int J Clin Pract 2008; 62: 575-84.

62

"A difference, in order to be a difference … MUST MAKE A DIFFERENCE"

David Plourd, M.D.
sitting on the boat one night
after 3 rum runners
circa July, 2013

63

Greater Differences in BMD Do Not Confer Greater Fracture Protection

Antiresorptive Therapy	BMD Increase (3 yr treatment)	Vertebral Fracture Risk Reduction (3 yr treatment)
Raloxifene[1]	2.6	50%
Ibandronate[2]	5.2	52%
Risedronate[3]	5.9	49%
Alendronate[4]	8.8	48%

Data are from separate placebo-controlled trials. These are not head-to-head trials in the same patient population, and therefore can not be used to compare clinical efficacy.

1. Ettinger, et al. *JAMA* 1999; 282(7): 637-645.
2. Chestnut, et al. *J Bone Miner Res* 2004; 19(8):1241-9.
3. Reginster, et al. *Osteoporosis International* 2000; 11: 83-91.
4. Liberman, et al. *NEJM* 1995; 333(22): 1437-1443.

64

Greater Differences in BMD Do Not Confer Greater Fracture Protection

Antiresorptive Therapy	FN BMD Increase (3 yr treatment)	Non-Vertebral Fracture Risk Reduction (3 yr treatment)
Risedronate[3]	1.6	39% (p=0.02)
Raloxifene[1]	2.1	10% (NS)*
Ibandronate[2]	2.6	0% (NS)
Alendronate[4]	5.9	21% (NS)

Data are from separate placebo-controlled trials. These are not head-to-head trials in the same patient population, and therefore can not be used to compare clinical efficacy.

1. Ettinger, et al. *JAMA* 1999; 282(7): 637-645.
2. Chestnut, et al. *J Bone Miner Res* 2004; 19(8):1241-9.
3. Harris, et al. *JAMA* 1999; 282:1344-52.
4. Liberman, et al. *NEJM* 1995; 333(22): 1437-1443.

65

Summary of the Effectiveness of Bisphosphonates

3-year prospective data:

Vertebral Fractures

Δ ~50% (p<0.001) reduction in risk

Hip Fractures

Δ 10--39% (p<0.001) reduction in risk

66

Which ONE of the Following Would NOT Be an Appropriate Intervention If a Woman's BMD Worsens After 2 Years on Bisphosphonate Therapy?

A. Evaluate for causes of secondary osteoporosis
B. Add a second agent to her existing regimen (begin combination Tx)
C. Change to a different agent
D. Refer to an endocrinologist or rheumatologist

CONTINUING EDUCATION COMPANY

67

Causes of Secondary Osteoporosis (A Short List)

- AIDS / HIV
- Anorexia nervosa
- Celiac disease
- Diabetes (types 1 and 2)
- Diminished ovarian reserve
- Gastric bypass
- Hyperparathyroidism
- Hypocalcemia
- Premature menopause
  - Including surgical or induced
- Primary ovarian insufficiency
  - Turner's syndrome
- Renal impairment
- Rheumatoid arthritis
- Vitamin D deficiency
- Medications

68

Medications Associated With Decreased BMD (A Short List)

- Steroids
- Aromatase inhibitors
- Proton pump inhibitors
- SSRI's
- Anticonvulsants
  - phenytoin, phenobarbital, carbamazepine, and primidone
- GnRH analogues
- heparin

69

Zoledronic Acid

- **HORIZON** (**H**ealth **O**utcomes **R**educed **I**ncidence with **Z**oledronic Acid **ON**ce Yearly)
  - Annual IV infusion – 5mg over ≥ 15 min
- 3-yr prospective follow-up data
  - **Vertebral Fractures**
    - 92 frx (Z-arm) [3.2%] vs 310 frx [10.9%]
    - **Δ 70%** (p<0.001) reduction in risk
  - **Hip Fractures**
    - 52 frx (Z-arm) [1.4%] vs 88 frx [2.5%]
    - **Δ 41%** (p<0.001) reduction in risk

Black D. NEJM 2007; 356: 1809-22.

70

Zoledronic Acid for Women with Osteopenia
(Low Bone Density)

- N=1,861
- 6-year F/U
- Placebo (925) ➡ 190 fragility fractures
- Zoledronate (936) ➡ 122 fragility fractures

} **37% reduction**

2018: new indication for zoledronic acid
For osteopenia (low bone density) T -1.0 to -2.5
5 mg IV infusion over >15 minutes **q 18 mos**

Reid I. NEJM. 2018.

71

When Should a Drug Holiday Be Considered
AACE 2020; AGOG 2024

- **For bisphosphonates**: after 5 yrs IF THE T-score improves to > -2.5, and pt remains fracture-free;
  - IF NOT, continue Rx for up to an additional 5 yrs
    - Grade A; Level 2
  - **For zoledronate**: after 3 yrs if the T-score has improved to > -2.5;
    - if NOT, continue for an additional 3 years
    - For VERY-HIGH Risk women: don't consider a drug holiday until after 6 years
      - Grade A; Level 2

LSC = least significant change

72

When to Resume Rx After a Drug Holiday

- **During a Drug Holiday**
  - Repeat DXA q 2-4 years
- **After the drug holiday, consider resuming therapy after**
  1. a fracture, or
  2. an increase in fracture risk, or
  3. after T-score declines by more than the LSC of the DXA machine
     - Grade A, Level 1

LSC = least significant change

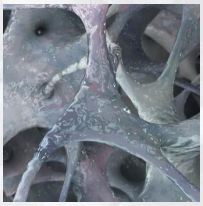
73

Risedronate May Not Allow for as Long of a Drug Holiday (vs. Alendronate)

- Risedronate has a shorter T ½ than alendronate
- Risedronate likely does not reside in the bone as long as alendronate
- Most drug holiday data was from the FLEX Trial, which involved alendronate
- This does NOT mean that alendronate should be preferred over risedronate
  - No difference in actual fracture risk reduction for up to 2 years
  - Risedronate accomplished a greater reduction in actual hip fractures after 2 years
  - Both drugs were given for ONLY 3 years before the drug holiday, followed by a 3-year holiday (Canadian study design)

- Hayes KN. J Clin Med. 2021; 10(5):1140.

74



That Was the Bisphosphonates…

Now, the Monoclonal Antibodies

(These Are Also Antiresorptive Agents)

75

Denosumab – Pivotal Fracture Trial

- DBPCRT n=7,808 women with postmenopausal osteoporosis
- Randomized 60 mg SQ q 6 mos x 36 mos vs placebo
- Endpoints at 36 months
  - **68% fewer vertebral fractures**
    - 0.32 [0.26-0.41]
  - **40% fewer hip fractures**
    - 0.60 [0.37-0.97]

Cummings S. NEJM. 2009; 361: 756-65.

76

Denosumab

PRO's

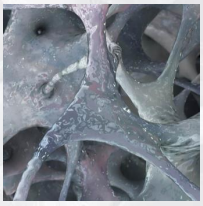
- Can continue without restriction on the maximum duration of use
- Well-tolerated GI
- OK with renal insufficiency (but not with ESRD or dialysis)
- Q 6-months subQ injection
  - HIGH QUALITY EVIDENCE of benefit -if patient prefers this as 1st line Rx
- No increased risk of ONJ

ESRD = End-Stage Renal Disease

CON's

- A monoclonal antibody – does not reside/linger in bone… so no drug holiday is feasible
  - So if you stop denosumab, must begin another antiresorptive agent
    - AACE 2020 (Grade A; Level 1)
- More AE's – rare anaphylaxis – observe x 15 min

77



That Was the Monoclonal Antibodies…

Now, Here Come the Anabolic Agents

78

ACP Recommendation- May, 2024
ONLY for Women with Primary Osteoporosis and a Very High Risk of Fracture

- Use a sclerostin inhibitor (romosozumab) (only ≤12 months) followed by a bisphosphonate or denosumab (MODERATE QUALITY EVIDENCE)…

OR

- or teriparatide or abaloparatide (only up to ≤24 months) followed by a bisphosphonate or denosumab (LOW QUALITY EVIDENCE) …

79

Use PTH-analogs (Teriparatide, Abaloparatide) as Initial Rx for Women at VERY-High Risk ACOG 2022

- HIGH-QUALITY EVIDENCE
  - For women at VERY high risk
  - For women who experience a fracture while on antiresorptive Rx
  - For women who demonstrate significant further bone loss (beyond the LSC of the DEXA machine/software)
  - For up to 24 months of use

80

Use PTH-analogs (Teriparatide, Abaloparatide) as Initial Rx for Women at VERY-High Risk

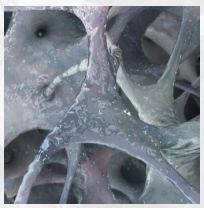
- Teriparatide

Metanalysis of 23 PCRT's/observational trials:

20µg daily SQ vs placebo

- Endpoints at 18 months (median)
  - **78% fewer vertebral fractures**
  - **56% fewer hip fractures**
- Abaloparatide claims a 17-22% better reduction in hip fractures (publication pending)
  - Eck M. Presented at the World Congress on Osteoporosis. April 11-14, 2024, London, U.K.

81



Summary of the Anti-Fracture Data

82

SUMMARY of the DATA: Anti-Fracture Effects

Drug	Vertebral	Hip
Alendronate	50%	20%
Risedronate	50%	40%
Raloxifene	50%	No
Ibandronate	50%	No
Zoledronate	70%	41%
Denosumab	68%	40%
Teriparatide	78%	50-56%
Abaloparatide	86%	? 59%
Romosozumab	73%	38%*

*vs alendronate @ 24 mos in the ARCH Trial

83

Reported Adverse Events of Antiresorptive Agents

COMMON:

- GI intolerance

RARE:

- Atypical mid-shaft femoral fractures
- Osteonecrosis of the jaw (mandible > maxilla)
- Atrial fibrillation
- Esophageal cancer

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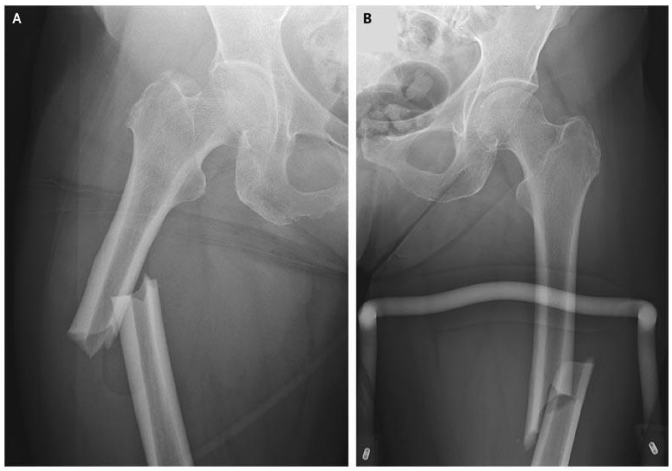
Radiographs of Atypical Mid-Shaft Fractures of the Femur



Lenart B et al. N Engl J Med 2008;358:1304-1306.

85

~~Oh NO !!!!~~: 25% Increase in Atypical Femoral Fractures with Long-Term Bisphosphonate Use

- Occur mostly after >5 years of Rx
- Rare – background rate: **28**/100K + 25% → **35**/100K
  - **7 MORE FRACTURES / 100K women**
- Weigh those 7 more against ~100 less spine frx's; and 30-50 less hip fractures

Oh YES !!!!

After 8+ years of bisphosphonate Rx, risk is **130**/100K

Zhong W. JBMR 2011; 26(3): 553. Black D. NEJM. 2020; 383: 743-53

86

Osteonecrosis Case Definition of "Jaw Rot"

Exposed bone in the maxillofacial region

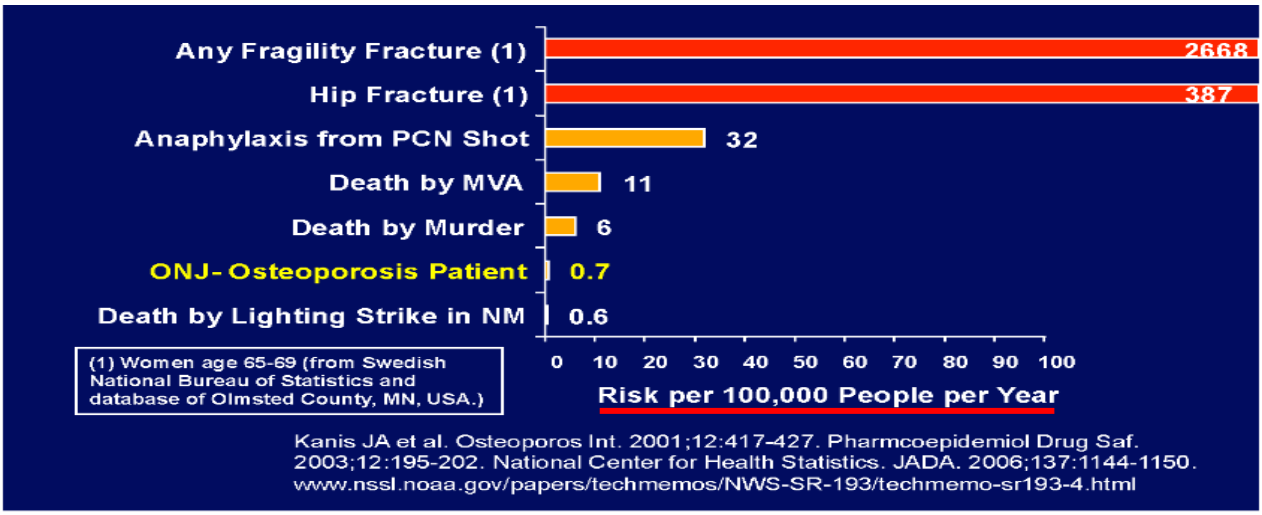
- Remains unhealed > 8 weeks
- No prior hx radiation to the region
- Not osteomyelitis

 AAOMS

- Khosla S. JBMR. 2007; 22: 1479-91

87

Communicating Risks



Postmenopausal Osteoporosis Guidelines, Endocr Pract. 2020;26(Suppl 1)

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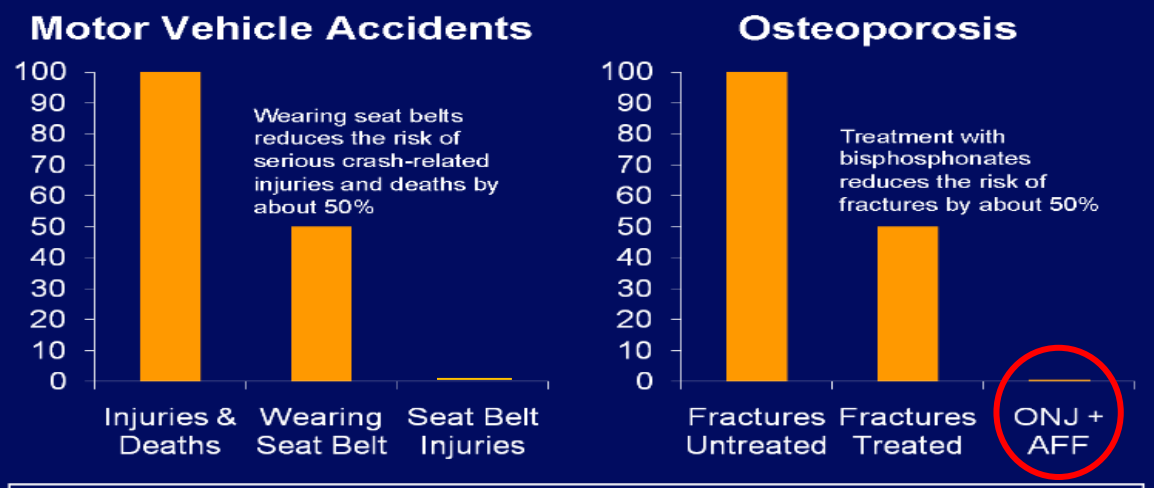
SUMMARY: Communicating Risks vs. Benefits



There are about 2.3 million adults treated in ERs each year for injuries from MVAs and about 2 million osteoporotic fractures each year. The risk of seat belt injuries and serious side effects from osteoporosis treatment is very small in proportion to the benefits. Data from multiple sources.

Postmenopausal Osteoporosis Guidelines, Endocr Pract. 2020;26(Suppl 1)

89

NOF: Osteonecrosis of Jaw Letter from YOU to Your Patient's Dentist/MFS

Dear Dr._____,

Our mutual patient _____ (DOB_____) is under my care for his/her diagnosis of osteoporosis and is currently treated with _____ to reduce his/her risk of osteoporotic fracture. I want to take this opportunity to summarize my recent discussion with our patient about his/her high risk of fracture compared to his/her real but very rare risk of MRONJ (Medication-related osteonecrosis of the jaw).

MRONJ is a rare event associated with the following medications: oral alendronate (Fosamax), oral risedronate (Actonel/Atelvia), oral or IV ibandronate (Boniva), IV zoledronic acid (Reclast), SQ denosumab (Prolia®), and SQ romosozumab (Evenity). MRONJ has NOT been associated with oral Raloxifene (Evista), SQ Teriparatide (Forteo®) , or SQ Abaloparatide (Tymlos®); therefore, there is NO recommendation for altering your standard dental plan if our patient is on one of these medications.

I know that you may have concerns about the risk of MRONJ; however, in a patient at high risk for fracture, the benefit of an approximate 40-70% reduction in fracture risk far outweighs the rare 1/10,000 to 1/100,000 risk of MRONJ. The most recent scientific summary reports by the ADA, AAOMS and the International Task Force for ONJ support this position. These societies also DO NOT recommend serum CTX testing.

In the publication of the FREEDOM extension trial (Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523), the real-world incidence of MRONJ in osteoporosis patients treated with denosumab (Prolia®) for up to 10 years was 5.2 cases per 10,000 subject years. It should be noted that denosumab (Xgeva®) and zoledronic acid (Zometa®) are used in the setting of cancer treatment in significantly higher doses and administered monthly instead of every 6-12 months. The risk of adverse events like MRONJ is much lower in the doses and frequency used for treating osteoporosis patients than in the treatment of oncology patients.

A tooth extraction or invasive jaw surgery may impart additional risk for MRONJ, especially if there is periodontal disease or chronic infection; however, routine cleanings, fillings, scaling/root planing, root canals and even implants do not appear to increase the risk of MRONJ. In all patients, but especially in those with additional risk factors such as diabetes, dry mouth, smoking, periodontal disease, poor fitting dentures or steroid use, the best course of action is appropriate dental hygiene and preventive dental care. You may consider oral antibiotics before and after procedures and/or antimicrobial rinses or local antimicrobial solution application if any of these risk factors are present or where you deem appropriate.

We do not recommend interruption of osteoporosis treatment for dental procedures in patients with high risk of fracture, especially if they are receiving denosumab (Prolia®) where the risk of multiple vertebral fractures is increased if denosumab (Prolia®) is discontinued or dosing is delayed without starting an alternative antiresorptive therapy.

I appreciate being able to care for our patient's bone health and would be happy to address any additional concerns that you may have.

Sincerely,

http://www.nof.org/wp-content/uploads/Dear-Dr-ONJ-letter-FINAL-FORM1.pdf

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Resources

- **National Osteoporosis Foundation Healthcare Professionals Toolkit**
  - https://www.bonesource.org/healthcare-professionals-toolkit
- **FRAX Calculator (& FRAXplus)**
  - https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9

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Summary

- Osteoporosis and its severe sequelae (fractures) represent a significant health burden to our patients, and a cost burden to the healthcare system
- The best estimate of real-life fracture risk can be achieved by the combination of FRAX® (or similar) screening tool and a central DXA scan
- First-line therapy for osteoporosis is most often a weekly bisphosphonate
- Combination therapy (concurrent agents) are generally not recommended; sequential therapy (e.g. an anabolic agent followed by an antiresorptive agent) is appropriate

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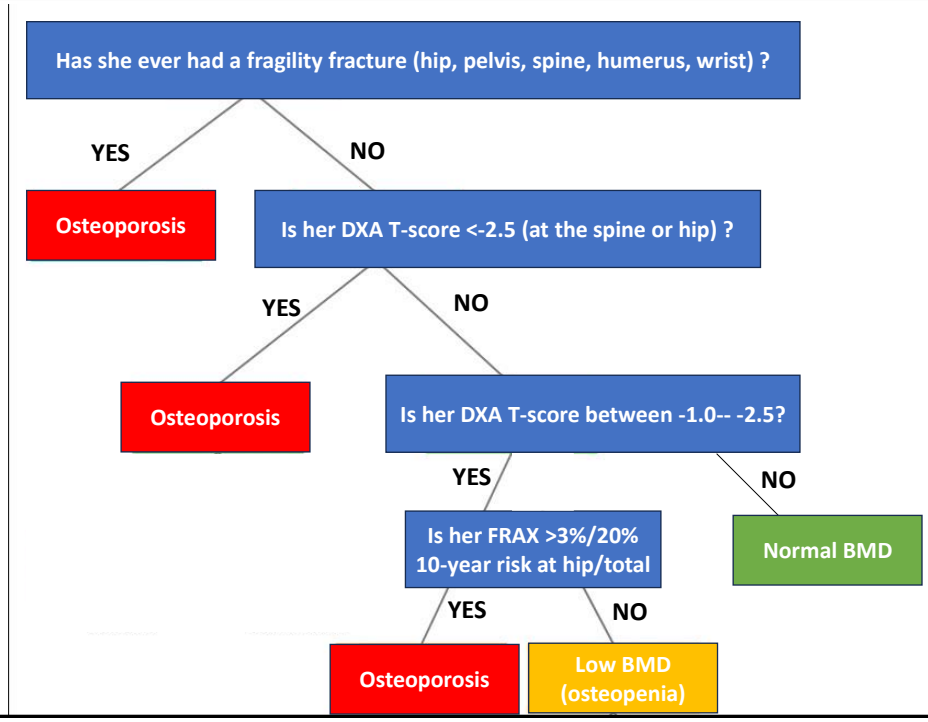

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APPENDIX SLIDES

94

Use a Sclerostin-binding Inhibitor (Romosozumab) as Rx for Women at VERY-High Risk ACOG 2022

- HIGH-QUALITY EVIDENCE
  - For women who experience a fracture while on antiresorptive Rx
  - For women NOT at increased risk of cardiovascular disease or stroke
  - For up to 12 months of use

95

When to Refer to a Subspecialist (Endocrinologist; Osteoporosis Specialist) ACOG 2022

- T-score < -3.0
- Any new fragility fracture
  - New fragility fracture on Rx
  - Fragility fracture with normal BMD
- Progressive decline in BMD while on antiresorptive Rx
- Endocrine or metabolic cause of secondary osteoporosis
  - Hyperthryroidism, hyperparathyroidism, hypercalciuria, elevated prolactin
- Comorbidities that complicate Rx
  - Significantly low GFR, malabsorption syndrome

96

Teriparatide (PTH 1-34)

- N=1,637 postmenopausal women w/ prior vertebral fracture(s)
- PCRT – 0, 20, 40 microGm SubQ qd
  - All received Ca++ and Vit D daily supplements
- F/U = 18 months

	Placebo (n=544) # /1000 pt-yrs (%)	20 microGM (n=541)	40 microGm (n=552)	
Vertebral Frx's	**136 (14%)**	**49 (5%)**	**30 (4%)**	**78%** ↓
Non Vert Frx's	**(6%)**	**(3%)**	**(3%)**	**50%** ↓

Neer R. NEJM. 2001; 344: 1434-41; . Diez-Perez A. Bone. 2019; 120:1-8

97

Abaloparatide - FDA Approved April 2017

- Mechanism: binds PTH receptor; Anabolic bone effect
- Regimen: daily subQ injection – 80 micrograms (pen contains 30 doses)
  - Does NOT require refrigeration (unlike TPD)
- **"ACTIVE"** Trial : **A**baloparatide **C**omparator **T**rial **I**n **V**ertebral **E**ndpoints
  - DBPCRT: N=2,463 women with postmenopausal osteoporosis
  - Abaloparatide 80 mcg (n=824)
  - vs. teriparatide 20 mcg (n=818)
  - vs. placebo (n=821)
- **F/U 18 months – 86% reduction in vert frx with ABL; vs. 78% with TPD**
- CONCLUSION: ABL is slightly superior to TPD in increasing BMD and in reducing major osteoporotic fractures, with a more rapid onset to benefit

Miller PD. Et al for the ACTIVE Study Investigators. *JAMA.* 2016;316(7):722-733. doi:10.1001/jama.2016.11136
Reginster JY. ACTIVE Trial: Expert Opin Pharmacother. 2017 Dec;18(17):1811-1813. doi: 10.1080/14656566.2017.1395021. Epub 2017 Nov 14

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Monoclonal Antibodies Against Sclerostin

- Sclerostin, produced by osteocytes, inhibits osteoblast activity
- **Romosozumab** – Human monoclonal antibody against sclerostin
  FDA approved April 9, 2019

INVESTIGATIONAL DRUG (still in development, December, 2024)

- Blosozumab – Phase III trial; LY2541546 ongoing
- Human monoclonal antibodies against sclerostin

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Romosozumab **FRAME** Study (PCRT) & **ARCH** Study (RCT vs. Alendronate)

- n=7,180 women with postmenopausal osteoporosis
- subQ injection 210mg (2 x 105mg prefilled syringes)
  q 4 weeks x 12 months
- F/U 12 months

- **73%** **fewer vertebral fractures** at 12 months **(rapid onset benefit)**
- **38%** **fewer hip fractures** at 12 months **(rapid onset benefit)**

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Limit the Durations of Certain Therapies

- LIMIT TPD & ABPD THERAPIES TO ≤ 24 MONTHS; LIMIT ROMO TO ≤ 12 MONTHS
  - Then follow the anabolic (teriparatide or abaloparatide) with an antiresorptive agent (e.g., a bisphosphonate or denosumab Rx)
    - Grade A; Level 1
  - P.S.
    - R/O Paget's disease (check the serum alkaline phosphatase) before prescribing an anabolic agent
    - Do not prescribe anabolics for patients with untreated hyperparathyroidism
    - Do not switch directly from denosumab to an anabolic agent
    - Do NOT use combination (concurrent) Rx therapies
- LIMIT ROMOSOZUMAB THERAPY TO ≤ 12 MONTHS
  - Then follow with bisphosphonate or denosumab Rx
    - Grade B; Level 1

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