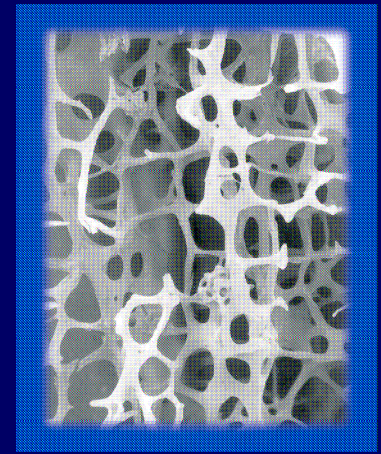
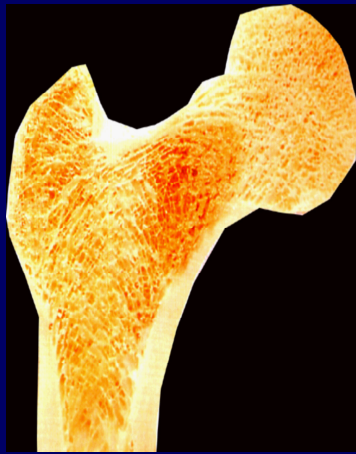


FRAX® FACTS: Update of Osteoporosis Treatment Guidelines

Medical Grand Rounds

Providence St Vincent Medical Center

February 24, 2009



Michael R. McClung, MD, FACP, FACE
Director, Oregon Osteoporosis Center
Member, WHO Fracture Risk Task Force

Disclosure and Conflict of Interest

I receive research grants and/or consulting fees from the following companies:

Amgen

Lilly

Novartis

sanofi-aventis

GlaxoSmithKline

Merck

Procter & Gamble

Takeda

Michael McClung, MD

February 2009



Osteoporosis Therapy

OBJECTIVES:

- Prevent new fractures

For patients with fractures

- Minimize symptoms
- Improve function
- Optimize quality of life



Postmenopausal Osteoporosis: Approved Treatment Options 2009

No head-to-head trials comparing fracture outcomes

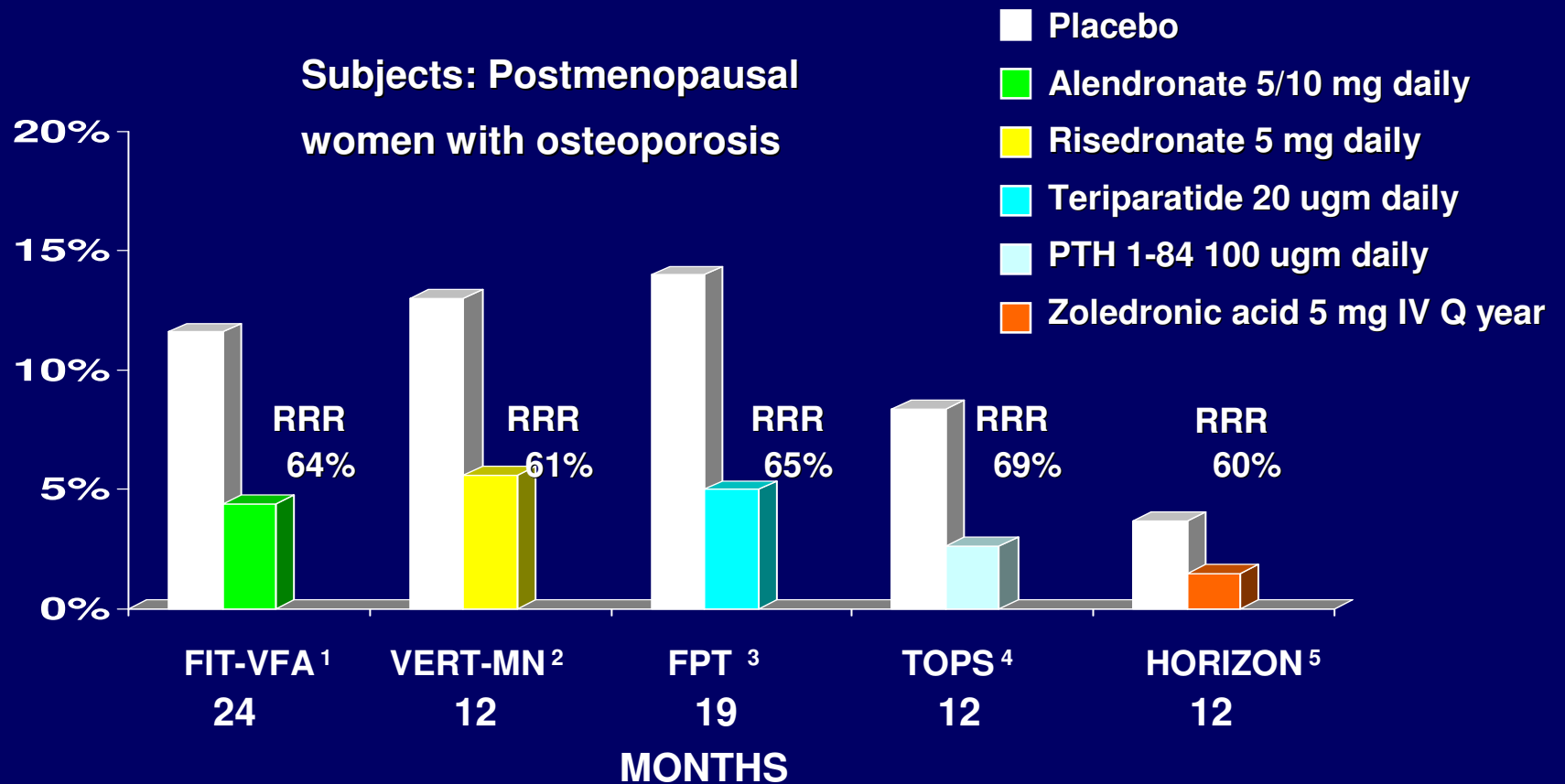
	Approved Indications *		Documented Fracture Reduction §			Comments
	Prevention	Treatment	Spine	Non-vertebral	Hip	
ANTIRESORPTIVE AGENTS						
Alendronate	X	X	X	X	X	Weekly dosing
Ibandronate	X	X	X			Monthly and IV dosing
Risedronate	X	X	X	X	X	Weekly and monthly dosing
Zoledronic acid	-	X	X	X	X	Annual IV dosing
Raloxifene	X	X	X			Prevention of breast cancer
Calcitonin	-	X	X			
Estrogen	X	-	X	X	X	Extra-skeletal effects
ANABOLIC AGENTS						
Teriparatide	-	X	X	X		

* X = FDA-approval § In clinical trials

Information from Package
Inserts of each agent



Vertebral Fracture Risk Reduction 12-24 months



RRR, relative risk reduction; FIT-VFA, Fracture Intervention Trial Vertebral Fracture Arm; VERT-MN, Vertebral Efficacy With Risedronate Therapy-Multinational; FPT, Fracture Prevention Trial; TOPS, Treatment of Osteoporosis with PTH Study

¹ Black DM, et al. *Lancet*. 1996;348:1535

² Reginster J, et al. *Osteoporos Int*. 2000;11:83

³ Neer RM, et al. *N Engl J Med*. 2001;344:1434

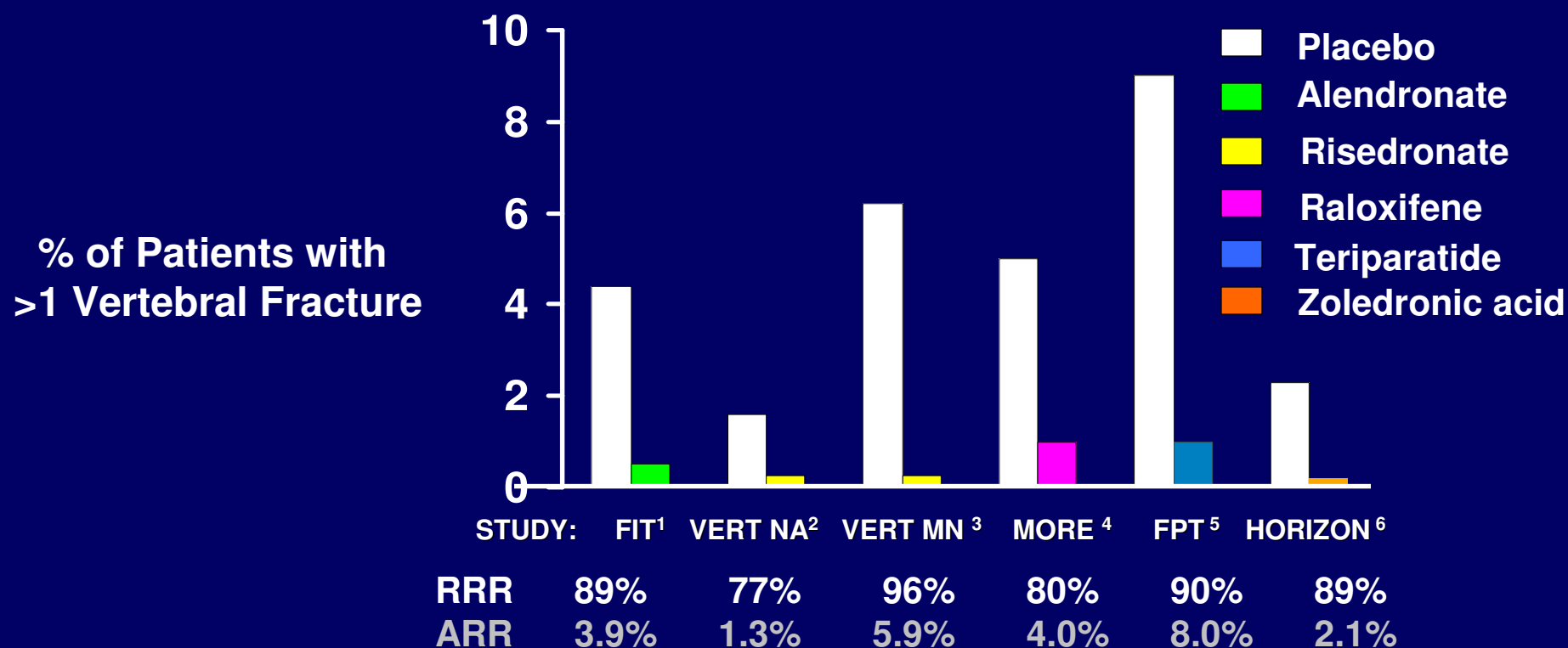
⁴ Greenspan SG et al. *Ann Intern Med*. 2007;146:326.

⁵ Black DM, et al. *N Engl J Med*. 2007;356:1809.



Therapy Interrupts Cycle of Multiple Vertebral Fractures

Patients: Low BMD with or without prevalent vertebral fracture



¹ Black DM, et al. *Lancet*. 1996;348:1535

² Harris ST, et al. *JAMA*. 1999;282:1344

³ Reginster J, et al. *Osteoporos Int*. 2000;11:83-91

⁴ Ettinger B et al, *JAMA*. 1999;282:637

⁵ Neer RM, et al. *N Engl J Med*. 2001;344:1434

⁶ Black DM, et al. *N Engl J Med*. 2007;356:1809.



Hip Fracture Risk Reduction

Not head-to-head: Studies cannot be directly compared



McClung MR, et al. *N Engl J Med.*
2001;344:333

Black DM, et al. *Lancet.*
1996;348:1535

Black DM, et al. *N Engl J Med.*
2007;356:1809



Osteoporosis Treatments

- We have very effective treatments to reduce fracture risk in patients with or at risk of osteoporosis

Delmas PD, *Lancet* 2000;359:2018

- New treatments, including some with novel mechanisms of action, will be available soon.
- The clinical challenges are
 - to select among the treatment options
 - to use the drugs in the most effective way
 - to identify the appropriate patients to treat



Selecting Patients for Therapy

- Efficacy has been documented in patients at moderate to high risk
- Therapy is not cost effective in patients at low risk
- Patient selection for treatment is best based on fracture risk
- BUT - there has been no consensus on how to do that



BMD and Osteoporosis

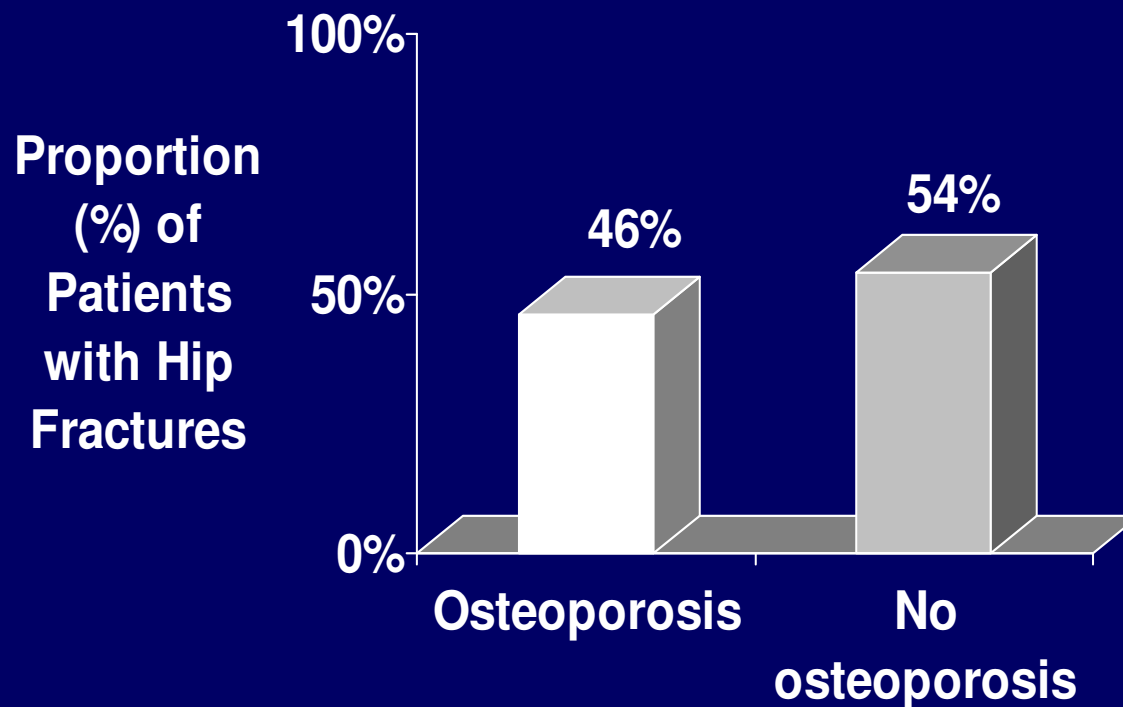
- **The operational definition of postmenopausal osteoporosis is based on BMD (T-score -2.5 or lower)**
- **For fracture risk prediction, the diagnostic threshold is modestly specific but not sensitive**

Most Hip Fractures Occur in Women Who Do Not Have “Osteoporosis”

SOF: 8065 women age 65 or older

17% had total hip T-score -2.5 or lower

3% experienced hip fracture

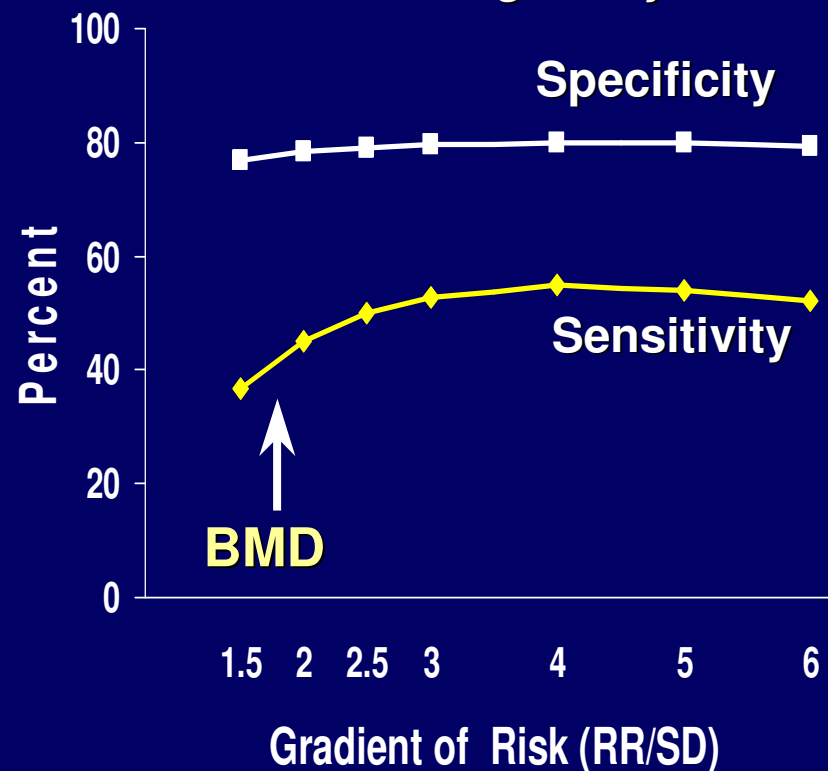


Gradient of Risk

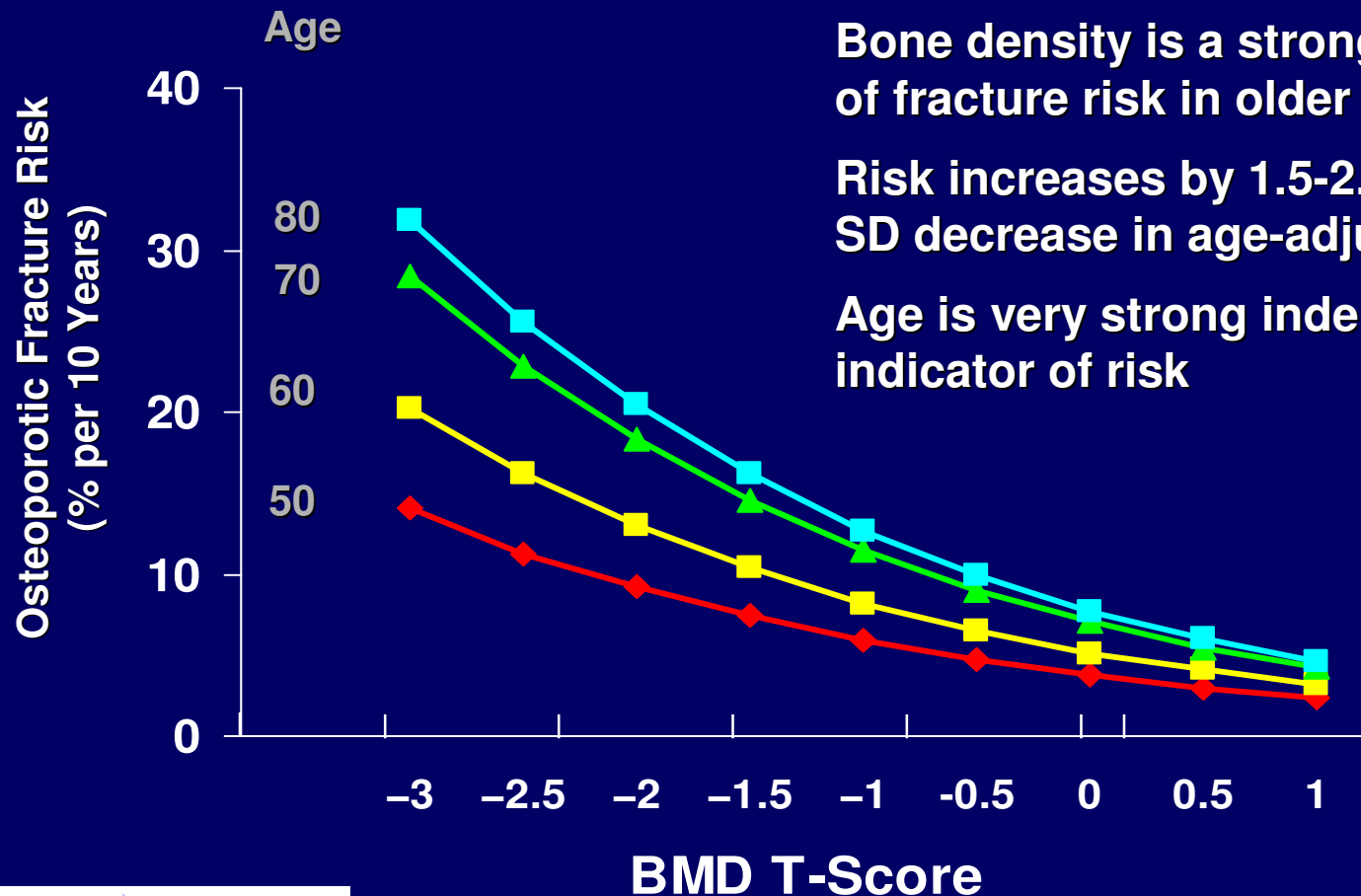
Using scores with higher risk gradients improves detection rate (sensitivity) without sacrificing specificity

Risk gradient of 3-4 is optimal
Risk gradient for BMD: 1.5 - 2

Estimates of sensitivity and specificity to predict any osteoporotic fracture in women aged 65 years



Bone Density and Fracture Risk



Bone density is a strong predictor of fracture risk in older adults

Risk increases by 1.5-2.5 fold for 1 SD decrease in age-adjusted BMD¹

Age is very strong independent indicator of risk



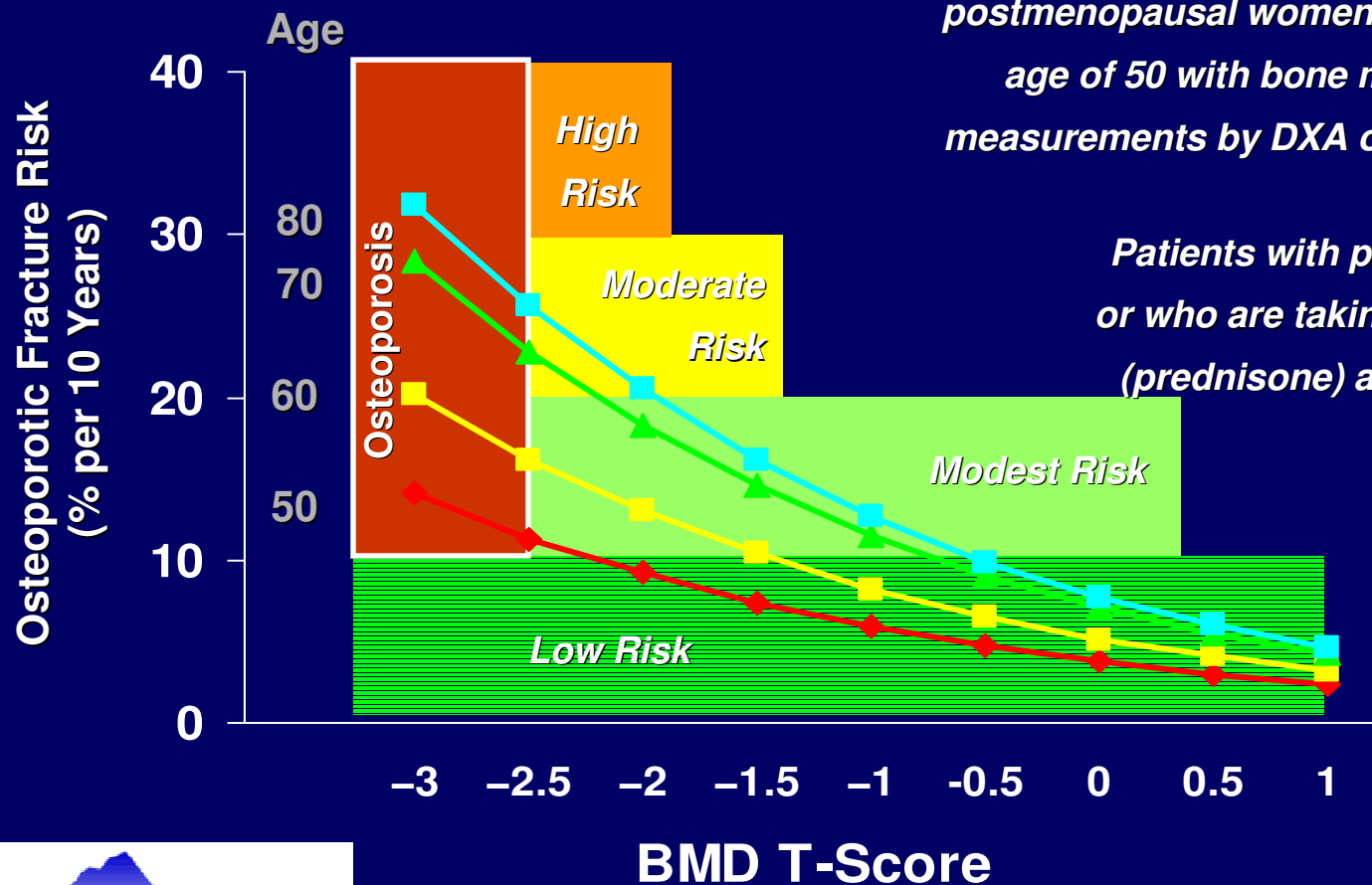
Core data from Kanis JA, et al. *Osteoporos Int.* 2001;12:989-995.

McClung MR. *Current Osteoporos Reports* 2005;3:57-63.

Bone Density Reporting: OOC

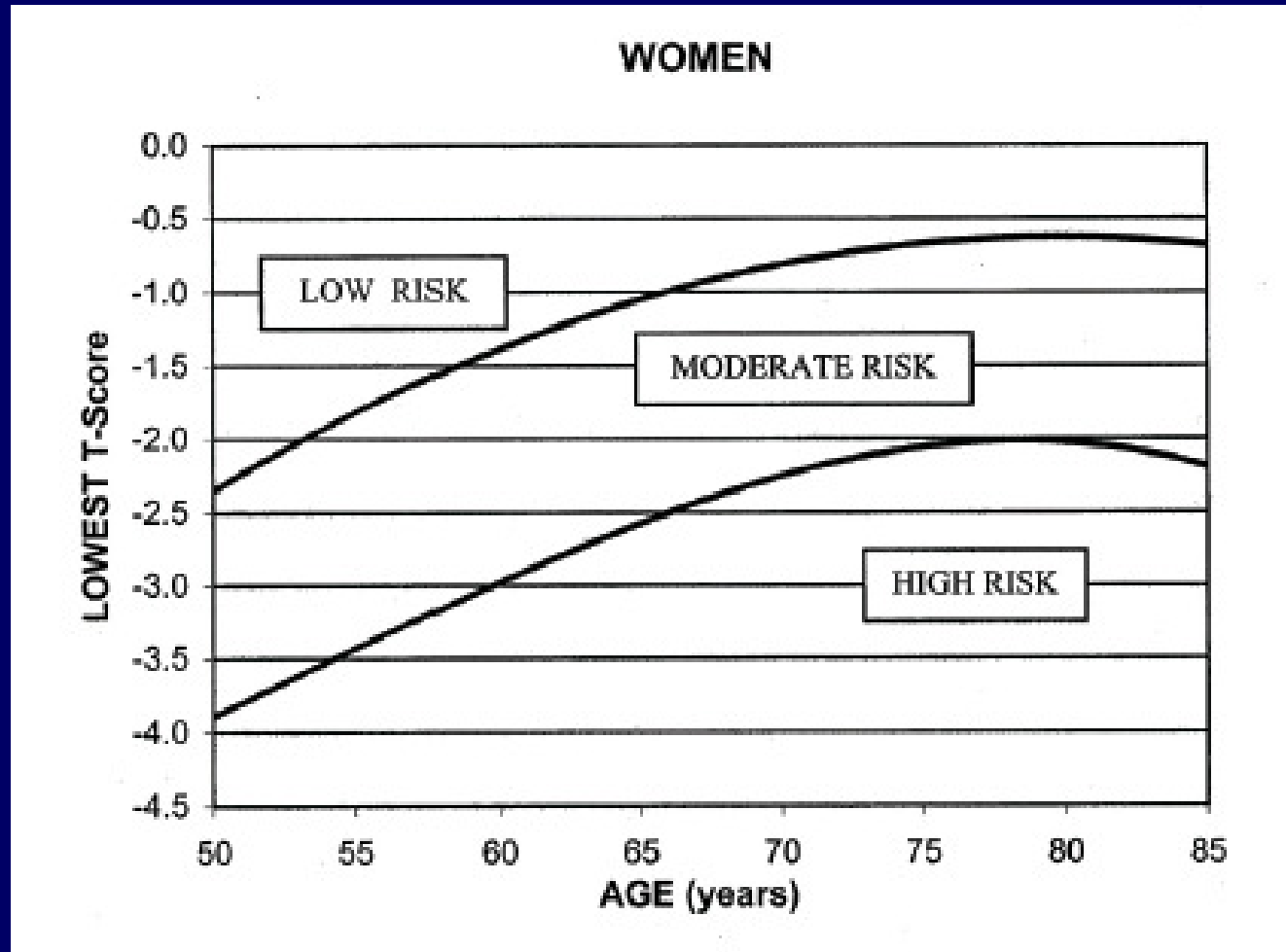
This information is to be used for postmenopausal women and men over the age of 50 with bone mineral density measurements by DXA of the spine or hip.

Patients with previous fractures or who are taking glucocorticoids (prednisone) are at higher risk.



Core data from Kanis JA, et al. *Osteoporos Int.* 2001;12:989-995.
 McClung MR. *Current Osteoporos Reports* 2005;3:57-63.

Bone Density Reporting: Osteoporosis Canada



WHO Scientific Group on Fracture Risk Reporting



OBJECTIVES

- to optimise sensitivity for fracture risk prediction
 - to identify patients to treat
- case finding strategy
- with or without BMD
- men and women
- globally applicable
- applicable to primary care setting
- cost-effective setting
- scientific rigour and international validity

FRAX[®] Cohorts Studied

EVOS / EPOS

Hiroshima

CaMoS

Rochester

Sheffield

Rotterdam

Kuopio

Gothenburg I

Gothenberg II

EPIDOS

Dubbo

OFELY

n = 59,232 person-years = 249,898

female = 74% male = 26%

Any fracture = 5,444 osteoporotic fractures = 3,495 hip fractures = 957



BMD-independent Risk Factors for Fracture in FRAX[®] Model

<u>Risk Factor</u>	<u>Without BMD</u>	<u>With BMD</u>
Prior fracture	++	++
Current age	++	+
BMI	++	-
Hip BMD	NA	++
Parent's hip fracture	+	+
Corticosteroids	++	++
Alcohol intake (>2/day)	+	+
Smoking (current)	+	+



FRAX - WHO Fracture Risk Assessment Tool - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9

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Norton Cards & Log-ins

FRAX[®] WHO Fracture Risk Assessment Tool

HOME CALCULATION TOOL PAPER CHARTS FAQ REFERENCES

Calcul

Please enter the details below to calculate the ten year probability of fracture with BMD.



Weight Conversion:
pound:
convert

Height Conversion:
inch:
convert

Country / ID : [About the risk factors](#) ⓘ

1. Age: Date of birth: / /

2. Sex: Male Female

3. Weight (kg):

4. Height (cm):

5. Previous fracture: No Yes

6. Parent fractured hip: No Yes

7. Current smoking: No Yes

8. Glucocorticoids: No Yes

9. Rheumatoid arthritis: No Yes

10. Secondary osteoporosis: No Yes

11. Alcohol 3 or more units per day: No Yes

12. Femoral neck BMD (g/cm²):

Select DXA:

Clear **Calculate**

FRAX - WHO Fracture Risk Assessment Tool - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9

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FRAX[®] WHO Fracture Risk Assessment Tool

HOME CALCULATION TOOL PAPER CHARTS FAQ REFERENCES

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.



Weight Conversion:

pound:

[convert](#)

130 pound = 58.97 kg

Height Conversion:

inch:

[convert](#)

64 inch = 162.56 cm

Country : **US (Caucasian)** Name / ID : [About the risk factors](#)

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age: Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture No Yes

6. Parent fractured hip No Yes

7. Current smoking No Yes

8. Glucocorticoids No Yes

9. Rheumatoid arthritis No Yes

10. Secondary osteoporosis No Yes

11. Alcohol 3 or more units per day No Yes

12. Femoral neck BMD (g/cm²)

Hologic **T-score: -2.2**

[Clear](#)

[Calculate](#)

BMI 22.3

The ten year probability of fracture (%)

with BMD

<input checked="" type="checkbox"/> Major osteoporotic	14
<input checked="" type="checkbox"/> Hip fracture	1.9

FRAX - WHO Fracture Risk Assessment Tool - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9

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FRAX[®] WHO Fracture Risk Assessment Tool

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[convert](#)

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4. Height (cm)

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8. Glucocorticoids No Yes

9. Rheumatoid arthritis No Yes

10. Secondary osteoporosis No Yes

11. Alcohol 3 or more units per day No Yes

12. Femoral neck BMD (g/cm²)

Hologic **T-score: -2.2**

[Clear](#)

[Calculate](#)

BMI 22.3

The ten year probability of fracture (%)



with BMD

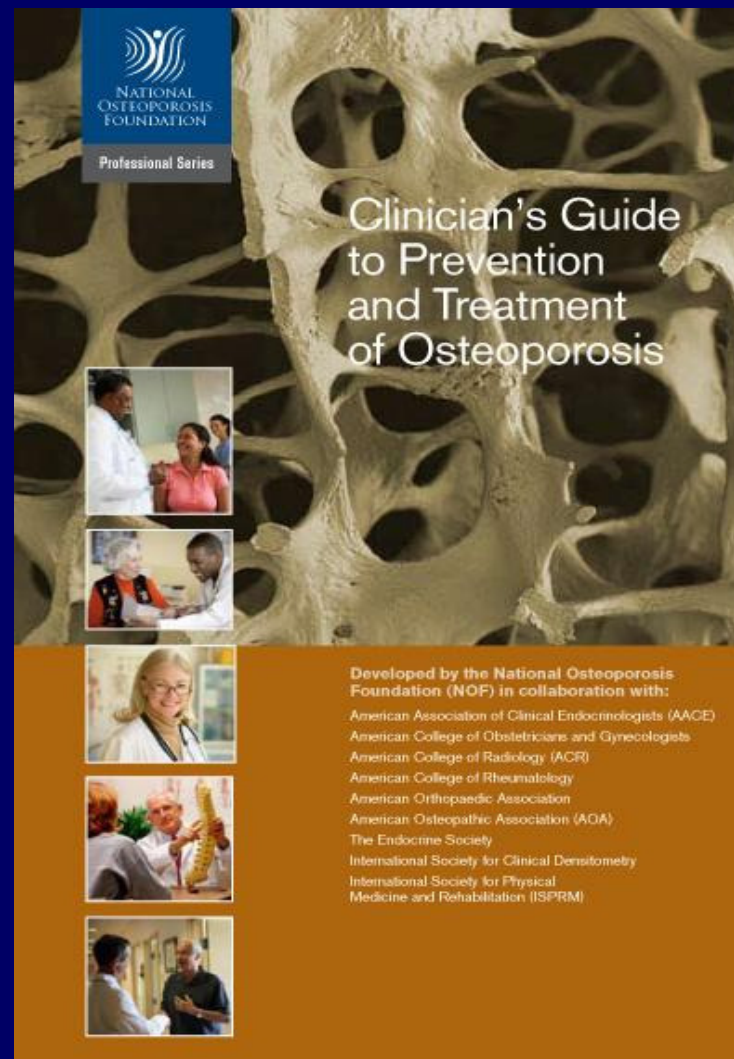
Major osteoporotic	23
Hip fracture	3.2

Intervention Thresholds

Fracture probability that one is willing to pay for

- **Efficacy, side-effects and costs of treatments**
- **Who pays**
- **Resources for health care**
- **Health care priorities**

Postmenopausal Osteoporosis: NOF-FRAX® Indications for Treatment



http://nof.org/professionals/Clinicians_Guide.htm

NOF Guidelines - 2008

Health Economic Considerations

- **Cost of drug - \$600/year**
- **Treatment for 5 years**
- **Offset of treatment effect over 5 years**
- **35% reduction in fracture risk**
- **100% adherence to therapy**
- **Cost effective threshold - \$60,000 per QALY**



NOF Guidelines - 2008

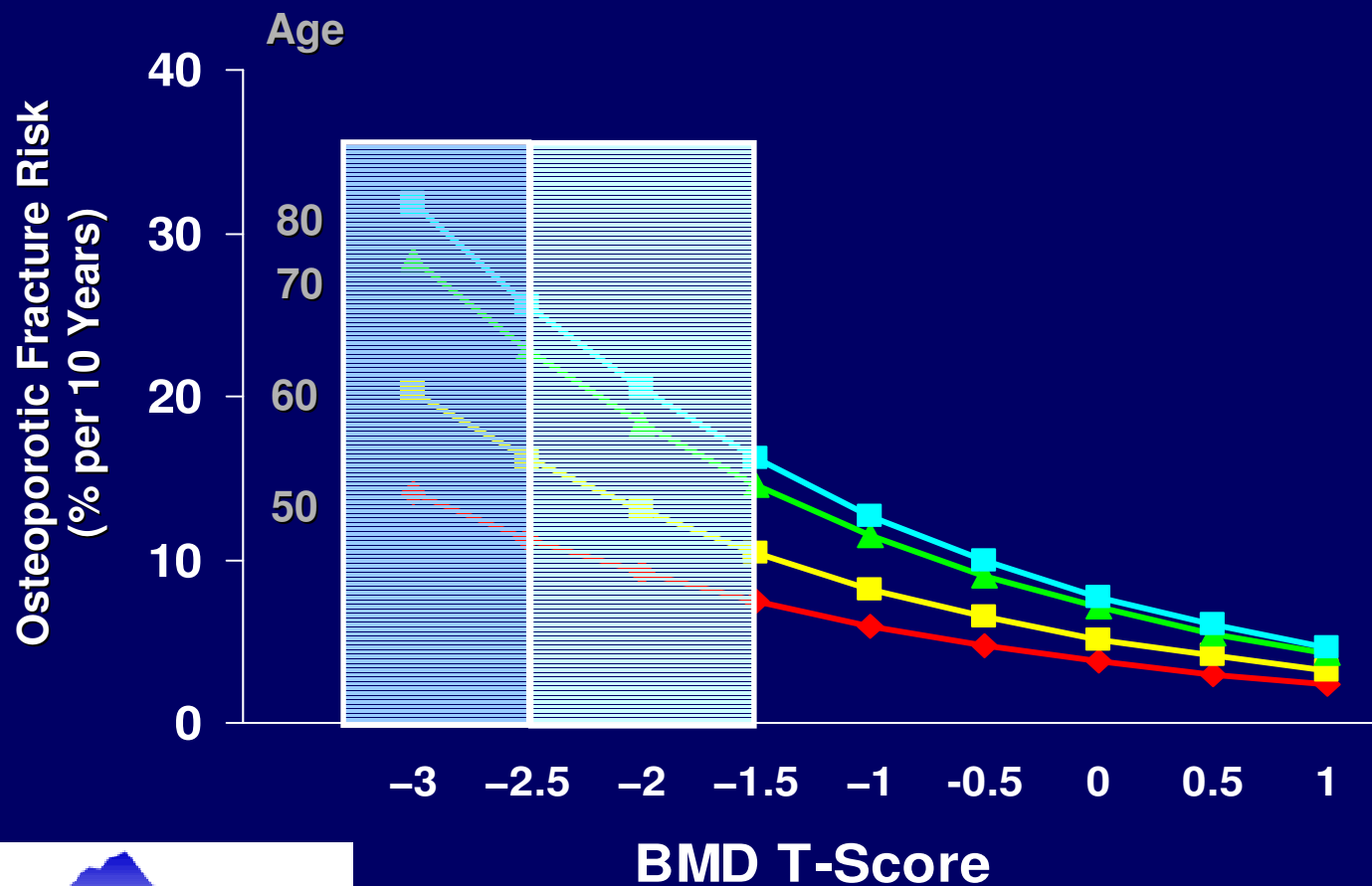
Indications for therapy in postmenopausal women and men over age 50

1. after hip or spine fracture
2. BMD T-score in spine or proximal femur ≤ -2.5
3. BMD between -1 and -2.5 and one of following:
 - a. 10 year risk of major fracture of 20% or more*
 - b. 10 year risk of hip fracture of 3% or more*

** Calculated by FRAX[®] algorithm*



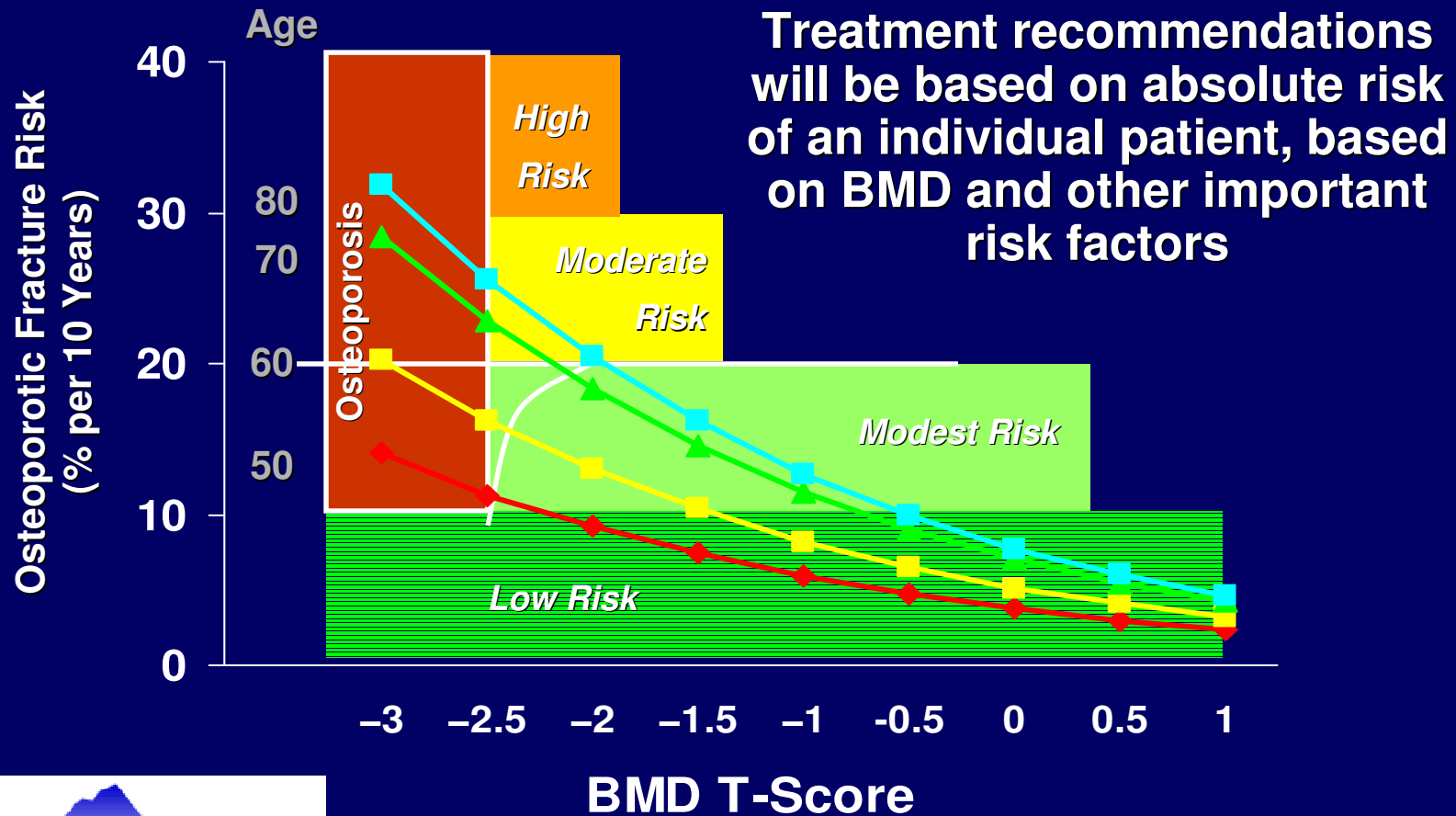
Previous Treatment Guidelines



Core data from Kanis JA, et al. *Osteoporos Int.* 2001;12:989-995.

McClung MR. *Current Osteoporosis Reports* 2005;3:57-63.

New Treatment Guidelines

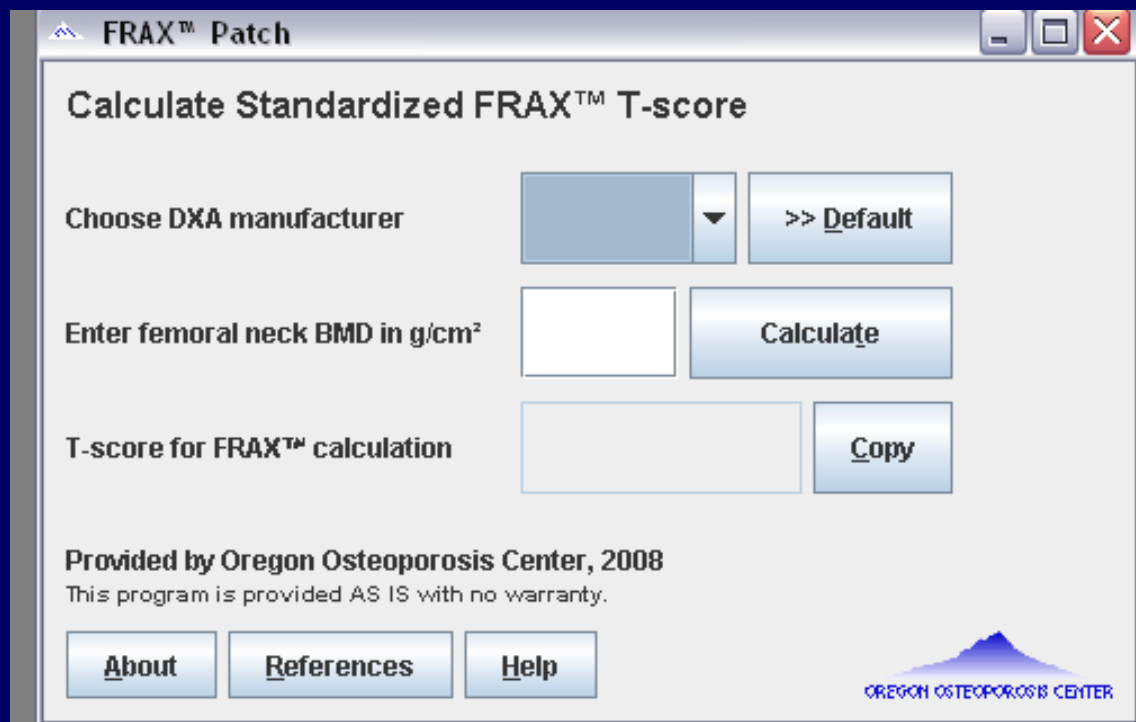


Core data from Kanis JA, et al. *Osteoporos Int.* 2001;12:989-995.

McClung MR. *Current Osteoporos Reports* 2005;3:57-63.

FRAX[®] - Problems

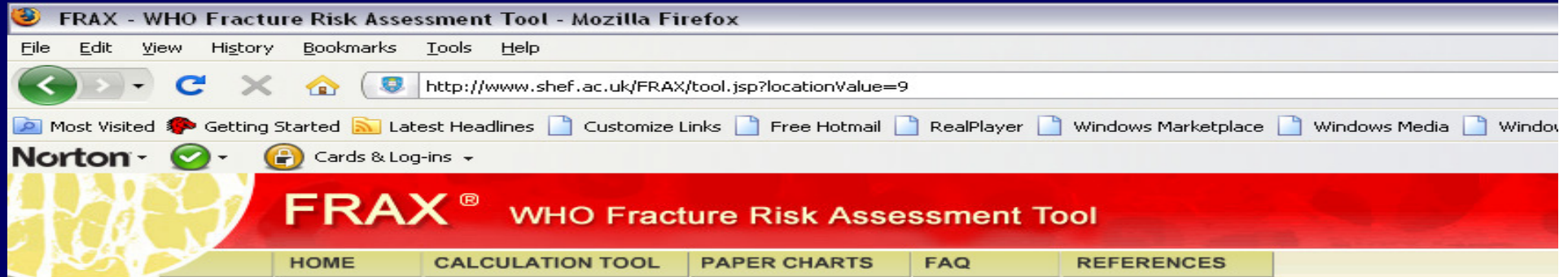
1. T-scores from DXA machines are not the right T-scores for FRAX[®]
- fixed with OOC FRAX[®] Patch



The screenshot shows a software window titled "FRAX™ Patch". The window contains the following elements:

- Title Bar:** "FRAX™ Patch" with standard window control buttons (minimize, maximize, close).
- Header:** "Calculate Standardized FRAX™ T-score"
- Form Fields:**
 - "Choose DXA manufacturer": A dropdown menu with a blue arrow button and a ">> Default" button.
 - "Enter femoral neck BMD in g/cm²": A text input field with a "Calculate" button.
 - "T-score for FRAX™ calculation": A text input field with a "Copy" button.
- Footer:**
 - Text: "Provided by Oregon Osteoporosis Center, 2008" and "This program is provided AS IS with no warranty."
 - Buttons: "About", "References", and "Help".
 - Logo: "OREGON OSTEOPOROSIS CENTER" with a stylized mountain graphic.





Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.



Weight Conversion:

pound:

130 pound = 58.97 kg

Height Conversion:

inch:

64 inch = 162.56 cm

Country : **US (Caucasian)** Name / ID : [About the risk factors](#) ⓘ

Questionnaire:

1. Age (between 40-90 years) or Date of birth
 Age: Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture No Yes

6. Parent fractured hip No Yes

7. Current smoking No Yes

8. Glucocorticoids No Yes

9. Rheumatoid arthritis No Yes

10. Secondary osteoporosis No Yes

11. Alcohol 3 or more units per day No Yes

12. Femoral neck BMD (g/cm²)
 T-score: -2.2

BMI 22.3
The ten year probability of fracture (%)

with BMD

Major osteoporotic	14
Hip fracture	1.9

FRAX[®] - Problems

1. T-scores from DXA machines are not the right T-scores for FRAX[®]
 - *fixed with OOC FRAX[®] Patch*
2. Major fracture risk was over-estimated in original version
 - *fixed*
3. Requires access to Internet
 - *will be on DXA software (later this year)*



FRAX[®] - NOF Guidelines: Strengths

1. Are tools and guidelines – not rules
2. Focuses on skeletal risk factors
3. Provides for the complex interplay among “not quite” independent risk factors
4. Includes men as well as women
5. Simple - uses easily available data



FRAX[®] - NOF Guidelines: Limitations

1. Identifies patients to treat where we have no evidence of treatment efficacy (non-osteoporotic)
2. Does not incorporate BMD except femoral neck (or total hip)
3. Does not include fall-related risk factors for fracture (not a true fracture risk predictor)
4. Makes some risk factors categorical vs variable
 - a. +/- glucocorticoid vs dose/duration, etc



FRAX[®] - NOF Guidelines: Limitations

5. Does not apply to many situations

- a) young adults
- b) patients on treatment
- c) early menopause
- d) stopping HRT
- e) hormone deprivation therapy
- f) beginning glucocorticoid therapy
- g) secondary osteoporoses



FRAX[®] - NOF Guidelines: Limitations

6. Does not incorporate the concept of drug treatment to “prevent osteoporosis”



Osteoporosis Treatment Guidelines: Summary

- **It is important to distinguish between diagnostic threshold (BMD-based) and intervention thresholds (risk-based)**
- **A very sophisticated, validated model will be available for assessing fracture probability in individual men and women**
- **Recommendations for treatment can now be based on estimates of skeletal contributions to fracture risk, not just BMD**
- **Therapy will be targeted at the population most in need of treatment**



Osteoporosis Therapy: Summary

- Our current treatment options are very effective agents for treatment of osteoporoses
- In general, our drugs are well tolerated and safe
- Acceptance and persistence with therapy are suboptimal
- In *appropriate patients*, benefits of treatment far outweigh possible risks of treatment
- We now have tools and guidelines to help identify those “appropriate” patients



Thank you



Michael R. McClung, MD, FACP, FACE
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mmclung@orost.com

