Brigham and Women's Hospital
Founding Member, Mass General Brigham

Osteoporosis

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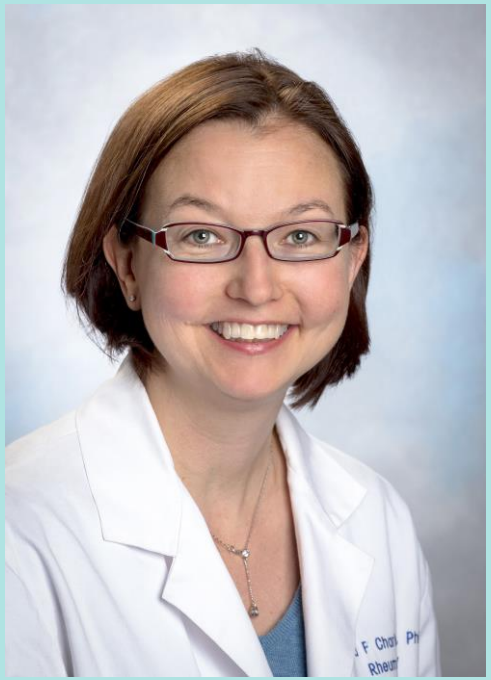


UCSF Medical School
BWH Internal Medicine
UCSF Rheumatology Fellowship

On faculty at BWH since 2011.

Clinical interests in osteoporosis, glucocorticoid induced osteoporosis, Paget's disease of bone, MSK complications of rare bone diseases.

I have run an outpatient Fracture Liaison program in the Department of Orthopaedic Surgery since 2017.

Literature review team for 2022 ACR guidelines update for GIOP

Disclosures

Advisory Boards: Kyowa Kirin, Alexion

Grant funding: Alexion

Author Royalties: Up to Date, Merck Manual

OBJECTIVES

- **Recognize patients at risk**
  - Identify risk factors
  - Review screening recommendations for osteoporosis
- **Interpret and apply diagnostic tools**
  - Interpret bone mineral density (BMD) results
  - Recognize the utility of trabecular bone scores (TBS)
  - Understand the use and limitations of FRAX
- **Initiate appropriate management**
  - Selection of pharmacologic agent
  - Monitoring treatment response
  - Managing long-term care and safety concerns.

Outline

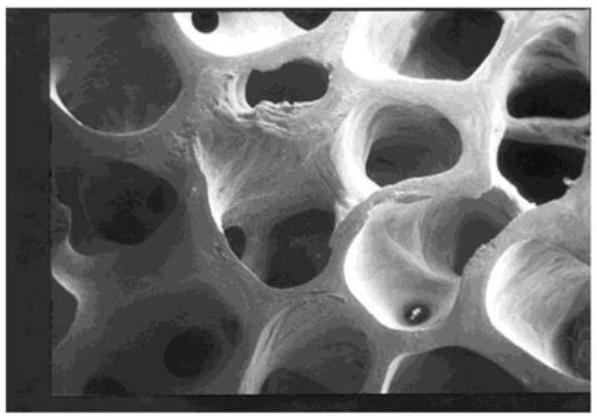
1. Introduction to Osteoporosis & Pathophysiology
2. Diagnosis of Osteoporosis/Osteopenia
3. Guidelines for Screening
4. Risk Factors
5. Recommended laboratory evaluation
6. Who should be treated?
7. Osteoporosis therapies: Benefits & Risks

Osteoporosis

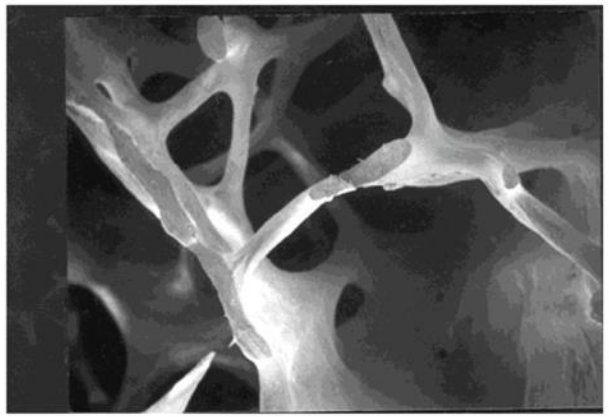
A skeletal disorder of compromised bone strength, predisposing to risk of fracture.

Bone strength depends on:

1. quantity – assessed by DXA or qCT
2. quality – microarchitectural changes - assessed by TBS



Normal bone

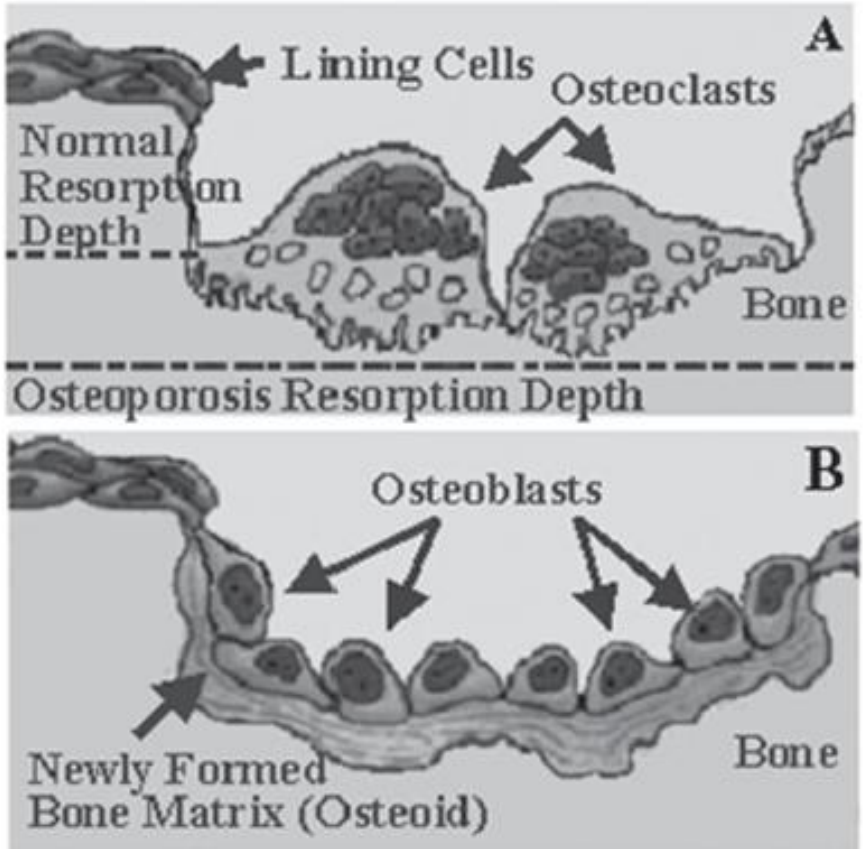


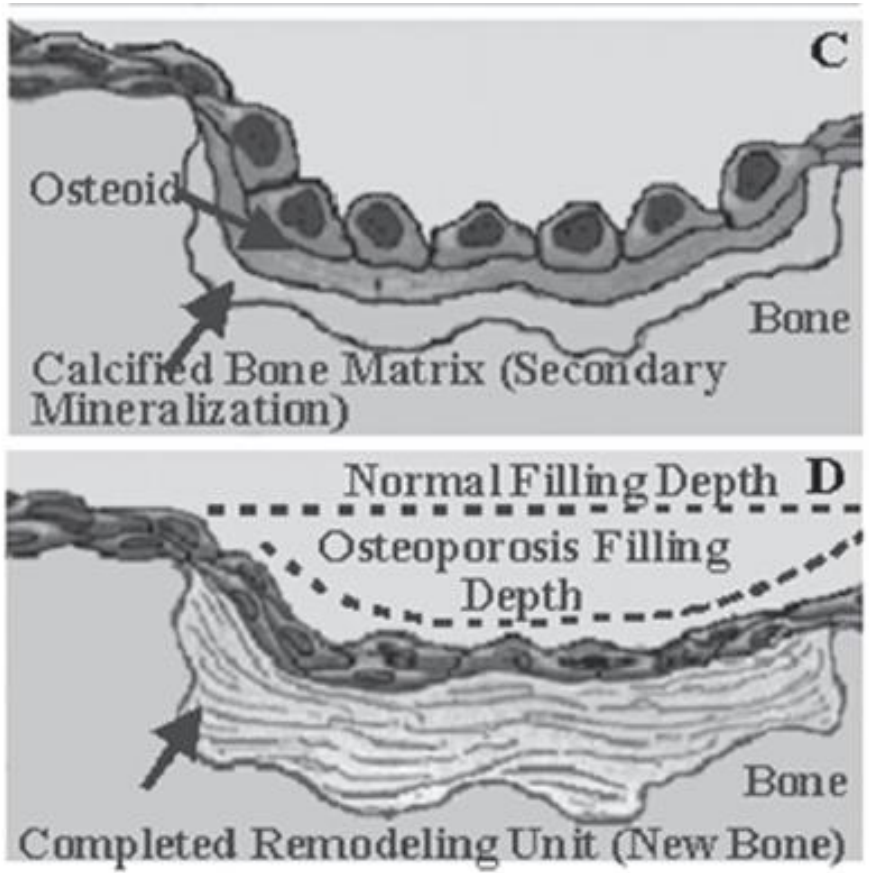
Osteoporotic bone

Bone loss: a two-fold problem

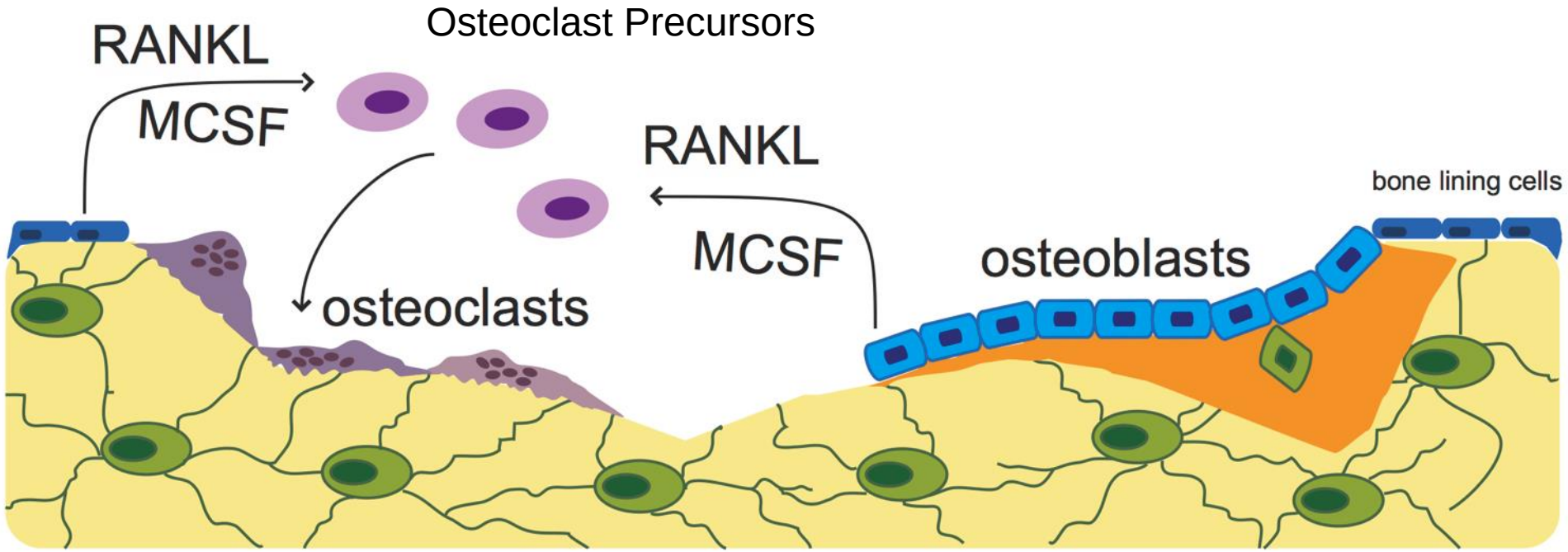
increased resorption

incomplete repair



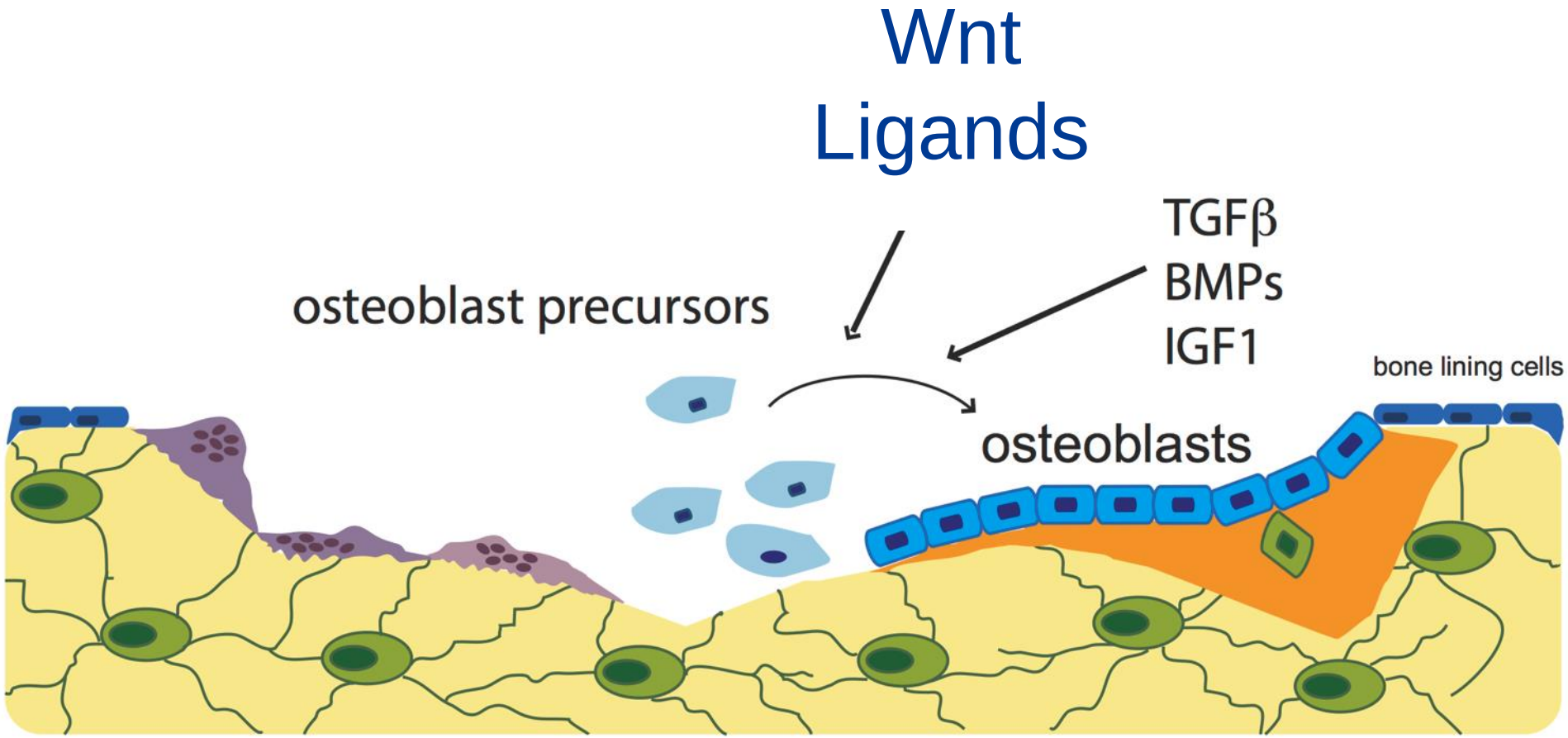


RANKL is the key cytokine driving osteoclast differentiation



Modified from Charles et al TMM, 2015

Multiple signaling pathways promote bone formation



Modified from Charles et al TMM, 2015

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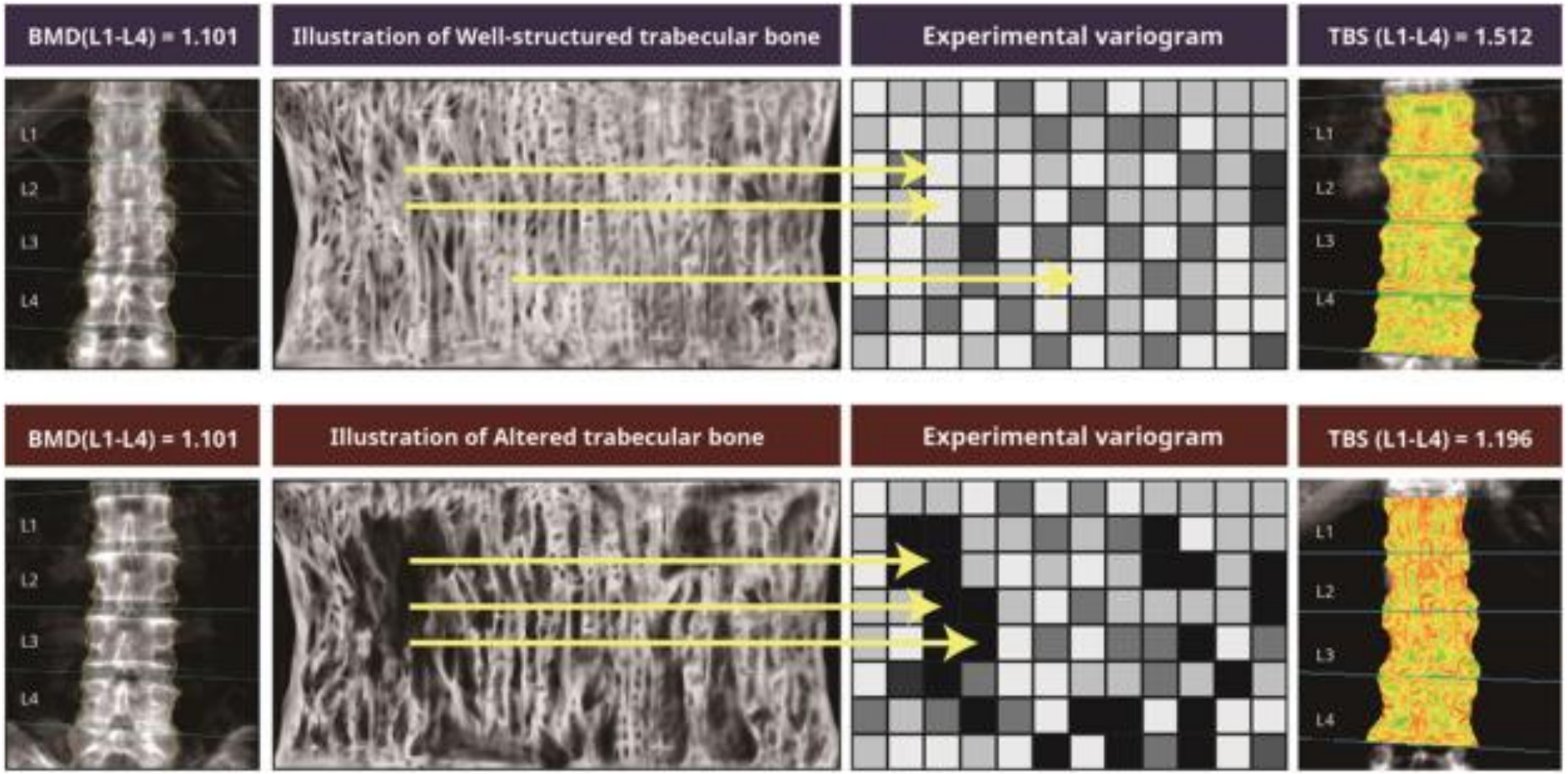
Osteoporosis: T score <-2.5 (postmenopausal women & men >50)

- Areal BMD
  - femoral neck
  - lumbar spine
  - distal radius
- No assessment of bone quality
- Lack of universal reference calibration

Dual Energy X-ray Absorptiometry

sequential scans should be performed on same machine

Trabecular Bone Score: a proxy for bone quality



Choi et al, Osteoporosis and Sarcopenia, 2016

Osteoporosis: Clinical Diagnosis

Fragility Fracture of the Vertebrae or Hip

- Adult age
- Absence of major trauma

  eg MVA, multi-story fall
- Clinical or morphometric vertebral fx

Osteoporosis: diagnosis in younger patients

For premenopausal women and men<50

- A Z-score of ≤ -2.0 is considered
  "Low bone density for chronologic age"

- A diagnosis of osteoporosis **is not based on BMD alone**

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Who should be screened?

Bone density measurement with DXA is recommended for:

- Women age 65 yrs and older
- Men age 70 and older
- Postmenopausal women and men age 50-69 with risk factors
- fracture > age 50

LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, Siris ES. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022

USPSTF guidelines for screening

Population	Recommendation	Grade
Women 65 years or older	The USPSTF recommends screening for osteoporosis to prevent osteoporotic fractures in women 65 years or older. See the "Practice Considerations" section for more information on screening tests.	B
Postmenopausal women younger than 65 years with 1 or more risk factors for osteoporosis	The USPSTF recommends screening for osteoporosis to prevent osteoporotic fractures in postmenopausal women younger than 65 years who are at increased risk for an osteoporotic fracture as estimated by clinical risk assessment. See the "Practice Considerations" section for more information on risk assessment and screening tests.	B
Men	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men. See the "Practice Considerations" section for suggestions for practice regarding the I statement.	I

US Preventive Services Task Force. Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2025

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Clinical Risk Factors

Advanced age
Women
Estrogen deficiency
Low BMI
Smoking
3 or more alcoholic drinks/day
Low physical activity
Vitamin D deficiency
Low calcium intake

Selected associated diseases

- Rheumatoid Arthritis
- SpA
- Inflammatory bowel disease
- Mastocytosis

- Vitamin D deficiency
- Hyperparathyroidism
- Hyperthyroidism
- Cushing's syndrome
- Hypogonadism

- Celiac disease
- Malabsorption
- Hypercalciuria

- Immobilization
- Renal/liver disease
- Multiple myeloma
- Post-transplant

Selected associated medications

- **Glucocorticoids**
- SSRIs
- Proton pump inhibitors
- GnRH agonists
- Loop diuretics
- Heparin

- Aromatase inhibitors
- Anticonvulsants
- Tenofovir (TDF)
- Excess thyroid hormone
- Thiazolidinediones

Case 1: 46 yo W with acute onset mid-back pain

- Healthy pre-menopausal woman
- Sudden onset of pain opening a window
- T spine films show new compression fracture T10
- DXA report from another facility

  spine T score of -2.5, Z score of -2.0

You give her a diagnosis of osteoporosis because:

A. spine T score is ≤-2.5
B. spine Z score is -2.0
C. T10 compression fracture is present

You give her a diagnosis of osteoporosis because:

A. spine T score is ≤-2.5

B. spine Z score is -2.0

C. T10 compression fracture is present

T score is not applicable in a premenopausal woman. Z score is "low bone density for age". Compression fracture is sufficient for a clinical diagnosis of osteoporosis.

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Laboratory Evaluation for Secondary Causes of Osteoporosis

No data to determine cost-effective approach

- CBC
- Complete chemistry screen
  - Creatinine
  - alk phos, albumin
- Ca, Phos, PTH
- 25(OH)Vitamin D
- TSH (when indicated)
- Testosterone (men)
- 24h urine calcium, creatinine
- SPEP/IFE
- Tissue Transglutaminase Ab
- Evaluation for CTD
- Tryptase
- Prolactin
- Homocysteine
- 24-hr urine cortisol
- Fe/TIBC, ferritin
- Bone biopsy

Laboratory Evaluation: Tier 1

- CBC
- Chemistry
  - Creatinine
  - alk phos, albumin
- Ca, Phos, PTH
- 25(OH)Vitamin D
- TSH (when indicated)
- Testosterone (men)
- 24h urine calcium, creatinine
- SPEP/IFE
- Tissue Transglutaminase Ab
- Evaluation for inflammatory disease
- Tryptase
- Prolactin
- Homocysteine
- 24-hr urine cortisol
- Fe/TIBC, ferritin
- Bone biopsy

Laboratory Evaluation: Tier 2

- CBC
- Chemistry
  - Creatinine
  - alk phos, albumin
- Ca, Phos, PTH
- 25(OH)Vitamin D
- TSH (when indicated)
- Testosterone (men)
- 24h urine calcium, creatinine
- SPEP/IFE

- Tissue Transglutaminase Ab
- Evaluation for inflammatory disease
- Tryptase
- Prolactin
- Homocysteine
- 24-hr urine cortisol
- Fe/TIBC, ferritin
- Bone biopsy

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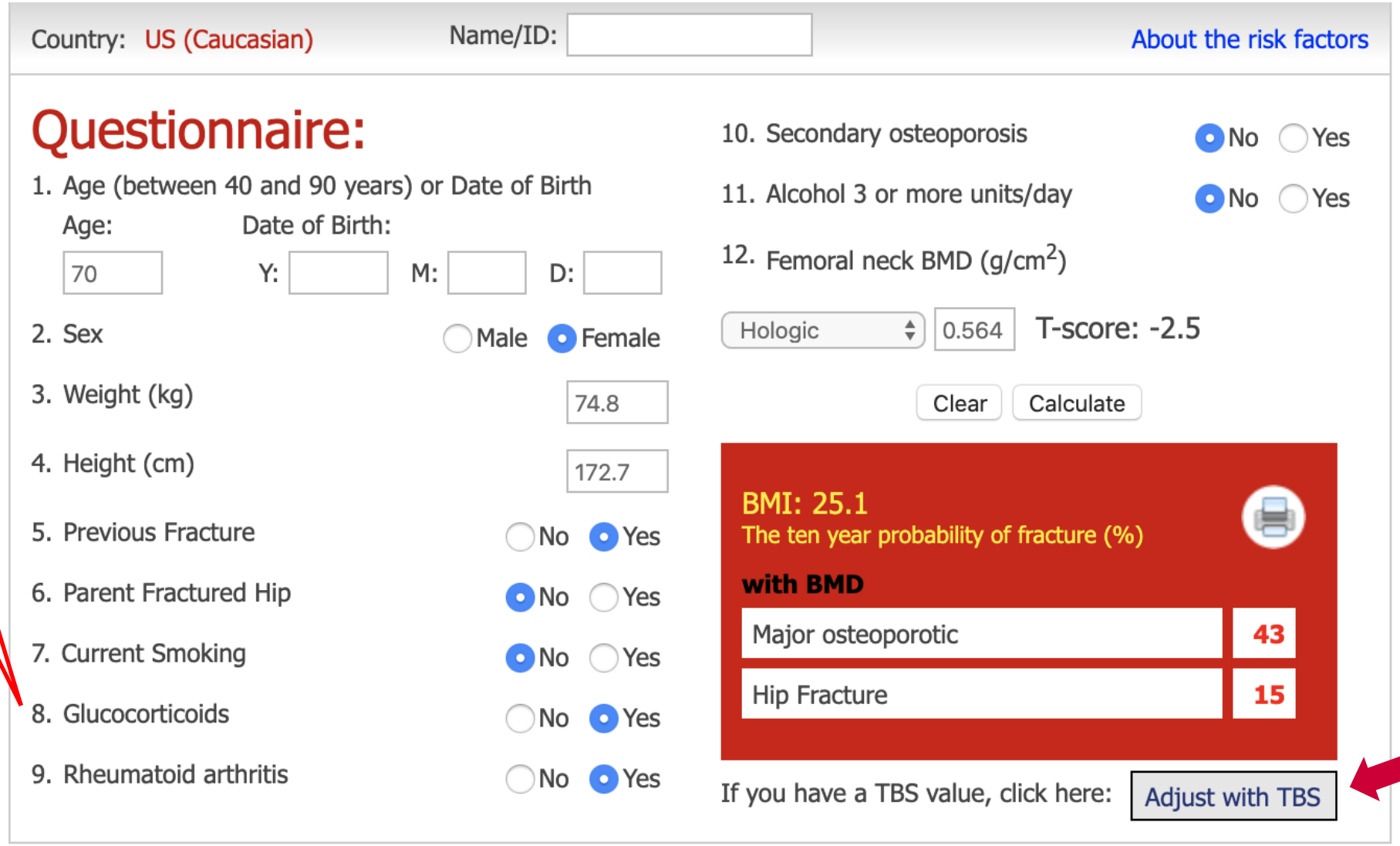
Who should be treated?

- Patients with vertebral or hip fractures
- Patients with T-score ≤ -2.5
- Patients with osteopenia or low bone density for age and history of fracture or high risk of fracture

FRAX® http://www.shef.ac.uk/FRAX



YES
if EVER
>3mo of
5mg
prednisone
or
equivalent

US Threshold for Treatment

Pharmacologic treatment is cost-effective if risk of fracture in 10 years is:

- **3% or greater** for hip fracture
- **20% or greater** for major osteoporotic fracture

Dawson-Hughes B et al. 2008 Osteoporos Int 19:449-458
Tosteson ANA et al. 2008 Osteoporos Int 19:437-447
http://www.nof.org/professionals/Clinicians_Guide.htm

Limitations of FRAX®

- Intended for use in post-menopausal women and men>50
- Not validated for patients currently or previously treated for osteoporosis
- Underestimates risk in patients with low spine BMD but relatively preserved hip BMD
  - *Spine-hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Leslie et al. Osteoporos Int. 2011*
- Does not include fall risk as a clinical factor
  - *Adjusting conventional FRAX estimates according to the number of prior falls in the preceding year. Kanis et al. Osteoporos Int. 2023*
- Underestimates risk in patients with multiple osteoporosis-related fractures

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3. Epidemiology and Risk Factors
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Treatment of Osteoporosis

- Universal Recommendations for Non-pharmacologic Interventions
- Pharmacologic interventions
  - Anti-resorptive agents
  - Anabolic agents

Monitoring Treatment in patients on pharmacologic therapy

- Periodic reassessment of
  - Interval history of fracture
  - Fracture risk
  - Adherence & satisfaction

- Perform serial BMD testing to assess response (typically every 1-2 years)

- ”Treat to Target” concept beginning to be applied in osteoporosis
  - Target is to reduce fracture risk to ’acceptable’ level
  - In practice, stability to improvement in BMD and no interval fracture

Universal recommendations

Adequate Calcium Intake

- 1000mg -1200mg a day
- Preferably dietary source

Adequate Vitamin D

- 600-1000IU/day (varying recommendations)
- Goal 25(OH)vitamin D of 30-50ng/mL

Weight bearing exercise

Smoking cessation

Avoid excess alcohol (>3 units/day)

Balance/ flexibility / fall avoidance

Pharmacologic Interventions

Anti-resorptives	Anabolic Agents
Raloxifene	Teriparatide
Bisphosphonates	Abaloparatide
Denosumab	Romosozumab
Calcitonin	
Estrogen-progesterone (prevention only)	

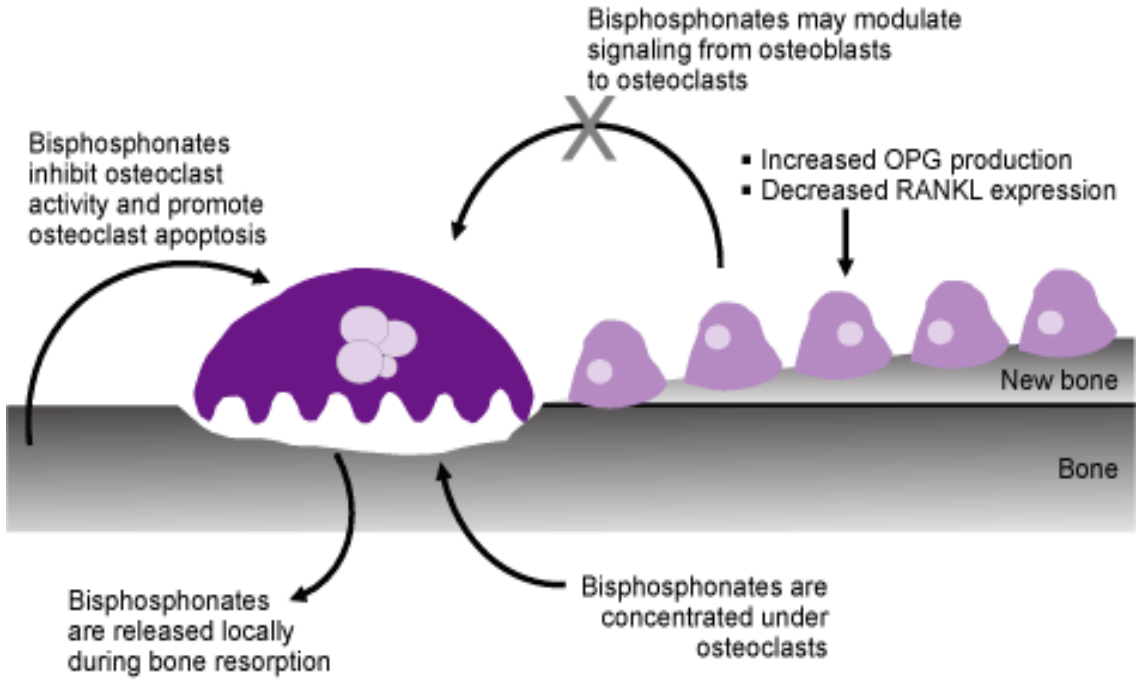
Raloxifene

- Selective Estrogen Receptor Modulator - Daily oral dosing
  - Modestly reduces fracture risk at spine only
  - Breast ca risk reduction in high-risk women
  - Not indicated for men
  - Contraindicated if history of thromboembolism
- Adverse Reactions of Note
  - Hot flashes
  - hypertriglyceridemia
  - DVT/PE
  - Increased risk of death from CVA

Bisphosphonates: Unique Aspects

- Inhibit G protein prenylation → cytoskeletal disorganization and loss of resorption capability & osteoclast apoptosis

- Prolonged Lifespan in Bone
  - Attracted to sites of rapid turnover
  - Not metabolized
  - Inactive, buried in bone for up to 10 years
  - activated by osteoclastic bone resorption



Bisphosphonates

ORAL AGENTS	IV AGENTS
➢ Alendronate (weekly) ➢ Risedronate (weekly) ➢ Ibandronate (monthly)	➢ Zoledronic acid (q12 OR **q18mo**) ➢ Ibandronate (q3mo)

Bisphosphonates

- Avoid if eGFR < 30 - 35 ml/min
- Correct vitamin D deficiency prior to administration
- Oral preparations
  - poorly absorbed (<1% under ideal circumstances)
  - must be taken in the morning on empty stomach, with glass of water; nothing else but water x 30-60 minutes; no lying down
  - Avoid if severe GERD, Barrett's or other esophageal pathology, hiatal hernia, gastric bypass

Bisphosphonates: Potential Adverse Events

ORAL AGENTS	IV AGENTS
GERD/Upper GI	Acute phase reaction
Hypocalcemia	Hypocalcemia
(Renal toxicity)	Renal toxicity
Atypical femur fracture	Atypical femur fracture
Osteonecrosis of the jaw	Osteonecrosis of the jaw
	Uveitis

Acute Phase Reaction after Zoledronic Acid Infusion

- Fever, myalgia, headache with elevated IFNγ and TNF
  - Thought to be caused by $\gamma\delta$T cell activation
- Common: 1 in 5 patients will have some symptoms
  1 in 20 will have more severe symptoms
  (eg fever>101˚C)
- *Risk factors:* young age, low vitamin D level, Asian race
- Prior BP exposure is protective
- acetaminophen or dex pretreatment reduces risk by ~50%
  - Acetominophen 500mg prior to then every 6h for 48 hours
  - Dexamethasone 4mg day of and for 2d after infusion

Roelofs et al BJH 2008; Reid et al JCEM 2010; Popp et al OI 2017; Wark et al OI 2012; Murdoch et al JBMR 2023

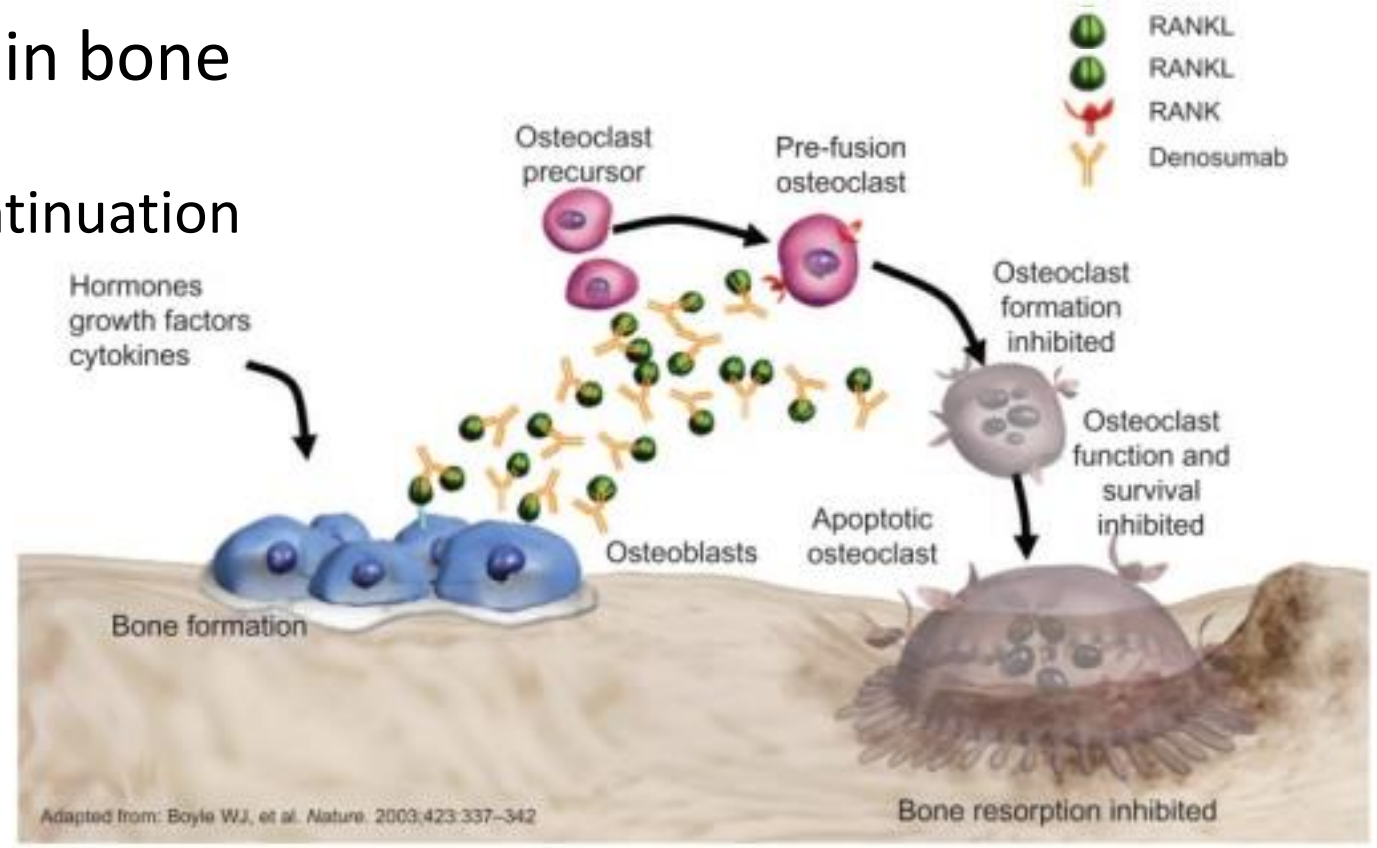
Denosumab: humanized neutralizing antibody to RANKL

- Every 6 month SQ injection
- No renal toxicity or adjustment for GFR

- Shorter-acting; does not reside in bone
  =>Rebound resorption
- BMD gains lost by 1 year after discontinuation

- BMD continues to increase over time without plateau (10-year data published)

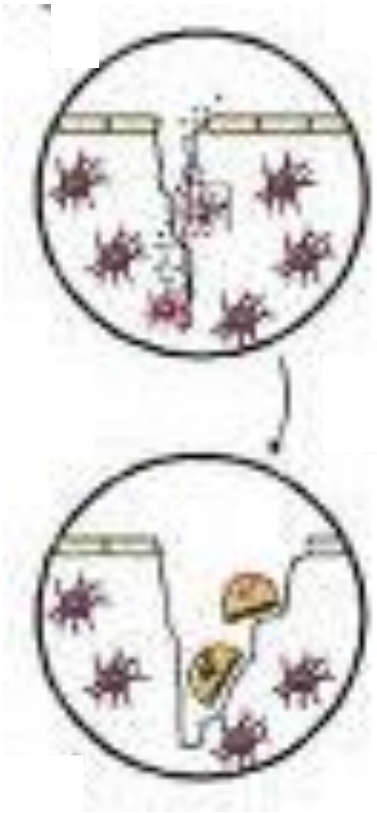
- No increase in AE rate with longer duration of dosing



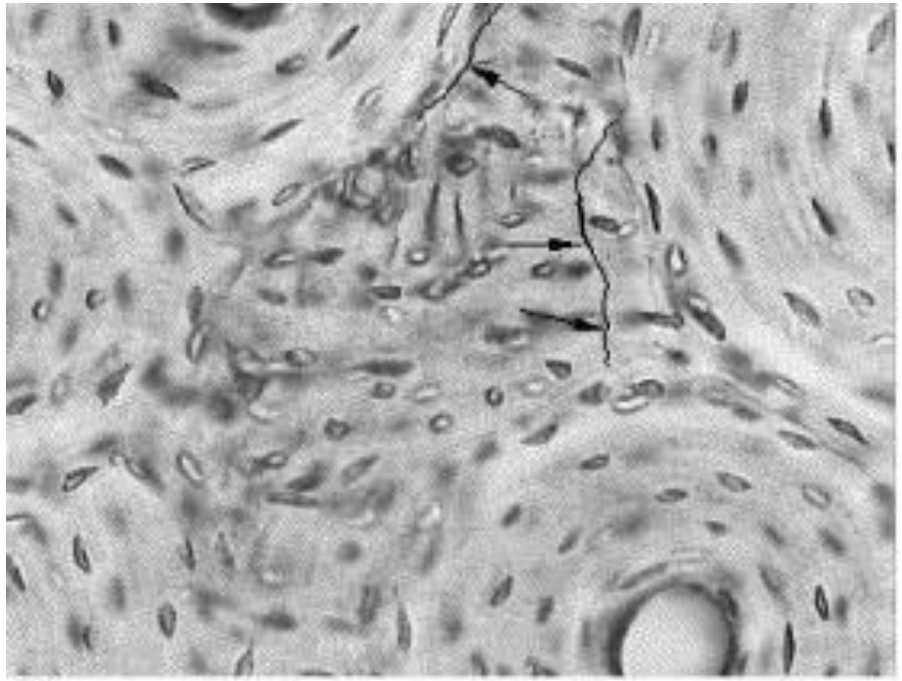
Bone et al, Lancet Diabetes Endocrinol, 2017

Prolonged suppression of bone turnover: Potential adverse effects

Microcrack Formation

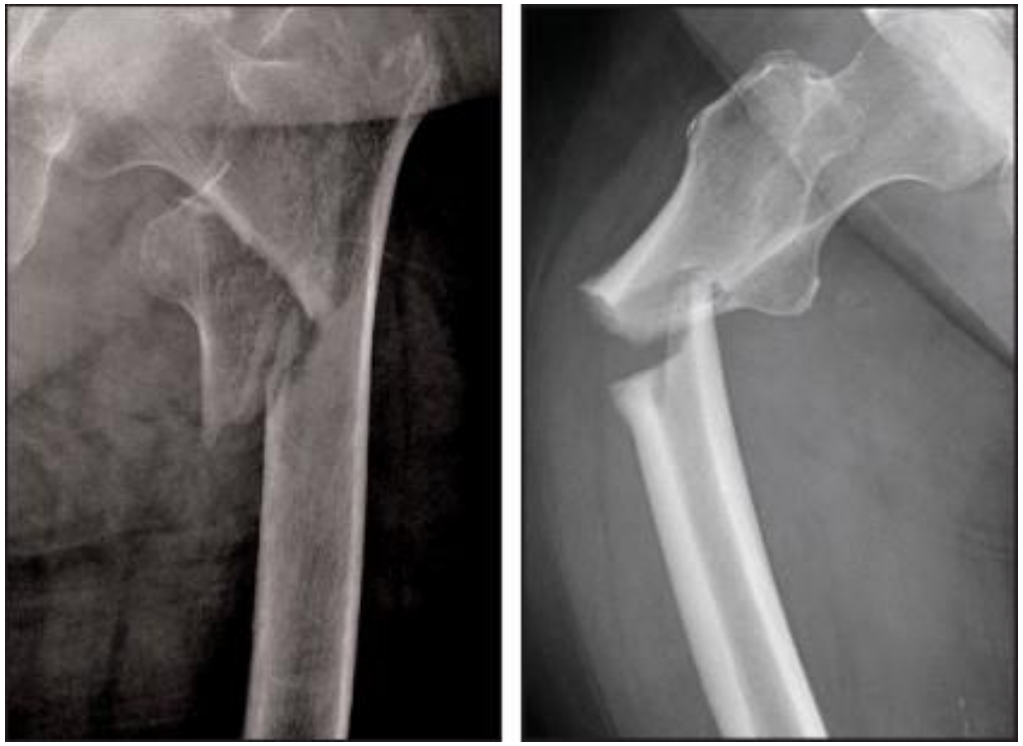


Osteoclast activation



(a)

Atypical femur fracture



Typical

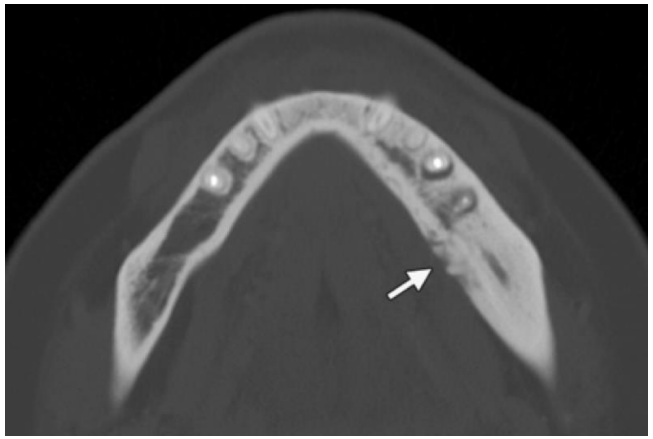
Atypical

- Approximately 3 in 100,000 patient years
- Transverse fractures originating at lateral cortex, located in the subtrochanteric femoral shaft lateral cortex
- Prodromal thigh or groin pain common
- Up to 1/3 are bilateral
- Median exposure to bisphosphonate of 7 years & risk increases with prolonged duration
- GC use increases risk
- *Management:* discontinue antiresorptive; prophylactic nail fixation for incomplete fractures with pain; consider teriparatide

Shane et al ASBMR 2nd Task Force, JBMR 2014

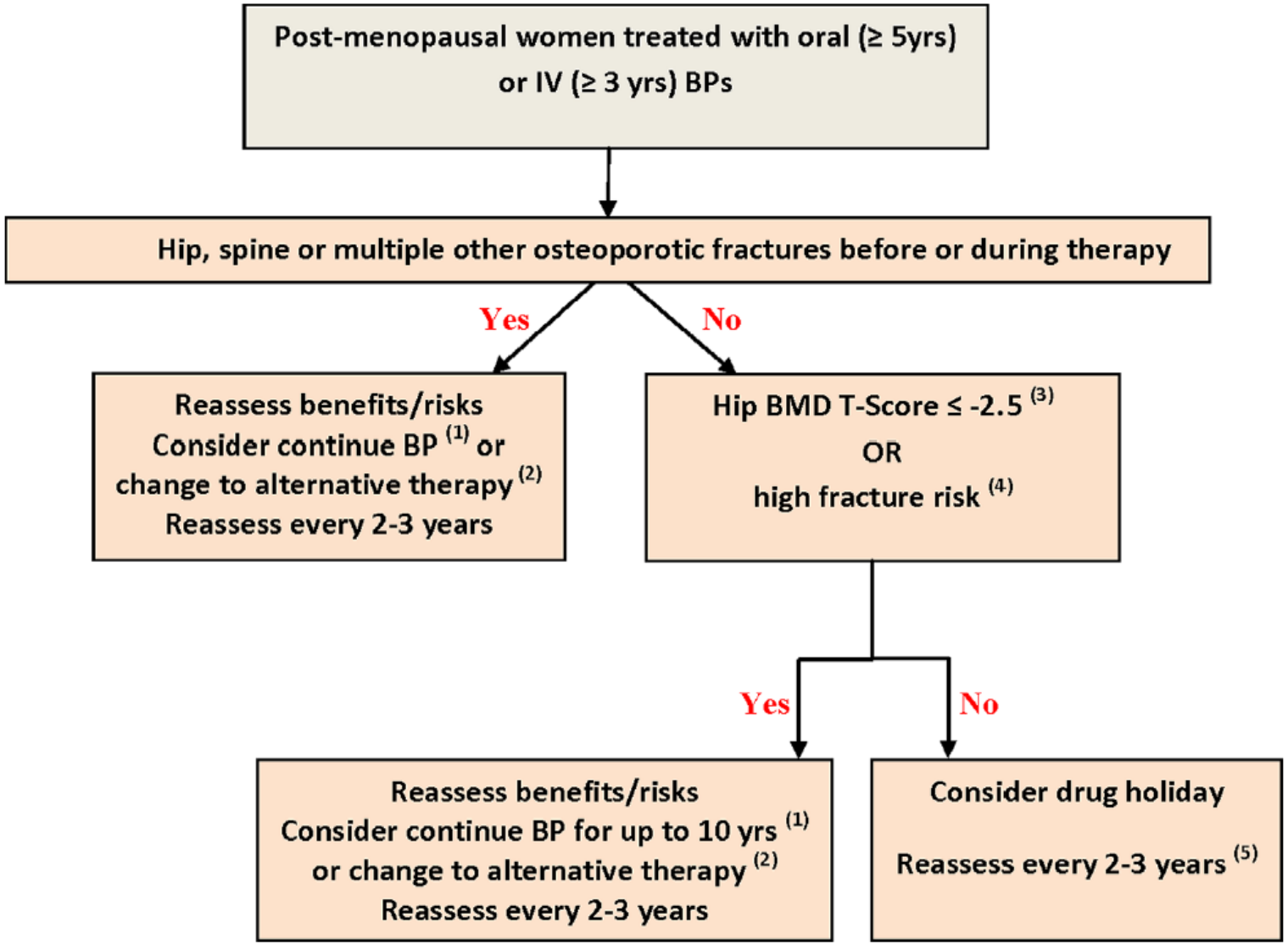
Osteonecrosis of the jaw

- 1 in 10,000
- Risk factors include
  - Dose and duration of therapy
  - IV administration
  - Dental extractions & implants
  - poorly fitting dentures
  - Anti-cancer treatments, glucocorticoids, smoking, DM
- *Prevention:* pre-treatment screening
- *Management:* pain management, antibacterial rinses, debridement as needed to control pain or infection



Khan et al, JBMR 2015
AAOMS position paper, 2014
Morag et al, RadiogGraphics RSNA, 2009

Recommendations for Considering Bisphosphonate Holiday



Adler RA et al. 2016 JBMR

Anabolic Agents: PTHR1 agonists

Teriparatide - recombinant fragment of human PTH, aa 1-34

Abaloparatide - Recombinant fragment of human PTHrP, aa 1-34

- Activate the PTH Receptor
- Intermittent dosing has an anabolic effect on bone
- Daily SQ injection for 18-24 months
- Must be followed with an anti-resorptive to maintain BMD gains

PTHR1 agonists:

Indicated for those at very high risk for fracture:

- T-score ≤ -3.5
- T-score ≤ -2.5 with fragility fractures
- Multiple risk factors (including steroids)
- Failed/intolerant of previous therapy

Teriparatide

approved for PMO, male osteoporosis, glucocorticoid induced OP

Abaloparatide

currently approved for PMO, male osteoporosis

PTHR1 agonists:
Contraindications & potential side effects

Contraindications	Potential Side Effects
Hyperparathyroidism	
Hypercalcemia	Hypercalcemia
Renal stones	Hypercalciuria Hyperuricemia (3%)
Prior radiation therapy involving the skeleton Open growth plates Paget's disease, unexplained high alk phos History of osteosarcoma/skeletal malignancy or metastasis	Concern for osteosarcoma

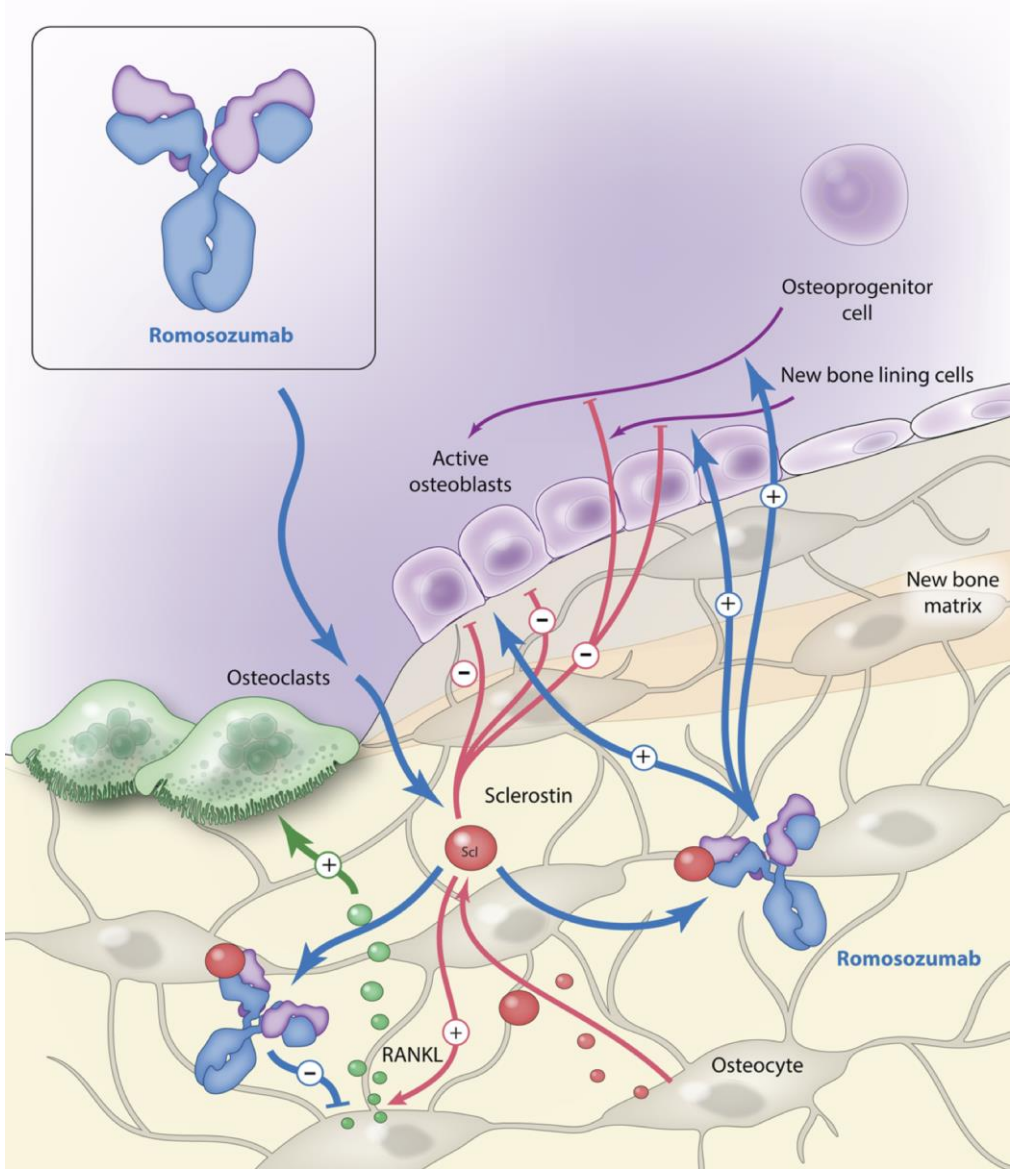
COMMON side effects: orthostatic hypotension, dizziness, palpitations, nausea

Romosozumab: humanized neutralizing antibody to Sclerostin

Anabolic (& anti-resorptive)

- neutralizes the Wnt pathway inhibitor sclerostin
- Increases Wnt signaling promotes OB function
- Inhibits RANKL to ↓bone resorption

- Clinician administered monthly for 12months (2 x 1.2 mL SC injections per visit)



Sølling, Ther Adv Msk Dis, 2018

Romosozumab:

- Approved for post-menopausal women
  - 2020 AACE guidelines suggests romosozumab use as
    - possible first line therapy in women at **very** high risk of fracture/prior fracture
    - Second line therapy in high-risk women failed/intolerant to other agents
- RCT shows benefit in men but not yet approved for men
- Increases spine BMD > alendronate
- Decreased risk of vertebral fracture, non-vertebral fracture, hip fracture compared to alendronate
- Course limited by loss of anabolic effect over time
- Must be followed by anti-resorptive to maintain BMD gains

Romosozumab

Contraindications

- Stroke or MI in last 12mo
- At risk for CV event (relative)
- Hypersensitivity
- Hypocalcemia

Possible Side Effects

- Headache
- Arthralgias
- Injection site reactions
- Hypocalcemia
- Stroke/MI/CV death

Two large RCT led to approval.

POOLED HR 1.3 for MACE

Considerations in Choosing Therapy:

- Efficacy against vertebral vs non-vertebral fractures
- Ease of administration
- Adverse effects
- Long-term safety
- Non-skeletal effects
- Cost and insurance coverage

Comparison of current osteoporosis therapies

	Mechanism of action	2-year spine BMD ↑	2-year hip BMD ↑	↓RR spine fx	↓RR non-spine
Raloxifene	SERM/anti-resorptive	2-3%	1%	50%	--
Oral BP	OC apoptosis/anti-resorptive	3-5%	2-3%	40-53%	0-20%
Zoledronic acid	OC apoptosis/anti-resorptive	5-6%	3-4%	70%	25%
Denosumab	RANKL inhibitor/anti-resorptive	6-8%	3-4%	68%	20%
Teriparatide	PTH analog/anabolic	8-10%	1.5-2%	65-70%	35%
Abaloparatide	PTHRP analog/anabolic	10%	2-3%	70-80%	40%
Romosozumab	Sclerostin inhibitor/anabolic	11% (1 yr)	4% (1 yr)	48% vs ALN	20% vs ALN

Black et al Lancet 1996; Neer et al NEJM 2001; Black et al NEJM 2007
Cummings NEJM 2009; Miller JAMA 2016; Saag NEJM 2017

MOC REFLECTIVE STATEMENT

- Screening with DXA is indicated for women over 65, younger individuals with risk factors, and (depending on guideline) men over 70.
- Diagnosis of osteoporosis can be made clinically (hip/spine fragility fracture) or based on DXA
- Pharmacologic therapy is indicated for individuals with osteoporosis and those whose FRAX calculated 10-year risk of fracture is >3% for hip fracture OR >20% for MOP
  - Initial therapy with osteo-anabolics indicated for those at very high risk of fracture
  - Osteo-anabolics must be followed by anti-resorptive therapy
  - Monitor response to therapy by serial re-assessment of fracture risk and BMD

References

- The clinician's guide to prevention and treatment of osteoporosis. LeBoff et al. Osteoporos Int. 2022
- Pharmacologic Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. Shoback et al. JCEM. 2020
- Managing osteoporosis in patients on long term bisphosphonates. Adler et al. JBMR. 2016.
- Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. Khan et al. JBMR 2015.
- Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. Shane et al. JBMR 2014.