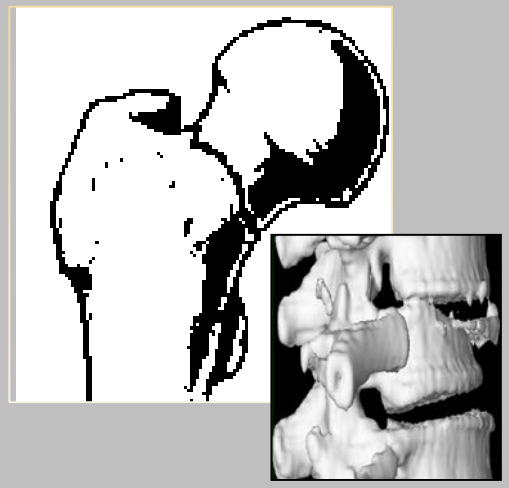
Clinical and research updates of osteoporosis in geriatric patients



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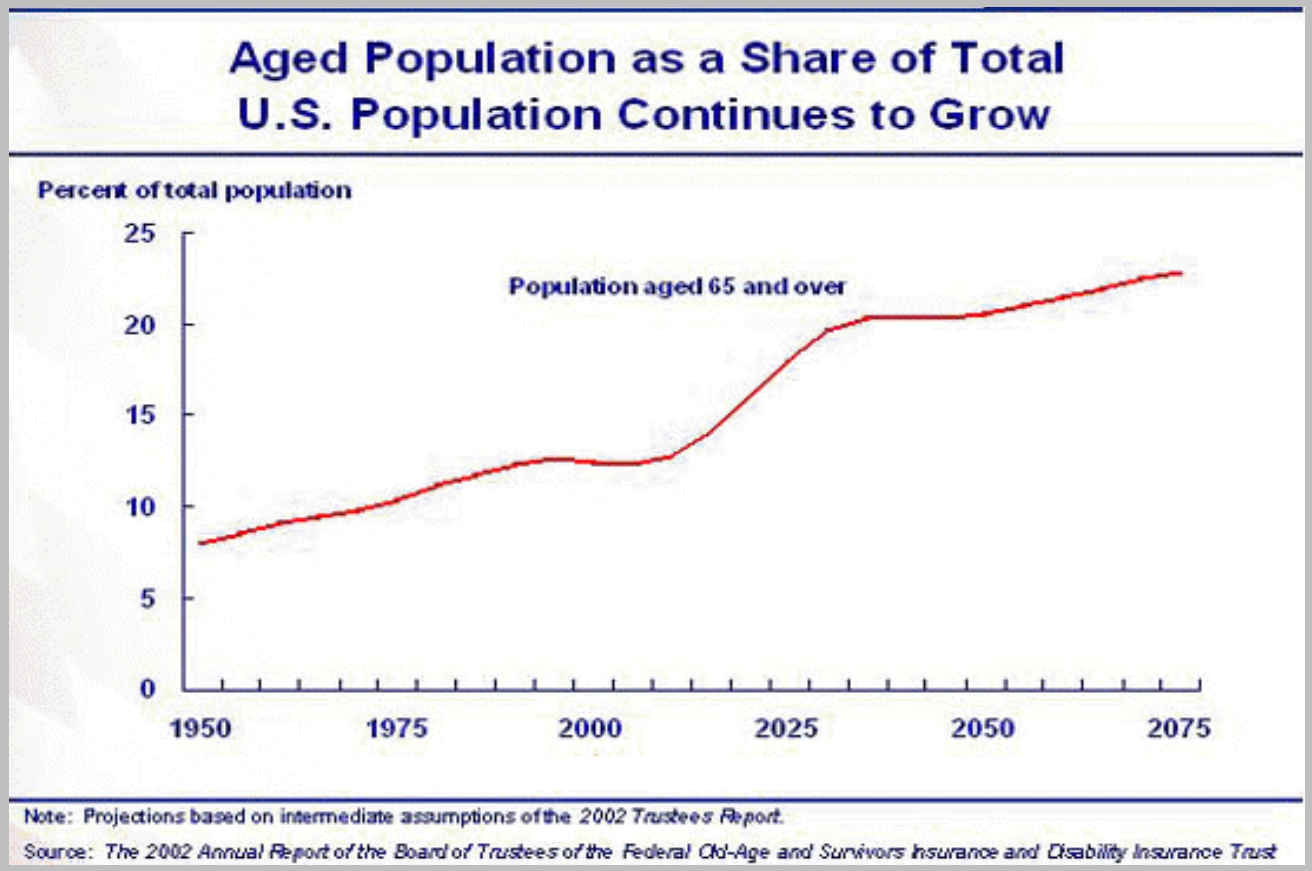
Learning objectives

- Attendees will recognize osteoporosis as an important public health problem in geriatric population
- Attendees will be able to screen & diagnose and treat osteoporosis
- Describe clinical progress in osteoporosis care for geriatric patients in relation to the recent scientific advancements

Disclosure

- None

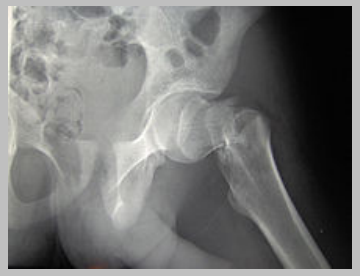
Geriatric population in the USA



- ~10,000 baby boomers turn 65 everyday with ≥65 yrs
  - 34 million in 1998 to ~ 70 million in 2030

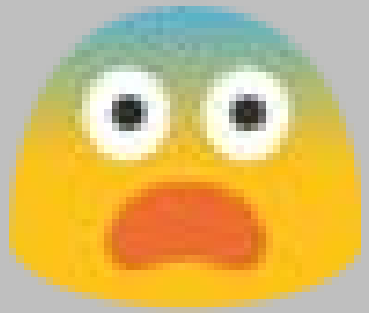
Osteoporosis: Health problem of old age & a public health concern

- 54 million Americans have osteoporosis or low bone mass
- ~1 in 2 women & 1 in 4 men ≥50 yrs will suffer a fragility fracture[NOF]
- Over 2 million fragility fractures a year
  - >combined incidence of MI, strokes & breast cancer
    - *27% vertebral fractures*
    - *19% wrist fractures*
    - *14% hip fractures*



Osteoporotic fractures: low impact trauma/fragility fracture

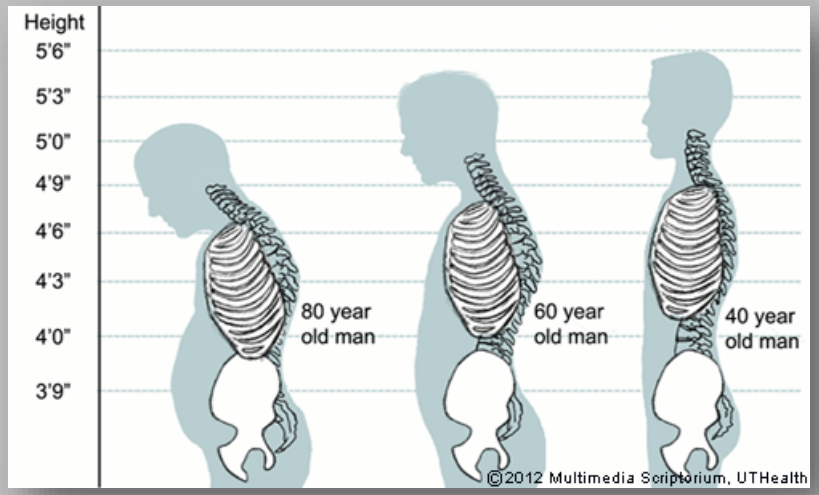
- Fractures without much force or any high impact trauma:
  - Turning in bed
  - Bent forward to do gardening
  - Lifted a trash can in the kitchen
  - Fall from wheel chair
  - Fall when transferring from bed to chair
  - Fall from standing height



Osteoporosis & quality of life

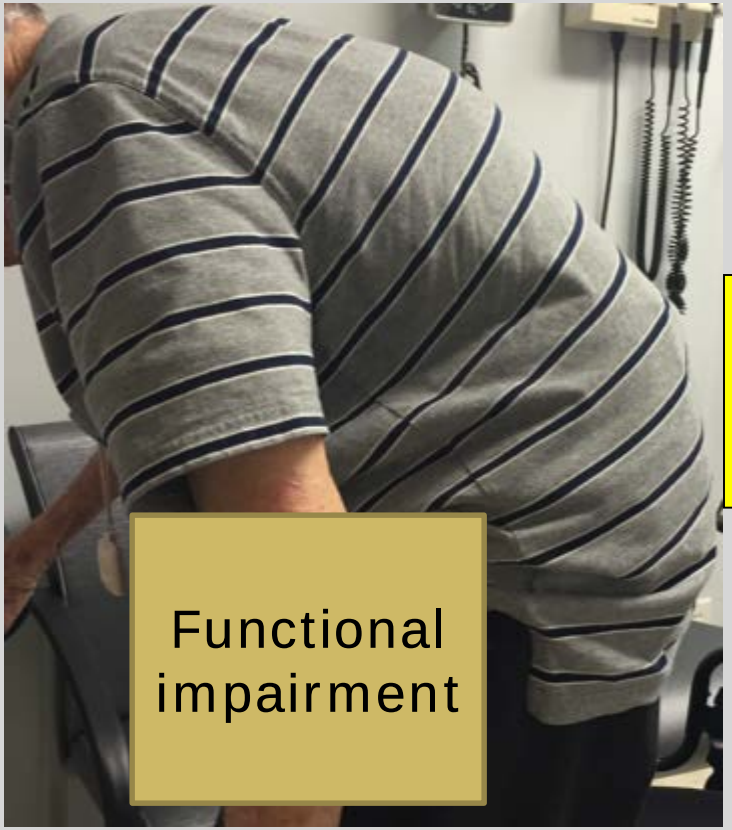
- Fractures can decrease quality of life:
  - *Physical*: pain, compressed abdomen, spinal deformity
  - *Functional*: decreased mobility
  - *Psychosocial*: depression
  - *Rate of recurrent vertebral fracture after the initial one:* ~5-20%

- Hip fracture
  - ~50% with hip fractures will never walk w/o assistance
  - ~25% will require long-term care



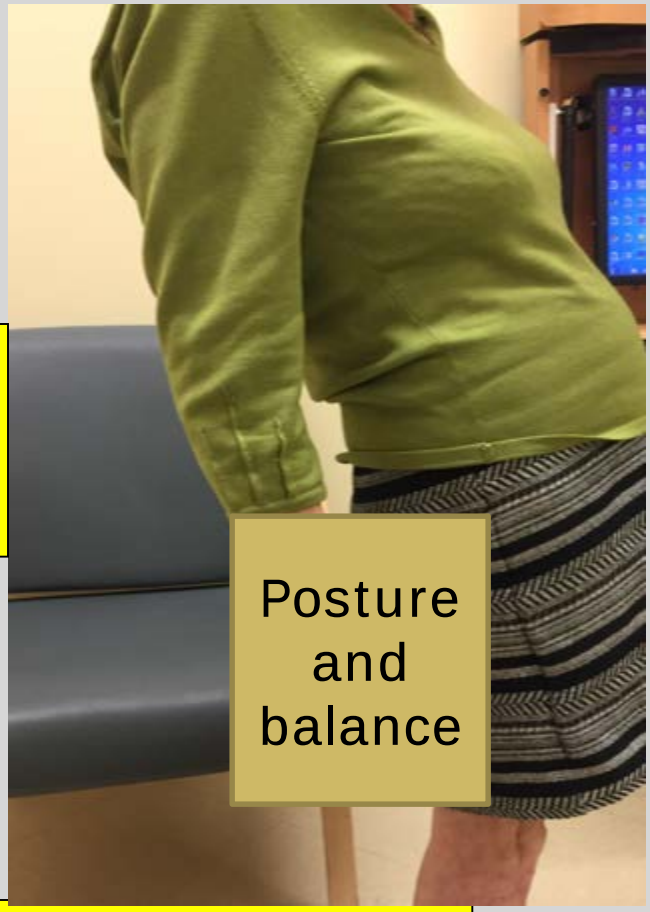
NOF

Life with osteoporosis



Limited mobility

Discomfort
Pain
Depression



High risk for Fall & Fragility Fractures

Health care cost

- ~ $22 billion is spent annually for osteoporosis and related fracture in the USA Blume & Curtis, 2010

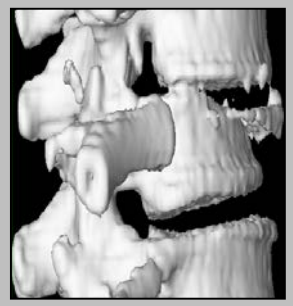
- ~ $7 billion is spent annually for breast cancer in the USA State of Health Care Quality, 2007

Concerns for geriatricians

- Concerns of under-recognition and under-treatment
  - ~20% f/u for treatment after fragility fractures Own the Bone
  - Fracture- often first sign of presence of osteoporosis
- ~ 50% osteoporosis related office visits managed by PCPs
  - HTN, ↑ lipid, OA, DM & depression - common in them
- Barriers for PCPs
  - For PCPs/Geriatricians: Competing chronic disease priorities
  - Lack of translational research
    - Tools available in clinical practice
    - Chronic diseases as risk of fracture
    - What is normal for the oldest of the old

Osteoporosis: definition

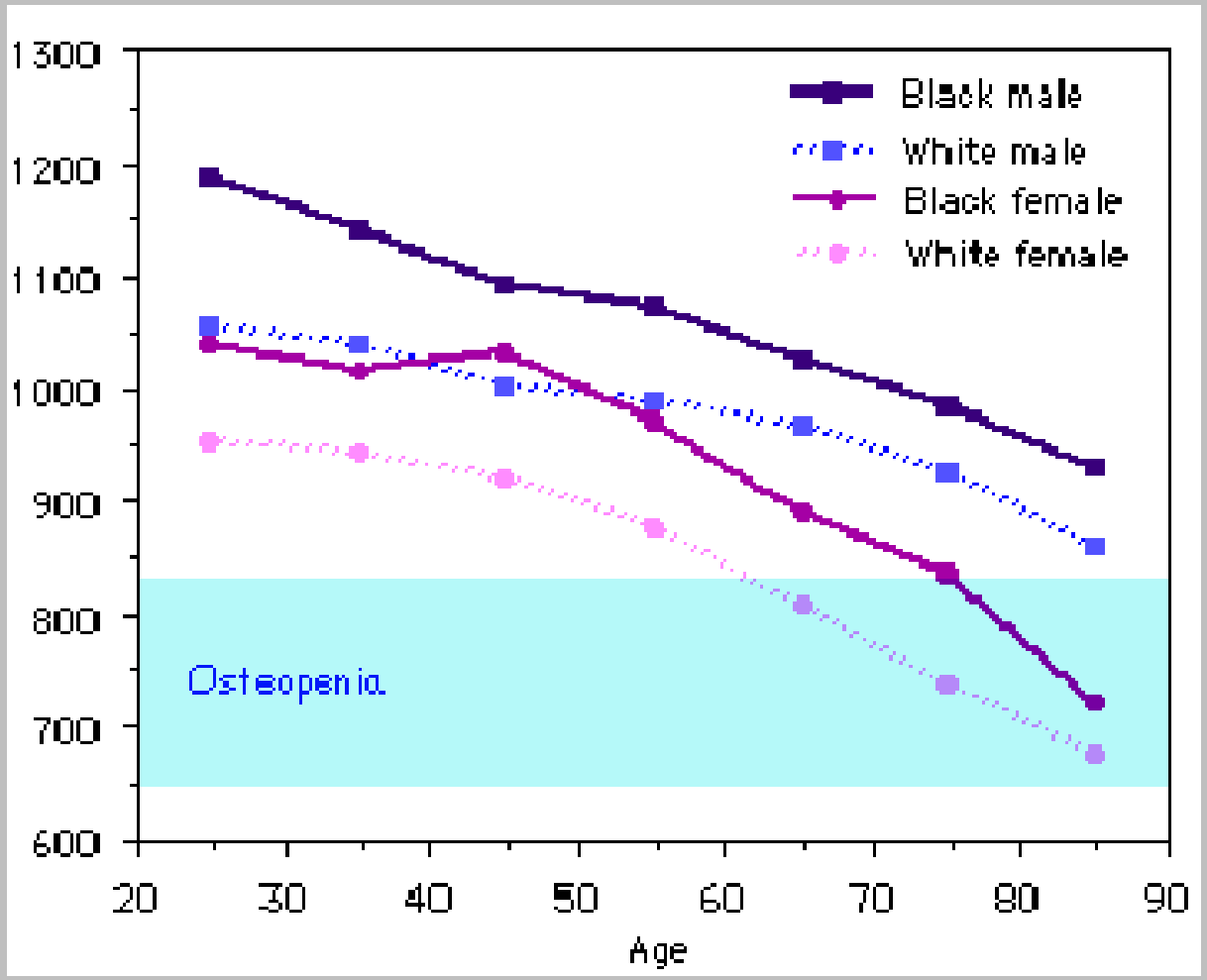
- Compromised bone strength that increases risk of fracture



  - Bone Strength is characterized by
    - Bone density &
    - Other bone qualities, e .g., micro-architecture influenced by bone remodeling, bone turnover, mineralization and other factors that are more difficult to quantify, such as “damage accumulation”

(NIH consensus conference 2000)

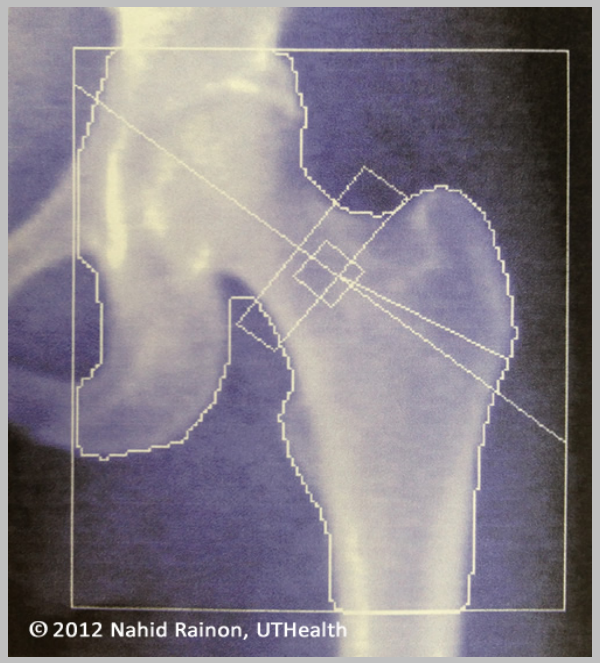
BMD changes with advanced age



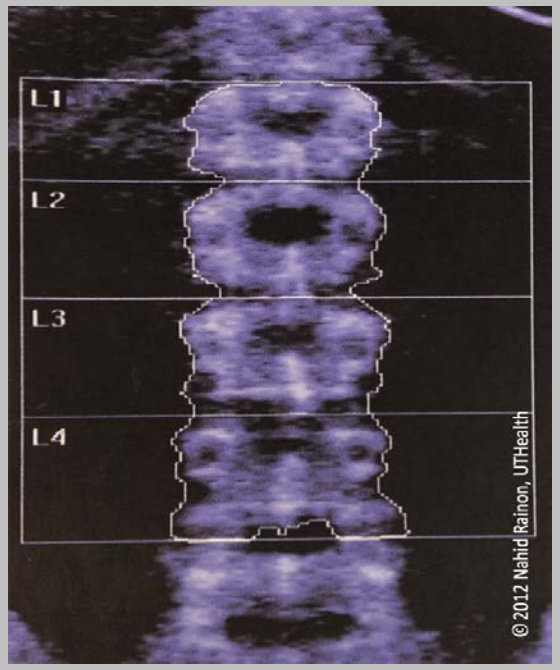
ASBMR 2011

Source: ASBMR using data from Looker A et al., 1998 Osteop. Intl

Clinical diagnosis of osteoporosis



DEXA scan - Left hip



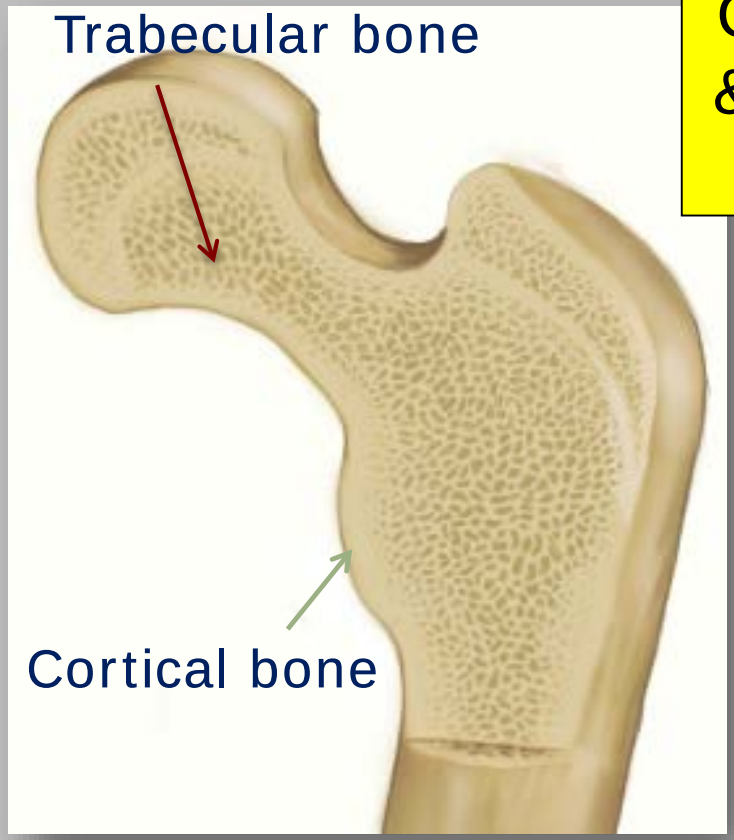
DXA scan - Lumbar spine

- Osteoporosis = A T- score of <-2.5 for BMD
- Osteopenia = A T-score of -1 to -2.5 for BMD

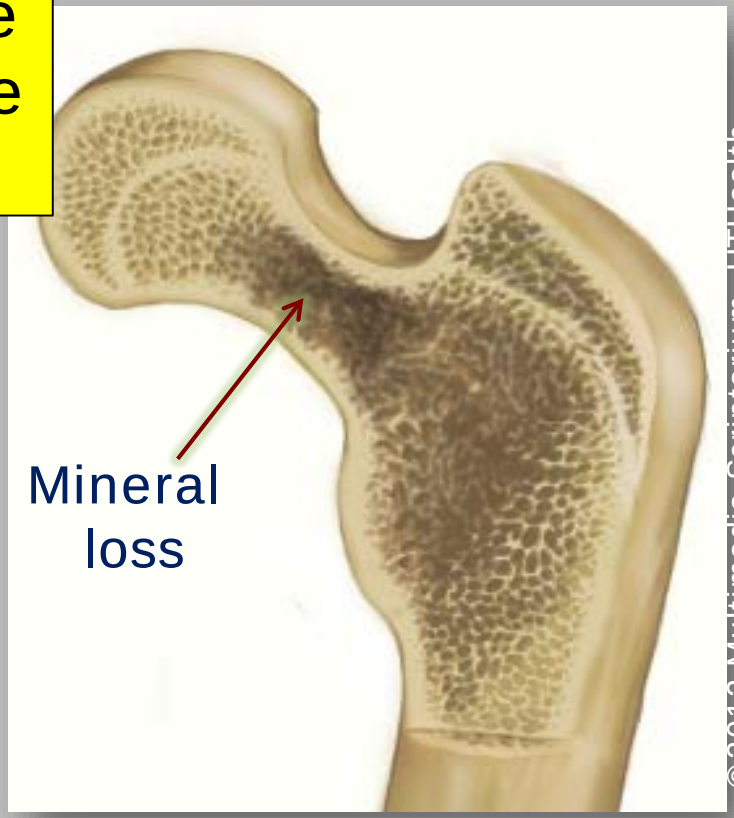
- Usual sites for DXA is lumbar spine and left hip

Osteoporotic bone

Quantitative & qualitative changes



Healthy femur



Loss of mineral & microstructure

Fragility Fractures

Who should we screen: USPSTF

Annals of Internal Medicine

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

USPSTF

SCREENING FOR OSTEOPOROSIS
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	**Women aged ≥65 years without previous known fractures or secondary causes of osteoporosis**	**Women aged <65 years whose 10-year fracture risk is equal to or greater than that of a 65-year-old white woman without additional risk factors**	**Men without previous known fractures or secondary causes of osteoporosis**
Recommendation	**Screen**		**No recommendation**
	Grade: B		**Grade: I (insufficient evidence)**

Risk Assessment	As many as 1 in 2 postmenopausal women and 1 in 5 older men are at risk for an osteoporosis-related fracture. Osteoporosis is common in all racial groups but is most common in white persons. Rates of osteoporosis increase with age. Elderly people are particularly susceptible to fractures. According to the FRAX fracture risk assessment tool, available at www.shef.ac.uk/FRAX/, the 10-year fracture risk in a 65-year-old white woman without additional risk factors is 9.3%.
Screening Tests	Current diagnostic and treatment criteria rely on dual-energy x-ray absorptiometry of the hip and lumbar spine.
Timing of Screening	Evidence is lacking about optimal intervals for repeated screening.
Interventions	In addition to adequate calcium and vitamin D intake and weight-bearing exercise, multiple U.S. Food and Drug Administration–approved therapies reduce fracture risk in women with low bone mineral density and no previous fractures, including bisphosphonates, parathyroid hormone, raloxifene, and estrogen. The choice of treatment should take into account the patient's clinical situation and the tradeoff between benefits and harms. Clinicians should provide education about how to minimize drug side effects.
Suggestions for Practice Regarding the I Statement for Men	Clinicians should consider: • Potential preventable burden: increasing because of the aging of the U.S. population • Potential harms: likely to be small, mostly opportunity costs • Current practice: routine screening of men is not widespread • Costs: additional scanners are required to screen sizeable populations. Men most likely to benefit from screening have a 10-year risk for osteoporotic fracture equal to or greater than that of a 65-year-old white woman without risk factors. However, current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, go to www.uspreventiveservicestaskforce.org.

Screening: other organizations

Organization	Recommendations	
	Women	men
NOF	BMD for all ≥65 y & postmenopausal <65 y, based on risk profile	BMD for all ≥70 y & 50-69 y, based on risk profile
WHO	Indirect evidence supports screening for ≥65 yo, but no direct evidence for widespread screening	
ACP		Older men at high risk & candidate for therapy
ACOG	BMD for all ≥65 y & postmenopausal <65 y who have ≥1 risk factor	

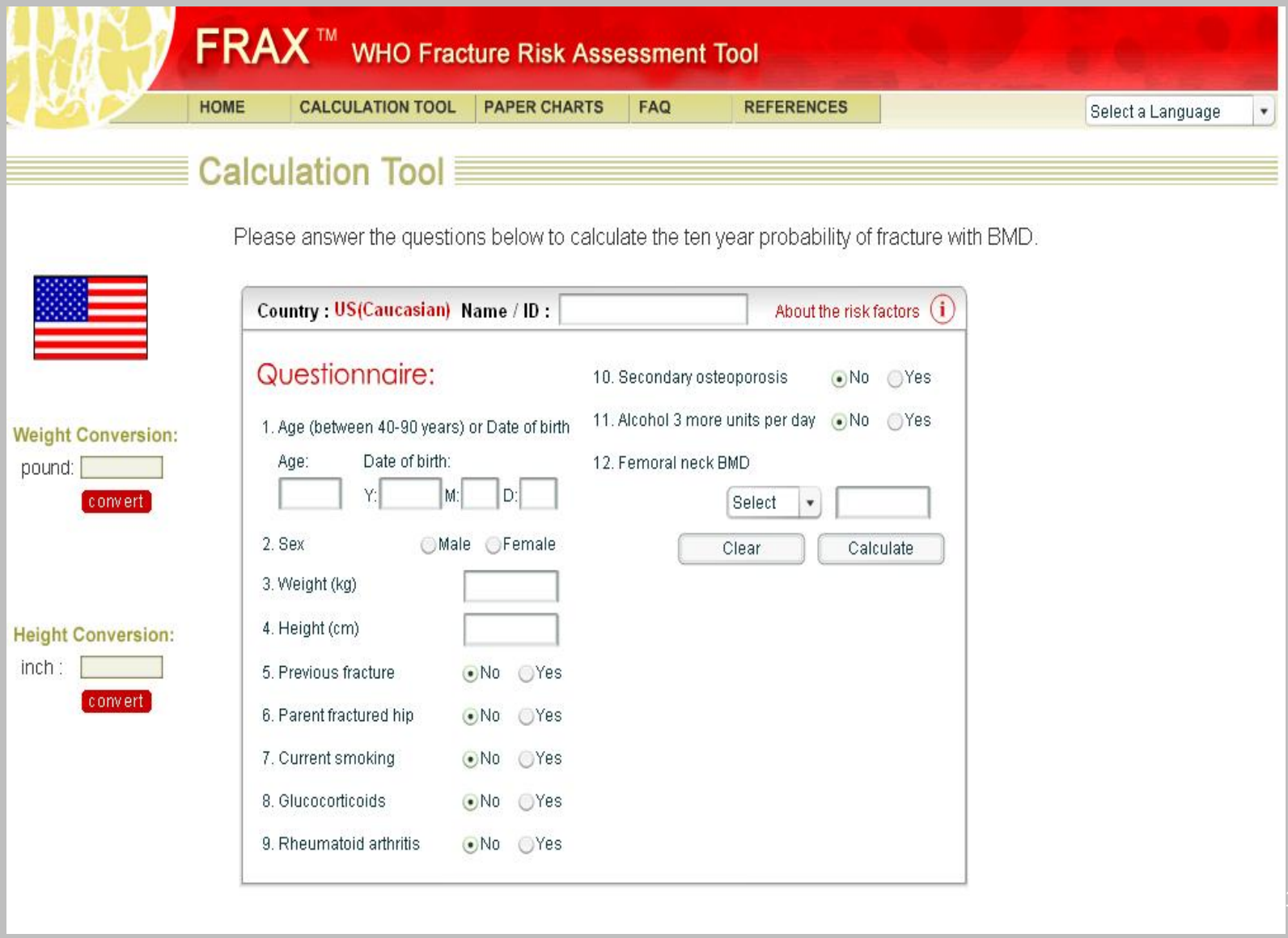
Ann Intern Med. 2011;154:356-364

Problem with fracture prevention based on BMD/T-score

- Fracture in patients with non-osteoporotic T score
- Assumptions that all older patients have high bone-turnover
- Unknown – What was baseline BMD before losing bone due to age
- Fracture before a screening DXA scan

- **WHO WILL HAVE A FRACTURE?**

WHO Fracture Assessment Tool
www.shef.ac.uk/FRAX



FRAX risk factors

- Age (40-90), gender, height & weight, race/ethnicity
- Previous fracture
- Hip fracture in parents
- Current smoking
- Alcohol
- Glucocorticoids (oral)≥ 3 months @ dose 5mg daily or more –
  - or equivalent doses of other glucocorticoids
- Rheumatoid arthritis
- 2ndary Osteoporosis
  - DM-I, OI in adults,
  - Untreated Hyper or Hypothyroidism,
  - Premature Menopause (<45 yrs),
  - Chronic malnutrition or malabsorption &
  - Chronic liver disease
- Bone mineral density (BMD)

Who needs treatment? (Men & Women)

- Hx of hip fracture
- Other prior fractures & T-score between -1.0 to -2.5 @ fem. neck, total hip or spine
  - Height loss (vert. frac.)*
- T-score ≤-2.5 @ fem. neck, total hip or spine

www.nof.org/professionals/clinical-guidelines
* Hannan et al., 2012 JBMR

- T-score between -1.0 to -2.5 @ fem. neck, total hip or spine **AND** 2ndary cause ↑ risk of fracture
  - Steroid use, total immobilization, men w/androgen deprivation therapy
- T-score between -1.0 to -2.5 @ fem. neck, total hip or spine **AND** 10-yr probability of hip fracture ≥ 3% or any major osteoporosis-related fracture ≥ 20% (FRAX)

Treatment Options

- **Antiresorptives**
- Bisphosphonates
  - Oral
    - Alendronate 10 mg qd or 70 mg wkly
    - Risedronate 5 mg qd or 35 mg wkly or 150 mg/mo
      - Ibandronate 150 mg/mo
  - Intra-venous
    - Zoledronic acid 5 mg/yr
- Denosumab
  - 60 mcg sc/q 6
    - Humanized monoclonal antibody

- **Anabolics**
- Teriparatide
  - 20 mcg sq daily
    - Recombinant human PTH (not >2 yrs)
    - Contra-indicated in cancer patients)
- Abaloparatide
  - 80 mcg sq daily
    - human PTHrP analog (not >2 yrs)
    - Not recommended for patients at risk of skeletal malignancies

- Calcium (1000-1200 mg) + Vitamin D (800-1000 IU daily)

www.nof.org/professionals/clinical-guidelines

Hormones as Treatment Options

- SERM
  - Raloxifene – not commonly used because it increases risk of DVT & increased hot flashes
- Estrogen/Progestin
  - Not encouraged due to increased risk of breast cancer, stroke, DVT and coronary diseases
- Testosterone
  - If hypogonadism is the cause of osteoporosis
  - Caution if history of prostate cancer

www.nof.org/professionals/clinical-guidelines

Adverse events/Tx Failure?: What to offer next

- For Bisphosphonates:
  - Atypical fracture
  - Jaw necrosis
  - Severe GERD/gastritis or GI bleed
  - Unimproved BMD despite treatment
  - Fracture while being on tx

- Intervention
  - Drug holiday
  - Monitor with DXA/1-2 yrs
  - Monitor bone markers/yr

- Alternate options
  - Switch to other agents

*Rianon N et al., 2011

Calcium and Vitamin D

- Calcium
  - 1000-1200 mg daily
  - Consider intake with diet
- Formulation:
  - Carbonate (with meal)
  - Citrate (fasting state)

- Vitamin D
  - Screen at risk patients
  - Check 25 hydroxy vitamin D total
  - Recommended level 30 ng/dl
- Ergo/Chole-calciferol
  - 800-1000 IU daily
  - Unless <30 – then 50000 IU q weekly for 8-12 wks

www.nof.org/professionals/clinical-guidelines;
IOM & Endocrine society guidelines

Monitoring Treatment Success

DXA Acquired BMD

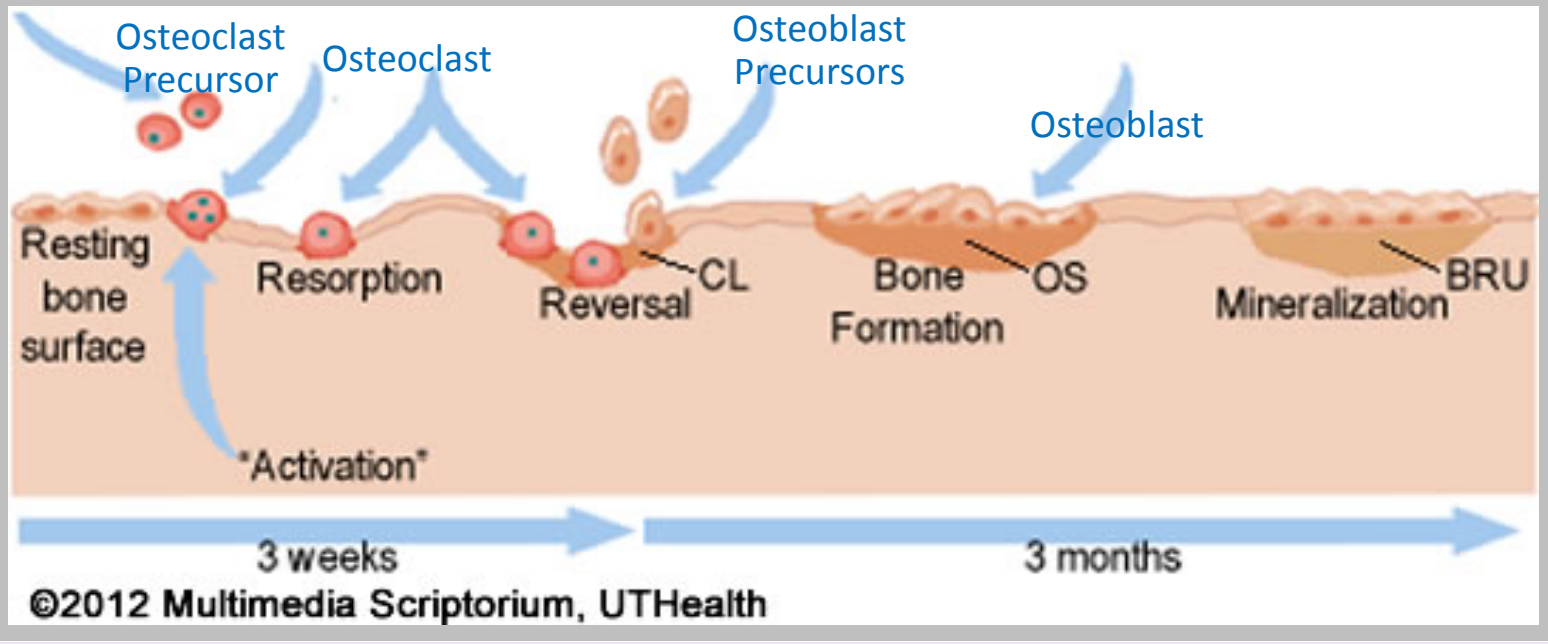
- Stable or improved BMD
- Loss of BMD < %CV showing no significant change over mechanical drift from QA report for DXA machine

Bone Markers

- Suppression of Bone markers
  - Both formation and resorption markers

Carey J, 2005; Delmas P et al., 2009; ASBMR

Physiology- Normal State



LEGEND: LC = Lining Cells CL = Cement Line OS = Osteoid BRU = Bone Remodeling Unit

Normal Bone Remodeling Sequence

Resorption = Formation No change in bone mass

Rianon- Osteoporosis UA, 2018

Pathogenesis: Unbalanced Remodeling

Resorption > Formation → **Net bone loss**

Inadequate calcium or vitamin D

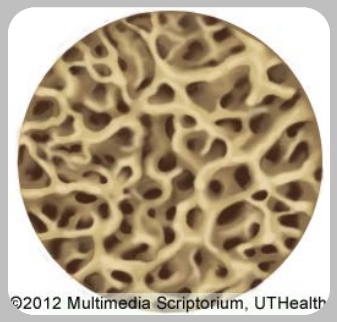
Menopause

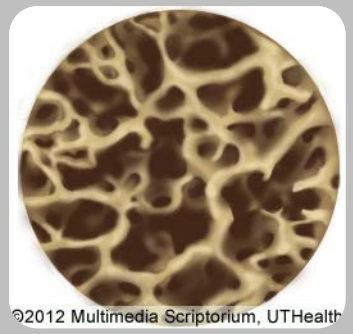
Aging

Medications or diseases

Osteoporosis

Normal Bone Structure





Osteoporotic Bone Structure

Bone Markers

Formation

- Serum bone specific alkaline phosphatase (BAP) (5.6-29 mcg/L)
- Serum pro-collagen type 1 amino-terminal propeptide (P1NP) (20-108 mcg/ml)
- Osteocalcin (8-32 ng/ml)

Resorption

- Serum C-terminal cross-linking telopeptide of type I collages (CTX)
- Urine N-terminal cross-linking telopeptide of type I collagen (NTX)
  - 2nd void sample in the AM (4-64 nmol BCE/mmol creatinine)

ASBMR: http://www.asbmr.org

Case 1

85 year old CF, BMI 21, lost about 4” since age 30s, no hx of cancer/known previous fx/other 2ndary risk of osteop, no known FHx of osteop or hip fx in parents, former smoker, social drinker, exercises regularly, hx of tx for osteoporosis w/ bisphosphonates for 14 yrs w/o much improvement in BMD. DXA acquired femur neck T scores since 1997 were:

T score Fem Neck	Year
-2.1	1997
-2.2	2006
-2.1	2008
-2.0	2010
Change from baseline was +2.0%	
DXA was done using the same machine at the same place	

U-NTX 18, P1NP 11, Vit D, Calc, PTH, Mg & Phos WNR.

- **What would you do at this point?**

Do we know it all

- **WHO WILL HAVE A FRACTURE?**
- **WHICH MEDICATION SHOULD BE USED?**

- **Limited options to treat**
- **First line agents- antiresorptive – new discussions on anabolic to be first line**
- **How and when to switch medications**
- **No clinical guidelines for starting treatment based on BTM status**
- **Concern - Lost to f/u & low rates of f/u**

Rianon- Osteoporosis UA, 2018

Gaps in current clinical practice: Opportunities to improve care

- aBMD offers information regarding the quantity of mineral in bone
  - Structure, material composition, turnover
  - 50% postmenopausal women with fragility fracture have “normal DXA BMD”
- High fracture risk in patients with chronic diseases, e.g., DMII, who have high BMD
  - How to think about older patients with osteoporosis and chronic diseases
    - ❖ Screening, Diagnosis, Treatment, Prevention

Chronic diseases

- HTN, DMII – common chronic diseases
  - Differences in metabolic changes
    - HTN – most likely similar to age-related changes but enhanced process
      - Low BMD
    - CAD – common risk factors
      - Low BMD
    - DMII – opposite of what is known as changes associated with normal aging
      - Normal or high BMD
  - Lack of preventive guidelines
  - Lack of clinical data to guide treatment methods

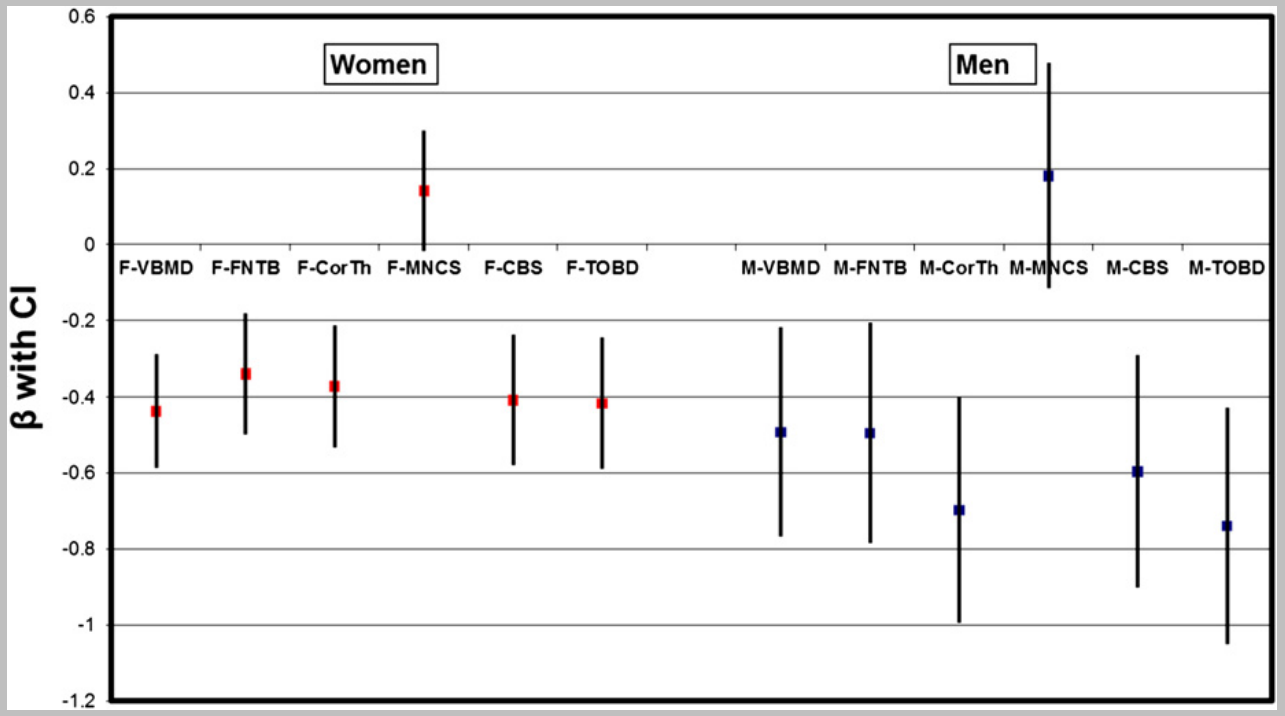
Medications – risks/benefits

- Risk of bone loss –
  - Antidepressants, e.g., SSRI – inconclusive
  - Anti-seizure – inconclusive
  - Anti-diabetics, e.g., Thiazolidinedione
    - ➢ Inconclusive guidelines – Gap in clinical research
- Beneficial –
  - Anti-hypertensives, e.g., ACEi/ARBs – early stages of translational research
  - Anti-cholesterol, e.g., statins
    - ➢ Lack of clinical data for treatment guidelines

Research

- Structural aspect
  - QCT/Finite element analysis
  - Ultrasound/acoustic bone measures
  - Trabecular Bone Score (TBS), using DXA scans
- Organic matrix, material composition
  - Raman spectroscopy (iRS)
- Serum or urine measurements of bone metabolism
  - Bone turnover
  - Clinical parameters for geriatric population
  - Cost
  - Knowledge

Fracture Risk Assessment in Older Adults Using a Combination of Selected Quantitative Computed Tomography Bone Measures: A Subanalysis of the Age, Gene/Environment Susceptibility-Reykjavik Study



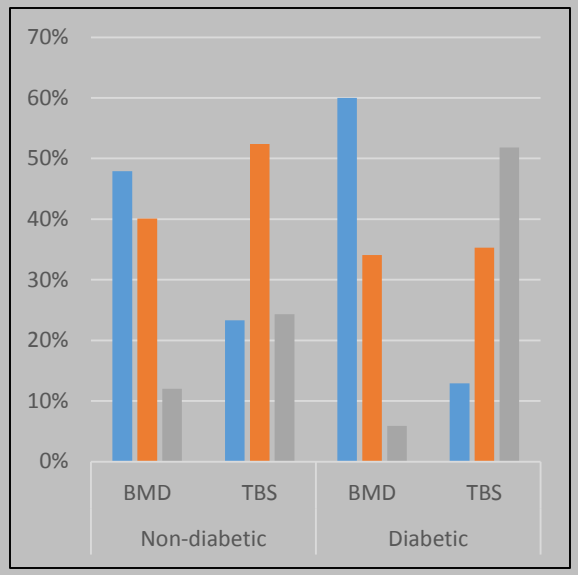
Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. ■, no. ■, 1–7, 2013

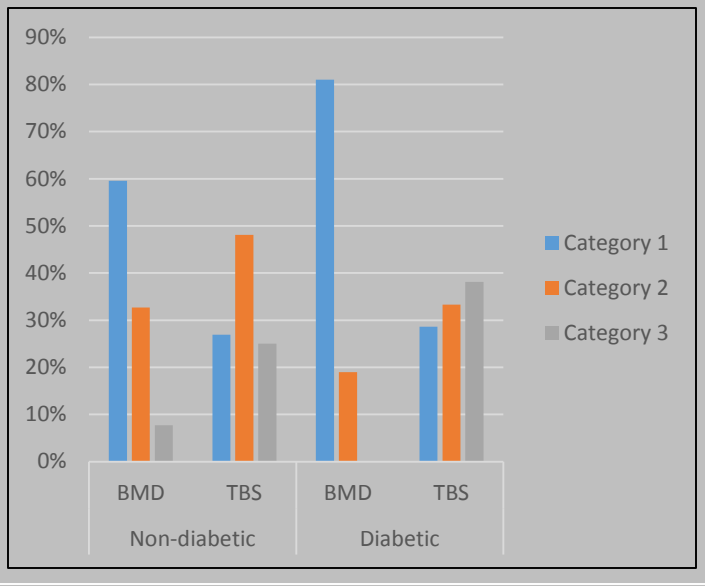
Rianon et al., 2013 - Associations between DXA BMD & other QCT acquired measures including BMD was not significantly different from each other to add any beneficial outcomes in fracture risk assessment in the older adults

Trabecular Bone Score

- The trabecular bone score (TBS), a texture parameter that measures the grey-scale variation within DXA images & significantly correlates with the 3-dimensional (3D) bone microarchitecture parameters Silva et al., *JBMR*, 2014
- TBS derived from DXA images - useful tool in predicting future fracture risk

Distributions of TBS and DXA categories in older women & men





Xue et al., 2017

TBS:

Category 1 = normal

Category 2 = partially degraded microarchitecture

Category 3 = degraded microarchitecture

BMD:

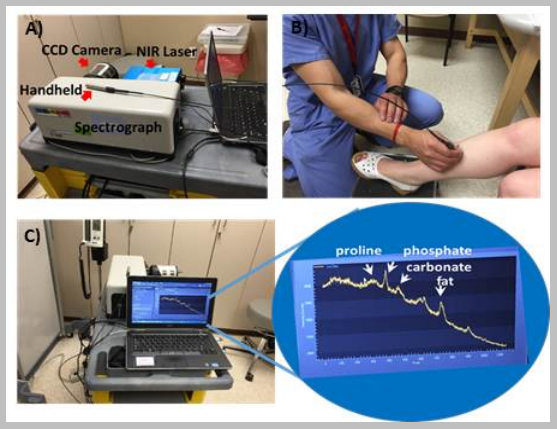
Category 1 = normal (t-score ≥ -1.0)

Category 2 = low bone mass (t-score between -2.5 & -1.0)

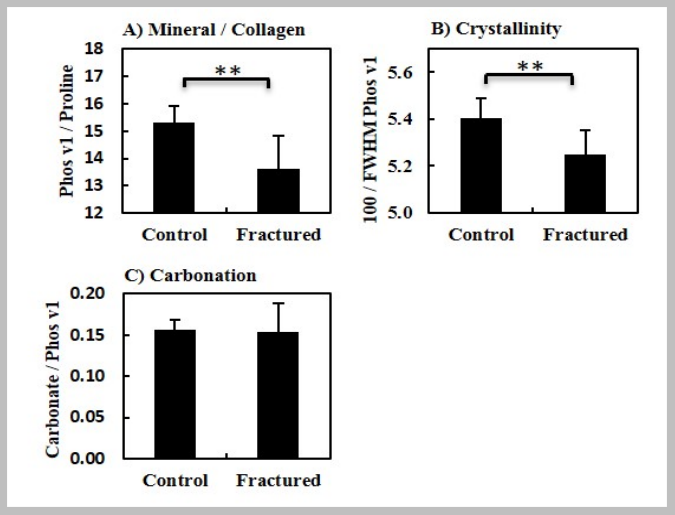
Category 3 = osteoporosis (t-score ≤ -2.5)

in-vivo Raman spectroscopy (iRS)

- Transcutaneous iRS, a vibrational spectroscopy technique
- Assesses bone mineral & matrix collagen; provides specific molecular information on compositional properties through which quality can be determined
- Compositional quality indicators correlate with bone metabolic markers & complementary to DXA Bi et al., 2017



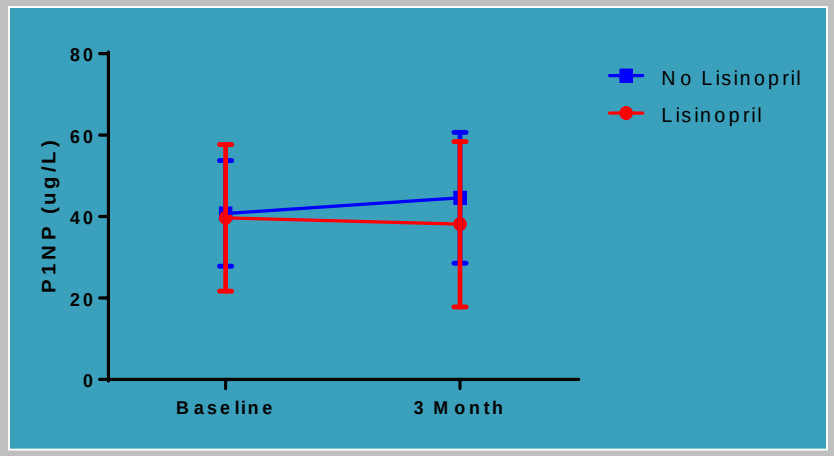
The portable iRS system



Bi et al., 2017 -

Raman spectral markers for bone quality: Comparison between fracture & non-fracture groups ($p<0.01$)

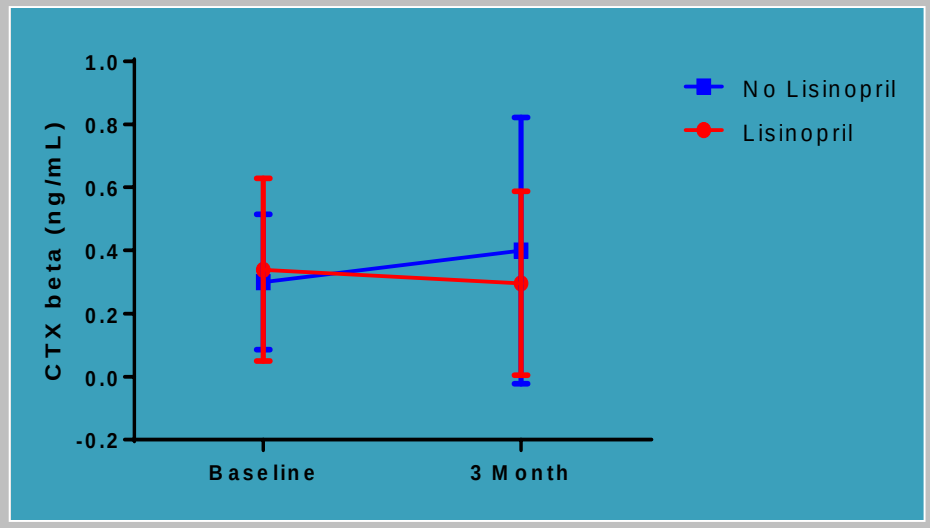
Mean (95% CI) changes in bone turnover after ACEi exposure for 3-months



- Age 57±7 years
- BMI 27±5 kg/m^2
- 25-hydroxyvitamin D was 66±17 nmol/L
- PTH 30±13 pg/ml.

After Lisinopril treatment:
- 11±27% ↓ in CTX
- 5%±15% ↓ in P1NP.

No Lisinopril group
- 41%±73% ↑ in CTX
- 10%±22% ↑ in P1NP



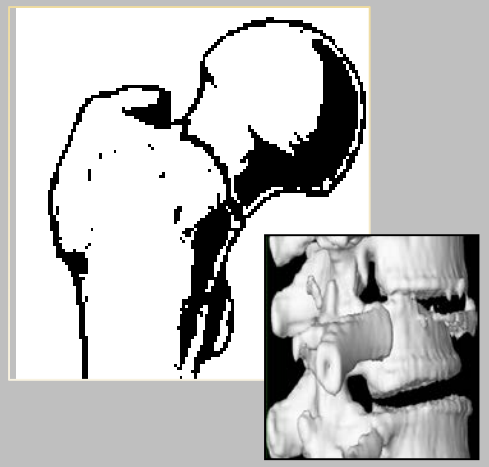
Rianon et al., 2016 (funded by NASA and RO3/NIA)

Clinical setting vs. Research setting: Screening, diagnosing & monitoring

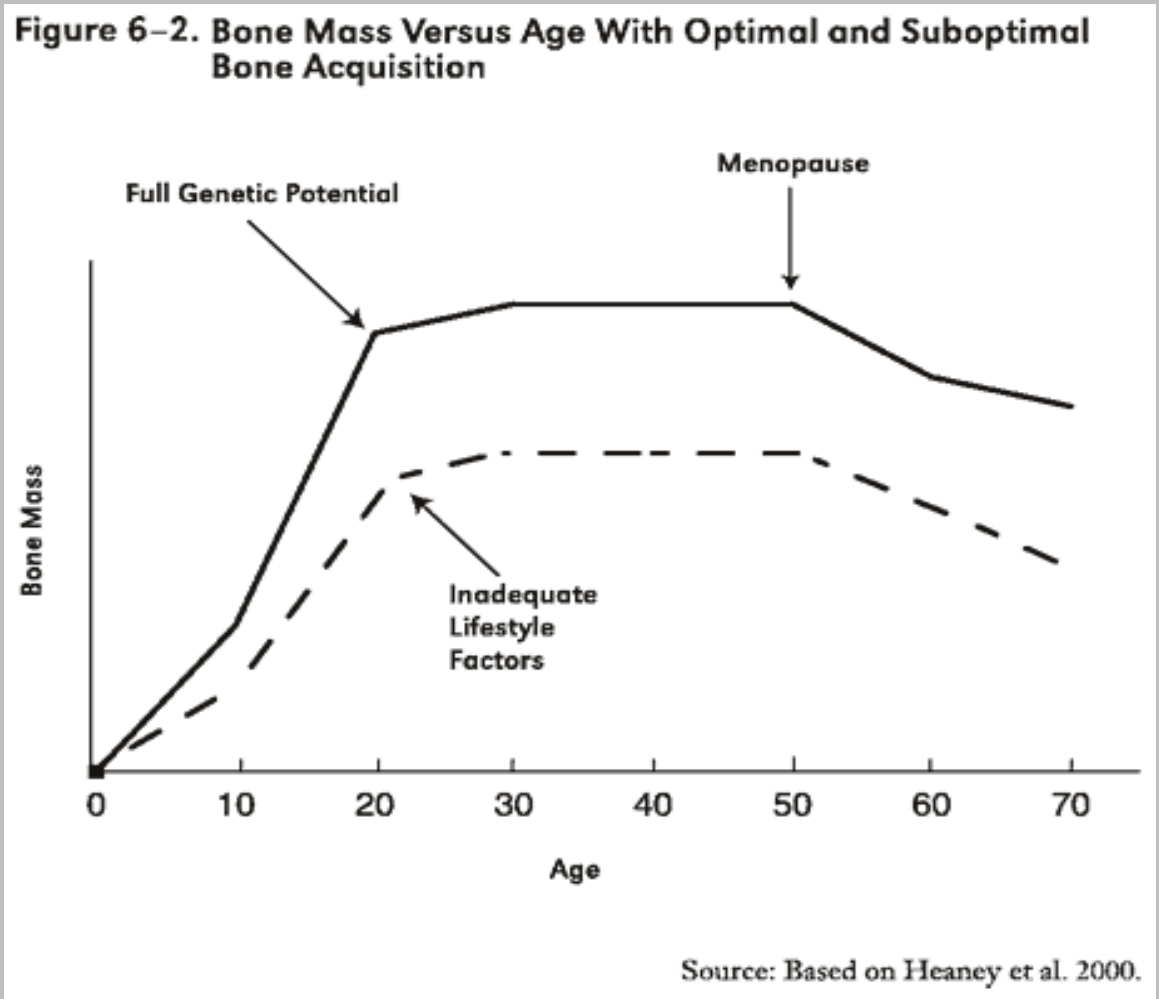
- QCT – not readily available
- Acoustic measures – not a gold standard and no standard re-imbursement policy
- iRS – great potential for clinical use
  - Needs further research
  - We are continuing research
- Bone metabolic work up
  - Some clinical use in practice
  - Needs further research
  - We are continuing our research

Clinical setting vs. Research setting: Treatment & Prevention

- New medications in pipeline
- Continue research on non-bone medications to prevent bone loss in older adults suffering from both osteoporosis and chronic diseases, e.g., HTN, DMII, CAD



Prevention: Aim at early age



http://www.surgeongeneral.gov/library/bonehealth/chapter_6.html#NutritionsImpactonBoneHealthAReviewoftheEvidence

Prevention

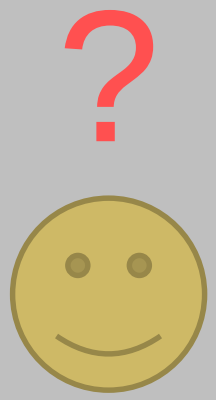
- Weight bearing exercise
  - Stimulates bone formation
  - 2.5 to 4 hours/wk of moderate to severe intensity physical activity
- Calcium and Vitamin D
  - Regular supplemental required dose
- Non-skeletal Environmental/Behavioral
  - Fall prevention
    - Improve balance & gait- PT/OT
  - Smoking cessation
  - Avoid risk level alcohol use
  - Avoid back flexion >45 degrees in patients with risk of or hx of vertebral fracture
- FLS (Fracture Liaison Services)
  - Network within the clinic, or group of providers

Chodzko-Zajko WJ et al., 2008 & ASBMR

Take Home Message

- Osteoporosis is a progressive & chronic metabolic bone disease that decreases bone density with deterioration of bone structure.
- Clinical Diagnosis = T- score of <-2.5 for BMD
- Prevention & treatment with a comprehensive and individualized approach.
- Goal oriented treatment plan – follow chronic disease management guidelines

Thank You!



Questions?