Biomarkers Development for Osteoporosis (OP)

Challenges and Opportunities

EFPIA – EMEA Meeting

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Challenges for Osteoporosis New Drug Development

- **Demonstration of efficacy**
  - fracture risk reduction required for new OP drug approval
- **Challenges**
  - *During past decade, multiple drugs approved*
    - *Placebo controlled trials with fracture endpoints*
  - *Feasibility of placebo controlled fracture trials*
    - *Increasingly limited by IRB approvals*
- **<u>Need to design fracture endpoint trials differently</u>**
    - *<u>in low risk population</u>*
      - *can outcomes apply to more severe population?*
    - *<u>or vs approved comparator</u>*
      - *what is an acceptable non inferiority margin?*
      - *what is a meaningful difference between groups?*
    - *<u>with dramatic increases in sample sizes</u>*

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Need for OP Biomarker Development

- **OP new drug development**
  - Ethical, methodological, scientific and costs challenges
- **Objectives for qualification of new biomarkers**
  - *better identify patients at risk of fracturing*
    - for CT enrichment (patient stratification and selection)
  - *facilitate decision making*
    - in clinical development
      - for new drugs from phase I to III
  - *support data insertion in regulatory labelling*
    - to better explain differences between drugs
      - in addition to fracture efficacy demonstration
        - e.g.effect of antiresorptive vs bone forming agents
  - *develop long term plan to validate fracture surrogate endpoints*

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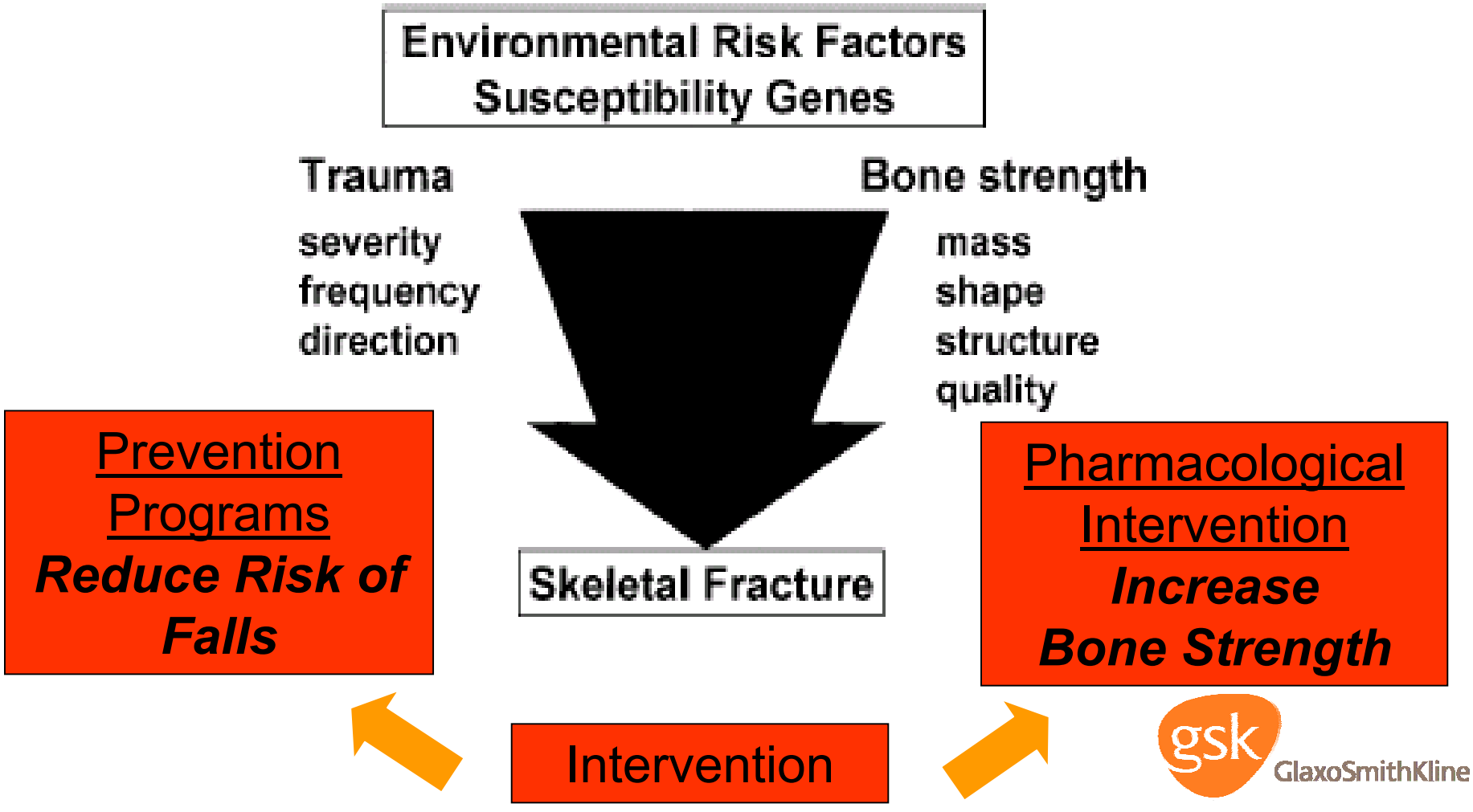
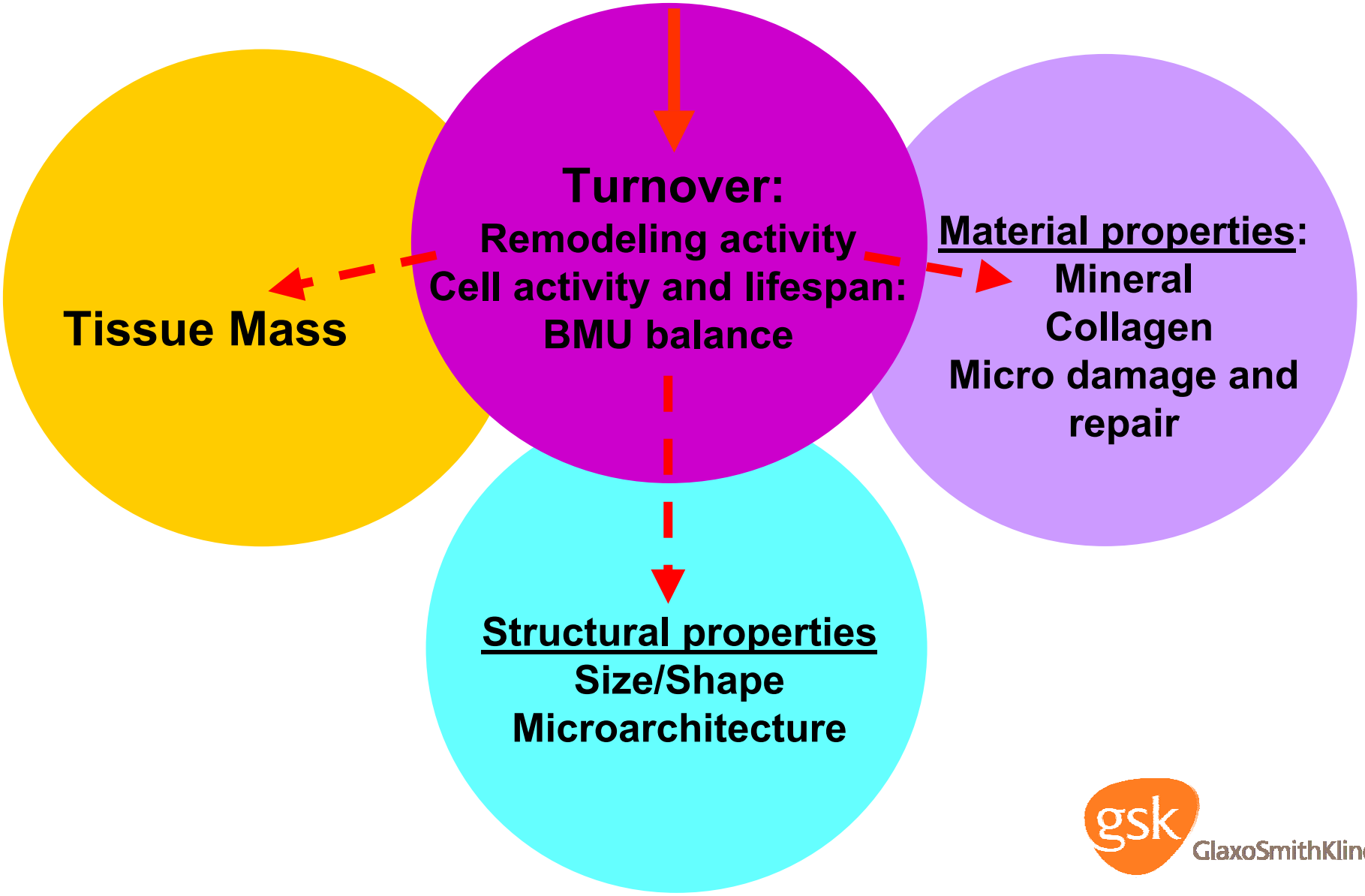
Bone Strength Concept and Fracture Risk

Drug Intervention Objective
"Make bones strong enough to withstand a fall"



Disease Progression
Response to Drug Intervention



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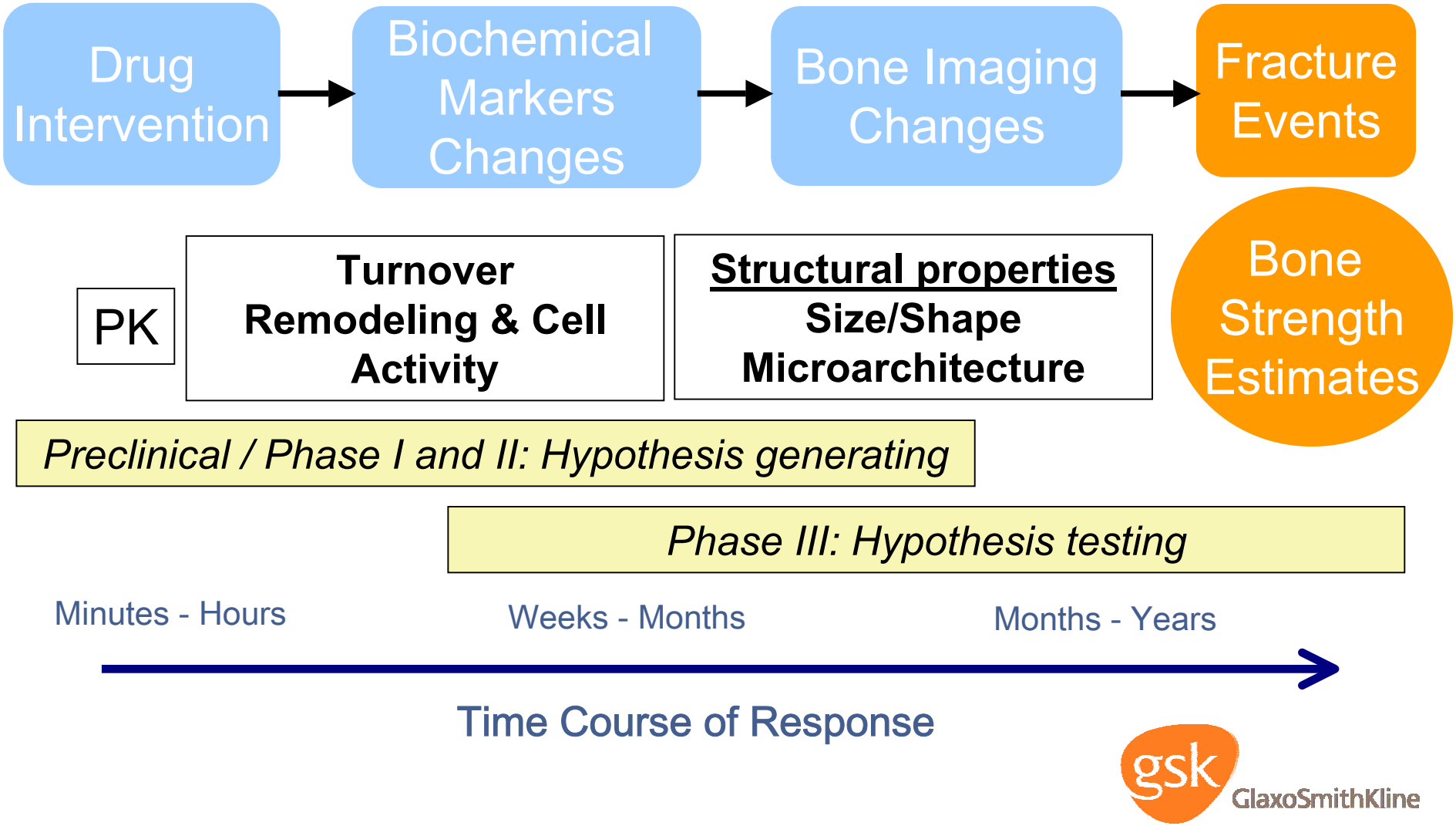
Drug Intervention in OP
Biomarkers Changes
Time Course of Response



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Currently Used Biomarkers for Prediction of OP Fracture Risk

Biochemical Markers of Bone Turnover

DXA BMD

Usefulness and Limitations

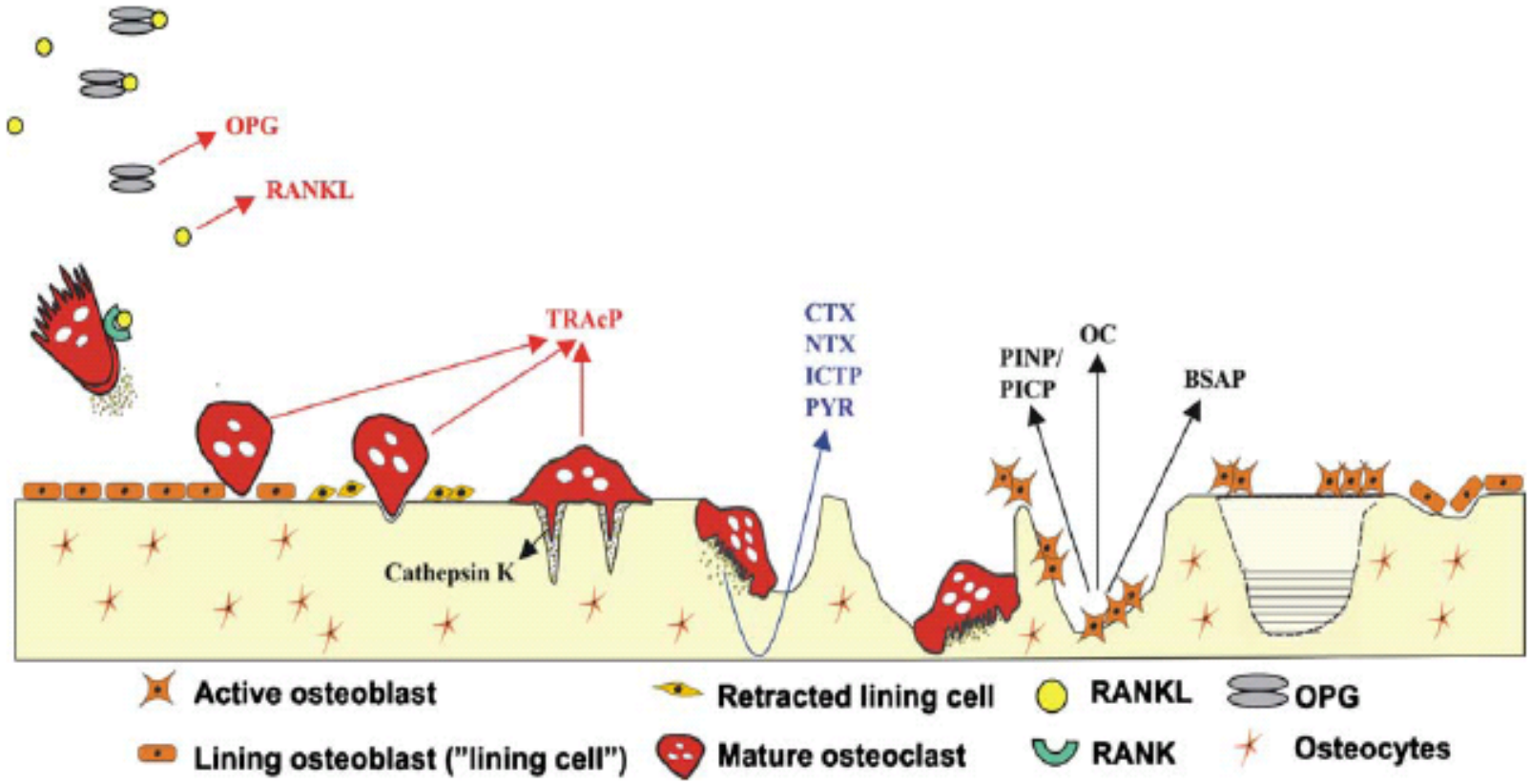
for

Assessment of Response

to Pharmacological Intervention

Biochemical Markers of Bone Turnover

Excellent measure of biological activity
Relationship of early changes with long term fracture risk?
Very MoA dependent: anti resorptives vs bone forming agents



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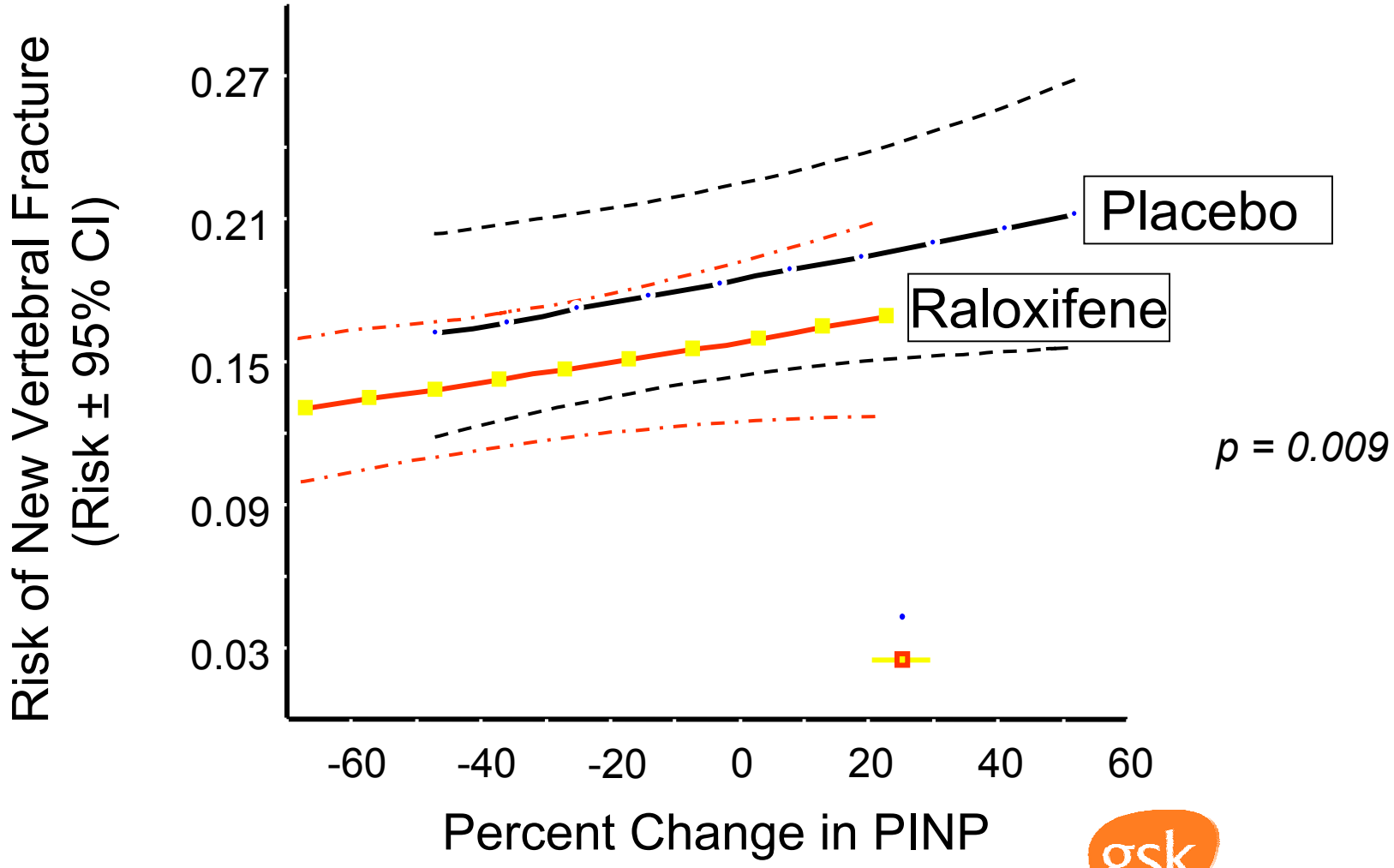
Percent Change in PINP at 1 Year and New Vertebral Fracture Risk at 3 Years



Reginster et al. *Bone* 34:344-351, 2003

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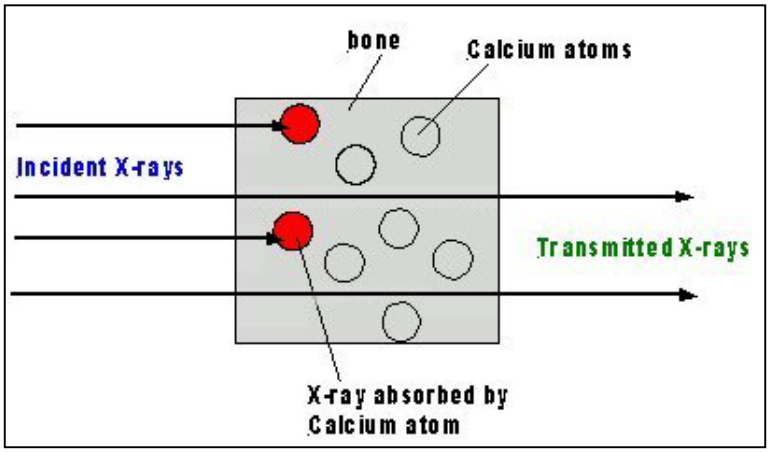
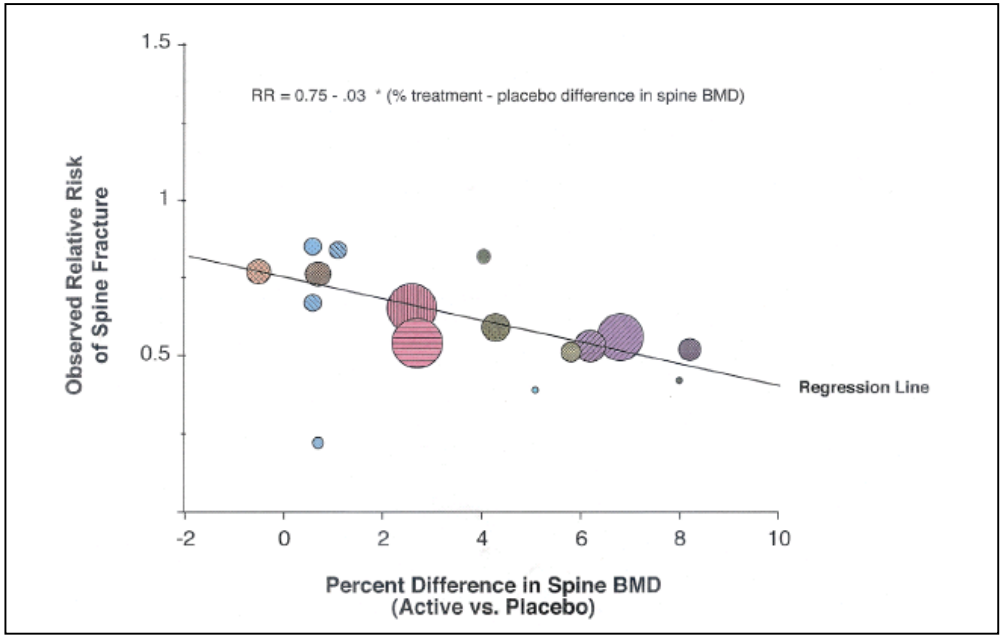
Relationship Spine Bone Density (DXA) and Reduction in Risk of Vertebral Fractures

Treatment with Antiresorptive Drugs





Improvement in spine bone mineral density during treatment with antiresorptive drugs accounts for a predictable but small part of the observed reduction in the risk of vertebral fracture.

S. Cummings et al, March 2002 The American Journal of Medicine

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Emerging Imaging Bone Biomarkers

- **Can new imaging biomarkers ?**
  - better assess bone strength
  - better predict fracture risk
  - alone or in combination with biochemical markers
  - than DXA BMD
- **What are the best current approaches for fracture risk estimates?**
  - measure of bone strength derived from imaging (QCT, MRI)
    - Finite Element Analysis (FEA)
- **What needs to be done ?**
  - to support bone strength data insertion in regulatory labelling
    - to better show differences between drugs
      - in addition to fracture efficacy demonstration
        - e.g.effect of antiresorptive vs bone forming agents

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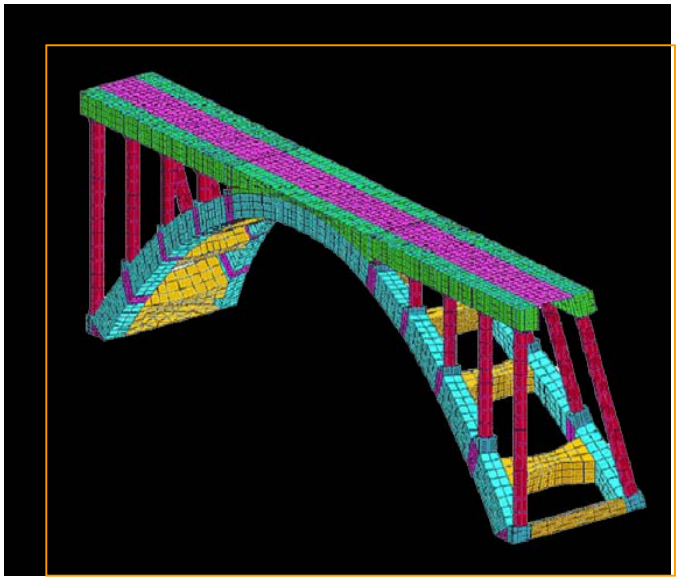
Finite Element Analysis (FEA)

- Well-established method for analysis of complex structures
- Model structure as collection of “finite elements”
- Assign material properties to each element and external forces to whole model
- Compute strength or other structural performance



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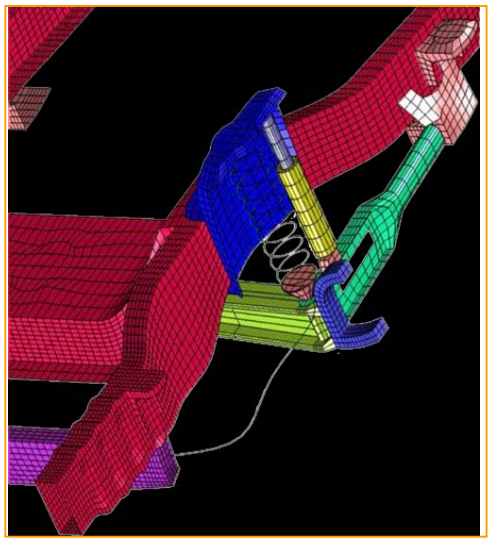

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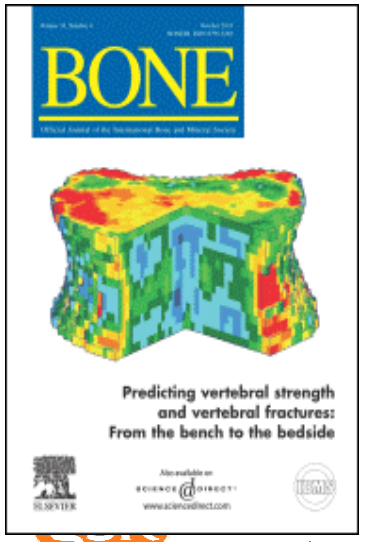
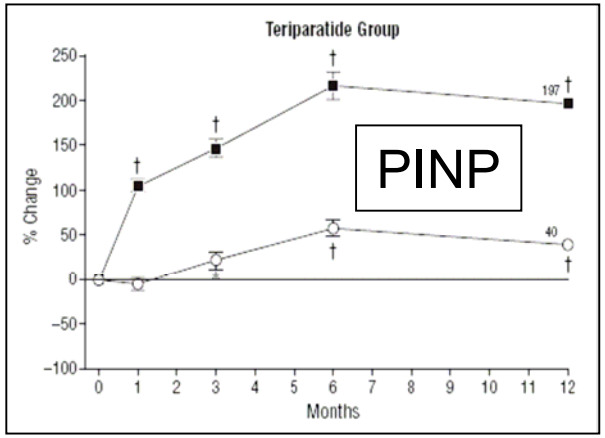
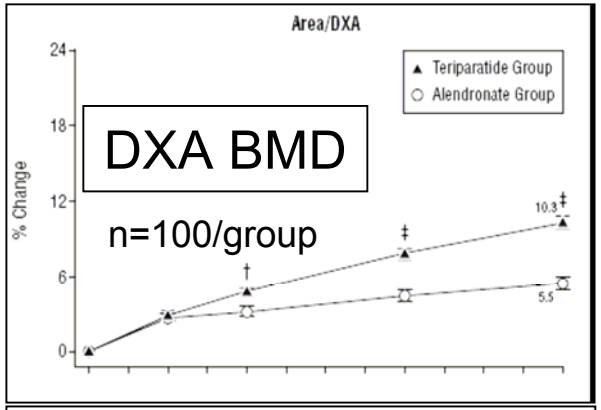
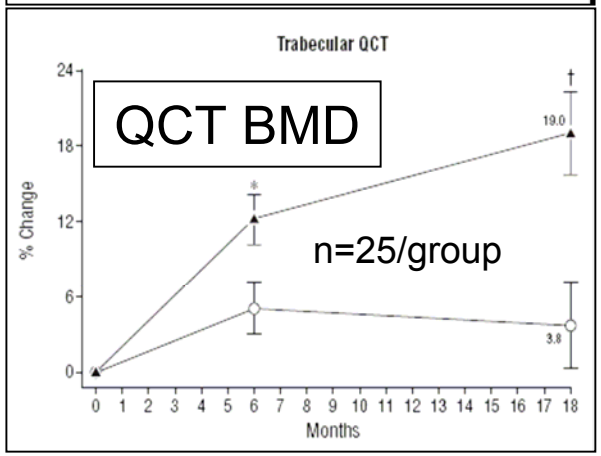


Crawford, Bone 2003

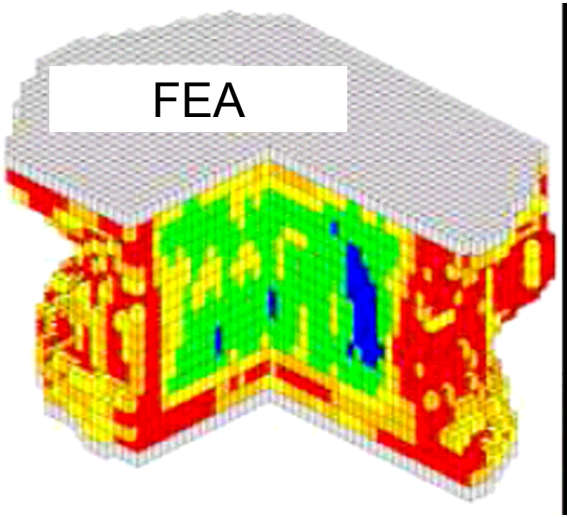
Hypothesis Generating Example







Strength: Density Ratio (Ncm3/mg)
6 months



Alendronate
2.2* (0.3, 4.5)

Teriparatide
6.0**# (2.6, 8.9)

Alendronate vs Teriparatide

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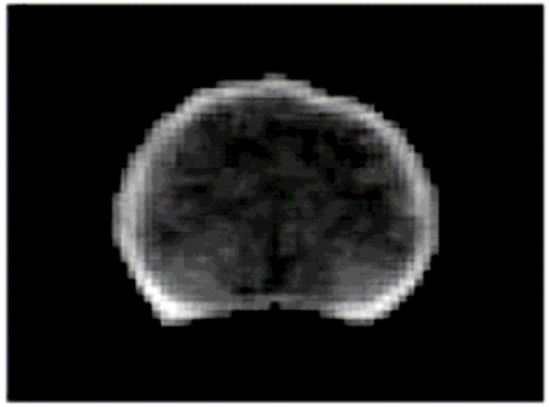
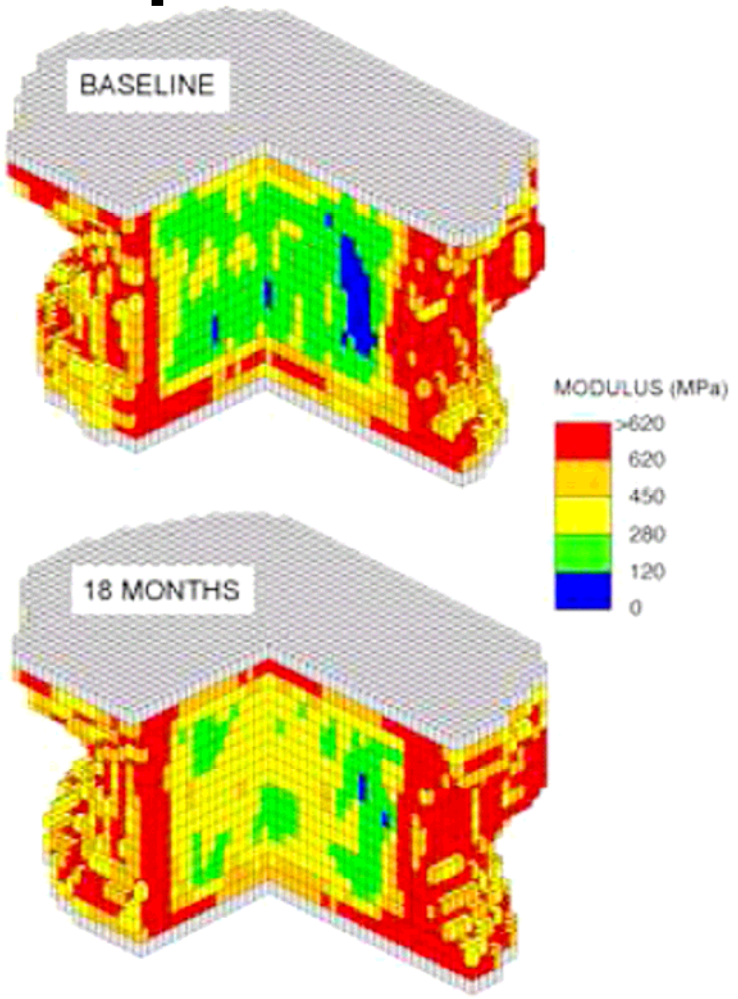
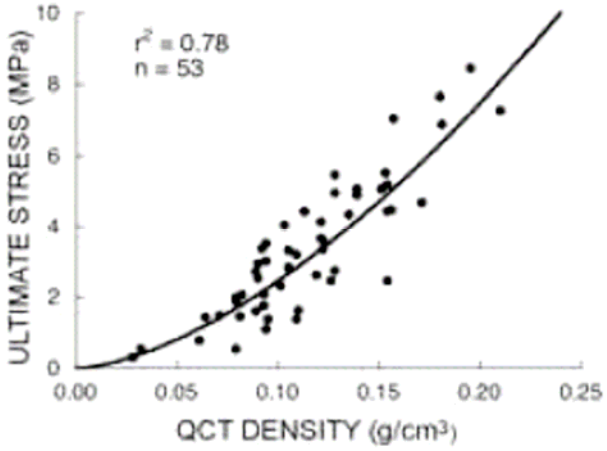
M. McLung et al. Arch Intern Med/Vol 165 Aug 8/22, 2005

T. Keaveny ASBMR 2005

Voxel QCT-based FEA Models of same Lumbar Spine Vertebra







Teriparatide treated patient

T. Keaveny, JBMR, in press, e-pub December 06

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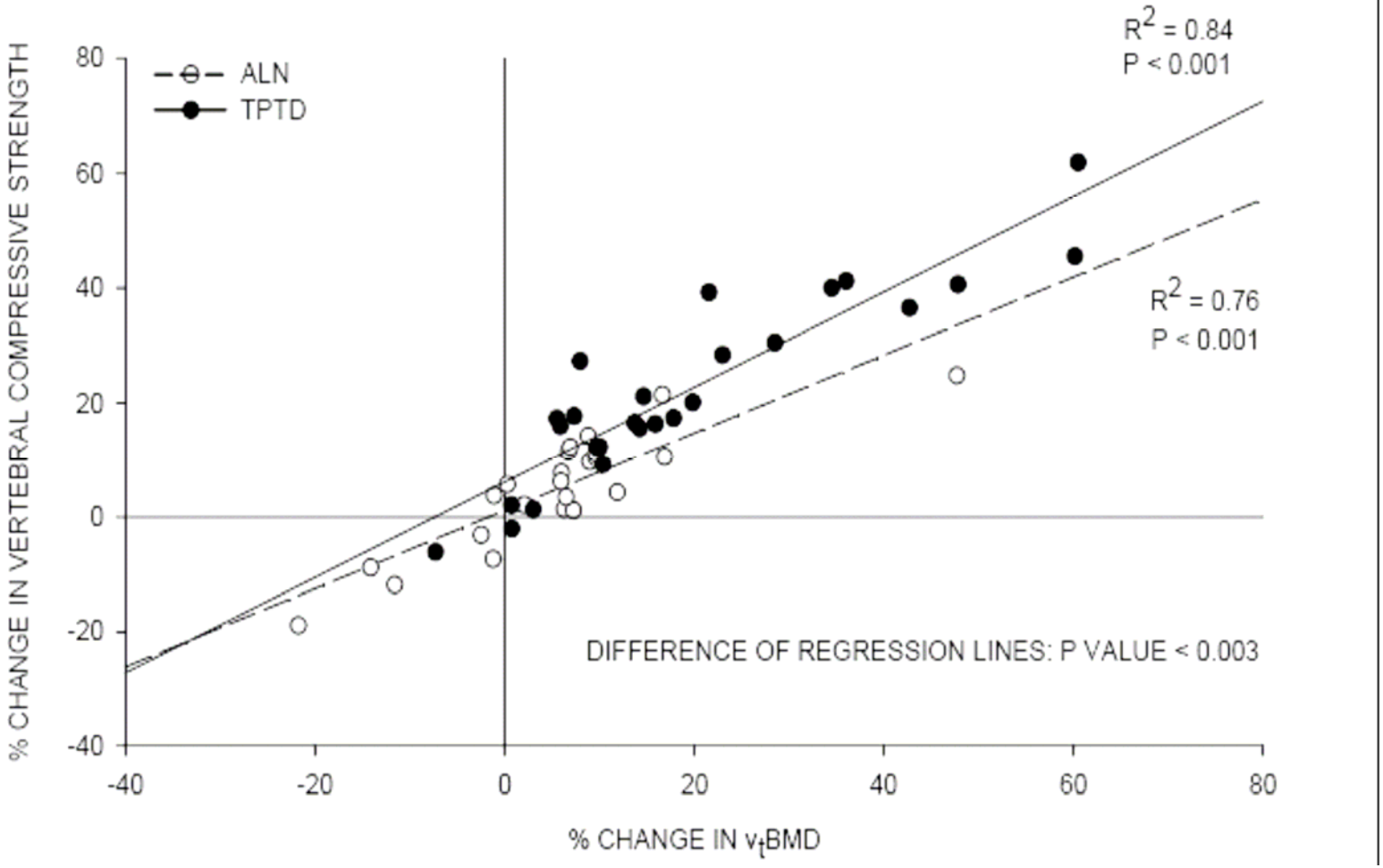
Effect of Teriparatide and Alendronate on Bone Strength



n=25/group

T. Keaveny, JBMR, in press, e-pub December 06

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What would be required to include bone strength data in labeling?

Drug X improves bone strength

Drug X improves bone strength more than Drug Y

Demonstrate that biomarker:

- is accurate, reproducible, standardized
- is correlated to whole bone strength in cadavers
- is correlated to whole bone strength in monkeys
- changes with drug intervention are associated with changes in bone strength in monkeys
- can predict fracture risk in patients
- changes with drug intervention in humans are greater with drug X than drug Y (head-to-head)
- changes with drug intervention correlate with fracture risk reduction

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Clinical Qualification Work to Be Done For Imaging Biomarkers

Qualification Work	QCT	QCT-FEA	µ-Arch MRI	µ-Arch XtremeCT
Cross-sectional (ages)	++	-	+ / -	+
Longitudinal (age-related changes)	+	-	-	-
Predict Frx Risk Case-control	+++	-	++	+
Predict Fx Risk Prospective	- (MrOS, AGES)	- (MrOS, AGES)	-	-
Treatment-related changes	++	+	+	-
Treatment Efficacy (ie Fx study)	-	-	-	-

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What Would Be a Surrogate Marker Evaluation Plan ?

- Design of Large Clinical Trial
  - 3-year, randomized, active-controlled study of 2 different MoAs
  - 12,000 OP patients at moderate-to-high risk of fracture
  - Biomarkers collected at baseline and every year thereafter
- Parallel, Open-Label Observational Study
  - Untreated OP patients across range of severity
  - Same duration, endpoints as randomized study
  - 2,000 patients
- Assessment of relationship
  - between biomarkers and fractures
  - across a range of treatment effects
- Develop model on first 8,000 patients enrolled
- Test model behavior (including predictiveness)
  - on last 4,000 patients enrolled
- Test hypotheses re: AUC of ROC on all 12,000 patients

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Future of OP Biomarkers

- **Imaging markers**
  - will differentiate drugs on mechanism of action
  - should generate comparative data effect on bone strength
- **Biochemical markers of bone turnover**
  - should become a key criteria
  - in combination with imaging markers
  - for decision making and dose selection
    - early in drug development process
- **Validation of true fracture surrogate marker endpoint**
  - will require
    - extensive hypothesis testing
    - analysis of multiple databases

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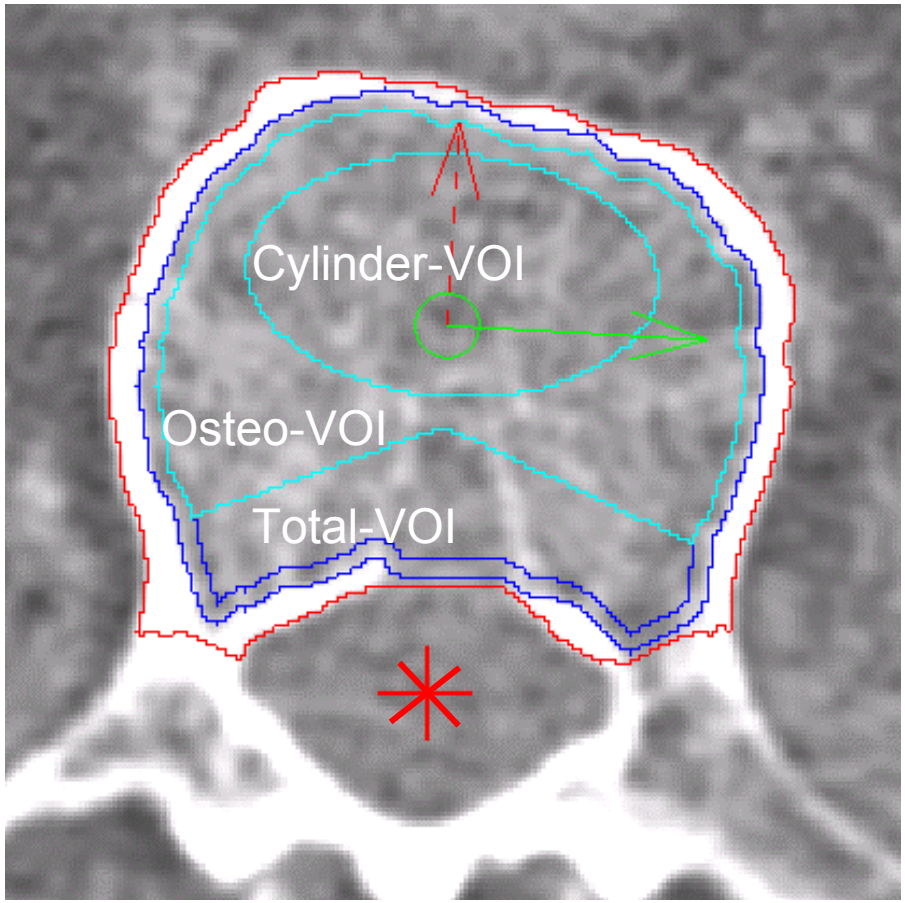
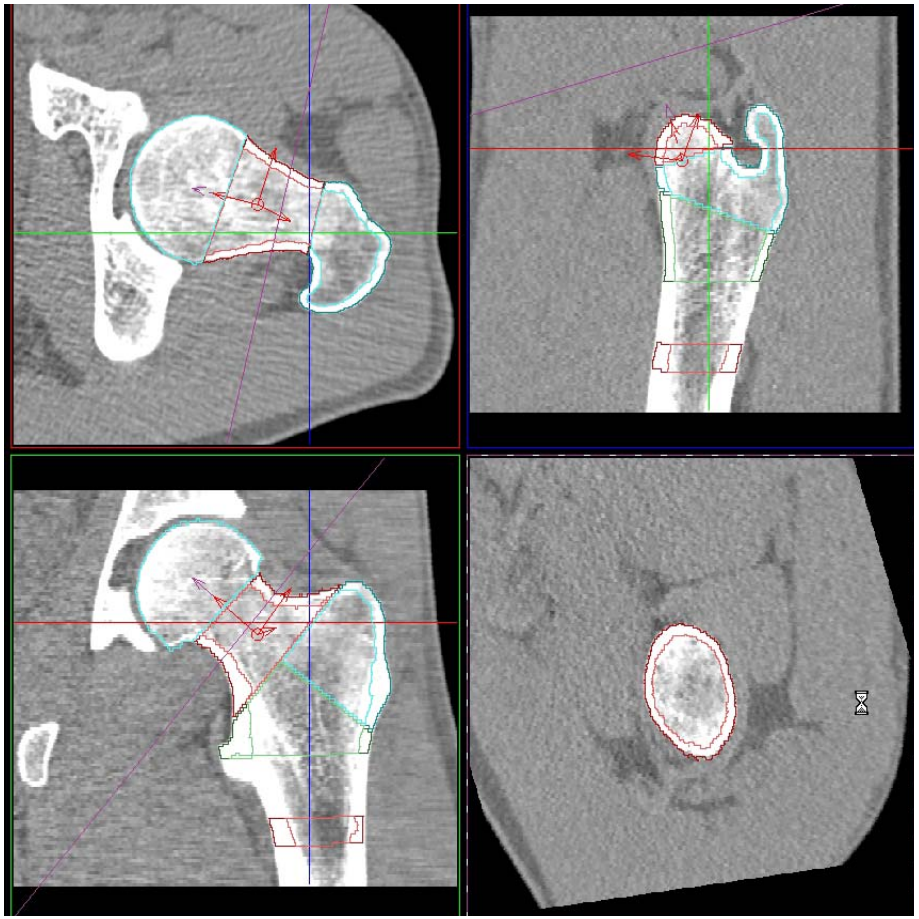
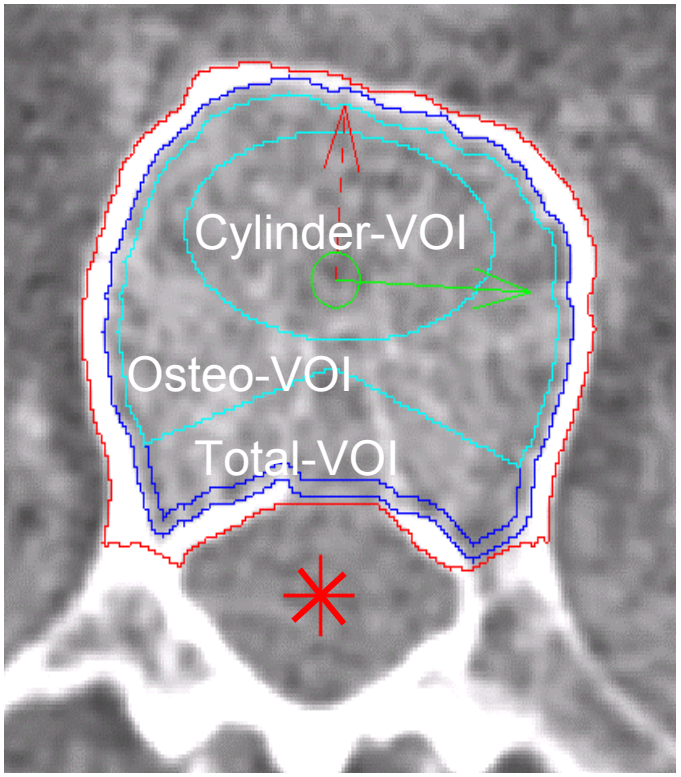
Backup Slides

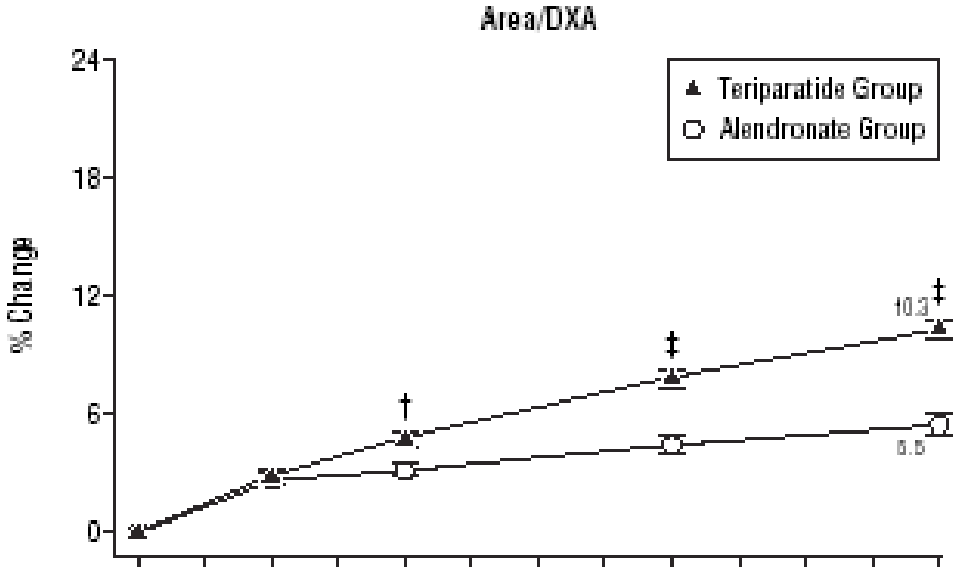
QCT
Trabecular & Cortical Bone / Geometry

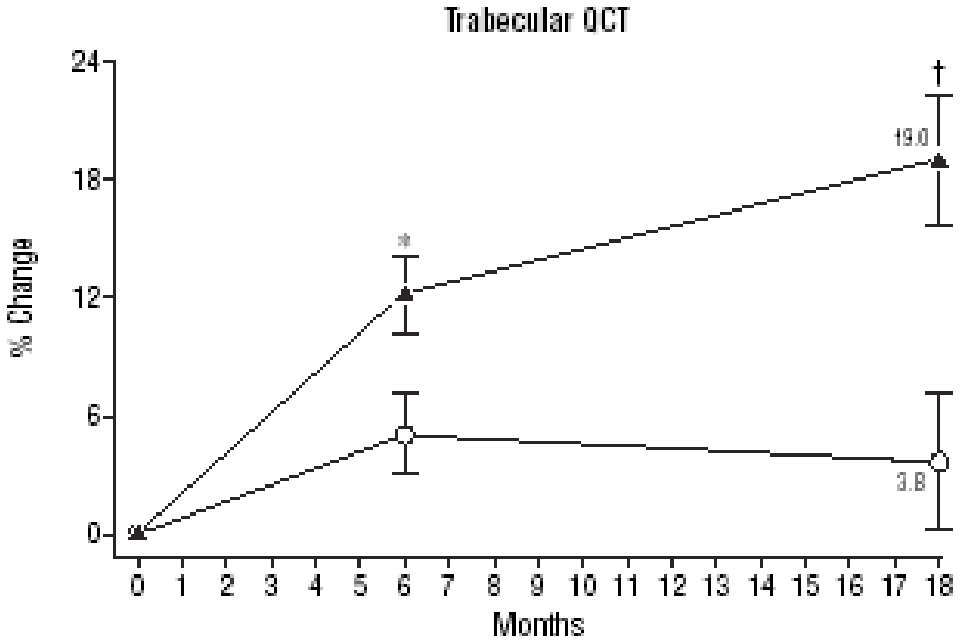




Differences between DEXA BMD and QCT Volumetric BMD Measurements

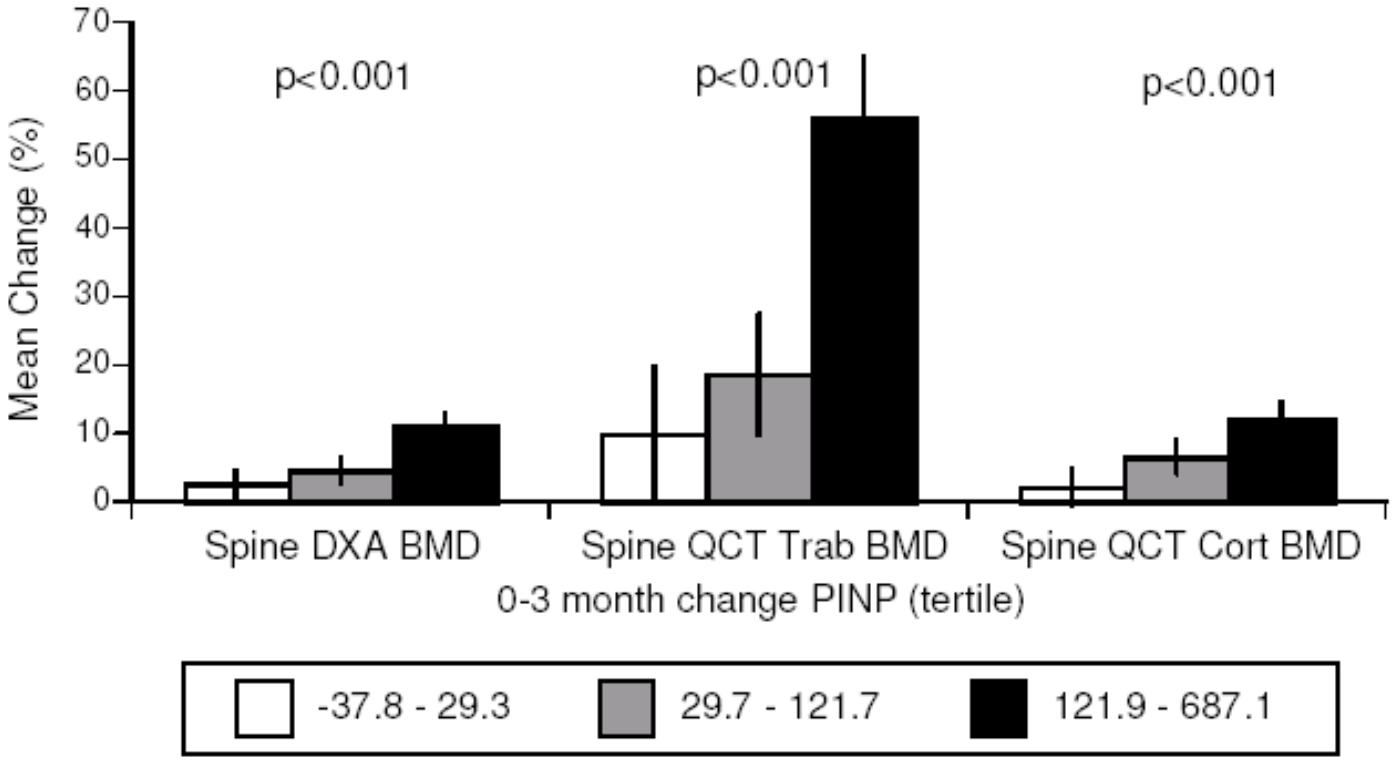






M. McLung et al. ARCH INTERN MED/VOL 165 AUG 8/22, 2005

One-year Change in Spine DXA and Spine QCT Trabecular BMD, and Cortical BMD by Tertile of 3-month Change in PINP Among PTH-treated Women P-value is across tertiles.



Baseline : 58.0 ± 34.5 ng/mL

J Clin Endocrin Metab. 91: 1370–1375, 2006

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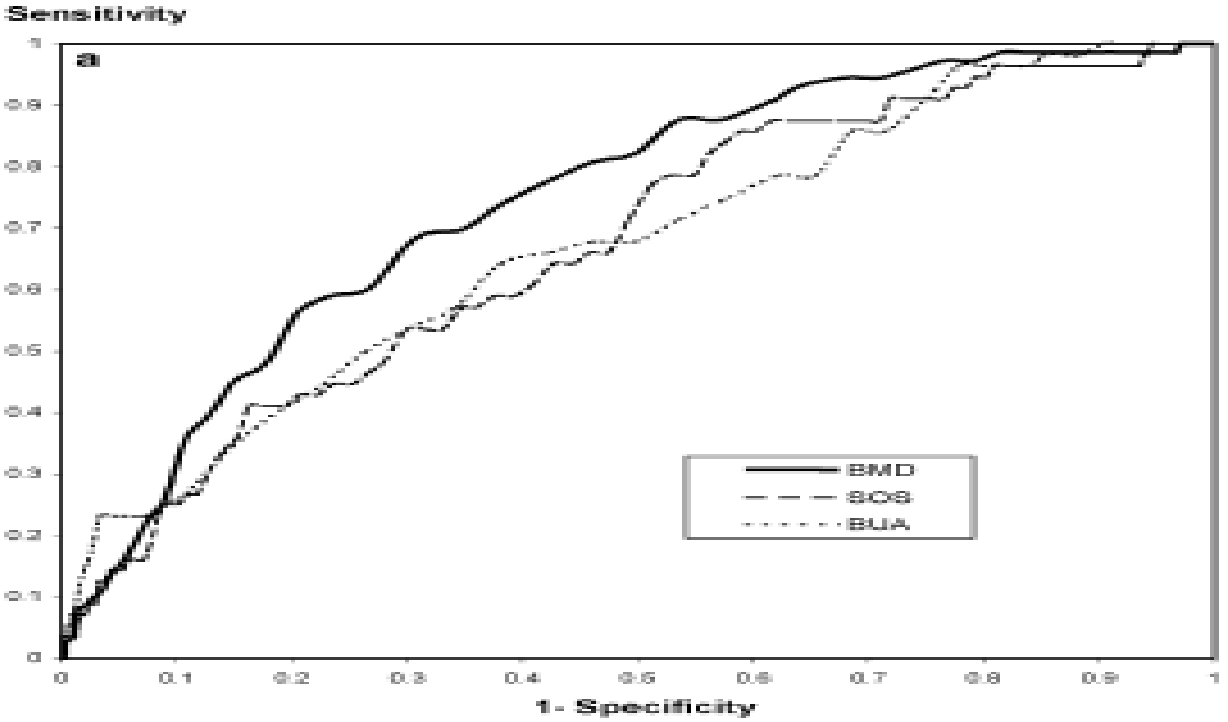

Table 4 Area under the ROC curves (AUC) obtained with BMD, BUA, and SOS for three age groups

	AUC (95% CI)	Group size	Women with hip fracture
Bone mineral density			
75–79 years	0.75 (0.73–0.76)	3,485	73
80–84 years	0.65 (0.63–0.67)	2,196	84
≥85 years	0.65 (0.61–0.68)	696	68
Broadband ultrasound attenuation			
75–79 years	0.67 (0.66–0.69)	2,796	56
80–84 years	0.66 (0.64–0.69)	1,755	66
≥85 years	0.63 (0.59–0.67)	544	56
Speed of sound			
75–79 years	0.67 (0.65–0.69)	2,796	56
80–84 years	0.60 (0.58–0.63)	1,755	66
≥85 years	0.61 (0.57–0.65)	544	56

Where are we today ?

TECHNICAL	QCT	QCT-FEA	µ-Arch MRI	µ-Arch XtremeCT
Standardized acquisition	?	?	?	+
Standardized analysis	-	+ / ?	-	+
Single site QC	+	+	+	+
Multi-center QC	?	?	?	?
Accuracy	+ / ?	?	+	+
Reproducibility - young	+	-	+	+
Reproducibility - old	-	-	-	-
Reproducibility - SCV	?	?	?	?

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Where are we today?

NON-CLINICAL	QCT	QCT-FEA	µ-Arch MRI	µ-Arch XtremeCT
Human cadaver - spine*	+	+	-	-
Human cadaver - hip*	+	+ / -	?	+/- (MSCT)
Primate - correlation to bone strength	+ (pQCT)	-	-	-
Primate - change under treatment	+ / - (pQCT)	-	-	-

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