National Aeronautics and Space Administration

Effect of Microgravity on Bones:

Challenges to Addressing Risks to Human Health & Performance

Endocrine Grand Rounds McGuire Veterans Affairs Medical Center

Jean D. Sibonga, Ph.D.
Lead, Bone Discipline
Human Research Program [HRP]
Johnson Space Center, Houston, TX

May 14, 2014

Overview

- NASA's challenges to addressing skeletal risks due to spaceflight: 3 C's
- Unique Skeletal Adaptations to Spaceflight
- Recommended Forward Actions for Risk Assessment and Management

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Mitigating Risks for the Human System in HRP

Inst of Medicine

Evidence Base – Flight and Ground
- **Science**
- **Clinical**
- **Operational experience**

Risks

Gaps

Standing Review Panels

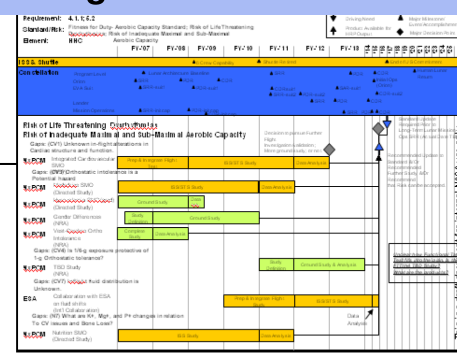
Prioritization & Implementation Approach

Constrained by
- Need dates
- Budgets
- Research platform availability

Exploration Missions & Architectures

NASA Spaceflight Human System Standards

Integrated Research Plan



Results and Deliverables

Solicitations & Directed Research

Customer Review

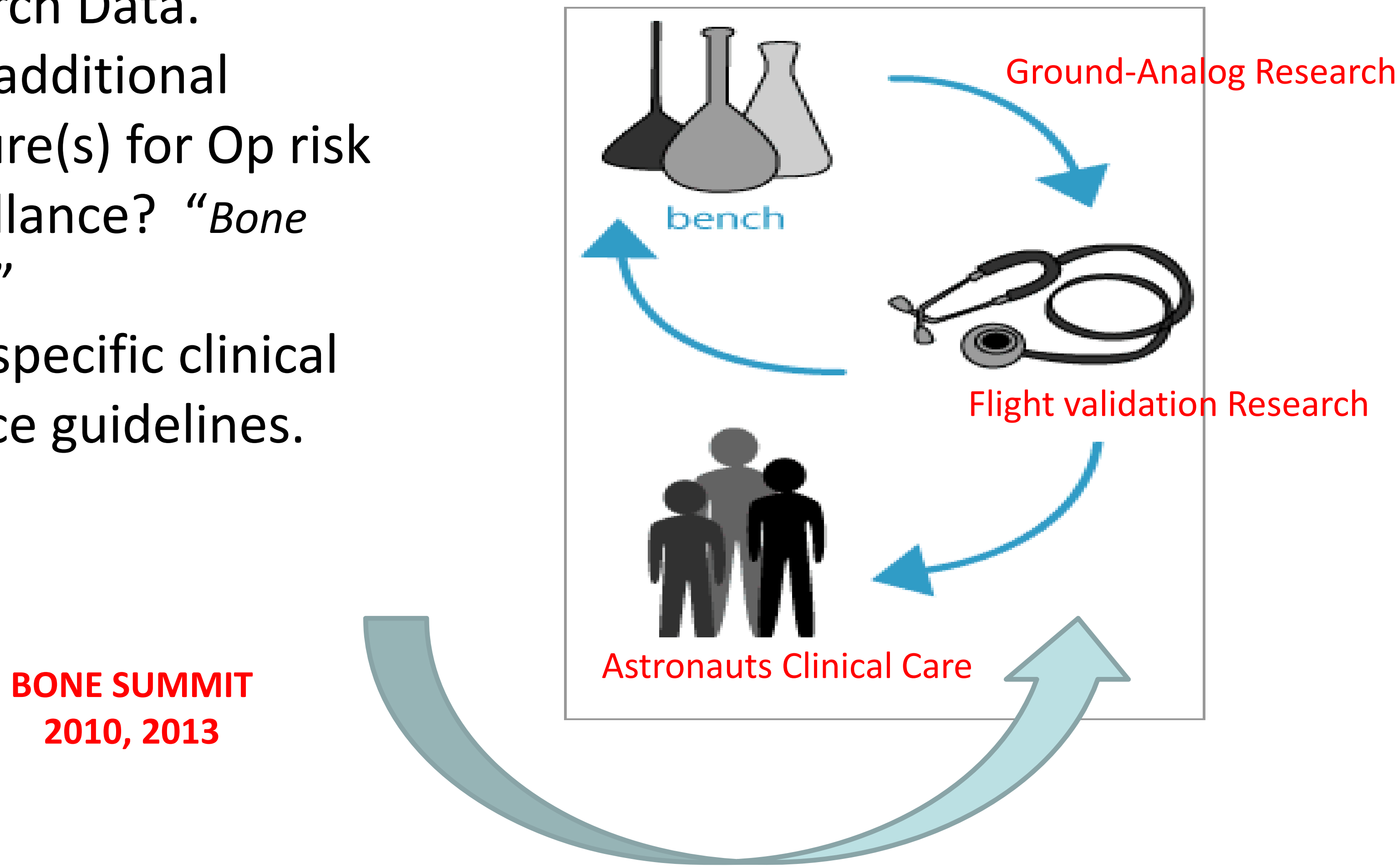
Peer Review

HRP slide courtesy C. Kundrot
Adapted Sibonga 2012

How should Space Medicine use Research Data in clinical care of astronauts?

1. Review of all Medical and Research Data.
2. What additional measure(s) for Op risk surveillance? "*Bone Quality*"
3. Need specific clinical practice guidelines.

Bone Research @ NASA



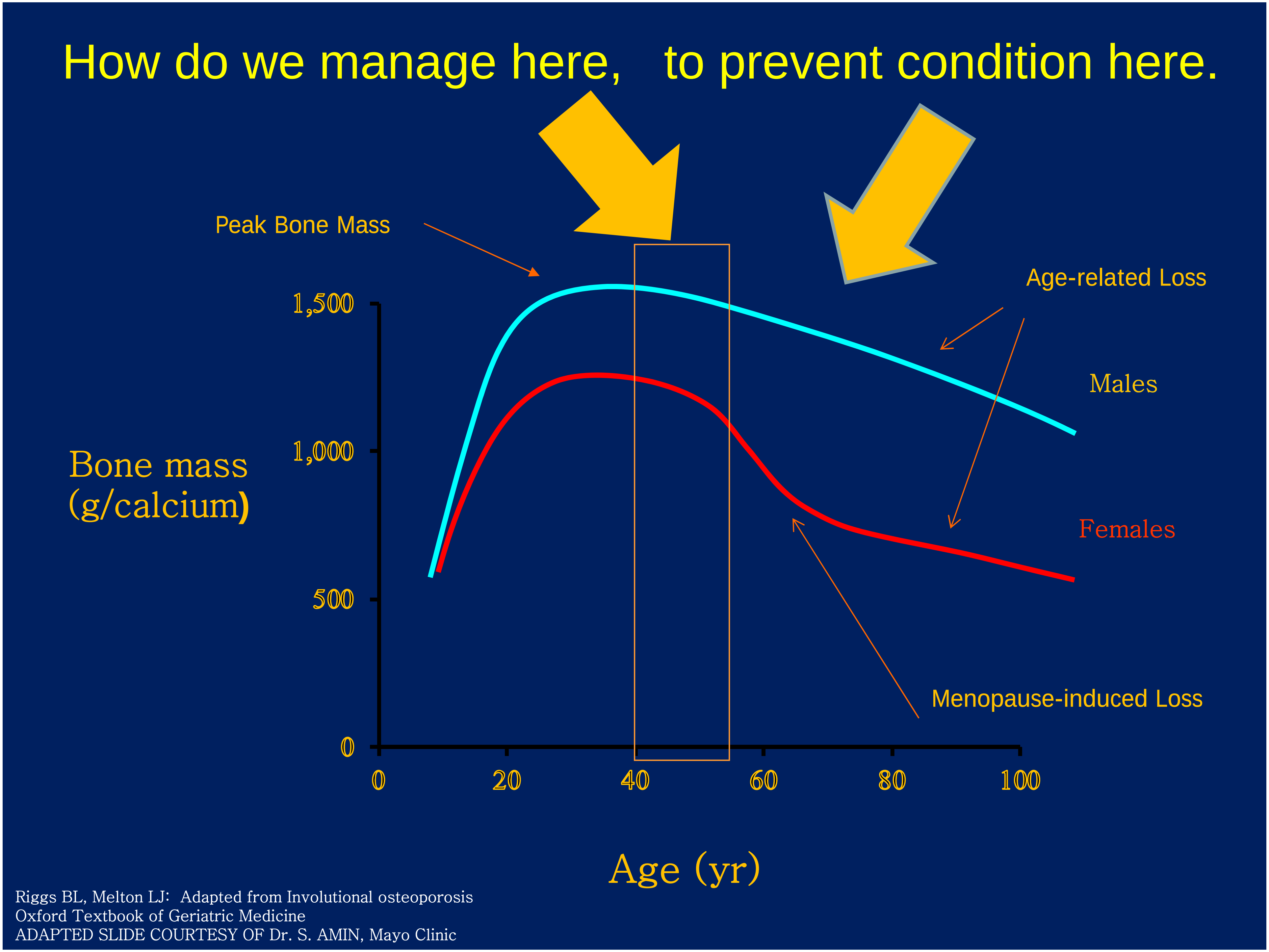
Journal of Bone and Mineral Research
Vol. 28, No. 6, June 2013, pp 1243–1255

REVIEW

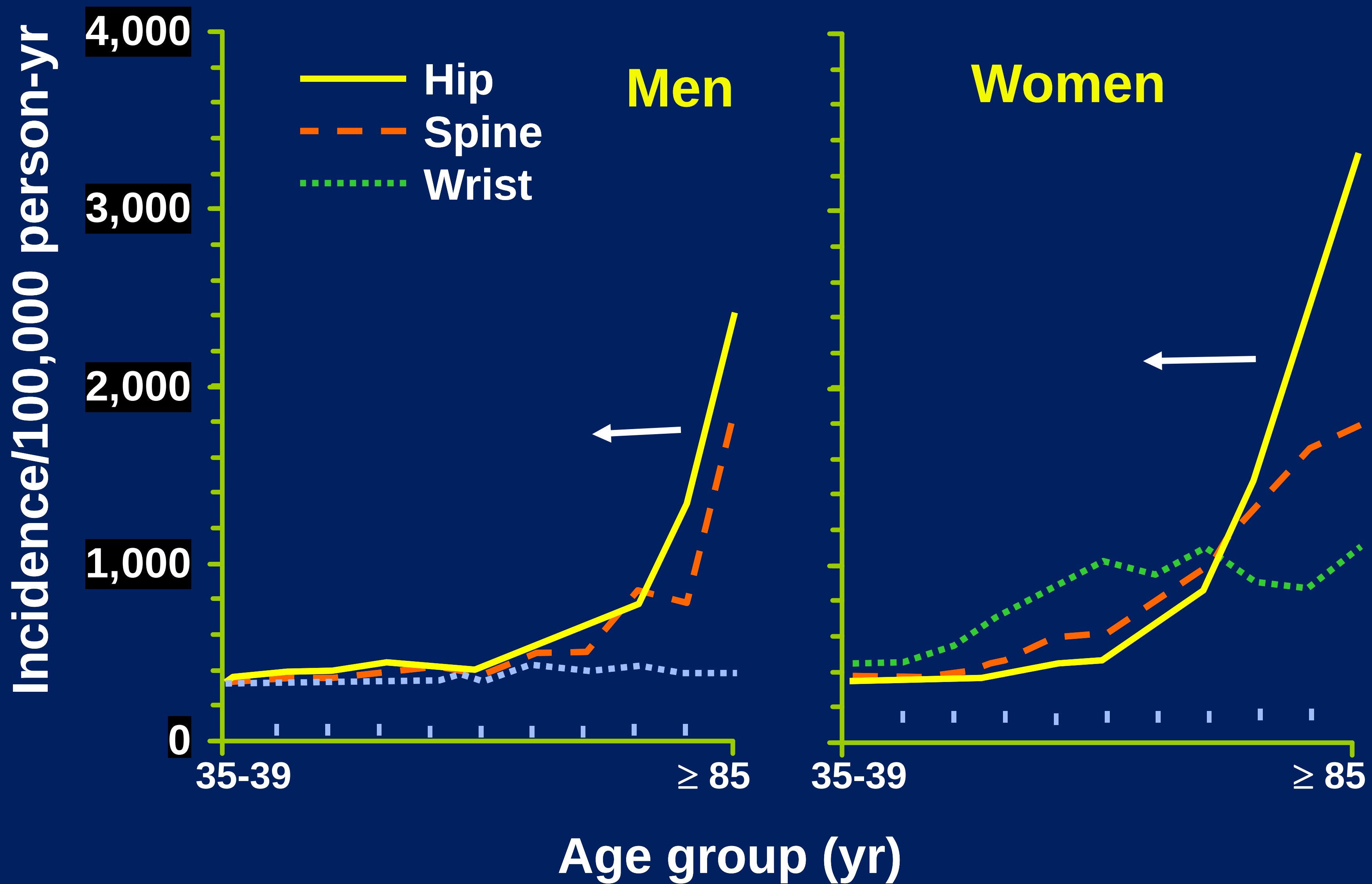
JBMR

Skeletal Health in Long-Duration Astronauts: Nature, Assessment, and Management Recommendations from the NASA Bone Summit

Eric S Orwoll,[1] Robert A Adler,[2] Shreyasee Amin,[3] Neil Binkley,[4] E Michael Lewiecki,[5] Steven M Petak,[6] Sue A Shapses,[7] Mehrsheed Sinaki,[8] Nelson B Watts,[9] and Jean D Sibonga[10]


How do we manage here, to prevent condition here.
Peak Bone Mass
Age-related Loss
Males
Females
Menopause-induced Loss
Bone mass (g/calcium)
1,500
1,000
500
0
0
20
40
60
80
100
Age (yr)
Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Issue: Recommendations in the absence of data.



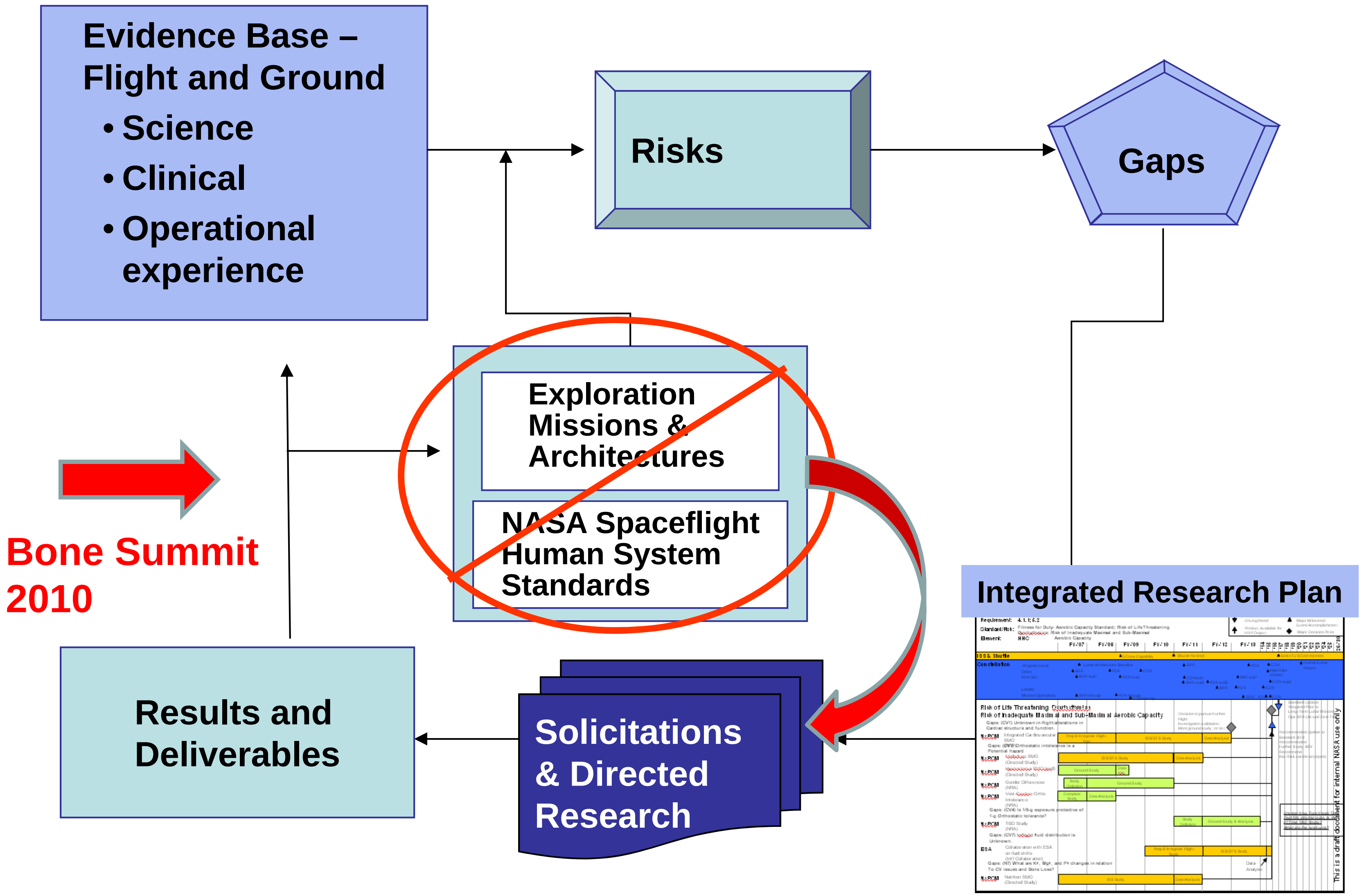
SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Cooper and Melton, 1992

Take Home Messages from Bone Summit

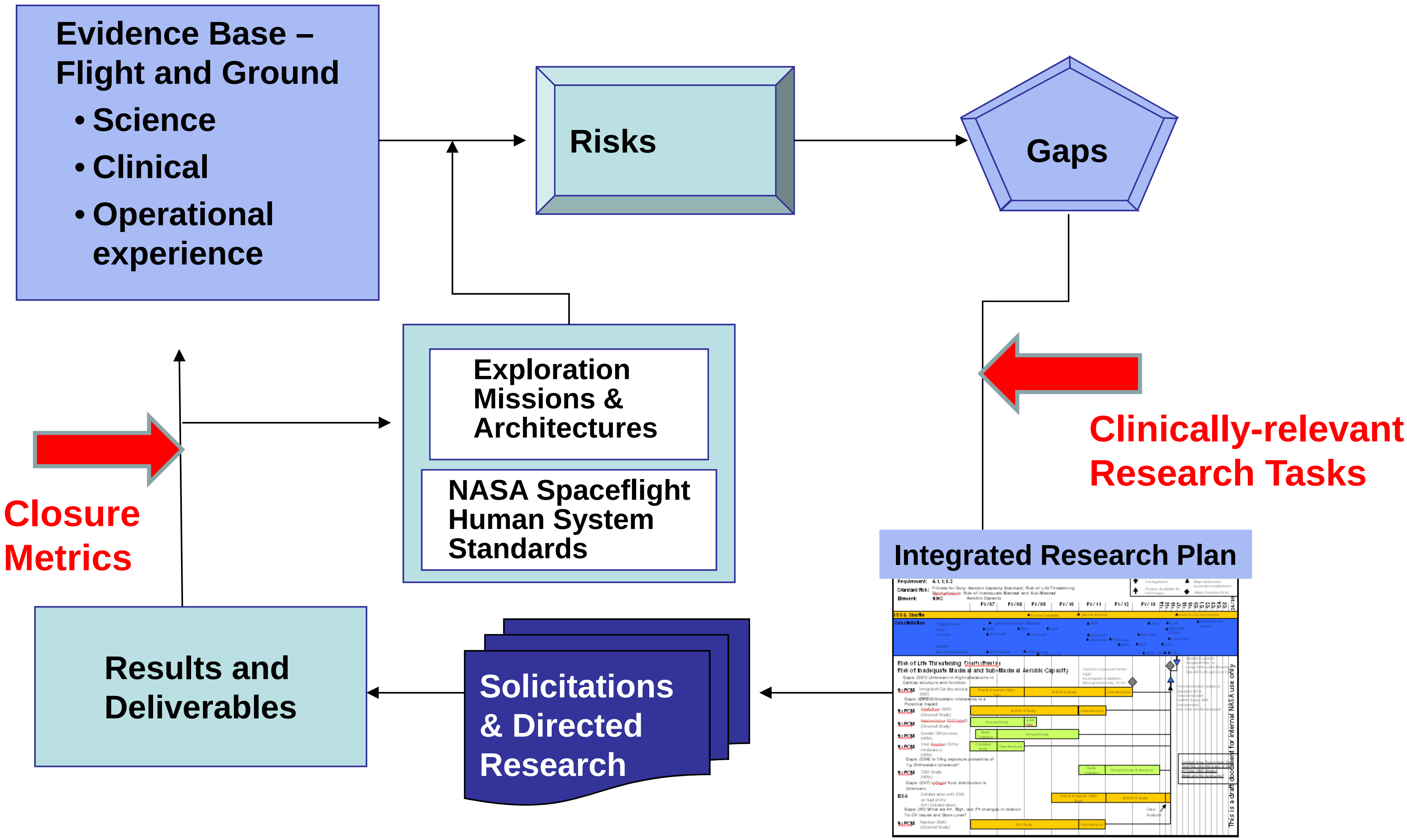
1. Bone is a complicated tissue.
2. NASA's constraints – not likely to reach Level of Evidence.
3. Astronauts are understudied group.
4. Spaceflight effects on bone are unique.
5. Clinically-accepted tests have limitations (JAMA).
6. Bone medical standards (based upon terrestrial guidelines) are not applicable to long-duration astronauts and require modification.
7. NASA circumstances may require transition of research technologies to clinical decision-making.

Bone Discipline Lead Briefs NASA HQ Chief Health & Medical Office [OCHMO]



HRP slide courtesy C. Kundrot
Adapted Sibonga 2012

Use of the *Research Clinical Advisory Panels* [RCAP] to focus NASA's Human Research for Bone Risks



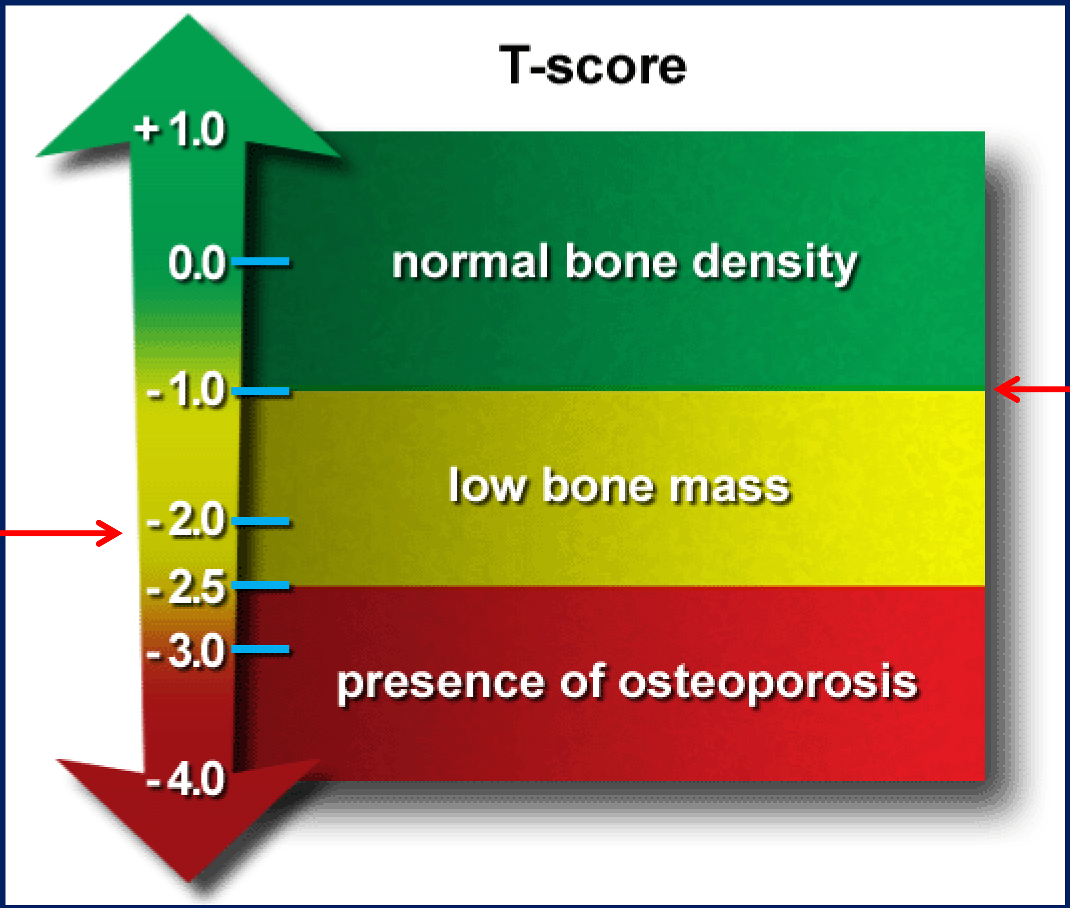
HRP slide courtesy C. Kundrot
Adapted Sibonga 2012

The long-duration astronaut – not typical subject to evaluate osteoporosis (4/2013).

- Typical space mission duration – 159 ± 32d (range 49-215d)
- Average Age – 47 ± 5 y (range 36 – 56)
- Male to Female Ratio – 4.4 : 1
- Current total # per astronauts in corps – 59 of 365
- # repeat fliers – 6
- BMI – Male BMI 25.7 ± 2.2 (range 21.2 to 30.7); Female BMI 22.2 ± 2.3 (range 20.1 to 25.9)
- Wt and Ht- Males: Males: 81 ± 9 (64 to 101); 176 ± 6 (163 to 185)
- Females: 64 ± 7 (54 to 81), 169 ± 4 (163 to 178)
- % Body Fat: Males 20 ± 4 (9 to 27); Females 27 ± 8 (19 to 41)
- ***MEDICAL PRIVACY A MAJOR CONSTRAINT***

NASA Standards for Crew Health
Based on World Health Organization (WHO)
Note: T-scores (Not BMD change).

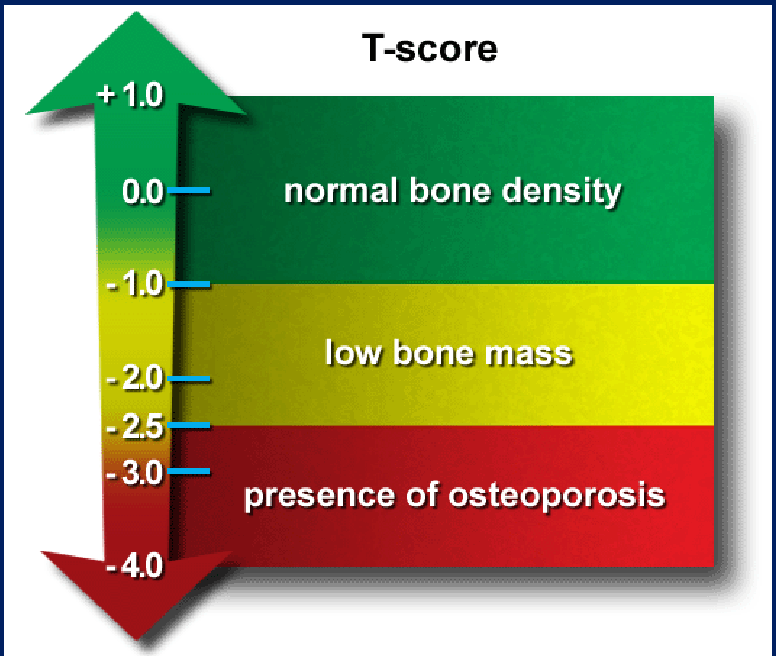
Permissible Outcome Limit

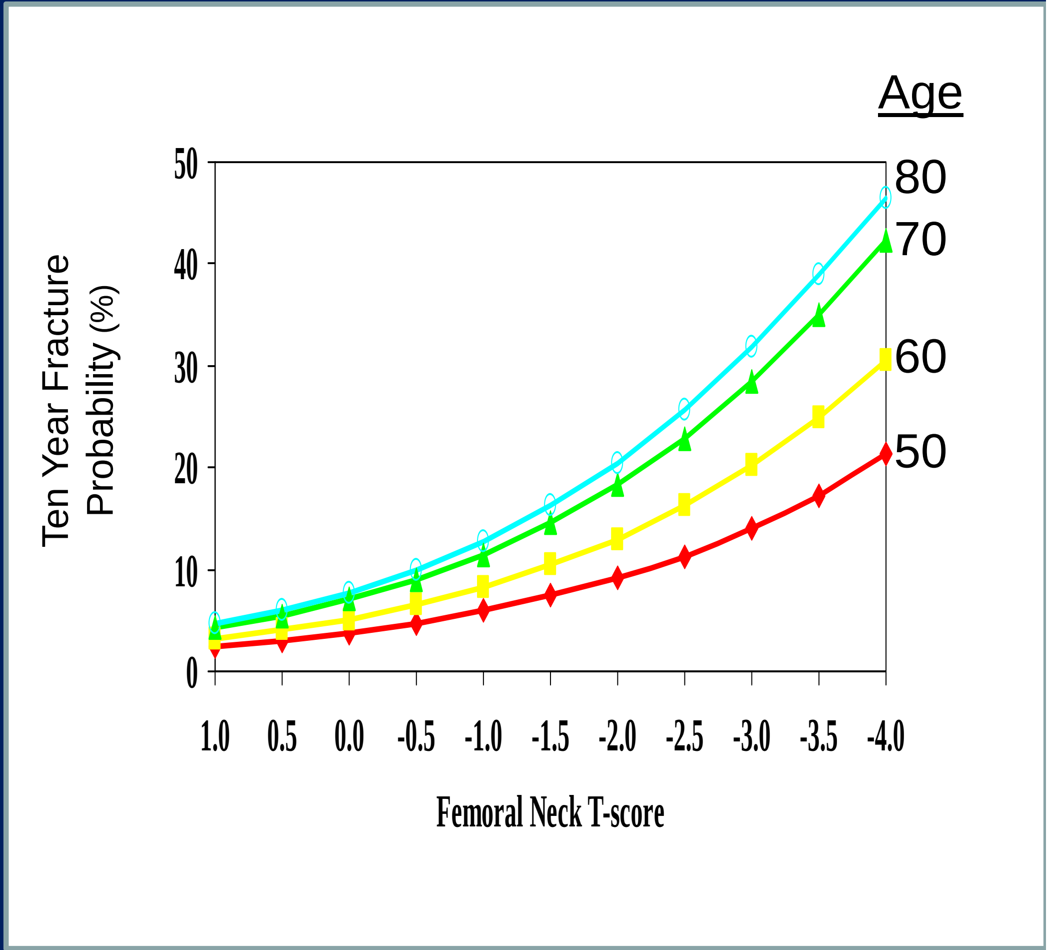


Fitness For Duty

T-score = # Standard Deviations from Normal bone mineral density [mean BMD] of young healthy persons.

WHO/ISCD* Guidelines developed for peri-, postmenopausal women and men > 50 yrs.
DXA screening & surveillance unique to NASA



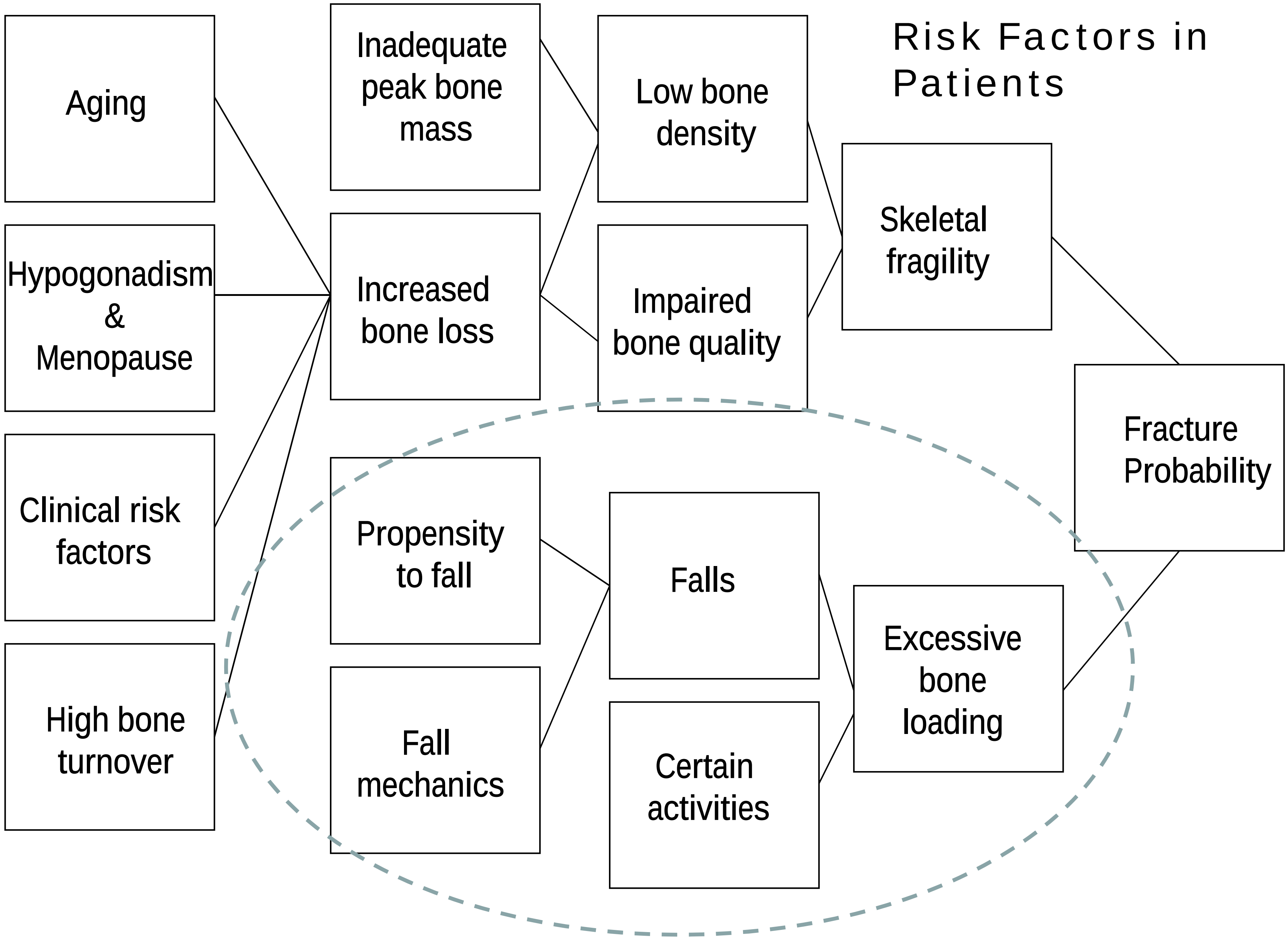


*Intl Society Clinical Densitometry

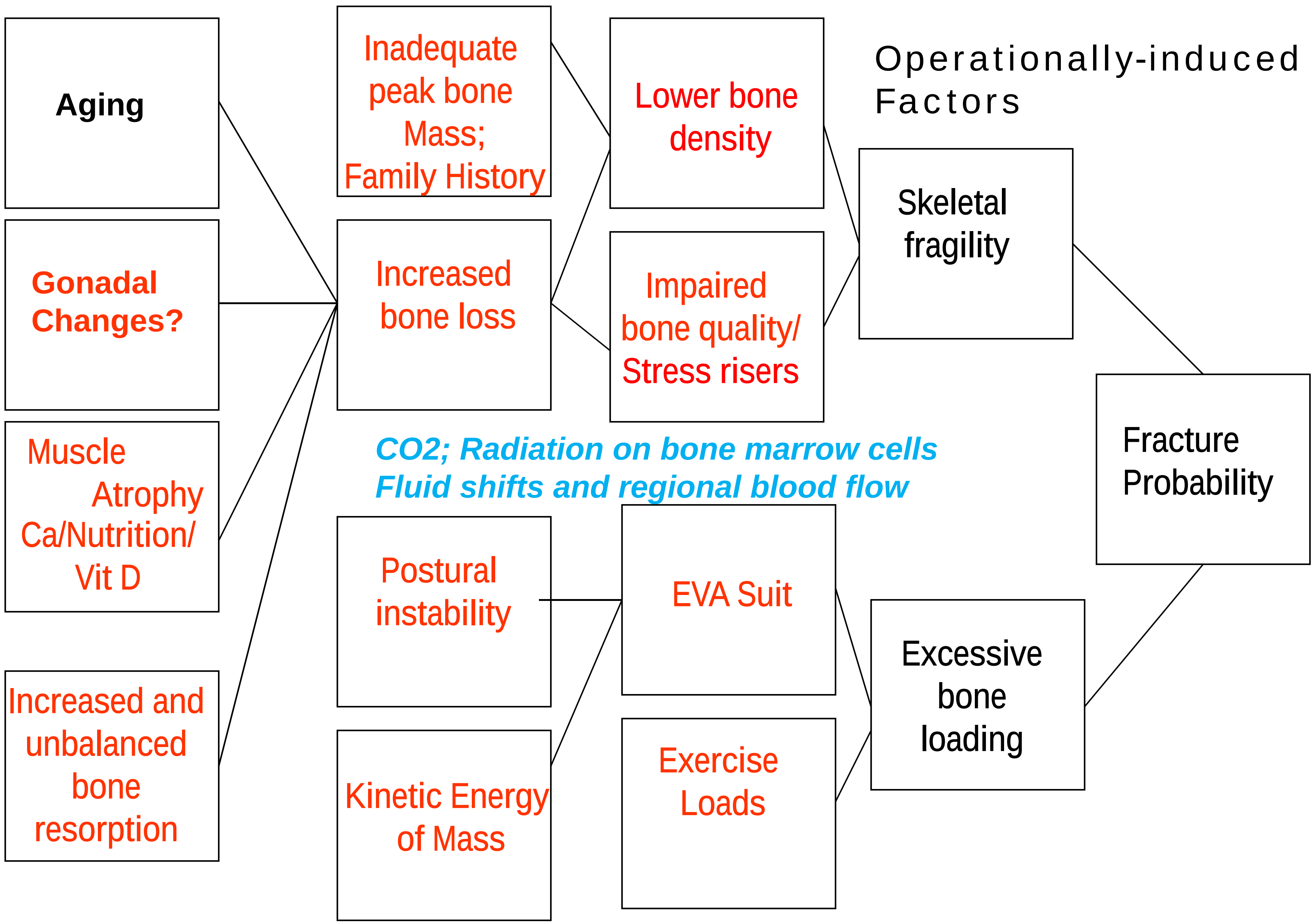
Fig. courtesy of S. Petak, MD

Adapted from:
Kanis JA et al. *Osteoporosis Int*. 2001;12:989-995

Risk Factors in Patients



Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C, Melton LJ



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Overview

- NASA's challenges to addressing skeletal risks due to spaceflight: 3 C's
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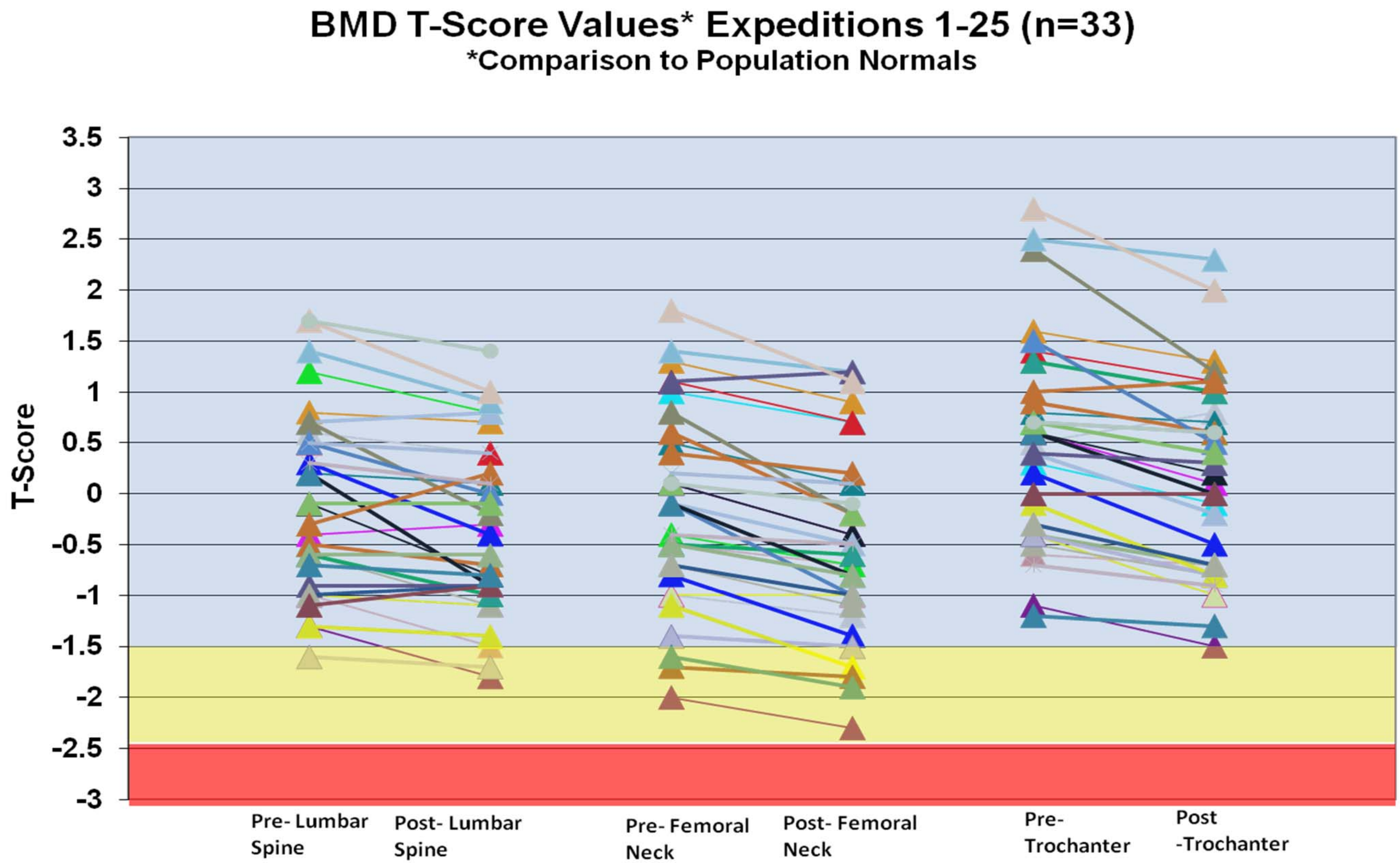
Diagnostic guidelines using areal BMD T-scores - not appropriate or predictive for fracture in astronaut population.



Paradigm Shift

- "Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality." JAMA 2001

Dual-energy X-ray Absorptiometry [DXA] BMD @ Johnson Space Center

- Monitor astronaut skeletal health
- Characterize skeletal effects of long-duration spaceflight
- Evaluate efficacy of bone loss countermeasures
- Verify restored health status

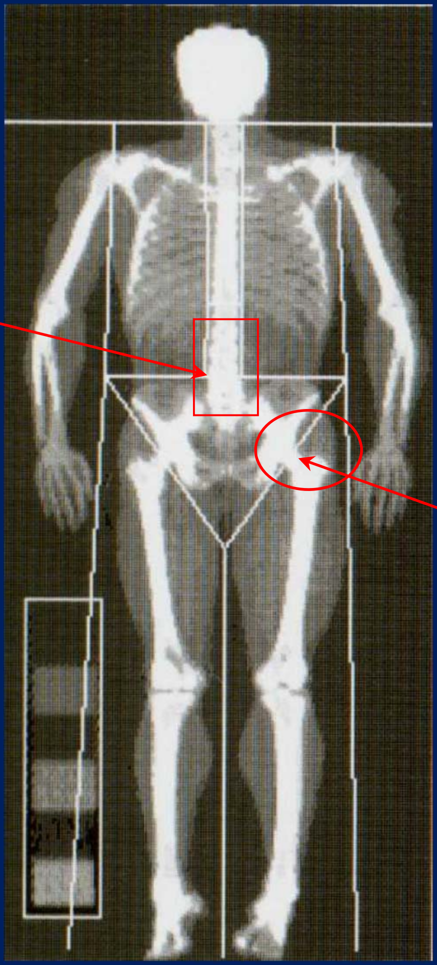
What are the risks for using inappropriate DXA-BMD based guidelines?

- Unnecessarily disqualifying applicants to Astronaut candidacy.
- Not fully understanding the effects of spaceflight on hip and spine integrity.
- Inadequately evaluating efficacy of countermeasures.

DXA: BMD losses are site-specific and rapid

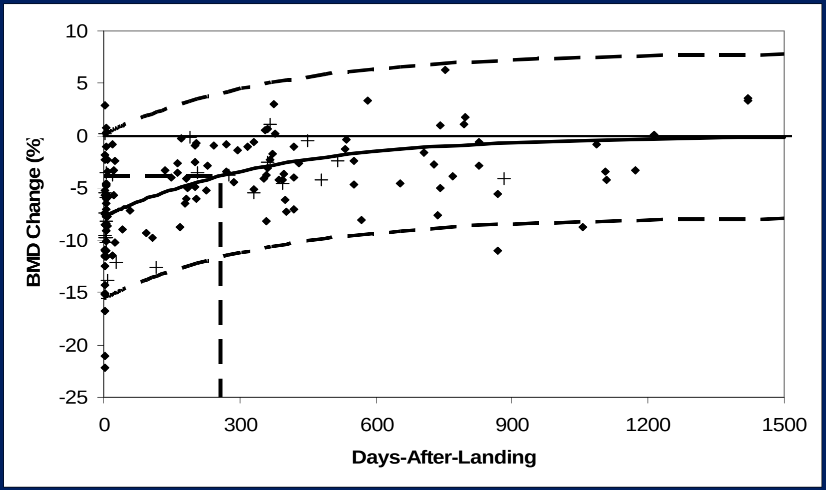
vs. 0.5 – 1.0 % BMD **loss/year** in the aged

Areal BMD g/cm2	**%/Month Change ± SD**
Lumbar Spine	-1.06±0.63*
Femoral Neck	-1.15±0.84*
Trochanter	-1.56±0.99*
Total Body	-0.35±0.25*
Pelvis	-1.35±0.54*
Arm	-0.04±0.88
Leg	-0.34±0.33*
*p<0.01, n=16-18	

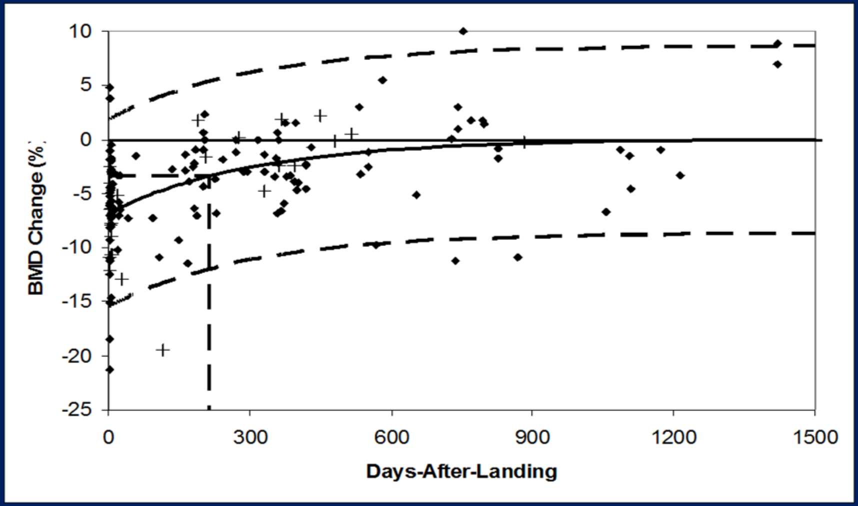


LeBlanc et al, J Musculoskeletal 2000

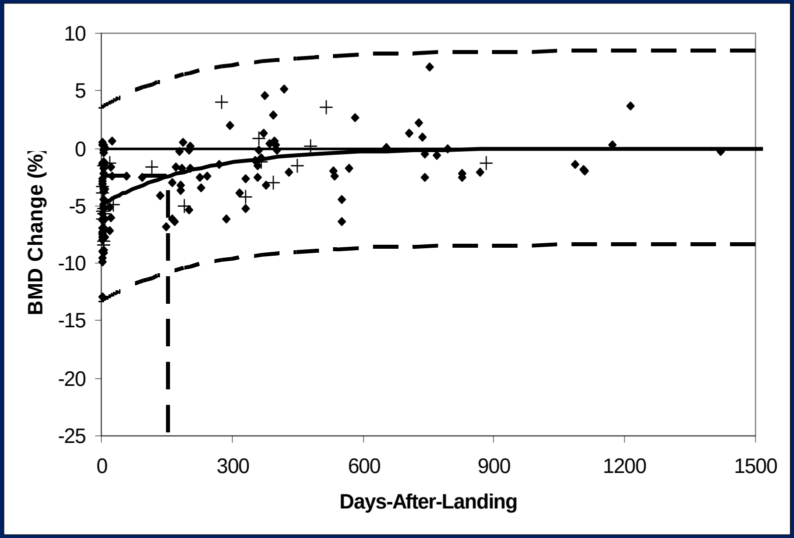
DXA BMD increases in Postflight – but not sufficient to assess recovery of *bone strength*.



Trochanter



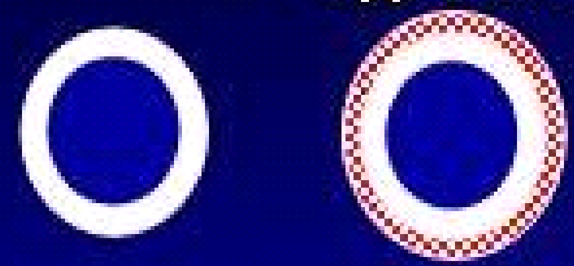
Femoral neck



Lumbar Spine

Sibonga et al. BONE 41:973-978, 2007

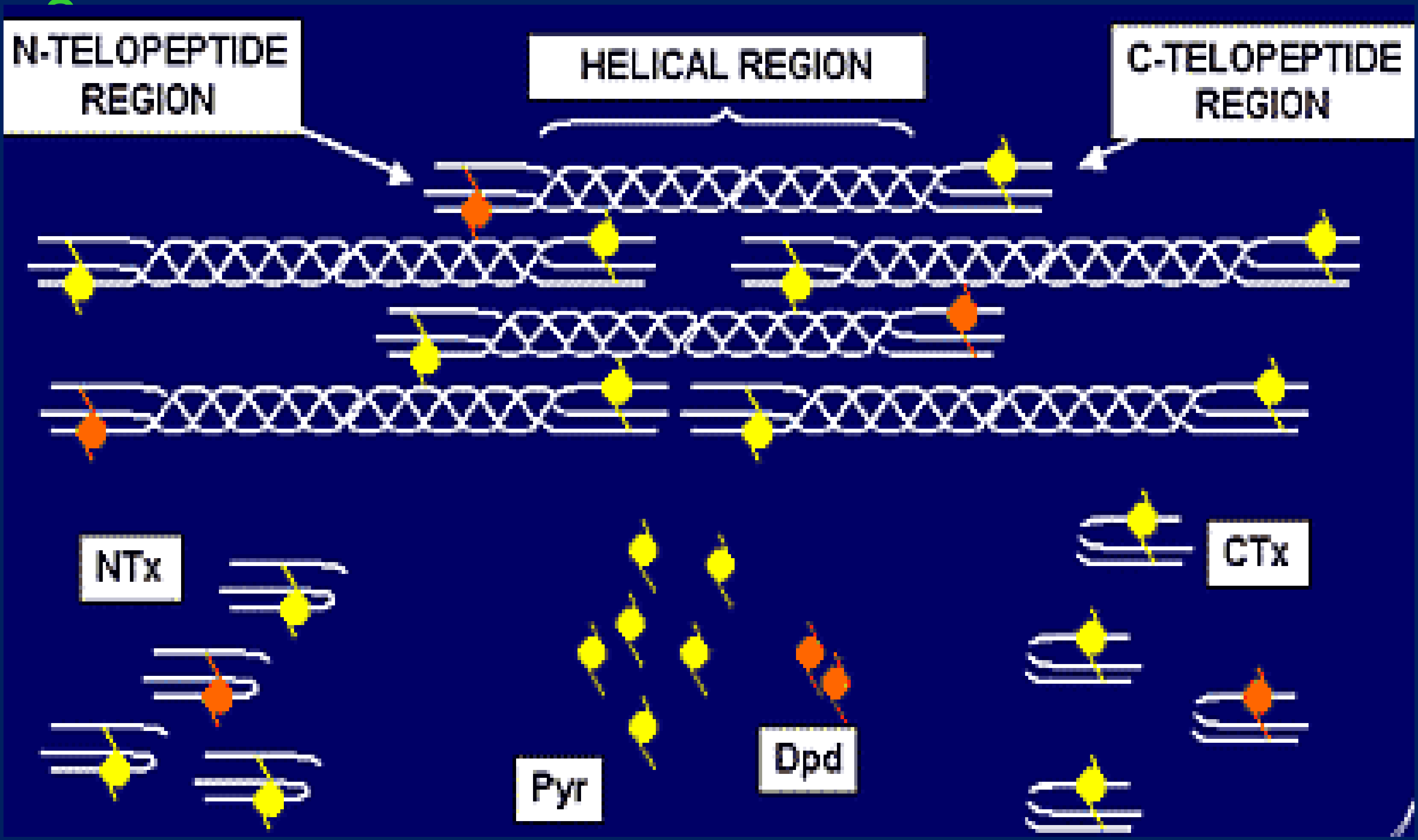
Changes in size, changes in bone strength.



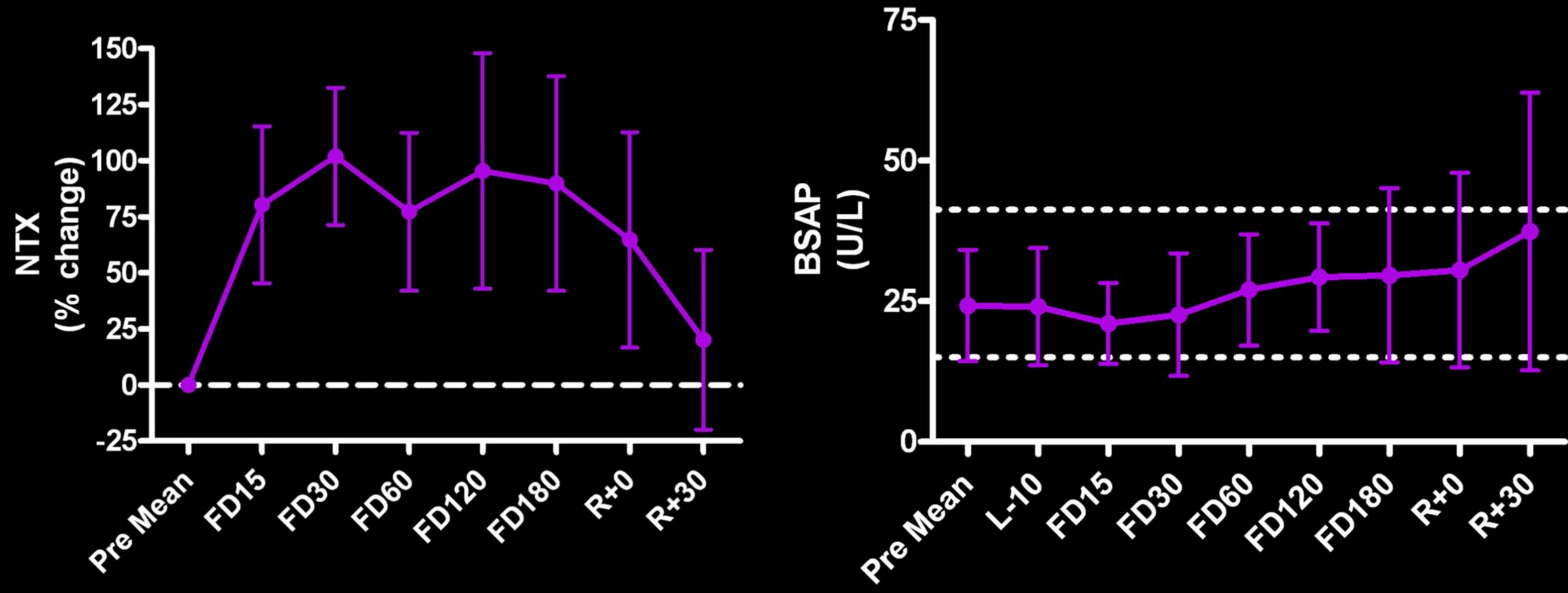
	Baseline	Periosteal Apposition	Endosteal Apposition
Periosteal Diameter	100 %	110 %	100 %
Endosteal Diameter	100 %	100 %	90 %
Compressive Strength	100 %	148 %	125 %
Bending Strength	100 %	168 %	116 %

Slide courtesy of M. Bouxsein, PhD – Bone Quality, 2005

Serum and urinary biomarkers reflect bone turnover and mineral metabolism.

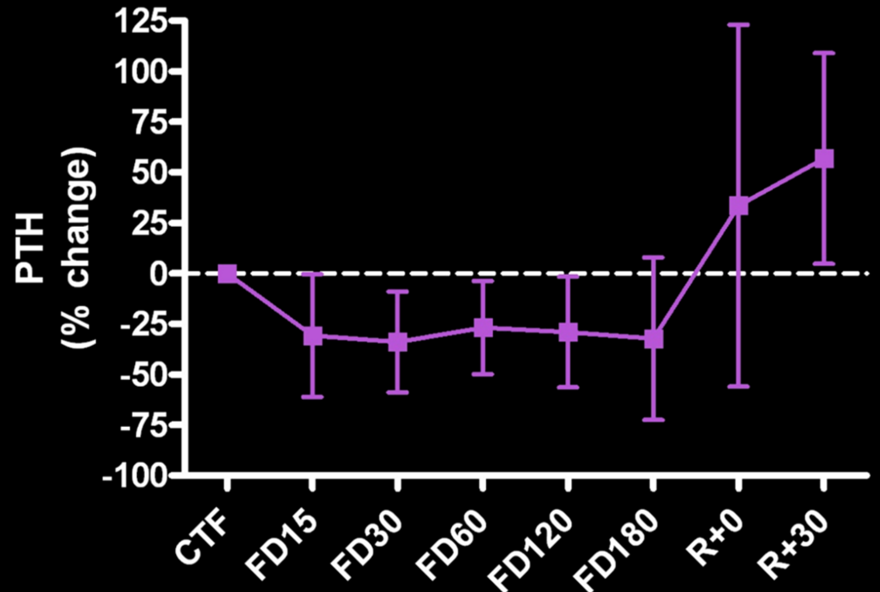


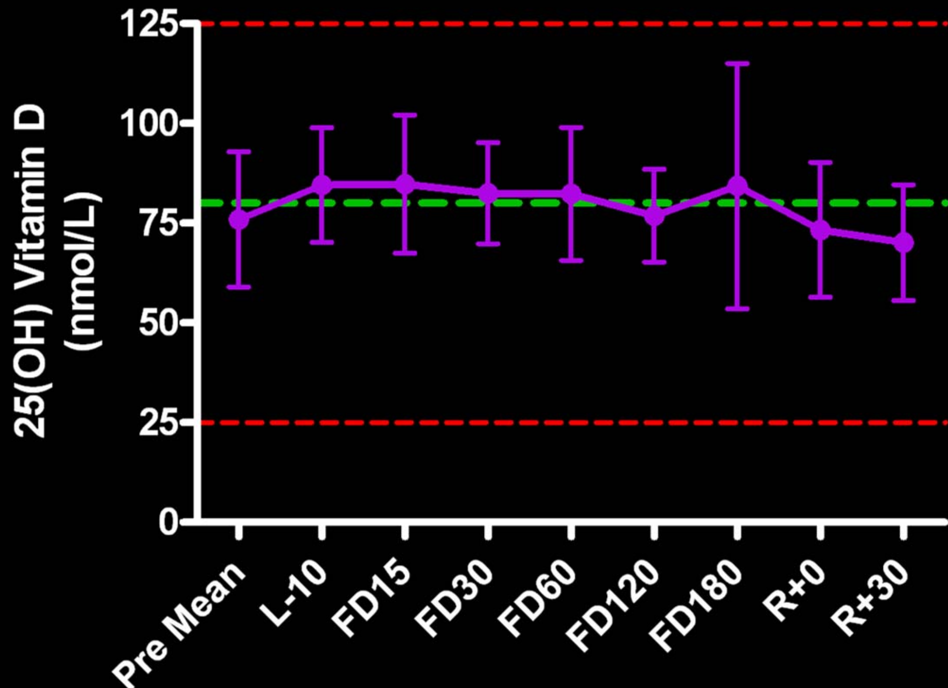
Bone Turnover Markers suggest a net loss in bone mass in the skeleton



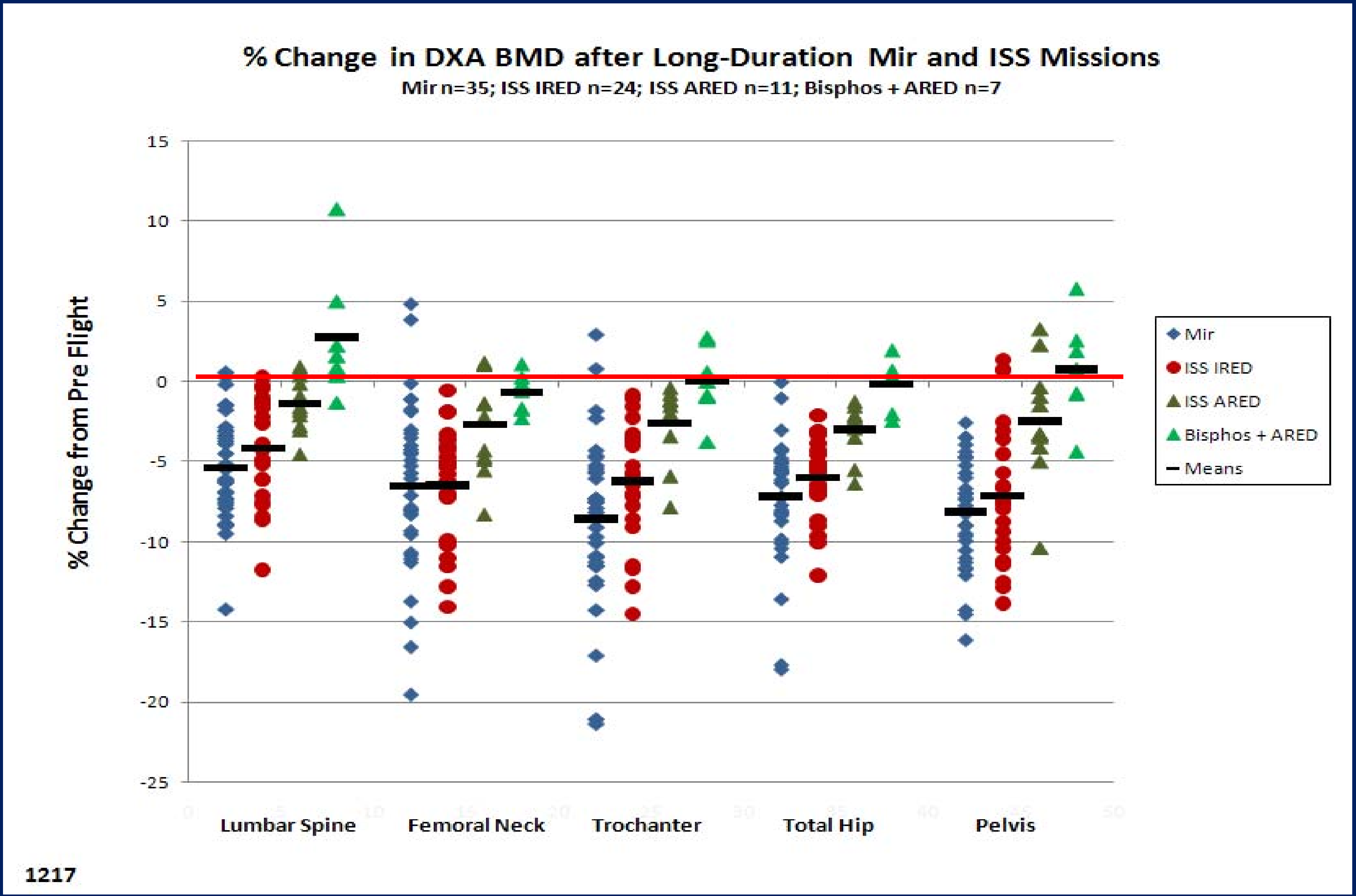
Slide Courtesy of Dr. SM Smith; Adapted by Sibonga

Calcium-regulating Hormones – Endocrine system is "normal" but perturbed.



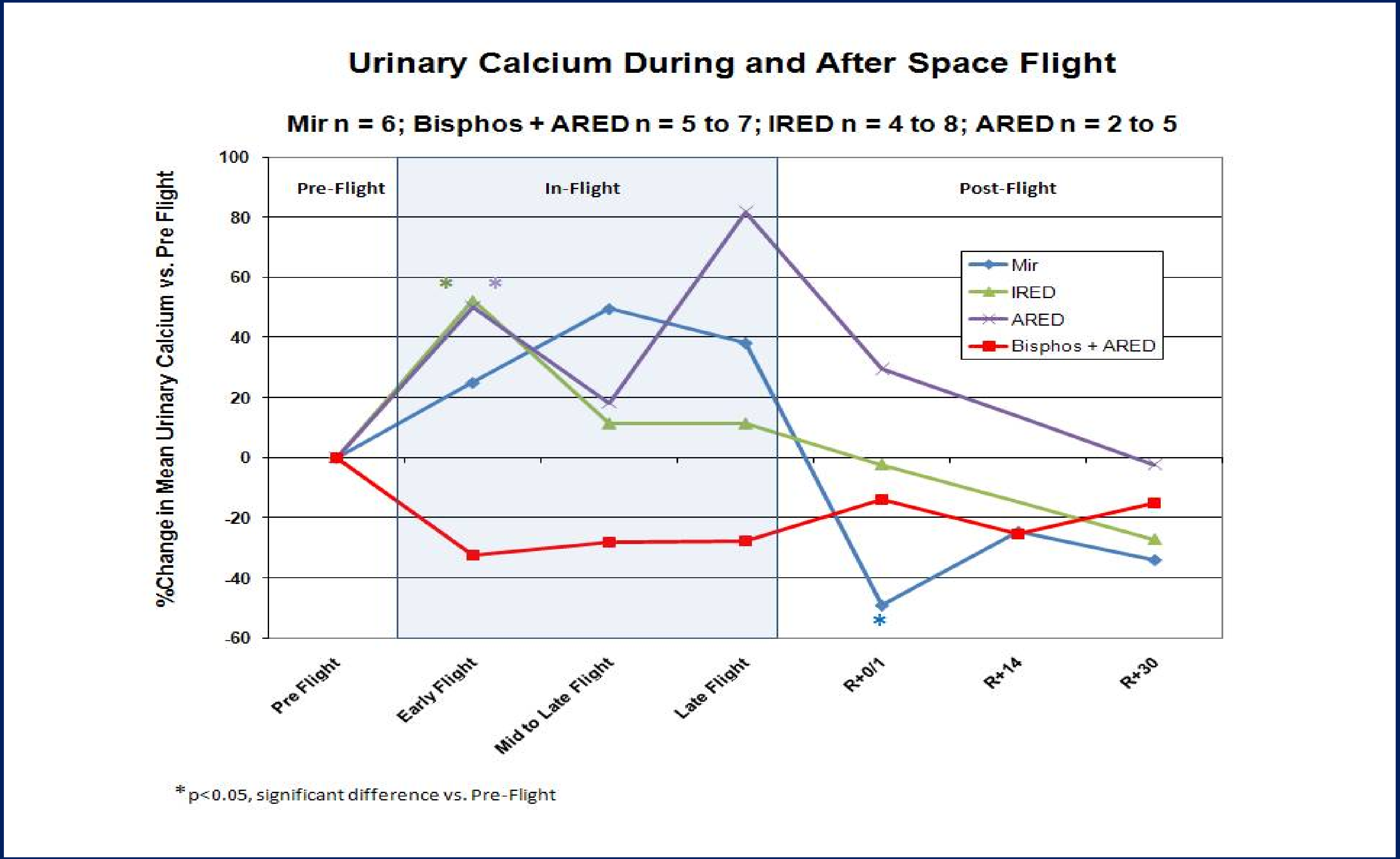


Nutrition SMO, unpublished data; Courtesy Dr. SM Smith



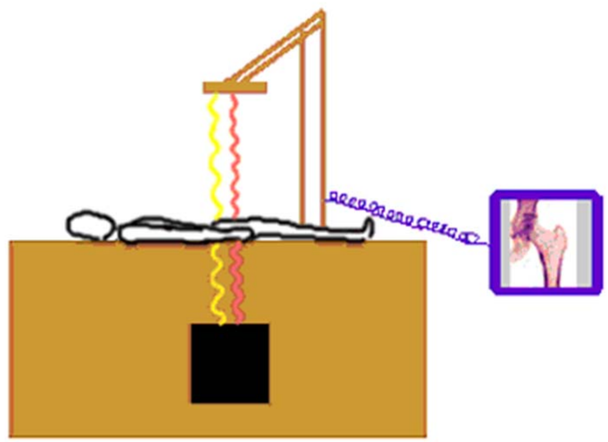
* Updated data since 2010 Bone Summit

Bisphosphonates as a Countermeasure to Spaceflight Effects - mitigates of urinary calcium excretion

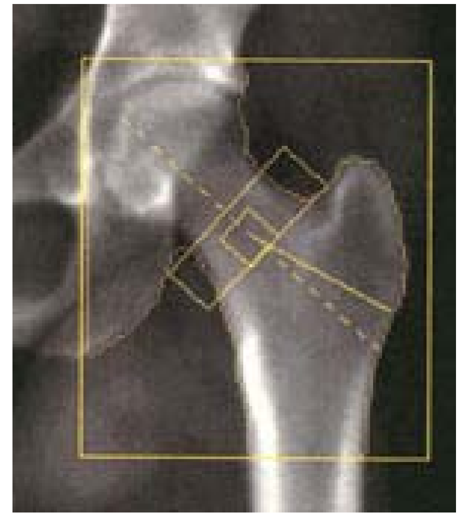


Slide courtesy of Dr. A. LeBlanc

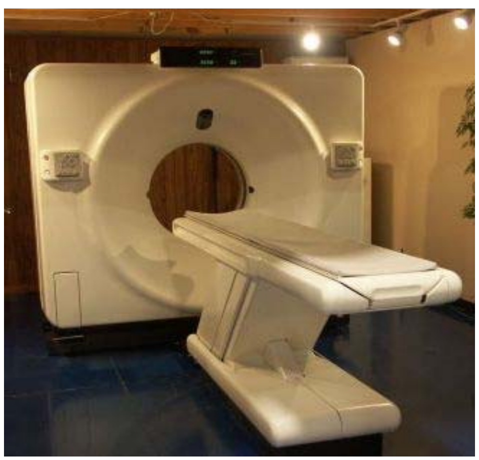
Densitometry & Reported Measurement



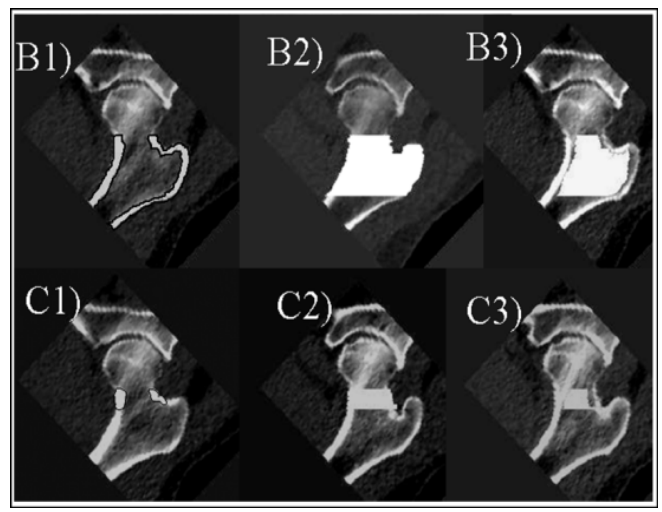
DXA reports areal BMD (aBMD)



g/cm^2 averaged for cortical + trabecular bone

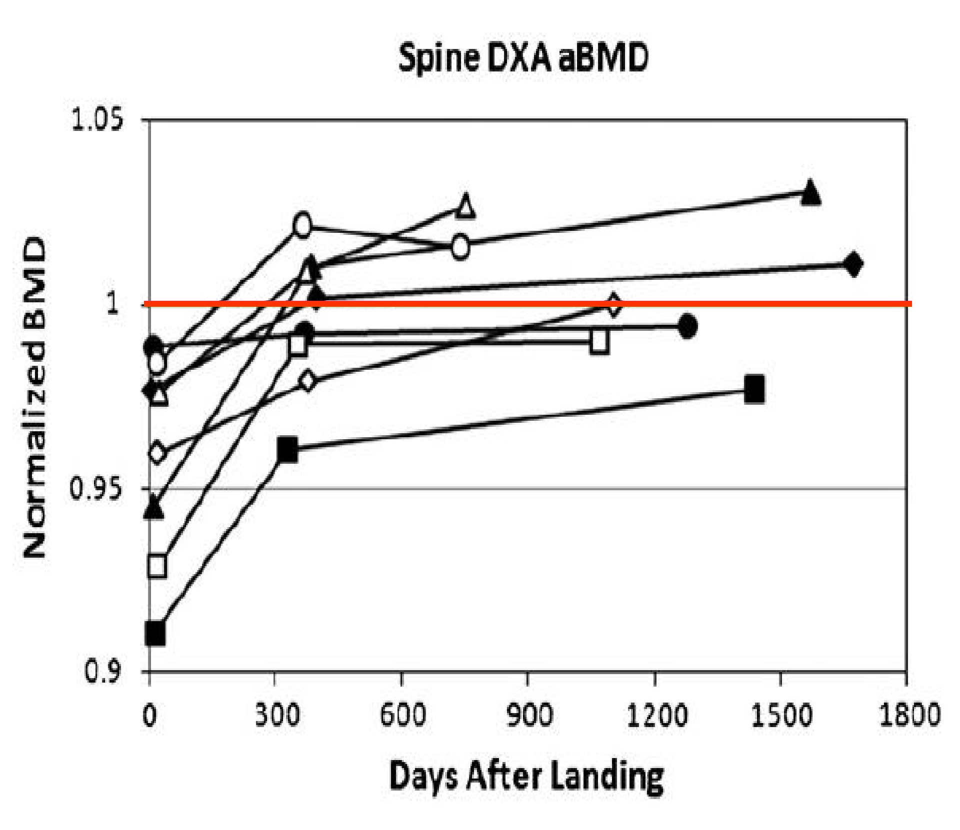


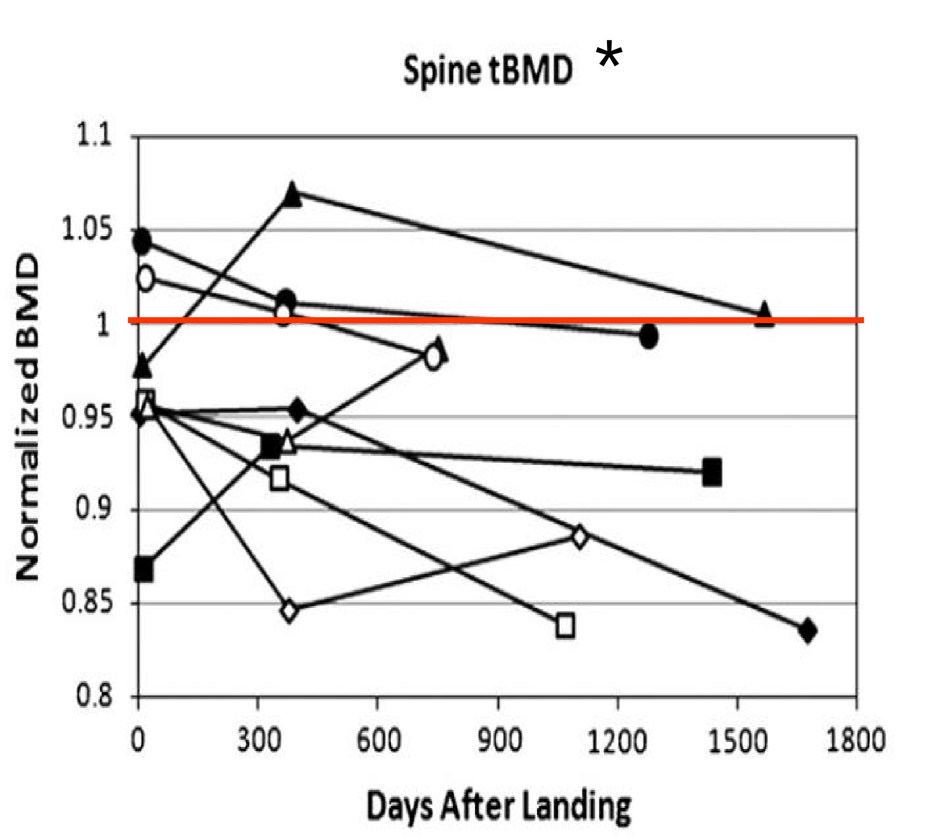
QCT quantifies volumetric BMD



g/cm^3 for separate cortical & trabecular bones

DXA vs. QCT Spine :
Discordant Recovery Patterns in Astronauts After Spaceflight



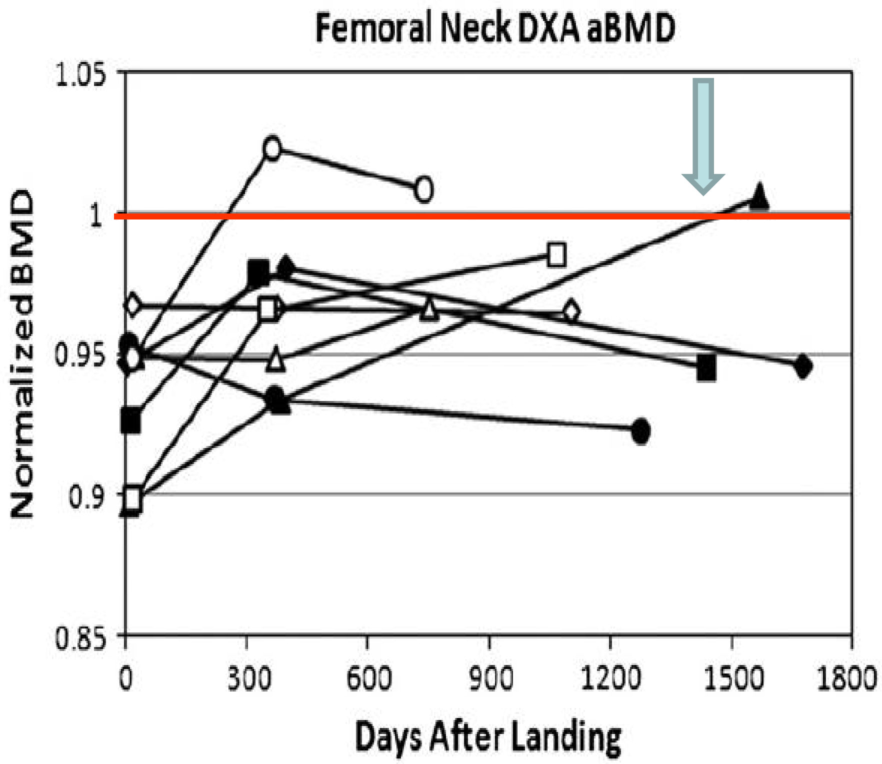


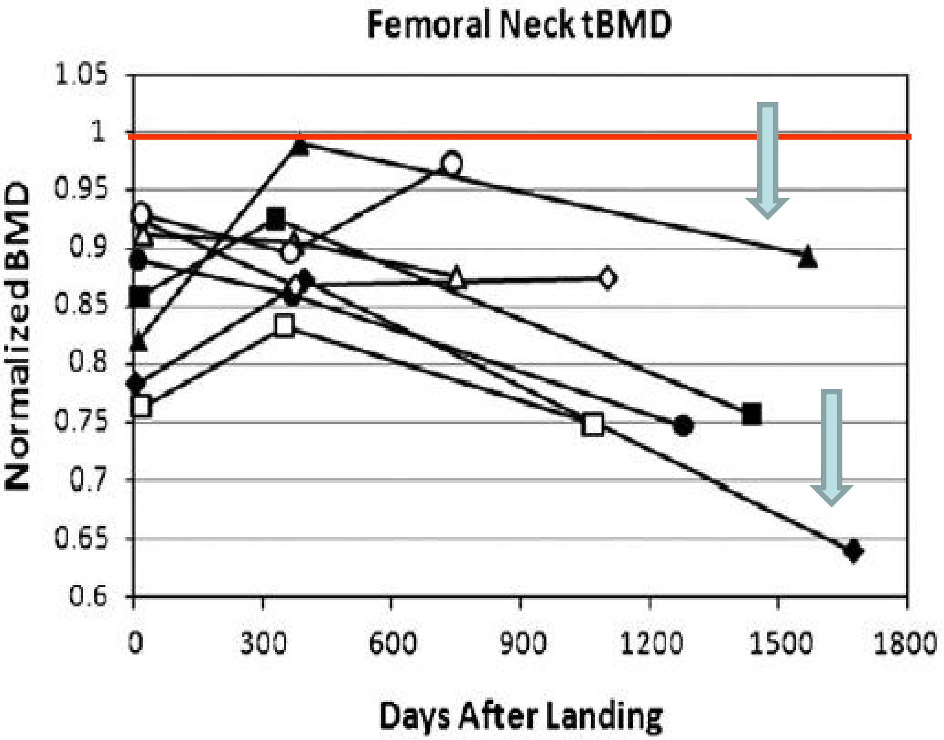
aBMD – areal bone mineral density g/cm^2

tBMD – trabecular volumetric bone mineral density g/cm^3

QCT Extension Study (n=8) Postflight Trabecular BMD in hip. Carpenter, D et al. Acta Astronautica, 2010.

Why the clinical concern?





aBMD – areal bone mineral density g/cm^2

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QCT Extension Study (n=8) Postflight Trabecular BMD in hip. Carpenter, D et al. Acta Astronautica, 2010.

QCT measures are independent predictor of hip fracture.

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 23, Number 8, 2008
Published online on March 17, 2008; doi: 10.1359/JBMR.080316

Proximal Femoral Structure and the Prediction of Hip Fracture in Men: A Large Prospective Study Using QCT*

Dennis M Black,[1] Mary L Bouxsein,[2] Lynn M Marshall,[3] Steven R Cummings,[4] Thomas F Lang,[5] Jane A Cauley,[6] Kristine E Ensrud,[7] Carrie M Nielson[3] and Eric S Orwoll[3] for the Osteoporotic Fractures in Men (MrOS) Research Group

Lower trabecular hip BMD is a predictor of hip fracture in aged men* (and in women, Bousson et al 2011)

SUMMIT RECOMMENDS AS THE <u>CLINICAL TRIGGER</u> FOR ASTRONAUTS.

This is the basis of Hip QCT flight study.

Overview

- NASA's challenges to addressing skeletal risks due to spaceflight: 3 C's
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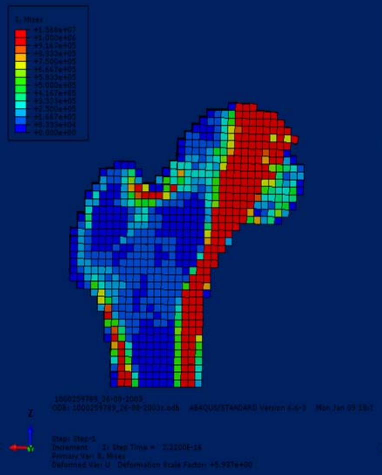
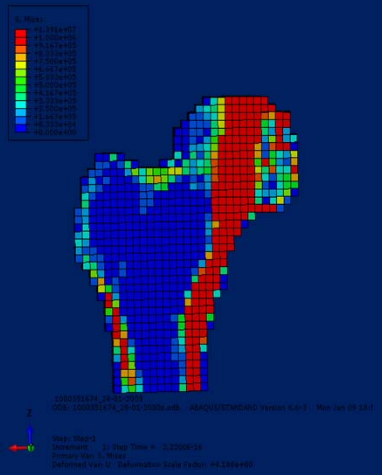
Investigate a new medical standard for BONE Finite Element Modeling [FEM] : What is it and what can it tell NASA about hip fracture risk in the long-duration astronaut?

Finite Element Models of QCT data – "FE modeling" is a computational tool to estimate failure loads ("strength") of complex structures.



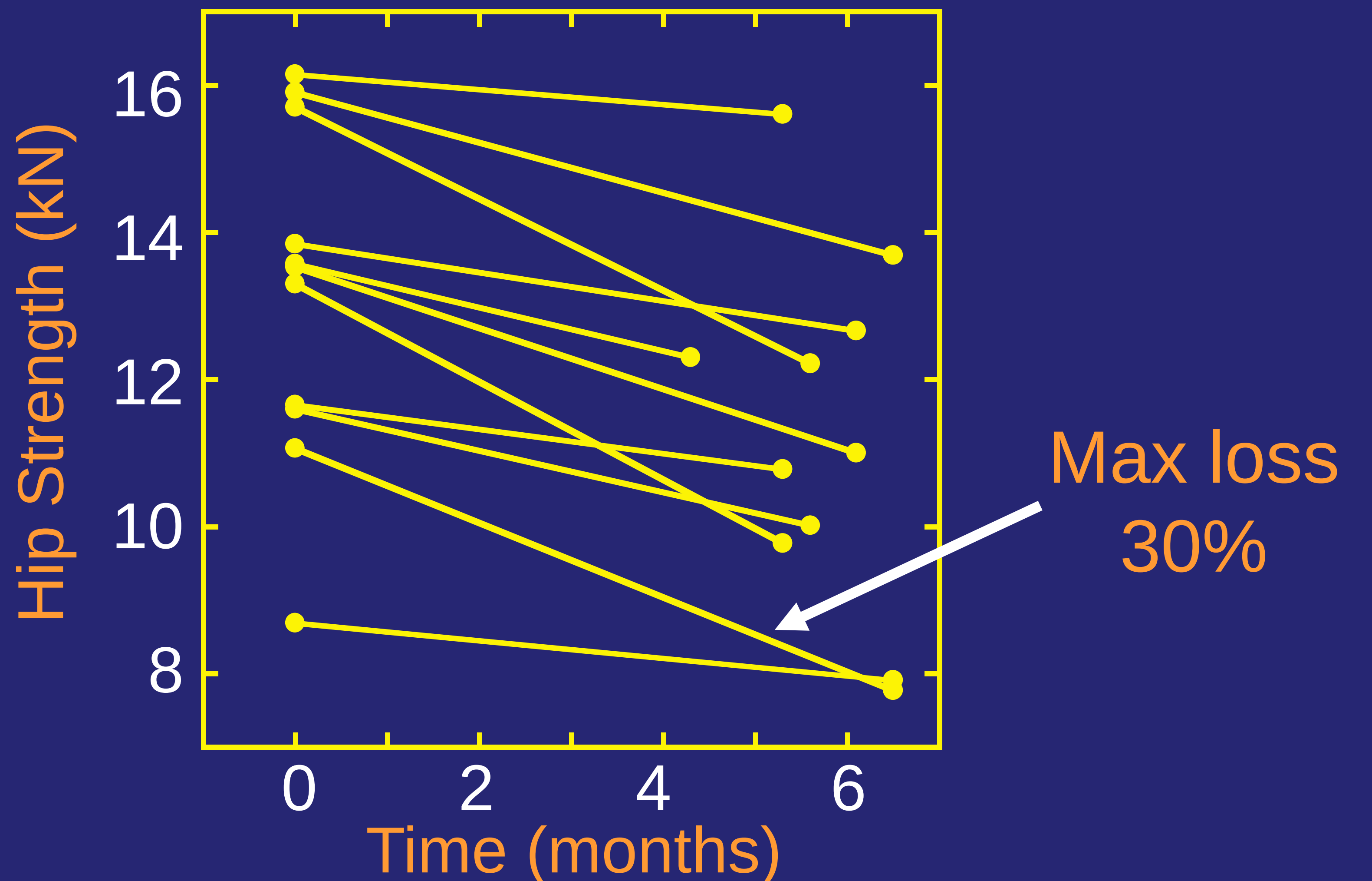


J. Keyak et al, 1998, 2001, 2005

Images courtesy of Dr. J Keyak

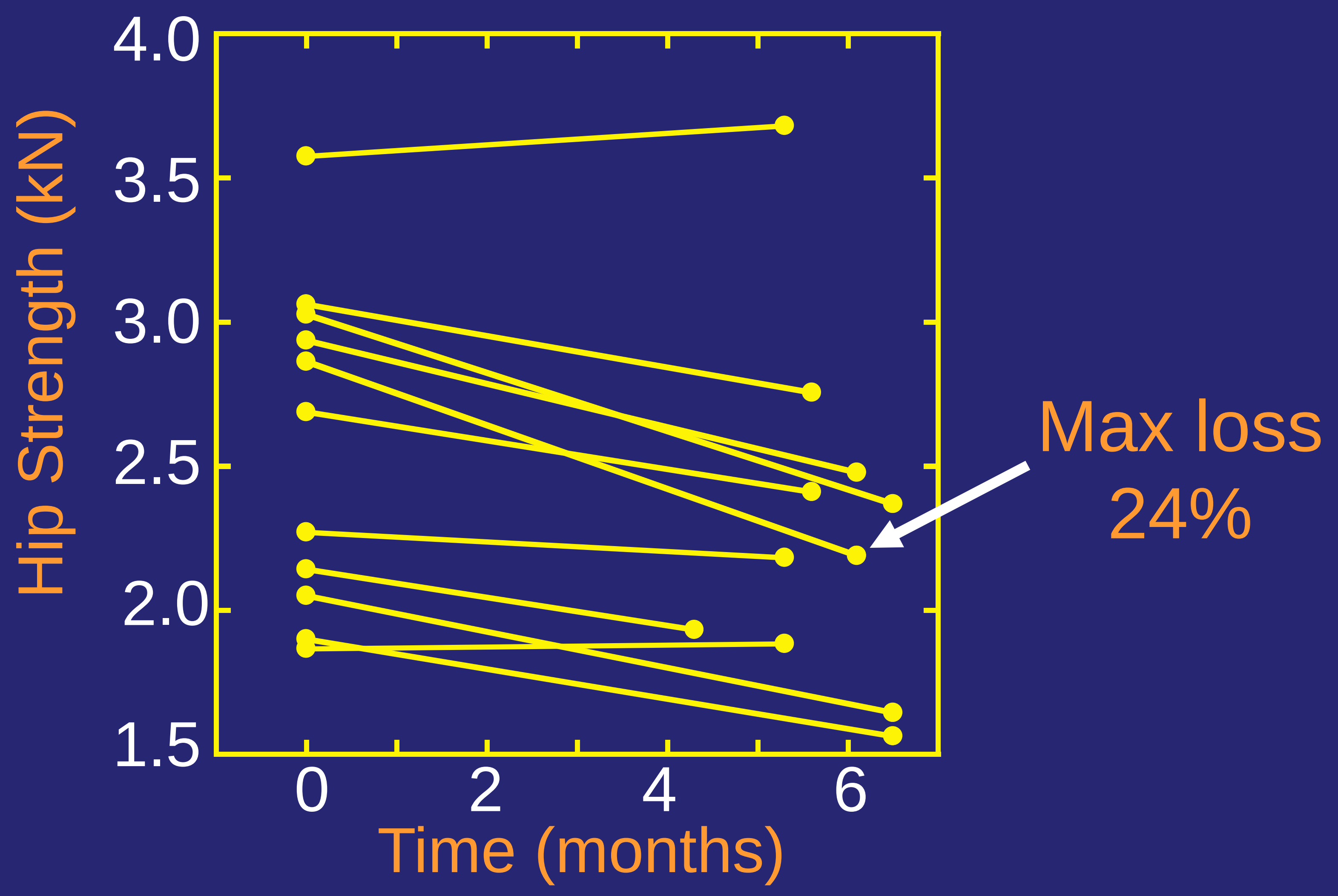
Individual Results

Stance Loading (4 to 30% loss in strength)

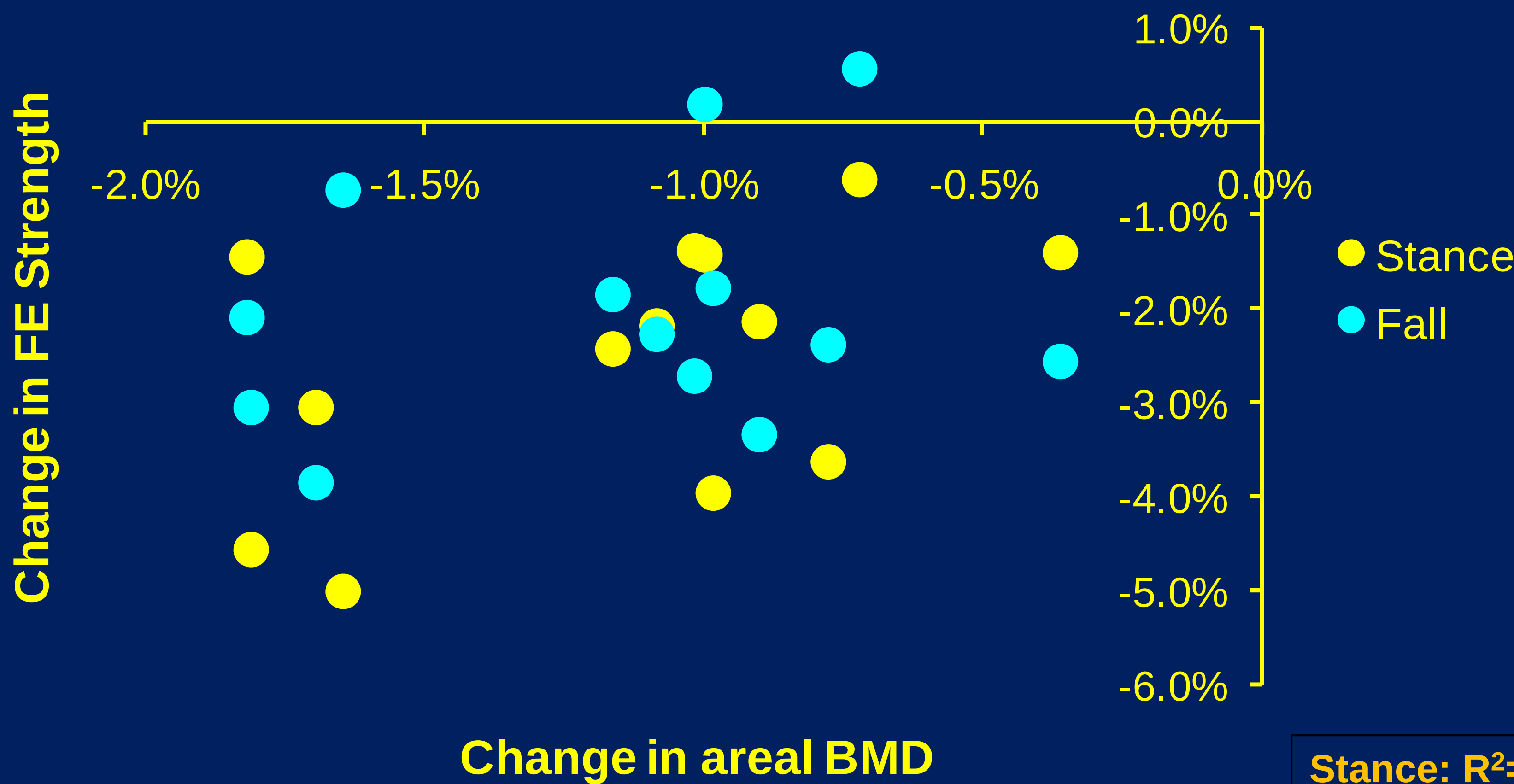


Individual Results

Fall Loading (3 gain to 24% loss in strength)



Two methods of monitoring space-induced changes in bone strength do not correlate.



Stance: R^2=0.23

Fall: R^2=0.05

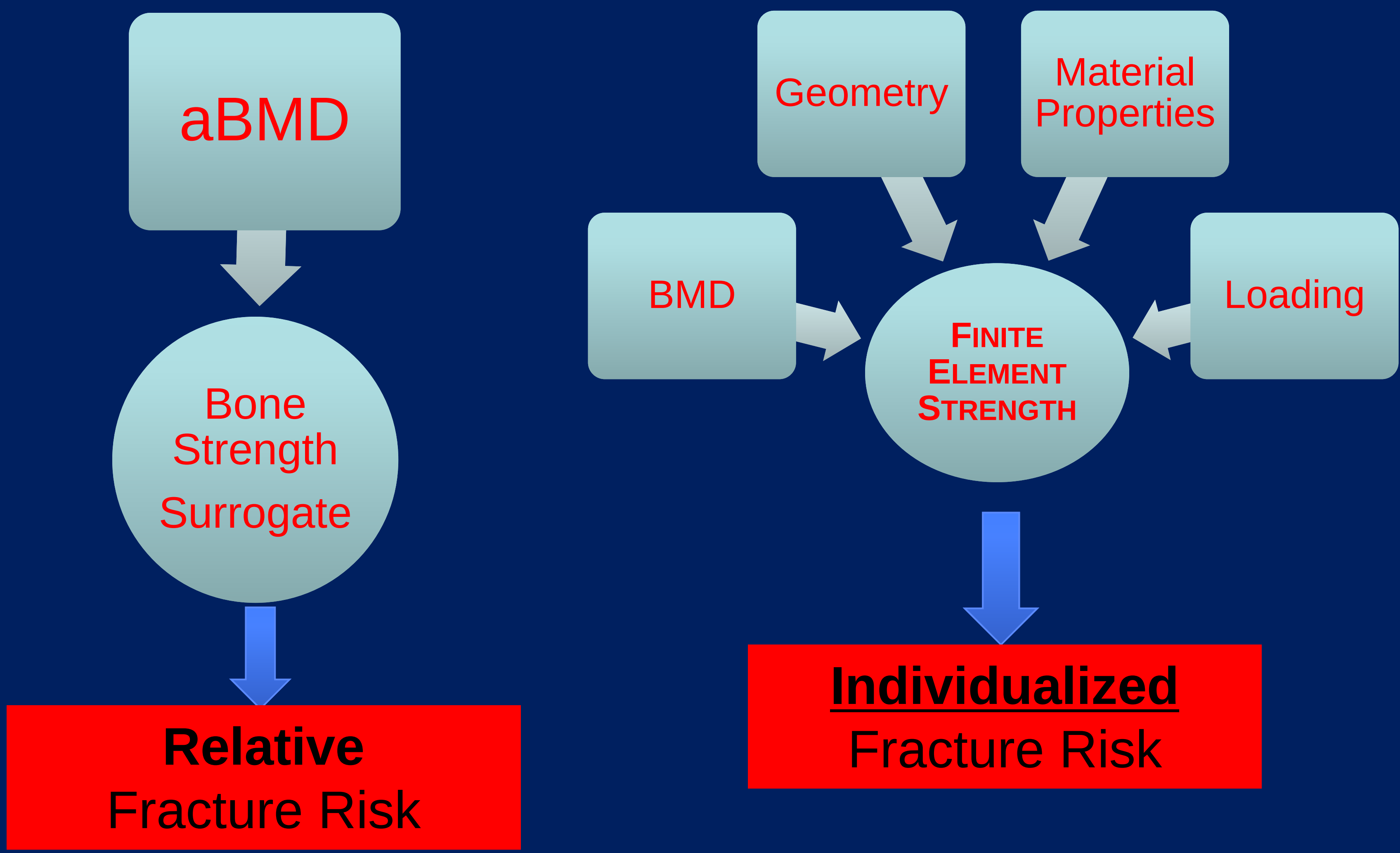
Slides courtesy of J Keyak; Bone. 2009 Mar;44(3):449-53.

Which is better?

Which is better?

Fracture risk by 1 measurement or by > 1 measurement?

It's not complicated.



Summit Recommendation

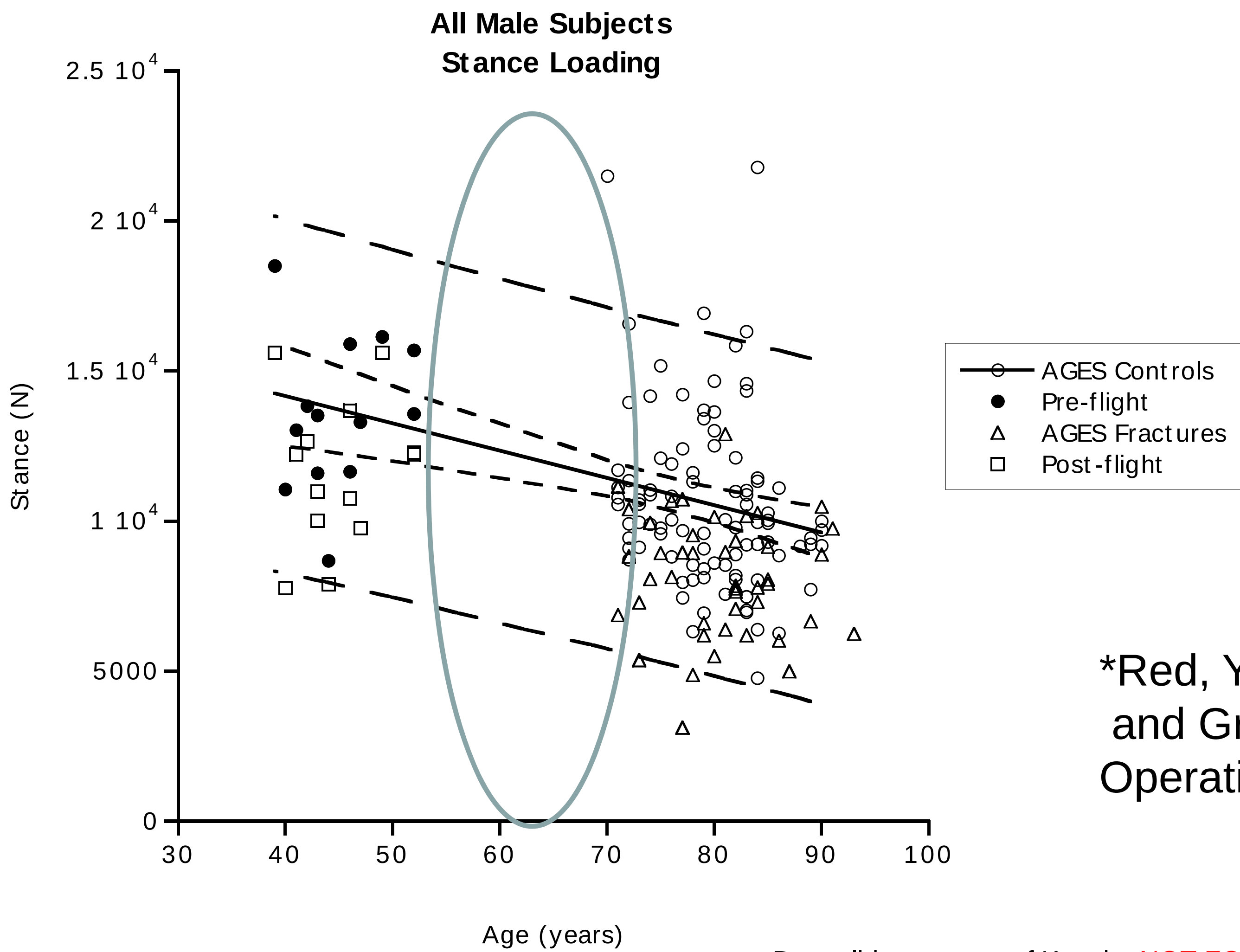
EXPLORE HOW FEM PREDICTS FRACTURE IN POPULATION STUDIES

Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.

- **Male-female differences in prediction of hip fracture during finite element analysis.** Keyak JH, Sigurdsson S, Karlsdottir G, Oskarsdottir D, Sigmarsdottir A, Zhao S, Kornak J, Harris TB, Sigurdsson G, Jonsson BY, Siggeirsdottir K, Eiriksdottir G, Gudnason V, Lang TR. Bone. 2011;48(6):1239-1245.
- **Association of hip strength estimates by finite –element analysis with fractures in women and men**. Amin S,, Kopperdahl DL, Melton LJ 3rd, Achenbach SJ, Therneau TM, Riggs BL, Keaveny TM, Khosla S. J Bone Miner Res. 2011;26(7):1593-1600.
- **Age-dependence of femoral strength in white women and men.** Keaveny TM, Kopperdahl DL, Melton III LJ, Hoffmann PF, Amin S, Riggs BL, Khosla S. J Bone Miner Res. 2010;25(5):994-1001.
- **Osteoporotic Fractures in Med Study Group. Finite element analysis of the proximal femur and hip fracture risk in older men**. Orwoll ES, Marshall LM, Nielson CM, Cummings SR, Lapidus J, Cauley JA, Ensrud K, Lane N, Hoffmann PR, Kopperdahl DL, Keaveny TM J Bone Miner Res. 2009;24(3):475–483.

FE Strength Cutoffs* Task Group

E. Orwoll MD, S Khosla MD, S Amin MD, T Lang PhD, J Keyak PhD, T Keaveny PhD, D Cody PhD, JD Sibonga, Ph.D.

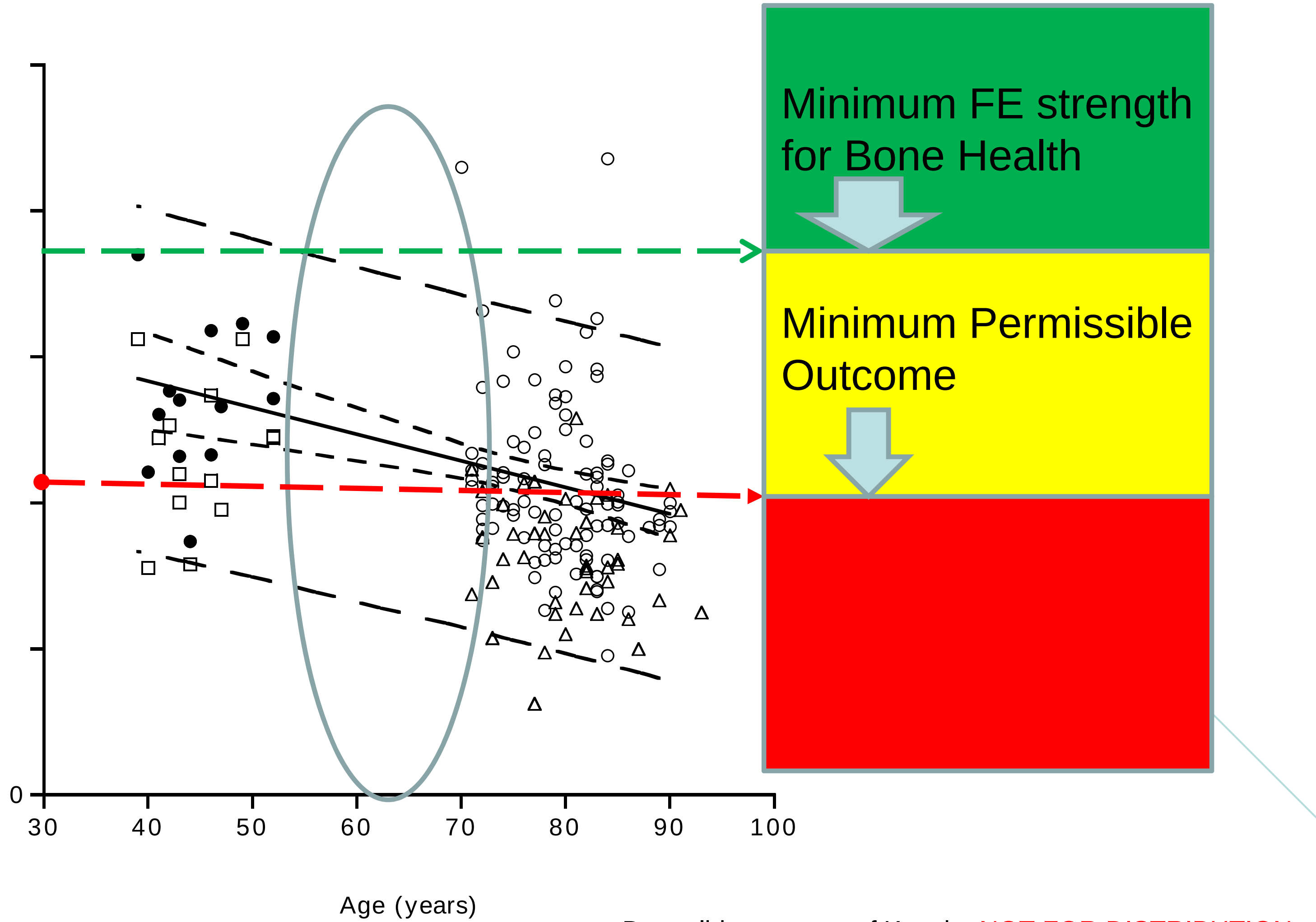


*Red, Yellow and Green Operating Bands

REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

RESEARCH: Selecting FE Cutoffs for “Bone Health”- i.e., hips strong enough to account for declines due to spaceflight and to aging- to be used together with DXA BMD Standards.



REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

Similar approach proposed for terrestrial medicine.

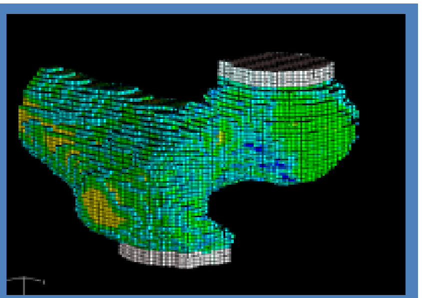
Improving Bone Quality Assessment
Biomarkers Consortium Project

Dennis Black, Ph.D.
Gayle Lester, Ph.D.
Federal Working Group on Bone Diseases
May 1, 2013

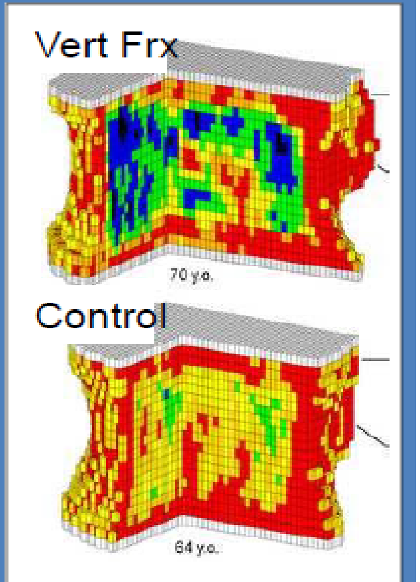
1

A new surrogate/patient management

Estimating bone strength by QCT-based finite element analysis (FEA)



- Standard engineering approach to evaluate mechanical behavior of complex structures
  - Integrates material & structural info from 3D QCT scans
  - Can provide multiple strength metrics
- Cadaver studies show that FEA predicts bone strength better than DXA-BMD
- Has been used *in vivo* to assess effect of treatments on bone strength and to predict fracture risk in untreated subjects



Melton, et al, JBMR 2008

Summary

- DXA –may be underestimating fracture probability and poorly estimating countermeasure efficacy for the astronaut population.
- Bone Discipline Research in progress to test QCT as a surveillance technology and to derive new cut-points for baseline bone health based upon finite element modeling.
- Bone Summit Panel is trying to formulate a therapeutic course of action, and the optimal timing of intervention.
- Leveraging Level 4 Evidence (expert opinion) from Bone Summit Panel as a means of defining and managing skeletal risks in astronauts in the absence of fracture evidence.

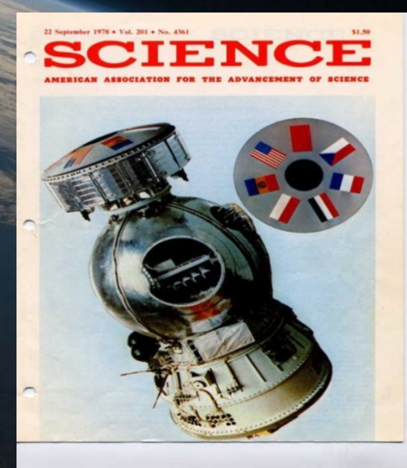
Thank you.

Acknowledgements

NASA & EXTRAMURAL

- Shreyasee Amin, M.D. (Mayo Clinic)
- Adriana Babiak-Vasquez (NASA JSC)
- Craig Kundrot (NASA JSC)
- Harlan J. Evans, Ph.D. (NASA JSC)
- Joyce H. Keyak; Ph.D. (UC Irvine)
- Thomas F. Lang; PhD. (UC San Francisco)
- Adrian D. LeBlanc, Ph.D. (USRA)
- Jerry Myers, Ph.D. (NASA GRC)
- Robert Ploutz-Snyder, Ph.D (NASA JSC)
- Clarence Sams, Ph.D (NASA JSC)
- Richard Scheuring, M.D. (NASA JSC)
- Linda C. Shackelford, M.D. (NASA JSC)
- Scott A. Smith (NASA JSC)
- Scott M. Smith, Ph.D. (NASA JSC)
- Elisabeth R. Spector (NASA JSC)
- Robert Wermers, M.D. (Mayo Clinic)

Emily Morey-Holton, Ph
David J. Baylink, M.D.



Backup Slides

The bridge as a metaphor for bone.

Official Minnesota Department of Transportation investigation photo of the I-35W bridge collapse in Minneapolis, taken Aug. 3, 2007.

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Endocrine disorders		
Adrenal insufficiency	Diabetes mellitus	Thyrotoxicosis
Cushing's syndrome	Hyperparathyroidism	
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
GI surgery	Pancreatic disease	
Hematologic disorders		
Hemophilia	Multiple myeloma	Systemic mastocytosis
Leukemia and lymphomas	Sickle cell disease	Thalassemia
Rheumatic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Miscellaneous conditions and diseases		
Alcoholism	Emphysema	Muscular dystrophy
Amyloidosis	End stage renal disease	Parenteral nutrition
Chronic metabolic acidosis	Epilepsy	Post-transplant bone disease
Congestive heart failure	Idiopathic scoliosis	Prior fracture as an adult
Depression	Multiple sclerosis	Sarcoidosis

tors in Patients

Skeletal fragility

Fracture Probability

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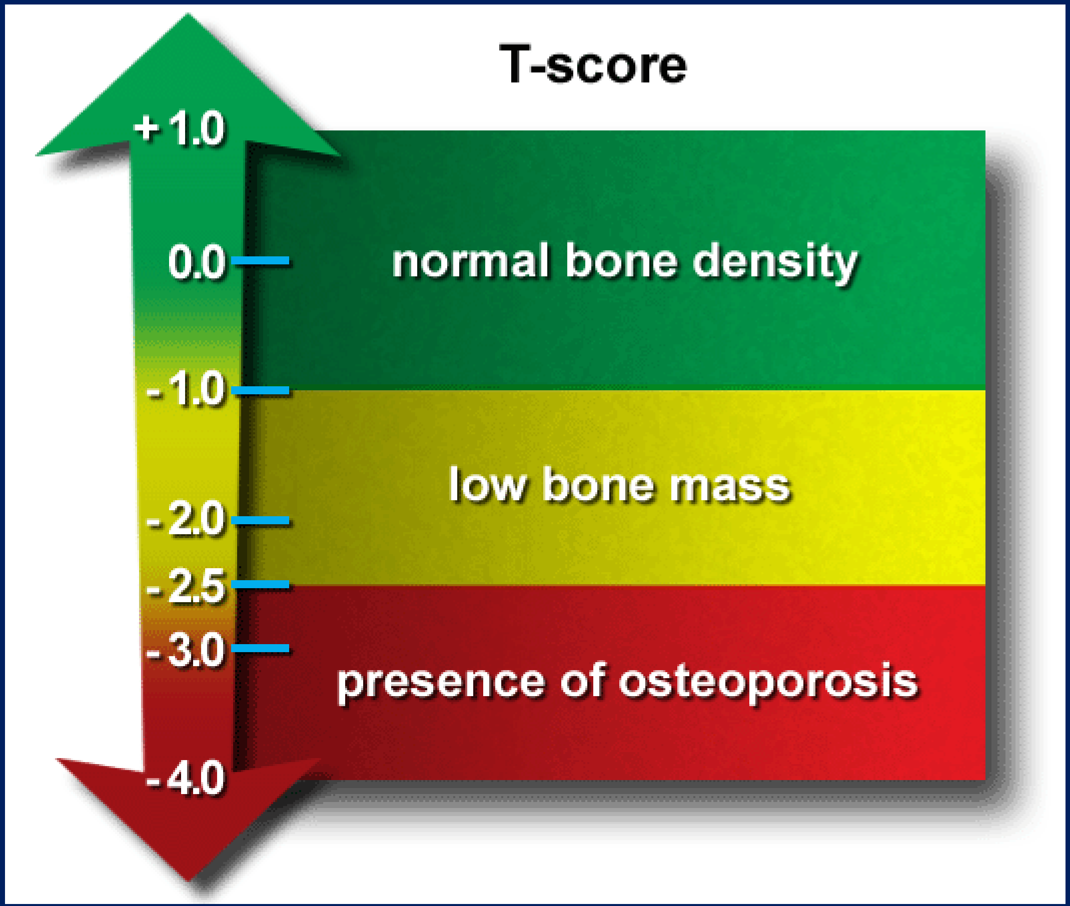
Adapted from: Pathogenesis of Osteoporosis-Related Fractures (NOF) Cooper C

Bone fragility is influenced by factors that are not detected by DXA BMD.

BMD accounts for 50-70% bone strength



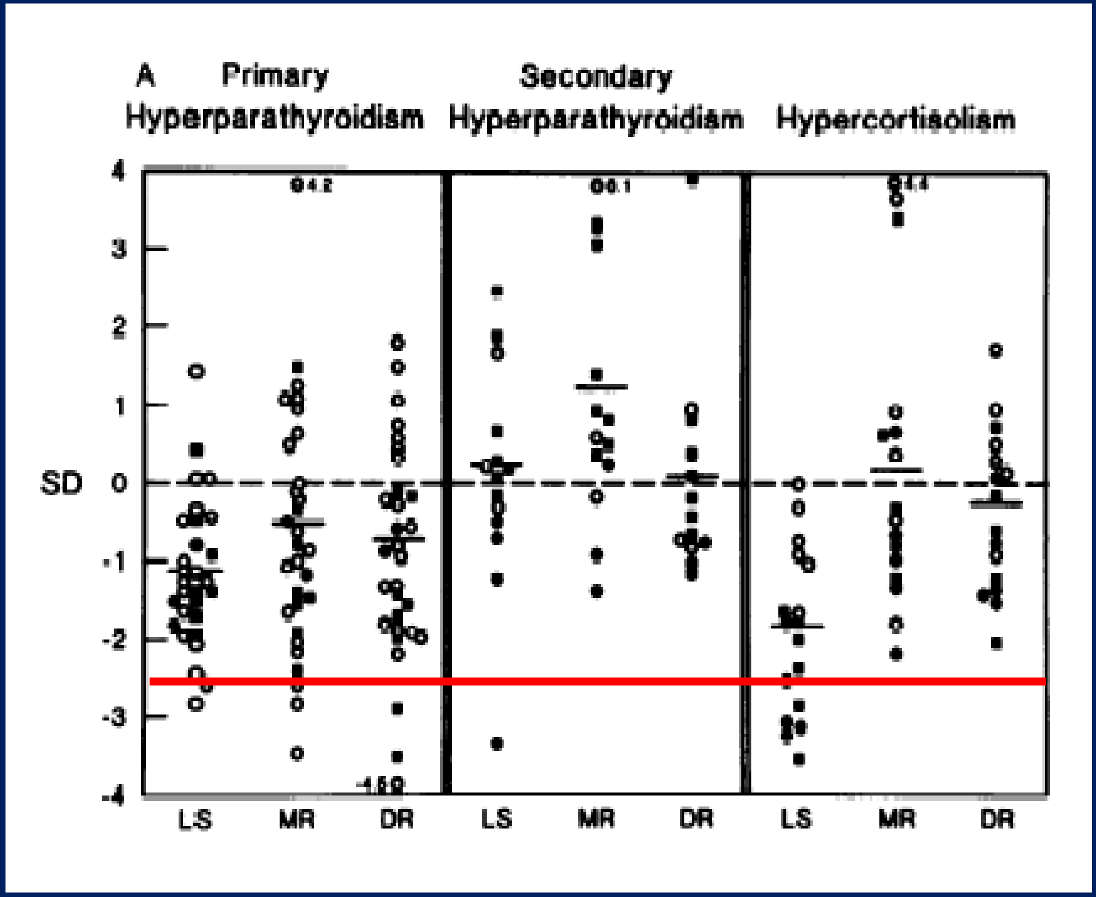
Disconnects discovered In population studies.

FRACTURE CASES

NON FRACTURES

Dual Photon Absorptiometry DPA)

- Differences in patterns of bone "loss" (cortical vs. trabecular) for different diseases…



Seeman, JCI 1992
Slide courtesy of Dr. Amin, MD

QCT provides useful information re: causation of hip fracture, evaluation of hip fracture risk and possible targets for intervention.

TABLE 4. HRs OF MULTIVARIATE MODELS OF SKELETAL PARAMETERS AT THE FEMORAL NECK FOR HIP FRACTURE ADJUSTED FOR CLINIC SITE, AGE, AND BODY MASS INDEX

	Model A (HR per SD decrease)			*Model B (HR per SD decrease)*			*Model C (HR per SD decrease)*		
	HR	*95% CI*	*p*	*HR*	*95% CI*	*p*	*HR*	*95% CI*	*p*
Trabecular bone, volumetric BMD (g/cm^3)	—			1.65	1.15, 2.37	0.007	1.29	0.84, 1.98	0.250
Percent cortical volume	—			3.19	2.23, 4.57	<0.001	2.42	1.56, 3.76	<0.001
Minimum cross-sectional area (cm^2)	—			1.59	1.24, 2.05	<0.001	1.48	1.14, 1.94	0.004
Areal BMD from DXA (g/cm^2)	4.13	2.67, 6.38	<0.001	—			1.91	1.06, 3.46	0.033

Area under the ROC curve for Models A, B, and C were 0.853, 0.855, and 0.860, respectively.

QCT + FEM has superior capabilities for estimating mechanical strength of ex-vivo specimens.

QCT estimates fracture loads better than DXA

QCT + FEM has superior capabilities for estimating fracture loads

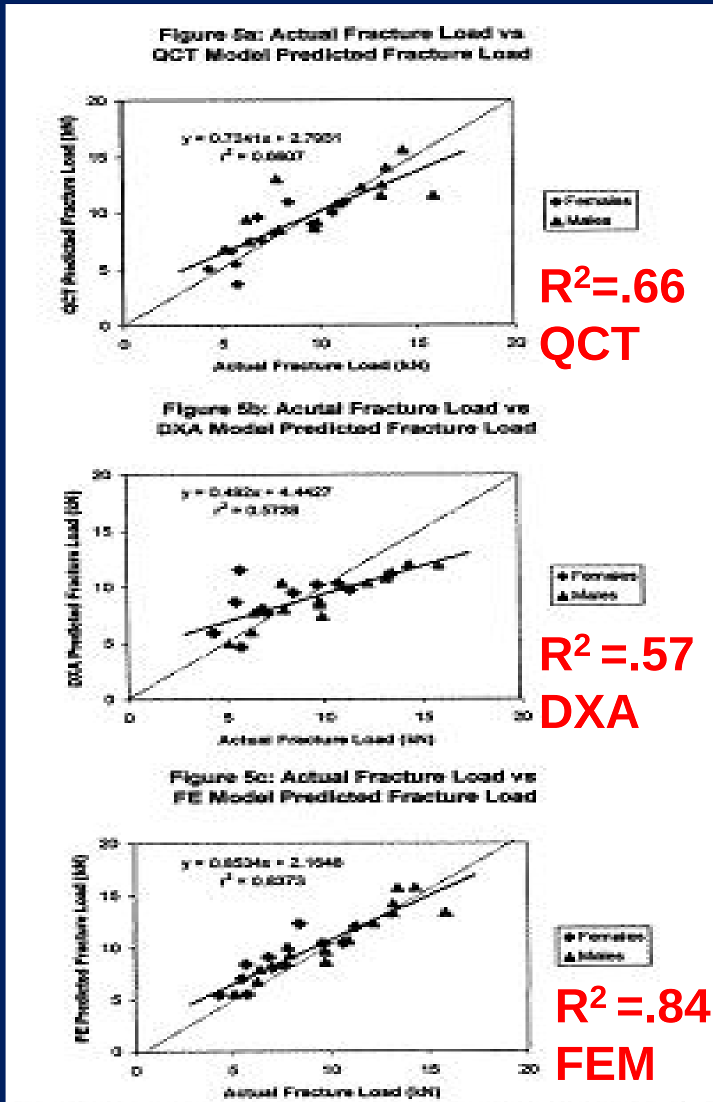


Fig. 5. The predicted strength of the specimens in the test set (developed from the models generated using the training set) plotted against their actual measured values for each of the three methods (a: QCT; b: DXA; c: FEM).

DD Cody: Femoral strength is better predicted by finite element models than QCT and DXA. J Biomechanics 32:1013 1999.

Astronaut Data– Reductions in Hip Strength with spaceflight.

N=11 crewmembers

Loading Condition	Mean (SD) Pre-flight	Mean (SD) Post-flight	*p*
Stance	13,200 N (2300 N)	11,200 N (2400 N)	<0.001
	2.2% loss/month		
Fall	2,580 N (560 N)	2,280 N (590 N)	0.003
	1.9% loss/month		

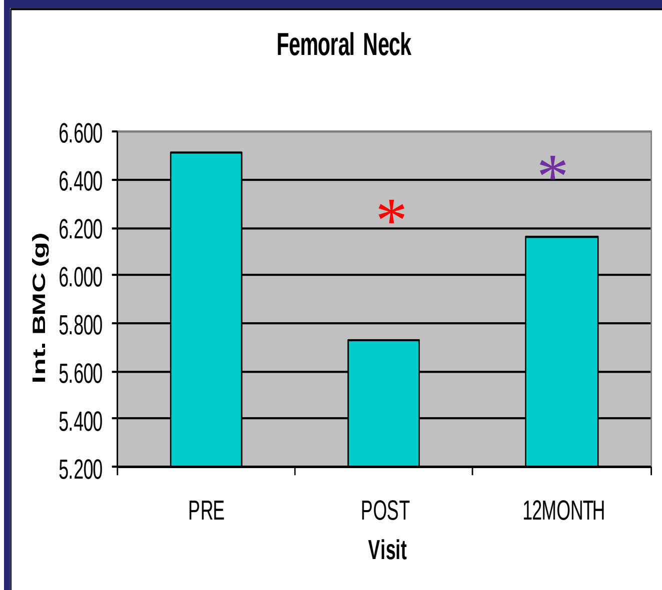
Research: QCT detects different rate of vBMD loss in separate bone compartments of hip. (n=16 ISS volunteers)

Index DXA	%/Month Change ± SD	Index QCT	%/Month Change ± SD
aBMD Lumbar Spine	1.06±0.63*	Integral vBMD Lumbar Spine	0.9±0.5
		Trabecular vBMD Lumbar Spine	0.7±0.6
aBMD Femoral Neck	1.15±0.84*	Integral vBMD Femoral Neck	1.2±0.7
		Trabecular vBMD Femoral Neck	2.7±1.9
aBMD Trochanter	1.56±0.99*	Integral vBMD Trochanter	1.5+0.9
*p<0.01, n=16-18		Trabecular vBMD Trochanter	2.2+0.9

LeBlanc, J Musculoskelet Neuronal Interact. 2000 ;
Lang , J Bone Miner Res, 2004;

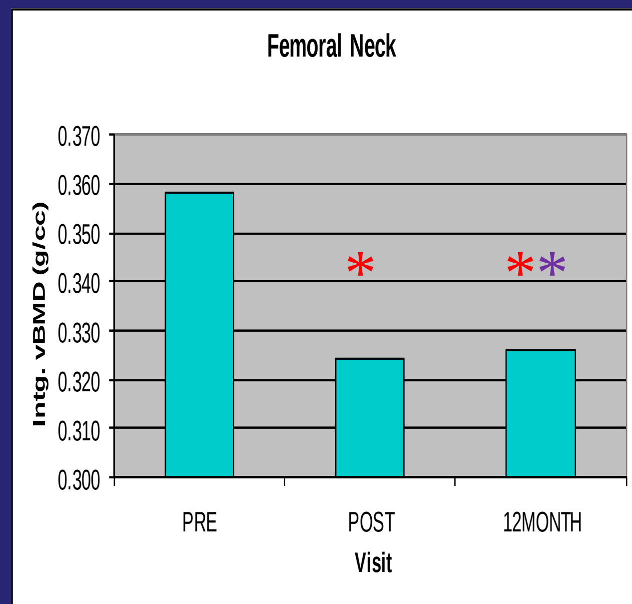
QCT Postflight – Changes in Femoral Neck structure detected 12 months after return

Bone Mineral Content
(g)



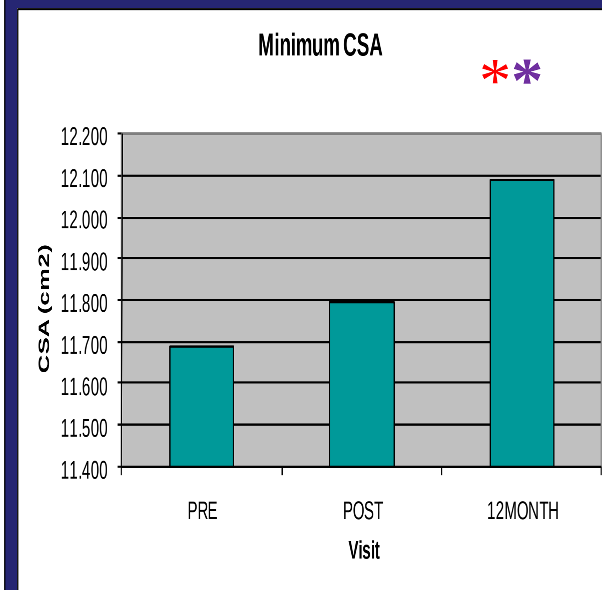
Pre Post 12

Volumetric Bone Mineral Density
g/cm^3



Pre Post 12

Minimum Cross-sectional Area
cm^2



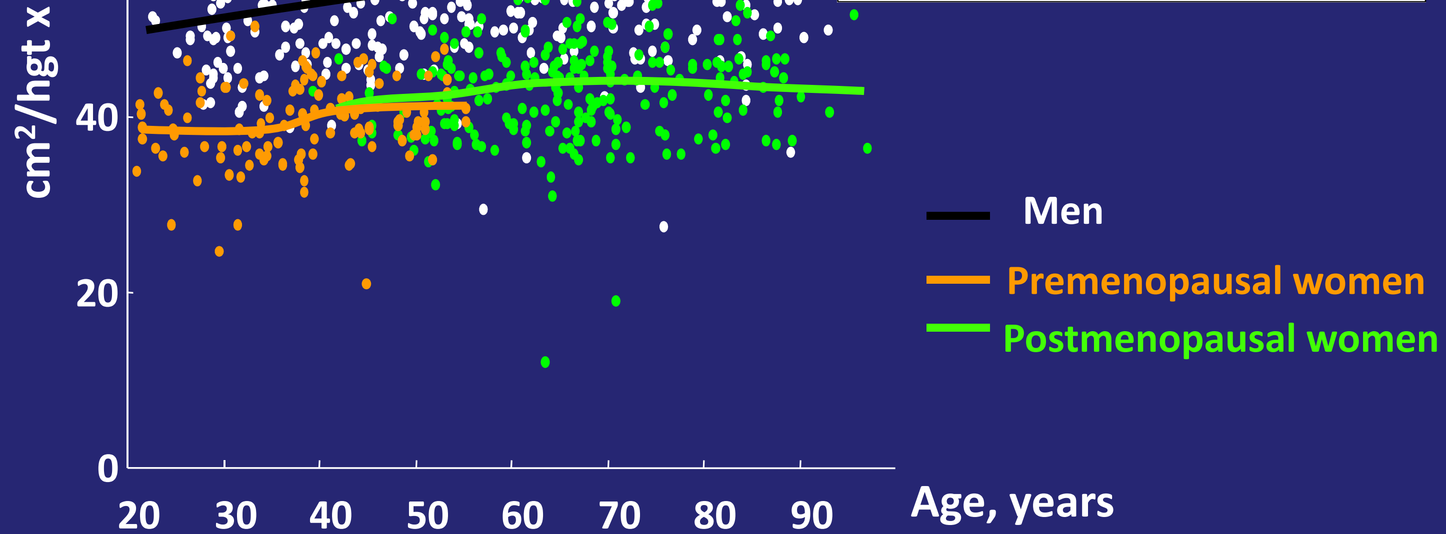
Pre Post 12

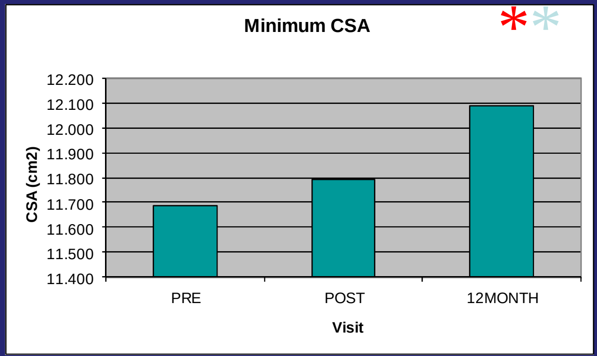
P < 0.05 with respect to preflight*, **postflight***

Slide adapted from T. Lang., JBMR 2006.

QCT in Population Study: Age-related Changes

Suggests that femoral neck total area increases by outward displacement when cortex thins with age

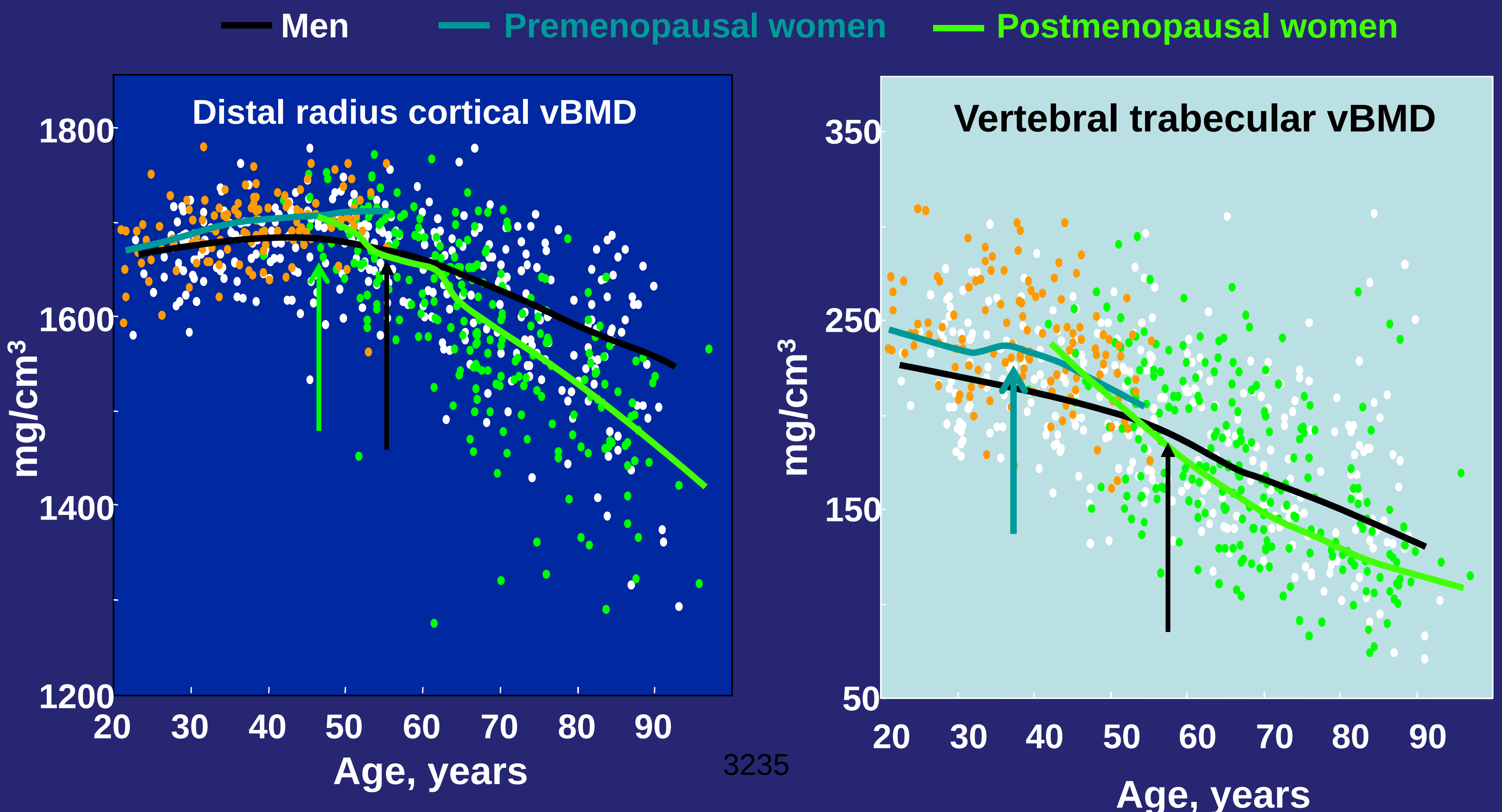




Riggs et al. JBMR19:1945, 2004.

AGE-REGRESSIONS: Bone loss occurs at earlier age than expected.

Riggs et al. JBMR19:1945, 2004.



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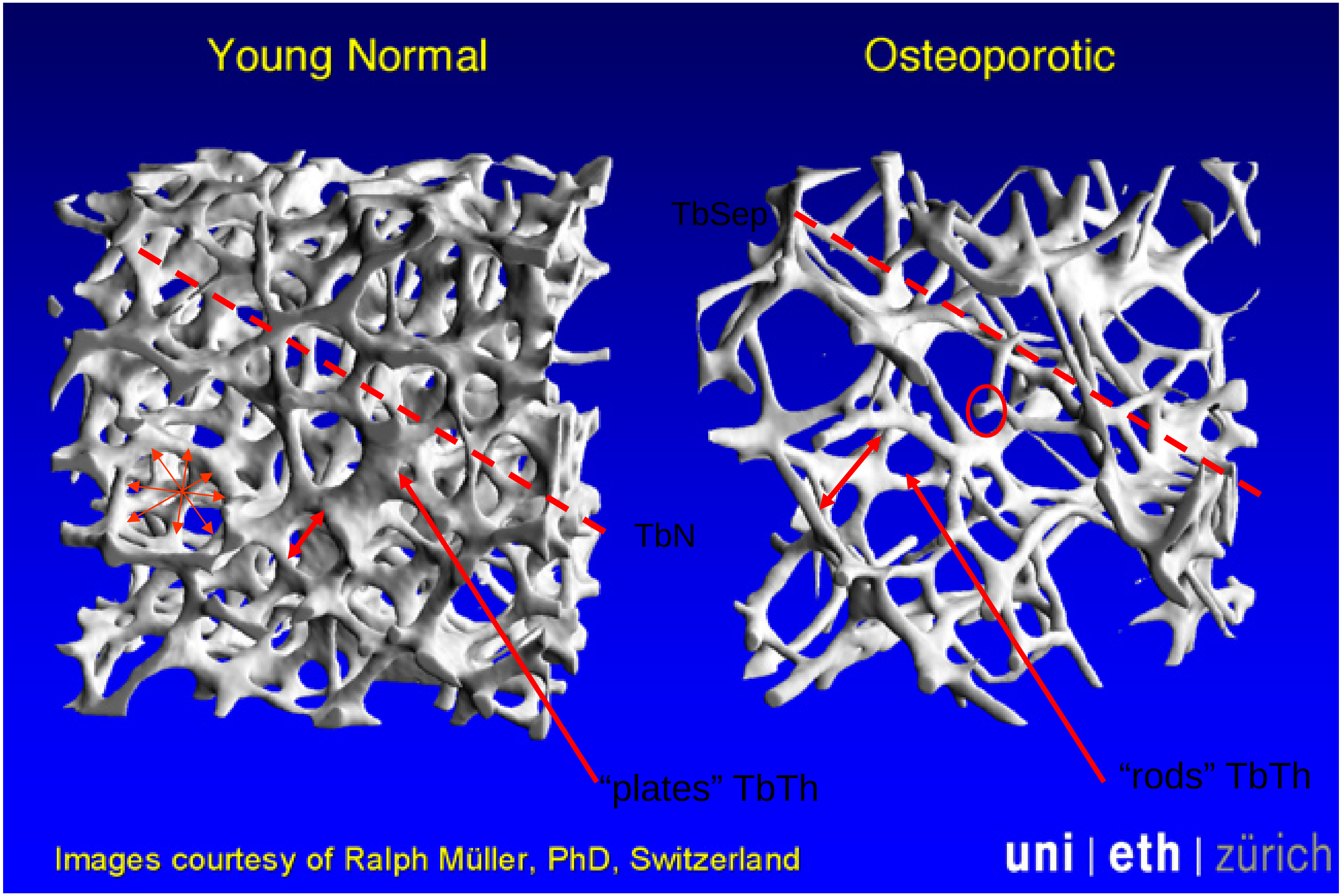
Microarchitectural Measures of Trabeculae and of Spatial Orientation



Adapted

Hip QCT Study

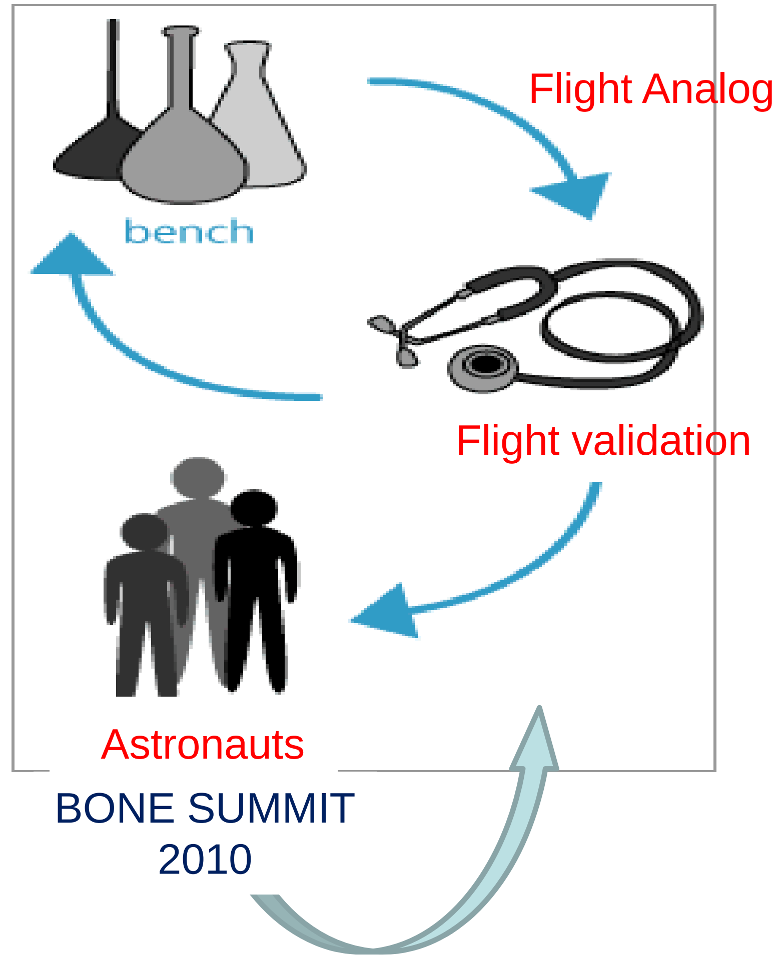
1. **Purpose of Hip QCT Surveillance is to implement recommendations of a clinical advisory panel of osteoporosis experts (Bone Summit 2010).**

2. **Collect specific QCT surveillance data** to develop clinical practice guidelines to recommend to space medicine.

3. **Evaluate recovery** at R+1 y and, if required, R+2 y.

4. **Research Study**: Describe how in-flight countermeasures or how post-flight **activities affect changes in bone strength and recovery**.

Translational Research @ NASA



Characterizing Bone Loss in Space