Risk for Early Onset Osteoporosis in *Long-duration* Astronauts due to Spaceflight

Requirement for Developing Clinical Practice Guidelines for Astronauts

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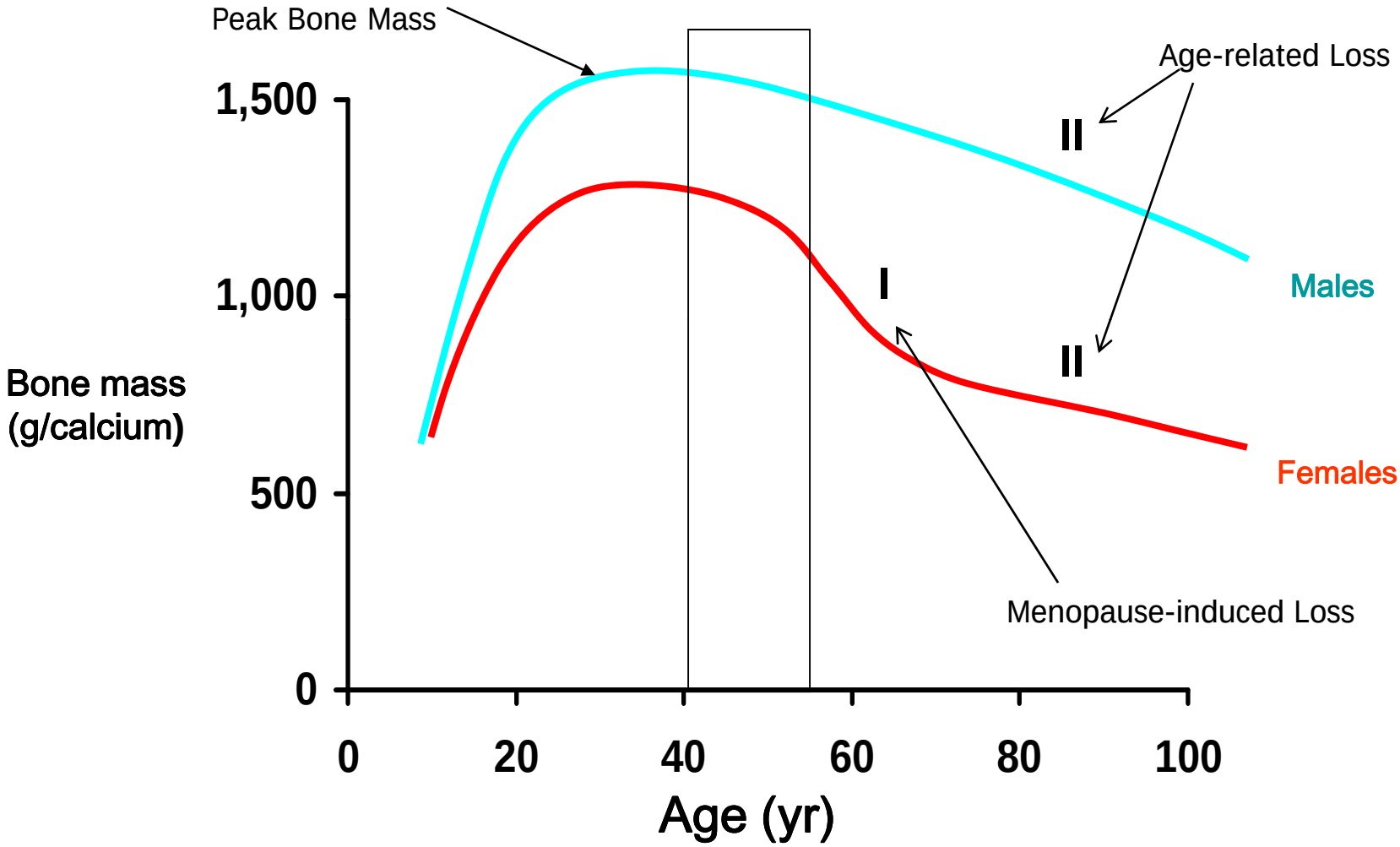
Disclosure Information

82nd Annual Scientific Meeting
Speaker's Name Here

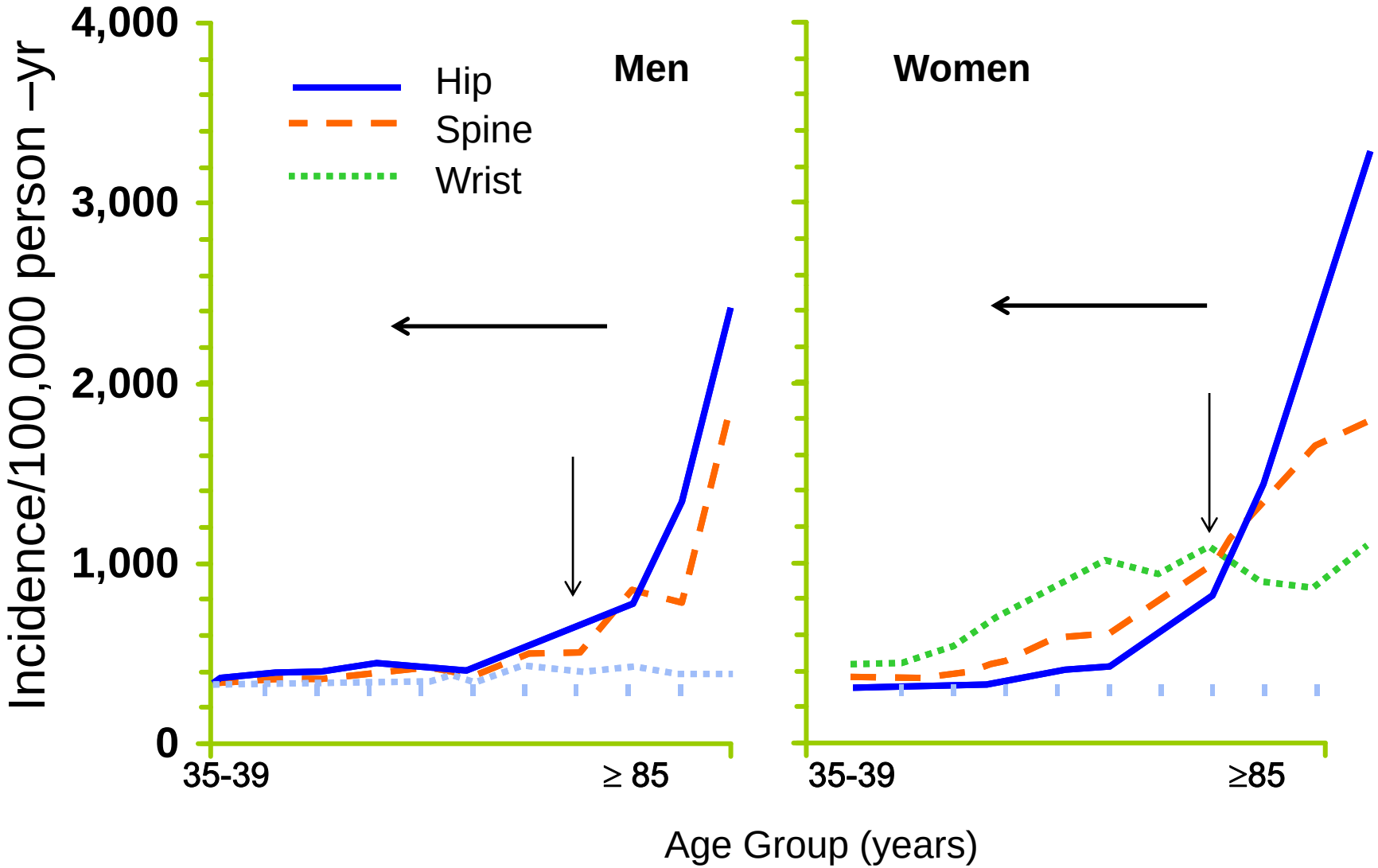
I will discuss the following off-label use and/or investigational use in my presentation: Quantitative Computed Tomography.

Does spaceflight result in irreversible changes to bone that combine with age-related losses?



Riggs BL, Melton LJ: Adapted from
Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Consequence: Premature Fractures?



SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic

Cooper and Melton, 1992

Perception: Subclinical data may not justify some RESEARCH, particularly studies which may introduce greater risk/benefit.

RMAT drives the need for a forum to communicate the UNCERTAINTIES to Space Medicine.

Why does this uncertainty exist?

- DXA BMD **T-score:** *Widely-applied* **surrogate** for bone strength and for fracture risk because grounded in abundance of population-based fracture data.
- Provides a *relative* risk for fracture – not enough information to assess *probability* fracture per *individual* which has greater clinical utility – the "so what?" question.
- Bone strength is influenced by factors that are not measured by DXA BMD (population data).
- Limitations of DXA technology
- Understudied cohort: younger, predominantly male, astronauts who are exposed to unique risk factor – spaceflight.*

Reported “Disconnects” and Limitations of DXA BMD

- **Riggs BL** et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 322(12):802-809, 1990.
- **Riggs BL** et al. Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. J Bone Miner Res. 9(2):265-275, 1994.
- **Cummings SR** et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998 280(24):2119-2120.
- **Gutteridge DH** et al. A randomized trial of sodium fluoride (60 mg) +/- estrogen in postmenopausal osteoporotic vertebral fractures: increased vertebral fractures and peripheral bone loss with sodium fluoride; concurrent estrogen prevents peripheral loss, but not vertebral fractures. Osteoporosis Int 13(2):158-170, 2002.
- **Black DM** et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 349(13):1207-1215, 2003. (DXA does not pick up significant impact of PTH detected by QCT.)
- **Chesnut CH** et al. Effects of salmon calcitonin on trabecular microarchitecture as determined by magnetic resonance imaging: results from the QUEST study. J Bone Miner Res. 2005 Sep;20(9):1548-61.
- **Lang T** et al. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Miner Res. 2004 Jun;19(6):1006-12.

After 40+ years in space, bone risk remains poorly understood.

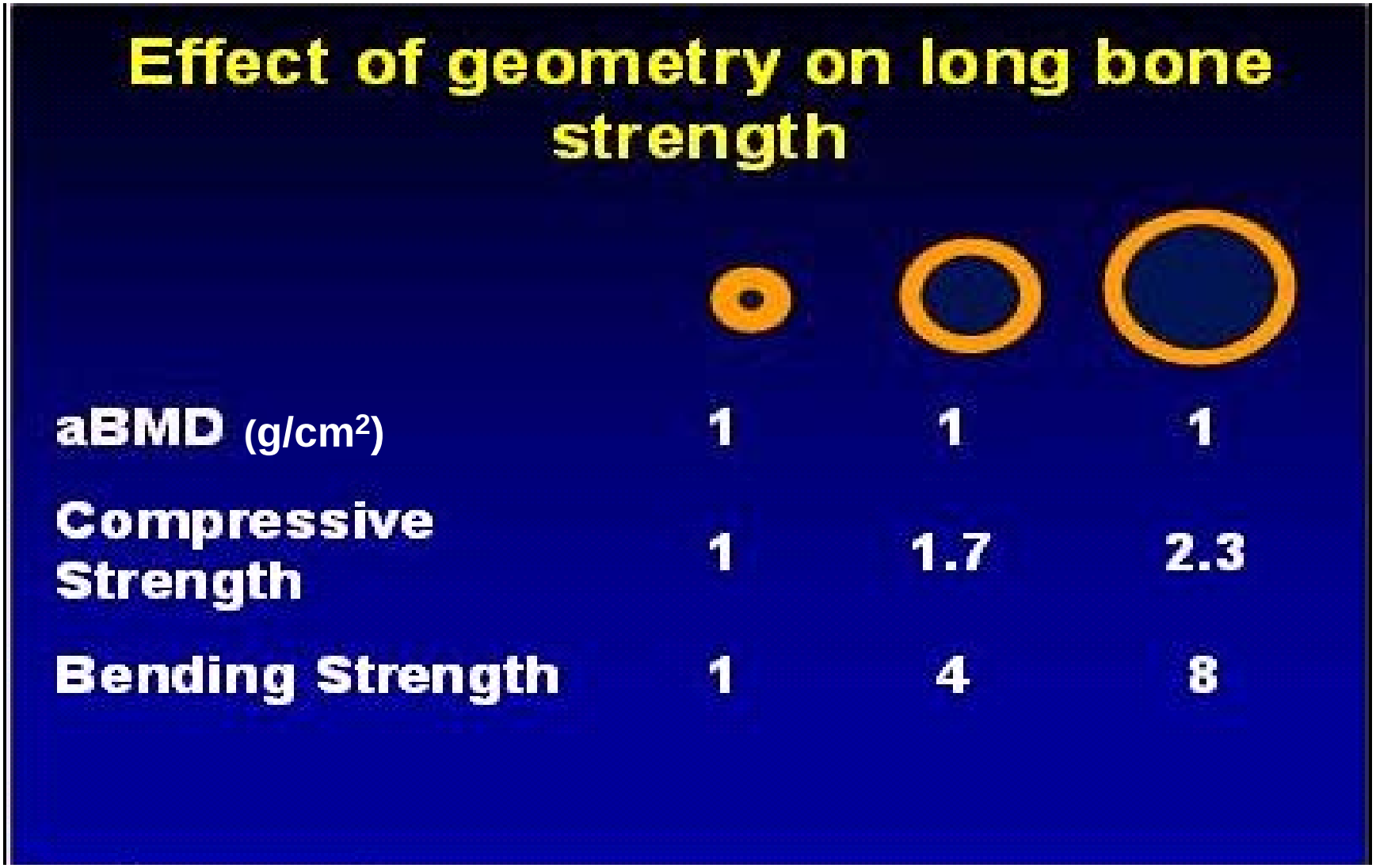
- "Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality."

JAMA. 2001

- "….Bone quality, in turn, is stated to refer to architecture, turnover, damage accumulation, (e.g., microfractures) and mineralization…."

Osteoporosis Int. 2002

One limitation: DXA does not account for different bone geometries.



Mary Bouxsein, Ph.D. Bone Geometry and Skeletal Fragility, May 2005

Why does this uncertainty exist?

- Widely-applied index for bone strength and fracture risk (DXA BMD T-score) grounded in abundance of population-based fracture data.
- Provides a *relative* risk for fracture – not enough information to assess *probability* fracture per *individual* which has greater clinical utility – the “so what?” question.
- Bone strength is influenced by factors that are not measured by DXA BMD.
- Limitations of DXA technology
- Understudied cohort: younger, predominantly male, astronauts who are exposed to unique risk factor – spaceflight.*

DXA BMD @ Johnson Space Center

- Monitor astronaut skeletal health
- Characterize skeletal effects of spaceflight
- Evaluate efficacy of in-flight countermeasures
- Verify restored health status

Does Medical Operations need a "new line in the sand" for skeletal integrity? YES

RMAT – Index for Skeletal Integrity

- **Human Health and Performance Standard**
  - ***HOW STRONG DO BONES HAVE TO BE AND HOW LOW CAN IT GO TO PERFORM MISSION TASKS? TO AVOID PREMATURE AGE-RELATED FRACTURES?***
- **Selection & Retention**
  - ***WHAT IS THE CUTOFF RANGE FOR FLIGHT IN LIGHT OF EXPECTED SKELETAL ASSAULT WITH SPACEFLIGHT? Specific architecture***
- **Clinical Risk Trigger(s)**
  - ***WHAT IS THE PHYSIOLOGICAL MEASURE THAT REQUIRES A CLINICAL RESPONSE or INTERVENTION?***
- **Current Mitigation Strategy**
  - ***WHAT INDEX FOR EFFICACY?***

Bone Summit Activity
to recommend clinical practice guidelines for risk management.

- Review ALL information* on individual basis that would assist clinical experts to understand

1) Why BMD changes in long-duration astronaut,

2) How those changes may relate to the spaceflight

3) How those changes may influence the probability for fracture: 1) premature age-related fractures and 2) fractures with *typical preflight* physical activity

- *All of these requirements could not be met. Still, Bone Summit provides opportunity to recommend forward actions*

Requirements for a Bone Summit Panel

- Specific expertise
- ✓ BMD in clinical practice
- ✓ Leaders in field and policy-makers
- ✓ Clinical expertise: male osteoporosis, bone turnover markers, bone epidemiology, endocrinology, exercise, vitamin D

- Add photo

Overarching themes that influenced panel recommendations.

1. Unlikely for NASA to obtain the volume of data normally required to formulate bone health policies.

2. Rare, poorly understood health risk in an unique population because of the very limited dataset.

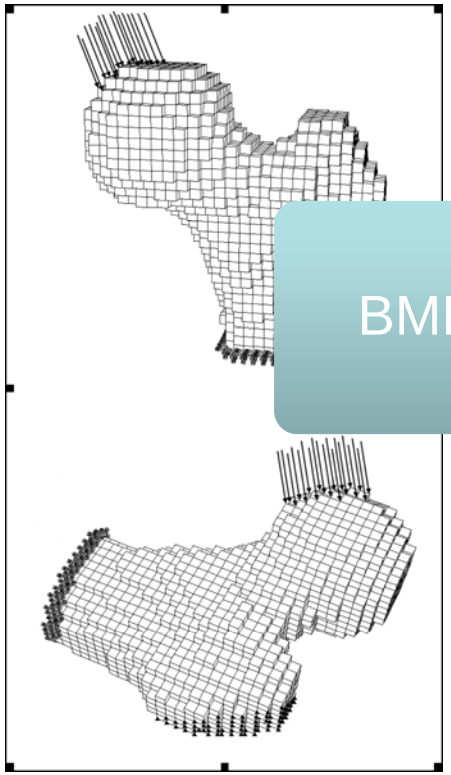
3. Surveillance data required to increase the understanding of spaceflight effects and reduce uncertainty re: probability of fracture.

Given NASA's constraints, these may be circumstances by which research technologies and analyses are transitioned to the clinical realm.

Recommendation: Index for decision-making (i.e., medical standards) based upon estimates of strength not surrogate measure, e.g., BMD.

How should bone strength be estimated?

Estimate hip bone strength by Finite Element Modeling (a computational tool).



Geometry

Material Properties

BMD

Finite Element Strength

Loading

Individualized Fracture Risk

Keyak et al, 1998, 2001, 2005

Slide courtesy of P. Truszkowski

FEM – a computational tool that uses QCT data to estimate Hip bone strength

QCT estimates fracture loads better than DXA

QCT + FEM has superior capabilities for estimating fracture loads

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

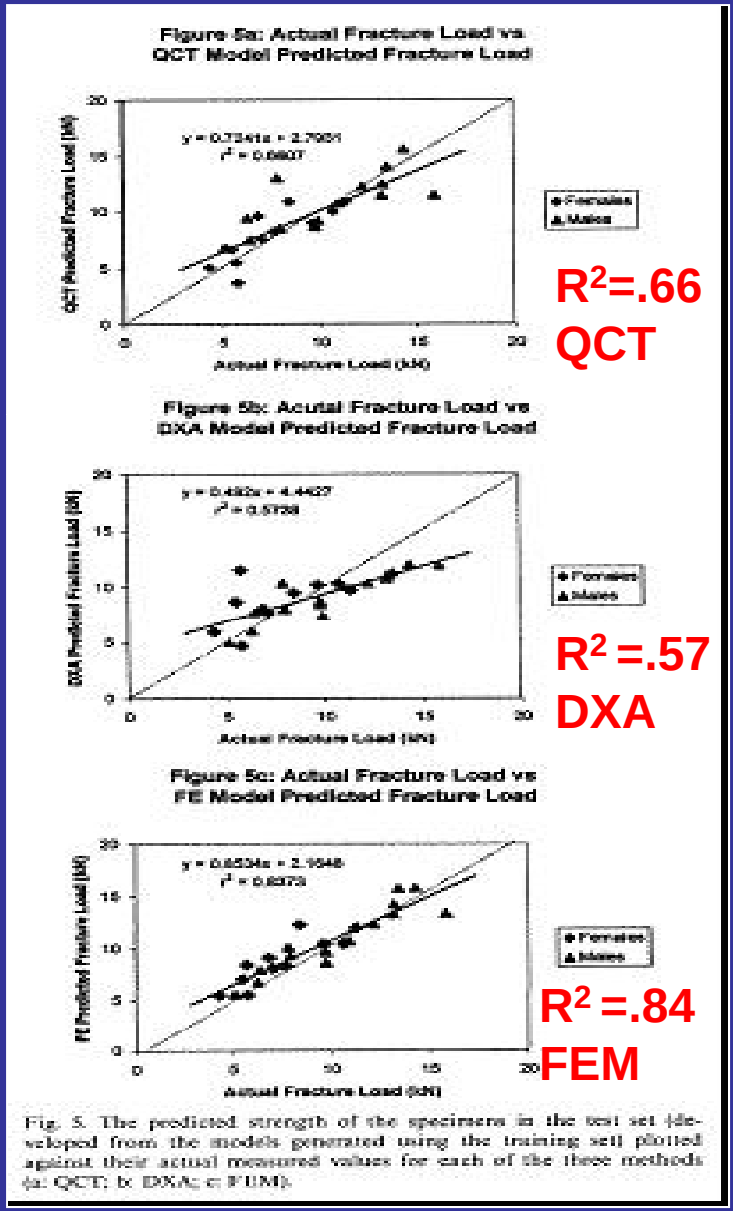
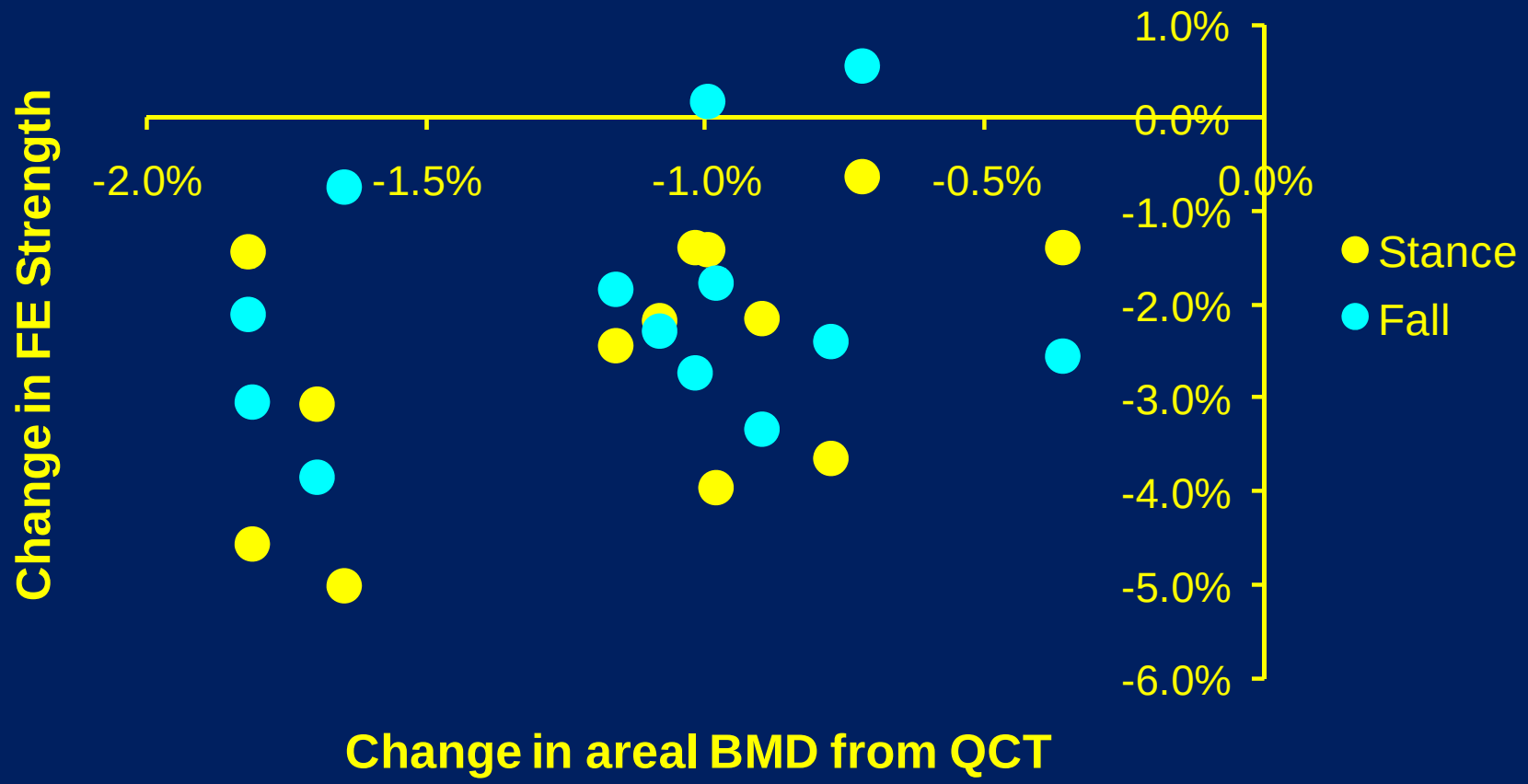


Fig. 5. The predicted strength of the specimens in the test set (developed from the models generated using the training set) plotted against their actual measured values for each of the three methods (a: QCT; b: DXA; c: FEM).

Astronaut Data: Surrogates of 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.

Summary & Conclusion

- Multiple levels of uncertainty with NASA's current assessment of skeletal integrity
- The RMAT-the driver to identify a clinical trigger and ultimately, to develop an index for skeletal integrity
- Required RMAT indices led to Action to convene Bone Summit Panel for clinical practice recommendations to manage occupational risks
- NASA needs to consider innovative research technology and analyses (with translation to fracture risk) to improve its estimation of fracture probability in LD astronauts.

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NASA BONE SUMMIT PANEL 6/2010

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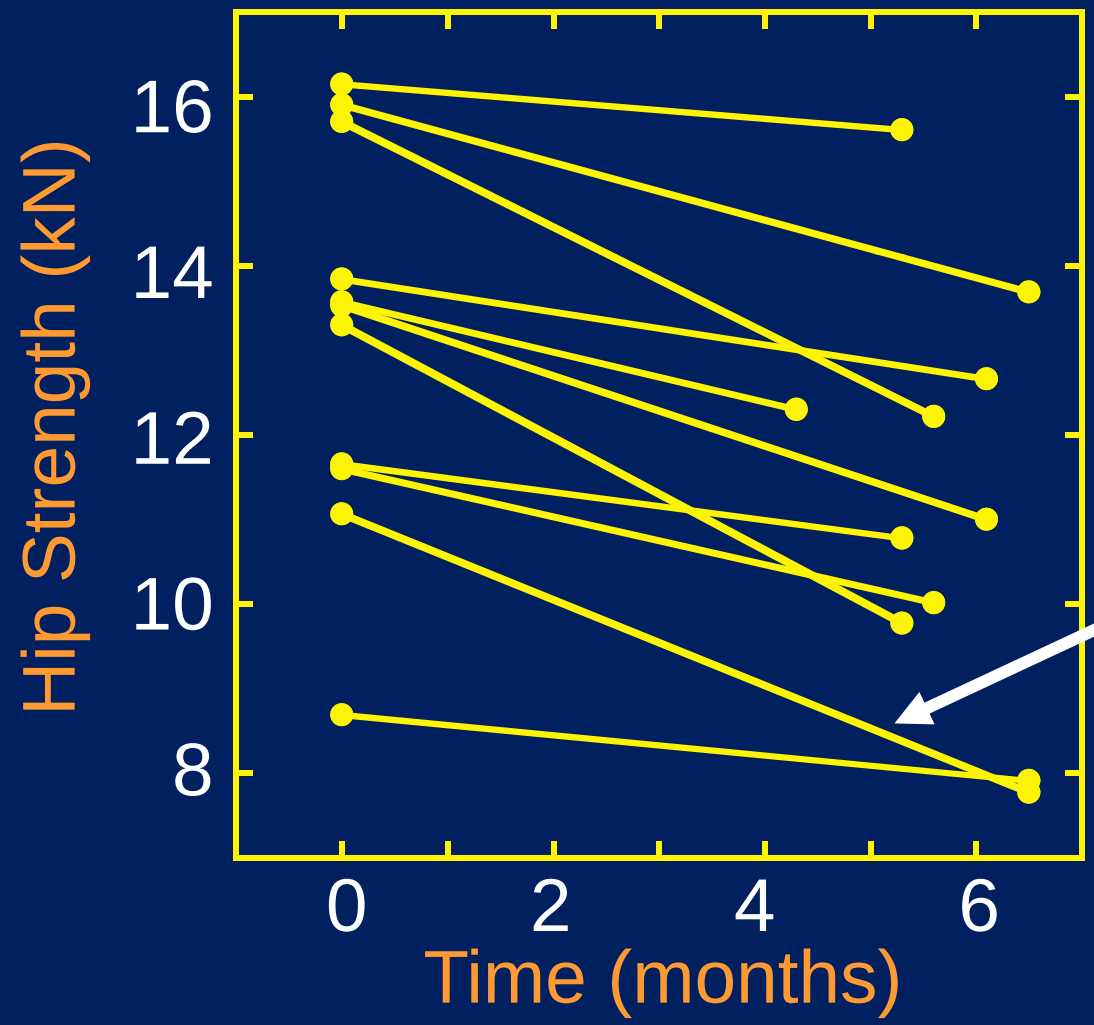
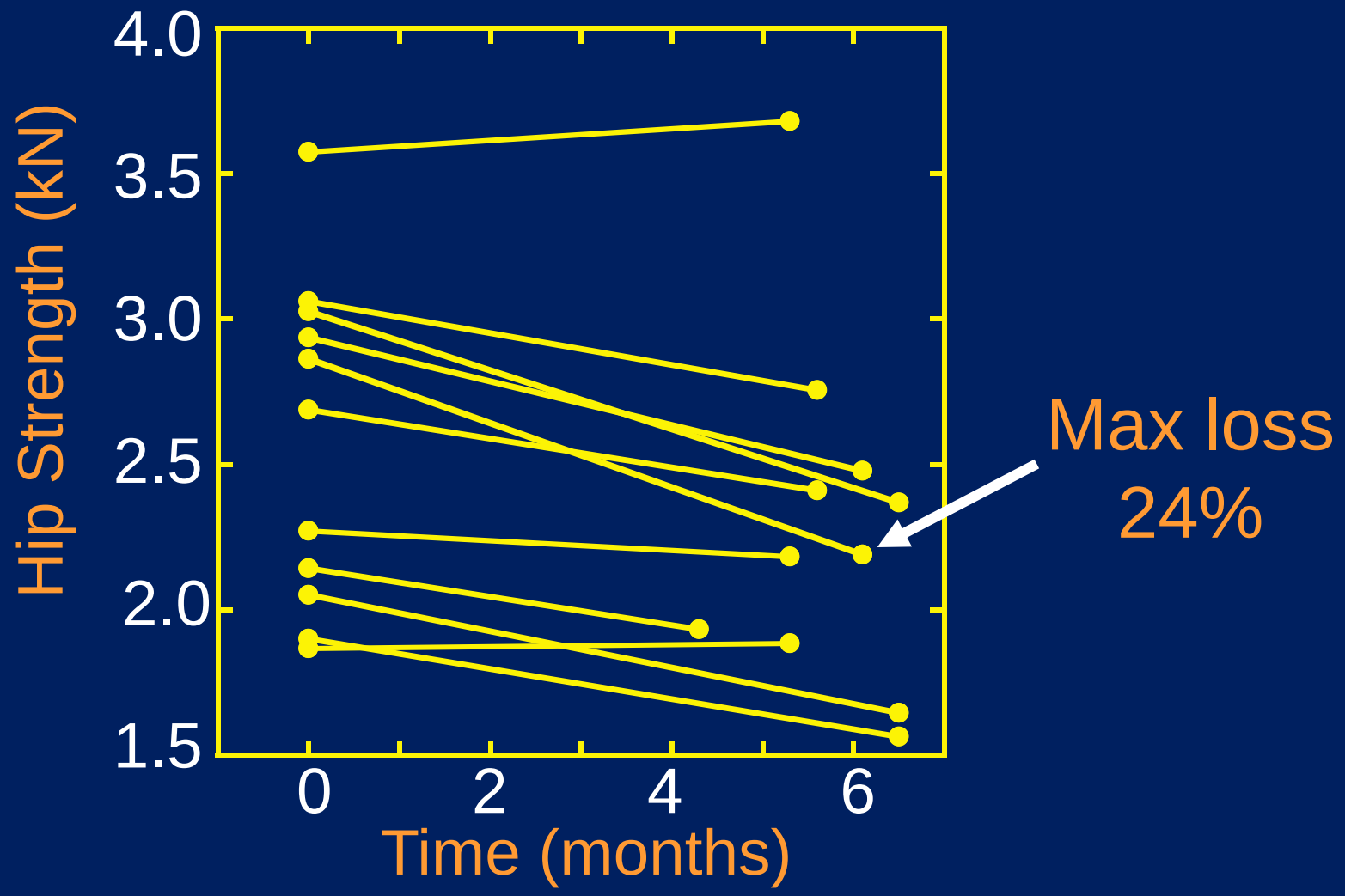
- Steven Petak, MD, JD, FACE
- Sue Shapses, PhD
- Mehrsheed Sinaki, MD, MS
- Nelson B. Watts, MD

Individual Results from ISS Stance Loading (4 to 30% loss in strength)

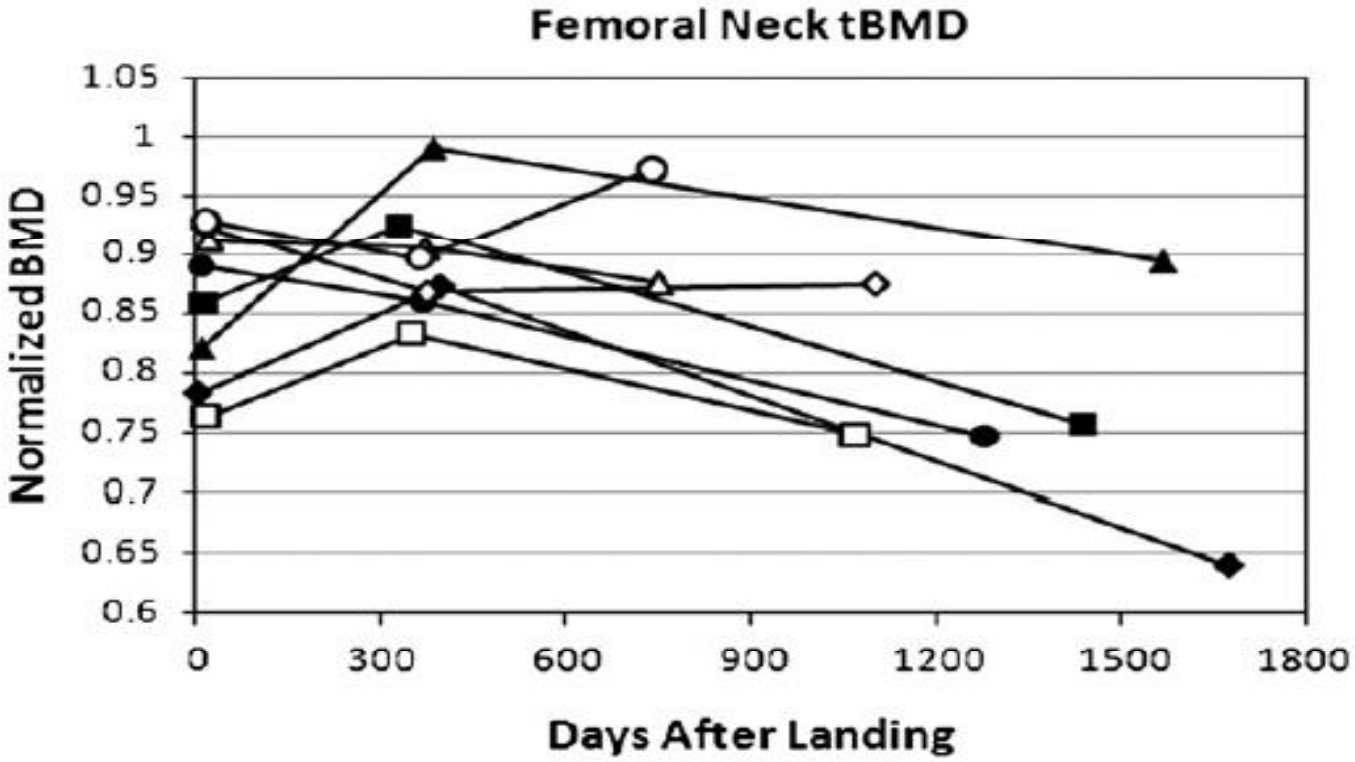


Max loss 30%

Individual Results from ISS Fall Loading (3 gain to 24% loss in strength)



QCT: Trabecular BMD at Femoral neck does not appear to show a recovery 2 to 4 years postflight



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