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

Requirement for Developing Clinical Practice Guidelines for Astronauts

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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?

Incidences/100,000 person–yr

Hip
Spine
Wrist

Men

Women

Age Group (years)

Cooper and Melton, 1992

SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
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


- **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.

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.

Effect of geometry on long bone strength

| aBMD (g/cm²) | 1 | 1 | 1 |
| Compressive Strength | 1 | 1.7 | 2.3 |
| Bending Strength | 1 | 4 | 8 |

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**
  - **What is the physiological measure that requires a clinical response or intervention?**

- **Clinical Risk Trigger(s)**
  - **What index for efficacy?**

- **Current Mitigation Strategy**
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

• Add photo

• 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
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).


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.
Astronaut Data: Surrogates of bone strength do not correlate.

Change in areal BMD from QCT

Stance: R²=0.23
Fall: R²=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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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.