Bone Changes During Spaceflight: The Path to Risk Reduction

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

April 8, 2014
At the end of this lecture, you should understand:

• The progression of bone research on the path to risk reduction for the human system.

• The view of DXA BMD as a surrogate for fracture risk in terrestrial medicine. Why “loss” is not measured by this test.

• Flight data describing the unique effects of spaceflight on skeletal sites at risk for age-related osteoporosis.

• Bold research approaches to a hip fracture surrogate in the context of NASA’s constraints.
Characterizing Bone Changes in Space

Mercury 1961-63
Gemini 1965-66
Apollo 1968-72
Skylab 1973-74
Shuttle 1981-2010
Intl Space Station 2000-present

Calcium balance
SPA of heel and wrist

Soyuz/Salyut 1974-85

Mir 1986-2000

SPA
Urine, fecal Ca
Heel, Wrist

DXA

DXA
QCT
pQCT
BTO

DXA=Single Photon Absorptiometry
DXA=Dual-energy X-ray Absorptiometry
QCT=Quantitative Computed Tomography
pQCT = peripheral QCT
BTO=biochemical markers of bone turnover
Skylab-Bone Mineral Density of Calcaneus (vs. wrist)

Skylab-Urinary Calcium Excretion

**Urinary Ca during Skylab**

(Mean + SEM)

-350 -300 -250 -200 -150 -100 -50 0 50 100 150

**Number of Flight Days**

**Urinary Ca after Return from Skylab**

0 10 20

**Days of Reambulation**
Two Functions of the Skeleton

- Internal support for the body
- Attachment for muscles / tendons for motion
- Protects vital organs
- Encloses blood-forming elements in marrow
- Mineral reservoir for Calcium (Ca\(^{2+}\)) homeostasis

*What potential risks to human health & performance?
Four identified “Bone” health risks for exploration missions.

1. Early Onset Osteoporosis (fragility fractures)
2. Bone Fracture (trauma fractures)
3. Formation of Renal Stones
4. Intervertebral Disc Injury (or Damage)
Four Identified “Bone” health risks for exploration missions.

1. Early Onset Osteoporosis

2. Bone Fracture

3. Formation of Renal Stones

4. Intervertebral Disc Injury (or Damage)
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 Sibonga10
1. What additional measure(s) do we need to monitor?
2. How frequently? For how long?
3. How should Med Ops use research data in its clinical practice?

Bone Research @ NASA

BONE SUMMIT 2010 and 2013
Take Home Messages from Bone Summit (2010)

1. Bone is a complicated tissue.
2. NASA has constraints: low subject #’s; slow data acquisition.
3. Astronauts are understudied group.
4. Spaceflight effects on bone are unique.
5. Clinically-accepted tests have limitations.
6. NASA’s medical standards for bone health (based upon terrestrial guidelines) are not applicable to long-duration astronauts.
7. Recommended exploring the transition of research approaches to clinical arena.
Risk: Different types of fractures

“Osteoporotic/Fragility Fractures” – low to atraumatic Fractures due to Osteoporosis (Causality - SKELETAL CONDITION)

You don’t have to be OLD.

Load > Bone Strength = FRACTURE

(Key Causality – BIOMECHANICS)

You don’t have to have OSTEOPOROSIS.
**RISK FOR FRAGILITY FRACTURES:** Does spaceflight result in irreversible changes to bone that combine with age-related losses? Then, what do we measure?

- **Bone mass (g/calcium)**
- **Age-related Loss**
- **Menopause-induced Loss**
- **Peak Bone Mass**

Riggs BL, Melton LJ: Adapted from Involutional osteoporosis

*Oxford Textbook of Geriatric Medicine*

ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
Increased risk in astronauts?
Limited time to count incidence of fractures.

Cooper and Melton, 1992
NASA measures Bone Mineral Density [BMD] by DXA as a surrogate for fracture just as clinical world. –T-scores (Not BMD change). circa 2000
“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 strength is influenced by additional factors that are not measured by DXA areal BMD.
Diagnostic Guidelines Not Meaningful for Astronauts
for peri- and postmenopausal women and men > 50 years.

BMD T-Score Values* Expeditions 1-25 (n=33)
*Comparison to Population Normals

![Graph showing BMD T-Score Values for different body parts and time points before and after space missions.]
Age is important risk factor for bone loss but the utility of BMD for < 50 years not clearly evident.*

Kanis et al JBMR 9(8):1137, 1994

* The use of DXA BMD for surveillance of active astronauts is a unique application.
Risk for osteoporotic fractures is lower at younger ages.

Given the probability of fracture drives the requirement for interventions, the necessity for testing younger aged is not evidence-based.

- Probability of first fracture of hip, distal forearm, proximal humerus, and symptomatic vertebral fracture in women of Malmö, Sweden.

Adapted from:

Slide Courtesy of S. Petak, MD.
Uncertainty exists. Are the long-duration astronauts at risk?

**WHAT COULD BE MEASURED TO DEFINE A RARE RISK IN YOUNGER PERSONS?**
### History of Bone Imaging in Space

<table>
<thead>
<tr>
<th>Year</th>
<th>Mission</th>
<th>Equipment and Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961-63</td>
<td>Mercury</td>
<td>X-ray densitometry</td>
</tr>
<tr>
<td>1965-66</td>
<td>Gemini</td>
<td>SPA heel and wrist</td>
</tr>
<tr>
<td>1968-72</td>
<td>Apollo</td>
<td>SPA heel and wrist</td>
</tr>
<tr>
<td>1973-74</td>
<td>Skylab</td>
<td>DXA whole body, CT of lumbar spine, BMD</td>
</tr>
<tr>
<td>2000-present</td>
<td>ISS</td>
<td>DXA, QCT, HR3DpQCT (ESA)</td>
</tr>
</tbody>
</table>

**1974-85 Soyuz/Salyut**
- SPA
- DPA

**1974-85 Mir**
- DXA whole body
- CT of lumbar spine
- BMD

[Slide courtesy of Mayo Clinic adapted from Dr. Jean Sibonga, NASA JSC]
Measurement of bone mineral in 2-d projection of bone $[\text{BMD}_a]$ g/cm²

- Improved precision; Low radiation; Shorter scan times; BMD measures over multiple skeletal sites
- Validated in numerous population studies for fracture prediction
- Long established, widely-applied surrogate for fracture outcome – become NASA standards, but T-scores give only Relative Risks
**DXA: BMD losses are site-specific and rapid** vs. 0.5 – 1.0 % BMD loss/year in the aged

<table>
<thead>
<tr>
<th>Areal BMD</th>
<th>%/Month Change ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>-1.06±0.63*</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>-1.15±0.84*</td>
</tr>
<tr>
<td>Trochanter</td>
<td>-1.56±0.99*</td>
</tr>
<tr>
<td>Total Body</td>
<td>-0.35±0.25*</td>
</tr>
<tr>
<td>Pelvis</td>
<td>-1.35±0.54*</td>
</tr>
<tr>
<td>Arm</td>
<td>-0.04±0.88</td>
</tr>
<tr>
<td>Leg</td>
<td>-0.34±0.33*</td>
</tr>
</tbody>
</table>

*p<0.01, n=16-18

LeBlanc et al, J Musculoskeletal 2000
Effects of exercise regimens described using DXA BMD

% Change in DXA BMD after Long-Duration Mir and ISS Missions
Mir n=35; ISS IRED n=24; ISS ARED n=11; Bisphos + ARED n=7

Note: No population data linking % BMD loss to Fracture Outcome

* Updated data since 2010 Bone Summit
A Limitation: DXA Cannot distinguish changes in bone size – a contributor to bone strength.

<table>
<thead>
<tr>
<th></th>
<th>Areal (g/cm²)</th>
<th>Compressive Strength</th>
<th>Bending Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>aBMD</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.7</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Mary Bouxsein, Ph.D. Bone Geometry and Skeletal Fragility, May 2005
Exercise changes geometry of whole bone (adult skeleton)- not detected by DXA.


Changes in size, changes in bone strength.
Two Functions of the Skeleton: increasing understanding by biochemistry

- Structural Framework
- Mineral Reservoir
- Resorption Biochemical Markers
- Bone Resorption
- Osteoblasts
- Bone Formation
- Osteoclasts
- Formation Biochemical Markers
- Cellular Basis of Imbalance in Skeletal Remodeling
Serum and urinary biomarkers are by-products of bone turnover and bone cell activity.
Bone breakdown is increased, formation is **uncoupled** from resorption, and bone gain and loss are unbalanced*

Reflects changes in **bone cells** but not **where** bone mass is lost.

*Could lead to net bone loss in skeleton.*
**HIGHLY-REGULATED ACTIONS OF BONE CELLS on BONE TURNOVER.**

Under-filling, over-filling, balanced filling of the bone remodeling unit [BRU] can impact overall structural strength of whole bone (skeletal region).

Remodeling of bone at the level of a single “BRU”

1-2 million BRUs in the adult skeleton
Some insight gained by comparison to Earth-based disorders of increased bone resorption.
Representative manifestation on bone microarchitecture. Clinical test not currently available for hip/spine.

(Mosekilde, 2000; Seeman, 2002; Silva, 1997; Kleerekoper, 1985)
Densitometry & Reported Measurement

DXA reports areal BMD (aBMD)

QCT quantifies volumetric BMD

$\text{g/cm}^2$ averaged for cortical + trabecular bone

$\text{g/cm}^3$ for separate cortical & trabecular bone
Research: QCT detects different rate of vBMD loss in separate bone compartments of hip. (n=16 ISS volunteers)

<table>
<thead>
<tr>
<th>Index (DXA)</th>
<th>%/Month Change ± SD</th>
<th>Index (QCT)</th>
<th>%/Month Change ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>aBMD Lumbar Spine</td>
<td>1.06±0.63*</td>
<td>Integral vBMD Lumbar Spine</td>
<td>0.9±0.5</td>
</tr>
<tr>
<td>Trabecular vBMD Lumbar Spine</td>
<td></td>
<td></td>
<td>0.7±0.6</td>
</tr>
<tr>
<td>aBMD Femoral Neck</td>
<td>1.15±0.84*</td>
<td>Integral vBMD Femoral Neck</td>
<td>1.2±0.7</td>
</tr>
<tr>
<td>Trabecular vBMD Femoral Neck</td>
<td></td>
<td></td>
<td>2.7±1.9</td>
</tr>
<tr>
<td>aBMD Trochanter</td>
<td>1.56±0.99*</td>
<td>Integral vBMD Trochanter</td>
<td>1.5±0.9</td>
</tr>
<tr>
<td>Trabecular vBMD Trochanter</td>
<td></td>
<td></td>
<td>2.2±0.9</td>
</tr>
</tbody>
</table>

*p<0.01, n=16-18

LeBlanc, J Musculoskeletal Neuronal Interact. 2000; Lang, J Bone Miner Res, 2004;
HOW CAN THESE RESEARCH DATA BE USED CLINICALLY IN THE ABSENCE OF FRACTURE DATA? So what?
DXA BMD increases in Postflight – but not sufficient to assess recovery of bone strength.

Sibonga et al. BONE 41:973-978, 2007
DXA & QCT Spine in 8 ISS astronauts: Expanding our Understanding of Recovery After Spaceflight

Clinical Evidence: QCT measures are independent predictors of hip fracture to supplement aBMD.

In Vivo Discrimination of Hip Fracture With Quantitative Computed Tomography: Results From the Prospective European Femur Fracture Study (EFFECT)
DXA BMD not as good of predictor of hip fractures for the “complicated patient” i.e., non-age-related bone loss

- Different patterns of bone “loss” (cortical vs. trabecular) with different metabolic disorders …analogous to spaceflight effects

Seeman, JCI 1992
Slide courtesy of Dr. Amin, MD
Dual Photon Absorptiometry (DPA)
Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.


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


Images courtesy of Dr. J Keyak
Individual Results

Stance Loading (4 to 30% loss in strength)

Max loss 30%

[Graph showing individual hip strength loss over time]
Individual Results

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

Max loss 24%
Astronaut Data (n=11): Space effects on surrogates of bone strength do not correlate.

Stance: $R^2=0.23$

Fall: $R^2=0.05$

Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.

Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.

Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.

Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.

Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.

Which is better?
Fracture risk by 1 measurement or by > 1 measurement?
It’s not complicated.
Additional cut-points for Bone Health: FE Modeling of QCT Scans from Population Studies

FE 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.

All Male Subjects
Stance Loading

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION

REPRESENTATIVE POPULATION DATA

Data slide courtesy of Keyak. NOT FOR DISTRIBUTION
Probabilistic Risk Assessments for Bone Fracture: NASA’s Model for Fracture Likelihood

Biomechanics and Mission Operations

Bone Loss in Space

Estimate of Fracture Probability

Clinical and Engineering Characteristics of Bone Strength

Figure 2. Summary of literature survey on fracture load as a function of femoral neck BMD

Beck et al, 1990
Hayes, Myers, 1996 (2mm/s)
Hayes, Myers, 1996 (100mm/s)
Kukla et al, 2002

Probability of event

Probability of Fracture

Probability bone will fail to support load

Slide courtesy of J Myers; Adapted by Sibonga
WHAT IS OUR PATH TO RISK REDUCTION?

For Exploration Class Missions
<table>
<thead>
<tr>
<th>Osteo 1: GUIDED, NEW</th>
<th>A new acceptable bone health standard using an improved surrogate for bone strength needs to be defined for the flight environment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteo 2: REPHRASED, MERGED</td>
<td>What is the incidence &amp; prevalence of early onset osteoporosis or fragility fractures due to exposure to spaceflight?</td>
</tr>
<tr>
<td>Osteo 3: GUIDED, MERGED</td>
<td>We need a validated, clinically-relevant method for assessing the effect of spaceflight on osteoporosis or fracture risks in long-duration [LD] astronauts.</td>
</tr>
<tr>
<td>Osteo 4: MERGED</td>
<td>We don’t know the contribution of each risk factor on bone loss and recovery of bone strength, and which factors are the best targets for countermeasure application.</td>
</tr>
<tr>
<td>Osteo 5: REPHRASED</td>
<td>We need an in flight capability to monitor bone turnover and bone mass changes during spaceflight.</td>
</tr>
<tr>
<td>Osteo 6: NEW</td>
<td>How do skeletal changes due to spaceflight modify the terrestrial risk of osteoporotic fractures?</td>
</tr>
<tr>
<td>Osteo 7: MERGED</td>
<td>We need to identify options for mitigating early onset osteoporosis before, during and after spaceflight.</td>
</tr>
</tbody>
</table>

**Bone Medical Standards update, Clinical Practice Guidelines [CPG]**

**Surveillance Program to data mine evidence of increased risk for fragility of low trauma fractures.**

Data for medical standards; surveillance data for CPG formulation; Clinical trigger; surveillance data

**Risk Characterization/Quantification**

Prototype In-flight monitoring device for bone mass and for bone biomarkers

**Risk Characterization: Probabilistic Risk Assessment Model/Tool to generate LxC; Input for clinical practice guidelines**

Integrated suite of countermeasures nutrition, exercise and pharmaceuticals
Schedules: ISS 2024

• Standards Update By FY14 End

• Spaceflight Effects Characterized \((as\ reasonably\ can\ be\ achieved)\) ~ FYs 19-20

• Countermeasures (validated efficacy for mitigating risk factors during flight, e.g., declines in BMD, turnover and strength) By FY 23
Summary

• DXA – widely-applied medical test for terrestrial medicine but may be too limiting for operational and clinical decision-making for bone health of astronauts.

• If skeletal integrity is assessed solely by a surrogate measure of bone strength (DXA – BMD) vs. an estimate of bone strength (e.g., FE modeling), then there may be a risk of underestimating fracture probability and poorly estimating countermeasure efficacy.

• In order to proceed down the path to risk reduction [PRR], Bone Research needs to take innovative approaches to characterizing risk and countermeasure effects.
Thank you.

QUESTIONS? COMMENTS?
Backup Slides
Study on Risk Surveillance: Hip QCT

- Test feasibility of QCT protocol for surveillance of clinical trigger.

- Accumulate surveillance data for development of clinical practice guidelines (QCT and FEM)

- Research: Demonstrate how QCT can delineate biochemical from mechanical countermeasures. “Proof of Concept” Pilot Study

Figures courtesy of T. Lang (UCSF) and D. Carter (Stanford U)
AGE-REGRESSIONS: Trabecular bone loss occurs at earlier age than expected.


Slide courtesy S. Khosla, adapted by Sibonga
Use of Osteoporosis Policy-makers help to translate research data to CPGs in absence of fracture data.

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

Risks

Gaps

Exploration Missions & Architectures

NASA Spaceflight Human System Standards

Results and Deliverables

Solicitations & Directed Research

Clinically-relevant Research Tasks

Integrated Research Plan
Effects on Different Compartments of Bone (cortical vs. trabecular BMDs)
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

DD Cody: Femoral strength is better predicted by finite element models than QCT and DXA. J Biomechanics 32:1013 1999.
ES Nelson et al. Development and validation of a predictive bone fracture risk model for astronauts NASA Glenn Research Center, Cleveland, OH

*Ann Biomed Eng, 37(11), 2009, pg. 2337 - 2359.*
Different ways to unbalance remodeling at bone surface.

Different levels of cell number and cell activities ending in deficit of bone at the BRU.
QCT provides useful information re: causation of hip fracture, evaluation of hip fracture risk and possible targets for intervention.

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A (HR per SD decrease)</td>
</tr>
<tr>
<td>HR</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Trabecular bone, volumetric BMD (g/cm²)</td>
</tr>
<tr>
<td>Percent cortical volume</td>
</tr>
<tr>
<td>Minimum cross-sectional area (cm²)</td>
</tr>
<tr>
<td>Areal BMD from DXA (g/cm²)</td>
</tr>
</tbody>
</table>

Area under the ROC curve for Models A, B, and C were 0.853, 0.855, and 0.860, respectively.
**ARED exercise appears** to mitigate decline in areal BMD.

(J Bone Mineral Research. Smith et al 2012) *this is not ref for figure.*
FE Standards Combine Aging and Spaceflight Changes to Hip Strength and used together with DXA BMD Standards.

<table>
<thead>
<tr>
<th>Minimum FE strength for Bone Health</th>
<th>“Go”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Permissible Outcome</td>
<td>“Wait”</td>
</tr>
<tr>
<td></td>
<td>“No Go”</td>
</tr>
</tbody>
</table>
Steven Goldstein, Ph.D.
“Bone Quality: A Biomechanical Perspective”
QCT Postflight – Changes in Femoral Neck structure detected 12 months after return

Bone Mineral Content (g)

Volumetric Bone Mineral Density g/cm³

Minimum Cross-sectional Area cm²

Pre  Post  12  Pre  Post  12  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

The long-duration astronaut – not typical subject to evaluate osteoporosis (2/2013).

• Typical space mission duration – 162 ± 36d (range 58-215d)
• Average Age – 47 ± 5 y (range 37 – 55)
• Male to Female Ratio – 4.8 : 1
• Current total # per astronauts in corps – 55 of 331
• # repeat fliers – 5
• BMI – Male BMI 25.8 ± 2.0 (range 21.2 to 30.7); Female BMI 23.4 ± 2.4 (range 20.4 to 25.9)
• Wt and Ht- Males: Males: 80 ± 6 (63 to 97); 176 ± 6 (163 to 185)
• Females: 67 ± 8 (57 to 82), 170 ± 4 (165 to 178)
• % Body Fat: Males 20 ± 4 (9 to 27); Females 27 ± 8 (19 to 41)
Bone Remodeling Sequence

- Oc Precursor: Osteoclast Precursor
- LC: Lining Cells
- Resting Bone Surface
- "Activation"
- Osteoclast
- Resorption
- Mononuclear Cells
- Reversal
- CL: Cement Line
- Bone Formation
- Ob Precursors
- Osteoblast
- OS: Osteoid
- BRU: Bone Remodeling Unit

Time:

- ~3 WEEKS
- ~3 MONTHS

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

Slide courtesy of Dr. R. Wermers, Mayo Clinic
RISK FOR FRAGILITY FRACTURES: Does spaceflight result in irreversible changes to bone that combine with age-related losses?

Peak Bone Mass

Age-related Loss

Bone mass (g/calcium)

Menopause-induced Loss

Females

Males

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

<table>
<thead>
<tr>
<th>Osteo #</th>
<th>Category</th>
<th>Subcategory</th>
<th>Customers</th>
<th>Deliverables</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Standards</td>
<td>New</td>
<td>OCHMO; Space &amp; Clinical Operations; Human Health Countermeasures [HHC]</td>
<td>Bone Health Standards update, Clinical Practice Guidelines</td>
</tr>
<tr>
<td>2</td>
<td>Knowledge Gap: Risk Characterization</td>
<td>Evidence</td>
<td>OCHMO; Space &amp; Clinical Operations</td>
<td>Evidence of increased risk for fragility of low trauma fractures.</td>
</tr>
<tr>
<td>3</td>
<td>Technology Gap Methology &amp; bone measurements</td>
<td>Clinical care; medical informatics</td>
<td>OCHMO; Space &amp; Clinical Operations; HHC</td>
<td>Data for medical standards (including index of countermeasure efficacy); Clinical trigger; surveillance data for Space Normal;</td>
</tr>
<tr>
<td>4</td>
<td>Knowledge Gap: Data, phenomenon, mechanism</td>
<td>Risk Factor</td>
<td>HHC, Biomed Research Div; Technology &amp; Engineering Division</td>
<td>Risk Characterization/Quantification-</td>
</tr>
<tr>
<td>5</td>
<td>Mitigation Gap- detect,monitor, treat</td>
<td>Prototype Hardware</td>
<td>Med Operations; Human Health Countermeasures; Systems Engineering</td>
<td>Prototype In-flight monitoring device for bone mass and for bone biomarkers</td>
</tr>
<tr>
<td>6</td>
<td>Mitigation- surveillance</td>
<td>Computational models, software</td>
<td>OCHMO; Space &amp; Clinical Operations; HHC</td>
<td>Risk Characterization: Probabilistic Risk Assessment Model/Tool to generate LxC; Input for clinical practice guidelines</td>
</tr>
<tr>
<td>7</td>
<td>Mitigation Prevention &amp; Treatment</td>
<td>Prescription(s)</td>
<td>Bone Summit-like Panel; Med Operations; OCHMO</td>
<td>Exercise prescription, metabolic countermeasures; validated pharm agent prescription; risk factor modifications; Recommended medical intervention.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol</td>
<td>Med Operations; OCHMO; HHC</td>
<td>Integrated suite of countermeasures nutrition, exercise and pharmaceuticals</td>
</tr>
</tbody>
</table>