Conference Proceedings - 2010 Bone Summit: Risk for Early Onset Osteoporosis

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December 2016
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Dedication

This report on Early Onset Osteoporosis is dedicated to the memory of Judith Liebenthal Robinson, PhD (1949-2010). Dr. Robinson was a vocal proponent for flight surgeons and life scientists working together to innovate health care for NASA’s Astronaut Corps. As the secretary for the Human System Risk Board, Dr. Robinson was well familiar with the issues of managing a health care system for the astronauts. While on medical leave at home, she remained a fervent advocate for the Bone Summit, which asked internationally-known osteoporosis clinicians to consider research technologies and data as they recommended clinical practice guidelines for mitigating early onset osteoporosis. Dr. Robinson graced the Bone Summit with her presence on June 7. Although she passed away on September 10, 2010, her presence and influence among us will be long felt.

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>aBMD</td>
<td>areal bone mineral density</td>
</tr>
<tr>
<td>ARED</td>
<td>advanced resistive exercise device</td>
</tr>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>CEVIS</td>
<td>cycle ergometer with vibration isolation and stabilization</td>
</tr>
<tr>
<td>CPHS</td>
<td>Committee for the Protection of Human Subjects</td>
</tr>
<tr>
<td>DXA</td>
<td>dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>Early Onset Op</td>
<td>early onset osteoporosis</td>
</tr>
<tr>
<td>ESA</td>
<td>European Space Agency</td>
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<tr>
<td>EMR</td>
<td>electronic medical record</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FE</td>
<td>finite element</td>
</tr>
<tr>
<td>FRAX</td>
<td>WHO Fracture Risk Assessment Tool</td>
</tr>
<tr>
<td>HRP</td>
<td>Human Research Program</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>iRED</td>
<td>interim resistive exercise device</td>
</tr>
<tr>
<td>ISCD</td>
<td>International Society for Clinical Densitometry</td>
</tr>
<tr>
<td>ISS</td>
<td>International Space Station</td>
</tr>
<tr>
<td>JAXA</td>
<td>Japan Aerospace Exploration Agency</td>
</tr>
<tr>
<td>JSC</td>
<td>Johnson Space Center</td>
</tr>
<tr>
<td>L - #</td>
<td>time (days/years) before launch</td>
</tr>
<tr>
<td>LSAH</td>
<td>Longitudinal Study (Lifetime Surveillance) of Astronaut Health</td>
</tr>
<tr>
<td>LSC</td>
<td>least significant change (Also see definition below)</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NASA</td>
<td>National Aeronautics Space Administration</td>
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<tr>
<td>NSBRI</td>
<td>National Space Biomedical Research Institute</td>
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<tr>
<td>QCT</td>
<td>quantitative computed tomography</td>
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<tr>
<td>RE</td>
<td>resistive exercise</td>
</tr>
<tr>
<td>RMAT</td>
<td>Risk Management Assessment Tool</td>
</tr>
<tr>
<td>R + #</td>
<td>time (d/yr) after return to Earth</td>
</tr>
<tr>
<td>SOLO</td>
<td>SOdium LOading in Microgravity</td>
</tr>
<tr>
<td>TVIS</td>
<td>treadmill with vibration isolation and stabilization</td>
</tr>
<tr>
<td>vBMD</td>
<td>volumetric bone mineral density</td>
</tr>
<tr>
<td>USRA</td>
<td>Universities Space Research Association</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>3D</td>
<td>three dimensional</td>
</tr>
</tbody>
</table>
### DEFINITIONS

<table>
<thead>
<tr>
<th>AGES</th>
<th>Age Gene/Environment Susceptibility - study cohort in Reykjavik, Iceland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areal BMD</td>
<td>BMD reported as bone mineral content per tissue area (g/cm²)</td>
</tr>
<tr>
<td>Fragility Fracture</td>
<td>A fragility fracture is defined as a pathologic fracture that results from minimal to zero trauma such as a fall from standing height or less. Typical sites of fragility fractures are vertebral bodies, femoral neck of hip and the wrist.</td>
</tr>
<tr>
<td>Least Significant Change</td>
<td>The smallest difference between serial measures of aBMD attributable to a real change and not to chance.</td>
</tr>
<tr>
<td>Volumetric BMD</td>
<td>Bone mineral density reported as bone mineral content per tissue volume (mg/cm³)</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY

NASA Space Flight Human System Standards are established not only to ensure human health and performance during spaceflight missions, but also to ensure that the service astronauts provide on long-duration missions, such as on the International Space Station (ISS), does not put them at risk for long-term health impairments. Consequently, the Bone Discipline Lead for NASA’s Human Research Program (HRP) was tasked by the Space Medicine Configuration Control Board and the Human System Risk Board to convene a panel of clinical experts in osteoporosis to address issues related to the HRP risk for Early Onset Osteoporosis (Early Onset Op) due to long-duration spaceflight missions. This Early Onset Op Bone Summit (Bone Summit) was intended to enable a panel of clinicians to review the medical and research evidence to-date to assess how the risk of Early Onset Op was being evaluated and managed by the Human Health and Performance Directorate. This panel was also requested to provide bone-specific input for a new category of astronaut data collection, that is, required assessments for the surveillance of occupational health risks due to spaceflight. Hence, the overarching question for the Bone Summit was: What should NASA be doing now for the astronaut to manage an occupational risk that may manifest later in life?

To this aim, the Bone Discipline Lead selected a panel composed of clinicians and clinical researchers who evaluate measures of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) technology as the primary endpoint for the clinical treatment of osteoporosis. Together with the Deputy Chief Medical Officer and the Space Medicine Operations and Biomedical Research & Environmental Services divisions, the Bone Discipline Lead provided a charge to the panel that would generate specific information required by NASA review boards to define, prioritize, manage, and move forward on health risks related to the space travel. The discussions and exchanges that ensued during the 2-day Bone Summit resulted in recommendations that can be categorized under 3 generalized topics that are discussed at length in this Executive Summary:

1. The implementation of quantitative computed tomography (QCT) for the surveillance of occupational risk due to spaceflight and how research data can be used in clinical management of the risk for Early Onset Op.

2. An evaluation of NASA’s current countermeasure research to address the risk of Early Onset Op in long-duration astronauts.

3. Recommendations for the Bone Health Program for the lifetime surveillance of health in active and retired astronauts.

The following overview lists the key comments and recommendations of the Bone Summit Panel (Panel):

- The Panel asserts: The “clinical trigger” in a long-duration astronaut, requiring a medical response by the flight surgeon, is the failure of volumetric bone mineral density (vBMD) in the cancellous bone compartments of the hip (femoral neck, trochanter, or total hip) to demonstrate complete recovery at 2 years after return to Earth (that is, vBMD within least significant change [LSC] of preflight vBMD measure). A total of 4 QCT scans for long-duration astronauts will be required for monitoring this clinical trigger (preflight, postflight, 1 year following return, and 2 years following return). The recommended response for clinical trigger: astronaut and
flight surgeon seek consultation with the contracted osteoporosis endocrinologist who will evaluate all relevant risk factors to discern the requirement for an intervention.

- The Panel states: The validation of all countermeasures that address the risks for fracture and for Early Onset Op requires an assessment of changes in the cancellous bone compartment (aka trabecular bone) of the hip to evaluate the mitigation of bone loss and possible irreversibility of deteriorated trabecular microarchitecture.

- The Panel warns: The concurrent in-flight evaluation of several countermeasures in an individual crewmember (for example, the combined application of exercise, pharmaceutical, and dietary interventions) will preclude the evaluation of any single countermeasure and will not optimally inform decision-makers regarding the utility of any single method for mitigation of skeletal health risks.

- The Panel recommendations for occupational risk surveillance are:
  - Requiring QCT, a technology for which there are no clinical guidelines yet, for astronaut risk surveillance to evaluate countermeasure efficacy, to monitor for the clinical trigger, and to enable the estimation of hip bone strength by finite element (FE) modeling.
  - Pursuing finite element (FE) modeling of QCT data to provide an individualized index of hip bone strength in astronauts. FE modeling would capture the unique adaptive changes of bone to spaceflight and would better support the clinical decisions for the novel scenarios that exist in the space program (for example, aggressive time schedules, small subject numbers, younger-aged cohort, rare skeletal changes, knowledge gaps, and technology challenges).
  - Developing an algorithm to drive NASA’s operational and clinical decisions based upon FE strength estimates. An algorithm using a distribution of FE strengths will be generated from emerging data relating FE strength and fracture risk, and will supplement and improve the current decision-making process.

Re-examining approaches for in-flight intervention by this Panel as data are acquired under the category of Occupational Risk Surveillance and for missions in excess of the typical 6-month ISS mission. The recommended use of QCT will be re-evaluated as data are collected to ensure that this new measurement continues to serve an important purpose (that is, in monitoring for bone structural changes associated with reduced strength with the possibility of clinical intervention).
PURPOSE

Background: One of the goals of Human System Risk Board (HSRB) is to dispose actions on the human health risks identified to be of high priority by the HRP. While most of these HRP risks relate to the maintenance of human health and performance of astronauts during spaceflight missions, there is also the requirement to address risks to long-term human health that are due to space exploration and habitation. One of these latter risks is the risk for Early Onset Op.

Medical Issue: For the Bone Discipline, Early Onset Op risk is probably the most recognized but poorly understood health risk brought on by spaceflight. Essentially, NASA needs to understand how prolonged space travel impacts the musculoskeletal health of astronauts and whether the persistence of the musculoskeletal de-conditioning predisposes astronauts to premature fragility fractures. To this aim, the Space Medicine Division is considering collection of astronaut data for the purposes of occupational risk surveillance.

Risk Management: Management of HRP health risks requires understanding the current evidence base for musculoskeletal de-conditioning in space and recognizing the gaps-in-knowledge. Many open issues exist and are related to the fact that long-duration astronauts compose a unique group of subjects that are not representative of the typical osteoporosis patient population here on Earth. Hence, the Bone Discipline Lead was subsequently tasked to convene a panel of osteoporosis clinicians to review the existing dataset collected on long-duration astronauts to make recommendations for clinical practice guidelines that are specific to the spaceflight-induced risk for Early Onset Op.

Summit Panel: The selected Panel consisted of clinical experts in fields of bone densitometry, endocrinology, male osteoporosis, gerontology, bone epidemiology, physical medicine, rehabilitation, vitamin D, and nutrition. Panel members are leaders in their expertise and experienced in developing bone health policy guidelines.

Summit Format: The Bone Summit was conducted in Houston, TX on June 7 and 8, 2010, by invitation only, at the Universities Space Research Association (USRA) facilities. Support scientists, extramural investigators, and NASA personnel that were involved in astronaut data acquisition and analysis were asked to support Panel discussions.

The Bone Summit involved a non-routine presentation of astronaut data for review by the panel. Because osteoporosis is a multi-factorial syndrome of musculoskeletal decline with resulting increased risk for fragility fracture, it was pertinent that the panel members be able to review any information (spaceflight and non-spaceflight related) that would assist them to understand the detected changes in BMD in the astronaut, how those changes may relate to the spaceflight mission, and how those changes may influence the risk for age-related fractures in the post-mission period. Astronaut data were presented as group means and trends and, in a closed session, reviewed in individual charts. Not all data from long-duration astronauts were available for review because of constraints related to privacy. Specifically, no data obtained from active research protocols, obtained under experiment-specific informed consent, or from non-U.S. astronauts (International Partners) were presented.

In addition to BMD data, reviewed charts included the astronaut birth date and flight dates, an account of risk factors and of physical activity, measures of calcitrophic hormones, measures of bone turnover markers, measures of bone-related cytokines, renal stone panel (urine
saturation levels), measures to reflect in-flight conditioning, and the identification of any in-flight musculoskeletal events.

In preparation for the Bone Summit, Panel members were provided with several published reports (Appendix A - Pre-Summit Reading Material) for an overview of the physiologic deconditioning with long-duration missions.

Summit Day 1 included presentations to provide the panel with an overview of how the risk is currently managed by medical standards, documented in the Risk Management Assessment Tool (RMAT) and monitored by the Bone Health Program for active and retired astronauts. Additional presentations highlighted observed trends in astronaut data: (1) exercise effects on bone mineral density, (2) bone biochemistry data, and (3) structural changes in bone and BMD recovery after return to Earth (Appendix B - Agenda).

Charts Reviewed: The reviewed charts (21 of 29 long-duration astronauts) were selected to represent a unique group or an extreme skeletal response to space. Reviewed data were from astronauts who were in the following categories: (a) female, (b) repeat long-duration missions, (c) users of ARED exercise hardware, (d) scanned by QCT, (e) hip bone strength estimated by FE modeling, and (f) BMD losses > 10% in either the hip or spine.

Keynote Presentations: The Chief for the Space Medicine Operations Division and an International Space Station (ISS) astronaut-physician gave keynote presentations to facilitate an understanding of NASA culture and the constraints within which clinical and operational decisions are made.

Speakers conveyed to the Panel members the rationale behind the aggressive preventive medicine program for the long-duration astronaut and the collective astronaut perception of medical risks in long-duration missions. In short, the Panel heard that, in the current absence of evidence for postflight low trauma fractures, astronauts are more interested in counteracting bone loss with resistive exercise and dietary approaches and in staying informed. Overall, the Panel heard that NASA and the astronauts take the risk seriously and are willing to act on validated risks with reasonable recommendations.

Summary of Summit Recommendations: The subsequent discussions and exchanges that ensued during the 2-day summit resulted in recommendations that are categorized in this report under the following headings:

1. QCT Technology for the Surveillance of Occupational Risk due to Spaceflight. The implementation of QCT technology and recommended uses of QCT data for clinical and operational decisions.

2. Status of Flight Experiments for Bone Loss Countermeasures. Comments related to current investigations conducted on ISS to address the risk of Early Onset Op, the requirements for intervention, and the timing of various interventions at different stages of a space mission.

PANEL RECOMMENDATIONS

1.0 QCT TECHNOLOGY FOR THE SURVEILLANCE OF OCCUPATIONAL RISK DUE TO SPACEFLIGHT

The Panel recommends QCT as surveillance technology for monitoring the hips of long-duration astronauts based on the following rationale and requirements discussed during the Bone Summit:

- QCT increases the understanding of spaceflight effects on bone structure
- QCT detects a bone trigger, as recommended by the panel, for seeking possible clinical intervention
- QCT validates the efficacy of countermeasures for reduced bone strength due to spaceflight
- QCT data can be translated to hip bone strength values via FE modeling
- QCT can be used to monitor recovery in bone mass, structure, and hip bone strength
- QCT can be used to supplement medical standards with measures of hip strength
- QCT can generate data with which to calculate probability of fracture

1.1 Spaceflight Effects on the Hip

Indices of bone structure (such as trabecular microarchitecture, whole bone geometry and cross sectional dimensions, cortical bone width) are key determinants of bone strength (Melton 2007). Hence, the impact of space-induced skeletal changes on hip bone strength will remain an open issue until those measures can be performed in long-duration astronauts. QCT is an imaging technology applied to a single prospective population studies (Black 2008). While it is not considered a standard clinical tool, QCT may need to be instituted for clinical decisions given the novel constraints and scenarios for which NASA must develop astronaut-specific health policies (for example, young age of target population, limited subject data, atypical changes to bone, induced risk factors).

Previously, QCT applications in NASA astronauts have been confined solely to the research realm. QCT scans were performed on ISS astronauts (n = 16) as a research study to describe the effects of long-duration spaceflight on bone mass and bone structure (Lang 2004). QCT is acknowledged as a technology to expand the understanding of spaceflight effects - and of recovery on Earth - because of its ability to capture structural changes during and between spaceflights with regard to whole bone size, cortical thickness, and bone mass distribution.

Hence, with QCT data to quantify changes to bone form, the changes to bone strength, and fracture risk (that is, bone function) can be estimated by advanced research analysis, that is, FE modeling.

Currently, flight surgeons rely strictly on the measurement of areal bone mineral density (aBMD) by DXA and on the official positions of the International Society for Clinical Densitometry (ISCD) for assessing the skeletal integrity of astronauts. However, this may not be the best approach for evaluating fracture risk in persons < 50 years or when used as the sole surrogate of bone strength. Although aBMD is an incomplete surrogate for bone strength it remains the most widely used predictor of fragility fracture risk because of the abundance of epidemiologic fracture data. Because DXA measures are limited to a 2-D projection of bone,
there is recognition that DXA fails to capture the unique spaceflight-induced changes to 3-D structures that would influence bone strength.

Alternatively, data derived from QCT scanning can be used in FE modeling of the hip. This modeling integrates the QCT BMD data for each point (each QCT voxel) in the bone to provide a complete 3-D description of how bone mass is distributed in the proximal femur. From this description, mechanical properties (for example, elastic modulus and strength) can be computed and subsequently used to construct a mathematical model of the 3-D hip structure. With this mathematical model, the force required to fracture the proximal femur (that is, the strength of the hip bone) can be calculated. This more accurate description of whole bone strength has been shown to provide more information about hip fracture risk in an elderly population than aBMD and therefore is likely to be a better predictor of fracture risk for individual astronauts than BMD (AGES Study - manuscript in preparation).

In addition, the adaptation of bone to space is not well defined; the number of astronauts with prolonged exposure to space is very small < 50; and it is not likely that substantial population data with fracture outcome will ever be achieved in the lifetime of a current long-duration astronaut. Furthermore, even with seemingly effective countermeasures that mitigate aBMD loss or increase aBMD, there is a concern for irreversible trabecular bone loss. DXA moreover cannot distinguish cortical restructuring (that is, modeling) that may occur with re-adaptation to Earth’s gravity or with exercise loading of bones. An increase in cortical bone may overwhelm the aBMD measure and mask the effects in trabecular bone. Structural changes that occur during a mission may not increase the fracture risk of an astronaut right after a spaceflight mission; however, structural changes that are irreversible are likely to combine with changes induced by the aging process and induce premature fractures.

It has been proposed that QCT and FE modeling can be used to monitor bone strength and fracture probability in the long-duration astronaut in association with the mission and for surveillance of long-term effects. The Occupational Risk Surveillance is a newly created category of compulsory data collection that is being considered by the Space Medicine Operations Division for the repository of these QCT data as performed in long-duration astronaut. Part of the charge to the Panel was to recommend how QCT scanning should be implemented to optimize the collection of surveillance data to define the risk for premature age-related fractures and potentially to develop clinical practice guidelines for intervention.

1.2 Timing of QCT for Long-Duration Astronauts

Panel Comments and Recommendations

- Perform QCT scans before and after flight using the same machine.
- Administer QCTs before launch as a reference value for postflight measurements.
  There was much discussion regarding the timing of this baseline QCT scan. The timing of the baseline scan before flight is contingent upon the purpose of the measure: for example,
    - To define risk for pre- and perimenopausal females.

Rationale: due to the limited but suggestive declines of trabecular bone in women before menopause, it is recommended that QCT scans be performed no greater than 3 to 6 months before launch in female astronauts of pre/perimenopausal status to better define the risk.
To separate out spaceflight-induced changes. 

**Rationale:** due to the possibility of a post-mission fracture, QCT scans should be performed as close as possible to launch and landing dates (bracketing mission duration) to better distinguish the contribution of spaceflight changes to fracture risk.

To accommodate scheduling constraints. 

**Rationale:** due to the stability of bone in young, healthy men, QCT scans can be performed as early as 1 year before launch if required by travel and work schedules.

- Conduct 3 postflight scans: As early as possible after return, at 1 year following return, and at 2 years following return. The scan at R + 2 years will be assessed for the clinical trigger (failure to detect trabecular vBMD of the hip to within least significant change [LSC] of preflight QCT measure).

### 1.3 QCT Measures for Clinical Decisions

Astronauts have been reported to show at least some degree of aBMD loss (≥ LSC) in at least one skeletal region scanned after a long-duration mission (LeBlanc 2007). As per a medical requirement at Johnson Space Center, the following regions are scanned by DXA for BMD assessment: the hip (femoral neck and trochanter), lumbar spine, heel and wrist. Astronaut fracture risk is assessed by the BMD gradient of fracture risk established by the WHO and according to ISCD guidelines. However, because DXA cannot distinguish changes in individual bone compartments, that is, DXA cannot distinguish the location of BMD gain or loss, DXA may provide misleading assessment of spaceflight effects and of any mitigation of those effects. Hence, the Panel is concerned most about irreversible changes to trabecular microstructure of hip. This concern is collectively based upon: (a) reports of very rapid bone loss (DXA data) (LeBlanc 2000) and aggressive osteoclastic resorption (Vico 1987; Thomsen 2005), (b) the unknown impact on trabecular connectivity (Kleerekoper, 1985; Van der Linden 2001), (c) the current lack of technologies to evaluate trabecular bone microarchitecture for central sites, and, most importantly, (d) upon the failure to see complete recovery with 2 to 4 years after return in hip trabecular compartment in eight astronauts (Carpenter 2010).

Following a crewmember’s initial mission, return to Earth’s gravity can result in compartment-specific adaptations (for example, periosteal expansion of cortical bone) that are manifest as changes to whole bone structure (increased cross-sectional area) (Lang 2006). These structural changes can be compounded by changes induced by a second flight as well as by aging (Riggs 2004, 2008). Further reported data reveal a low correlation between change in aBMD and FE strength, suggesting that FE strength reveals unique, space-induced changes to bone that DXA cannot capture (Keyak 2009). Finally, the precipitous rate of BMD decline and aggressive osteoclast activity observed in iliac crest biopsies of skeletally-unloaded bed rest subjects (Vico 1987, Thomsen 2005) suggests that the space-induced changes to bone quality puts an astronaut at a different fracture risk than the average Earth-based person with the same aBMD.

**Panel Comments and Recommendations**

- Occupational risk surveillance will consist of four QCT scans: a preflight baseline scan, a postflight scan, and two scans at 1-year intervals after return. These scans shall be used by the endocrinologist on contract with Space Medicine to monitor recovery of hip trabecular vBMD. Recovery of trabecular vBMD shall be established
when vBMD value has returned to baseline vBMD (within precision error of QCT [LSC]).

- The failure to completely recover trabecular vBMD in the hip (total hip, femoral neck, and trochanter) at 2 years following return to Earth, should serve as the clinical trigger for referral to the contracted endocrinologist.

- The Panel indicated that the impact of space on trabecular microarchitecture is a critical knowledge gap and that technologies to conduct evaluations in central skeleton of astronauts should be discovered, developed or applied.

1.4 QCT-derived FE Strength (Developing an Algorithm for Decision Making)

QCT is a research tool for which there are no current clinical guidelines for its use, and thus is not ready yet to replace DXA clinically. Nevertheless, QCT is capable of expanding and improving the knowledge base from which clinical and operational decisions for the space program could be based. For instance, QCT is required to detect the critical index (as recommended by the Panel) for a clinical intervention decision for astronauts. Currently, operational and clinical decisions are based upon relative fracture risks derived from aBMD measurements conducted in population studies. That is, DXA is grounded on large epidemiologic studies with excellent Earth-based fracture data. As previously mentioned, the astronaut corps is a unique subset of subjects exposed to novel environmental risk factors for which the number of subjects will not reach the level from which health policies and guidelines are typically developed. Thus, the Panel suggested that these may be the circumstances in which research technologies should be transitioned to the clinical realm.

For clinical decisions, QCT can describe the effects of spaceflight on hip structure and on mass distribution in bone compartments and should be used to monitor the clinical trigger in astronauts after return. Since the basis of osteoporosis therapy is prophylactic, QCT also enables the estimation of hip bone strength by FE modeling that can obviate the need for evidence of fragility fractures. The translation of QCT data to FE strength provides a functional mechanism for the hip (hip bone failure load for a specific load vector) that is individualized per astronaut; this index is possibly the single best composite number of strength because of its ability to integrate applied loads with the 3-D geometry and distribution of material properties (bone mineral density, elastic modulus, and yield strength), that is, the 3-D bone structure.

Because fracture prevention ultimately drives the requirement for interventions, it is prudent to use a more sophisticated measure of bone strength, instead of limited surrogates for bone strength (for example, aBMD), to enhance estimation of fracture probability in this unique astronaut population. Ultimately, QCT technology will enable the surveillance of hip bone strength and fracture risk estimation as it changes in the long-duration astronaut with re-adaptation to Earth or with aging.

Because the current gold standard surrogate of fracture risk, DXA BMD, is insufficient for the astronaut population, and because it would take an extensive number of years to determine fracture outcome, the Panel recommends using FE bone strength as a new, improved surrogate for assessing fracture risk.

For operational decisions, QCT-FE strength can be used to supplement the existing medical standards that have been based to-date upon DXA BMD to reflect skeletal integrity. The collective evidence from flight is a reminder that prolonged space habitation appears to affect the
skeleton in such a way that declines in mechanical strength may not be detected by current clinical technologies. These observations are in spite of the pristine medical history and extreme physical fitness of the typical astronaut. In addition, there are accumulating data that FE strength is strongly related to fracture risk, even more so than aBMD (Orwoll 2009, AGES Study).

Hence, it is the expert opinion of this panel that there should be an attempt to use the most powerful research technologies and analyses available to identify those astronauts who may be at risk for developing Early Onset Op (premature low-trauma fractures or fragility fractures).

For apparent reasons, the development of clinical guidelines for mitigating the risk for premature fragility fractures should not be held to the same standards that osteoporosis clinicians are accustomed (that is, fracture outcome data from large population studies). It is the combination of space effects with aging effects that may predispose long-duration astronauts to fragility fractures at an earlier age. FE modeling performed in an aging population may provide a distribution of FE strengths, associated with incident hip fractures that could be used to identify those astronauts at increased risk for fracture for their age (AGES Study). The Panel recognizes, however, that the development of a clinical trigger for astronauts - based upon FE strength - is a herculean feat and may be modestly imperfect.

Panel Comments and Recommendations

- QCT is capable of delineating and measuring cortical from trabecular bone and provides predictors of fracture that are independent of aBMD - one of which is trabecular vBMD of the femoral neck (Black 2208). Hence, the Panel strongly recommended that QCT be a required technology to evaluate the ability of in-flight countermeasures to prevent or mitigate declines in the trabecular vBMD of the hip (total hip, trochanter and femoral neck).

- QCT-derived FE strength of the hip shall be used to improve the understanding of spaceflight effects on hip bone strength and on subsequent fracture risk after a mission.

- The Panel proposed to evaluate FE strengths, derived from FE modeling of fracture risk in an aged population cohort, (AGES Study) in an attempt to develop an algorithm to estimate the probability of fracture in astronauts after return from long-duration spaceflight.

- This algorithm could be for use in both operational and clinical decisions by NASA. Applications for consideration by the space program include astronaut candidate selection to the Corps, astronaut certification for long-duration missions, and for clinical intervention in an astronaut with high fracture risk.

- The Panel recommended using FE strength to qualify astronauts who would have been disqualified by BMD-based standard. This standard should confirm the more pertinent issue - are the hip bones strong enough?

- This algorithm would be used to certify astronauts for a second long-duration flight based upon acceptable probability for fracture (input by NASA) and the risk for early onset fragility fractures (input from Panel).

- This algorithm (probability for fracture based upon FE) should also include the rate of strength loss during Flight 1 as a variable.
• It was proposed that QCT and FE strength can also be used to inform the Integrated Medical Model (developed at NASA Glenn Research Center, Cleveland, OH), which conducts probabilistic fracture risk assessments for mechanically-loaded mission tasks. This probabilistic fracture module (Nelson 2009) can be used in the context of exercise conducted on ARED to evaluate the risk of an on-orbit injury - a concern voiced during Panel discussion.

• The Panel also highlighted the existing knowledge and technology gaps in understanding the impact of spaceflight on bone microarchitecture of hip and spine; microarchitectural disruptions are a hallmark of osteoporosis and a technology for assessing trabecular microarchitecture of the hip is required to optimally estimate hip fracture risk.

1.5 Additional Uses of QCT and FE Strength

The Panel offered additional considerations as to how the Space Medicine Operations Division can use research data generated by QCT surveillance and FE strength modeling as part of its clinical care guidelines.

Panel Comments and Recommendations

• As previously alluded to, FE modeling performed in the AGES (Reykjavik, Iceland cohort) will be analyzed to provide a reference range of FE strengths whereby fractures are likely to occur in an Earth-based, non-astronaut population. A distribution of FE strength might provide a range of FE strength that astronauts must exceed for certification for second flight.

• The Panel emphasized that a selected range of FE strengths is NOT based upon a presumed increase of fracture on the subsequent mission recognizing that the fracture risk while in the ISS in low-Earth orbit is low. Instead, this FE range will be selected upon considering the combined effect of 2 long-duration missions interacting with the expected changes due to aging in the returned astronaut.

• In a post-Panel discussion, the Panel confirmed that QCT detection of bone structure could be used further to direct bone rehabilitation efforts with exercise. Such rehabilitation approaches should be managed by an on-site clinical expert in physical medicine and rehabilitation for osteoporosis fractures who would work with astronaut trainers.

• It was further agreed that the probability of fracture can be mitigated with knowledge of bone failure loads and adjustments to physical activity upon return to Earth (for example, restrictions of certain weight-bearing activities) could be implemented and modified according to recovery of bone strength.

• The application of QCT and FE data for probabilistic modeling for fracture risk (PRAs - probabilistic risk assessments) in the returned astronaut should be explored.

• The Panel also indicated that QCT and FE strength are required to confirm response to therapy and effective rehabilitation.
As QCT and FE surveillance data accumulate, the variability in measures for the astronaut population will inform decision-makers, especially with regards to future, extended missions on near-Earth orbit asteroids.

1.6 Use of DXA for Surveillance

For astronaut returning after a long-duration mission with a DXA T-score < -2.0, serial DXA scans at 6-month intervals are implemented until aBMD returns within 2% of preflight value. Once DXA establishes the stability of recovery, scans are conducted on a triennial basis for continued surveillance of astronaut bone health. There is an abundance of Earth-bound epidemiologic data that makes DXA the principal tool for skeletal assessment and for fracture prediction in the general population. For astronaut surveillance, DXA generates a minimal cumulative radiation exposure and also enables simultaneous monitoring of changes in body composition.

Panel Comments and Recommendations

- The current DXA monitoring schedule should continue as it has minimal radiation exposure, allows for continued follow up after the final QCT, adds to the available, historical dataset for surveillance, and remains the most widely used predictor of fracture risk in spite of its limitations.

- However, the lower exposure to ionizing radiation with DXA, even with its BMD-based inferences of bone structure with as hip structural analysis (Hologic), does not outweigh the additional data gained with QCT assessment (including the detection of the clinical trigger).

- Clinical and operational decisions as a consequence of spaceflight-induced skeletal effects will not rely solely upon DXA-derived BMD.

- Specific disruptions in trabecular bone microarchitecture (reduced trabecular number and increased trabecular spacing and trabecular separation versus reduced trabecular thickness) are associated with reduced mechanical strength and increased fracture risk in vertebral bodies; how prolonged spaceflight influences trabecular microarchitecture of the hip and its contribution to whole bone hip strength needs to be quantified in addition.

- The Panel stated that MRI is an attractive future imaging option but not yet useful for whole bone strength determinations. MRI correlations with QCT FE will require further development and financial support.

2.0 STATUS OF COUNTERMEASURE RESEARCH FOR EARLY ONSET OP

There is a body of evidence in bioastronautics literature that has shown that a lack of mechanical loading on the skeleton, compounded by hormonal alterations and operational constraints to preserving bone health, result in bone atrophy in astronauts serving on long-duration missions. Changes in aBMD are evident in those astronauts conducting extended missions (typically 6 months) on the ISS. Although it is recognized that a loss of bone mass may reduce bone strength and may increase the fracture risk of returning astronauts, there is a lack of surveillance data to fully assess the risk of early-onset osteoporosis and to substantiate the premature occurrence of fragility fractures.
In the absence of fragility fractures detected in the existing long-duration astronaut population, the Panel was asked to review individual charts of the long-duration astronauts. The Panel engaged in a discussion session of Day 2 that centered on the following key query: Do the data suggest that an intervention is required to mitigate the risk of premature fragility/osteoporotic fractures?

**Panel Comments and Recommendations**

- It is the Panel’s collective expert opinion that an intervention is needed for long-duration astronauts to mitigate the risk of Early Onset Op (and age-related fractures).
- This assessment is based upon the following:
  - A precipitous rate of BMD loss that, at the very least, models the losses observed with the onset of menopause (LeBlanc 2000).
  - Structural changes to proximal femur (cortical thinning) in astronauts (Lang, 2004).
  - Complete recovery of vBMD for the trabecular compartment of the hip is not observed in 8 crewmembers anywhere between 2 to 4 years after return (Carpenter 2010).
  - The impact on bone microarchitecture of the hip (and spine) is unknown.
  - The changes induced by spaceflight are likely to compound with the changes induced by aging (Riggs 2004, 2008).
  - Deficit in the trabecular vBMD of the femoral neck is a predictor of hip fracture (independent of aBMD) in elderly men (Black 2008).

In its charge, the Panel was also asked to consider and discuss various means of intervention at different stages of a spaceflight mission or of an astronaut’s life:

- **Before a mission:** Can prophylactic therapies be implemented before flight to prevent bone loss during a mission? Could medical standards be modified to ensure selecting astronauts of optimal bone health and with minimal risk factors? Should our standards for certifying long-duration astronauts detail more disqualifying conditions?
- **During a mission:** Will it be enough to mitigate risk factors secondary to the adaptation to weightlessness? For example, controlling dietary intake, providing resistive exercise capability.
- **After a mission:** Should intervention be delayed and therapy applied to reverse spaceflight-induced skeletal changes? What index should serve as the clinical trigger? Or, instead mitigate expected declines with the aging process?

### 2.1 Preflight Interventions

Current NASA guidelines dictate that within a year before flight, astronauts receive a DXA scan to assess their preflight bone status. While it is not considered a disqualifying conditioning for astronauts to have a hip or spine BMD measure that is 1.5 standard deviation or greater below the mean BMD of young, sex-matched persons, astronauts undergo an endocrine evaluation to determine if low bone mass can be attributed to a treatable metabolic condition and to receive the most appropriate course of action. Notably, the World Health Organization (WHO)
diagnostic classifications of osteopenia and osteoporosis apply only to men ≥ age 50, to perimenopausal women and to postmenopausal women. To apply these diagnoses to persons outside these groups implies that they have a disease state, which may not be the case. However, astronauts with ≤ -1.5 T-score for hip and spine are not automatically assigned to a flight. The basis for this BMD guideline is the presumption that at a constant, averaged rate of BMD loss of 1% to 2% per month, an astronaut may return from a 6-month mission with a T-score < -2.0 (NASA denotes this non-permissible outcome).

In addition, the current musculoskeletal medical standard for selection into the Astronaut Corps, which is similarly based upon DXA T-scores for hip, was considered highly conservative by the Panel. The Panel agreed that the selection standard might unnecessarily disqualify persons based upon their genetic make-up (that is, being female or small boned). While smaller bones are considered a risk factor for fracture, the Panel suggested that FE strength (as previously discussed, Section 1.4) may provide a better estimation of strength because it integrates other determinants (such as geometry, cross-sectional area or trabecular bone density. Standards for optimal bone health used at astronaut selection and for flight certification provide another means (a preflight intervention) of mitigating the risk for Early Onset Op.

Teriparatide, a synthetic form of human parathyroid hormone, has been shown to stimulate trabecular bone formation. Forteo®, teriparatide’s trade name, is FDA-approved for the treatment of osteoporosis in both men and women with various off label uses noted, including improved fracture healing in athletes. It may therefore be possible to use Forteo® to augment the trabecular bone of low BMD astronauts but any such use of Forteo® would be individualized and require consultation with Dr. Stevan Petak (NASA-contracted endocrinologist).

- Certain Panel members suggested that Forteo® may provide some benefits preflight but strongly stressed the importance of further research, especially since this would be an off-label use of an FDA-approved drug.
- Forteo® given to astronauts should be an option for treatment only according to current clinical guidelines.
- The inclusion of Forteo® in the flight medical kit for fracture healing, however, should be seriously considered for Exploration-class missions.

2.2 In-flight Interventions

Currently in-flight interventions have two approaches: (1) eliminating or mitigating risk factors for bone loss (Plan A) and (2) using pharmaceutical anti-resorptives (Plan B). Recognized risk factors for bone loss include reduced physical and resistive activity in the weightless environment and inadequate nutrition during flight.

Plan A: Historically, resistive and aerobic exercises, to mitigate the effect of reduced physical activity or of mechanical unloading, have been the cornerstone of bone loss interventions during missions. Recently the advanced resistive exercise device (ARED) was flown to the ISS (December 2008) to supplement the interim resistive exercise device (iRED), the cycle ergometer (CEVIS) and treadmill exercise (TVIS) hardware (flown since 2000). The ARED increased resistive loading up to 600 lb (2-fold > than iRED) and improved the type of loading, being more analogous to the resistive exercise performed with free weights in the 1g environment. This suite of hardware provides resistive and aerobic exercise capabilities where exercise regimens are individually prescribed for each astronaut. In addition, the allotted time for
exercise is 2.5 h/d for 6 d/wk, where the actual time performing exercise amounts to approximately 1.5 h/d due to setting-up and re-stowing of hardware. While these exercise opportunities were/are available for all ISS long-duration astronauts, there were 7 long-duration astronauts, who served on the earlier Mir spacecraft (1995-1998), who did not have access to either the ARED or the iRED.

There are additional Plan A countermeasures aimed at reducing dietary risk factors: the contribution of salt restriction (SOLO) and acid/base modifications (ProK) are being investigated in flight research studies. These dietary countermeasures are offered to consented participants.

Because DXA-measurement of aBMD is a required medical assessment test in long-duration astronauts, DXA BMD is the only index used to evaluate spaceflight-induced changes in bone mass in response to exercise using ARED and to dietary approaches to mitigating bone loss.

Incidentally, over the ~20-year course of long-duration spaceflights (Mir and ISS), the largest dataset available to assess spaceflight as a risk factor for Early Onset OI is composed of DXA BMDs. Those measures have been supplemented by assays of bone turnover markers and as of 2000 both datasets (aBMD and bone turnover markers) were generated by required medical assessment tests for all long-duration astronauts. There is a small amount of QCT information (reported from 16 ISS crewmembers) to describe the adaptation of bone structure during prolonged spaceflight (Lang 2004) and an even smaller amount (iliac crest biopsies from II non human primates) that describe the histomorphometry of space-induced bone loss (Zerath 1996, 2002). QCT remains a research technology that can be applied to a limited number of astronauts who consent to participate in-flight studies designed to use QCT measures as an experimental outcome.

The Bone Summit chart reviews of DXA BMD evidence indicated that spaceflight resulted in substantial deficits (exceeding 10%) in the lumbar spine and the hip over the course the mission for a number of long-duration astronauts (n = 6 of 29).

Panel Comments and Recommendations

- The Panel underscored the fact that the concurrent applications of countermeasures in an individual astronaut during flight will confound the ability to validate individual countermeasure approaches.

- Due to a lack of information about possible drug-induced side effects under weightless conditions and the severity of complications should they occur during a mission, the Panel recommended a continued focus on exercise and diet countermeasures (Plan A) as the primary method of bone loss prevention before employing Earth-based pharmaceutical interventions (Plan B).

- The newly installed ARED has returned promising results on aBMD (DXA) yet the effects on compartment-specific bone adaptation are still unknown. Because bone compartments lose bone mass at different rates, and because QCT can measure vBMD in separate bone compartments, QCT is critical for understanding the effect of interventions. With the current lack of critical QCT data, the Panel was prevented from drawing any strong conclusions regarding currently tested in-flight interventions designed to mitigate risk factors for bone loss.
To characterize spaceflight effects and to determine the effectiveness of current in-flight interventions for space-induced bone adaptation, the Panel strongly recommended that QCT scans be a required technology to validate the efficacy of all in-flight countermeasures to bone loss and structural changes.

**Plan B:** Very few studies of osteoporosis pharmaceutical drug therapies have been carried out on the ISS, most notable of these being the ongoing study with Fosamax® (alendronate). The flight experiment, which is a joint experiment with the Japan Aerospace Exploration Agency (JAXA), actually tests II pharmaceutical agents in the class of bisphosphonates (Fosamax® [alendronate] and Reclast® [zoledronic acid]) for the ability to prevent losses in bone mass and changes to bone structure in long-duration astronauts; the experiment is powered for n = 8 astronauts with statistical comparison to 16 historical controls (Lang 2004). Only alendronate, however, is offered to US astronauts because of NASA’s concern for the safety profile of zoledronic acid. The primary index of efficacy is the mitigation of decline in the vBMD of trabecular compartment in the hip as determined by QCT. As mentioned, effective mitigation will be determined by statistical comparison to historical controls (ISS astronauts from previous ISS mission scanned by QCT) none of whom had access to ARED (Lang 2004).

**Panel Comments and Recommendations**

- In Panel discussions it was noted that the fracture risk in space is very low. Consequently, a pharmaceutical intervention may not be justified during flight but may be more appropriate after an astronaut has returned to Earth. However, a concern for in-flight stress fractures and fractures during in-flight exercise performance had also been raised. This issue may be resolved at a later time as bone strength data begin to accumulate and probabilities for fracture can be estimated.

- The current lack of information about possible risks associated with different pharmaceuticals and their effects during spaceflight precluded the Panel from suggesting a specific drug-based intervention at this time.

- The preliminary but very limited flight data of alendronate are encouraging and suggest that the bisphosphonate alendronate may be beneficial to astronauts by preventing bone loss in the hip during flight. However, the Panel cautioned that this study coincides with the implementation of new ARED hardware; therefore, it may be not possible to determine the contribution of each intervention on the prevention of BMD loss or the underlying structural changes.

- To help elucidate the distinct effects of the Fosamax® study from exercise, it was recommended that a placebo group of 8 individuals be included in a randomized study. This would allow for a blinded comparison of combined alendronate and ARED-exercise interventions with only the ARED-exercise intervention.

- However, the Panel stated, that regardless of the Fosamax® study findings, pharmaceuticals such as bisphosphonates, should remain a “Plan B” approach if exercise proved to be ineffective. In the extreme environment and austere confines of the ISS, the relatively minor complications on Earth, such as nausea and heartburn, may prove extremely dangerous for crewmembers in space. And while the rare, severe complication of esophageal ulcer is better understood and considered an
acceptable risk for the general population, such an event would prove disastrous for an astronaut in space.

- The Panel on the whole strongly disagreed with the NASA decision not to offer Reclast® (zoledronic acid) as a bisphosphonate option for the in-flight experiment. The safety of the drug is high for the doses used to treat osteoporosis.
  - If an on-orbit pharmaceutical intervention is deemed to be necessary, for example, with longer Exploration-class missions, then the administration of a pharmaceutical before flight would be preferred as this allows for addressing on Earth any issues that may arise. In the case of bisphosphonates, the Panel commented that a single IV infusion of Reclast® (zoledronic acid) is preferred to weekly oral alendronate, because of its associated side effects.
  - New pharmaceutical agents (for example, denosumab) are appealing. The clinical data, however, are emerging and may require a wider use in clinical medicine before the revelation of rare adverse events.

2.3 Postflight Interventions

Currently, there are no specific guidelines for postflight intervention to address the risk of Early Onset Op due to spaceflight. Dr. Steven Petak is the endocrinologist on-contract to the Space Medicine Division. Dr. Petak has, and shall employ, an individualized approach to treating astronauts whose DXA scans of hip and spine indicate a BMD T-score < -2.0 or a failure to demonstrate recovery of space-induced BMD deficits.

Panel Comments and Recommendations

- The previously-mentioned Forteo® is not FDA-approved for young, non-osteoporotic individuals. However, its ability to greatly improve trabecular strength might be effective for crewmembers that are unable to regain BMD over an extended period with conventional treatments.
- Panel recommended that surveillance QCT scans be performed at 1 and 2 years after return. If no change in hip trabecular vBMDs between 1 and 2 years, then QCT scans can cease.
- Recovery of trabecular vBMD will be evaluated in long-duration astronauts at 2 years after return with QCT. The failure to completely recover vBMD in the total hip, femoral neck and trochanter shall serve as a clinical trigger even if DXA indicates sufficient BMD improvement.
- The heterogeneous changes in the spine preclude its evaluation as a clinical trigger for a medical response but this site should be monitored and not ignored. The frequency of QCT scans for spine, however, requires further discussion and no recommendation is available at this time.
- If a clinical trigger is detected at the 2-year time point, the long-duration astronaut and flight surgeon shall seek a clinical evaluation by Dr. Petak for possible intervention.
- Any subsequent QCT scanning, for example, to evaluate response to intervention, is per medical order.
3.0 LIFETIME SURVEILLANCE OF ASTRONAUT HEALTH

3.1 Integration of Medical and Research Data to Define Bone Health Risks

Panel Comments and Recommendations

- Because there are sex-specific patterns as to how humans lose bone mass as they age, the Panel recommended that data for male and female astronauts should not be combined when presented. NASA will need to address privacy issues (due to small number of possibly identifiable females) to consider this recommendation.

- Not all data from biochemical assays for mediators or markers of bone regulation, (for example, levels of gonadal hormone) was available for review by the Panel. Some data were of active flight experiments. Additionally, biochemical data on the same subject, sometimes from identical biological specimens, yielded divergent results likely due to tests performed by different laboratories and using different methods. The Panel recommended that key biochemical regulators of bone volume should be required medical assessment tests to be conducted in all astronauts and that these tests should be performed by one central laboratory, ideally with stable or calibrated methodology over time.

- As a follow-up action, the Bone Discipline Lead will distribute to the Panel a list of clinical biochemical indices and assay methods (established and putative effectors and/or markers of bone turnover) that are conducted in astronauts either as a medical test or an experimental endpoint. Panel members will recommend an optimized list of medically-required biochemical assays, with preferred methods, specific to supporting clinical decisions for bone risks.

- Panel members recommended the use of an external Data Safety Monitoring Board to evaluate and oversee the quality of astronaut dataset.

- It was also recommended that biological specimens for research studies should be aliquoted, stored, or archived until research assays can be conducted in one batch to minimize assay variability.

3.2 Facilitating Use of Clinical Medical Records to Support Research Studies

During the closed sessions of the Summit, there was a disclosure of private medical information related to the in-flight intake of medications that have known effects on bone volume (for example, glucocorticoids, and/or estrogens). These “private medical conferences” are not accessible or readily known except to the flight surgeon and the astronaut. The inability to access such information could contribute to incorrectly-drawn conclusions from epidemiological research studies or from other similar data-mining analyses.

Panel Comments and Recommendations

- The Panel recommended that standardized procedures be developed for accessing all information (research or clinical) required for developing clinical practice guidelines (that is, for summit activities) or for any IRB-approved research study.

- In addition, clinical medical records are not always research-friendly; clinical records currently do not include the additional questionnaire administered by the Bone Mineral Lab with each DXA scan to collect FRAX-related risk factor information.
The Panel recommended integrating questions of the Bone and Mineral Lab (where astronaut DXA scans are performed) into the emergency medical record (EMR) of the Flight Medicine Clinic (where astronaut annual exams are performed) to avoid redundancy and discouraging astronauts from follow-up DXA scans.

- The medical record merger shall enable electronic access to medical history by the DXA technologist during the scheduled DXA scan. Before each scan, rather than administering a new questionnaire, the ISCD-trained, DXA technologist would ask the astronaut to review previously entered information and provide updates if necessary.

- In addition, the Panel recommended modifying the verbiage of the questions to elicit information in a clinically meaningful manner. For example, fracture history, fracture site, fracture event, age at fracture are all critical to understanding whether a fracture is due to osteoporosis; the current EMR at the Flight Medicine Clinic, with its answer-dependent follow-up questions, will simplify the entry of the bone-relevant medical data.

- Integrating research questions/data into the EMR raises concerns about access to confidential medical information of an already easily-identifiable patient population. To ensure continued patient confidentiality, researchers should be granted access only to the portion of the EMR deemed relevant to their IRB-approved project.

3.3 **FE strength for Surveillance of Fracture Risk**

*Panel Comments and Recommendations*

- The application of FE strength to monitor fracture can be extended over the remaining lifetime of the long-duration astronaut.

- The frequency of QCT scans for the retired ISS astronaut, or possibly any astronaut suspected of being at risk shall be deliberated further by the Panel.

- It is recommended that the Panel be reconvened as QCT and FE surveillance data are acquired to re-evaluate the dataset as it pertains to the lifetime surveillance of the long-duration astronaut.

**FORWARD ACTIONS**

On behalf of the Panel, a manuscript will be prepared for submission to the journal *Osteoporosis International* on the Panel’s recommendations to NASA for bone health surveillance in astronauts. A formal report will later be presented to NASA’s Aerospace Medicine Board to consider the recommended approaches for surveillance of bone loss to reduce fracture risk in the astronaut population and the recommended use of whole bone strength to direct rehabilitation approaches and to assist in the selection of astronauts for specific mission architectures or second long-duration missions.
REFERENCES


APPENDIX A - PRE-SUMMIT READING MATERIAL

Future human bone research in space. LeBlanc A, Shackelford L, Schneider V. 1998, Bone 22(5):113S-116S.


Epidemiologic analyses of risk factors for bone loss and recovery related to long-duration space flight. Amin S. 2010, HRP Investigator Workshop, Houston, TX.


# APPENDIX B - AGENDA

**June 7-8, 2010**

**NASA Johnson Space Center and Universities Space Research Associates, Houston, TX**

## Sunday, June 6

| All Day | Panel members arrive in Houston; check-in at the Hilton Hotel |

## Monday, June 7

| 7:30 AM | Arrive at USRA, check-in |
| 7:55 AM | Summit Rules-of-Engagement. Introduction of Summit Participants |
| 8:00 AM | Welcome - Summit Chair: J. Mike Duncan, MD, Deputy Chief Medical Officer |
| 8:30 AM | Presentations and Discussion |
| a. Medical Standards for Bone and the Risk Management Assessment Tool [RMAT] - Jennifer Fogarty, PhD |
| b. Review of Physiological Deconditioning - Clarence Sams, PhD |
| c. Trends in Astronaut Bone Biochemical Data - Scott M. Smith, PhD |
| d. Bone Evaluations in Astronauts: Group Trends - Jean D. Sibonga, PhD |
| e. Current Bone Health Program for Active and Retired Astronauts - James Locke, MD |
| 11:30 am | Break |
| **PM Sessions** | Closed to nonmedical personnel and JSC personnel not directly involved in generation and presentation of data |
| 12:00 pm | Working Lunch, Review of Bone Health Surveillance Questions for Bone Health Program |
| 1:00 pm | Panel Review of Selected Crewmember Data |
| 5:00 pm | Adjourn for the day |
| 6:30 pm | No-host dinner with NASA stakeholders at Perry’s Italian Grille Astronaut Michael Barratt, MD and J. D. Polk, DO |

## Tuesday, June 8

| 7:30 AM | Check in (lunch order) and Coffee |
| 8:00 AM | Morning Session: Continued review of individual crewmember data |
| 12:00 PM | Working Lunch |
| 1:00 PM | Afternoon Session: Continued review (if required) and discussion: Charge-to-the-Panel |
| 4:00 pm | Recommendations and Forward Actions of the Panel |
| 5:00 pm | Closing Remarks |
APPENDIX C - CHARGE TO PANEL FOR SUMMIT ON EARLY ONSET OP IN LONG-DURATION ASTRONAUTS

The NASA Astronaut Corps is not the typical cohort for evaluating osteoporosis or determining age-related fracture risk. Astronauts are young, ranging between 25 to 55 years of age, and are made-up predominantly of men (male: female ratio of 3:1). Individuals are selected into the Corps by a stringent set of medical standards to ensure a long, healthy and safe career in the space program; their fitness level should enable them to endure the rigors of training, flights on high performance aircraft, exposure to hypobaric and hyperbaric conditions in addition to the effects of microgravity. Moreover, the skeletal adaptation to space has not been fully described for the long-duration astronaut because of the additional factors of prolonged space occupation that may contribute to the deconditioning of bones. In particular, the lack of weight-bearing and aerobic activities, muscle atrophy, 10 to 20 fold increased atmospheric CO₂, constrained dietary intake, inhibited vitamin D metabolism (by ultraviolet shielding), reduced plasma volume, and cephalic fluid shifts could exacerbate skeletal adaptation. Furthermore, the constraints of mission operations such as up-mass, volume, power, time and remote medicine hinder the application of known Earth-based countermeasures to bone loss.

Thus, this panel of bone experts is charged with reviewing 29 case reports (long-duration astronauts) to evaluate if there is enough evidence to address the following questions:

1. Does the evidence-to-date suggest that an intervention is required now (versus continuing research) to prevent early onset osteoporosis? Can a clinical threshold be identified at which intervention should be implemented?

2. If so, what kind of intervention is recommended, when, and what should be the “driver” for its implementation:
   - Before mission - For example, can prophylactic therapies be implemented before flight to prevent bone loss during a mission? Could medical standards be modified to ensure selecting astronauts of optimal bone health and with minimal risk factors?
   - Should our standards for certifying long-duration astronauts detail more disqualifying conditions?
   - During mission - Will it be enough to mitigate risk factors secondary to the adaptation to weightlessness? For example, supplementing vitamin D, controlling dietary intake, providing resistive exercise capability.
   - After a mission - Based upon the evidence, is it possible to reverse spaceflight-induced skeletal changes or do we mitigate expected decline with aging?

3. Is there enough evidence to indicate that an intervention during spaceflight missions will do more good than harm in this younger, healthy population?

4. Direct question from the flight surgeons: How can they use research data in clinical practice? Specifically, how do they apply the following information: QCT data on bone geometry and bone compartmental vBMD; the estimations of bone failure loads by Finite Element Modeling, the current calculations of Factor-of-Risk based upon falls from standing height, estimations of bone strength by BMD or biomechanical algorithms for compressive and bending strengths.
5. If intervention is not required during a mission is there a permissible outcome limit and for which criterion (for example, is there an acceptable BMD loss, an acceptable decline in bone structure, and is restoration of preflight bone turnover level sufficient)?

6. If the recommendation is to “watch and monitor” what information should be acquired and what specific measures should be conducted to monitor this osteoporosis risk? What data should be acquired during a mission? What medical tests and analyses should be conducted during the post-mission period and during Lifetime Surveillance of Astronaut Health (LSAH)?

7. If a postflight fracture should occur, is it possible to discriminate the contributions of spaceflight exposure vs. aging for this fracture occurrence? Is there an “end of liability” for NASA if a long-duration astronaut fractures in the post-mission time period?

8. Direct question from Human System Risk Board: what is the clinical trigger in a long-duration astronaut (physiological measure, BMD decline) that will require space medicine to respond clinically? When is a referral to bone endocrinologist required? If a fracture occurs, should there be additional follow-up beyond the orthopedic surgeon?
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*Bone Summit Data Coordination Team*
APPENDIX G - USE OF QCT TECHNOLOGY FOR CLINICAL AND OPERATIONAL DECISIONS

Use of Bone Imaging Technology for Clinical and Operational Decisions

Recommendations from an Expert Panel for Consideration by NASA

PRE-FLIGHT 1

Is L2-1y DXA T-score above 1.0?  

Additional clinical info?

Endocrine Evaluation (for possible treatment)

No pre-flight intervention required

Eligible for Further Screening

Is OCT derived FE strength above (TBD)?

Inseligible for Candidacy unless waiver granted.

APPLICANTS FOR ASTRONAUT CANDIDACY

Is DXA T-score* above -2?  

yes

no

POST-FLIGHT 1

Is R2+ly DXA T-score above -2?  

Send to Osteoporosis Expert

yes

no

Is R1+lyDXA T-score within 2% of preflight?

Is R1+lyDXA T-score within 2% of preflight?

Is R1+lyDXA T-score within 2% of preflight?

Is R2+lyDXA T-score within 2% of preflight?

Is R2+lyDXA T-score within 2% of preflight?

Conduct routine DXA every 3 years from date of DXA indicating recovery within 2% of preflight

Send to Osteoporosis Expert

R2+ly DXA

R1+ly QCT*: FE strength and trabecular recovery

R1+ly QCT*: FE strength and trabecular recovery

R1+ly QCT*: FE strength and trabecular recovery

POST-FLIGHT 2

Is OCT derived FE strength at time of recanalization above (TBD)?

Is DXA T-score above -1.5?

Pre-flight intervention required

Consult Osteoporosis Expert

Certified for second flight

No pre-flight intervention required

Flight 2

Flight 1

Is R2+ly DXA T-score above -2?  

Does R2+ly QCT* indicate trabecular bone recovery within 2% of preflight or FE strength < (TBD)*?

Send to Osteoporosis Expert

Conduct routine DXA every 3 years from date of DXA indicating recovery within 2% of preflight

Send to Osteoporosis Expert

R2+ly DXA

R1+ly QCT*: FE strength and trabecular recovery

R1+ly QCT*: FE strength and trabecular recovery

R2+ly QCT*: FE strength and trabecular recovery

R1+ly QCT*: FE strength and trabecular recovery

R1+ly QCT*: FE strength and trabecular recovery

R1+ly QCT*: FE strength and trabecular recovery

R2+ly DXA

*All designated QCT scans are for occupational surveillance purposes.
* T1: Total Hip, Femoral Neck, Trochanter, and LS
* As per 2019 Med Vol 6 in 2019
### Title and Subtitle
Conference Proceedings - 2010 Bone Summit: Risk for Early Onset Osteoporosis

### Authors
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### Abstract
The Bone Discipline Lead for NASA’s Human Research Program was tasked by the Space Medicine Configuration Control Board and the Human System Risk Board to convene a panel of osteoporosis clinicians to review the existing dataset collected on long-duration astronauts to make recommendations for clinical practice guidelines that are specific to the spaceflight-induced risk for Early Onset Osteoporosis (Early Onset Op). The selected Panel consisted of clinical experts in fields of bone densitometry, endocrinology, male osteoporosis, gerontology, bone epidemiology, physical medicine, rehabilitation, vitamin D, and nutrition. The Bone Summit was conducted in Houston, TX on June 7 and 8, 2010, by invitation only, at the Universities Space Research Association facilities. Support scientists, extramural investigators, and NASA personnel that were involved in astronaut data acquisition and analysis were asked to support Panel discussions.

### Subject Terms
- long-duration spaceflight
- bone density
- bone mineral density
- osteoporosis
- early onset osteoporosis
- exercise

### Security Classification
- Unclassified

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