Bellagio II Report: Terrestrial Applications of Space Medicine Research

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INTRODUCTION: For over 50 yr, investigators have studied the physiological adaptations of the human system during short- and long-duration spaceflight exposures. Much of the knowledge gained in developing health countermeasures for astronauts onboard the International Space Station demonstrate terrestrial applications. To date, a systematic process for translating these space applications to terrestrial human health has yet to be defined.

METHODS: In the summer of 2017, a team of 38 international scientists launched the Bellagio ll Summit Initiative. The goals of the Summit were: 1) To identify space medicine findings and countermeasures with highest probability for future terrestrial applications; and 2) To develop a roadmap for translation of these countermeasures to future terrestrial application. The team reviewed public domain literature, NASA databases, and evidence books within the framework of the five-stage National Institutes of Health (NIH) translation science model, and the NASA two-stage translation model. Teams then analyzed and discussed interdisciplinary findings to determine the most significant evidence-based countermeasures sufficiently developed for terrestrial application.

RESULTS: Teams identified published human spaceflight research and applied translational science models to define mature products for terrestrial clinical practice.

CONCLUSIONS: The Bellagio ll Summit identified a snapshot of space medicine research and mature science with the highest probability of translation and developed a "Roadmap" of terrestrial application from space medicine-derived countermeasures. These evidence-based findings can provide guidance regarding the terrestrial applications of best practices, countermeasures, and clinical protocols currently used in spaceflight.

KEYWORDS: Space medicine, countermeasures, translation science, risk mitigation, terrestrial application, human health performance.

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INTRODUCTION

Section Leads: Marian B. Sides and Brent Monseur

Background

For more than 50 yr, research scientists have studied the impact of the space environment on the human body and the consequences of these exposures on long-term human health, performance, and longevity. Much of the knowledge gained in developing countermeasures to help astronauts live in the unique habitat of the International Space Station (ISS) is applicable to humans on Earth. While valuable information to enhance human health is available from space medicine, a systematic process for translating space applications to human health on Earth has not been clearly defined.

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Future space missions beyond low Earth orbit will be highly constrained without medical evacuation possibilities or real-time telemedicine and procedural support. Research into the effects on the human system and subsequent countermeasure development for these long-duration space missions will further increase the body of space medicine literature with potential terrestrial application.

Bellagio II Summit

In the summer of 2017, a team of 38 international scientists launched the Bellagio II Summit Initiative. The goals of the Summit were to identify space medicine findings and countermeasures with the highest probability for future terrestrial applications, and to develop a roadmap for translation of these countermeasures to future terrestrial application to enhance human health, performance, and longevity. The objectives were to contribute to the science of aerospace medicine, mentor the next generation of scientists, engage multidisciplinary mindsets in an international venue, and to contribute to the education of professional and lay communities through outreach activities and publications. The team reviewed NASA databases and evidence books within the framework of the five-stage National Institutes of Health (NIH) translation science model and the NASA two-stage translation model. Following the literature reviews, teams analyzed interdisciplinary findings to determine the most significant and mature evidence-based countermeasures ready for translation from the space environment to terrestrial application. This data analysis shaped the 4-d summit held in September 2017 in Moltrasio, near Bellagio, Italy. Five research themes were defined: 1) Space Travel and Genetics; 2) Habitat and Environment; 3) Nutrition; 4) Physiological Fitness and Exercise Countermeasures; and 5) Behavioral Health. Participants in the Summit engaged in multidisciplinary discussions and deliberations to develop abstracts on mature space medicine countermeasures demonstrating readiness for clinical application and practice on Earth.

The Translational Sciences Model

The Bellagio II Summit sought to identify mature science in space medicine research with current terrestrial application for human health and longevity. The Bellagio team adopted the NIH Translational Science Spectrum as a conceptual model to analyze public-facing NASA databases, technical documents, and the scientific literature for the available, mature science. The NIH Translational Science Model (**Fig. 1**) demonstrates a multidirectional flow of information through five stages, from basic research through to readiness to apply to population-level health here on Earth.

During the literature review process, note was made of various patterns of information flow. Incongruent with the well-known, linear, step-by-step process of the Technology Readiness Levels (TRLs) in engineering, the science has often jumped from preclinical to operational procedure. This highlights the flexibility and dynamism of the space medicine field where high-quality research can drive operational procedures, despite small *N*-values. In this report of the Bellagio II findings, we highlight examples of bidirectional and multidirectional information flow of research findings that have potential for terrestrial application. The development and application of countermeasures to protect the astronaut corps require research at multiple levels of maturity. Translating research and practice at various levels within the NIH translational stages model may inform novel countermeasures with potential terrestrial spin-offs.

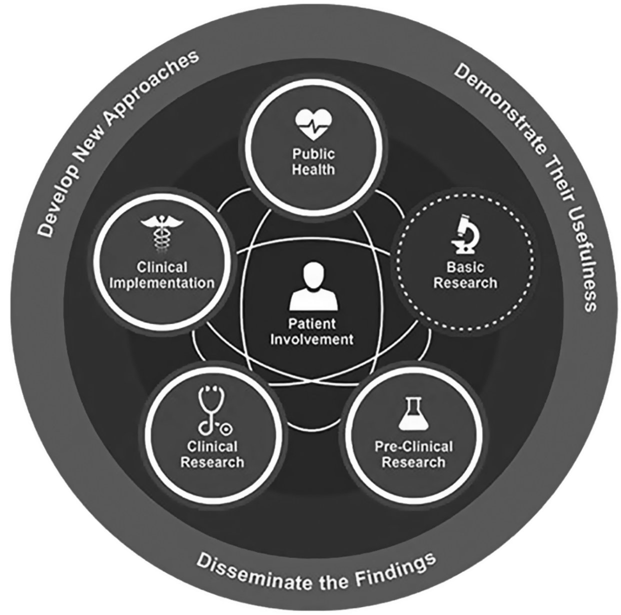

Fig. 1. The National Institute for Health (NIH) Translational Science Spectrum diagram demonstrating the nonlinear transfer of information and potential from various stages of clinical research.

CORONARY ARTERY DISEASE RISK MITIGATION STRATEGIES

Section Leads: Smith L. Johnston III and Jan Stepanek

Background

The potential for incapacitation due to cardiovascular event during spaceflight is a concern that has driven robust and evidence-based monitoring programs for astronaut and cosmonaut cardiac health. As prevention of cardiovascular disease relies on risk prediction and associated modifications of diet, exercise, and medication regimens, accurate and reliable cardiovascular risk prediction has received significant attention within the field of aerospace medicine. NASA's current protocol for identification and management has demonstrated early detection, stabilization, and even reversal or regression of coronary artery disease as measured by computed tomography (CT) angiogram and coronary artery calcium (CAC) scoring. Furthermore, identification, management, and utilization of the ASTRO-CHARM scoring model has reduced spaceflight-certified individuals to an estimated cardiac risk of ≤ 0.5% per year.

The current aerospace medicine approach to screening and monitoring astronauts and cosmonauts for cardiovascular disease is designed to identify subtle and cumulative changes to cardiovascular health. Cardiovascular screening efforts include review of family history, use of risk-stratification scores, exercise stress testing, echocardiography, biomarkers, and standard hemodynamic clinical monitoring. Further, astronauts and cosmonauts undergo regular monitoring of CAC scores, carotid intimal media thickness (CIMT) measurements, and cardiovascular angiographic imaging techniques, if clinically indicated.

In 2012, NASA and the National Space Biomedical Research Institute (NSBRI) convened an expert panel to provide recommendations regarding early interventions for maintenance of cardiovascular health based upon best terrestrial practices. These experts reviewed the Multi-Ethnic Study of Atherosclerosis (MESA)[2] as a source of primary guidance. The MESA models likely cardiovascular risk in otherwise healthy individuals based upon various factors including age, sex, coronary artery calcification (CAC), race/ethnicity, cholesterol, blood pressure, family history, smoking status, current medications, and comorbid diabetes.[2] The expert panel considered this approach and then tailored their recommendations to a younger (45-65 yr-old) and highly fit population representative of the active astronaut corps, including additional risk factors such as fitness score and high-sensitivity C-reactive protein levels. Adjustment of risk based on fitness and statin use was validated by a study published by Hallal et al.[44] in 2012 and further refined by Radford et al.[88] in 2018.

Current Approaches for Astronauts

The expert panel presented a list of recommended practices that included:

- Use of MESA to calculate 10-yr risk, based on CACs and Framingham Risk Factors
- Adjustment of risk based on statin use as follows:
  - o 30% reduction for statin use meeting 100 mg/dL LDL target;
  - o 35% reduction for statin use meeting 70 mg/dL LDL target.
- Adjustment of risk based on fitness as follows:
  - o 40% reduction for VO_2max > 10 METs < 11.5 METS;
  - o 45% reduction for VO_2max > 11.5 METs < 13 METS;
  - o 50% reduction for VO_2max > 13 METs.
- Adjustment of risk based on high-sensitivity C-reactive protein (hsCRP) as follows:
  - o 5% risk reduction for hsCRP < 0.5;
  - o 5% risk increase for hsCRP > 3.0 < 10.

Through analysis and refinement of these methods, the astronaut cardiovascular health and risk modification model, ASTRO-CHARM, was developed.[57] This risk assessment tool was developed specific to the astronaut population for the comprehensive assessment of atherosclerotic cardiovascular disease. To develop ASTRO-CHARM, Khera et al. combined participant level data from three population-based cohorts: the Dallas Heart Study, MESA, and the Prospective Army Coronary Calcium (PACC) study.[57] Cox proportional hazard models were created with traditional risk factors as the independent variables (age, sex, race, total cholesterol, high-density lipoprotein (HDL), systolic blood pressure, use of antihypertensive medications, smoking history, and glucose levels). Family history of myocardial infarction, hsCRP levels, and statin use were also tested to determine if they were independently associated with the outcome and improved model-fit statistics. This risk model was internally and externally validated.[57] The ASTRO-CHARM tool is the first integrated atherosclerotic cardiovascular disease risk calculator to incorporate risk factor and CAC data.

Simultaneously, onboard use of ultrasound technology has allowed for sonographic evaluation of carotid intimal media during flight. This noninvasive technique can identify alterations of carotid wall thickness and the development of atherosclerotic vessel wall changes, providing early indication for mitigation strategies of any developing disease.[113] A study published in 2016 by Arbeille et al. described the use of onboard ultrasound by minimally trained astronauts to obtain adequate imaging of the carotid artery for telemetered evaluation,[5] demonstrating the simplicity of such techniques for atherosclerotic screening and risk evaluation.

Terrestrial Applications

These risk mitigation strategies are not uniquely indicated for the astronaut population, and translation of the cardiovascular risk modification pathways utilized for the astronaut corps to terrestrial populations could provide valuable tools for clinicians in the risk stratification and management of cardiovascular disease in their patients. Evidence-based insights and countermeasures identified for potential utilization by health practitioners on their terrestrial patients to identify asymptomatic atherosclerotic soft plaques for stabilization and regression include:

1. Easy, affordable identification of atherosclerotic soft plaques by noninvasive and low-radiation coronary calcium heart scanning techniques and CIMT testing;
2. Analysis of laboratory and genetic markers including cholesterol profiles, Lipo(a), apolipoprotein E4 (APOE4), and similar;
3. Optimization of cholesterol profile and hsCRP (ideally total cholesterol < 150, low-density lipoprotein (LDL) < 80, hsCRP < 1.0) with:
   a. Diet (emphasizing plant based complex carbohydrates and lean meats with an N-6/N-3 ratio of < 3.4, avoidance of simple sugars)
   b. Environmental (good air quality/avoidance of smoking or encouraging smoking cessation)
   c. Fitness, with exercise goals at least 150 min/week at a minimum of 5 METS combined with strength training
   d. Medications (e.g., statins, proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitors, ezetimibe, and others) to manage cholesterol profile

e. Sleep and stress management (including diagnoses and management of obstructive sleep apnea (OSA), awareness of the impact of circadian dysregulation, etc.);

4. Monitoring via periodic biomarkers, imaging (including carotid intimal media testing, CAC, advanced tomographic angiography of coronary vessels, etc.) and risk modeling (such as with the ASTRO-CHARM model, available for public use at http://astrocharm.org).

While developed for specific application in the astronaut population, clinical assessment tools and associated mitigation techniques provide a comprehensive understanding of cardiovascular risk and subsequent clinical interventions. These tools can be implemented for terrestrial applications to augment current clinical practice in patients of similar age and sex.

MUSKULOSKELETAL RESISTIVE EXERCISE COUNTERMEASURES

Section Leads: Michael B. Gallagher and Judith Hayes

Background

Astronauts experience deconditioning during exposure to microgravity associated with spaceflight. This phenomenon has been considered as analogous to accelerated aging, particularly with respect to the musculoskeletal system. Astronauts and cosmonauts travel to space with minimal risk of fracture.[101] Microgravity exposure results in increased bone turnover and decreased bone mineral density (BMD) as well as increases in markers of bone resorption, including urinary deoxypyridinoline, urinary N-telopeptide, and urinary pyridinium crosslinks.[101,111] Loss of muscle mass is also recognized as a problem following microgravity exposure. Previous studies have delineated these losses through studies of isokinetic strength of various muscle groups in astronauts pre- and postflight.[32] Exercise has historically been used as a countermeasure in the U.S. space program to mitigate physiological impacts of microgravity exposure.[50] Research has been conducted over decades by the international community to refine the countermeasure prescriptions and thereby optimize astronaut performance while mitigating effects on the cardiovascular, sensorimotor, and musculoskeletal systems.[50,98,131] Currently, astronauts on the ISS are scheduled for 2.5 h per day, 6 d per week of dedicated exercise, with 30–45 min for aerobic exercise and approximately 45 min for resistive exercise.[50,98] The ISS is outfitted with cycle ergometers (U.S. and Russian), treadmills (U.S. and Russian), and resistive exercise devices. Though significant advances in exercise countermeasures have been made, further research on optimizing individual prescriptions of varying body types is needed.[98]

To combat bone and muscle loss in spaceflight, the ISS was initially equipped with an interim resistive exercise device (iRED) for the first 18 ISS mission increments. Unfortunately, iRED was no more effective than aerobic exercise at preventing bone loss in prolonged microgravity.[109] Terrestrial knowledge indicates the importance of eccentric loading versus concentric loading in heavy resistive exercise.[101] The advanced resistive exercise device (ARED) replaced the iRED after its arrival to the ISS in 2008.[59] Compared to iRED, the ARED provides astronauts with greater absolute loads, options for constant loading or variable force, an improved eccentric:concentric ratio (90%), a greater variety of possible exercises, and for targeting of mechanical loads to body sites that experience the greatest reductions in bone mass.[59,109] For crewmembers who used ARED on the ISS, their pelvic BMD, bone mineral content, hip femoral neck BMD, trochanter BMD, and total hip BMD remained essentially unchanged after flight compared to preflight measurements.[109] While the ARED marks a significant improvement compared to the capabilities of the iRED, the ARED is still not a perfect countermeasure for bony remodeling and resorption in microgravity. Recent evidence shows that while ARED protects cortical volumetric BMD (vBMD) at the femoral neck, trabecular vBMD at the hip is not protected with current prescriptions.[100]

Six degrees head-down-tilt (HDT) bed rest studies on Earth have been used as an analog to understand the effects of long-term microgravity in humans. Bone loss has been observed in the lumbar spine, femoral neck, trochanter, tibia, forearm, calcaneus, and in the entire body of bed rest subjects.[62] Muscle loss has been observed.[87] Interestingly, these individuals' skulls gained bone mass. Exercise countermeasures to mitigate bone loss have been studied in this setting. Ploutz-Snyder et al. conducted a 70-d HDT bed rest study randomizing 34 subjects to one of four intervention groups: the first using traditional exercise equipment similar to that found on the ISS without supplementation (Ex); the second using traditional equipment similar to what is on ISS along with testosterone supplementation (ExT); the third using a single compact flywheel providing both aerobic rowing and resistance exercise (FLY); and the fourth doing no exercise whatsoever and serving as a control group (CONT).[87] Quadriceps and soleus muscle atrophy was significantly attenuated by the exercise countermeasures. However, no significant effect of exercise was observed on BMD or its molecular markers with the exception of urinary calcium, which was significantly decreased in both FLY and ExT groups compared with the CONT group.[87]

A good diet and targeted vitamin supplementation during long-duration spaceflight holds promise for mitigating bone loss. Astronauts who consumed higher energy or protein amounts on orbit had lower losses of pelvic bone mineral content.[111] However, while subjects assigned to ARED tended to consume higher amounts of energy and protein than those using the iRED, determining the degree of influence nutrition had versus the type of resistive exercise employed was difficult. Despite astronauts taking Vitamin D supplements on orbit, the amount of it in their bodies appeared to be compromised. The active form of Vitamin D, 1,25-dihydroxycholecalciferol, was lower in astronauts during spaceflight in both ARED and iRED groups.[111] Also, 25-hydroxycholecalciferol in astronauts postflight was decreased despite Vitamin D supplementation. Interestingly, 1,25-dihydroxycholecalciferol was unchanged in their bodies after landing in this study.

Current Approaches for Astronauts

NASA has developed an individualized approach to astronaut bone health. Key to the current regimen is monitoring and customized exercise prescriptions from a NASA flight surgeon in collaboration with laboratory exercise physiologists and an Astronaut Strength, Conditioning, and Rehabilitation (ASCR) specialist. The ASCRs, working under the direction of a licensed physician, are a group that includes an exercise physiologist and licensed athletic trainers, all certified as strength and conditioning specialists. Through their observation, testing, and guidance, individualized prescriptions, in the form of an exercise plan, for each astronaut prepares the crewmember for the flight level of physical fitness required, prevention of in-flight injuries, as well as managing postflight rehabilitation. There is active education for the crewmember on injury prevention and early diagnosis of musculoskeletal injuries. This individualized therapy is achieved through one-on-one training and observation.

Clinical surveillance of mission-assigned astronauts to monitor astronaut health and performance as well as countermeasure effectiveness include[50]:

- Isokinetic skeletal muscle strength and endurance evaluations (pre- and postflight);
- Functional fitness tests (pre- and postflight);
- Cycle ergometer aerobic capacity VO_2-max test (pre, in-, and postflight);
- Dual-energy X-ray absorptiometry scan (pre- and postflight);
- Biomarker monitoring (pre- and postflight);
- n-telopeptide monitoring (pre- and postflight);
- Vitamin D monitoring (pre- and postflight);
- On-orbit strength and conditioning monitoring (in-flight daily exercise logs).

Terrestrial Applications

Lessons learned from astronauts on the ISS may have direct application to elderly patients at risk of hip fractures. In the elderly, hip fractures can be devastating. Many experience significant decreases in their activities of daily living (ADL) and independent activities of daily living (IADL) 1 yr after such an injury with mortality rates of 10–35% during this timeframe.[68] Contributing factors to hip fractures in the elderly include an increased propensity to fall, lower BMD, fatigue damage to bone from microfractures, thinning of cancellous and cortical bone structures, and, in females, changes in femoral neck geometry.[95] Certain exercise programs in the elderly can improve BMD, but could be optimized to ensure consistent results. Elderly subjects exposed to 40-wk-long resistance training programs experienced a significant increase in BMD at their lumbar spines and hips.[15] However, in another study conducted on middle-aged and older men doing resistance and high-impact loading exercises for 9 mo, no significant improvement in BMD was seen compared with a control group.[18]

In the immediate postflight phase, astronauts also have a higher susceptibility to fall as compared to their preflight status based on measures of postural stability via computerized dynamic posturography.[131] This is a concern as long-duration mission astronauts may have compromised their bone density and architecture so that their fracture risk may be heightened. While the on-orbit countermeasures address aerobic, anaerobic, and musculoskeletal conditioning, some in-flight resistance activities ‘requiring stable manipulation of external loads’ during lower-body resistance exercise may support positive sensorimotor outcomes postflight.[131] In addition, the daily, personalized astronaut reconditioning programs initiated immediately on return from the ISS contribute to recovery astronaut health and performance.

From iRED to ARED to dietary interventions, the space program has strived to mitigate microgravity’s harmful effects on the musculoskeletal systems of astronauts. Lessons learned in long-duration spaceflight can be applied to improve exercise prescriptions in the elderly to mitigate hip fractures and other harmful effects of osteoporosis. The fact that ARED was designed to provide more types of in-flight exercises, higher intensity exercise prescriptions, and an improved loading profile that simulates constant mass and the inertia of free weights[59,109] gives credence to the notion that exercise prescriptions in the elderly could be optimized by using free weights for resistance training rather than other devices. The bed rest study by Ploutz-Snyder et al. demonstrates that even 1 h per day of exercise can mitigate 23 h per day of unloading via bed rest.[87] Though many hospitalized elderly patients likely cannot achieve the intensity of exercise in this study, the types of exercise that bed rest subjects completed could hold clues to what may improve the exercise regimens prescribed to elderly patients with osteoporosis.

LOWER BODY COMPRESSION GARMENT FOR MITIGATING ORTHOSTATIC INTOLERANCE

Section Leads: Stuart M.C. Lee and Michael B. Stenger

Background

Approximately 25% of astronauts participating in short-duration and > 60% of astronauts who complete long-duration spaceflight (> 4 mo) become presyncopal during a 10-min 80° head-up tilt test on landing day.[64,74] Orthostatic intolerance after spaceflight is a potentially serious health risk for astronauts and cosmonauts during re-entry and landing, particularly if the crew are oriented in the upright, seated position or are required to participate in the piloting of the vehicle. To protect against this, NASA has employed countermeasures that have included in-flight exercise,[68] fluid loading,[22] whole body cooling,[84] and lower body compression garments.[84,86] The Russian Space Agency has implemented a similar suite of countermeasures in which all individuals returning on the Soyuz spacecraft also must participate, including the use of their lower-body compression garment.[60] Analogous interventions have been prescribed to combat orthostatic intolerance in patient populations with varying levels of efficacy.

NASA and the Russian Space Agency had successfully used their respective compression garments, the Anti-Gravity Suit (AGS) and the "Kentavr" (кентавр, translation: "centaur"), for many years.[84,121] The intent of NASA's effort to develop a "next-generation" lower-body compression garment sought to incorporate the best elements of each while addressing some recognized concerns. Laboratory testing previously demonstrated the efficacy of both current garments to prevent presyncope during a 15-min 80° head-up tilt test,[86] a protocol similar to that used when testing astronauts on landing day,[64,74] in subjects who were hypovolemic to levels similar to the plasma volume loss induced by spaceflight.[61,74] With these results in mind and in consideration of observations following spaceflight exposures,[84,121] the baseline requirements for the next-generation compression garments included that mean pressure applied by the garments should be between 40 and 80 mmHg, the range of compression levels provided the AGS and the Kentavr. Other considerations included: continuous coverage from the feet to the abdomen; sizing that was individually customized to the crewmember's anthropometry[86]; construction that would not inhibit movement[16,65]; garments that were easy to don and doff[51]; and gradient compression, applying the highest levels at the lower legs with decreasing pressures at the thighs and abdomen. The goal was to develop a garment that would be worn during re-entry and landing and comfortably protect the crewmember for several hours after landing in the event that medical support personnel were not immediately available to assist the crew in an off-nominal situation.[85]

Research and development at NASA, in collaboration with industry experts, resulted in a three-piece gradient compression garment (GCG) (**Fig. 2**) that could be donned by the wearer with relative ease in less than 5 min.[115] Donning of the garments is eased by including zippers in the shorts and in the ankles of the thigh-high, lower-extremity garments that could be opened to relieve pressure while donning and then closed to provide the appropriate level of compression.

Three studies were performed which demonstrated the efficacy of the GCG to protect against orthostatic intolerance following exposures to simulated and actual microgravity. In one, none of the 16 subjects became presyncopal during a 15-min tilt test following 14 d of 6° head-down tilt bed rest, despite significant losses in plasma volume and indices of decreased left ventricular mass and function.[114] In fact, contrary to tilt test results from other studies, the change in heart rate and stroke volume from supine to head-up tilt was less after bed rest when wearing the GCG than before bed rest without the GCG. Importantly, none of the subjects participated in any other countermeasures (e.g., fluid loading, cooling) before or during the postbed rest tilt test. Additionally, though female astronauts have a high rate of postspaceflight presyncope during tilt tests on landing day,[37,124] none of the four women subjects became presyncopal while wearing the GCG during postbed rest testing. In a study of U.S. Space Shuttle astronauts, seven subjects

Fig. 2. The graded compression garment (GCG) consists of two stockings covering the feet to the top of the thighs, which are pulled up one at a time, and a pair of "biker-style" shorts that are pulled on last, covering the upper thighs, hips, buttocks, and abdomen. Limb (every 1.5 inches from the base of the toes to the top of the thigh) and body circumferences (at the level of the hips and abdomen) are measured to construct a custom garment that provides compression of 55 mmHg at the ankle, 35 mmHg at the knee, 18 mmHg at the top of the leg, and 16 mmHg over the abdomen.

wore the GCG during a 3.5-min stand test conducted within 2 h of landing and their results were compared to astronauts performing the same stand test without the GCG.[115] Although the stand-test duration was chosen such that no astronauts became presyncopal on landing day, the effectiveness of the garment was evident. The GCG prevented the tachycardia and reduced stroke volume and cardiac output normally associated with standing after spaceflight. Most recently, 10 astronauts who completed long-duration missions on the ISS were studied and, within hours of landing, participated in the same stand test described previously during which heart rate and blood pressure were measured. Wearing the GCG prevented both the tachycardic response and the decrease in mean arterial pressure commonly observed while standing on landing day.[63]

Current Approaches for Astronauts

Although postspaceflight orthostatic intolerance was recognized as a negative consequence to weightlessness early in the NASA space program, orthostatic intolerance countermeasures were not tested until the last two Apollo missions. Based upon the reports from longer spaceflights undertaken by the Soviet space program, there was a concern that Skylab astronauts would require more protection against orthostatic intolerance when undertaking much longer missions than NASA had yet attempted.[51] Consequently, "cardiovascular counter pressure garments" were flown for each of the three Skylab missions. The astronauts donned the garments before re-entry and then inflated the pneumatic garments with a hand bulb, either during or after landing.[53] Given that astronauts were seated upright, pneumatic lower-body compression garments also were utilized during Space Shuttle re-entry and landing. Additionally, during the Space Shuttle program, end-of-mission oral fluid loading[22] and use of liquid cooling garments under the Launch and Entry Suit and Advanced Crew Escape Suit[84] became operational practices to restore plasma volume and prevent excessive heating, respectively. During the Shuttle-Mir and early ISS programs, astronauts and cosmonauts returning on the Space Shuttle used compression garments, participated in fluid loading, and wore the liquid cooling garment as other Space Shuttle astronauts did, but they also were returned to the Earth in the recumbent posture.[45] Astronauts returning from space in the Soyuz capsule, particularly after the retirement of the Space Shuttle, wear the Kentavr and largely have adopted the Russian protocol for end-of-mission oral fluid loading. In general, astronauts continue to wear lower-body compression garments after landing whenever they are not recumbent or sleeping until the time that symptoms of orthostatic intolerance have largely resolved. Although recovery of cardiovascular responses to gravity to preflight levels can be prolonged after long-duration missions,[64] the rate of recovery varies across individuals. Some astronauts will not wear compression garments after the first day of landing, some will be encouraged to wear garments at a lower level of compression, and some will wear garments for several days, progressively stepping down in compression each day.[114] Assigned crew surgeons monitor the condition of their astronauts after landing and consider the planned activities while providing guidance for the strategies undertaken to protect against orthostatic intolerance and encouraging a safe recovery from spaceflight adaptations.

Terrestrial Applications

Interventions that protect astronauts from orthostatic intolerance after spaceflight also can benefit clinical populations, including individuals with autonomic failure, recurrent syncope, and postural orthostatic tachycardia syndrome, as well as those who are bedridden for an extended duration.[114] Effective treatment for these patients is a high priority for physicians because, even in otherwise healthy, young individuals, orthostatic intolerance can result in an inability to participate in normal activities of daily life.[53] To assess the efficacy of the GCG in a clinical setting, patients – with a range of maladies inducing orthostatic intolerance or orthostatic hypotension – participated in either a stand test or a tilt test with and without wearing GCGs. Patients wearing a GCG experienced fewer symptoms, lower heart rates, and better blood pressure control during a short orthostatic challenge compared to their experiences when they attempted the same test without garments.[67] Gradient compression garments like those designed for use by astronauts after spaceflight can be adapted for everyday use in some patient populations to reduce symptomatology and improve quality of life on Earth.

NASA NUTRITIONAL GUIDELINES

Section Leads: Scott M. Smith, Sara R. Zwart, and Grace Douglas

Food and nutrition are important countermeasures guaranteed to be on every long-duration space exploration mission, regardless of duration or destination. From human performance and crew morale, to support of virtually every physiological system, food and nutrition have proven critical in the success (or sometimes failure) of exploration missions on Earth, and the same will be true as we seek to leave Earth's gravitational pull.

Nutritional requirements for space missions have been defined based largely on terrestrial guidelines with augmentation from knowledge gained from spaceflight and from ground-analog research. Terrestrial guidelines most often seek to define nutrient intakes to mitigate nutrient deficiency, and they are not designed to prevent disease and maintain optimal health.[134] While preventing deficiency is absolutely critical, we truly seek to define food systems which provide nutritional support to mitigate the risk of disease in astronauts, including musculoskeletal losses, cardiovascular degradation, ocular pathologies, neuropathy, dementia, and cancer, and to optimize the DNA repair processes, cognition, sleeping patterns, and overall health. The optimized food and nutrition to provide this support is unknown terrestrially and, at this point, is even less defined for astronauts.

Current Approaches for Astronauts

Inferring from available knowledge related to musculoskeletal health on Earth, NASA has developed and is currently testing nutritional guidelines for health and performance for astronauts on long-duration space missions. Specific guidelines include:

- Maintain energy intake, body mass;
- 2-3 servings fish/week (N-6:N-3 ratio < 3.4);
- > 6 servings fruits and vegetables/day;
- > 5 servings lycopene-rich foods/week;
- > 2 flavonoid-rich foods/day;
- Maintain protein intake at 1.2-2.0 g/kg body weight;

- Maintain potassium intake at > 2600 mg · d^{-1} in women, and > 3400 mg · d^{-1} in men;
- Maintain calcium intake at 1000-1200 mg · d^{-1};
- Sodium intake near or below 2300 mg · d^{-1};
- Iron intake close to 10 mg · d^{-1} or lower;
- Vitamin D3 intake > 800 IU/day.

These guidelines are based on the National Academy of Medicine's Dietary Reference Intakes for North Americans,[80] position of the Academy of Nutrition and Dietetics, Dietitians of Canada, and the American College of Sports Medicine for nutrition and athletic performance,[117] and other ground-based literature.[43,83,118,128] These guidelines highlight the importance of balanced energy intake and the critical need for nutritionally stable processed food sources. Supplementation is typically not required (nor is it desired), with the exception of Vitamin D. These guidelines provide both food-based recommendations along with individual nutrient goals, both of which are important elements. Energy intake remains a key requirement and focusing on vitamin/mineral supplements will distract from this fact. If the nutritional content of the food system is degrading, the quality likely is as well, which means crews will eat less. The best option is to define and incorporate the technologies that provide nutritious, high-quality foods through the mission, which will obviate the need for supplementation. Highlighting the importance of whole food-based sources of nutrients also brings back the impact of the psychological impact of food during isolated and challenging space missions. Testing of these recommendations not only on musculoskeletal but also on immune and microbiome health is underway in both ground and flight research. Ultimately, these guidelines could be used by the terrestrial population, as optimal human health depends on food and nutrition regardless of the environment.

NASA provides comprehensive dietary recommendations to develop and maintain the fitness and physiological status of astronauts. Validation of the effectiveness of these dietary recommendations during flight is required before crews are sent on exploration missions.

Terrestrial Applications

NASA studies in spaceflight and ground analogs provide evidence-based recommendations for dietary countermeasures that may be similarly applied on Earth and further support for Earth-based study outcomes. Accurate dietary compliance and tracking over prolonged periods in human studies on Earth can be challenging, whereas the closed food system and tracking in spaceflight provides greater certainty of accurate dietary accounting and associations with physiological changes. Fish intake has been associated with reduced loss of BMD both in spaceflight[136] and terrestrial populations.[1,41,70,82] Additionally, an association of single-nucleotide polymorphisms with one-carbon metabolism and ophthalmic changes indicates there may be cases where B-vitamin supplementation may provide an advantage,[110,135] even where the diet may supply adequate amounts. Ongoing interdisciplinary evaluations of the impacts of dietary improvements on nutritional markers of health status, the immune system, and the microbiome are expected to further support targeted nutritional countermeasures using whole food systems for both Earth and space exploration.

ULTRASOUND TECHNOLOGY MITIGATING NEPHROLITHIASIS

Section Leads: Adam Sirek and Ashot Sargsyan

Background

Microgravity exposure produces certain changes in human metabolism and physiology, increasing the potential for the formation of nephrolithiasis. Early metabolic studies demonstrated that calcium oxalate and uric acid stone formation risk was increased because of the hypercalcuria, hypocitraturia, and intravascular volume depletion which occur during spaceflight[126] and immediately postflight.[127] Ground-based models of spaceflight physiology have corroborated the results of previous flight studies. A 90-d bed rest study to analyze the mechanism of stone formation and evaluate effects from exercise and oral bisphosphonates demonstrated similar rates of stone formation in control and exercise groups, but no stone formation in the bisphosphonate group.[81] Intravenous bisphosphonates in another bed rest study showed similar protective effect against renal stone formation.[123] It appears that exercise counteracted bone loss by promoting osteoblastic activity but did not suppress bone resorption sufficiently to protect against renal stone formation.

Human studies on the ISS have provided greater insight to bone metabolism and the risk of renal stone formation. Preflight and postflight analysis of long-duration missions over a 12-yr period (2000–2012) demonstrated similar findings in male and female crewmembers, with equivalent changes in BMD, biochemical markers, and some increase in urinary supersaturation.[112] Spaceflight appears to create a "hyper-resorptive" bone metabolism pattern. Markers of both bone resorption and bone growth have been shown to increase during spaceflight.[108] Thus, despite the favorable outcomes of ISS missions in two decades of continuous habitation, the perception of risks to crew health and mission from nephrolithiasis remains sufficiently high to sustain interest in the spaceflight community and promote efforts to develop and implement effective risk modification and mitigation strategies. This is especially important for the highly constrained exploration missions beyond low Earth orbit without medical evacuation possibilities or real-time telemedicine and procedural support.

For several decades, astronaut selection has prescreened for the presence or history of urinary tract calculi.[7] Evidence-based medical standards and advanced imaging technologies in the ISS program have changed the approach for managing potential urolithiasis. Countermeasures include readily available telemedicine on the ISS, ultrasound imaging, robust pharmacy, and potentially medical evacuation to mitigate any residual risk of urolithiasis. For long-duration space missions, a similar approach is likely to be taken with a stronger emphasis on prevention and risk modification and in-flight tools supporting crew medical autonomy for in-flight imaging and management on the other.

Acknowledging the risk of symptomatic urolithiasis during a mission, which could rapidly evolve into an urgent medical event, NASA experts and funded investigators continue efforts to improve stone detection and characterization capabilities for ongoing surveillance of astronauts and for urinary tract imaging in the context of missions of different profiles. Focus on advanced ultrasound technology relies on solid terrestrial evidence supporting its use in various nephrolithiasis scenarios. Both focused ultrasound (emergency department) and comprehensive ultrasound (radiology) have been shown to be similarly effective compared to computed tomography (CT) in the management of symptomatic urolithiasis.[107]

In the context of nephrolithiasis, modern ultrasound devices offer a broad variety of grayscale (B-mode) image optimization techniques as well as additional modes that prove increasingly useful in stone detection and characterization. May et al. studied stone-specific imaging, termed "S-mode," to improve stone detection by enhancing stone visibility and surface delineation.[73] Many commercial ultrasound devices have preprogrammed stone-sensitive modes.

An important additional mode to enhance stone detection is the color Doppler mode, which maps ultrasound frequency shifts over the anatomical image. In addition to the Doppler effect from moving cells in blood vessels, this mode detects ultrasound frequency dispersion (similar to acoustical "white noise") by solid stationary targets, including mineralized material. While these non-Doppler frequency shifts are far greater than those from the true Doppler effect, they exceed the scale of the color spectrum, and aliasing causes a "twinkling" pattern (hence the term "twinkling artifact"). Some investigators suggest that this phenomenon also improves determination of stone size. Terrestrial clinical trials have compared the accuracy of stone detection between color Doppler technique and CT, finding color Doppler to have a 94% positive predictive value[58] and 99% specificity.[130] A group of NASA investigators studied the mechanisms for the "twinkling artifact" and suggested that it was caused by microbubbles on the surface of the stone and may be influenced by carbon dioxide levels in the atmosphere.[102,103] The authors concluded that the "twinkling artifact" may not be as readily elicited in conditions of spaceflight.

Current Approaches for Astronauts

Space medicine depends on ultrasound imaging more than most other clinical disciplines because of the absence of other diagnostic imaging modalities and the operational nature of the setting with limited resources and the very limited ability to safely and quickly evacuate the ill or injured crewmember. Depending on the clinical and operational circumstances, a focused diagnostic examination in space with a single binary clinical question (emergency medicine model) can evolve into a broader, comprehensive, and specific imaging application (radiology model). Therefore, space medicine experts have a great interest in established and emerging ultrasound applications, monitoring the accelerating adoption of bedside ultrasound techniques in terrestrial medicine, novel devices, telemedicine solutions, and advances in ultrasound skill management and machine learning.

Current ISS medical requirements do not include any renal imaging in asymptomatic astronauts, who are assumed to have been stone free at launch and unlikely to develop clinically significant (i.e., larger than 4.5 mm) renal stones during the mission. However, the risk of urolithiasis has been among the top reasons for recognizing ultrasound imaging as a required capability on ISS for augmentation of medical support since 2003. As part of experiments and medical technology demonstrations, multiple renal imaging trials have been conducted since 2002 with successful acquisition of intended data. The ISS paradigm for ultrasound imaging relies on real-time tele-ultrasound with an experienced remote guide at NASA's Mission Control Center. This model will have to yield to a substantially different set of solutions to sustain the imaging capability in exploration mission settings. NASA uses the ISS as a testbed to develop novel, skill-management solutions for procedural autonomy.

Ongoing surveillance of astronauts for occult mineralized deposits and small calculi is a sensible means to minimize the overall impact of nephrolithiasis in spaceflight programs. While the clinical practice at large still prefers CT as "gold standard" for diagnosing manifest nephrolithiasis, its use for surveillance of healthy individuals is not justifiable due to radiation, cost, and lower sensitivity in very small (< 3 mm) in-situ mineralized deposits. In contrast, ultrasound, is a safe, repeatable, and low-cost modality for detection and monitoring of mineralized foci that do not yet meet diagnostic criteria for nephrolithiasis but could potentially evolve to larger stones. However, such surveillance program must be built to address multiple complicated factors associated with equipment, operators, imaging protocol and procedure, extraction and interpretation of results, and communication between the program and the attending flight surgeons.

All partner medical organizations in the ISS program perform periodic sonographic screening of their crew cohorts for nephrolithiasis, to meet or exceed the joint requirement of abdominal sonography once every 5 yr. Besides optimized settings in standard imaging modes, the protocol includes the use of color Doppler mode to detect the phenomenon of spectral dispersion (commonly known as "twinkling artifact") as well as the more sensitive spectral Doppler mode to objectively document the presence of dispersion. Thanks to formalized tracking of each suspected focus, overall accuracy of ultrasound is expected to increase with each annual repetition. The pending analysis of accumulated experience will provide uniquely important evidence for space medicine as well as for the medical community at large.

Due to the limited sensitivity of the twinkling artifact in very small, mineralized deposits, the current NASA surveillance program uses, in addition to the color Doppler mode, a targeted spectral Doppler mode to obtain proof of even low-amplitude frequency dispersion. This allows increasing sensitivity of the surveillance program to include smaller mineralized deposits that do not cause appreciable twinkling in color yet can be included in long-term tracking for surveillance purposes.

Terrestrial Applications

Terrestrially, small occult calculi remain undetected until they become symptomatic or they are discovered incidentally in an imaging study for another cause. Once a stone is detected, management becomes the primary concern. Large or symptomatic stones are commonly managed via rehydration, analgesia, lithotripsy, stenting, surgical procedures, or a combination of the above. Ultrasound therapy is also suggested and favors pulse wave in a ramping format with good results.[92] Recent advances in ultrasound technology have allowed for increased focus in power and target of the array such that the ultrasound itself may be capable of relocating the stone. Transcutaneous stone propulsion rates of 1 cm · s^{-1} were originally demonstrated in a porcine model with implanted human stones.[99] Further studies refined the technique and reduced the risk of tissue thermal injury from the high intensity beams by altering the burst pattern while still being able demonstrate stone movement from the calyx to the renal pelvis, ureteropelvic junction, or proximal ureter.[49] Specific studies of tissue injury in a porcine model demonstrated no tissue injury when the ultrasound burst was shortened to 50 ms with 1-s bursts.[48] Human studies successfully moved renal stones and fragments up to 10 mm with minimal discomfort.[47] The space medicine community carefully follows the developments in this area and may consider inclusion of high-intensity ultrasound capability in the medical systems of future programs.

Terrestrially, rates of renal stone formation are increasing. An estimated 10% of the population will be affected with renal stones at some time during their life. The risk and cost of a potential renal stone-related event in spaceflight has resulted in a framework for early and accurate noninvasive, radiation-free detection of nephrolithiasis, with identification and refinement of ultrasound imaging technologies and techniques based on both existing evidence and essential experience from spaceflight. Ultrasound uses in human spaceflight also provide methods for management, treatment guidance, and follow-up, including both temporizing measures and a potentially definitive treatment modality. These spaceflight-focused technology applications could be translated to the terrestrial clinical environment, offering a potential reduction in healthcare cost and morbidity among the general population. Especially important are the prospects of using the spaceflight-driven constructs as well-studied examples and precedents of successful operation in a limited-resource environment. Maximizing the use of affordable ultrasound technology, which may be the only imaging modality readily available in many remote locations around the globe, has the potential of improving care for millions of patients with nephrolithiasis and optimizing the use of scarce healthcare resources. Human spaceflight can also raise the radiation awareness in the medical community and the general public since ultrasound imaging technology, based on ample evidence, could assume the role of a primary imaging modality for most nephrolithiasis-related needs.

DYNAMIC LIGHTING SYSTEMS TO MITIGATE CIRCADIAN DYSSYNCHRONY IN OPERATIONAL ENVIRONMENTS

Section Leads: Erin E. Flynn-Evans, Steven W. Lockley, Smith L. Johnston III, and Nicolas G. Nelson

Background

Dysregulation of circadian rhythms is detrimental to human health and performance, contributing to suboptimal sleep and impaired alertness while complicating other multisystem pathologies.[6,72,94] Astronauts scheduled for non-24-h operations or exposed to 92-min orbital light-dark cycles become biologically misaligned from their imposed sleep-wake schedule, increasing the potential for sleep loss, which in turn increases the risk of accidents.[35]

Light is the body's primary "time-giver" – the environmental cue that calibrates our circadian clocks. For most individuals, circadian entrainment occurs through passive exposure to the solar light-dark cycle. Visible light stimulates specialized cells in the retina, which elicits synchronization of the central circadian pacemaker in the hypothalamic suprachiasmatic nuclei, suppresses melatonin release from the pineal gland, triggers direct alerting effects, and defines an overall "biological time."[20,21,90] During spaceflight, circadian misalignment can result from non-24-h schedules, "shiftwork" because of vehicle docking or other time-critical procedures, or from the inappropriate timing, intensity, or wavelength of light exposure. On Earth, circadian desynchrony is a common condition for shift workers, military populations, and people experiencing jetlag.

Visible light is a nonpharmacological countermeasure that can be used in two ways:

1. Light, when appropriately timed, can entrain crews to a new circadian phase (e.g., a different time zone[19,94]) or period (i.e., a non-24-h schedule[69,90]); and
2. As a direct altering agent during times of anticipated sleepiness (i.e., when working overnight, when sleep deprived, or during a particularly hazardous operation).

The properties of light are important – altering the light intensity, timing, or wavelength can improve the efficacy of its use as a countermeasure. For example, white light that is enriched in the short-wavelength part of the spectrum (in the 480 nm range) is most effective at resetting the circadian system[125] and alerting the brain.[23,120]

Current Approaches for Astronauts

NASA has funded the research, development, and implementation of dynamic lighting systems. Studies in controlled laboratory environments have shown that humans can entrain to the Mars day length, or sol, which is 24.65 h.[42,96] Fatigue management interventions have utilized short-wavelength enriched light devices in a number of operational settings. For example, mission staff were able to entrain to the non-24-h Martian sol during the Pheonix Lander mission and suffered less sleep loss.[9] Blue-enriched white lights have also been shown to improve performance during overnight work at mission control.[8] Light-emitting diodes (LED) are being investigated as an in-flight countermeasure against circadian desynchrony, sleep disruption, and deficits in alertness and cognitive performance[20] and high fidelity analogs such as NASA's Human Exploration Research Analog (HERA)[89] and Antarctica.[36,78] Dynamic multi-LED arrays provide at least as much visibility and color discrimination as fluorescent lights, with the advantage of greater flexibility in the intensity and spectrum of light emitted as well as potentially longer product life and reduction of potential pollutants such as mercury. Reduction of intensity and short-wavelength content of white light before bed can also reduce alertness and improve sleep quality.[25,91] Such light exposure regimes – blue-enriched white light upon waking and red-enriched white light before sleep – are currently being tested onboard the ISS.[19]

Terrestrial Applications

Over two decades of research support the efficacy of light as a countermeasure to promote alertness during spaceflight, and some findings have already been translated into Earth-based spin-offs for shift workers, patients with sleep disorders, travelers, athletes, and the military.[6,19,20] Short-wavelength lighting countermeasures have led to clinical benefits like phototherapy for the treatment of psychiatric conditions like seasonal affective disorder (SAD) (recurrent major depressive episodes that typically begin late autumn and remit in spring[3,39]), fatigue associate with traumatic brain injury,[104] or chemotherapy.[55] Similar applications have been used to help sleep and depression in care home residents[33,34,52] and in a number of occupational environments such as offices,[124] schools,[105] and industrial settings.[106]

Light can also potentially be used to help synchronize the diverse range of functions controlled by the circadian clock including hormone secretions, intracranial pressure, microbiome activity, and other emergent processes.[6,21,97] The science of chronobiology could further inform the management of sleep disorders, depression, and other chronic conditions; circadian desynchrony has been associated with the etiology of metabolic pathologies like diabetes.[71] Ultimately, chronobiology could lead to the development of time-optimized cancer therapies and a better understanding of oncology.[28,116]

In summary, dynamic-lighting countermeasures against spaceflight-associated circadian desynchrony have reshaped our appreciation of the solar cycle's influence over the human body and mind. With proper scheduling, bright-blue light has demonstrated success in a variety of applications: entraining circadian phases, enhancing alertness, adjusting circadian periods, and treating psychiatric conditions like SAD. Future research into chronobiology promises new phototherapies, optimized infrastructural lighting, novel strategies for preventing and managing chronic conditions, personalized scheduling, and other advancements in human health and performance. Eons of evolution engineered the biochemical clockwork encoded in our genes, and with the use of dynamic lighting systems, we are learning to synchronize it with a few quanta of light.

FATIGUE RISK MANAGEMENT SERVICE

Section Leads: Smith L. Johnston, Steven W. Lockley, and Mathias Basner

Background

Sleep deficiency is a common terrestrial condition with significant cost to healthcare and industry productivity. This is also the case during space missions as crews often experience sleep and circadian desynchrony in preflight, in-flight, and postflight, and for mission control ground crew who provide round-the-clock support from mission control.

Current Approaches for Astronauts

NASA has developed an integrated suite of best practices and countermeasures to help crewmembers improve sleep and circadian outcomes on Earth and in space. NASA has established a fatigue management service (FMS), a central component in translating sleep and circadian research outcomes into operations. This service provides crewmembers with a structured implementation plan for fatigue risk management training and personalized guidance on the use of circadian shift schedules, which include advice on light exposure, light avoidance, melatonin, caffeine, and other pharmacologic hypnotic and alertness countermeasures to optimize the pre, in-, and postflight sleep opportunities. NASA-funded research has identified circadian misalignment as a major cause of sleep deficiency and cognitive impairment among crewmembers. NASA has developed and tested protocols for providing wavelength-specific light exposure to help crewmembers adapt to new schedules and time zones both on Earth and, following installation of new lighting onboard the ISS, during spaceflight.[19] These light exposure regimes have been paired with personalized schedules based on an individual's chronotype

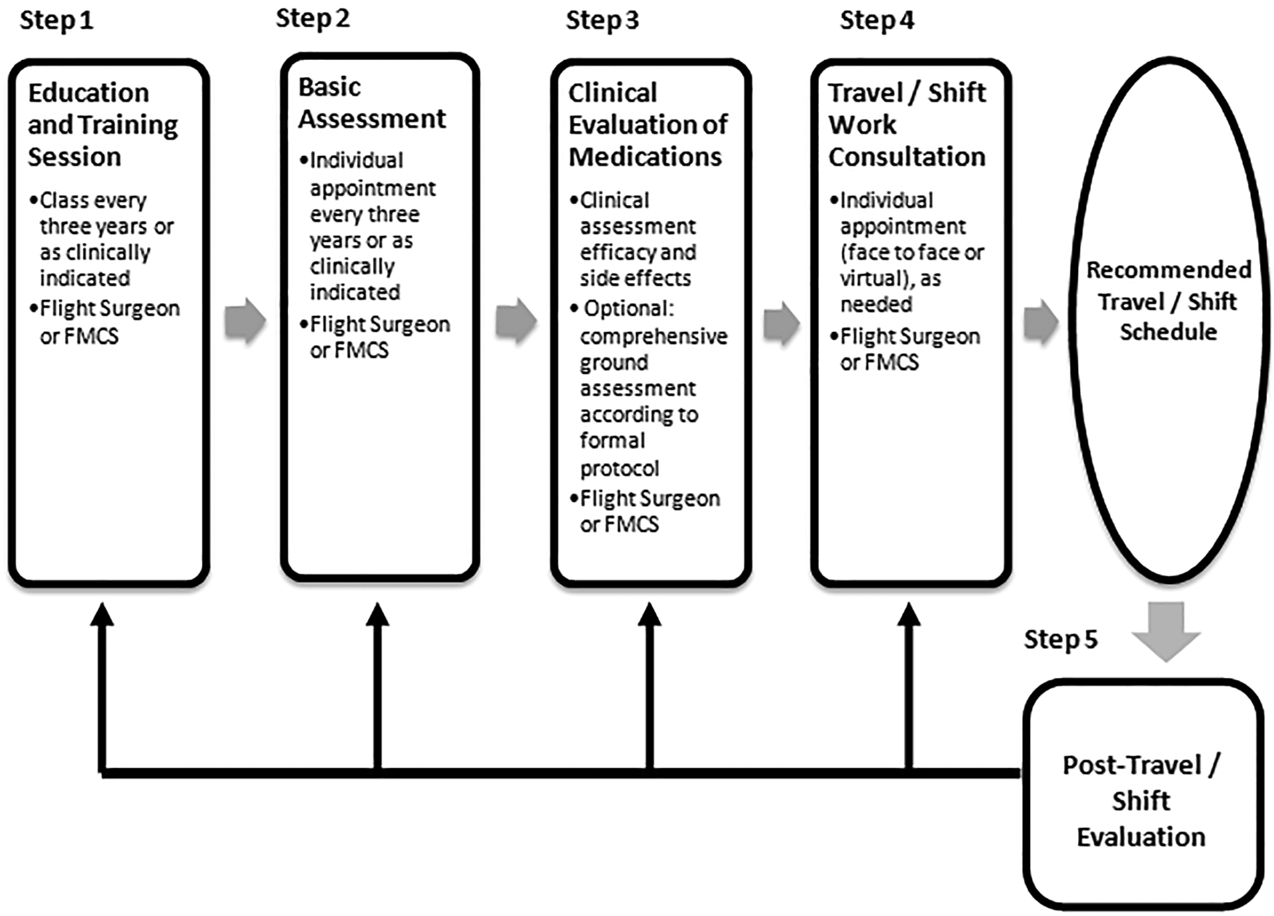

Fig. 3. Process used to provide fatigue management services to crewmembers during the pre-mission training phase, from the Clinical Practice Guidelines for Management of Circadian in ISS Operations.

and sleep preferences, unique ground testing protocols for chronobiologics (e.g., melatonin and light/darkness[9,20,42,132]), short-acting benzodiazepine agonist hypnotics (e.g., zaleplon and zolpidem[30]) and alertness medications (e.g., modafinal and caffeine[40,133]), and a personalized sleep training program provided to crewmembers and flight controls by the FMS to facilitate the fastest possible adaptation and performance benefits. Objective measures of sleep and performance (e.g., 3-min psychomotor vigilance test [PVT][12] and cognition battery[14,79]) with debrief questionnaires are also employed for feedback, as illustrated in **Fig. 3** countermeasures implementation plan. All these best practices can be entered into a uniquely designed electronic medical record for patient and data management.

Terrestrial Applications

Sleep of adequate duration and quality is critical for optimal alertness and performance and depends in large part on the circadian timing of sleep, length of a workday, and sleep quantity and quality over the previous few days.[26] Utilization of personalized approaches to help improve sleep outcomes, particularly during episodes of circadian misalignment, has potential benefits to terrestrial populations including military personnel, shift workers, and travelers experiencing jet lag. Usage of chronobiologics have already been implemented for U.S. military personnel in aviation environments[24] as countermeasures to rotating shift schedules and disruption in sleep schedules.

The experience gained in NASA's work in sleep management has contributed to the development of a commercially available application for individuals to utilize when planning a trip to help management jet lag and fatigue. This application is utilized by commercial airlines and frequent fliers. Future editions are being developed with further options for military and operational environments as well as shift workers. This product has also been successfully used with professional athletes from Olympians to national sports teams. The 3-min version of the PVT was developed with NASA-funding and has been used as a sensitive tool for alertness decrements related to sleep loss or circadian misalignment in several terrestrial research studies.[11,13] The broader cognition test battery[14] was specifically developed for high-performing astronauts and consists of 10 brief tests that cover a range of cognitive domains relevant for spaceflight. It is also currently being used to assess performance in high-performing terrestrial populations (e.g., Navy personnel, physicians).

PROBABILISTIC RISK ASSESSMENT

Section Leads: Erik L. Antonsen and Ari Epstein

Background

As NASA transitions from flight operations limited to low Earth orbit to exploration missions, NASA will face novel challenges to the health and safety of its crew. Over the last 19 yr of continuous human presence on the ISS, the delivery model for medical care in spaceflight has worked for that environment. However, the model has been limited by minimally integrated data systems infrastructure and medical "kit" planning dominated by expert opinion rather than evidence-based drivers for system needs. This process cannot adequately address the increasing likelihood of medical conditions inherent to increasing mission duration that occur as vehicle constraints tighten. Interplanetary missions will grapple with these challenges:

1. Significantly reduced mass and volume for medical resources;
2. Potential power and data bandwidth restrictions;
3. More limited resupply capabilities driven by increasing distance from Earth;
4. Increased need for autonomous medical capacity due to changes in operational paradigms expected with communication time delays;
5. Increased evacuation times or no evacuation capability for ill or injured crew.

Probabilistic risk assessment (PRA) provides a quantitative framework that can help prioritize medical capabilities in a process that respects mass and volume limitations to help guide systems engineering processes. The total risk that a planetary mission faces can be described as a balance between medical and nonmedical risk. In short-duration missions, the medical risk impact to total risk is generally small because of the selection of healthy individuals and limited exposure to spaceflight hazards that have a degrading effect over time. As mission duration and distance from Earth increase, the proportion of risk carried by the human system increases, and the need for mission-appropriate medical support is likely to increase.

In spaceflight, a larger medical capability traditionally translates to increased mass and volume that, compared to the ISS, will decrease in future exploration vehicles. When mass and volume are allocated to a system in excess of the need, the result is waste that may have increased risk in another area of the mission by causing omission of other important items; thus, assigning an unnecessarily large footprint to medical resources or crew training could ultimately improve medical risk (with potentially diminishing returns) at the expense of total increased mission risk. Ideally, system designers would appropriately trade medical and nonmedical mass and volume to identify the nadir of total mission risk as illustrated in **Fig. 4**.

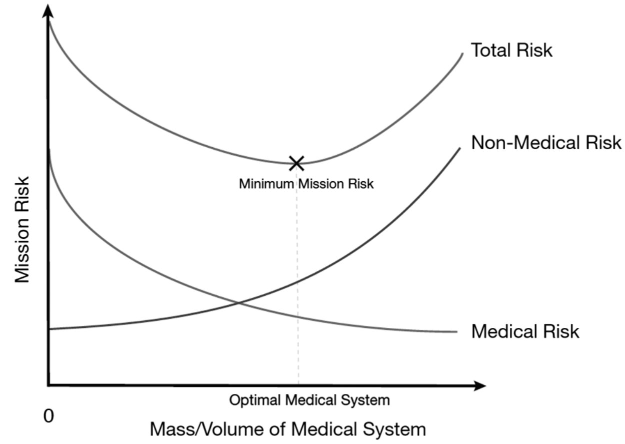

Fig. 4. Illustration of mission risk as a function of medical system mass and volume allocation. As medical system mass and volume increase, other important mission items may be excluded, resulting in elevated total mission risk. The minimum mission risk point "x" demonstrates the ideal optimal medical system and volume that is sought through utilization of the PRA approaches.

Current Approaches for Astronauts

To approach this risk nadir and improve recommendations to optimize medical system capabilities and resources, NASA created a mixed PRA model called the integrated medical model (IMM). This tool estimates probabilities of medical events occurring during missions and models the impact of resource availability for medical care on risk outcomes of interest to mission planners.[38,57,75] The probability distributions for modeled medical conditions helped inform the prioritization of medical capabilities that should be considered for inclusion in vehicle medical systems during mission and vehicle design and development. The probabilities are also used with other assessments of medical priority to identify which medical conditions are likely to contribute meaningfully to risk reduction when planning for mission medical needs such as diagnosis and treatment capability.[4,17,129]

The IMM merges spaceflight and terrestrial medicine evidence bases to feed Monte Carlo simulations that estimate the probability and likelihood of unplanned medical conditions, effects on resource utilization, and crew functional impairment on the ISS.[77,129] These outputs estimate mission risk parameters including the likelihoods of loss of crew life (LOCL), need for medical evacuation (EVAC), and crew performance decrements expected from medical issues (Crew Health Index [CHI]).[4,57] While imperfect, this is the only tool available to quantitatively inform exploration medical needs beyond low-Earth orbit. NASA's Exploration Medical Capability (ExMC) Element employs a model-based systems engineering framework to define and align stakeholder expectations when planning for exploration mission needs. The PRA provides quantitative inputs for trade space analysis (typically used by NASA in terms of searching for the optimal boundary by trading off a cost in one cost center for a cost in another cost center)

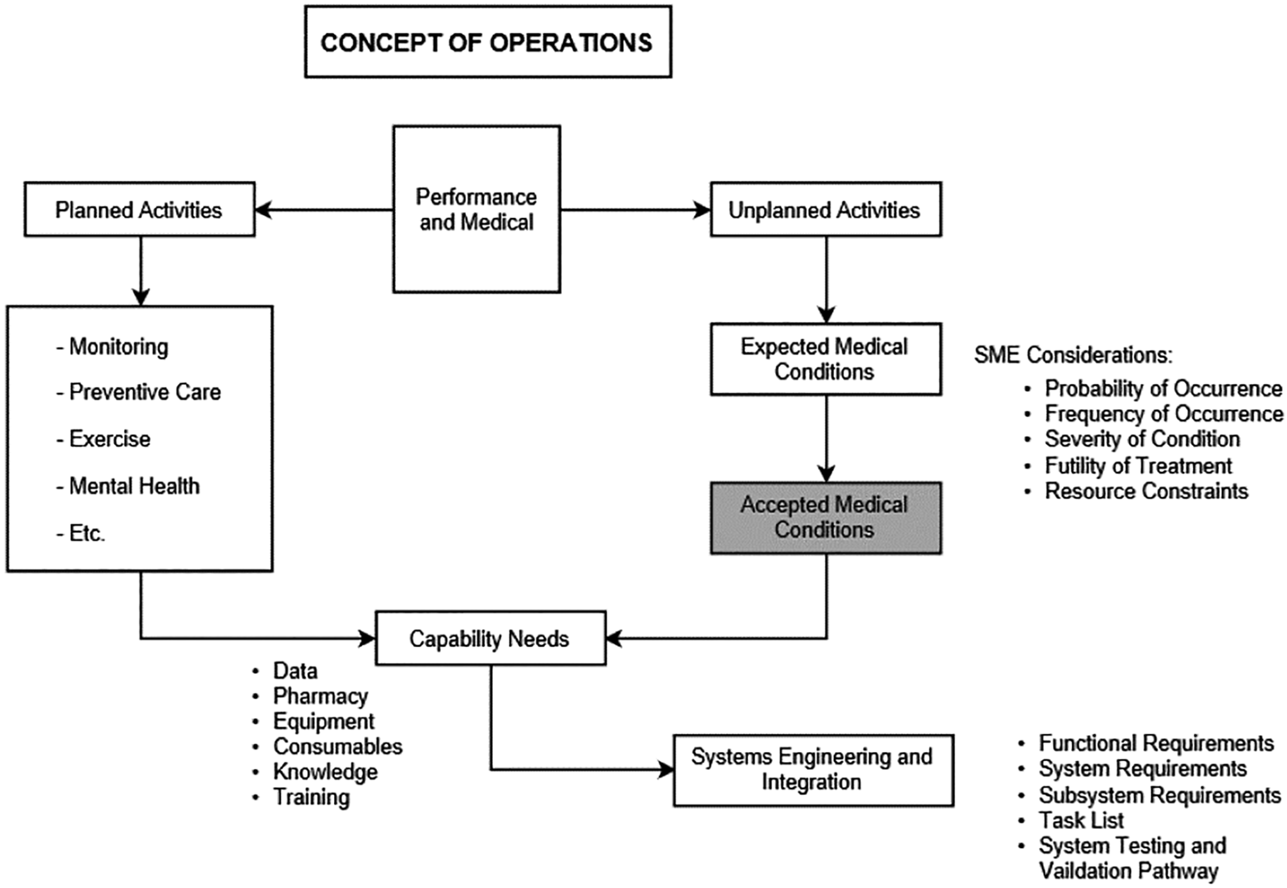

Fig. 5. The process starting with the mission Concept of Operations provides a walkthrough of the elements of a repeatable process that is informed by the mission activities that are planned (preventative health care) and those that are unplanned (acute health care). Systematic approaches enable repeatable derivation of the appropriate medical capabilities that can be provided to systems engineering processes for trade space analysis.

for exploration medical systems.[4] This enables improved alignment of medical needs with systems designs to improve crew autonomy.[47,76]

Using probability of occurrence for medical conditions in mission calculated by the IMM, the ExMC institutes a repeatable, traceable process that leverages subject matter experts (SMEs) of various clinical backgrounds (flight surgeons, pharmacists, and nurses) and the PRA to derive an accepted medical conditions list (AMCL)[17] designed to inform medical systems planning. The integrated medical exploration database (iMED) definitions for best and worst case care are reviewed in surveys by SMEs, who interpret and assign scores for a futility index and a complexity index for each medical condition with the goal of prioritizing the most appropriate medical conditions to drive recommended medical capabilities for the exploration mission parameters (**Fig. 5**).

Terrestrial Applications

Although this decision-support approach has been developed for exploration spaceflight, the applicability extends to other logistics and planning domains. Regulatory agencies have used PRA methods to help regulate carcinogens in foods, consumer products, environment, and the workplace[93] as well as hazardous waste site remediation.[119] Civilian health and military systems face some of the same logistical challenges as human spaceflight. Leveraging medical evidence-based PRA analysis methods to inform repeatable prioritization approaches provides an effective blueprint for mapping between the disparate expertise-bases of medicine and systems engineering. Civilian regional health systems with both public and mixed funding sources navigate operational challenges in: 1.) Identifying which systematic healthcare risks to target; and 2.) Prioritizing finite mitigation resources to optimize public health or disease responses.[10] PRA provides a quantitative framework that could be useful to develop stakeholder insight for decisions impacting efficient and equitable distribution of healthcare.[27,77]

This approach could similarly be applied to military deployment of forces, commodities, and logistics. In both combat and peacetime-deployed settings, sustainment teams balance several competing requirements, such as personnel rotation; joint reception, staging, onward movement and integration (JRSOI); resourcing; mortuary affairs, casualty tracking and patient evacuation; transportation and lift; and key leader engagement (KLE). In austere or remote environments, this type of planning demands significant lead time.[29] By expanding risk assessments beyond their current use for food/water mission requirements and supply chain management,[31] military operators could gain a quantitative framework to better support decisions that optimize medical resource allocation to support mission success.

As humans return to exploration spaceflight, medical operations require decision support tools that integrate medical systems into the larger engineering processes. Medical PRA tools can provide input for transparent, repeatable processes to improve trade space analysis and systems engineering and match medical capabilities with expected mission needs.

BELLAGIO II CONCLUSIONS

Human research has been a major focus of the ISS and the U.S. space program since its inception. Investigating the effect of microgravity on human physiology has extended our capabilities off the planet while increasing medical capabilities to deal with aberrant physiology terrestrially. Experience with short- and long-duration spaceflight has uncovered novel homeostatic pathways, as well as unexpected pathophysiology. Ultimately, the findings have led to the development of various countermeasures to maintain the human element at peak performance during the missions.

The ISS has established itself as an important research platform and test bed for various scientific research and technology demonstrations. To maintain the need for advancement, understanding the human system remains critical. The environment of the ISS is inherently dangerous to a human being and long-term microgravity exposure has been likened in many ways to the normal terrestrial aging process; the astronauts themselves have thus become critical research elements for the terrestrial human platform.

The Bellagio II Project conducted an extensive search of the available data bases to review mature science available in the public domain. This manuscript outlines the status of sciences and technologies with direct terrestrial application at the time of publication. It is a snapshot of mature science that demonstrates a pathway for translation of evidenced based countermeasures that have effectively mitigated risk to astronaut health and are ready for translation as solutions to analogous biological health problems on Earth.

Countermeasures of mature science selected to demonstrate a pathway for translation include clinical assessment tools to mitigate coronary artery disease; exercise prescriptions to mitigate fractures and effects of osteoporosis; use of GCGs to mitigate episodes of orthostatic intolerance; and nutritional guidelines and evidence based dietary recommendations to maintain fitness and optimal physiology. Space medicine research has demonstrated early and accurate renal stone detection through ultrasound; dynamic lighting systems to mitigate altered sleep patterns and circadian dysynchrony; fatigue risk management; and probabilistic risk assessment within a framework of systems engineering for optimal resource allocation for austere operations.

Future Research

In addition to mature science, the Bellagio II Summit proceedings identified research in progress, at different stages of maturity, with probability for future terrestrial application. Numerous articles and research veins demonstrated great merit but incomplete readiness at this time. Although not presented in this manuscript, examples of these works in progress include: artificial intelligence; the microbiome; virtual, augmented and mixed reality; stem cell and tissue engineering; melanoma screening in high risk populations; space radiation; plant growth in differential gravity and radiation fields; genetics; and astronaut selection. Research in these areas is ongoing, and progress toward maturity will be monitored for readiness to terrestrial application. We anticipate that, as research continues, more data will be available to expand the realm of scientific knowledge from space to Earth.

Partnership

The Bellagio initiative is characterized by a multidisciplinary effort with international collaboration, that generated partnerships among entities including NASA, the Aerospace Medical Association (AsMA) and its constituents, the NIH, and international space agencies. Representatives from 13 countries participated in person at the Bellagio II Summit. Through the process of analyzing the evidence present in published literature, relationships and ideas were freely exchanged and discourse over a variety of viewpoints aligned the course of the project through recognition of the mature science. The momentum and concept generation from the collaboration and interdisciplinary partnerships strengthened collaborative and teamworking skills of the participants.

Such coordinated efforts need to continue as we move forward into the era of commercial spaceflight, long-duration space travel, and the enhancement of safety and health in space exploration as well as clinical operations on Earth. Efforts will need to be directed at improvement of interdisciplinary case management teams, effective leadership, qualified and certified personnel, clinical practice guidelines, best practice models, protocols for application of space medicine countermeasures and solutions.

Mentorship, Outreach, and Advocacy

The post-Bellagio ll Summit spirit and enthusiasm continues to influence the medical community and the general public through action-oriented activities that stimulate awareness and inform the public regarding career paths in aviation and space medicine. Such activities include speaking engagements at career days, giving talks to elementary schools, high schools, colleges and alma maters, our children's sciences classes, and job fairs. Much of the research carried out by the scientific community has tremendous benefits for the general public.

As we pursue the advancement of aviation and space medicine through ongoing research, a key objective in this process is to create a next generation of scientists through effective mentorship. The Bellagio ll initiative engaged many young, aspiring scientists along this journey, providing opportunities to prepare and deliver scientific papers, pursue dialogue and collaborate in scientific think tanks, publish journal articles, and strengthen their career paths.

Dissemination of information to educate, inspire, and empower the people of our communities through presentations, publications, and various avenues of networking is encouraged and will continue. The ultimate goal from a medical perspective is to improve human health, performance, and longevity and to improve quality of life for all humanity.

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REFERENCES

1. Abdelhamid A, Hooper L, Sivakaran R, Hayhoe RPG, Welch A, Group P. The relationship between omega-3, omega-6 and total polyunsaturated fat and musculoskeletal health and functional status in adults: a systematic review and meta-analysis of RCTs. Calcif Tissue Int. 2019; 105(4): 353–372.
2. Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2006; 48(6):1190–1197.
3. Anderson JL, Glod CA, Dai J, Cao Y, Lockley SW. Lux vs. wavelength in light treatment of Seasonal Affective Disorder. Acta Psychiatr Scand. 2009; 120(3):203–212.
4. Antonsen EL, Mulcahy RA, Rubin D, Blue RS, Canga MA, Shah R. Prototype development of a tradespace analysis tool for spaceflight medical resources. Aerosp Med Hum Perform. 2018; 89(2):108–114.
5. Arbeille P, Provost R, Zuj K. Carotid and Femoral Artery Intima-Media Thickness During 6 Months of spaceflight. Aerosp Med Hum Perform. 2016; 87(5):449–453.
6 Astaburuaga R, Basti, A., Li, Y., Herms, D., Relógio, A.Circadian regulation of physiology: relevance for space medicine. REACH: Reviews in Human Space Exploration. 2019:100029.
7. Aubert AE, Larina I, Momken I, Blanc S, White O, et al. Towards human exploration of space: the THESEUS review series on cardiovascular, respiratory, and renal research priorities. NPJ Microgravity. 2016; 2(1):16031.
8. Barger L, Sullivan J, Bollweg L, Lockley S, Czeisler C.Experimental trial of fatigue countermeasure program in operational flight controllers. NASA Human Research Program Investigators' Workshop. Galveston, TX, February 11–14, 2013. Houston (TX): NASA; 2013.
9. Barger LK, Sullivan JP, Vincent AS, Fiedler ER, McKenna LM, et al. Learning to live on a Mars day: fatigue countermeasures during the Phoenix Mars Lander mission. Sleep. 2012; 35(10):1423–1435.
10. Barrett DH, Ortmann LW, Brown N, DeCausey BR, Saenz C, Dawson A. Public health research. In: Barrett DH, Ortmann LW, Dawson A, Saenz C, Reis A, Bolan G, eds. Public health ethics: cases spanning the globe. Cham (CH): Springer; 2016:285–318.
11. Basner M, Asch DA, Shea JA, Bellini LM, Carlin M, et al. Sleep and alertness in a duty-hour flexibility trial in internal medicine. N Engl J Med. 2019; 380(10):915–923.
12. Basner M, Mollicone D, Dinges DF. Validity and sensitivity of a brief Psychomotor Vigilance Test (PVT-B) to total and partial sleep deprivation. Acta Astronaut. 2011; 69(11–12):949–959.
13. Basner M, Rubinstein J. Fitness for duty: a 3-minute version of the Psychomotor Vigilance Test predicts fatigue-related declines in luggage-screening performance. J Occup Environ Med. 2011; 53(10):1146–1154.

14. Basner M, Savitt A, Moore TM, Port AM, McGuire S, et al. Development and validation of the cognition test battery for spaceflight. Aerosp Med Hum Perform. 2015; 86(11):942–952.
15. Bemben DA, Bemben MG. Dose-response effect of 40 weeks of resistance training on bone mineral density in older adults. Osteoporos Int. 2011; 22(1):179–186.
16. Bishop PA, Lee SM, Conza NE, Clapp LL, Moore AD, Jr., et al. Carbon dioxide accumulation, walking performance, and metabolic cost in the NASA launch and entry suit. Aviat Space Environ Med. 1999; 70(7):656–665.
17. Blue R, Nusbaum D, Antonsen E. Development of an accepted medical condition list for exploration medical capability scoping. Houston (TX): NASA Johnson Space Center; 2019.
18. Bolam KA, Skinner TL, Jenkins DG, Galvao DA, Taaffe DR. The osteogenic effect of impact-loading and resistance exercise on bone mineral density in middle-aged and older men: a pilot study. Gerontology. 2015; 62(1): 22–32.
19. Brainard GC, Barger LK, Soler RR, Hanifin JP. The development of lighting countermeasures for sleep disruption and circadian misalignment during spaceflight. Curr Opin Pulm Med. 2016; 22(6):535–544.
20. Brainard GC, Coyle W, Ayers M, Kemp J, Warfield B, et al. Solid-state lighting for the International Space Station: tests of visual performance and melatonin regulation. Acta Astronaut. 2013; 92(1):21–28.
21. Braun R, Kath WL, Iwanaszko M, Kula-Eversole E, Abbott SM, et al. Universal method for robust detection of circadian state from gene expression. Proc Natl Acad Sci USA. 2018; 115(39):E9247–E9256.
22. Bungo MW, Charles JB, Johnson PC, Jr. Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. Aviat Space Environ Med. 1985; 56(10):985–990.
23. Cajochen C. Alerting effects of light. Sleep Med Rev. 2007; 11(6):453–464.
24. Caldwell JA, Caldwell JL. Fatigue in military aviation: an overview of US military-approved pharmacological countermeasures. Aviat Space Environ Med. 2005; 76(7, Suppl):C39–C51.
25. Chellappa SL, Steiner R, Oelhafen P, Lang D, Gotz T, et al. Acute exposure to evening blue-enriched light impacts on human sleep. J Sleep Res. 2013; 22(5):573–580.
26. Czeisler CA, Gooley JJ. Sleep and circadian rhythms in humans. Cold Spring Harb Symp Quant Biol. 2007; 72(1):579–597.
27. Daniels N. Just health: meeting health needs fairly. New York: Cambridge University Press; 2008.
28. deHaro D, Kines KJ, Sokolowski M, Dauchy RT, Streva VA, et al. Regulation of L1 expression and retrotransposition by melatonin and its receptor: implications for cancer risk associated with light exposure at night. Nucleic Acids Res. 2014; 42(12):7694–7707.
29. Deployable Training Division (DTD) Joint Staff J7. Sustainment Insights and Best Practices Focus Paper. 2018; fourth edition. [Accessed 2018 May]. Available from: https://www.jcs.mil/Portals/36/Documents/Doctrine/fp/sustainment_fp.pdf?ver=2018-05-17-102011-017.
30. Dinges DF, Basner M, Ecker AJ, Baskin P, Johnston SL. Effects of zolpidem and zaleplon on cognitive performance after emergent morning awakenings at Tmax: a randomized placebo-controlled trial. Sleep. 2019; 42(3):zsy258.
31. Loredo EN, Raffensperger JF, Moore NY. Measuring and managing Army supply chain risk: a quantitative approach by item number and commercial entity code. 2015. [Accessed 6 May 2021]. Available from: https://www.rand.org/content/dam/rand/pubs/research_reports/RR900/RR902/RAND_RR902.pdf.
32. English KL, Lee SMC, Loehr JA, Ploutz-Snyder RJ, Ploutz-Snyder LL. Isokinetic strength changes following long-duration spaceflight on the ISS. Aerosp Med Hum Perform. 2015; 86(12, Suppl):A68–A77.
33. Figueiro MG, Plitnick B, Roohan C, Sahin L, Kalsher M, Rea MS. Effects of a tailored lighting intervention on sleep quality, rest-activity, mood, and behavior in older adults with Alzheimer disease and related dementias: a randomized clinical trial. J Clin Sleep Med. 2019; 15(12):1757–1767.
34. Figueiro MG, Plitnick BA, Lok A, Jones GE, Higgins P, et al. Tailored lighting intervention improves measures of sleep, depression, and agitation in persons with Alzheimer's disease and related dementia living in long-term care facilities. Clin Interv Aging. 2014; 9:1527–1537.
35. Flynn-Evans EE, Barger LK, Kubey AA, Sullivan JP, Czeisler CA. Circadian misalignment affects sleep and medication use before and during spaceflight. NPJ Microgravity. 2016; 2(1):15019.
36. Francis G, Bishop L, Luke C, Middleton B, Williams P, Arendt J. Sleep during the Antarctic winter: preliminary observations on changing the spectral composition of artificial light. J Sleep Res. 2008; 17(3):354–360.
37 Fritsch-Yelle JM, Whitson PA, Bondar RL, Brown TE. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. J Appl Physiol(1985). 1996; 81(5):2134–2141.
38 .Gilkey K, Myers J, McRae M, Griffin E, Kallrui A. Bayesian analysis for risk assessment of selected medical events in support of the integrated medical model effort. Cleveland (OH): NASA-Glenn Research Center, 2012; NASA/TP 2012-217120.
39. Glickman G, Byrne B, Pineda C, Hauck WW, Brainard GC. Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). Biol Psychiatry. 2006; 59(6):502–507.
40. Grady S, Aeschbach D, Wright KP, Jr., Czeisler CA. Effect of modafinil on impairments in neurobehavioral performance and learning associated with extended wakefulness and circadian misalignment. Neuropsychopharmacology. 2010; 35(9):1910–1920.
41. Griel AE, Kris-Etherton PM, Hilpert KF, Zhao G, West SG, Corwin RL. An increase in dietary n-3 fatty acids decreases a marker of bone resorption in humans. Nutr J. 2007; 6(1):2.
42. Gronfier C, Wright KP, Jr., Kronauer RE, Czeisler CA. Entrainment of the human circadian pacemaker to longer-than-24-h days. Proc Natl Acad Sci USA. 2007; 104(21):9081–9086.
43. Gunn CA, Weber JL, McGill AT, Kruger MC. Increased intake of selected vegetables, herbs and fruit may reduce bone turnover in post-menopausal women. Nutrients. 2015; 7(4):2499–2517.
44. Hallal PC, Lee IM. Prescription of physical activity: an undervalued intervention. Lancet. 2013; 381(9864):356–357.
45. Hamilton D. Cardiovascular aspects of spaceflight. In: Barratt MR, Baker ES, Pool SL, eds. Principles of clinical medicine for space flight. New York (NY): Springer Science+Business Media LLC. 2019:673–710.
46. Hanson A, Mindock J, Okon S, Hailey M, McGuire K, et al.A model-based systems engineering approach to exploration medical system development. 2019 IEEE Aerospace Conference; June 20, 2019; Big Sky, MT. Piscataway (NJ): IEEE; 2019:1–19.
47. Harper JD, Cunitz BW, Dunmire B, Lee FC, Sorensen MD, et al. First in human clinical trial of ultrasonic propulsion of kidney stones. J Urol. 2016; 195(4 Pt 1):956–964.
48. Harper JD, Dunmire B, Wang YN, Simon JC, Liggitt D, et al. Preclinical safety and effectiveness studies of ultrasonic propulsion of kidney stones. Urology. 2014; 84(2):484–489.
49. Harper JD, Sorensen MD, Cunitz BW, Wang YN, Simon JC, et al. Focused ultrasound to expel calculi from the kidney: safety and efficacy of a clinical prototype device. J Urol. 2013; 190(3):1090–1095.
50. Hayes J. The first decade of ISS exercise: lessons learned on Expeditions 1–25. Aerosp Med Hum Perform. 2015; 86(12, Suppl):A1–A6.
51. Hoffler GW, Jr. Apollo flight crew cardiovascular evaluations. In: Johnston RS, Berry CA, Dietlein LF, eds. Biomedical results of Apollo. Washington (D.C.): Scientific and Technical Information Office, National Aeronautics and Space Administration; 1975:227–264.
52. Hopkins S, Morgan PL, Schlangen LJM, Williams P, Skene DJ, Middleton B. Blue-enriched lighting for older people living in care homes: effect on activity, actigraphic sleep, mood and alertness. Curr Alzheimer Res. 2017; 14(10):1053–1062.
53. Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. Am J Med Sci. 1999; 317(2):88–101.

54. Johnson JA, Garland SN, Carlson LE, Savard J, Simpson JSA, et al. Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. J Cancer Surviv. 2018; 12(2):206–215.
55. Johnson RLHG, Nicogossian AE, Bergman SA, Jr., Jackson MM. Lower body negative pressure: third manned Skylab mission. In: Johnston RS, Dietlein LF, eds. Biomedical results from Skylab. Washington (D.C.): Scientific and Technical Information Office, National Aeronautics and Space Administration; 1977:284–312.
56. Keenan A, Young M, Saile L, Boley L, Walton M, et al.The Integrated Medical Model: A probabilistic simulation model predicting in-flight medical risks. 45th international Conference on Environmental Systems. July 12–16, 2015; Bellevue, WA. 2015.
57. Khera A, Budoff MJ, O'Donnell CJ, Ayers CA, Locke J, et al. Astronaut cardiovascular health and risk modification (Astro-CHARM) coronary calcium atherosclerotic cardiovascular disease risk calculator. Circulation. 2018; 138(17):1819–1827.
58. Kielar AZ, Shabana W, Vakili M, Rubin J. Prospective evaluation of Doppler sonography to detect the twinkling artifact versus unenhanced computed tomography for identifying urinary tract calculi. J Ultrasound Med. 2012; 31(10):1619–1625.
59. Korth DW. Exercise countermeasure hardware evolution on ISS: the first decade. Aerosp Med Hum Perform. 2015; 86(12, Suppl):A7–A13.
60. Kozlovskaya IB, Pestov ID, Egorov A. The system of preventive measures in long space flights. Hum Physiol. 2010; 36(7):773–779.
61. Leach CS, Alfrey CP, Suki WN, Leonard JI, Rambaut PC, Inners LD, et al.Regulation of body fluid compartments during short-term spaceflight. J Appl Physiol (1985). 1996 Jul;81(1):105–116.
62. Leblanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM. Bone mineral loss and recovery after 17 weeks of bed rest. J Bone Miner Res. 1990; 5(8):843–850.
63. Lee SM, Ribeiro L, Laurie S, Feiveson A, Kitov V, et al. Efficacy of gradient compression garments in the hours after long-duration space flight. Front Physiol. 2020; 11:784.
64. Lee SMC, Feiveson AH, Stein SP, Stenger MB, Platts SH. Orthostatic intolerance after International Space Station and Space Shuttle missions. Aerosp Med Hum Perform. 2015; 86:A54–A67.
65. Lee SMC, Guined JR, Brown AK, Stenger MB, Platts SH. Metabolic consequences of garments worn to protect against post-spaceflight orthostatic intolerance. Aviat Space Environ Med. 2011; 82(6):648–653.
66. Lee SMC, Moore ADJ, Fritsch-Yelle JM, Greenisen MC, Schneider SM. Inflight exercise affects stand test responses after space flight. Med Sci Sports Exerc. 1999; 31(12):1755–1762.
67. Lee SMC, Stenger MB, Platts SH, Levine BD, Qi F, Norsk P. Orthostatic intolerance after spaceflight: Countermeasures for astronauts and clinical populations. [Abstract 238]. Aerosp Med Hum Perform. 2018; 89:241–242.
68. Lin PC, Chang SY. Functional recovery among elderly people one year after hip fracture surgery. J Nurs Res. 2004; 12(1):72–82.
69. Lockley SW, Evans EE, Scheer FA, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep. 2006Feb 29(2):161–168.
70. Mangano KM, Kerstetter JE, Kenny AM, Insogna KL, Walsh SJ. An investigation of the association between omega 3 FA and bone mineral density among older adults: results from the National Health and Nutrition Examination Survey years 2005–2008. Osteoporos Int. 2014; 25(3): 1033–1041.
71. Mäntele S, Otway DT, Middleton B, Bretschneider S, Wright J, et al. Daily rhythms of plasma melatonin, but not plasma leptin or leptin mRNA, vary between lean, obese and type 2 diabetic men. PLoS One. 2012; 7(5):e37123.
72. Maury E. Off the clock: from circadian disruption to metabolic disease. Int J Mol Sci. 2019; 20(7):1597.
73. May PC, Haider Y, Dunmire B, Cunitz BW, Thiel J, et al. Stone-mode ultrasound for determining renal stone size. J Endourol. 2016; 30(9):958–962.
74. Meck JV, Reyes CJ, Perez SA, Goldberger AL, Ziegler MG. Marked exacerbation of orthostatic intolerance after long- vs. short-duration spaceflight in veteran astronauts. Psychosom Med. 2001; 63(6):865–873.
75. Minard CG, de Carvalho MF, Iyengar MS. Optimizing medical resources for spaceflight using the integrated medical model. Aviat Space Environ Med. 2011; 82(9):890–894.
76. Mindock J, Reilly J, Rubin D, Urbina M, Hailey M, et al. Reyes, D. Systems engineering for space exploration medical capabilities. AIAA SPACE and Astronautics Forum and Exposition.12–14 September 2017; Orlando, FL. Reston (VA): American Institute of Aeronautics and Astronautics; 2017.
77. Myers JG, Garcia Y, Arellano J, Boley L, Goodenow DA, et al. Validation of the NASA integrated medical model: a space flight medical risk prediction tool. Probabilistic Safety Assessment and Management PSAM 14, September 2018, Los Angeles, CA. Washington (DC): NASA; NTRS 2018. Available from: https://ntrs.nasa.gov/api/citations/20180006877/downloads/20180006877.pdf.
78. Najjar RP, Wolf L, Taillard J, Schlangen LJ, Salam A, et al. Chronic artificial blue-enriched white light is an effective countermeasure to delayed circadian phase and neurobehavioral decrements. PLoS One. 2014; 9(7):e102827.
79. Nasrini J, Hermosillo E, Dinges DF, Moore TM, Gur RC, Basner M. Cognitive performance during confinement and sleep restriction in NASA's Human Exploration Research Analog (HERA). Front Physiol. 2020; 11:394.
80. National Academy of Sciences. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC): NAS; 2001.
81. Okada A, Ichikawa J, Tozawa K.[Kidney stone formation during space flight and long-term bed rest]. [JPN] Clin Calcium. 2011; Oct 21(10):1505–1510.
82. Orchard TS, Ing SW, Lu B, Belury MA, Johnson K, et al. The association of red blood cell n-3 and n-6 fatty acids with bone mineral density and hip fracture risk in the women's health initiative. J Bone Miner Res. 2013; 28 (3):505–515.
83. Oria M, Harrison M, Stallings VA.In: Oria M, Harrison M, Stallings VA, editors. Dietary Reference Intakes for Sodium and Potassium. Washington (DC): National Academies Press, 2019.
84. Perez SA, Charles JB, Fortner GW. Hurst Vt, Meck JV. Cardiovascular effects of anti-G suit and cooling garment during space shuttle re-entry and landing. Aviat Space Environ Med. 2003; 74(7):753–757.
85. Pettit D. Mars landing on Earth: an astronaut's perspective. J Cosmol. 2010; 12:3529–3536. [Available from: http://journalofcosmology.com/Mars125.html].
86. Platts SH, Tuxhorn JA, Ribeiro LC, Stenger MB, Lee SMC, Meck JV. Compression garments as countermeasures to orthostatic intolerance. Aviat Space Environ Med. 2009; 80(5):437–442.
87. Ploutz-Snyder LL, Downs M, Goetchius E, Crowell B, English KL, et al. Exercise training mitigates multisystem deconditioning during bed rest. Med Sci Sports Exerc. 2018; 50(9):1920–1928.
88. Radford NB, DeFina LF, Leonard D, Barlow CE, Willis BL, et al. Cardiorespiratory fitness, coronary artery calcium, and cardiovascular disease events in a cohort of generally healthy middle-age men: results from the Cooper Center Longitudinal Study. Circulation. 2018; 137(18):1888–1895.
89. Rahman S, Kent B, St. Hilaire M, Clark T, Hanifin J, et al.Lighting protocols for exploration – HERA campaign. NASA Human Research Program Investigators' Workshop. Jan. 27–30, 2020; Galveston, TX; 2020. Houston (TX): Baylor College of Medicine; 2020.
90. Rahman SA, Flynn-Evans EE, Aeschbach D, Brainard GC, Czeisler CA, Lockley SW. Diurnal spectral sensitivity of the acute alerting effects of light. Sleep. 2014; 37(2):271–281.
91. Rahman SA, St Hilaire MA, Lockley SW. The effects of spectral tuning of evening ambient light on melatonin suppression, alertness and sleep. Physiol Behav. 2017; 177:221–229.

92. Rassweiler JJ, Knoll T, Kohrmann KU, McAteer JA, Lingeman JE, et al. Shock wave technology and application: an update. Eur Urol. 2011; 59(5):784–796.
93. Rodricks JV. When risk assessment came to Washington: a look back. Dose Response. 2019; 17(1):1559325818824934.
94. Roenneberg T, Merrow M. The circadian clock and human health. Curr Biol. 2016; 26(10):R432–R443.
95. Rubin CD. Southwestern Internal Medicine Conference: prevention of hip fractures in the elderly. Am J Med Sci. 1995; 310(2):77–85.
96. Scheer FA, Wright KP, Jr., Kronauer RE, Czeisler CA. Plasticity of the intrinsic period of the human circadian timing system. PLoS One. 2007; 2(8):e721.
97. Schwartz WJ, Klerman EB. Circadian neurobiology and the physiologic regulation of sleep and wakefulness. Neurol Clin. 2019; 37(3):475–486.
98. Scott JPWT, Green DA. Optimization of exercise countermeasures for human space flight – lessons from terrestrial physiology and operational considerations. Front Physiol. 2019; 10:173.
99. Shah A, Harper JD, Cunitz BW, Wang YN, Paun M, et al. Focused ultrasound to expel calculi from the kidney. J Urol. 2012; 187(2):739–743.
100. Sibonga J, Matsumoto T, Jones J, Shapiro J, Lang T, et al. Resistive exercise in astronauts on prolonged spaceflights provides partial protection against spaceflight-induced bone loss. Bone. 2019; 128:112037.
101. Sibonga JD, Spector ER, Johnston SL, Tarver WJ. Evaluating bone loss in ISS astronauts. Aerosp Med Hum Perform. 2015; 86(12, Suppl): A38–A44.
102. Simon JC, Sapozhnikov OA, Kreider W, Breshock M, Williams JC, Bailey MR. The role of trapped bubbles in kidney stone detection with the color Doppler ultrasound twinkling artifact. Phys Med Biol. 2018; 63(2):025011.
103. Simon JC, Wang YN, Cunitz BW, Thiel J, Starr F, et al. Effect of carbon dioxide on the twinkling artifact in ultrasound imaging of kidney stones: a pilot study. Ultrasound Med Biol. 2017; 43(5):877–883.
104. Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SM. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. Neurorehabil Neural Repair. 2014; 28(4):303–313.
105. Sleegers P, Moolenaar N, Galetzka M, Pruyn A, Sarroukh B, van der Zande B. Lighting affects students' concentration positively: Findings from three Dutch studies. Light Res Technol. 2013; 45(2):159–175.
106. Sletten TL, Ftouni S, Nicholas CL, Magee M, Grunstein RR, et al. Randomised controlled trial of the efficacy of a blue-enriched light intervention to improve alertness and performance in night shift workers. Occup Environ Med. 2017; 74(11):792–801.
107. Smith-Bindman R, Aubin C, Bailitz J, Bengiamin RN, Camargo CA, Jr., et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. N Engl J Med. 2014; 371(12):1100–1110.
108. Smith SM, Heer M, Shackelford LC, Sibonga JD, Spatz J, et al. Bone metabolism and renal stone risk during International Space Station missions. Bone. 2015; 81:712–720.
109. Smith SM, Heer MA, Shackelford LC, Sibonga JD, Ploutz-Snyder L, Zwart SR. Benefits for bone from resistance exercise and nutrition in long-duration spaceflight: Evidence from biochemistry and densitometry. J Bone Miner Res. 2012; 27(9):1896–1906.
110. Smith SM, Zwart SR. Spaceflight-related ocular changes: the potential role of genetics, and the potential of B vitamins as a countermeasure. Curr Opin Clin Nutr Metab Care. 2018; 21(6):481–488.
111. Smith SM, Zwart SR, Block G, Rice BL, Davis-Street JE. The nutritional status of astronauts is altered afterlong-term space flight aboard the International Space Station. J Nutr. 2005; 135(3):437–443.
112. Smith SM, Zwart SR, Heer M, Hudson EK, Shackelford L, Morgan JL. Men and women in space: bone loss and kidney stone risk after long-duration spaceflight. J Bone Miner Res. 2014; 29(7):1639–1645.
113. Srámek A, Bosch JG, Reiber JH, Van Oostayen JA, Rosendaal FR. Ultrasound assessment of atherosclerotic vessel wall changes: reproducibility of intima-media thickness measurements in carotid and femoral arteries. Invest Radiol. 2000; 35(12):699–706.
114. Stenger MB, Lee SM, Ribeiro LC, Phillips TR, Ploutz-Snyder RJ, et al. Gradient compression garments protect against orthostatic intolerance during recovery from bed rest. Eur J Appl Physiol. 2014; 114(3):597–608.
115. Stenger MB, Lee SM, Westby CM, Ribeiro LC, Phillips TR, et al. Abdomen-high elastic gradient compression garments during post-spaceflight stand tests. Aviat Space Environ Med. 2013; 84(5): 459–466.
116. Stevens RG, Brainard GC, Blask DE, Lockley SW, Motta ME. Breast cancer and circadian disruption from electric lighting in the modern world. CA Cancer J Clin. 2014; 64(3):207–218.
117. Thomas DT, Erdman KA, Burke LM. Position of the Academy of Nutrition and Dietetics, Dietitians of Canada, and the American College of Sports Medicine: Nutrition and Athletic Performance. J Acad Nutr Diet. 2016; 116(3):501–528.
118. Trumbo P, Yates AA, Schlicker S, Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. J Am Diet Assoc. 2001; 101(3):294–301.
119. U.S. EPA. Risk Assessment Guidance for Superfund (RAGS). Human Health Evaluation Manual (HHEM) (Part A, Baseline Risk Assessment), vol. I. Washington (DC): EPA Office of Emergency and Remedial Response; 1989.
120. Vandewalle G, Maquet P, Dijk DJ. Light as a modulator of cognitive brain function. Trends Cogn Sci. 2009; 13(10):429–438.
121. Vil-Viliams IFKA, Gavrilova LN, Lukjanuk VYu, Yarov AS. Human +Gx tolerance with the use of anti-G suits during descent from orbit of the Soyuz space vehicles. J Gravit Physiol. 1998; 5(1):P129–P130.
122. Viola AU, James LM, Schlangen LJ, Dijk DJ. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scand J Work Environ Health. 2008; 34(4):297–306.
123. Watanabe Y, Ohshima H, Mizuno K, Sekiguchi C, Fukunaga M, et al. Intravenous pamidronate prevents femoral bone loss and renal stone formation during 90-day bed rest. J Bone Miner Res. 2004; 19(11):1771–1778.
124. Waters WWZM, Meck JV. Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. J Appl Physiol. 2002; 92(2):586–594.
125 West KE, Jablonski MR, Warfield B, Cecil KS, James M, Ayers MA, et al. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. J Appl Physiol(1985). 2011; 110(3): 619–626.
126. Whitson PA, Pietrzyk RA, Pak CY. Renal stone risk assessment during Space Shuttle flights. J Urol. 1997; 158(6):2305–2310.
127. Whitson PA, Pietrzyk RA, Pak CY, Cintron NM. Alterations in renal stone risk factors after space flight. J Urol. 1993; 150(3):803–807.
128. Willems HME, van den Heuvel E, Schoemaker RJW, Klein-Nulend J, Bakker AD. Diet and exercise: a match made in bone. Curr Osteoporos Rep. 2017; 15(6):555–563.
129. Williams RS, Doarn C, Shepanek M. Engineering, life sciences, and health/medicine synergy in aerospace human systems integration: the Rosetta Stone Project. Washington (DC): NASA,Office of the Chief Health and Medical Officer; 2017:73–84.
130. Winkel RR, Kalhauge A, Fredfeldt KE. The usefulness of ultrasound colour-Doppler twinkling artefact for detecting urolithiasis compared with low dose nonenhanced computerized tomography. Ultrasound Med Biol. 2012; 38(7):1180–1187.
131. Wood SJ, Paloski WH, Clark JB. Assessing sensorimotor function following ISS with computerized dynamic posturography. Aerosp Med Hum Perform. 2015; 86(12, Suppl):A45–A53.
132. Wright KP, Jr., Hughes RJ, Kronauer RE, Dijk DJ, Czeisler CA. Intrinsic near-24-h pacemaker period determines limits of circadian entrainment to a weak synchronizer in humans. Proc Natl Acad Sci USA. 2001; 98 (24):14027–14032.
133. Wyatt JK, Cajochen C, Ritz-De Cecco A, Czeisler CA, Dijk DJ. Low-dose repeated caffeine administration for circadian-phase-dependent

performance degradation during extended wakefulness. Sleep. 2004; 27(3):374–381.
134. Yetley EA, MacFarlane AJ, Greene-Finestone LS, Garza C, Ard JD, et al. Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. Am J Clin Nutr. 2017; 105(1):249S–285S.
135. Zwart SR, Gibson CR, Gregory JF, Mader TH, Stover PJ, et al. Astronaut ophthalmic syndrome. FASEB J. 2017; 31(9):3746–3756.
136. Zwart SR, Pierson D, Mehta S, Gonda S, Smith SM. Capacity of omega-3 fatty acids or eicosapentaenoic acid to counteract weightlessness-induced bone loss by inhibiting NF-kappaB activation: from cells to bed rest to astronauts. J Bone Miner Res. 2010; 25(5):1049–1057.