# Evidence Report:

# Risk of Adverse Health Outcomes and Decrements in Performance due to In-Flight Medical Conditions

## Human Research Program
## Exploration Medical Capabilities Element

**Approved for Public Release: Month DD, YYYY**

**National Aeronautics and Space Administration**
**Lyndon B. Johnson Space Center**
**Houston, Texas**

CURRENT CONTRIBUTING AUTHORS

| | |
|---|---|
| Erik Antonsen | Baylor University |
| Tina Bayuse | KBRwyle |
| Rebecca Blue | UTMB |
| Vernie Daniels | KBRwyle |
| Melinda Hailey | KBRwyle |
| Sam Hussey | NASA |
| Eric Kerstman | UTMB |
| Mike Krihak | NASA |
| Kara Latorella | NASA |
| Jennifer Mindock | KBRwyle |
| Jerry Myers | NASA |
| Robert Mulcahy | UTMB |
| Rebekah Reed | NASA |
| David Reyes | UTMB |
| Michelle Urbina | MEI Technologies |
| Marlei Walton | KBRwyle |

PREVIOUS CONTRIBUTING AUTHORS

Ross Archibald
Michael Barratt
Lauren Best
Grandin Bickham
Doug Butler
Lisa Scott Carnell
John Charles
Duane Chin
Katherine Daues
Victor Hurst
Aric Katterhagen
Kevin Kelleher
Craig Kundrot
Jancy McPhee
John McQuillen
Sandra Olson
Jack Rasbury
David Rubin
Lynn Saile
Rick Senter
Ronak Shah
Susan Steinberg
Bill Thompson
Paul Vargas
Sharmila Watkins
Aaron Weaver
John Zoldak

# Table of Contents

## I. Executive Summary

The drive to undertake long-duration space exploration missions at greater distances from Earth gives rise to many challenges concerning human performance under extreme conditions. At NASA, the Human Research Program (HRP) has been established to investigate the specific risks to astronaut health and performance presented by space exploration, in addition to developing necessary countermeasures and technology to reduce risk and facilitate safer, more productive missions in space (NASA Human Research Program 2009). The HRP is divided into five subsections, covering behavioral health, space radiation, habitability, and other areas of interest. Within this structure is the ExMC Element, whose research contributes to the overall development of new technologies to overcome the challenges of expanding human exploration and habitation of space. The risk statement provided by the HRP to the ExMC Element states: "Given that medical conditions/events will occur during human spaceflight missions, there is a possibility of adverse health outcomes and decrements in performance in mission and for long term health" (NASA Human Research Program 2016). Within this risk context, the Exploration Medical Capabilities (ExMC) Element is specifically concerned with establishing evidenced-based methods of monitoring and maintaining astronaut health. Essential to completing this task is the advancement in techniques that identify, prevent, and treat any health threats that may occur during space missions.

Establishing capabilities to provide long-term preventive and autonomous healthcare becomes particularly important as future missions, such as those to a near-Earth asteroid, the Moon, and Mars, are longer and more isolated from the Earth. In the event of a medical emergency during these missions, the possibility of returning to Earth or consulting via long distance communications may be challenging or impractical. There are many factors associated with long-duration space missions that make the provision of autonomous medical care particularly problematic, including limitations on available medical equipment and supplies owing to mass and volume constraints, a lack of comprehensively trained medical personnel in the mission crew, and the potential for encountering unfamiliar medical conditions and hazards particular to the space environment. Proposed solutions to these problems include diagnostic technologies, medical record-keeping systems, and guided treatment methodologies. These solutions are the focus of current ExMC Element research activities.

The ultimate goal of the ExMC Element is to develop and demonstrate a pathway for medical system integration into vehicle and mission design to mitigate the risk of medical issues. Integral to this effort is inclusion of an evidence-based medical and data handling system appropriate for long-duration, exploration-class missions. This requires a clear Concept of Operations, quantitative risk metrics or other tools to address changing risk throughout a mission, and system scoping and system engineering. Because of the novel nature of the risks involved in exploration missions, new and complex ethical challenges are likely to be encountered. This

document describes the relevant background and evidence that informs the development of an exploration medical system.

## II. Introduction

A human mission to Mars is a challenge outside of the bounds of human experience, but within the grasp of our technology and imagination. It is critical to both draw lessons from prior spaceflight experience and to recognize the limits of that experience. Relying too heavily on prior spaceflight experience creates a risk of not challenging assumptions inapplicable to planetary exploration. Each medical system designed for earlier human spaceflight was developed for a close-proximity Earth-centered mission that enjoyed the advantages of real-time telemedical support, consumable resupply, and medical evacuation when necessary. Operating outside low Earth orbit, without these advantages, requires a closer alignment between vehicle engineering and medical system development.

In a real sense, success in a human Mars mission will depend on a comprehensive and mission-enabling astronaut healthcare system as well as an understanding of how such a system will be integrated and implemented within an exploration mission. All other design, requirements, and research within exploration medicine will be driven by these two goals; thus, these goals form the conceptual cornerstone that defines the medical system design and the supporting research pathway. Using this framework, the ExMC Element works to envision the medical needs for a human Mars mission, identify operational barriers to meeting those needs, and implement a research pathway in the support of agency requirements and stakeholder interests.

The medical challenges expected in a human Mars mission are unlike any prior manned spaceflight experience. As a result, provision of medical care within the limitations of such a mission requires a paradigm shift in the understanding and acceptance of risk, the ethical framework of experimental flight, and the trading of medical capabilities against other vehicle components within a vehicle architecture limited by mass, volume, power, telemetry, and many other factors unique to distant and interplanetary travel. Manned spaceflight has reached a critical moment where the transition to a human-centric mission architecture must become reality if exploration missions are to succeed. Medical system requirements and vehicle design must share dependence to minimize the risks to crews, and flexible and minimized technologies must factor heavily in system design to elevate a medical capability without sacrificing other systems components designed to keep our crews safe. It is imperative that the medical system be optimized within these constraints to ensure that crew health and performance is maintained and mission risks are minimized.

## III. Evidence

The NASA Categories of Evidence are used to help characterize the type of evidence provided in this report. The categories are adapted from, and are comparable to, more familiar versions of Levels of Evidence scales (Silagy and Haines 2001). The four categories of evidence identified at NASA include:

- Category I data: based on at least one randomized controlled trial

- Category II data: based on at least one controlled study without randomization, including cohort, case-control, or subject operating as own control
- Category III data: non-experimental observations or comparative, correlation, and case (or case-series) studies
- Category IV data: expert committee reports or opinions of respected authorities that are based on clinical experiences, bench research, or "first principles"

While ideally all scientific practices pursued in manned spaceflight would be based upon the highest level of terrestrial and spaceflight evidence, realistically this is not always feasible. In particular, an Element dedicated to the science of exploration missions, those missions that have yet to be achieved and whose risks are yet undefined, must often rely on best-practice decisions made on the basis of historical evidence and expert opinion. Even more so, this practice must often be applied to parameters outside of the original intent of the research, evidence, or opinion, in an effort to provide any source of reasonable knowledge base to inform decision-making. Even the most robust data become theoretical or based upon expert opinion when applied to interplanetary spaceflight. In many of the cases presented in this document, the evidence categories presented above do not directly apply because of these limitations; as a result, this document will present evidence with a description of source and purpose, but will not attempt to force the evidence into artificial categories that are not applicable to the exploration paradigm.

Determining the risk of unacceptable health and mission outcomes due to limitations of in-flight medical capabilities first requires consideration of which medical scenarios are most likely to arise during a mission as well as those presenting the highest risk. Further, it is important to identify available capabilities that can most efficiently support crew medical needs, while simultaneously minimizing the medical system footprint. For exploration medicine, the evidence base is drawn from various sources, including data from previous spaceflight missions, ground-based studies in 'analog' environments, general population-based studies of disease and healthcare incidences, and computer-based simulations.

Studies of astronaut health pre-flight, in-flight, and post-flight allow the incidences of medical conditions during space missions to be established where possible, highlighting, where known, the common and high-risk conditions that could require medical attention during long-duration exploration missions. While often limited in applicability to the exploration environment, and simultaneously limited by a small population size that precludes statistical analysis for clinical significance, these data can help to provide context for exploration science or informed probabilistic risk modeling. The NASA Lifetime Surveillance of Astronaut Health (LSAH) project collects data on astronaut medical care and workplace exposures, including those occurring in the training and spaceflight environments, and conducts occupational surveillance to monitor for trends in exposure and health outcomes. NASA's Life Sciences Data Archive also includes data from human subjects derived from both

past and current spaceflight as well as data from analog studies. Several publications provide an overview of in-flight medical condition incidences (Davis 1999; Summers et al. 2005; Stewart et al. 2007). Tables 1 and 2 provided in the Appendix demonstrate the occurrences of medical conditions that have arisen in NASA astronauts during previous space missions.

Several of these conditions are not high-risk or emergent in nature, requiring a relatively low level of treatment resources such as medication and basic medical officer input. Non-emergent conditions that have occurred during space missions include dermatological, musculoskeletal, cardiovascular, and mild psychiatric conditions, as well as minor trauma and burns. Of greater concern, particularly for longer and more remote exploration missions, is the potential for more serious or life-threatening medical conditions during a spaceflight mission. Both benign and more serious cardiac dysrhythmias (supraventricular and ventricular tachycardia) have been reported during previous Mir, Skylab, and Apollo missions (Fritsch-Yelle et al. 1998); one case of dysrhythmia required that crewmembers be brought back to Earth (Summers et al. 2005). Additionally, dental (Berry 1974) and urological emergencies (Cockett 1964; Stepaniak et al. 2007) have been documented among astronauts.

Further evidence addressing the potential occurrence of medical conditions during exploration missions is drawn from studies in harsh environments that may be considered analogs of the space environment, such as submarine and Antarctic research expeditions. A range of medical conditions has been reported in these settings; most of these were non-emergent in nature though some required immediate evacuation (Ball and Evans 2001). Though these analog environments differ from those encountered by astronauts, there are some very important similarities that must be noted. The first is that, in both cases, crews are highly screened and must meet specific health criteria to participate in a mission. Both environments are also limited in their capacity to diagnose and treat medical conditions by lack of medical capability and resources. There are also occasional gaps in medical staff knowledge in both settings that require communication with outside specialists to help initiate and guide treatment.

For longer exploration missions, estimations of the expected rate of a significant medical event have been made based on the analysis of data from submarines, Antarctic expeditions, military aviation, and U.S. and Russian space missions (Billica et al. 1996). Risk estimations made using analog population data are limited in how they may be extrapolated for use in exploration mission risk assessments, as they do not account for the unique problems associated with the space environment such as radiation effects or physiological problems associated with microgravity.

General population-based studies are helpful where a basis for comparison with astronaut health data is required or when concerning the gold standard treatment options within a medical system. Particularly when considering the development of medical technologies or system-wide data architecture, an understanding of the

current state of medical practice as a whole provides great insight regarding available technologies or capabilities that could be incorporated into exploration medical system design.

## IV. Risk in Context of Exploration Mission Operational Scenarios

### A. Constraints for Exploration Missions

Exploration mission design is significantly different from previous spaceflight missions, with limitations in habitat volume, mass, and power, communication and data telemetry, and alterations to important human factors, including isolation and confinement for much longer timeframes and over greater distances from the Earth than any mission to date. This section will attempt to identify and briefly outline such constraints to provide a clear understanding of the environment within which an exploration medical system must perform.

#### *1. Habitat Design Constraints*

Restrictions in available mass, power, and volume within a space vehicle limit the medical equipment, consumables, and, consequently, the conditions that may be addressed within a medical system architecture. Currently, habitat designs are informed by mission requirements through the use of parametric sizing models, such as EXAMINE (Komar et al. 2008). This approach provides the capability for rapid quantification of trade considerations in mission and habitat design. At the architectural level, habitable volume and dimensions are specified, but typically the allocation of these to specific spaces that can be assigned to various systems needs is a process defined late in the process of vehicle development. Human Factors and Behavioral Performance personnel conduct habitability investigations of current crew and environment fit and model postures of specific tasks, particularly those that are envisioned to scope the largest volume for a dedicated subspace within a habitat. At present there is no direct linkage between the architecture (habitat, mission) design effort and medical system requirements. This linkage is necessary to ensure that medical items and environmental characteristics are assessed and interpreted by habitat designers to support health maintenance and care for the crew.

Sizing tools are also used in the development of an integrated Mass Equipment List (MEL), a list of all the equipment and supplies required to support a planned mission in consideration of the mission objectives, duration, and crew number and needs. MELs generally provide mass, power, and volume of required equipment and supplies. At the architectural level, it is typical for "Crew Healthcare" to be a single line item in a habitat MEL. For example, a notional deep-space habitat design reference mission for 380 days in duration with four crewmembers was estimated to require 250kg of dry mass (Toups et al. 2012). While these estimates are based on historical data, specifications at this level rarely differentiate equipment and supplies or their relative mass and volume requirements. Further, other line items in habitat (non-healthcare) MELs can include items that could be considered within the realm of medical capability support. For example, lines associated with Crew

Accommodations, Miscellaneous Provisions, Waste Collection and Personal Hygiene, Operational Supplies, and Maintenance Equipment and Spares could all include medical system-dedicated resources (Toups et al. 2012).

The general approach to address these disconnects is to develop, within the ExMC Element effort, the tools and guidance that permits more well-defined description of the requirements for medical capability support. Further, these tools and guidance must support the requirements of the iterative nature of habitat and mission design by providing a Medical MEL as well as layout and volumetric guidance. This guidance must be capable of scaling with mission characteristics, including duration, crew type and size, operational tasks and duration of surface operations, and the like. Further, medical guidelines must be able to support reconsideration as new capabilities become available to support crew health maintenance. Successful integration of a medical system into a vehicle architecture is enabled by early and consistent integration with engineering and design teams. In the past, NASA has typically not brought medical systems engineering efforts into the larger vehicle design or mission architecture.

### *2. Communication, Telemetry, and Data Constraints*

Current medical operations on the International Space Station (ISS) are actively supported by regular communication with ground support teams, including flight surgeons, biomedical engineers, and numerous consultants available as needed for specific medical concerns. However, in a long-duration exploration mission outside of low Earth orbit, communication with the ground will be limited in the best of circumstances by latency secondary to distance, with delays of up to 50 minutes for round trip communications near Mars (Hamilton et al. 2008; Baisden et al. 2008). Further, available bandwidth for deep-space communications is likely to be severely limited, restricting available time for crew-to-ground consultation possibly to as little as one hour in a 24 hour period. Aside from verbal communication, there will likely be significant constraints on data package telemetry, limiting the ability of ground crews to monitor vehicle and crew data, including health parameters, and restricting the ability to update onboard resources such as software-based medical knowledge support systems. These limitations lead to a need for a highly robust, autonomous, and self-supported medical system, including both onboard resources as well as high-level, internalized crew medical knowledge (Bridge and Watkins 2011).

### *3. Evacuation Capability Constraints*

While evacuation and return-to-Earth during even a low Earth orbit mission would require significant cost and resources, such a capability is possible and provides for a definitive option for the treatment of medical events during spaceflight. In an exploration mission to Mars, crews will be unable during most of the flight to abandon the mission and simply return to Earth, given limitations of fuel and distance as well as relative orbital mechanics. As a result, the vehicle must provide as complete a medical system as possible allowing for robust care for a variety of medical concerns (Baisden et al. 2008). Further, for conditions that cannot be

managed by the limited resources available in an exploration vehicle, a palliative capability must be available (Hamilton et al. 2008).

### B. Additional Stressors for Exploration Missions

Historically, illness and injury are the most common causes of mission delay or failure (Baisden et al. 2008). Exploration missions will include greater physiological, psychological, and environmental stressors than previously experienced in any spaceflight to date, increasing the potential for illness or injury with resultant mission impact. Aside from the habitat, communication, and distance limitations as described above, it is important to consider the specific health threats to a deep-space mission as independent factors that can significantly impact human health during such a mission. For example, the deep space radiation environment carries significantly higher risk than that of low Earth orbit, with an increased potential for exposure-induced illnesses in crew (Cucinotta et al. 2013; Cucinotta 2015). Additionally, the isolation and confinement of a deep space mission raises concern regarding psychological impact, group dynamics, and similar challenges to mental health during long-duration missions (Manzey 2004; Basner et al. 2014). The new challenges posed by the unique environment of a deep-space mission must be considered within the constraints of such a mission, and a robust medical system must be versatile enough to manage these concerns while still adhering to the limitations imposed by mass, volume, and power described above.

## V. Concept of Operations and Mission Design

### A. Development of a Concept of Operations for a Transit Mission to Mars

Per the NASA Procedural Requirements document for NASA Systems Engineering Processes and Requirements (NPR 7123.1B), a Concept of Operations (ConOps) is developed in the early phase of a systems engineering development process to describe the "overall high-level concept of how the system will be used to meet stakeholder expectations…and help facilitate an understanding of the system goals" (NASA Systems Engineering Processes and Requirements 2013). Currently, there is no overarching and validated ConOps for a Transit Mission to Mars; the lack of such a guidance document creates uncertainty regarding the mission components, capabilities, and constraints to be considered in medical system development for such a mission.

ConOps are regularly used throughout U.S. governmental agencies. For example, the Air Force Policy Directive 63-1, among other documents, establishes the need for a ConOps as discussed by the Systems Engineering sector of the Office of the Deputy Assistant Secretary of Defense (Department of Defense 2011; United States Air Force 2016). Many private sector industries rely upon the ConOps design to establish high-level guidance for production and operations. For example, the International Counsel of Systems Engineering recommends systems engineering processes for guidance on project developments, providing ConOps-level direction (INCOSE 2016). Within NASA, multiple historical ConOps and similar and related

guidance documents have been developed to identify, guide, and satisfy mission requirements for various aspects of manned spaceflight.

In 2009, the Space Medicine Exploration Medical Condition List (EMCL, JSC-65722), was developed to present medical conditions that are of concern to human health an performance in future flights and should be considered with regards to exploration medical capabilities (Watkins 2010; NASA Space Medicine Division 2012; Saile et al. 2014). This list forms the basis for the Integrated Medical Model (IMM). The IMM is predictive model that provides an estimation of risk to help identify a scale of clinical priority for mitigation of the EMCL medical conditions through adequate onboard resources within a given mission design (Saile et al. 2014). While the EMCL has been useful for previous work under the umbrella of the exploration mission architecture and is certainly applicable to interplanetary missions, Mars Transit missions (and the potential medical risks specific to such missions) are not specifically addressed by this list or the work that has followed.

The Exploration Medical Conditions Concept of Operations (JSC-65973) was baselined in 2010 and documents the operational concept and rationale for the prevention, diagnosis, and treatment of medical concerns for various exploration missions, including lunar sorties and outposts. Within this document, a number of medical strategies for exploration mission support were identified and pursued. The Exploration Medical Capability (ExMC) ConOps (HRP-48002) was baselined in 2013 and most recently updated in 2014 (Exploration Medical Capability Element 2013). The ExMC ConOps focused on design solutions to specific problems identified by the ExMC Element, outlining tasks designed to address knowledge gaps and management of specific medical concerns with regards to the development of an exploration medical architecture for future missions.

Similarly, a Telemedicine Operational Concepts for Human Exploration Missions to Near Earth Asteroids was completed in 2014 and documents the vision of the NASA space medicine community for telemedicine, serving as a roadmap for future research and technology development in the area of telemedicine for longer duration and more distant missions (Barsten et al. 2014). It presents the operational concepts for an end-to-end telemedicine system specific to a Near Earth Asteroid exploration-class mission; many of the medical capabilities described within are applicable to other interplanetary or long-duration exploration missions. These documents could be assessed for applicability to a Mars Transit ConOps but in their current form do not address such mission architecture.

Despite these precedents, there is a need for clarification of a ConOps for Mars Transit and dedicated to the development of a robust and comprehensive medical system, specific to the needs of the Mars Transit mission architecture. Current spaceflight operations are based on low Earth orbit in a vehicle that enables real-time ground based support and an expedited return to a higher level of medical care if needed. Future exploration missions will require greater autonomy, especially in the context of healthcare, due to extended mission duration, limited ability to

resupply or update onboard resources, and inability to evacuate to definitive medical care. A dedicated ConOps, specific to a Mars exploration mission, will provide a common vision of medical care for developing a medical support system for such a mission, documenting goals expected of a medical system and providing examples of the types of activities that the system will be used in support of this goal. This ConOps will ultimately inform the engineering effort to define the technical needs to be met by the mission medical system, which will subsequently develop functional requirements, system architectures, interfaces, and verification and validation approaches for the medical system. As previous requirements for standard of medical care have been vague, fundamental to this effort will be the identification of the level and types of medical care needed in a given mission architecture so that an appropriate medical system can be designed and integrated into the overall vehicle and mission subsystem (NASA 2014). The development of requirements for, and prioritization of, medical operations design, medical procedures, training plans, and the corresponding hardware and software is essential to reduce the risk of adverse health outcomes and decrements in performance due to in-flight medical conditions.

**B. Ethical Considerations**

At a fundamental level, the first astronauts that embark upon exploration missions beyond low Earth orbit are participating in experimental activities, just as the vehicles on which we transport them are fundamentally experimental. The space environment beyond low Earth orbit is not fully defined, operational concepts are untested, and the long-term impact of the space environment on the human explorers is not fully understood (Ball and Evans 2001; Cucinotta et al. 2013). Explorers will be accepting a high level of mission risk independent of the health consequences of their exposure to the space environment (Ball and Evans 2001). In some instances, due to limited mass, volume, and systems capability on exploration vehicles, our ability to protect the crew against health impacts may be traded against our ability to reduce overall mission and vehicle risks.

Ethical decisions concerning crew health and medical capabilities must be balanced with the contribution of countermeasures to overall mission success. For example, when considered in isolation, a full surgical suite would appear potentially very useful on a planetary mission, would buy down medical risk, and would appear to be an ethically sound decision. However, providing that capability would mean that the weight-limited vehicle would be unable to transport sufficient fuel and redundant systems to complete its transit to Mars successfully, and the crew would require significant training investment to realize a surgical capability, drawing precious training time from other mission needs. Ultimately, there may be instances where protecting the health of one crewmember could mean increasing the risk of harm to the other crew due to resource sacrifices. As a result, an ethical framework for exploration medical care will have to include not only clinical ethics directed at the care of each individual, but also the implications of decisions on the well-being of the entire crew. Finally, because these missions carry significant value for the nation and for humanity despite their high risk (Ball and Evans 2001; Institute of

Medicine 2014a), there may be instances where mission success outweighs individual interests.

Based upon standards established by the Belmont Report, NASA has provided policy definitions of the ethical principles it will use in making decisions that affect the health of crewmembers to include avoiding harm, beneficence, favorable balance of risk and benefit, respect for autonomy, fairness, and fidelity (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; Institute of Medicine 2014b; Office of the Chief Health & Medical Officer 2016). Currently, NASA reviews the ethical implications of a given mission architecture at several levels (Institute of Medicine 2014b). First, with regards to mission planning, there is an ethical need to understand the overall risk of loss of crew and the potential environmental exposures within a given mission design, including the risks to the crew themselves as well as the greater risk to society in the case of mission loss. Second, with regards to crew selection, there are clear ethical guidelines based on historical precedent in manned spaceflight regarding the ethical selection of crew for particularly dangerous missions (Reed and Antonsen 2017). Established ethical principles require that "burdens and benefits [of mission assignment] be distributed fairly, and that fair processes be created and followed" (Institute of Medicine 2014b). NASA strives to ensure that, to the extent practicable, crew are informed of the health risks of their participation in the mission. Further, NASA attempts to ensure that the crew selected are those best suited to successfully complete a mission without unacceptable long-term health consequences while also ensuring equality of opportunity (Institute of Medicine 2014b). This is one of the most ethically challenging areas of exploration medicine, because it balances issues of paternalism and autonomy against the obligations for beneficence and to minimize harm.

At a minimum, a continued standard of fair practice in selection and honest and thorough presentation of mission risks for true informed consent has guided crew selection in the past and should continue to be practiced in exploration missions. With an inability to predict exactly what resources will be needed in mission, understanding of the impacts of inclusion and exclusion of medical capability are necessary for the agency to make informed decisions regarding medical risk and to communicate that risk to crew for appropriate informed consent. Ultimately, NASA will need to refine and exercise its processes for the identification and review of the ethical implications of exploration mission, vehicle, and system design; for evaluating crew selection and assignment criteria; and for clinical decision-making during exploration missions with limited real-time communications and onboard capabilities.

## VI. Exploration Mission Medical Systems

### A. Modeling and Predicting Risk

In order to scope an exploration medical system, a precursor ability to model and predict risk is required. The best evidence must be used to address the following questions:

1. What medical issues do we think will occur?
2. How many times do we think those medical issues will occur?
3. What medical capabilities would we like to provide in order to identify and address those issues?
4. What subset of our desired capability is realistic given the mission mass, volume, power, data, and ethical constraints?

This section will review the evidence developed to this point to support risk analysis in the context of medical system scoping.

NASA's approach to risk prediction has varied over the history of manned spaceflight. Prior to 1986, NASA and other technology-driven organizations depended on failure mode and effects analysis (FMEA) and hazard analysis as their primary means to assess mission risk (Stamatelatos and Dezfuli 2011). Similar to a multidisciplinary root cause analysis, FMEA relies upon the calculation of a risk priority number on a scale of severity, occurrence, and detectability, and then provides a risk assessment based on the analysis of multidisciplinary teams at target institutions. This risk analysis, when applied to healthcare, is approached in a prospective rather than retrospective manner (Marx and Slonim 2003). However, such analysis focuses on local institutional assessment of risk and therefore lacks the ability to identify complex system and multifactorial effects, reducing its efficiency when applied to new technology development or large, system-wide health architecture.

Qualitative risk analysis approaches, such as FMEA, have proven successful in improving healthcare practices. Such activities have also improved acceptance of quantitative healthcare risk assessment processes, such as those based on fault tree and probabilistic risk analysis (PRA) approaches. PRA techniques have been designed with a focus on the outcomes of interest associated with event trees and fault trees that can lead to the related outcomes. By populating these event trees with associated likelihood probabilities and uncertainties of the critical and fault events, a quantitative assessment of the risk of the defined outcomes can be assessed through Markov-Chain Monte Carlo type approaches (Stamatelatos and Dezfuli 2011). As early as the 1980s, the nuclear power industry refined and regularly implemented PRA techniques as a quantitative means of assessing complex technological risk. In 1986, following the Challenger Space Shuttle mishap, NASA began utilizing PRA as an alternative approach to risk prediction. By 1994, the National Research Council recommended the use of PRA methods to quantitatively address uncertainty, variability and complexity of risk in complex system technologies that impact public safety. Technology-driven industries, such

as food safety and environmental protection, adopted the regular use of such techniques to prospectively evaluate existing risks and the cost-benefit of new technologies, processes, and the optimization of resources (Thompson 2002).

The healthcare industry has similarly begun utilizing various aspects of PRA techniques in risk prediction. In particular, the relatively recent healthcare focus on informed decision-making has benefitted from quantitative risk modeling by improving the evidence supporting design and funding capture for development of new healthcare technologies (Briggs et al. 2004). Resource allocation in the planning for natural disaster response and disease outbreaks benefitted from such evidence modeling support (Sobieraj et al. 2007; Zolfaghari and Peyghaleh 2015). PRA-derived techniques, such as Sociotechnical PRA (ST-PRA), have proven to be important risk vs. cost vs. outcomes utility estimate tools for medical staff, hospital administrators, and government decision-makers when compared to qualitative techniques (Marx and Slonim 2003; Comden et al. 2005; Garside et al. 2007). Hospital admittance practices and resource planning have utilized PRA-type methods, such as probabilistic mortality models, to improve other risk-scoring admittance techniques and as a means to stratify treatment resource allocations (Iezzoni et al.; Gandjour and Weyler 2006; Kansagara et al. 2011; Hippisley-Cox and Coupland 2013; Lich et al. 2014). Further application in these areas has led to implementation of optimization techniques to refine resource allocation and placement in general healthcare and disaster settings (Parker et al. 1998; Moore et al. 2012; Zolfaghari and Peyghaleh 2015). Markov probabilistic models related to the risk of specific applications or treatment processes have become relatively prevalent in current risk-prediction literature. Predicting falls, caries, stroke outcomes, hospital re-admittance after cardiac events, and diabetes treatment impacts are just a sampling of the myriad applications to which probabilistic techniques have been used to evaluate healthcare treatment and technology (Moss and Zero 1995; Selker et al. 1997; Singh et al. 2004; Oostenbrink et al. 2005; Rutten-van Mölken et al. 2007; Page et al. 2011; Palmer et al. 2013).

NASA has adopted PRA techniques in the assessment of medical conditions related to the unique aspects of spaceflight, particularly those lacking insight secondary to a lack of observable events such as bone fracture (Nelson et al. 2009; Sulkowski et al. 2011), head injury (Weaver et al. 2013), and decompression sickness (Conkin et al. 1996). Models and relational databases are being developed to allow computational analysis of multiple factors and enable NASA medical and engineering communities to communicate. The approach utilizes probabilistic and statistical models, in combination with relational databases, in an approach similar to engineering and to other technical organizations. The similarity is intended to provide medical information in a familiar risk characterization that enables quantitative discussions with vehicle designers and engineering teams. Specific applications of this approach for exploration-class missions include the EMCL, the IMM project, and the Medical Optimization Network for Space Telemedicine Resources (MONSTR) project.

- *The Exploration Medical Conditions List and the Integrated Medical Model*

As described above (see section *Va*), the EMCL consists of a list of 100 medical conditions that have either occurred or are of significant concern for affecting crew survival or threatening mission objectives in the event that they do occur in future missions (Watkins 2010; Antonsen et al. 2016; Canga et al. 2016). This List provides a minimum set of criteria that must be addressed by the space medical system; specifically, any operational system must provide in-flight capabilities needed for screening, diagnosis, and treatment of the conditions that comprise the EMCL (Watkins 2010; Saile et al. 2014). Initially developed in 2009, the EMCL has been used to develop a framework of medical concerns that has helped to provide context for further exploration-class developments within ExMC.

Developed in parallel with the EMCL, the IMM is a Monte Carlo simulation approach to spaceflight missions that explores the event space for medical concerns during a given reference mission. The IMM was designed to be a probabilistic model system and database of supporting medical conditions used to provide the relative risk, including likelihood and severity of outcomes, for the list of medical conditions. The IMM uses a medical evidence base from both spaceflight and terrestrial literature as well as a database of available treatment capabilities derived from the ISS medical kit, with mass and volume for all components and assignment of resources needed for treatment. The quantitative outputs provided by the IMM include medical condition probability of occurrence, event distribution, likelihood of medical evacuation criteria being met, likelihood of loss of crew life, and crew health index. The applicable range of IMM is limited by a number of necessary assumptions, such as the framework that all treatment and outcomes extend from reference sources associated with how medicine is to be practiced on the ISS; as a result, resource limitations and alterations to standard of care can change outcome parameters from the IMM.

As mentioned above, the IMM has been previously utilized for specific risk applications, particularly where specific medical events or conditions have not occurred in prior spaceflight experience. For example, the Bone Fracture Risk Module, a computational model subset of the IMM, was constructed to calculate the risk of bone fracture given specific flight conditions, with skeletal loading, altered activity, sex, body mass, altered bone strength dependent on mission length and type, and similar factors all considered by the model (Nelson et al. 2009). The model was able to provide a prediction of risk of bone fracture during reference missions to the moon and Mars, demonstrating higher risk on Mars due to compromised bone integrity from long-duration flight, and even demonstrated the ability to predict risk based upon bone load orientation and subject flexibility (Nelson et al. 2009). Results of the model's predictive capabilities were reported in the NASA Human Research Program Evidence Book (McPhee and Charles 2009). In 2011, Sulkowski et al published data regarding prediction of the risk of astronaut bone fracture related to extravehicular activity (EVA) utilizing the modeling capabilities of the IMM (Sulkowski et al. 2011). The model provided a conservative risk assessment that was deemed to be more realistic than prior risk prediction approaches, given the

high fidelity of the EVA suit analog and bone analogs used in the development of the model (Sulkowski et al. 2011).

Similarly, a Head Injury Model was developed as a further subset of the IMM tool to provide predictive capabilities regarding the risk of head injury aboard the ISS (Weaver et al. 2013). Head injury is among the EMCL conditions that do not have adequate observational data regarding prior head injury events in obit, nor are there many analogs available for representative study on the ground (Weaver et al. 2013). The IMM Head Injury Model provided a means to assess this risk without significant supporting data, instead relying upon head acceleration response models modified for use in the microgravity environment (Weaver et al. 2013). The model was demonstrated to be valid and reliable and provided a needed risk assessment regarding a medical condition with fortunately few actual historical events (Weaver et al. 2013).

- *The Medical Optimization Network for Space Telemedicine Resources Project*

To supplement the predictive power of the IMM, the MONSTR project was designed to explore the physician call space across the medical conditions of interest using a terrestrial standard of care to identify, per condition, what capabilities, actions, and resources are required or desired to implement the components of medical care that are indicated by the EMCL. The information contained in the MONSTR database has been obtained from the general medical community with an effort to capture the best technological approaches for best outcome in the treatment of EMCL medical conditions during long-duration flight. In its inception, MONSTR was designed to help identify high-yield research investments in capabilities that will mitigate medical risk through maximizing flexible medical capability. The current version (MONSTR 2.0) allows for physician ranking of actions and resources, as well as probability of occurrence for a given medical condition, utilizing the IMM modeling power to prioritize medical capabilities of interest for research investment.

Currently, MONSTR exists as a pilot project designed to demonstrate whether or not such a database provides valuable input for mission planners with regards to the medical capabilities trade space. Providing a reference for a terrestrial standard of care allows mission planners to identify resources required to address all medical concerns, then weighs the risks and benefits of eliminating any of those resources to save mass or space in future vehicle and system design (Antonsen et al. 2016; Canga et al. 2016). Deconstruction of medical resources in this manner allows for the development of relative weighting by both criticality and by probability of occurrence, as predicted by the IMM, allowing for a reasonable comparison of the relative utility of various medical resources, and further facilitating trades in medical resource mass and volume (Minard et al. 2011; Antonsen et al. 2016; Canga et al. 2016). With EMCL, IMM, and MONSTR capabilities, prediction of medical risk and weighted risk of inclusion or exclusion of various medical resources can evaluated with greater fidelity, allowing for earlier and more accurate input into the evidence-based development of a more robust medical system for future exploration-class missions.

- *Autonomous Risk Assessment and Dynamic Probabilistic Risk Analysis*

Current modeling techniques, including the IMM, provide probabilities based upon the resources onboard the ISS. Given that medical system parameters for a future exploration mission, including Mars Transit, have yet to be defined, it is currently not possible to develop a model based upon these undefined system parameters. However, the ideal PRA model would be one that accounts for all onboard resources throughout a specific exploration mission, but further factors in any change in mission parameters, including time remaining before return to Earth as well as the resources already exhausted in earlier medical events, to provide a dynamic, changing, probabilistic analysis throughout the mission. Monitoring the depletion of resources could provide significant insight into an adjusting risk prediction and could provide crewmembers and ground support with necessary information to facilitate decision-making regarding any necessary alterations or adjustments to mission parameters, goals, or operations.

Dynamic PRAs are currently of interest in the medical community, particularly with regards to economic modeling and use of resources across a larger medical system or hospital unit. Predictive modeling tools are being developed to address optimization of multifaceted population health systems, addressing, for example, deficiencies in technological factors, accessibility concerns, workflow optimization, and resource utilization to augment a health system as a single entity (Johnson et al. 2015). Similarly, dynamic modeling is applied to local- and state-level emergency preparedness, providing risk prediction for various disaster capabilities that is responsive to changing resources and current medical burdens (Rosenfeld et al. 2009). While even those who are actively making use of these models recognize their limitations, dynamic models are already being recognized for their enhancement of system understanding, particularly in providing early identification of system vulnerabilities and in guiding adjustment of appropriate responses to resource limitations (Rosenfeld et al. 2009).

Development of such a model for exploration missions, or adjustment of current models in use in other health applications to make these models useful in the aerospace environment, would be dependent upon first developing the medical system to be included in an exploration vehicle, and therefore must wait until the medical system is realized. However, such dynamic predictive capabilities would ultimately provide important insight for crew and ground alike, and as such would be highly desirable as an onboard resource for an exploration-class mission.

## B. Medical Mission Components

### *1. Consumables*

- *Onboard Pharmaceuticals*

A comprehensive medication formulary ideally is designed to accommodate the size and space limitations of the spacecraft while addressing the individual medication needs and preferences of the crew. Challenges in the provision of such a pharmacy

for exploration class missions include: the negative outcome of a degrading inventory over time, the inability to resupply before expiration dates, and the need to properly forecast the best possible medication candidates to treat conditions that will occur in the future.

Current provision of a pharmacy for the ISS is heavily dependent on the ability to resupply medications that have been used. In a planetary mission expected to have a duration of 2.5-3 years and include exposure to a previously unexperienced radiation environment, the stability of pre-supplied medications is suspect. Using FDA standards, only 16% of the 107 medications in the current ISS formulary would last 2.5 years by expiration date when accounting for ordering and packing times typical of pre-mission launch phases (Bayuse 2016). Little is publically known about most medications stability beyond expiration dates, and information is often challenging to gather due to pharmaceutical company proprietary concerns. Existing records of medication usage during prior human spaceflight are insufficient to draw conclusions on an appropriate prioritization of medications for exploration class missions.

Faced with the obstacle of access to in-flight medical care, and limitations of vehicle space, time, and communications, it is necessary to prioritize what medical consumables are manifested for the flight and which medical conditions are addressed. Studies of astronaut health establish the incidence of common and high-risk medical conditions that require medical intervention during long-duration exploration missions. In 2000, the Institute of Medicine convened a committee of experts, Committee on Creating a Vision for Space Medicine during Travel beyond Earth Orbit, to examine the issues surrounding astronaut health and safety for long-duration space missions. Two themes run throughout the committee's final report: first, that not enough is known about the risks to human health during long-duration missions beyond Earth's orbit or about what can effectively mitigate those risks to enable humans to travel and work safely in the environment of deep space, and second, that everything reasonable should be done to gain the necessary information before humans are sent on missions of space exploration (Ball and Evans 2001).

Although several spaceflight-focused pharmaceutical research studies have been conducted, few have provided sufficient data regarding medication usage or potency changes during spaceflight. The Du pharmaceutical stability study assessed medications flown on Space Shuttles to and from the ISS from 2006 until 2008; their study found that some medications were still viable beyond their expiration dates (Du et al. 2011). However, as with many spaceflight studies, the small sample size associated with this study limits the ability to draw strong conclusions. Other recent studies have provided information regarding medication usage, indications, and efficacy gleaned from spaceflight records (Barger et al. 2014; Basner and Dinges 2014; Wotring 2015, 2016). Although some conclusions can be drawn from these studies, the inability to fully quantify medication usage, indications, side effects, and

effectiveness limits insight as to which medications should be prioritized for further research.

The Food and Drug Administration (FDA) conducted a terrestrial study to evaluate pharmaceuticals that were stored beyond their original expiration date based on a comprehensive testing program The Federal Shelf Life Extension Program (SLEP) Program was established in 1986, and administered by the U.S. Department of Defense in cooperation with the FDA, to defer replacement costs of stockpiled medications and materials by extending their expiration dates. The FDA conducted all quality testing and medication evaluations for the SLEP Program. Potency was evaluated for all products by conducting active ingredient assays, and regression analyses of real-time assay data determined if shelf life extensions were granted. Results indicated that the actual shelf life of products tested may be longer than their labeled expiration dates, depending on their storage conditions (Lyon et al. 2006). The study summarized the long-term stability of 122 medications stored in original packaging from 3005 different lots tested using U.S. pharmacopeia and FDA stability testing standards to determine shelf life extension data. Overall, 2650 (88%) of the 3005 lots tested were extended past their original expiration dates, with an average extension of 66 months (Lyon et al. 2006). However, only 7 pharmaceutical compounds tested in the SLEP program are represented in the current ISS operational flight formulary (including amoxicillin, atropine, ceftriaxone, clindamycin, diphenhydramine, doxycycline, epinephrine, diazepam, lidocaine, methylprednisolone, phenytoin, and promethazine).

Cantrell et al. conducted a study evaluating eight long-expired medications with 15 different active ingredients that were discovered in a retail pharmacy in original, unopened containers (Cantrell et al. 2012). The medications had all expired 28 to 40 years prior to analysis. Three dosage units of each medication were analyzed, and each sample tested 3 times. Twelve of the 14 drug compounds tested (86%) were present in concentrations at least 90% of the labeled amounts, the generally recognized minimum-acceptable potency. Three of these compounds were present at greater than 110% of the labeled content. Two compounds, aspirin and amphetamine, were present in amounts of less than 90% of labeled content. One compound, phenacetin, banned by the FDA in 1983 for use in the U.S., was present at greater than 90% of labeled amounts from one medication sample tested, but less than 90% in other medication samples of that compound. In this study, 12 of 14 medications retained full potency for at least 336 months, and 8 of these for at least 480 months. The results of this study provides additional evidence that many medications retain their full chemical potency for decades beyond their manufacturer labeled expiration dates (Cantrell et al. 2012).

Du, et al., conducted an investigation into 33 pharmaceutical products, 22 solids, 7 semisolid, and 4 liquid formulations, packaged in payload medication kits that were flown to, and returned from, the ISS via the Space Shuttle (Du et al. 2011). Ground controls stored in an environmental chamber were available for comparison. Four payloads were returned after an on-orbit duration ranging from 13 to 880 days.

Cumulative radiation dose during the 880 days was observed to be linear over time. The study found that the number of formulations that did not meet content requirement of Active Pharmaceutical Ingredient (API) was higher in flight kits, as compared to the corresponding control kits from all four payloads (Du et al. 2011). Additionally, it was noted that the number of unstable formulations between flight and control increased as a function of storage time in space. However, although degradation was found to be faster in space than on the ground for most of the APIs, loss of API content was generally less than 20% of label claim (Du et al. 2011).

Dr. Virginia Wotring of the Baylor College of Medicine's Center for Space Medicine conducted an opportunistic, observational, pilot-scale investigation to test the hypothesis that ISS-aging does not cause unusual degradation (Wotring 2016). Nine medications were analyzed for active pharmaceutical ingredient (API) content and degradant amounts; results were compared to 2012 U.S. Pharmacopeia (USP) requirements. The medications were two sleep aids, two antihistamines/decongestants, three pain relievers, an antidiarrheal, and an alertness medication. Because the samples were obtained opportunistically from unused pharmacy supplies, each medication was available at only one time point and no control samples (samples aged for a similar period on Earth) were available. One medication (acetaminophen) met USP requirements 5 months after its expiration date. Four of the nine medications tested (44%, including loratadine, pseudoephedrine, zolpidem, and aspirin) met USP requirements 8 months post-expiration. Another three medications (33%, including loperamide, modafinil, and ibuprofen) met USP guidelines 2–3 months before expiration. One compound, a dietary supplement used as a sleep aid (melatonin), failed to meet USP requirements at 11 months post-expiration. No unusual degradation products were identified (Wotring 2016). These results agree with those of other studies of medication potency.

A report by Kim and Plante in 2015 assessed the potential effects of radiation on food and pharmaceutical storage during a 3 year spaceflight journey outside the protection of the geomagnetosphere (Kim and Plante 2015). Investigators calculated the mean number of charged particle hits and the radiolytic yields in the target materials of freeze-dried food, intermediate moisture food, and liquid formulation pharmaceuticals. For this assessment, the exterior background radiation environment at deep solar minimum was assumed to be uniform, isotropic, and constant throughout the entire round-trip journey to Mars. This study predicted an unlikelihood of background radiation to cause a rapid change of functional properties in pharmaceuticals stored inside the vehicle, but rather suggested that progressive functional defects would occur over time. These functional defects would depend on energy deposition, yields of radiolytic species, bond-dissociation frequency, or any other break-type chemistry phenomena. The study also proposed that the radiation dose received during a 3 year mission to Mars would be several orders of magnitude lower than that received during manufacturer sterilization or preservation procedures, and that the probability of space radiation hitting the individual molecules comprising consumables is very

low. The summary further suggests that radiolytic species may not be generated in solid dosage forms due to water removal during manufacturing. Therefore, the authors concluded that space radiation is not a concern for long-term preservation pharmaceuticals (Kim and Plante 2015).

As suggested by the Kim and Plante report, gamma irradiation has been used as a method of microbial sterilization in the food and medical devices industries, but to a lesser extent in the pharmaceutical industries. Contrary to this summary, however, the use of gamma irradiation on pharmaceutical products can result in a loss of API potency, the creation of radiolysis byproducts, and a reduction of the molecular weight of polymer excipients, and can influence drug release from the final product (Garcia et al. 2004). Despite these risks, use of gamma sterilization has continued to increase and demonstrate strong applicability to a wide range of pharmaceutical products. For example, water dissociates as a result of exposure to radiation and is a major source of free radicals; those free radicals can cause chemical compromise. Therefore, drugs with higher water content tend to respond poorly to irradiation (Garcia et al. 2004).

A recent literature review article (Hasanain et al. 2014) discussed how potentially harmful high ionization energy from gamma irradiation could be harnessed and optimized by formulation changes, such as the addition of radioprotectants, or by varying the irradiation conditions, including temperature, product state, oxygen environment, dose, and dose rate. The advancements made in gamma sterilization research may have further application for pharmaceutical products used during an exploration spaceflight mission. However, the potential damage and subsequent solutions for these products when they are exposed to forms of ionizing radiation found in deep space (i.e. galactic cosmic rays, solar energetic particles) may be considerably different from damage resulting from gamma sterilization and solutions to prevent or counteract such damage. Ideally, stability studies would be capable of characterizing quality, chemical integrity, and safety of medications exposed to the deep space environment. However, in the absence of obtaining those characterizations from deep space exposure, a close environmental analog such as the ISS or targeted radiation exposure could reveal additional insight that could bring us closer to that safe and effective exploration mission medication formulary.

Glenn Research Center released a NASA Technical Report, "Pharmaceuticals Exposed to the Space Environment: Problems and Prospects" (Jaworske and Myers 2016). This report reviewed several NASA and external reports evaluating pharmaceutical stability and shelf life extension. The report acknowledged that previous studies and NASA Evidence Reports have illustrated that selected pharmaceuticals on the ISS may have a shorter shelf life in space than on Earth, and offers a compelling argument for continuing opportunistic retrieval of medications returned from all spaceflight opportunities, including medications retrieved from the ISS, as well as passive payloads missions returned from outside of Earth's magnetic field. The report further suggests that data obtained from the analyses of

these medication samples returned from spaceflight would enhance statistical databases for probabilistic risk assessments and predictive modeling.

Another option to address radiation-related pharmaceutical degradation is storage at cryogenic temperatures. A study conducted by Meents et al. illustrated that when cubic insulin crystals were stored at 50 K, radiation damage to disulfide bridge structures were reduced by a factor of 4 when compared to analogous observations at 100 K (Meents et al. 2010), suggesting that cryogenic storage may be a viable option to reduce damage from the radiation environment. Similarly, Garcia et al. suggested that performing irradiation on drug products in a frozen state could mitigate irradiation effects (Garcia et al. 2004). While promising, this method is dependent upon the ability of the product to be safely frozen and thawed. That said, freezing a drug traps free radicals in the ice crystals, thereby reducing their freedom to move about; this may induce the molecules to recombine with each other, rather than cause disruption in the compound. This process could possibly improve drug stability and simultaneously impart resistance to degradation due to irradiation. Garcia and colleagues also recommended other options such as freeze-drying and using free-radical scavengers to alleviate degradation effects resulting from irradiation (Garcia et al. 2004).

The electronic Medicines Compendium (eMC) contains up-to-date information about medicines licensed for use in the United Kingdom (UK). All information on the eMC website comes directly from the 200 pharmaceutical companies that subscribe to the eMC; many of these have corporate headquarters in the United States. Pharmaceutical companies submit and update the Summaries of Product Characteristics (SPCs) provided by the eMC. Review of the eMC SPCs revealed that the maximum shelf life, or maximum amount of time the medication meets regulatory standards for potency based on drug stability testing, is reported as greater than 3 years for most medications in the eMC (eMC 2017). SPC shelf life information was identified for 40 of the 63 medications on NASA's prioritized medication formulary list, with 63% reported as having 3 or more years of shelf life.

It is clear that pharmaceutical intervention is an essential component of risk management planning for astronaut healthcare during exploration missions. However, the challenge still remains of how to assemble a formulary that is comprehensive enough to prevent or treat anticipated medical events and is also chemically stable, safe, and robust enough to have sufficient potency to last for the duration of an exploration space mission. In cases where a pharmaceutical agent will not have sufficient potency for a full mission, addressing this capability gap may require exploration of novel drug development techniques, dosage forms, and dosage delivery platforms that enhance chemical stability as well as therapeutic effectiveness.

- *Consumable Tracking*

In addition to decisions regarding which pharmaceuticals to include in an exploration mission, there are questions regarding how much medication will be

needed and how to ensure that such medication resources are managed to ensure availability when they are needed, even late in a mission timeline. Inclusion of an adequate pharmacy designed to address all potential needs of a long-duration, exploration-class crew raises concerns regarding mass and resource utilization. On the ISS, current onboard pharmaceuticals are minimized, given the option of evacuation and return to Earth for any significant medical condition. In an interplanetary mission, early mission termination and evacuation is unlikely to be a feasible option, increasing the need for a larger and more comprehensive pharmacy.

Current pharmaceutical use during spaceflight is not comprehensively monitored due to the balance between crew time demands and a decreased need for usage rate information in a setting where resupply is possible (Wotring 2015). As a result, our understanding of the frequency of medication uses, as well as an understanding of the quantity of medications needed over a given mission duration, could be improved. In order to better understand the volume and mass of pharmaceuticals needed for a long-duration, exploration class mission, a valid and robust means of medication tracking is needed.

Such systems already exist aboard the ISS for non-pharmaceutical purposes. For example, nutritional requirements are closely monitored, utilizing a robust dietary intake tracking method to ensure adequate caloric and nutritional intake and identifying volumetric food requirements for future missions. Astronauts track their food intake, as well as preferences and dislikes, utilizing tracking technology developed for efficiency and accuracy. The ISS Food Intake Tracker allows for item input by way of selection from a list, photographic food items, barcode scanning, voice recording, or manual keypad input (NASA Mission Pages 2013; Smith et al. 2014). This tracking system has greatly improved the awareness of the volume, type, and nutritional content of the foods consumed during a given mission, and has provided important insight regarding the volume and mass of foods necessary for longer or more distant missions. Early prototypes of a similar system for pharmaceutical monitoring are in development, with experiments aboard the ISS ongoing. For example, the Medical Consumables Tracking project uses radio-frequency identification codes to track medications and medical supplies on the ISS, allowing ground support to track which medical resources are used and when replenishment would be required (NASA 2017a). Similarly, the Dose Tracker project was designed to track crew medication uses, associated symptoms or relief, and any adverse effects to identify whether medications act differently on humans in space compared to terrestrial norms (NASA Mission Pages 2017). If successful, such capabilities could provide much-needed awareness regarding these parameters for pharmaceuticals.

Ground-based systems are in common use in most healthcare facilities. Automated medication storage and distribution systems have become the gold-standard in hospital wards, providing easy and rapid access to single-dose medications with accurate tracking of medications administered, time of dosage, and the patient receiving the medications (Canadian Agency for Drugs and Technologies in Health

(CADTH) 2010). Most systems utilize identifiers including barcode scanning, personnel identification numbers, and patient identifiers to ensure that the right patient receives the right medication, as ordered (and often pre-approved) through an electronic medical system. Implementation of such technology has been both economically and organizationally praised. Economically, automated distribution systems allow for improved billing, reduce the need for unnecessary stocking of minimally-used medications, and reduce the risk of medical error and the costs associated with such (Kheniene et al. 2008; Canadian Agency for Drugs and Technologies in Health (CADTH) 2010). With regards to safety and organizational impacts, these systems have been demonstrated to reduce medical error, improve time-to-first-treatment, improve identification of expired medications, improve timely stocking and ensure appropriate availability of highly utilized medications, and to reduce overall time spent on pharmaceutical-related paperwork, freeing up significant time for hospital personnel (Lee et al. 1992; Kheniene et al. 2008; Canadian Agency for Drugs and Technologies in Health (CADTH) 2010; Bourcier et al. 2016).

Installation of a fully automated dispensing cabinet will most likely require mass and volume that is incompatible with exploration mission-class vehicles. However, utilization of similar technological applications is likely feasible. Alteration of the food tracking system to include pharmaceutical tracking, or further development of a parallel medication tracking system, is one option for future missions. Development of similar tracking devices, such as barcode scanners or list identifiers of medications dispensed, would improve upon pharmaceutical tracking capabilities, whether or not a fully controlled dispensing cabinet is included. Development of such onboard capabilities in the near-term, with near-Earth mission implementation, would provide much-needed information regarding medication usage habits, future mission needs, and the like, and the technologies developed would undoubtedly be useful for resource management during a longer exploration mission in the future.

- *Personalized Medicine*

Personalized medicine will be an important element of exploration medical capabilities. In particular, providing interventions tailored to individual crew members through pharmacogenetics and pharmacogenomics will improve outcomes and minimize mass requirements of the onboard pharmacy by optimizing the drug selection for the crew complement. Over time, enhanced insight into the genomics and phenotypes of individual crew will help NASA to develop more effective countermeasures and interventions to address the effects of spaceflight on the human.

Personalized medicine is not novel in spaceflight. In both the Space Shuttle and ISS Programs, NASA used personalized medicine, in the form of individualized drug tolerance testing, to personalize sleep and alertness interventions for crew (Johnston et al. 2015). On the ISS today, personalized pharmaceutical prescriptions are paired with complementary behavioral and environmental interventions such as

sleep schedules and smart lighting (Brainard et al. 2013; Scheuring and Johnston 2015; Flynn-Evans et al. 2016). Recent research has demonstrated significant genetic variability among individuals that affects need for sleep and the cognitive effects of sleep deprivation (Goel and Dinges 2012). Work is underway to develop genetic markers that will inform personalized countermeasures to cognitive or operational limitations due to sleep loss, optimization of sleep scheduling, and determination of a crewmember's need for onboard pharmaceutical interventions (Goel and Dinges 2012). Sleep will likely remain a focus of personalized medicine in exploration medicine.

Terrestrial pharmacogenetics is making significant strides that will support exploration medicine in the future. Ground-based pharmaceutical studies have demonstrated significant genetic- and population-based differences in response to various drugs. For example, response to medication can be significantly altered by age, possibly secondary to DNA methylation or similar age-related degradation or alteration of gene expression (Fitzpatrick and Wilson 2003). Pharmaceutical response can be varied by sex, as demonstrated by differences between male and female responses to cardiovascular pharmacotherapy (Jochmann et al. 2005). Race and ethnicity can also affect drug response; examples include: cardiovascular medications only effective in persons of African descent (Taylor et al. 2002); altered metabolism of sedative medication in persons of East Asian descent (Tang et al. 1983); and differences in the metabolism of antihypertensives in persons of African and Chinese heritage when compared to those of European descent (Kalow 2001).

The source of these differences may be due to varied expression of specific genes. Cytochromatic expression, for example, has been identified in numerous studies to be the basis of significant alterations in drug metabolism and response, including cytochrome CYP2D6 and response to metoprolol (Schwartz and Turner 2004) and cytochrome CYP2C9 and response to warfarin (Herman et al. 2005). Similarly, the presence of N-acetyltransferase activity prevents many of the unpleasant side effects associated with the administration of isoniazid (Bonicke and Reif 1953). Research are looking at similar enzyme-driven response aboard the ISS. Early results suggest that as many as a third of the drugs available on the ISS are regulated by enzymatic response (such as the cytochrome system) potentially leading to significant response variance among individuals (Stingl et al. 2015).

Personalized medicine as a field is in its infancy. In terrestrial medicine other federal agencies are working to realize the potential of this field in the larger medical arena (Hamburg and Collins 2010). For NASA, additional research on genetic and genomic information to inform personalized medicine poses both logistical and regulatory challenges. There are few astronauts who have experienced extended stays in space, and few analogs to identify spaceflight-induced genetic changes. Terrestrial medical research is exploring different techniques in clinical medicine that include tracking the individual rather than average responses to therapies (Schork 2015) that may be more applicable to the challenges NASA faces with small crews and long duration missions. In studying our

current astronauts, NASA is bound by Federal law that limits the collection and use of genetic information. For instance, NASA may use genetic information for occupational surveillance and countermeasure development, but not for crew selection and assignment decisions (Reed and Antonsen 2017). Even working within these constraints, there is much NASA can accomplish to improve the ability to deploy personalized medicine on exploration missions, particularly by building on advances in terrestrial personalized medicine.

### *2. System Capabilities*

Prolonged microgravity exposure is known to cause significant deconditioning of the musculoskeletal system, placing crew at risk of injury when they return to a normal gravitational environment. Similarly, crew arriving to the Mars surface will face an increased risk of injury if musculoskeletal health is not maintained, and sustained planetary activities will contribute further to physiological stressors. In addition, any illness experienced during the flight between the Earth and Mars could result in significant cardiovascular or musculoskeletal deconditioning. Much like on Earth, where prolonged bed rest is associated with decreased strength and cardiovascular reserve, illness in spaceflight could similarly reduce the physical capabilities of afflicted crewmembers. As a result, an onboard medical system must have the capability to provide rehabilitation techniques to mitigate such risk. Further, a system knowledge resource that could provide guidance to an onboard medical officer, directing decision-making with regards to rehabilitation regimes or specific interventions, could offer much-needed support in the absence of regular communication or intervention by ground support. These considerations will be discussed at length below.

- *Rehabilitation*

Experience in low Earth orbit has demonstrated that many injuries occurring during flight are musculoskeletal in nature (Scheuring et al. 2009). In addition, there are numerous studies regarding the significant atrophy of skeletal muscle and bone during long-duration spaceflight secondary to the unloading of axial stress in the microgravity environment (Ploutz-Snyder et al. 2015). To date, most medical events that have occurred in-mission have been self-limiting, minor, or easily treated with existing vehicle medical capabilities (Scheuring et al. 2009). For more serious conditions, evacuation to definitive medical care is available and there is no need for prolonged in-mission rehabilitation capability. Without the ability to evacuate an injured crewmember, in-mission rehabilitation capabilities may be required.

Longer stays in Earth orbit have necessitated the development of countermeasures to prevent, or at least limit, the atrophic effect of microgravity, prepare astronauts for the return to Earth and its gravitational environment, and to prevent injury secondary to muscle or bone atrophy during flight, and serve the basis of evidence for potential countermeasures for future exploration missions (Hawkey 2003; Orwoll et al. 2013; Ploutz-Snyder et al. 2015). While countermeasure capabilities are aimed towards prevention of deconditioning, there is a close correlation between such preventive efforts and exploration mission injury and rehabilitation

concerns. As future exploration missions increase time and distance from Earth, there is the possibility that medical events will occur that result in significant crew functional impairment requiring in-mission rehabilitation (Hamilton et al. 2008). In particular, the need for immediate physical performance and operational capabilities upon arrival to a distant planetary surface like Mars could place deconditioned crew at increased risk for injury. As in terrestrial rehabilitation efforts, use of exercise equipment will likely form a large part of the preventive and recuperative rehabilitative capabilities onboard an exploration vehicle. Given the correlation between deconditioning countermeasures, injury risk, and rehabilitation needs, a brief introduction to countermeasures is provided below for context.

Multiple countermeasure devices have been utilized aboard the ISS and other historical spacecraft. Current devices in use aboard the ISS include the cycle ergometer with vibration isolation and stabilization (CEVIS), treadmill with vibration isolation and stabilization system (second generation, called T2), and the Advanced Resistive Exercise Device (ARED), which replaced the interim Resistive Exercise Device (iRED) in 2010 (Ploutz-Snyder et al. 2015). The CEVIS and T2 provide cardiovascular conditioning through running or cycling, allowing for maintenance of cardiovascular reserve, preventing orthostasis, hypotension, and cardiovascular stress upon return to a gravitational environment after landing (Ploutz-Snyder et al. 2015; Petersen et al. 2016). These devices are notorious for onboard failures leading to reduced availability; particularly during early ISS missions, it was rare that all exercise devices were working, making it difficult for crew to maintain cardiovascular conditioning during long-duration missions (Ploutz-Snyder et al. 2015).

The iRED is an elastomer-based resistance hardware device, utilized during long-duration missions until the introduction of the ARED in 2010. In studies regarding spaceflight-related musculoskeletal alterations, data demonstrated successful muscular activation and strength training using iRED with muscle responses similar to that seen with ground-based use of free weights (Schneider et al. 2003). However, iRED failed to stimulate bone and prevent atrophy during flight, demonstrating a need for improved countermeasure strategies for long-duration missions to prevent microgravity deconditioning (Schneider et al. 2003; Ploutz-Snyder et al. 2015). The addition of the ARED allowed for varied and improved resistant exercise regimes. The ARED uses vacuum canisters to provide up to 600 pounds of resistance, mimicking inertial loads generated by the use of free weights on Earth (Ploutz-Snyder et al. 2015). Ground-based studies demonstrated protection of both muscle mass and bone mineral density with use of the ARED (Loehr et al. 2011). Aboard the ISS, crewmembers show improved protection and even gain of muscle mass as well as protection of bone density during flight through ARED use (Smith et al. 2012; Ploutz-Snyder et al. 2015).

Despite these advances, rehabilitation capabilities for exploration-class missions are still lacking. While the ARED has significantly improved upon exercise-related rehabilitation and mitigation of microgravity-induced musculoskeletal detriments,

the mass and volume required for a system like the ARED are prohibitively large when considering the limitations of an interplanetary mission. Smaller devices, such as the iRED, have been less successful and are likely insufficient for successful mitigation of atrophy during a multi-year mission. Further, while exercise has been the primary countermeasure for deconditioning during prolonged microgravity exposure and mitigating negative physiological change, they have been associated with numerous musculoskeletal injuries in the past (Scheuring et al. 2009). There is a need for effective but volume-reduced rehabilitation countermeasures that provide effective mitigation at minimal risk to the crew for exploration-class missions.

New devices are under investigation for exercise-related countermeasure and rehabilitation efforts. For example, the Resistive Overload Combined with Kinetic Yo-Yo Device (ROCKY) was developed by Zin Technologies, Ohio, to provide a robust exercise capability at an exponential decline in mass and volume requirements (Garcia 2016; Zin Technologies 2016). Alternatives to exercise-mitigation of microgravity deconditioning are also of interest. For example, lower-body negative pressure (LBNP) devices have demonstrated some success in mitigating post-flight orthostatic intolerance; these devices are often relatively compact, requiring less mass and volume than many of the historic and current exercise devices described above (Murthy et al. 1994; Trappe et al. 2007). However, the effects of LBNP tend to be best obtained when the capability is used in conjunction with cardiovascular exercise (Murthy et al. 1994; Trappe et al. 2007). Further, LBNP does not provide effective mitigation of musculoskeletal atrophy in long-duration exposure to microgravity.

An onboard medical capability must be able to prevent injury, including prevention of deconditioning that will lead to increased physical risk. It is likely that, in the absence of ground instruction, the crew will look to an onboard medical officer to guide rehabilitation and training regimes, tailoring them to specific injuries and weaknesses or to declining functional performance capabilities that follow prolonged illness or convalescence. One consideration for future long-duration missions is the inclusion of guided rehabilitation regimes with use of telerehabilitation to tailor specific exercise countermeasures to a given crewmember, addressing any known limitations, injuries, or similar factors. On Earth, rehabilitation techniques typically involve an extensive complement of medical expertise and equipment, including physicians, nurses, therapists, and specialized equipment that are specifically tailored to a given patient's needs (Frontera 2013). To address out-of-hospital needs, telerehabilitation is currently being developed for patients in remote terrestrial locations (Schmeler et al. 2009). As telerehabilitation often requires a less extensive array of on-site medical personnel and makes use of often limited equipment, telerehabilitation capabilities could be important components of an in-flight rehabilitation capability in a similarly limited resource environment of an exploration mission (Kumar and Cohn 2013; Papali 2016).

While techniques or equipment have yet to be developed to meet the specific needs of exploration or interplanetary spaceflight, the risk of injury or deconditioning during longer missions is quite real, and poses a significant threat to crews that must be capable of physical performance upon reaching their destination. Development of appropriate technology or telerehabilitation techniques to mitigate specific injury or atrophy that meet mass and volume constraints for long-duration, exploration-class missions will be an important component of future mission design.

- *Decision Support and Onboard Knowledge Resources*

Current missions aboard the ISS rely heavily upon ground support and telemedical capabilities in the way of live remote guidance, monitoring, and coverage to assist in the diagnosis, treatment, and other management of acute medical issues and needs during flight (Hamilton et al. 2008; Bridge and Watkins 2011; Blue et al. 2014). In an exploration-class mission, immediate terrestrial support may be unavailable; in emergent situations, communication delays or blackouts may limit the ability for ground-based support to assist crew decision-making. A shift in the current telemedicine paradigm is needed to support real-time clinical decision-making in a remote environment. More autonomous data systems must be developed that are robust enough to allow the crew to independently and rapidly diagnose illness and assess the best available treatments, evaluate the likelihood of success of treatment, and determine the implications for the rest of the crew and the mission regarding the use of the resources required to treat an injured crewmember.

With regards to specific onboard resources, there are a number of guidance programs available to assist in diagnostic examination as well as interpretation of test results. For example, multiple guided imaging programs exist for the assistance of sonographic techniques. To improve upon operator skill in ultrasound, developers have designed robotic imaging technology that provides point-of-care guidance on probe placement, image acquisition, and telemedical interfaces (Monfaredi et al. 2015). Similar technologies have been developed for use on the ISS, including the Advanced Diagnostic Ultrasound in Microgravity (ADUM) project. The ADUM system uses remote guidance, telemedical interfaces, and just-in-time instruction techniques to guide minimally trained crewmembers in acquisition of adequate imaging that could be used for diagnostic purposes (Foale et al. 2005; Hamilton et al. 2011; NASA Mission Pages 2016a). Follow-on studies aim to expand upon this technology, allowing for more computer-based guidance and relying less upon telemedical support from ground crews. For example, the "Clinical Outcome Metrics for Optimization of Robust Training" (COMFORT) study aims to develop clinical outcome metrics and guided training tools for physician and non-physician crew medical officers for use in exploration medicine (Ebert 2017).

In terrestrial medicine, similar techniques are being developed for other medical applications, such as robotic guidance for invasive procedures such as percutaneous needle guidance (Cleary et al. 2006; Kettenbach and Kronreif 2015). Robotic assistance for telemedicine is occasionally used for remote physician presence in underserved regions; while many of these resources focus primarily on video

conferencing, some incorporate other tools including remote bedside monitoring and medical decision-making algorithms for assisted decision support (Ackerman et al. 2010). It is important to remember that the benefits of these technological advances must be weighed against the associated mass and volume requirements of flying equipment needed to support the technology. However, robotic guidance for procedural support or assisted decision-making has the potential to greatly amplify autonomous crew medical capabilities, allowing for point-of-care guidance for interventions in which the crew receives minimal training or procedures that are outside of the expertise of the onboard Physician Astronaut. At the moment, these technologies are early, and applicability to the challenges of spaceflight is currently outside of the scope of these technologies. Further, any technology included in an exploration medical system must be near autonomous and robust enough to be reliable for the duration of the mission; this, too, is not achievable with today's technologies.

In addition to procedural assistance, onboard knowledge support technologies will be necessary to enhance medical capabilities on a long-duration mission. At a very basic level, the onboard Physician Astronaut will likely have need for educational resources and refresher materials, such as computerized clinical knowledge systems like UpToDate®, eMedicine™, Wheeless Online, and other online resources available in most hospitals (Medscape 2017; UpToDate 2017; Wheeless 2017). Retrospective and non-blinded comparative studies have demonstrated improvement in patient outcome, decreased length of stay, and reduced resource utilization in hospital systems that allow physicians to directly access such knowledge supplements during clinical activities (Bonis et al. 2008; Isaac et al. 2012). Knowledge resources are ideally rapidly accessed, with directed information indexed by simple search terminology such as diagnostic criteria, symptomatology, and clinical signs, and provide specific information regarding treatment options, prognosis, and the like. Such resources would undoubtedly provide much-needed knowledge resources in the case of an in-mission medical event.

While a basic searchable text of knowledge would certainly complement the Physician Astronaut capabilities, a more robust system could provide higher-level decision support technologies. For example, artificial intelligence technologies have been developed that apply algorithms to medical diagnostic criteria, providing decision support regarding best treatment options, ideal medication and dosing information, and similar. Such systems have been used in clinical diagnosis protocols, image analysis, and complex data interpretation, and the application of these technologies is being explored in multiple fields of medicine (Henson et al. 1997; Pesonen et al. 1998; Ramesh et al. 2004; de Bruijne 2016). If these systems were adjusted for aerospace medical considerations, protocol guidance and assisted decision-making technologies could provide support for medical response in an exploration mission where communication with ground support and telemedical capabilities are limited. While promising, there is a need for significant development of these technological advances before such techniques are clinically robust enough for incorporation into an exploration medical system, and the ExMC Element

continues to assess the likely maturity of these systems in anticipation of a Mars mission.

## C. Medical Mission Considerations

### *1. Risk Mitigation*

- *Selection of the Physician Astronaut and Pre-mission Medical Training*

Current pre-mission medical training for ISS missions is based upon the present paradigm of an assigned crew medical officer. Presently, a mission's crew medical officer is any individual chosen to be responsible for acute medical care aboard the ISS; this individual may or may not have had any prior medical training or experience (Bridge and Watkins 2011). ISS standards include designation of one medical officer per every three-person crew (Hamilton et al. 2008). Prior to launch, this medical officer receives approximately 40 hours of instruction in the use of onboard resources and a basic education regarding the presentation of common medical conditions and related superficial treatment options (Bridge and Watkins 2011). This includes approximately 4 hours of lecture on medical diagnostics, 5 hours on therapeutic interventions, and 10 hours of basic life support (BLS) and advanced cardiac life support (ACLS) algorithm training to American Heart Association standards (Bridge and Watkins 2011). ISS crew medical officers may choose to further shadow medical providers in various clinical scenarios, including an emergency or trauma center or pre-hospital care settings (Bridge and Watkins 2011; Blue et al. 2014). Finally, all crew medical officers are provided guidance regarding clinical indications to involve telemedical intervention and ground medical support (Bridge and Watkins 2011; Blue et al. 2014).

NASA standards require a designated medical officer, trained to the level of a physician, as part of the onboard astronaut skill mix for planetary missions longer that 210 days given the increased duration, uncertainty and complexity surrounding medical care in this environment (National Aeronautics and Space Administration 2016). Thus, future mission planning to mitigate medical and human performance risk for planetary missions will need to consider what type of prior training (i.e. what type of physician training or background is most suited to the mission needs) as well as providing redundancy for the physician-trained medical officer, referred to here as Physician Astronaut (Bridge and Watkins 2011). Physician Astronauts supporting planetary missions must have sufficient education and technical competency to provide medical decision-making and provision of treatment for any number of varied medical events that could occur during flight. Physician-level medical training typically takes at least seven dedicated years of medical school and residency training to achieve the capability to practice independently in the United States. This level of training is unrealistic to duplicate within the astronaut training regime; thus, an individual with an appropriate skill set must be selected, with training pathways designed for maintenance of skills prior to a mission, and training needs identified for in-mission knowledge and skills maintenance (Blue et al. 2014).

In the context of a more distant exploration-class mission, pre-flight training for the Physician Astronaut would need to focus on familiarization with common ailments or injuries, as well as onboard capabilities and resources (Blue et al. 2014). NASA has assessed the needs for exploration missions and found common medical capabilities and management strategies that should be emphasized for Physician Astronaut training, including dental procedures, behavioral health issues, and musculoskeletal injury. All of these have been identified as potentially frequent and/or incapacitating without effective intervention (Scheuring et al. 2009; Blue et al. 2014). Onboard medical equipment, particularly hardware and pharmaceuticals, should be familiar enough that Physician Astronauts can rapidly access assets in case of emergency (Blue et al. 2014). Specialized training in the classic and even non-conventional capabilities of onboard resources, such as expanded sonographic techniques if an ultrasound is included within the medical system, could ensure that the Physician Astronaut can make full use of such resources and even potentially improvise an alternative solution in the case of an injury that is outside the classic indications of onboard resources (Fincke et al. 2005; Sargsyan et al. 2006; Kwon et al. 2007; Kirkpatrick et al. 2007; Jones et al. 2009a; Sirek et al. 2014). Further pre-flight training may be needed for specific illnesses or injuries anticipated in a given mission that fall outside a Physician Astronaut's field of knowledge or personal experience (Blue et al. 2014). Given that a Physician Astronaut will likely be many years removed from their original medical training, pre-fight refresher training may be required in areas of practice that require manual skill, complex thinking, or rapid and critical decision-making.

In addition, the Physician Astronaut would need to be familiar with the effects of long-duration flight on the human body, particularly with regards to musculoskeletal and cardiovascular deconditioning, neurovestibular alterations, immune suppression, effects of chronic radiation exposure, behavioral health implications, and effects on metabolism and endocrine activity (Grigoriev et al. 2002; Pool and Davis 2007; Baisden et al. 2008; Bridge and Watkins 2011). The ability to recognize signs or symptoms of significant deconditioning and to implement countermeasures may be critical in the case of interplanetary flight, where crewmembers would require physical agility and strength immediately after landing for likely mission-critical activities (Bridge and Watkins 2011). Awareness and training in in-flight rehabilitation and countermeasure resources, as described above, would help the Physician Astronaut recognize deconditioning and make full use of onboard resources to counteract such trends. A pre-flight awareness and understanding of aerospace physiology would provide significant insight regarding risks and potential opportunities for intervention during an exploration mission.

- *Continuing Education and Just-In-Time Training*

Continuing education that includes repeat patient exposure is critical for maintenance of competency for any clinician (ACGME 2016). The content, frequency, and amount of that exposure to maintain minimum levels of competency is not clearly defined outside of regulatory body requirements for licensing and likely varies clinician to clinician. Current ISS astronauts can have delays of many

years between selection and mission assignment, and during this time period they are cross-trained in multiple professional fields in preparation for future mission assignments (Barshi and Dempsey 2016). It is critical to ensure that core clinical skills and competencies are maintained during this time frame between hire and mission assignment while managing competing priorities for work time. Further, as all potentially necessary medical procedural skills are not likely to be trained prior to a mission, an evidence based approach to just-in-time learning strategies needed from an exploration medical system must be scoped, researched, and eventually tested (Blue et al. 2014). Clinically competent Physician Astronauts and those designated as backups will also require spaceflight-specific medical training during this time period to familiarize them with the medical operational environment of their spacecraft and habitat.

Currently, ISS crew medical officers are able to reference knowledge resources, including tutorials and study materials, for point-of-care training for various medical scenarios or resource usage (Foale et al. 2005; Blue et al. 2014). Further, ground-based medical support is available for conference, assisted decision-making, and provision of additional resources as needed (Blue et al. 2014). For the rare and generally minor injuries or medical events that have occurred to date, this capability has been sufficient to ensure that the necessary medical care is available in low Earth orbit. However, exploration-class missions outside of low Earth orbit are unlikely to be able to emergently utilize ground-based assets given communication limitations imposed by distance and technology or bandwidth restrictions. Physician astronauts and backup medical officers need onboard resources to assist in the case of a medical event outside their area of medical expertise to provide point-of-care or just-in-time training (Blue et al. 2014).

One training modality that has been demonstrated to be effective in even critical operations is the use of integrated simulation (Blue et al. 2014). Simulations have been demonstrated effective in improving crew resource management, leadership, team integration, communication, mission-specific training, and critical performance metrics (Davidson et al. 2012; Blue et al. 2014). Medical simulation in particular has been demonstrated to be more effective than lectures or similarly formatted discussions when training for skill performance (Cook et al. 2011, 2012). It has been further demonstrated to improve skill retention and provide effective re-training in previously learned techniques (Gaba 2004; Ander et al. 2009; Didwania et al. 2011). Currently, ISS astronauts utilize simulation to practice cardiopulmonary resuscitation and similar basic life support skills needed for medical emergency (Barshi and Dempsey 2016). Incorporation of further simulation-based training may be an effective means of maintaining clinical skills in longer-duration missions.

Just-in-time training is used aboard the ISS for other skills, including acquisition or refreshment of skills related to onboard experiments and planned procedures for extravehicular activities (EVAs) (Barshi and Dempsey 2016). Such training programs have been received with varying degrees of success, and astronauts have commented on inconsistency in implementation or varying efficacy of available

training resources (Barshi and Dempsey 2016). In general, the more interactive and high-fidelity the training modality, the higher the likelihood that it will be found useful by crewmembers. Even so, current just-in-time training modalities generally work from the assumption that training crews have the support of ground-based assets, including trainers, experimental leads, and other support staff to ensure adequate understanding of the onboard materials. Transition to a fully autonomous training system for exploration missions will be a challenge in future mission development.

In addition to identifying successful training techniques, there is a need for effective tools to identify competency in medical skills during flight. Such evaluations could provide evidence of both pre-flight mastery of required skills and just-in-time demonstration of retention of needed critical capabilities in the case of medical emergency (Blue et al. 2014). There are numerous studies demonstrating various options for validation of effective training, including written examinations, mini-clinical evaluations, direct observation by subject matter experts, case-based discussion or simulation, and objective-structured clinical examinations (OSCEs) (Blue et al. 2014). For use in an in-flight environment, OSCE and simulation-based examinations are most likely to be useful (Blue et al. 2014). These examinations are based upon simulated clinical scenarios, where trainees are required to meet standardized and pre-established checklist criteria or skills (Sloan et al. 1995; Durning et al. 2002; Kreiter and Bergus 2009). Failure to meet objectives, or other evidence of waning performance, could prompt increased training through onboard simulation or resource utilization to ensure maintenance of skills throughout the duration of the mission (Blue et al. 2014). However, such simulations must work within the constraint that they cannot impact consumables that are needed for operational capabilities or future medical response. Therefore, alternative technologies that utilize virtual reality or simulated procedures without requiring consumable equipment may prove to be better alternatives for onboard training (McWilliams and Malecha 2017).

### *2. Identified Threats and Focused Mitigation*

NASA's Human Systems Risk Board has identified specific medical conditions that are deemed high risk to exploration-class missions; subsequently, the dedicated effort to mitigate such risk has been made a priority for exploration science (NASA Human Research Program 2009). The mitigation of these risks requires a fundamental understanding of these problems within the spaceflight environment, challenges in the development of preventive countermeasures, incorporation of such modalities into an exploration medical system, and the need for development of capability in relevant components of medical care that will aid in diagnosis and treatment options for these conditions. A number of these risks require medical awareness and response capability. The specific medical risks considered here include bone fracture, planetary dust exposure, and renal stone formation. Given the specificity of these risks and the evidence presented here, we will provide case-by-case evidence categorization for clarity of strength of evidence; evidence presented in this section is Category III except where otherwise indicated.

- *Bone Fracture*

Bone mineral loss occurs in microgravity due to unloading of the skeletal system, with average loss rates of approximately 1% per month (LeBlanc et al. 2000). It is unclear whether bone mineral density will stabilize at a lower level or continue to diminish with longer microgravity exposure. It is also unknown if fractional gravity, present on the moon and Mars, would mitigate some or all of the loss. This level of bone loss does not create an unacceptable risk of fractures for ISS missions, but could pose a greater risk during future longer or more distant missions.

The definitive index for a fracture risk due to spaceflight is an increased incidence of fractures in long-duration crewmembers relative to a comparable, non-flying population. The astronaut cohort, however, is statistically underpowered to substantiate an increased fracture risk by epidemiology in a reasonable time period. Specifically, there are data regarding only around 70 crewmembers to date with long-duration spaceflights; the average age of long-duration crewmembers is 47 years (range 36-58 years), and there are only around ten long-duration astronauts currently in this database between the ages of 60-75. Currently, NASA uses measured areal bone mineral density (aBMD), by dual-energy x-ray absorptiometry (DXA), as a surrogate for fracture risk, but the clinical assessment to date suggests that long-duration astronauts do not have an increased relative risk for fragility fractures (i.e. fractures due to age-related osteoporosis) (Sibonga et al. 2015). However, the reliance on this assessment for fracture risk is likely insufficient for understanding the risk in the astronaut cohort with its novel skeletal insult secondary to deconditioning (NIH Consensus Development Panel on Osteoporosis Prevention et al. 2001; Orwoll et al. 2013). Further, population studies have revealed declines in the specificity and sensitivity of aBMD for predicting those persons who fracture in the aging population (Schuit et al. 2004; Wainwright et al. 2005; Sornay-Rendu et al. 2005). In 2010, subject-matter experts in osteoporosis and bone densitometry reviewed the accumulating clinical and research data from long-duration astronauts to assist the NASA Directorate with assessing skeletal health and fracture risk [Category IV evidence] (Orwoll et al. 2013). These experts expressed that clinical testing by DXA technology and biochemical assays was not sufficient to capture and understand the unique effects of spaceflight because many of these changes are unlike skeletal changes observed in comparable terrestrial populations or with clinically-relevant age-related bone loss [Category III and IV evidence] (NASA Conference Proceedings; Orwoll et al. 2013).

One reason why DXA measurement of aBMD would be considered insufficient as a test for astronauts is that it averages total bone mineral content in a two dimensional areal projection of bone; subsequently, DXA fails to capture changes due to spaceflight or countermeasures in bone size, geometry, or in the three dimensional distribution of mass between cortical and trabecular bone sub-regions. In contrast, research data acquired by quantitative computed tomography (QCT) have characterized three-dimensional changes in trabecular and cortical hip bone sub-regions during spaceflight and recovery (Lang et al. 2004, 2006; Dana Carpenter et al. 2010). These conventional QCT hip indices, including trabecular volumetric

BMD, minimum cross-sectional diameter of femoral neck, and percent cortical bone volume, do not out-perform DXA aBMD as a predictor of age-related fragility fractures, but do provide additional measurements to understand how spaceflight might influence hip fracture probability or to understand the etiology of hip fractures (Black et al. 2008; Bousson et al. 2011). This expanded evaluation is necessary because spaceflight changes are unlike clinically-assessed terrestrial changes to bone (NASA Conference Proceedings; Orwoll et al. 2013). Moreover, finite element models were generated from those QCT data and, upon analysis, indicated a significant reduction in hip bone strength during spaceflight [Category II evidence] (Keyak et al. 2009). Consequently, clinical experts asserted that the systematic use of QCT imaging could enhance the overall management of skeletal health in astronauts, but would be necessary to detect an appropriate clinical trigger for possible intervention (Orwoll et al. 2013). In a pilot study to monitor for the clinical trigger, such as a lack of recovery in a reasonable post-flight time frame to baseline BMD, the addition of QCT to DXA in ten astronauts revealed that QCT, but not DXA, could detect space-induced deficits in hip trabecular volumetric BMD (vBMD) after spaceflight and a lack of recovery at two years after return (Sibonga 2017). In addition, biochemical assays of bone turnover from in-flight specimens consistently characterized significant bone resorption during spaceflight, even in the context of stimulated bone formation in response to high-fidelity resistive exercise (Smith et al. 2012, 2015). Based upon three separate reviews of biomedical data of long-duration astronauts accumulated since 2010, the clinical panel of experts recommended that bisphosphonate treatment be considered for all astronauts serving on spaceflights greater than 6 months. Research in this domain continues.

QCT data for analysis of finite element model carries some additional radiation burden for a crew (Griffith and Genant 2008). The ExMC Element has an interest in exploring alternative methodologies for trabecular structure interrogation that do not rely on the increased radiation load and may provide an alternative or even point-of-care means of assessing the likelihood of fracture in exploration crews that will already be exposed to a high radiation environment. The National Space Biomedical Research Institute (NSBRI) has previously supported Dr. Yi-Xian Qin from the State University of New York at Sunnybrook in the development of ultrasound capability to characterize bone trabecular structure as well as methods for using ultrasound to accelerate bone healing in the case of fracture [Category II evidence] (Lam and Qin 2008; Qin and Lam 2009; Qin et al. 2010; Lam et al. 2011). One advantage of these approaches is that quantitative diagnosis and therapeutic ultrasound techniques are being designed to integrate with flexible ultrasound capabilities intended for implementation aboard the ISS and future vehicles, potentially allowing such techniques to be available for point-of-care use in future flight. In addition, research efforts in collaboration with the IMM predictive capability have developed the Bone Fracture Risk Model, described above (see section VI.A) (Nelson et al. 2009). Advances in these areas of prognostic risk and mitigation techniques are important for future exploration medical capabilities addressing the specific risk of bone fracture during long-duration spaceflight.

- *Dust Exposure*

Dust exposure from non-terrestrial sources will pose several challenges to crew health on future exploration missions to the moon and Mars. Planetary surfaces are largely covered by a hard, abrasive dust and loose rock known as regolith, the composition of which has been studied extensively (Colwell et al. 2007; Park et al. 2008; Cooper et al. 2010; Taylor et al. 2010; Liu and Taylor 2011; McKay et al. 2015). Both the diagnostic and therapeutic approach to the management of pulmonary or systemic conditions resulting from exposure to non-terrestrial dust will be challenging during a space mission due to limited onboard resources.

Apollo missions to the lunar surface provided significant experience with dust exposure and related concerns. After crewmembers perform EVAs on a planetary surface, they may introduce dust into the habitat from deposits that have collected on their spacesuits. Cleaning of the suits between EVAs and changing of the Environmental Control Life Support System filters could similarly result in direct exposure to celestial dusts. In addition, if the spacesuits used in exploration missions abrade the skin, as current EVA suits have, contact with these wounds would provide a source of transdermal exposure. Further, if celestial dusts gain access to a suit's interior, as was the case during the Apollo missions, the dust could serve as an additional source of abrasions or enhance suit induced injuries [Category III and IV evidence] (Armstrong et al. 1969; Conrad et al. 1969; Center 1971; Shepard et al. 1971; Young et al. 1972; Cernan et al. 1973). When a crew leaves the surface of a celestial body and returns to microgravity, the dust that is introduced into the return vehicle will "float," thus increasing the opportunity for ocular and respiratory exposure and subsequent injury [Category II-IV evidence] (Wagner 2006; Scheuring et al. 2008; Meyers et al. 2012; Theriot et al. 2014).

NASA has conducted several studies utilizing lunar dust simulants and authentic lunar dust to determine the unique properties of lunar dust that affect physiology, assess the dermal and ocular irritancy of the dust, and establish a permissible exposure limit (PEL) for episodic exposure to airborne lunar dust during missions that would involve no more than 6 months stay on the lunar surface (Jones et al. 2009b). Studies with authentic lunar soils from both highland (Apollo 16) and mare (Apollo 17) regions demonstrated that the lunar soil is highly abrasive to a high-fidelity model of human skin (Jones et al. 2009b); anecdotally, this supports reports made by Apollo astronauts after their own missions (Armstrong et al. 1969; Conrad et al. 1969; Center 1971; Shepard et al. 1971; Young et al. 1972; Cernan et al. 1973). Studies of lunar dust returned during the Apollo 14 mission from an area of the moon in which the soils were comprised of mineral constituents from both highlands and mares demonstrated only minimal ocular irritancy and pulmonary toxicity that was less than the highly toxic terrestrial crystalline silica (PEL 0.05 $mg/m^3$), though more toxic than the nuisance dust titanium dioxide [Category II and III evidence] (TiO2, PEL 5.0 $mg/m^3$) (Meyers et al. 2012; James et al. 2013; Lam et al. 2013). A PEL for episodic exposure to airborne lunar dust during a six month stay on the lunar surface was established at 0.3 $mg/m^3$ in consultation with an

independent, extramural panel of expert pulmonary toxicologists (James et al. 2014).

The PEL provided for lunar dust is limited to the conditions and exposure specified; additional research is needed to further address other factors of dust exposure, the effects of more unique lunar or Martian geology (Glotch et al. 2010; Greenhagen et al. 2010), the potential toxicological effects of inhaled or ingested dust upon non-pulmonary organ systems including cardiovascular (Brook et al. 2010; Rich et al. 2010) and nervous systems (Nakane 2012), the effects of acute exposure to massive doses of dust such as may occur during off-nominal situations, and the risks associated with the prolonged exposures that could occur during exploration missions. Work to support the establishment of PELs for Martian dust and dusts of asteroids has yet to be accomplished.

As part of exploration mission planning for a Mars transit mission, there has been some level of discussion about unique health challenges associated with asteroids or Martian dust exposures including the effects of environmental factors, such as windstorms or other sources of increased exposure, and unique chemical components of Mars-specific exposures (Schuerger et al. 2012; Davila et al. 2013). As specific mission destinations and timelines are not yet established, NASA has sought a pragmatic research strategy to continue to prepare for future missions in a flexible manner while not embarking on large-scale investigations which may not be appropriate at this time. This strategy has several dimensions and is risk-driven and collaborative. Much of the strategy is centered on an attempt to appropriately relate the body of scientific evidence generated for lunar dust to other celestial locations. The lunar dust standard states that the existing PEL is specifically relevant to a lunar mission, and that its direct applicability to other mission destinations should not be presumed (James et al. 2014). However, if Mars or other celestial destinations can be related to lunar dust through geological or chemical similarities, it is likely that lunar dust findings can be at least partially leveraged to the assessment of risk for future missions. Recent research efforts have been dedicated to these efforts. In 2015, Dr. Chiu Wing Lam produced a white paper on Martian Dust Chemical Risk Assessment. In this paper, Dr. Lam addressed the chemical components of Martian dust to help identify risk contributors and to help identify their potential impact to crew health (Chiu Wing Lam 2015). In 2016, the NASA HRP helped to design a call for collaborative research in regard to celestial dust and risk assessment techniques, issued in the Celestial Dust Data Mining Solar System Exploration Research Virtual Institute Cooperative Agreement Notice (NASA 2016). That same year, a Mars Dust Technical Information Exchange meeting was held to coordinate knowledge sharing between health scientists, Environment Control and Life Support Systems experts, and operational planners, focusing on the challenges of Martian dust exposure (McCoy 2016). Research in all of these important areas is ongoing.

- *Renal Stone Formation*

Renal stone formation in the unique spaceflight environment has been identified by NASA as a specific condition risk requiring mitigation. The formation of renal stones

poses an in-flight health risk of high severity, not only because of the impact of renal colic on human performance, but because of complications that could possibly require crew evacuation such as hematuria, infection, or hydronephrosis (Jones et al. 2008). An untreated kidney stone on a long-duration, exploration-class mission can result in severe pain, dysuria, hematuria, nausea, and vomiting (Jones et al. 2008). Generally, stones greater than 5mm in diameter are less likely to be passed spontaneously (Jones et al. 2008). When treatment or definitive medical management is unavailable, and particularly when stone progression occurs with growth to greater than 5mm, nephrolith impaction may lead to ureteral obstruction causing hydronephrosis, acute renal failure, infection, or sepsis (Jones et al. 2008). Consequently, kidney stone formation and passage has the potential to greatly impact crewmember health for long-duration missions and, subsequently, threaten mission success. Given the higher probability of kidney stone formation in crewmembers during long-duration missions (Gilkey et al. 2012; Myers 2015), capabilities for in-flight screening, prevention, diagnosis, and treatment are highly desirable.

Evidence for risk factors comes from urine analyses of crewmembers documenting changes to the urinary environment that are conducive to increased saturation of stone-forming salts, which are the driving force for nucleation and growth of a stone nidus (Whitson et al. 1993, 1999; Pietrzyk et al. 2007). Given the severity of the risk for renal stone formation, it is important to characterize the spaceflight conditions that promote nephrolithiasis in order to take appropriate steps to mitigate the risk. One of the primary risk factors for renal stone formation in space is the increased excretion of calcium due to the resorption of bone (Jones et al. 2008). Other contributing risk factors include dehydration, diet (high sodium, high animal proteins), low urinary citrate, pathological (Randall's plaques), genetics, and environmental derangements such as alteration of ambient temperature. These factors can contribute to urinary supersaturation of salts, high urine acidity, and reduced urine volumes, all of which create favorable conditions for crystallization (Jones et al. 2008).

There has been one reported case of a symptomatic renal stone in spaceflight, wherein a cosmonaut experienced severe lower abdominal pain that spontaneously resolved. However, the cosmonaut's symptoms were severe enough to prompt initial planning for an emergency de-orbit; while resolution of his symptoms prevented mission termination, this case highlighted the potential mission risk of nephrolithiasis (Lebedev 1990). As of July 2015, NASA astronauts have had 37 symptomatic kidney stones in 23 crewmembers (before or after flight), but no reported in-flight events.

The current evidence base of data in low Earth orbit does not allow us to predict what will happen when crewmembers are exposed to the spaceflight environment for longer exploration missions. As a result, development of applicable models provides the best methods for prediction of the likelihood of a renal stone event. A model developed by Kassemi and Thompson uses renal biochemical profiles of a

subject as input and predicts the steady-state distribution of nucleating, growing, and agglomerating calcium oxalate crystals during transit through the kidney (Kassemi and Thompson 2016a). The Kassemi model indicates that the predicted renal calculi size distribution for a microgravity astronaut is closer to that of a recurrent stone former on Earth rather than to a normal subject in normal gravity (Kassemi and Thompson 2016a). The model also indicates that an increase in citrate levels beyond average ground-based urinary values can be beneficial in the prevention of nephrolith formation, but only to a limited extent (Kassemi and Thompson 2016b). However, any decline in the citrate levels during space travel below its normal urinary values on Earth can easily move the astronaut into the stone-forming risk category (Kassemi and Thompson 2016b). Further work on this model will provide a better understanding and risk prediction of renal stone events in microgravity.

Prevention strategies are in place to minimize the risk of stone formation. All astronauts are screened by ultrasound pre-flight for the presence of renal stones, and all receive a urinary biochemical assessment through measurement of stone risk parameters such as urinary pH, volume, and supersaturation of calcium oxalate, calcium phosphate, and uric acid (Reyes 2016). In 2016, post-flight renal ultrasounds were added to assess the potential contribution of microgravity exposure to the development of stone (Reyes 2016). If evidence of increased nephrolith risk is identified, pharmacological treatment is available and may be used to reduce the potential for stone formation. For example, potassium citrate is used clinically to minimize the development of crystals and the growth of renal stones by increasing urinary citrate concentration and urine pH (Whitson et al. 2009). The citrate complexes with calcium, decreasing ion activity, and, subsequently, reducing urinary supersaturation and crystallization of calcium oxalate and brushite. Administration of bisphosphonates in combination with a resistive exercise regimen appears to improve bone health and decrease urinary calcium excretion, and thus may reduce the risk of stone formation during and possibly after long-duration spaceflight (LeBlanc et al. 2013). All astronauts are educated in the in the benefits of increased hydration during flight, as increasing fluid intake (thereby increasing urine volume) can provide favorable changes in the urinary supersaturation of the stone-forming salts (Whitson et al. 2001).

Recently, the research community has provided evidence demonstrating the capability of ultrasound to diagnose and monitor stone formation. Clinical evidence has supported the ability to image renal stones and studies conducted during spaceflight have shown the use of ultrasound can be used to localize and measure ureteral stone size, or detect the presence of obstruction or alternative diagnoses [Category II and III evidence] (Sargsyan et al. 2005; Jones et al. 2009a; Smith-Bindman et al. 2014). A flexible ultrasound capability is currently being developed to target therapeutic sonography, with possible interventions including transcutaneous repositioning of a stone or stimulation of ureteral peristalsis to enhance ureteral stone expulsion (Sorensen et al. 2013; Harper et al. 2016). The addition of this capability to existing imaging technology would provide a treatment

arm to the current capability of monitoring and diagnosing an in-flight renal stone, potentially reducing the need for further intervention. Additionally, research into using the same technology to fragment stones with ultrasound, providing an effective transcutaneous lithotripsy capability, is considered high-value future research (Maxwell et al. 2015).

### *3. Technological Innovation and Design*

- *In-Flight Data Utilization*

Handling of medical information requires a fundamental understanding how medical data are gathered, used, stored, and recalled. Some key capabilities in onboard medical capabilities during a given mission include capture of relevant medical history and exams in an electronic medical record, control of available medical diagnostics and related devices, streaming and processing data in real-time, storage and retrieval of diagnostic imaging and laboratory results, sampling of environmental data from a vehicle, providing a knowledge base of medical reference materials, and the provision of video, audio, and augmented reality assistance and training on demand. To reduce crew time for medical data handing during exploration missions and to ensure data is seamlessly and accurately recorded and transferred to medical support staff and archival databases, it is essential that data transfer becomes much more autonomous.

In the terrestrial setting, electronic medical record (EMR) systems are central to the medical data architecture that performs these functions. Many large EMR systems, such as EpicCare or Centricity, are server-based systems that can span a large medical enterprise, across large distances, serving all specialties and aspects of medical care (Mehta et al. 2016; EpicCare 2017; GE Healthcare 2017). Terrestrial medical systems typically employ large-scale data architecture targeted at the healthcare industry. These systems often control data for hundreds of thousands of patients, and include insurance and other ancillary information in addition to patient care records. The additional complexity of high patient volume, billing and insurance capabilities, and high-level administrative functionality is not required in the spaceflight setting. Although the Centricity EMR from General Electric (GE Healthcare 2017) is used at the NASA Flight Medicine Clinic to track astronaut healthcare records, and occasionally employed to manually record some in-flight medical events relayed to the ground, this system is not currently used in-flight. Further flight and health data are recorded in the LSAH repository or in a Mission Medical Repository database and may not be recorded in the EMR (Johnson-Throop 2016). An onboard EMR system that serves as a hub of medical data collection, record keeping, and training suitable for exploration missions does not currently exist.

The federal government drives the adoption of EMRs through the Health Information Technology for Economic and Clinical Health Act of 2009, which provided incentives for health care providers and organizations to adopt EMRs (National Center for Health Statistics 2016). The Centers for Medicare and Medicaid

Services also drives universal EMR adoption by the development of EMR use and reporting standards (Centers for Medicaid and Medicare Services 2017). The widespread adoption of EMRs in the U.S. is relatively recent, and nearly all EMRs and medical devices use proprietary forms of data exchange. As different EMR platforms are not standardized, interoperability between systems and devices require that unique application interfaces be written for each new device to automate the input of data into any given EMR or for EMRs to transfer data between differing systems and vendors (duPont et al. 2009). Data communication standards for medical devices have been developed and are just now being adopted by industry (IEEE Standards Association 2013). As a result, it is not possible to predict which medical technologies and data protocols will be in use at the time of an exploration vehicle design freeze. Thus, the design of future medical data architecture must focus on the development of a conceptual model that is agnostic to the final technology and data communication standards employed.

Currently, medical data management aboard the ISS is not designed for efficient clinical care, requiring excessive crew time to collect, store, and transmit data regarding any medical event, data collection, or even routine examination. While some health and medical devices on the ISS have the ability to transmit data directly via ISS network resources, others require the manual transfer of data by crewmembers from these devices to other ISS computers for eventual transfer to the ground. Crew-generated data is often manually entered into various data collection applications or transmitted verbally through voice communications to the ground support teams. For example, crew audiology exam data from the ISS have been download as a MatLab file, with subsequent post-processing and manual entry into the EMR for medical cross-referencing (Dicken 2012). Health and medical data thus exist in a variety of formats and in numerous locations within the ISS environment, and current record-keeping options are less than ideal.

Several open source EMR systems exist that may be suitable or modified for deep-space use and improved data management (FreeMed Software Foundation 2016; Open EMR 2016; Open MRS 2016). However, challenges persist in integration and data management secondary to the diversity of these data sources (Mezghani et al. 2015), as there are currently no standard data protocols for medical data system interoperability (Fenton et al. 2013). Additional challenges in the space environment include data rate constraints secondary to telemetry bandwidth limitations that hinder the synchronization of medical information between the vehicle and the ground. Further, the medical system for the space vehicle may need additional functions not typically seen in terrestrial EMRs, such as medical references, medical training programs, and vehicle environmental data integration. Thus, a single commercial solution will not be suitable for space exploration missions, and a more robust solution remains to be found.

In 2015, the Exploration Medical System Demonstration (EMSD) project was undertaken to show that several medical technologies needed for an exploration mission, including medical informatics tools for managing evidence and decision-

making, can be integrated into a single system and used by an exploration crew in an efficient and meaningful manner (Rubin and Watkins 2014). The ESMD system was successfully demonstrated during a Human Exploration Research Analog (HERA) mission at NASA Johnson Space Center and was further discussed with international partners at the Canadian Space Agency to facilitate interagency collaboration for an integrated medical data management and clinical decision support system for future missions (Rubin and Watkins 2014). Similarly, the SpaceMED project under the NSBRI (NSBRI 2016) demonstrated an integrated medical system capability to automatically collect data from a variety of sources. Aims of this project included the development of a prototype platform for future medical capabilities integration and validation for the integration of telemetrically-gathered physiological data from varied devices for point-of-care decision-making assistance. These prototype projects have demonstrated the feasibility of an all-encompassing medical data support system and prompted ExMC to invest in the development of a more robust medical data architecture. An operationally sound system has yet to be completed, and a holistic data architecture approach to manage data source heterogeneity and scalability is still needed.

- *Multipurpose Design and Technology Development and Sourcing*

Medical capabilities that are capable of addressing multiple needs are essential to create an efficient and effective medical system. Ideal medical capabilities cut across multiple applications, meeting diverse operational needs while minimizing mass, volume, and the need for crew training. While current medical technologies attempt to address this issue by expanding traditional use of available modalities to include off-label or non-conventional techniques, there is a need for improved technological applications, or improved technological design, to advance the efficiency and minimize the design impacts of exploration-class medical resources while ensuring robust system capabilities. Three areas identified in which development of multipurpose designs or non-conventional expansion of off-the-shelf technology would be of particular use in exploration missions are imaging modalities, laboratory analyzers, and biomonitoring devices.

*Imaging*

One example of a multipurpose medical technology is seen in the current use of ultrasound imaging in low Earth orbit. Ultrasound imaging has been used to address conditions identified in the EMCL for diagnosis or preventive monitoring, and ultrasound applications have been continuously expanded since the introduction of ultrasound technology aboard the ISS in 2002. Initial ultrasound indications were limited to retroperitoneal and pelvic examination (NASA Mission Pages 2016b); however, an onboard exercise in 2002 demonstrated the utility of ultrasound in microgravity for a Focused Assessment in Sonographic Technique (FAST) exam, a rapid ultrasound examination to rule out internal bleeding in the case of traumatic abdominal injury (Sargsyan et al. 2005). Of note, this exam was performed by minimally trained crewmembers through remote guidance; despite ground-to-ISS communication latency, clinical results and speed of imaging were deemed better than adequate for effective FAST evaluation (Sargsyan et al. 2005). In 2005,

ultrasound imaging was again used in a demonstration of a rapid ocular evaluation for trauma-related injury, with minimally trained crew again successful in obtaining adequate diagnostic imaging through remote guidance (Chiao et al. 2005). Since that time, ultrasound technology has been utilized as an imaging modality for the monitoring and diagnosis of ocular changes related to the spaceflight environment (Martin et al. 2012) as well as many other broad applications of the imaging modality for varied medical conditions and concerns (Fincke et al. 2005; Sargsyan et al. 2006; Kwon et al. 2007; Kirkpatrick et al. 2007; Jones et al. 2009a; Sirek et al. 2014).

While ultrasound imaging is used frequently, often secondary to its availability in lieu of any other imaging technologies in orbit as well as its small physical footprint and power requirements, there are problems with relying on current ultrasound technology for all imaging needs. While many studies in both the space environment (Sargsyan et al. 2005; Fincke et al. 2005; Chiao et al. 2005) and in analog terrestrial environments (Shah et al. 2009, 2016) demonstrate that motivated persons can be readily trained in effective use of ultrasound for medical diagnosis, ultrasound is often critiqued for its non-intuitive images, long learning curve, and dependence on operator skill (Kijowski and De Smet 2006; Lew et al. 2007), and it can be difficult for minimally trained operators to get high diagnostic quality images without some formalized training. Even with appropriate training, some anatomical structures, like the cranium or lungs, are poorly imaged using ultrasound, where an alternative modality such as radiography would greatly complement ultrasound imaging.

Advanced ultrasound is being developed for diagnosing or treating certain conditions; however, integrating new technologies into traditional ultrasound capabilities can be a challenging, though not insurmountable, process. Advanced clinical modalities such as therapeutic ultrasound and three-dimensional ocular scanning often require development of special software or the use of custom hardware. Typical FDA-approved clinical scanners do not readily accommodate these special software and hardware components. As mentioned above (See VI.C.2), a flexible ultrasound capability is currently being developed to target therapeutic sonography, with possible interventions including transcutaneous repositioning of a stone or stimulation of ureteral peristalsis to enhance ureteral stone expulsion (Sorensen et al. 2013; Harper et al. 2016). Additionally, research into using the same technology to fragment stones with ultrasound, providing an effective transcutaneous lithotripsy capability, is considered high-value future research (Maxwell et al. 2015). Other research focuses on the development of ultrasound capability to characterize bone trabecular structure as well as methods for using ultrasound to accelerate bone healing in the case of fracture (Lam and Qin 2008; Qin and Lam 2009; Qin et al. 2010; Lam et al. 2011). The addition of these capabilities to existing imaging technology would provide a treatment arm to monitoring and diagnosing in-flight medical issues. Similarly, technology that can autonomously guide ultrasound scanning by minimally-trained crewmembers is highly desirable. Virtual guidance is an area where a flight precedent has been established (Martin et

al. 2012) and will likely continue to produce beneficial results as these technologies advance.

*Laboratory Analysis*

Similar to imaging challenges, there are limitations to current technologies for laboratory analysis of human biomedical samples during spaceflight. At present, ISS crews freeze urine and blood samples for analysis upon eventual return to Earth. This strategy has proven adequate for research-oriented analysis; however, terrestrial experiments determined that some blood analytes degrade within 24 hours after phlebotomy when placed in controlled storage, rendering samples inadequate for more detailed or sensitive analysis (Zwart et al. 2009). As analysis of blood and other bodily fluids is an essential component of medical diagnosis, long-duration flight and autonomous capabilities call for blood analysis to satisfy timely clinical diagnostic and research needs. Portable point-of-care blood analyzers hold enormous potential for revolutionizing terrestrial medicine by providing real-time diagnostic data in clinics, emergency rooms, surgeries, and austere locations. However, research on such point-of-care biomedical devices has largely focused on development of device components, such as sample pretreatment, reagent mixing, and filtration, rather than the development of a robust general analyzer (Nelson 2011; Chin et al. 2012; Sharma et al. 2015).

NASA has evaluated commercial point-of-care devices for on-orbit blood analysis, such as Abbott Laboratories' i-STAT™ analyzer (Jacobs et al. 1993). However, use of such devices in spaceflight carries potential limitations, including any effects of microgravity on device operation, the need for an extremely long shelf life, minimally-trained personnel requiring automated, easy-to-use protocols, and the lack of refrigerated storage constraints (Nelson 2011). Other aspects of the spacecraft environment, such as the impact of radiation, may play a role in the degradation of reagents and other supplies (Du et al. 2011; Jaworske and Myers 2016), although evidence is lacking in this area. Further, spacecraft are closed environments, and as such extreme caution is necessary in materials selection and device design secondary to concerns of off-gassing and toxicity in a closed environment. Finally, spaceflight-specific laboratory needs may be significantly removed from normal off-the-shelf applications. For example, effective diagnostics for bone loss, muscle atrophy, and other spaceflight-specific medical issues require measurements of analytes that may be outside of the range of normal, terrestrial clinical practice (Smith et al. 2005; Zwart et al. 2009). Finally, resource constraints will require multipurpose devices that can analyze many measurements from a single blood or other bodily fluid sample.

For example, one of the major constraints in space-based blood analysis for long-duration flight is the need for long reagent shelf life, potentially lasting 3 years or more. The i-STAT™ test cartridges for clinical chemistry can maintain stability for up to one year, which is beyond the manufacturer specifications (Smith et al. 2004), but other crucial blood assays degrade faster. In contrast, urinalysis test strips maintain the reagents in a dry condition before use, which is more conducive to long

shelf life. For example, Roche Diagnostics Chemstrips™ have been used successfully on the ISS (Smith et al. 2004) and are rated by the manufacturer up to its labeled expiration data or two years after opening its sealed container (Roche Diagnostics Corporation 2001).

NASA has closely follows the explosion of research and development in point-of-care devices through market surveys and assessment of commercial and nearly commercial platforms in industry and academia (Nelson and Chait 2010; Krihak et al. 2011). One significant challenge for developers is that the market for point-of-care blood analysis has been dominated by large industry providers, leaving small companies with new technologies struggling to find or create a niche for commercial viability (Nelson 2011). In order to promote development of a flightworthy blood analyzer from even a small or unknown developer, NASA has engaged promising platform developers in technology development. Two developers were funded by NASA and the NSBRI to develop platforms for analysis of white blood cells and differentials: Prof. Yu-Chong Tai, California Institute of Technology, Pasadena, CA, and Dr. Eugene Chan, DNA Medicine Institute, Cambridge, MA. Both developers created benchtop flow cytometers, although neither reached the standard of automation that was desired. A later prototype of the DNA Medicine Institute's rHEALTH design functioned appropriately in the reduced gravity of parabolic flight (NASA Small Business Innovation Research 2016). NASA continues to fund and monitor ongoing research and development efforts of portable blood analyzers for exploration medical use.

*Biomonitoring*

Biomonitoring is an area of great interest for future exploration-class missions. The ability to monitor an astronaut's vital signs and response to strenuous activity such as exercise, either intermittently or in real-time, is applicable to both clinical and research needs in spaceflight. The current monitoring system is adequate for basic monitoring on an as-needed basis aboard the ISS. U.S. capabilities include rhythm monitoring via 12-lead wired electrocardiogram (ECG), semi-automated blood pressure assessment, and non-invasive blood oximetry via finger probe that measures oxygen saturation, carbon monoxide, methemoglobin, and perfusion index (Barratt and Pool 2008). Russian capabilities are similar with regards to basic biomedical monitoring capabilities (Barratt and Pool 2008). However, this system is time consuming to use; the ECG requires shaving for application of adhesive electrodes and requires software initiation and signal checks; the blood pressure device is sensitive to operator error and cuff size selection, patient movement, and noise. The oximeter display is not user-friendly even for trained medical professionals. All devices require manual data entry and file transfer to information systems and ground monitors, further consuming crew time. Finally, all devices show significant wear-and-tear after multiple uses and extensive cleaning, especially as devices are often used during exercise. A more efficient system is needed to save crew time and reduce the volume and mass of consumable components, particularly for exploration missions. Some advanced capabilities, such as automated blood pressure devices, have been flown for research intent, but

have yet to be incorporated into the onboard medical system architecture. The integration of small, easy-to-use, preferably wireless biomedical sensors that will have the ability to measure, store, and transmit physiological parameters would provide a wealth of data for the medical and research communities.

Devices that measure physiological parameters in space have slightly different requirements than those used terrestrially. For example, most ECG machines used on Earth are large and bulky with numerous leads and electrodes, and interpretation of ECGs requires training and medical knowledge. In order to ensure an operation that was neither complex nor invasive, there is interest in dry cloth electrodes and patches that could wirelessly transmit ECG data (Chen et al. 2013; Dai et al. 2016). Built-in software that provides real-time analysis of data output has been developed for off-the-shelf products, including fitness monitoring and sleep patterns, and could potentially provide real-time feedback to crewmembers during a mission regarding adherence to a countermeasure and fitness regimen, success of a personalized sleep schedule, and the like (Markwald et al. 2016; Jones et al. 2016; Jee 2017; Grigsby-Toussaint et al. 2017). With regards to blood pressure monitoring, it is preferable to obtain real-time, continuous, and non-invasive measurements for more accurate and useful monitoring; therefore, there is interest in automatic wireless cuffs or methods that do not require a cuff at all (Smulyan and Safar 2011; Gaurav et al. 2016). Even so, use of real-time, wireless, noninvasive biomonitoring raises new challenges related to patient privacy and autonomy when measured in the context of a work environment. Research is ongoing in each of these areas, and as of yet there is no ideal device that provides non-invasive, accurate measurements that meet the needs of the both the medical and scientific interests of exploration missions. However, the rapid pace of market technological development will likely outpace NASA-funded or directed research efforts; as a result, continued effort dedicated to monitoring market and commercial devices that can meet these needs is likely to be more successful than an attempt to develop novel devices that aim to fill this gap.

**VII. Gaps**

At the time of writing, the ExMC Element has identified 13 research knowledge gaps directly related to the risk of adverse health outcomes and decrements in performance due to in-flight medical conditions. These are:

- Med01: We do not have a concept of operations for medical care during exploration missions.
- Med02: We do not have the capability to provide a safe and effective pharmacy for exploration missions.
- Med03: We do not know how to apply personalized medicine effectively to reduce health risk for a selected crew.
- Med04: We do not have a defined rehabilitation capability for injured or deconditioned crewmembers during exploration missions.
- Med05: We do not know how to define medical planning or operational needs for ethical issues that may arise during exploration missions.
- Med07: We do not have the capability to comprehensively process medically relevant information to support medical operations during exploration missions.
- Med08: We do not have quantified knowledge bases and modeling to estimate medical risk incurred on exploration missions.
- Med09: We do not have the capability to predict estimated medical risk posture during exploration missions based on current crew health and resources.
- Med10: We do not have the capability to provide computed medical decision support during exploration missions.
- Med11: We do not have the capability to minimize medical system resource utilization during exploration missions.
- Med12: We do not have the capability to mitigate select medical conditions.
- Med13: We do not have the capability to implement medical resources that enhance operational innovation for medical needs.

## VIII. Conclusions

Evidence gathered from spaceflight, computer simulation, and ground analogs, including long-duration isolation in remote and austere environments, demonstrates that sudden, incapacitating medical events can rapidly compromise the success of a mission. The ability of a robust medical system to address such events, or the limitations of such a system within the mission architecture, will determine the risk of unacceptable health and mission outcomes. Limitations arise from vehicular constraints in mass, power, and volume, as well as gaps in current medical knowledge and technologies available to adequately screen for, diagnose, and treat a range of medical conditions. The ExMC Element has established specific knowledge and system gaps that, if addressed, could significantly improve upon onboard medical capabilities while minimizing the overall footprint and burden, with regards to financial expense and the cost of crew training time, of an exploration medical system.

While specific medical concerns will vary depending on the features of an exploration mission, efforts that strive towards creation of a robust and comprehensive medical capability will enhance the potential for mission success, no matter the destination. This review of evidence reveals that much work has been done in an effort to achieve these goals; however, as manned spaceflight continues to venture ever further towards more distant and challenging destinations, there will continue to be a need for dedicated efforts in providing the most capable medical support system to protect and provide for our crews. The ExMC Element will continue to work towards achieving this mission, addressing the gaps defined above, to provide effective countermeasures, capable resources for medical response, and ever-improving technologies to enable mankind to leave low Earth orbit and continue its exploration of space.

## IX. References


ACGME (2016) Clinical Learning Environment Review: Patient Safety. http://www.acgme.org/Portals/0/PDFs/CLER/ACGME_CLER_Patient-Safety_Digital.pdf. Accreditation Council for Graduate Medical Education

Ackerman MJ, Filart R, Burgess LP, et al (2010) Developing next-generation telehealth tools and technologies: patients, systems, and data perspectives. Telemed J E-Health Off J Am Telemed Assoc 16:93–95. doi: 10.1089/tmj.2009.0153

Ander DS, Heilpern K, Goertz F, et al (2009) Effectiveness of a simulation-based medical student course on managing life-threatening medical conditions. Simul Healthc J Soc Simul Healthc 4:207–211. doi: 10.1097/SIH.0b013e3181a9dd84

Antonsen E, Hanson A, Shah R, et al (2016) Conceptual Drivers for an Exploration Medical System. 67th International Astronautical Congress, Guadalajara, Mexico

Armstrong N, Collins M, Aldrin E (1969) Apollo 11 Technical Crew Debriefing. NASA Johns Space Cent Houst TX 9–24.

Baisden DL, Beven GE, Campbell MR, et al (2008) Human health and performance for long-duration spaceflight. Aviat Space Environ Med 79:629–635.

Ball J, Evans C (2001) Safe Passage: Astronaut Care for Exploration Missions. National Academies Press, Washington, D.C.

Barger LK, Flynn-Evans EE, Kubey A, et al (2014) Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. Lancet Neurol 13:904–912. doi: 10.1016/S1474-4422(14)70122-X

Barratt MR, Pool SL (eds) (2008) Principles of clinical medicine for space flight. Springer, New York

Barshi I, Dempsey D (2016) Risk of Performance Errors Due to Training Deficiencies. National Aeronautics and Space Administration

Barsten K, Baumann D, Byrne V, et al (2014) Telemedicine Operational Concepts for Human Exploration Missions to Near Earth Asteroids. National Aeronautics and Space Administration, NASA Johnson Space Center

Basner M, Dinges DF (2014) Lost in space: sleep. Lancet Neurol 13:860–862. doi: 10.1016/S1474-4422(14)70176-0

Basner M, Dinges DF, Mollicone DJ, et al (2014) Psychological and behavioral changes during confinement in a 520-day simulated interplanetary mission to mars. PloS One 9:e93298. doi: 10.1371/journal.pone.0093298

Bayuse T (2016) Personal Communication, NASA Pharmacology.

Berry CA (1974) Medical legacy of Apollo. Aerosp Med 45:1046–1057.

Billica RD, Simmons SC, Mathes KL, et al (1996) Perception of the medical risk of spaceflight. Aviat Space Environ Med 67:467–473.

Black DM, Bouxsein ML, Marshall LM, et al (2008) Proximal Femoral Structure and the Prediction of Hip Fracture in Men: A Large Prospective Study Using QCT. J Bone Miner Res 23:1326–1333. doi: 10.1359/jbmr.080316

Blue R, Bridge L, Chough N, et al (2014) Identification of Medical Training Methods for Exploration missions. National Aeronautics and Space Administration

Bonicke R, Reif W (1953) [Enzymatic inactivation of isonicotinic acid hydrizide in human and animal organism]. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol 220:321–323.

Bonis PA, Pickens GT, Rind DM, Foster DA (2008) Association of a clinical knowledge support system with improved patient safety, reduced complications and shorter length of stay among Medicare beneficiaries in acute care hospitals in the United States. Int J Med Inf 77:745–753. doi: 10.1016/j.ijmedinf.2008.04.002

Bourcier E, Madelaine S, Archer V, et al (2016) Implementation of automated dispensing cabinets for management of medical devices in an intensive care unit: organisational and financial impact. Eur J Hosp Pharm 23:86–90. doi: 10.1136/ejhpharm-2014-000604

Bousson VD, Adams J, Engelke K, et al (2011) In vivo discrimination of hip fracture with quantitative computed tomography: Results from the prospective European Femur Fracture Study (EFFECT). J Bone Miner Res 26:881–893. doi: 10.1002/jbmr.270

Brainard GC, Coyle W, Ayers M, et al (2013) Solid-state lighting for the International Space Station: Tests of visual performance and melatonin regulation. Acta Astronaut 92:21–28. doi: 10.1016/j.actaastro.2012.04.019

Bridge L, Watkins S (2011) Impact of Medical Training Level on Medical Autonomy for Long-Duration Space Flight. National Aeronautics and Space Administration

Briggs A, Sculpher M, Dawson J, et al (2004) The use of probabilistic decision models in technology assessment : the case of total hip replacement. Appl Health Econ Health Policy 3:79–89.

Brook RD, Rajagopalan S, Pope CA, et al (2010) Particulate Matter Air Pollution and Cardiovascular Disease. Circulation 121:2331–2378. doi: 10.1161/CIR.0b013e3181dbece1

Canadian Agency for Drugs and Technologies in Health (CADTH) (2010) Technologies to reduce errors in dispensing and administration of medication in hospitals: clinical and economic analyses. CADTH Technol Overv 1:e0116.

Canga M, Shah R, Mindock J, Antonsen E (2016) A Strategic Approach to Medical Care for Exploration Missions. 67th International Astronautical Congress, Guadalajara, Mexico

Cantrell L, Suchard JR, Wu A, Gerona RR (2012) Stability of active ingredients in long-expired prescription medications. Arch Intern Med 172:1685–1687. doi: 10.1001/archinternmed.2012.4501

Center MS (1971) Apollo 15 Technical Debrief.

Centers for Medicaid and Medicare Services (2017) Electronic Health Records (EHR) Incentive Programs.

Cernan E, Evans R, Schmitt H (1973) Apollo 17 Technical Debrief, MSC-07631.

Chen C-Y, Chang C-L, Chang C-W, et al (2013) A low-power bio-potential acquisition system with flexible PDMS dry electrodes for portable ubiquitous healthcare applications. Sensors 13:3077–3091. doi: 10.3390/s130303077

Chiao L, Sharipov S, Sargsyan AE, et al (2005) Ocular examination for trauma; clinical ultrasound aboard the International Space Station. J Trauma 58:885–889.

Chin CD, Linder V, Sia SK (2012) Commercialization of microfluidic point-of-care diagnostic devices. Lab Chip 12:2118–2134. doi: 10.1039/c2lc21204h

Chiu Wing Lam (2015) Assessment of Health Risks from Exposures to Martian Dust Containing Perchlorate and Other Chemicals of Toxicological Concern. Toxicology & Environmental Chemistry Group/NASA JSC

Cleary K, Melzer A, Watson V, et al (2006) Interventional robotic systems: applications and technology state-of-the-art. Minim Invasive Ther Allied Technol MITAT Off J Soc Minim Invasive Ther 15:101–113. doi: 10.1080/13645700600674179

Cockett AT (1964) The Urological Problems in Space Medicine. J Urol 92:564–567.

Colwell JE, Batiste S, Horányi M, et al (2007) Lunar surface: Dust dynamics and regolith mechanics. Rev Geophys 45:RG2006. doi: 10.1029/2005RG000184

Comden SC, Marx D, Murphy-Carley M, Hale M (2005) Using Probabilistic Risk Assessment to Model Medication System Failures in Long-term Care Facilities.

Conkin J, Kumar K V, Powell MR, et al (1996) A probabilistic model of hypobaric decompression sickness based on 66 chamber tests. Aviat Space Environ Med 67:176–83.

Conrad C, Gordon Jr R, Bean A (1969) Apollo 12 Technical Crew Debriefing. NASA Johns Space Cent Houst TX 1:9–11.

Cook DA, Brydges R, Hamstra SJ, et al (2012) Comparative effectiveness of technology-enhanced simulation versus other instructional methods: a systematic review and meta-analysis. Simul Healthc J Soc Simul Healthc 7:308–320. doi: 10.1097/SIH.0b013e3182614f95

Cook DA, Hatala R, Brydges R, et al (2011) Technology-enhanced simulation for health professions education: a systematic review and meta-analysis. JAMA 306:978–988. doi: 10.1001/jama.2011.1234

Cooper BL, McKay D, Riofrio L, et al (2010) Sub-10-micron and respirable particles in lunar soils. In: Lunar and Planetary Science Conference. p 2279

Cucinotta FA (2015) Review of NASA approach to space radiation risk assessments for Mars exploration. Health Phys 108:131–142. doi: 10.1097/HP.0000000000000255

Cucinotta FA, Kim M-HY, Chappell LJ, Huff JL (2013) How safe is safe enough? Radiation risk for a human mission to Mars. PloS One 8:e74988. doi: 10.1371/journal.pone.0074988

Dai M, Xiao X, Chen X, et al (2016) A low-power and miniaturized electrocardiograph data collection system with smart textile electrodes for monitoring of cardiac function. Australas Phys Eng Sci Med 39:1029–1040. doi: 10.1007/s13246-016-0483-5

Dana Carpenter R, LeBlanc AD, Evans H, et al (2010) Long-term changes in the density and structure of the human hip and spine after long-duration spaceflight. Acta Astronaut 67:71–81. doi: 10.1016/j.actaastro.2010.01.022

Davidson IJA, Lok C, Dolmatch B, et al (2012) Virtual reality: emerging role of simulation training in vascular access. Semin Nephrol 32:572–581. doi: 10.1016/j.semnephrol.2012.10.009

Davila AF, Willson D, Coates JD, McKay CP (2013) Perchlorate on Mars: a chemical hazard and a resource for humans. Int J Astrobiol 12:321–325. doi: 10.1017/S1473550413000189

Davis JR (1999) Medical issues for a mission to Mars. Aviat Space Environ Med 70:162–168.

de Bruijne M (2016) Machine learning approaches in medical image analysis: From detection to diagnosis. Med Image Anal 33:94–97. doi: 10.1016/j.media.2016.06.032

Department of Defense (2011) Deputy Assistant Secretary of Defense for Systems Engineering Instruction.

Dicken T (2012) Data Acquisition, Management, and Analysis in Support of the Audiology & Hearing Conservation and the Orbital Debris Program Office.

Didwania A, McGaghie WC, Cohen ER, et al (2011) Progress toward improving the quality of cardiac arrest medical team responses at an academic teaching hospital. J Grad Med Educ 3:211–216. doi: 10.4300/JGME-D-10-00144.1

Du B, Daniels VR, Vaksman Z, et al (2011) Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. AAPS J 13:299–308. doi: 10.1208/s12248-011-9270-0

duPont NC, Koeninger D, Guyer JD, Travers D (2009) Selecting an electronic medical record system for small physician practices. N C Med J 70:399–403.

Durning SJ, Cation LJ, Markert RJ, Pangaro LN (2002) Assessing the reliability and validity of the mini-clinical evaluation exercise for internal medicine residency training. Acad Med J Assoc Am Med Coll 77:900–904.

Ebert D (2017) Clinical Outcome Metrics for Optimization of Robust Training. http://nsbri.org/researches/clinical-outcome-metrics-for-optimization-of-robust-training/.

eMC (2017) Electronic Medicines Compendium. https://www.medicines.org.uk/emc/.

EpicCare (2017) EpicCare. http://www.epic.com/software.

Exploration Medical Capability Element (2013) Exploration Medical Capability Concept of Operations.

Fenton S, Giannangelo K, Kallem C, Scichilone R (2013) Data standards, data quality, and interoperability (updated). J AHIMA 84:64–69.

Fincke EM, Padalka G, Lee D, et al (2005) Evaluation of shoulder integrity in space: first report of musculoskeletal US on the International Space Station. Radiology 234:319–322. doi: 10.1148/radiol.2342041680

Fitzpatrick DR, Wilson CB (2003) Methylation and demethylation in the regulation of genes, cells, and responses in the immune system. Clin Immunol Orlando Fla 109:37–45.

Flynn-Evans EE, Gregory K, Arsintescu L, Whitmire A (2016) Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload. National Aeronautics and Space Administration

Foale CM, Kaleri AY, Sargsyan AE, et al (2005) Diagnostic instrumentation aboard ISS: just-in-time training for non-physician crewmembers. Aviat Space Environ Med 76:594–598.

FreeMed Software Foundation (2016) FreeMed Software Foundation: Opensource Electronic Medical Software. http://freemedsoftware.org/.

Fritsch-Yelle JM, Leuenberger UA, D'Aunno DS, et al (1998) An episode of ventricular tachycardia during long-duration spaceflight. Am J Cardiol 81:1391–1392.

Frontera W (ed) (2013) DeLisa's Physical Medicine and Rehabilitation: Principles and Practice. Lippencott Williams & Wilkins, Philadelphia, PA

Gaba DM (2004) The future vision of simulation in health care. Qual Saf Health Care 13 Suppl 1:i2-10. doi: 10.1136/qhc.13.suppl_1.i2

Gandjour A, Weyler E-J (2006) Cost-effectiveness of referrals to high-volume hospitals: an analysis based on a probabilistic Markov model for hip fracture surgeries. Health Care Manag Sci 9:359–69.

Garcia M (2016) ROCKY Exercise Device is a Real Knockout. https://www.nasa.gov/feature/exercise-device-for-orion-to-pack-powerful-punch.

Garcia R, Howard B, LaRue R, et al (2004) Strategies for Gamma Sterilization of Pharmaceuticals. Pharm. Med. Packag. News

Garside R, Pitt M, Anderson R, et al (2007) The cost-utility of cinacalcet in addition to standard care compared to standard care alone for secondary hyperparathyroidism in end-stage renal disease: a UK perspective. Nephrol

Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc 22:1428–36. doi: 10.1093/ndt/gfl774

Gaurav A, Maheedhar M, Tiwari VN, Narayanan R (2016) Cuff-less PPG based continuous blood pressure monitoring: a smartphone based approach. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf 2016:607–610. doi: 10.1109/EMBC.2016.7590775

GE Healthcare (2017) Centricity EMR. http://www3.gehealthcare.com/en/products/categories/healthcare_it/electronic_medical_records/centricity_emr.

Gilkey KM, Myers JG, McRae MP, et al (2012) Bayesian Analysis for Risk Assessment of Selected Medical Events in Support of the Integrated Medical Model Effort.

Glotch TD, Lucey PG, Bandfield JL, et al (2010) Highly Silicic Compositions on the Moon. Science 329:1510–1513. doi: 10.1126/science.1192148

Goel N, Dinges DF (2012) Predicting Risk in Space: Genetic Markers for Differential Vulnerability to Sleep Restriction. Acta Astronaut 77:207–213. doi: 10.1016/j.actaastro.2012.04.002

Greenhagen BT, Lucey PG, Wyatt MB, et al (2010) Global Silicate Mineralogy of the Moon from the Diviner Lunar Radiometer. Science 329:1507–1509. doi: 10.1126/science.1192196

Griffith JF, Genant HK (2008) Bone mass and architecture determination: state of the art. Best Pract Res Clin Endocrinol Metab 22:737–764. doi: 10.1016/j.beem.2008.07.003

Grigoriev AI, Kozlovskaya IB, Potapov AN (2002) Goals of biomedical support of a mission to Mars and possible approaches to achieving them. Aviat Space Environ Med 73:379–384.

Grigsby-Toussaint DS, Shin JC, Reeves DM, et al (2017) Sleep apps and behavioral constructs: A content analysis. Prev Med Rep 6:126–129. doi: 10.1016/j.pmedr.2017.02.018

Hamburg M, Collins F (2010) The Path to Personalized Medicine. N Engl J Med 363:301–4.

Hamilton D, Smart K, Melton S, et al (2008) Autonomous medical care for exploration class space missions. J Trauma 64:S354-363. doi: 10.1097/TA.0b013e31816c005d

Hamilton DR, Sargsyan AE, Martin DS, et al (2011) On-orbit prospective echocardiography on International Space Station crew. Echocardiogr Mt Kisco N 28:491–501. doi: 10.1111/j.1540-8175.2011.01385.x

Harper JD, Cunitz BW, Dunmire B, et al (2016) First in Human Clinical Trial of Ultrasonic Propulsion of Kidney Stones. J Urol 195:956–964. doi: 10.1016/j.juro.2015.10.131

Hasanain F, Guenther K, Mullett WM, Craven E (2014) Gamma sterilization of pharmaceuticals--a review of the irradiation of excipients, active pharmaceutical ingredients, and final drug product formulations. PDA J Pharm Sci Technol 68:113–137. doi: 10.5731/pdajpst.2014.00955

Hawkey A (2003) The importance of exercising in space. Interdiscip Sci Rev ISR 28:130–138.

Henson DB, Spenceley SE, Bull DR (1997) Artificial neural network analysis of noisy visual field data in glaucoma. Artif Intell Med 10:99–113.

Herman D, Locatelli I, Grabnar I, et al (2005) Influence of CYP2C9 polymorphisms, demographic factors and concomitant drug therapy on warfarin metabolism and maintenance dose. Pharmacogenomics J 5:193–202. doi: 10.1038/sj.tpj.6500308

Hippisley-Cox J, Coupland C (2013) Predicting risk of emergency admission to hospital using primary care data: derivation and validation of QAdmissions score. BMJ Open 3:e003482. doi: 10.1136/bmjopen-2013-003482

IEEE Standards Association (2013) U.S. Federal Government Recognizes IEEE 11073™ Standards for Medical-Device Communication.

Iezzoni LI, Shwartz M, Ash AS, Mackiernan YD Predicting in-hospital mortality for stroke patients: results differ across severity-measurement methods. Med Decis Mak Int J Soc Med Decis Mak 16:348–56.

INCOSE (2016) The International Council on Systems Engineering: Strategic Objectives.

Institute of Medicine (2014a) Pathways to Exploration: Rationales and Approaches for a U.S. Program of Human Space Exploration. National Academies Press, Washington, D.C.

Institute of Medicine (2014b) Health Standards for Long Duration and Exploration Spaceflight: Ethics Principles, Responsibilities, and Decision Framework. National Academies Press (US), Washington (DC)

Isaac T, Zheng J, Jha A (2012) Use of UpToDate and outcomes in US hospitals. J Hosp Med 7:85–90. doi: 10.1002/jhm.944

Jacobs E, Vadasdi E, Sarkozi L, Colman N (1993) Analytical evaluation of i-STAT Portable Clinical Analyzer and use by nonlaboratory health-care professionals. Clin Chem 39:1069–1074.

James J, Lam C, Scully R, et al (2014) Lunar Dust Toxicity Final Report.

James JT, Lam C-W, Santana PA, Scully RR (2013) Estimate of safe human exposure levels for lunar dust based on comparative benchmark dose modeling. Inhal Toxicol 25:243–256. doi: 10.3109/08958378.2013.777821

Jaworske D, Myers J (2016) Pharmaceuticals Exposed to the Space Environment: Problems and Prospects. National Aeronautics and Space Administration

Jee H (2017) Review of researches on smartphone applications for physical activity promotion in healthy adults. J Exerc Rehabil 13:3–11. doi: 10.12965/jer.1732928.464

Jochmann N, Stangl K, Garbe E, et al (2005) Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. Eur Heart J 26:1585–1595. doi: 10.1093/eurheartj/ehi397

Johnson TL, Brewer D, Estacio R, et al (2015) Augmenting Predictive Modeling Tools with Clinical Insights for Care Coordination Program Design and Implementation. EGEMS Wash DC 3:1181. doi: 10.13063/2327-9214.1181

Johnson-Throop K (2016) 50+ Years of NASA Astronaut Data - Architecting the Data and Analytics System. National Aeronautics and Space Administration

Johnston SL, Dinges DF, Basner M (2015) Operational Ground Testing Protocol to Optimize Astronaut Sleep Medication Efficacy and Individual Effects II. National Aeronautics and Space Administration, NASA Johnson Space Center

Jones D, Skrepnik N, Toselli RM, Leroy B (2016) Incorporating Novel Mobile Health Technologies Into Management of Knee Osteoarthritis in Patients Treated With Intra-Articular Hyaluronic Acid: Rationale and Protocol of a Randomized Controlled Trial. JMIR Res Protoc 5:e164. doi: 10.2196/resprot.5940

Jones JA, Pietrzyk RA, Whitson PA (2008) Chapter 13: Renal and Genitourinary Concerns. In: Barratt MR, Pool SL (eds) Principles of Clinical Medicine for Space Flight. Springer Science & Business Media,

Jones JA, Sargsyan AE, Barr YR, et al (2009a) Diagnostic Ultrasound at MACH 20: Retroperitoneal and Pelvic Imaging in Space. Ultrasound Med Biol 35:1059–1067. doi: 10.1016/j.ultrasmedbio.2009.01.002

Jones L, Jacques S, Tranfield S, et al (2009b) NASA Human Research Program Investigators' Workshop. League City, TX

Kalow W (2001) Interethnic differences in drug response. In: Pharmacogenomics, Second. Marcel Dekker Inc., New York, pp 51–80

Kansagara D, Englander H, Salanitro A, et al (2011) Risk Prediction Models for Hospital Readmission. JAMA 306:1688. doi: 10.1001/jama.2011.1515

Kassemi M, Thompson D (2016a) Prediction of renal crystalline size distributions in space using a PBE analytic model. 1. Effect of microgravity-induced biochemical alterations. Am J Physiol - Ren Physiol 311:F520–F530. doi: 10.1152/ajprenal.00401.2015

Kassemi M, Thompson D (2016b) Prediction of renal crystalline size distributions in space using a PBE analytic model. 2. Effect of dietary countermeasures. Am J Physiol - Ren Physiol 311:F531–F538. doi: 10.1152/ajprenal.00402.2015

Kettenbach J, Kronreif G (2015) Robotic systems for percutaneous needle-guided interventions. Minim Invasive Ther Allied Technol MITAT Off J Soc Minim Invasive Ther 24:45–53. doi: 10.3109/13645706.2014.977299

Keyak JH, Koyama AK, LeBlanc A, et al (2009) Reduction in proximal femoral strength due to long-duration spaceflight. Bone 44:449–453. doi: 10.1016/j.bone.2008.11.014

Kheniene F, Bedouch P, Durand M, et al (2008) [Economic impact of an automated dispensing system in an intensive care unit]. Ann Fr Anesth Reanim 27:208–215. doi: 10.1016/j.annfar.2007.11.026

Kijowski R, De Smet AA (2006) The role of ultrasound in the evaluation of sports medicine injuries of the upper extremity. Clin Sports Med 25:569–590, viii. doi: 10.1016/j.csm.2006.03.004

Kim M, Plante I (2015) An Assessment of How Radiation Incurred During a Mars Mission Could Affect Food and Pharmaceuticals. Wyle Science, Technology, and Engineering Group

Kirkpatrick AW, Jones JA, Sargsyan A, et al (2007) Trauma sonography for use in microgravity. Aviat Space Environ Med 78:A38-42.

Komar D, Hoffman J, Olds A, Seal M (2008) Framework for the Parametric System Modeling of Space Exploration Architectures. National Aeronautics and Space Administration, NASA Langley Research Center

Kreiter CD, Bergus G (2009) The validity of performance-based measures of clinical reasoning and alternative approaches. Med Educ 43:320–325. doi: 10.1111/j.1365-2923.2008.03281.x

Krihak M, Abrams H, Katterhagen A, Fung P (2011) ISS Laboratory Analysis: HHC Market Survey: Post-Functional Requirements.

Kumar S, Cohn ER (eds) (2013) Telerehabilitation. Springer London, London

Kwon D, Bouffard JA, van Holsbeeck M, et al (2007) Battling fire and ice: remote guidance ultrasound to diagnose injury on the International Space Station and the ice rink. Am J Surg 193:417–420. doi: 10.1016/j.amjsurg.2006.11.009

Lam C, Scully RR, Zhang Y, et al (2013) Toxicity of lunar dust assessed in inhalation-exposed rats. Inhal Toxicol 25:661–678. doi: 10.3109/08958378.2013.833660

Lam H, Hu M, Qin Y-X (2011) Alteration of contraction-to-rest ratio to optimize trabecular bone adaptation induced by dynamic muscle stimulation. Bone 48:399–405. doi: 10.1016/j.bone.2010.09.018

Lam H, Qin Y-X (2008) The effects of frequency-dependent dynamic muscle stimulation on inhibition of trabecular bone loss in a disuse model. Bone 43:1093–1100. doi: 10.1016/j.bone.2008.07.253

Lang T, LeBlanc A, Evans H, et al (2004) Cortical and Trabecular Bone Mineral Loss From the Spine and Hip in Long-Duration Spaceflight. J Bone Miner Res 19:1006–1012. doi: 10.1359/JBMR.040307

Lang TF, Leblanc AD, Evans HJ, Lu Y (2006) Adaptation of the Proximal Femur to Skeletal Reloading After Long-Duration Spaceflight. J Bone Miner Res 21:1224–1230. doi: 10.1359/jbmr.060509

Lebedev V (1990) Diary of a Cosmonaut: 211 Days in Space. Bantam Books

LeBlanc A, Matsumoto T, Jones J, et al (2013) Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight. Osteoporos Int 24:2105–2114. doi: 10.1007/s00198-012-2243-z

LeBlanc A, Schneider V, Shackelford L, et al (2000) Bone mineral and lean tissue loss after long duration space flight. J Musculoskelet Neuronal Interact 1:157–60.

Lee LW, Wellman GS, Birdwell SW, Sherrin TP (1992) Use of an automated medication storage and distribution system. Am J Hosp Pharm 49:851–855.

Lew HL, Chen CPC, Wang T-G, Chew KTL (2007) Introduction to musculoskeletal diagnostic ultrasound: examination of the upper limb. Am J Phys Med Rehabil 86:310–321. doi: 10.1097/PHM.0b013e31803839ac

Lich KH, Tian Y, Beadles CA, et al (2014) Strategic planning to reduce the burden of stroke among veterans: using simulation modeling to inform decision making. Stroke 45:2078–84. doi: 10.1161/STROKEAHA.114.004694

Liu Y, Taylor LA (2011) Characterization of lunar dust and a synopsis of available lunar simulants. Planet Space Sci 59:1769–1783. doi: 10.1016/j.pss.2010.11.007

Loehr JA, Lee SMC, English KL, et al (2011) Musculoskeletal adaptations to training with the advanced resistive exercise device. Med Sci Sports Exerc 43:146–156. doi: 10.1249/MSS.0b013e3181e4f161

Lyon RC, Taylor JS, Porter DA, et al (2006) Stability profiles of drug products extended beyond labeled expiration dates. J Pharm Sci 95:1549–1560. doi: 10.1002/jps.20636

Manzey D (2004) Human missions to Mars: new psychological challenges and research issues. Acta Astronaut 55:781–790.

Markwald RR, Bessman SC, Reini SA, Drummond SPA (2016) Performance of a Portable Sleep Monitoring Device in Individuals with High Versus Low Sleep Efficiency. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med 12:95–103. doi: 10.5664/jcsm.5404

Martin DS, Caine TL, Matz T, et al (2012) Virtual guidance as a tool to obtain diagnostic ultrasound for spaceflight and remote environments. Aviat Space Environ Med 83:995–1000.

Marx D a, Slonim a D (2003) Assessing patient safety risk before the injury occurs: an introduction to sociotechnical probabilistic risk modelling in health care. Qual Saf Health Care 12 Suppl 2:ii33-i38. doi: 10.1136/qhc.12.suppl_2.ii33

Maxwell AD, Cunitz BW, Kreider W, et al (2015) Fragmentation of Urinary Calculi In Vitro by Burst Wave Lithotripsy. J Urol 193:338–344. doi: 10.1016/j.juro.2014.08.009

McCoy T (2016) Martian Dust “Roundtable.”

McKay DS, Cooper BL, Taylor LA, et al (2015) Physicochemical properties of respirable-size lunar dust. Acta Astronaut 107:163–176. doi: 10.1016/j.actaastro.2014.10.032

McPhee J, Charles J (2009) Human Health and Performance Risks of Space Exploration Missions. National Aeronautics and Space Administration

McWilliams LA, Malecha A (2017) Comparing Intravenous Insertion Instructional Methods with Haptic Simulators. Nurs Res Pract 2017:1–11. doi: 10.1155/2017/4685157

Medscape (2017) eMedicine. http://emedicine.medscape.com/.

Meents A, Gutmann S, Wagner A, Schulze-Briese C (2010) Origin and temperature dependence of radiation damage in biological samples at cryogenic temperatures. Proc Natl Acad Sci 107:1094–1099. doi: 10.1073/pnas.0905481107

Mehta R, Radhakrishnan NS, Warring CD, et al (2016) The Use of Evidence-Based, Problem-Oriented Templates as a Clinical Decision Support in an Inpatient Electronic Health Record System. Appl Clin Inform 7:790–802. doi: 10.4338/ACI-2015-11-RA-0164

Meyers VE, Garcìa HD, Monds K, et al (2012) Ocular toxicity of authentic lunar dust. BMC Ophthalmol 12:26. doi: 10.1186/1471-2415-12-26

Mezghani E, Exposito E, Drira K, et al (2015) A Semantic Big Data Platform for Integrating Heterogeneous Wearable Data in Healthcare. J Med Syst 39:185. doi: 10.1007/s10916-015-0344-x

Minard CG, de Carvalho MF, Iyengar MS (2011) Optimizing medical resources for spaceflight using the integrated medical model. Aviat Space Environ Med 82:890–894.

Monfaredi R, Wilson E, Azizi Koutenaei B, et al (2015) Robot-assisted ultrasound imaging: overview and development of a parallel telerobotic system. Minim Invasive Ther Allied Technol MITAT Off J Soc Minim Invasive Ther 24:54–62. doi: 10.3109/13645706.2014.992908

Moore JA, Gordon JJ, Anscher M, et al (2012) Comparisons of treatment optimization directly incorporating systematic patient setup uncertainty with a margin-based approach. Med Phys 39:1102–11. doi: 10.1118/1.3679856

Moss ME, Zero DT (1995) An overview of caries risk assessment, and its potential utility. J Dent Educ 59:932–40.

Murthy G, Watenpaugh DE, Ballard RE, Hargens AR (1994) Exercise against lower body negative pressure as a countermeasure for cardiovascular and musculoskeletal deconditioning. Acta Astronaut 33:89–96.

Myers J (2015) IMM/iMED Data Report Request D-20150730-330. National Aeronautics and Space Administration

Nakane H (2012) Translocation of particles deposited in the respiratory system: a systematic review and statistical analysis. Environ Health Prev Med 17:263–274. doi: 10.1007/s12199-011-0252-8

NASA (2014) NASA Spaceflight Human System Standards - NASA Standard 3001. National Aeronautics and Space Administration, NASA Johnson Space Center

NASA (2017a) Medical Consumables Tracking. https://www.nasa.gov/mission_pages/station/research/experiments/1259.html.

NASA (2016) Cooperative Agreement Notice (CAN): Solar System Exploration Research Virtual Institute.

NASA (2017b) Integrated Medical Model Incidence Update for the Exploration Medical Capability Evidence, Update 2017. National Aeronautics and Space Administration, NASA Johnson Space Center

NASA Conference Proceedings 2010 Bone Summit: Risk for Early Onset Osteoporosis.

NASA Human Research Program (2009) NASA Human Research Program Plan, Revision A. National Aeronautics and Space Administration

NASA Human Research Program (2016) Human Research Program Roadmap. https://humanresearchroadmap.nasa.gov.

NASA Mission Pages (2013) International Space Station - Food Intake Tracker. https://www.nasa.gov/content/international-space-station-food-intake-tracker.

NASA Mission Pages (2017) Dose Tracker Application for Monitoring Medication Usage, Symptoms, and Adverse Effects During Missions. https://www.nasa.gov/mission_pages/station/research/experiments/1933.html#publications.

NASA Mission Pages (2016a) Advanced Diagnostic Ultrasound in Microgravity (ADUM).

NASA Mission Pages (2016b) Human Research Facility Ultrasound on the International Space Station.

NASA Small Business Innovation Research (2016) DNA Medicine Institute. https://sbir.gsfc.nasa.gov/sites/default/files/DNA_Medicine_Institute.pdf.

NASA Space Medicine Division (2012) Space Medicine Exploration Medical Condition List.

NASA Systems Engineering Processes and Requirements (2013) NASA Systems Engineering Processes and Requirements. National Aeronautics and Space Administration

National Aeronautics and Space Administration (2016) NASA Space Flight Human System Standards. National Aeronautics and Space Administration

National Center for Health Statistics (2016) Adoption of Certified Electronic Health Record Systems and Electronic Information Sharing in Physician Offices: United States, 2013 and 2014.

Nelson E (2011) Design principles for biomedical microfluidics in space. In: Fasel R (ed) Biomedical Engineering.

Nelson E, Chait A (2010) Portable diagnostics technology assessment for space missions. National Aeronautics and Space Administration

Nelson ES, Lewandowski B, Licata A, Myers JG (2009) Development and Validation of a Predictive Bone Fracture Risk Model for Astronauts. Ann Biomed Eng 37:2337–2359. doi: 10.1007/s10439-009-9779-x

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy (2001) Osteoporosis prevention, diagnosis, and therapy. JAMA 285:785–795. doi: 10.1001/jama.285.6.785

NSBRI (2016) Distributed System for Spaceflight Biomedical Support.

Office of the Chief Health & Medical Officer (2016) NASA Health and Medical Requirements for Human Space Exploration. National Aeronautics and Space Administration

Oostenbrink JB, Rutten-van Mölken MPMH, Monz BU, FitzGerald JM (2005) Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health 8:32–46. doi: 10.1111/j.1524-4733.2005.03086.x

Open EMR (2016) Open EMR. http://www.open-emr.org/.

Open MRS (2016) Open MRS. http://openmrs.org/.

Orwoll ES, Adler RA, Amin S, et al (2013) Skeletal health in long-duration astronauts: Nature, assessment, and management recommendations from the NASA bone summit: SKELETAL HEALTH IN LONG-DURATION ASTRONAUTS. J Bone Miner Res 28:1243–1255. doi: 10.1002/jbmr.1948

Page KN, Barker AL, Kamar J (2011) Development and validation of a pressure ulcer risk assessment tool for acute hospital patients. Wound Repair Regen Off Publ Wound Heal Soc Eur Tissue Repair Soc 19:31–7. doi: 10.1111/j.1524-475X.2010.00647.x

Palmer AJ, Mount Hood 5 Modeling Group, Clarke P, et al (2013) Computer modeling of diabetes and its complications: a report on the Fifth Mount Hood challenge meeting. Value Health J Int Soc Pharmacoeconomics Outcomes Res 16:670–85. doi: 10.1016/j.jval.2013.01.002

Papali A (2016) Providing health care in rural and remote areas: lessons from the international space station. Bull World Health Organ 94:73–74. doi: 10.2471/BLT.15.162628

Park J, Liu Y, Kihm KD, Taylor LA (2008) Characterization of lunar dust for toxicological studies. I: Particle size distribution. J Aerosp Eng 21:266–271.

Parker EC, Survanshi SS, Massell PB, Weathersby PK (1998) Probabilistic models of the role of oxygen in human decompression sickness. J Appl Physiol Bethesda Md 1985 84:1096–102.

Pesonen E, Ohmann C, Eskelinen M, Juhola M (1998) Diagnosis of acute appendicitis in two databases. Evaluation of different neighborhoods with an LVQ neural network. Methods Inf Med 37:59–63.

Petersen N, Jaekel P, Rosenberger A, et al (2016) Exercise in space: the European Space Agency approach to in-flight exercise countermeasures for long-duration missions on ISS. Extreme Physiol Med 5:9. doi: 10.1186/s13728-016-0050-4

Pietrzyk RA, Jones JA, Sams CF, Whitson PA (2007) Renal Stone Formation Among Astronauts. Aviat Space Environ Med 78:A9–A13.

Ploutz-Snyder L, Ryder J, English K, et al (2015) Risk of Impaired Performance Due to Reduced Muscle Mass, Strength, and Endurance. National Aeronautics and Space Administration

Pool SL, Davis JR (2007) Space medicine roots: a historical perspective for the current direction. Aviat Space Environ Med 78:A3-4.

Qin Y-X, Lam H (2009) Intramedullary pressure and matrix strain induced by oscillatory skeletal muscle stimulation and its potential in adaptation. J Biomech 42:140–145. doi: 10.1016/j.jbiomech.2008.10.018

Qin YX, Lam H, Ferreri S, Rubin C (2010) Dynamic skeletal muscle stimulation and its potential in bone adaptation. J Musculoskelet Neuronal Interact 10:12–24.

Ramesh AN, Kambhampati C, Monson JRT, Drew PJ (2004) Artificial intelligence in medicine. Ann R Coll Surg Engl 86:334–338. doi: 10.1308/147870804290

Reed R, Antonsen E (2017) Personalizing Space Medicine: The Genetic Information Non-Discrimination Act (GINA) and NASA Occupational Surveillance and Research.

Reyes D (2016) Clinical Practice Guideline for the Monitoring and Management of Renal Stones.

Rich DQ, Kipen HM, Zhang J, et al (2010) Triggering of Transmural Infarctions, but Not Nontransmural Infarctions, by Ambient Fine Particles. Environ Health Perspect Res Triangle Park 118:1229–34.

Roche Diagnostics Corporation (2001) Urinalysis Today.

Rosenfeld LA, Fox CE, Kerr D, et al (2009) Use of computer modeling for emergency preparedness functions by local and state health officials: a needs assessment. J Public Health Manag Pract JPHMP 15:96–104. doi: 10.1097/01.PHH.0000346004.21157.ef

Rubin D, Watkins S (2014) Exploration Medical System Demonstration. National Aeronautics and Space Administration

Rutten-van Mölken MPMH, Oostenbrink JB, Miravitlles M, Monz BU (2007) Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ HEPAC Health Econ Prev Care 8:123–35. doi: 10.1007/s10198-007-0039-4

Saile L, Kerstman E, Shah R, Van Baalen M (2014) Human Research Program Integrated Medical Model List of Medical Conditions. National Aeronautics and Space Administration

Sargsyan AE, Hamilton DR, Jones JA, et al (2005) FAST at MACH 20: Clinical Ultrasound Aboard the International Space Station. J Trauma-Inj Infect 58:35–39.

Sargsyan AE, Hamilton DR, Melton SL, Young J (2006) The International Space Station Ultrasound Imaging Capability Overview for Prospective Users. National Aeronautics and Space Administration

Scheuring R, Johnston SL (2015) Fatigue in US Astronauts Onboard the International Space Station: Environmental Factors, Operational Impacts, and Implementation of Countermeasures.

Scheuring RA, Jones JA, Novak JD, et al (2008) The Apollo Medical Operations Project: Recommendations to improve crew health and performance for future exploration missions and lunar surface operations. Acta Astronaut 63:980–987. doi: 10.1016/j.actaastro.2007.12.065

Scheuring RA, Mathers CH, Jones JA, Wear ML (2009) Musculoskeletal injuries and minor trauma in space: incidence and injury mechanisms in U.S. astronauts. Aviat Space Environ Med 80:117–124.

Schmeler MR, Schein RM, McCue M, Betz K (2009) Telerehabilitation clinical and vocational applications for assistive technology: research, opportunities, and challenges. Int J Telerehabilitation 1:59–72.

Schneider SM, Amonette WE, Blazine K, et al (2003) Training with the International Space Station interim resistive exercise device. Med Sci Sports Exerc 35:1935–1945. doi: 10.1249/01.MSS.0000093611.88198.08

Schork N (2015) Personalized Medicine: Time for one-person trials. Nature 520:609–11.

Schuerger AC, Golden DC, Ming DW (2012) Biotoxicity of Mars soils: 1. Dry deposition of analog soils on microbial colonies and survival under Martian conditions. Planet Space Sci 72:91–101. doi: 10.1016/j.pss.2012.07.026

Schuit SCE, van der Klift M, Weel AEAM, et al (2004) Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 34:195–202. doi: 10.1016/j.bone.2003.10.001

Schwartz GL, Turner ST (2004) Pharmacogenetics of antihypertensive drug responses. Am J Pharmacogenomics Genomics-Relat Res Drug Dev Clin Pract 4:151–160.

Selker HP, Griffith JL, Beshansky JR, et al (1997) Patient-specific predictions of outcomes in myocardial infarction for real-time emergency use: a thrombolytic predictive instrument. Ann Intern Med 127:538–56.

Shah S, Epino H, Bukhman G, et al (2009) Impact of the introduction of ultrasound services in a limited resource setting: rural Rwanda 2008.

Shah S, Shah S, Fils-Aime R, et al (2016) Focused cardiopulmonary ultrasound for assessment of dyspnea in a resource-limited setting.

Sharma S, Zapatero-Rodríguez J, Estrela P, O'Kennedy R (2015) Point-of-Care Diagnostics in Low Resource Settings: Present Status and Future Role of Microfluidics. Biosensors 5:577–601. doi: 10.3390/bios5030577

Shepard A, Roosa S, Mitchell E (1971) Apollo 14 Technical Crew Debriefing. NASA Johns Space Cent Houst TX 9–17.

Sibonga JD (2017) Personal Communication.

Sibonga JD, Spector ER, Johnston SL, Tarver WJ (2015) Evaluating Bone Loss in ISS Astronauts. Aerosp Med Hum Perform 86:A38–A44. doi: 10.3357/AMHP.EC06.2015

Silagy C, Haines A (2001) Evidenced Based Practice in Primary Care, 2nd edn. BMJ Books, London

Singh S, Sun H, Anis AH (2004) Cost-effectiveness of hip protectors in the prevention of osteoporosis related hip fractures in elderly nursing home residents. J Rheumatol 31:1607–13.

Sirek AS, Garcia K, Foy M, et al (2014) Doppler Ultrasound of the Central Retinal Artery in Microgravity. Aviat Space Environ Med 85:3–8. doi: 10.3357/ASEM.3750.2014

Sloan DA, Donnelly MB, Schwartz RW, Strodel WE (1995) The Objective Structured Clinical Examination. The new gold standard for evaluating postgraduate clinical performance. Ann Surg 222:735–742.

Smith MD, Davis-Street JE, Calkins DS, et al (2004) Stability of i-Stat EC6+ cartridges: effect of storage temperature on shelf life. Clin Chem 50:669–673. doi: 10.1373/clinchem.2003.028936

Smith S, Zwart SR, Heer M (2014) Human Adaptation to Spaceflight The Role of Nutrition. United States Govt Printing Office

Smith SM, Heer M, Shackelford LC, et al (2015) Bone metabolism and renal stone risk during International Space Station missions. Bone 81:712–720. doi: 10.1016/j.bone.2015.10.002

Smith SM, Heer MA, Shackelford LC, et al (2012) Benefits for bone from resistance exercise and nutrition in long-duration spaceflight: Evidence from biochemistry and densitometry. J Bone Miner Res 27:1896–1906. doi: 10.1002/jbmr.1647

Smith SM, Wastney ME, O'Brien KO, et al (2005) Bone markers, calcium metabolism, and calcium kinetics during extended-duration space flight on the mir space station. J Bone Miner Res Off J Am Soc Bone Miner Res 20:208–218. doi: 10.1359/JBMR.041105

Smith-Bindman R, Aubin C, Bailitz J, et al (2014) Ultrasonography versus Computed Tomography for Suspected Nephrolithiasis. N Engl J Med 371:1100–1110. doi: 10.1056/NEJMoa1404446

Smulyan H, Safar ME (2011) Blood pressure measurement: retrospective and prospective views. Am J Hypertens 24:628–634. doi: 10.1038/ajh.2011.22

Sobieraj JA, Reyes J, Dunemn KN, et al (2007) Modeling hospital response to mild and severe influenza pandemic scenarios under normal and expanded capacities. Mil Med 172:486–90.

Sorensen MD, Bailey MR, Hsi RS, et al (2013) Focused Ultrasonic Propulsion of Kidney Stones: Review and Update of Preclinical Technology. J Endourol 27:1183–1186. doi: 10.1089/end.2013.0315

Sornay-Rendu E, Munoz F, Garnero P, et al (2005) Identification of Osteopenic Women at High Risk of Fracture: The OFELY Study. J Bone Miner Res 20:1813–1819. doi: 10.1359/JBMR.050609

Stamatelatos M, Dezfuli H (2011) Probabilistic Risk Assessment Procedures Guide for NASA Managers and Practitioners. NASA Tech Rep SP-2011-34:323. doi: NASA/SP-2011-3421

Stepaniak PC, Ramchandani SR, Jones JA (2007) Acute urinary retention among astronauts. Aviat Space Environ Med 78:A5-8.

Stewart LH, Trunkey D, Rebagliati GS (2007) Emergency medicine in space. J Emerg Med 32:45–54. doi: 10.1016/j.jemermed.2006.05.031

Stingl JC, Welker S, Hartmann G, et al (2015) Where Failure Is Not an Option - Personalized Medicine in Astronauts. PloS One 10:e0140764. doi: 10.1371/journal.pone.0140764

Sulkowski CM, Gilkey KM, Lewandowski BE, et al (2011) An extravehicular suit impact load attenuation study to improve astronaut bone fracture prediction. Aviat Space Environ Med 82:455–62.

Summers RL, Johnston SL, Marshburn TH, Williams DR (2005) Emergencies in space. Ann Emerg Med 46:177–184. doi: 10.1016/j.annemergmed.2005.02.010

Tang BK, Kalow W, Inaba T, Kadar D (1983) Variation in amobarbital metabolism: evaluation of a simplified population study. Clin Pharmacol Ther 34:202–206.

Taylor AL, Cohn JN, Worcel M, et al (2002) The African-American Heart Failure Trial: background, rationale and significance. J Natl Med Assoc 94:762–769.

Taylor LA, Pieters C, Patchen A, et al (2010) Mineralogical and chemical characterization of lunar highland soils: Insights into the space weathering of soils on airless bodies. J Geophys Res Planets 115:E02002. doi: 10.1029/2009JE003427

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Department of Health, Education, and Welfare

Theriot C, Glass A, CW L, et al (2014) Chronic Lunar Dust Exposure on Rat Cornea: Evaluation by Gene Expression Profiling. NASA Human Research Program Investigators' Workshop, Galveston, TX

Thompson KM (2002) Variability and uncertainty meet risk management and risk communication. Risk Anal Off Publ Soc Risk Anal 22:647–54.

Toups L, Simon M, Smitherman D, Spexarth G (2012) Design and Parametric Sizing of Deep Space Habitats Supporting NASA's Human Spaceflight Architecture Team. National Aeronautics and Space Administration, NASA Johnson Space Center

Trappe TA, Burd NA, Louis ES, et al (2007) Influence of concurrent exercise or nutrition countermeasures on thigh and calf muscle size and function during 60 days of bed rest in women. Acta Physiol Oxf Engl 191:147–159. doi: 10.1111/j.1748-1716.2007.01728.x

United States Air Force (2016) Air Force Policy Directive 63-1.

UpToDate (2017) UpToDate. www.uptodate.com.

Wagner SA (2006) The Apollo experience lessons learned for constellation lunar dust management.

Wainwright SA, Marshall LM, Ensrud KE, et al (2005) Hip Fracture in Women without Osteoporosis. J Clin Endocrinol Metab 90:2787–2793. doi: 10.1210/jc.2004-1568

Watkins SD (2010) Space Medicine Exploration: Full Medical Condition List. National Aeronautics and Space Administration, Washington, DC

Weaver AS, Zakrajsek AD, Lewandowski BE, et al (2013) Predicting head injury risk during International Space Station increments. Aviat Space Environ Med 84:38–46.

Wheeless C (2017) Wheeless' Textbook of Orthopedics. http://www.wheelessonline.com/.

Whitson PA, Pietrzyk RA, Jones JA, et al (2009) Effect of Potassium Citrate Therapy on the Risk of Renal Stone Formation During Spaceflight. J Urol 182:2490–2496. doi: 10.1016/j.juro.2009.07.010

Whitson PA, Pietrzyk RA, Pak CY, Cintrón NM (1993) Alterations in renal stone risk factors after space flight. J Urol 150:803–807.

Whitson PA, Pietrzyk RA, Sams CF (1999) Space flight and the risk of renal stones. J Gravitational Physiol J Int Soc Gravitational Physiol 6:P87-8.

Whitson PA, Pietrzyk RA, Sams CF (2001) Urine volume and its effects on renal stone risk in astronauts. Aviat Space Environ Med 72:368–372.

Wotring VE (2015) Medication use by U.S. crewmembers on the International Space Station. FASEB J Off Publ Fed Am Soc Exp Biol 29:4417–4423. doi: 10.1096/fj.14-264838

Wotring VE (2016) Chemical Potency and Degradation Products of Medications Stored Over 550 Earth Days at the International Space Station. AAPS J 18:210–216. doi: 10.1208/s12248-015-9834-5

Young J, Mattingly T, Duke JR C (1972) Apollo 16 Technical Crew Debriefing. NASA Johns Space Cent Houst TX 10–17.

Zin Technologies (2016) Zin Technologies, Inc.

Zolfaghari MR, Peyghaleh E (2015) Implementation of equity in resource allocation for regional earthquake risk mitigation using two-stage stochastic programming. Risk Anal Off Publ Soc Risk Anal 35:434–58. doi: 10.1111/risa.12321

Zwart SR, Wolf M, Rogers A, et al (2009) Stability of analytes related to clinical chemistry and bone metabolism in blood specimens after delayed processing. Clin Biochem 42:907–910. doi: 10.1016/j.clinbiochem.2009.02.010

## X. List of Acronyms

aBMD: areal bone mineral density
ADUM: Advanced Diagnostic Ultrasound in Microgravity
API: active pharmaceutical ingredient
ARED: advanced resistive exercise device
BMD: bone mineral density
CEVIS: cycle ergometer with vibration isolation and stabilization
ConOps: Concept of Operations
CT: Computed tomography
DXA: dual-energy x-ray absorptiometry
ECG: electrocardiogram
eMC: electronic Medicines Compendium
EMCL: Exploration Medical Condition List
EMR: Electronic Medical Record
EMSD: Exploration Medical System Demonstration
EVA: Extravehicular Activity
ExMC: Exploration Medical Capability
FAST: Focused Assessment in Sonographic Technique
FDA: Food and Drug Administration
FMEA: Failure Mode and Effects Analysis
HERA: Human Exploration Research Analog
HRP: Human Research Program
IMM: Integrated Medical Model
iRED: interim resistive exercise device
ISS: International Space Station
LBNP: Lower body negative pressure
LSAH: Lifetime Surveillance of Astronaut Health
MEL: Mass Equipment List
MONSTR: Medical Optimization Network for Space Telemedicine Resources
NIH: National Institute of Health
NSBRI: National Space Biomedical Research Institute
OSCE: objective-structured clinical examinations
PEL: permissible exposure limit
PRA: Probabilistic risk analysis
QCT: quantitative computed tomography
SLEP: Shelf Life Extension Program
SPC: Summaries of Product Characteristics
T2: second generation treadmill with vibration isolation and stabilization
USP: United States Pharmacopeia
vBMD: volumetric bone mineral density

## XI. Appendix

Table 1: Medical events and symptoms occurring during ISS missions (through ISS Expedition 40). Number of events, person-year incidence, and number of events attributed to extravehicular activity (EVA) are provided. (NB: Data are as comprehensive as possible through ISS Expedition 40. Some expeditions had more reports and information than others, so data may be heavily influenced by certain missions or crewmembers.) LSAH Data Request ID: #10912.

| Category | Complaint | N | Person-Year Incidence | EVA Attributed |
|---|---|---|---|---|
| Orthopedics | Arm | 2 | 0.14 | 2 |
| | General | 1 | 0.07 | 1 |
| | Groin | 2 | 0.14 | 1 |
| | Hamstring | 5 | 0.34 | |
| | Hip | 6 | 0.41 | |
| | Knee | 9 | 0.62 | |
| | Leg | 3 | 0.21 | |
| | Neck | 2 | 0.14 | |
| | Shoulder | 8 | 0.55 | 2 |
| | Unknown | 2 | 0.14 | |
| | Wrist | 3 | 0.21 | |
| | Total | 43 | 2.96 | 6 |
| Skin | Abrasion | 9 | 0.62 | 3 |
| | Dry Skin | 4 | 0.28 | |
| | Irritation | 10 | 0.69 | 2 |
| | Itch | 3 | 0.21 | |
| | Laceration | 1 | 0.07 | |
| | Rash | 10 | 0.69 | |
| | Total | 37 | 2.55 | 5 |
| Headache | | 33 | 2.27 | |
| | Total | 33 | 2.27 | |
| Nasal | Congestion | 28 | 1.93 | 1 |
| | Dry | 1 | 0.07 | |
| | Irritation | 1 | 0.07 | |
| | Nose Bleed | 2 | 0.14 | |
| | Total | 32 | 2.20 | 1 |
| Back Pain | | 29 | 1.99 | 2 |
| | Total | 29 | 1.99 | 2 |
| Eye | Abnormality | 9 | 0.62 | |
| | Debris | 4 | 0.28 | |
| | Dry Eyes | 4 | 0.28 | |
| | Irritation | 5 | 0.34 | |
| | Puffy | 1 | 0.07 | |

| | | | | |
|---|---|---|---|---|
| | **Watery** | 4 | 0.28 | |
| | **Total** | 27 | 1.86 | |
| GI | **Constipation** | 9 | 0.62 | 1 |
| | **Diarrhea** | 2 | 0.14 | |
| | **Hemorrhoid** | 1 | 0.07 | |
| | **Indigestion** | 8 | 0.55 | |
| | **Nausea** | 1 | 0.07 | |
| | **Stomach** | 1 | 0.07 | |
| | **Total** | 22 | 1.51 | 1 |
| Sleep | | 1 | 0.07 | |
| | **Disruption** | 1 | 0.07 | |
| | **Hypersomnia** | 1 | 0.07 | |
| | **Insomnia** | 19 | 1.31 | |
| | **Total** | 22 | 1.51 | |
| Systemic | **Fatigue** | 21 | 1.44 | 5 |
| | **Total** | 21 | 1.44 | 5 |
| SMS | | 16 | 1.10 | |
| | **Total** | 16 | 1.10 | |
| VIIP | | 14 | 0.96 | |
| | **Total** | 14 | 0.96 | |
| Urinary | | 1 | 0.07 | |
| | **Decreased Urination** | 2 | 0.14 | |
| | **Dysuria** | 2 | 0.14 | |
| | **Hematuria** | 1 | 0.07 | |
| | **Incontinence** | 1 | 0.07 | |
| | **Increased Urination** | 2 | 0.14 | |
| | **Nocturia** | 1 | 0.07 | |
| | **Retention** | 1 | 0.07 | 1 |
| | **Urine Reflux** | 1 | 0.07 | |
| | **Total** | 12 | 0.83 | 1 |
| Hand | | 9 | 0.62 | 7 |
| | **Total** | 9 | 0.62 | 7 |
| Psych | | 9 | 0.62 | |
| | **Total** | 9 | 0.62 | |
| Elbow Pain | | 6 | 0.41 | 1 |
| | **Total** | 6 | 0.41 | 1 |
| Mouth Ulcer | | 6 | 0.41 | |
| | **Total** | 6 | 0.41 | |
| Vestibular | | 6 | 0.41 | |
| | **Total** | 6 | 0.41 | |
| Bruising Due to Blood Draw | **Arm** | 5 | 0.34 | |
| | **Total** | 5 | 0.34 | |
| Ear | **Congestion** | 5 | 0.34 | 1 |

| | | | | |
|---|---|---|---|---|
| | **Total** | 5 | 0.34 | 1 |
| Neurologic | **Loss of Feeling** | 5 | 0.34 | 2 |
| | **Total** | 5 | 0.34 | 2 |
| ENT | **Sneezing** | 2 | 0.14 | |
| | **Sore Throat** | 2 | 0.14 | |
| | **Total** | 4 | 0.28 | |
| Fingernail | **Delamination** | 1 | 0.07 | 1 |
| | **Pain** | 3 | 0.21 | 3 |
| | **Total** | 4 | 0.28 | 4 |
| Fluid Shift | **Composition Change** | 1 | 0.07 | |
| | **Facial Fullness** | 3 | 0.21 | |
| | **Total** | 4 | 0.28 | |
| Thermal Comfort | | 1 | 0.07 | 1 |
| | **Feet** | 1 | 0.07 | 1 |
| | **Hands** | 2 | 0.14 | 2 |
| | **Total** | 4 | 0.28 | 4 |
| Bruise | **Arm** | 1 | 0.07 | 1 |
| | **Hand** | 1 | 0.07 | 1 |
| | **Shoulder** | 1 | 0.07 | 1 |
| | **Total** | 3 | 0.21 | 3 |
| Dehydration | | 2 | 0.14 | |
| | **Total** | 2 | 0.14 | |
| Respiratory | **Bronchitis** | 1 | 0.07 | |
| | **Total** | 1 | 0.07 | |
| **Grand Total** | | **381** | **26.21** | **43** |

Table 2. Number of occurrences of medical conditions that have affected NASA astronauts during previous space missions (NASA 2017b). Data are obtained from LSAH records for medical conditions that occurred among US astronauts during the Space Shuttle Program, Mir, and ISS (through Expedition 13 in 2006) missions. EVA: extravehicular activity

| Medical Condition | Events | Medical Condition | Events |
|---|---|---|---|
| Allergic reaction (mild to moderate) | 11 | Mouth ulcer | 9 |
| Ankle sprain/strain | 11 | Nasal congestion (space adaptation) | 389 |
| Back injury | 31 | Neck injury | 9 |
| Back pain (space adaptation) | 382 | Nose bleed (space adaptation) | 6 |
| Barotrauma (ear/sinus block) | 31 | Otitis externa | 3 |
| Choking/obstructed airway | 3 | Otitis media | 3 |
| Constipation (space adaptation) | 113 | Paresthesias | 26 |
| Diarrhea | 33 | Pharyngitis | 11 |
| Elbow sprain/strain | 12 | Respiratory infection | 33 |
| Eye abrasion (foreign body) | 70 | Shoulder sprain/strain | 22 |
| Eye chemical burn | 6 | Sinusitis | 6 |
| Eye infection | 5 | Skin abrasion | 94 |
| Finger dislocation | 1 | Skin infection | 13 |
| Fingernail delamination (EVA) | 16 | Skin laceration | 1 |
| Gastroenteritis | 4 | Skin rash | 94 |
| Headache ($CO_2$ induced) | 20 | Smoke inhalation | 3 |
| Headache (late) | 49 | Space motion sickness (space adaptation) | 325 |
| Headache (space adaptation) | 233 | Urinary incontinence (space adaptation) | 5 |
| Hemorrhoids | 2 | Urinary retention (space adaptation) – female | 5 |
| Herpes Zoster reactivation (shingles) | 1 | Urinary retention (space adaptation) – male | 4 |
| Indigestion | 6 | Urinary tract infection – female | 5 |
| Influenza | 1 | Urinary tract infection – male | 4 |
| Insomnia (space adaptation | 299 | Visual impairment/increased intracranial pressure (space adaptation) | 15 |
| Insomnia (late) | 133 | Wrist sprain/strain | 5 |
| Knee sprain/strain | 7 | | |