



Review of NASA's Evidence Reports on Human Health Risks: 2016 Letter Report

DETAILS

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Review of NASA's Evidence Reports on Human Health Risks

2016 LETTER REPORT

Committee to Review NASA's Evidence Reports
on Human Health Risks

Board on Health Sciences Policy

Carol E. H. Scott-Conner, Daniel R. Masys, and
Catharyn T. Liverman, *Editors*

Health and Medicine Division

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Marcia J. Rieke**, University of Arizona. She was responsible for making certain

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that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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HEALTH AND MEDICINE DIVISION
Board on Health Sciences and Policy

December 28, 2016

John Charles, Ph.D.
Lyndon B. Johnson Space Center
2101 NASA Parkway
Houston, TX 77058

Dear Dr. Charles:

The National Academies of Sciences, Engineering, and Medicine (the National Academies), at the request of the National Aeronautics and Space Administration (NASA) and with guidance from the National Academies' Standing Committee on Aerospace Medicine and the Medicine of Extreme Environments, has established the Committee to Review NASA's Evidence Reports on Human Health Risks. This letter report is the fourth in a series of five reports (IOM, 2014, 2015, 2016). The committee will provide an independent review of the more than 30 evidence reports that NASA has compiled on human health risks for long-duration and exploration spaceflights. This 2016 letter report builds on the work of the 2008 Institute of Medicine (IOM) report and examines eight evidence reports:

1. *Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure* (Patel et al., 2016)
2. *Risk of Radiation Carcinogenesis* (Huff et al., 2016)
3. *Risk of Acute Radiation Syndromes Due to Solar Particle Events* (Carnell et al., 2016)
4. *Risk of Acute and Late Central Nervous System Effects from Radiation Exposure* (Nelson et al., 2016)
5. *Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders* (Slack et al., 2016)

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6. *Risk of Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication, and Psychosocial Adaptation Within a Team* (Landon et al., 2016)
7. *Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload* (Flynn-Evans et al., 2016)
8. *Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Space Flight* (Bloomberg et al., 2016)

COMMITTEE'S TASK AND OVERARCHING ISSUES

To review the eight NASA evidence reports, the National Academies assembled a 13-member committee with expertise in aerospace medicine, occupational health, radiation medicine and radiological research, human performance, internal medicine, physiology and exercise science, behavioral health, sleep and circadian rhythms, psychiatry, aerospace engineering, otolaryngology, and biomedical informatics. Committee biographical sketches are included in Appendix B.

The committee's task, detailed in Box 1, was to review each evidence report in response to nine specific questions. In summary, this report examines the quality of the evidence, analysis, and overall construction of each report; identifies existing gaps in report content; and provides suggestions for additional sources of expert input. This report also builds on the 2008 IOM report *Review of NASA's Human Research Program Evidence Books: A Letter Report*, which assessed the process for developing NASA's evidence reports and provided an initial and brief review of NASA's original evidence report.¹

The committee approached its task by analyzing each evidence report's overall quality, which included readability; internal consistency; the source and breadth of cited evidence; identification of existing knowledge and research gaps; authorship expertise; and, if applicable, response to recommendations from the IOM letter report previously described.

The committee commends NASA for its guidance to report authors to explicitly note the categories of evidence incorporated into reports, ranging from expert opinion to controlled trials. This practice is now in-

¹The original evidence book was "a collection of evidence reports created from the information presented verbally and discussed within the NASA HRP [Human Research Program] in 2006" (NASA, 2013a).

cluded comprehensively in most, but not all reports, with exceptions noted in relevant sections below. As noted in prior letter reports (IOM, 2014, 2015, 2016), substantial variability exists in the formatting, internal consistency, and completeness of the references among individual evidence reports, making it difficult to compare cited evidence for related human health risks. NASA is encouraged to select a preferred citation format for all evidence reports and to require all writing teams to use that format.

BOX 1

Review of NASA's Evidence Reports on Human Health Risks

Statement of Task

NASA has requested a study to provide an independent review of more than 30 evidence reports on human health risks for long-duration and exploration spaceflight. The evidence reports, which are publicly available, are categorized into five broad categories: (1) behavioral health and performance; (2) human health countermeasures (with a focus on bone metabolism and orthopedics, nutrition, immunology, cardiac and pulmonary physiology); (3) radiation; (4) human factors issues; and (5) exploration medical capabilities. The reports are revised on an ongoing basis to incorporate new scientific information. In conducting this study, an ad hoc committee will build on the 2008 Institute of Medicine (IOM) report *Review of NASA's Human Research Program Evidence Books*. That report provided an assessment of the process used for developing the evidence reports and provided an initial review of the evidence reports that had been completed at that time.

Each year, NASA staff will identify a set of evidence reports for committee review. Over the course of the study all evidence reports will be reviewed. The committee will hold an annual scientific workshop to receive input on the evidence reports it is reviewing that year and an update on the recent literature. The committee will issue an annual letter report that addresses the following questions relevant to each evidence report:

1. Does the evidence report provide sufficient evidence, as well as sufficient risk context, that the risk is of concern for long-term space missions?
2. Does the evidence report provide evidence that the named gaps are the most critical presented?
3. Are there any additional gaps or aspects to existing gaps that are not addressed for this specific risk?
4. Does the evidence report address relevant interactions among risks?
5. Is input from additional disciplines needed?

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6. Is the breadth of the cited literature sufficient?
7. What is the overall readability and quality?
8. Is the expertise of the authors sufficient to fully cover the scope of the given risk?
9. Has the evidence report addressed previous recommendations made by the IOM in the 2008 letter report?

In addition to analyzing the content of individual letter reports, the committee also gathered evidence from existing literature and relevant experts in the field. The committee held three conference call meetings and one in-person meeting, with the latter held in conjunction with a public workshop (see Appendix A). At the workshop, the committee invited individuals with expertise related to at least one of the eight evidence reports to analyze NASA's evidence reports and engage in discussions with the committee, focusing on the questions enumerated by NASA in the study task.

This report follows the format of the prior letter reports, which includes the committee's responses to each of the questions listed in its statement of task for each of the eight evidence reports. Although no formal recommendations are included in this report, the committee's observations are intended to help inform and improve NASA's ongoing efforts to update the content of individual evidence reports.

THE NASA HUMAN RESEARCH ROADMAP

The evidence reports reviewed in this National Academies' report are part of a larger roadmap process developed and under implementation by NASA's Human Research Program. The goals of the program are to "provide human health and performance countermeasures, knowledge, technologies, and tools to enable safe, reliable, and productive human space exploration" (NASA, 2014). As outlined in Figure 1, the evidence reports are the first part of the roadmap, which is followed by clarifying the risks, specifying the research gaps to address those risks, implementing research tasks, and obtaining deliverables. These steps are then assessed to ascertain progress in preventing or mitigating the risk to astronaut health. NASA updates its progress on risk reduction for four design reference missions: (1) 12-month mission on the International

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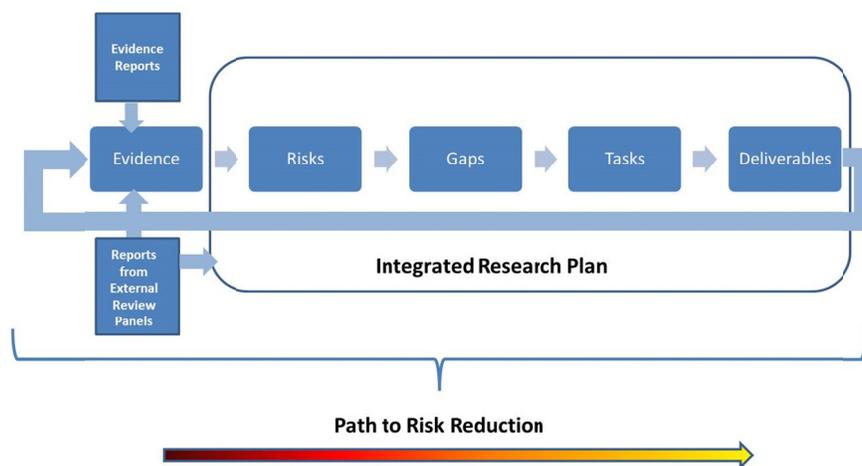


FIGURE 1 NASA's human research roadmap.
SOURCE: Adapted from NASA, 2014.

Space Station (ISS); (2) lunar (outpost) mission; (3) deep space journey mission (e.g., near Earth asteroid); and (4) planetary mission (e.g., Mars) by identifying the extent to which there is evidence that the plans for that mission will meet existing crew health standards or that countermeasures exist to control the risk (NASA, 2013b).

RISK OF CARDIOVASCULAR DISEASE AND OTHER DEGENERATIVE TISSUE EFFECTS FROM RADIATION EXPOSURE

As discussed in the evidence report *Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure* (Patel et al., 2016), epidemiologic studies of populations exposed to ionizing radiation (primarily x-rays or gamma rays) show an increased incidence of degenerative tissue effects such as cataracts and cardiovascular disease (atherosclerosis); the effects of space radiation on such degenerative effects, however, are largely unknown. The underlying mechanisms are also not fully understood, but likely involve oxidative damage and inflammation as well as more direct damage to tissues. The committee's responses to the key review questions are summarized below.

The committee noted that the four NASA evidence reports on radiation (Carnell et al., 2016; Huff et al., 2016; Nelson et al., 2016; Patel et

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al., 2016), taken in the aggregate, provide an extremely comprehensive introduction to radiation biology, dosimetry, and the space radiation environment. In some instances, aspects of this background information are best covered in one report and (appropriately) not in such depth in others. Additional cross-referencing among these evidence reports might be considered as a way to efficiently cover all of this material.

**Does the Evidence Report Provide Sufficient Evidence,
as Well as Sufficient Risk Context, That the Risk Is of Concern
for Long-Term Space Missions?**

This evidence report effectively presents the current state of knowledge (and lack thereof) in regard to risk of cardiovascular disease and other degenerative tissue effects from ionizing radiation exposure (Patel et al., 2016). Indeed, sufficient evidence and risk context are provided to support the conclusion that the risk of degenerative diseases from long-term exposure to space radiation may be of much greater concern than previously believed: “For a Mars mission, the accumulated dose is sufficiently high that epidemiology data and preliminary risk estimates suggest a significant risk for cardiovascular disease” (Patel et al., 2016, p. 5).

The association between ionizing radiation exposure and long-term development of degenerative pathologies (late effects), such as cardiovascular disease, cataracts, immune and endocrine dysfunction, and premature aging is well established for moderate to high doses of low linear energy transfer (LET) radiation. Indications are that other potential ionizing radiation-related degenerative effects involve respiratory and digestive systems. However, the risks for these diseases from low dose/low dose-rate (more chronic) exposures relevant to spaceflight, particularly to high-LET and high-Z high-energy (HZE) nuclei, are largely unknown and much more difficult to assess due to their multifactorial nature (the influence of many other flight factors, e.g., microgravity) and long latency periods. It is also currently unclear as to whether low-dose exposures (<0.5 Gy) influence the same biological pathways known to be involved in disease progression following moderate- to high-dose ionizing radiation exposures.

Astronauts will spend extended periods of time in deep space during long-term lunar or Mars missions, where exposure to galactic cosmic rays (GCRs) will be chronic and at relatively low fluence. This scenario is of concern because the risk of developing cardiovascular disease

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and/or other degenerative tissue effects (including accelerated aging) associated with low dose/low dose–rate exposures relevant to spaceflight—particularly to high-LET radiation and GCR—is largely unknown, yet has the potential to influence performance during long-duration missions.

Does the Evidence Report Provide Evidence That the Named Gaps Are the Most Critical Presented?

The report adequately supports the named gaps as the most critical to improving understanding of and appreciation for the risk of cardiovascular disease and other degenerative tissue effects from radiation exposure. Specific comments are provided below on each of the gaps discussed in the report.

Degen-1 (*How can tissue specific experimental models be developed for the major degenerative tissue risks, including cardiovascular, lens, and other tissue systems [e.g., immune, endocrine, respiratory and/or digestive] in order to estimate space radiation risks for degenerative diseases?*): The evidence report sufficiently conveys concern regarding the appropriateness of mouse/rodent models for estimating risk in humans and outlines evidence of the need for other types of models. For example, radiation has delayed effects (e.g., cardiovascular disease) that take time to manifest and the degenerative pathologies are in general associated with age; for these types of risks the mouse/rodent models are not relevant. Therefore, it is critical that valid animal models are developed for each specific tissue or system affected by space-relevant ionizing radiation–induced degenerative effects (e.g., cardiovascular, lens, immune, endocrine, respiratory, and/or digestive systems) in order to more accurately estimate space radiation risks for human degenerative diseases.

Degen-2 (*What are the mechanisms of degenerative tissue changes in the cardiovascular, lens, digestive, endocrine, and other tissue systems? What surrogate endpoints do they suggest?*): Mechanisms of space-relevant ionizing radiation–induced degenerative tissue changes in the cardiovascular, lens, digestive, endocrine and other tissue systems need to be characterized (e.g., persistent ionizing radiation–induced oxidative stress) and surrogate biomarkers and endpoints identified (e.g., telomere length changes with time/age). There is also a need for studies to explore the potential existence of dose thresholds (the shape of the dose response curves is largely unknown), as well as to establish relative

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biological effectiveness (RBE) relationships and dose-rate dependencies for different types of space radiation.

Degen-3 (*What are the progression rates and latency periods for radiation-induced degenerative diseases, and how do progression rates depend on age, sex, radiation type, or other physiological or environmental factors?*): Progression rates and latency periods for space-relevant ionizing radiation–induced degenerative tissue changes/disease, as well as how they depend on age, sex, radiation type/quality, or other physiological or environmental factors need to be determined.

Degen-4 (*How does individual susceptibility, including hereditary predisposition, alter radiation-induced degenerative disease processes and risk estimates?*): There is a need to incorporate personalized medicine (e.g., “omics”) approaches to identify (and monitor) potential individual susceptibilities that may alter ionizing radiation–induced degenerative effects/risks and susceptibilities and would include sex differences.

Degen-5 (*What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?*): This gap addresses the need for accurate models to extrapolate risks from existing models to astronauts and furthermore, the need to identify space-relevant ionizing radiation–exposed human populations.

Degen-6 (*What are the most effective biomedical or dietary countermeasures to mitigate degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these [countermeasures] additive, synergistic, or antagonistic to other risks?*): This gap addresses the need for countermeasures to mitigate space-relevant ionizing radiation–induced degenerative tissue risks (e.g., biomedical [drug development] or dietary [vitamins C and E] interventions), to improve understanding of their mechanisms of action, and to determine whether the effects are additive, synergistic, or antagonistic with other risks.

Degen-7 (*Are there synergistic effects from other spaceflight factors [e.g., altered gravity (μ -gravity), stress, altered circadian rhythms, altered immune function, or other] that modify space radiation-induced degenerative diseases in a clinically significant manner?*): This gap addresses the need to identify potential synergistic interactions with other spaceflight factors that may alter ionizing radiation–induced degenerative effects/risks and emphasizes the need for the topic of this evidence

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report to be discussed in other evidence reports, such as those on sleep and on immune function (Crucian et al., 2009; Flynn-Evans et al., 2016).

Degen-8 (*Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation circulatory disease risk estimates?*): Tobacco use is one of a number of environmental and lifestyle risks that could be considered to be addressed in this gap.

**Are There Any Additional Gaps in Knowledge or Aspects
to Existing Gaps That Are Not Addressed
for This Specific Risk?**

No biophysical model can project all possible degenerative tissue effects/risks for the entire range of particle types and energies found in space. Once models are developed and the risks are better defined, there is further need for consensus on what exactly are acceptable space-relevant ionizing radiation–induced degenerative risks for astronauts.

No human data are currently available on the effects of high-LET on development of degenerative heart and cardiovascular complications. Differences and similarities in male versus female responses are also largely absent. Not only are less heterogeneous and more comparable populations needed to generate meaningful risk coefficients, it is “essential that additional data with HZE particles be acquired using relevant model systems and relevant doses to refine the current model of cardiovascular disease risk from space radiation” (NCRP, 2014, p. 17). Additionally, consideration must be given to characterizing individual, ion-specific alterations of ionizing radiation–induced degenerative effects/risks, in order to better understand more representative mixed-field GCR simulations as they become available.

In regard to individual susceptibility and differences between men and women, recent and rapid advances in genomics research, as well as NASA’s first foray into “omics” based investigations with the Twins Study, suggest it is time to consider incorporating “personalized medicine” research components to identify specific genetic signatures that influence risk of space-relevant ionizing radiation–induced cancer and non-cancer (degenerative) effects. Such information could be used to guide individual selection into the astronaut core, as well as post-mission as a means of identifying individuals at particular risk of developing late, degenerative effects.

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An additional gap is the possible role of chronic inflammation and increased oxidative stress associated with space radiation/GCR exposure and degenerative risks.

Additionally, as astronauts venture into deep space and mission duration increases, degenerative risks to other tissues (e.g., digestive and pulmonary) will need to be addressed.

An important long-term goal will be to consider all possible changes in animal validation studies once those are conducted at the extended-duration GCR simulator facility under development at NASA's Space Radiation Laboratory.

The accepted relationship of low-LET ionizing radiation exposure with accelerated aging and associated degenerative diseases is discussed in the evidence report. The report also notes that the space environment includes many other stressors (e.g., microgravity, altered oxygen levels, nutritional deficiencies, immune dysregulation, psychological, etc.), which can influence and are unknown modifiers of cardiovascular disease and degenerative disease risks. There is a need to establish the effects of long-term high-LET ionizing radiation exposure on aging and associated degenerative diseases, including characterizing the interactions and synergies among stressors and identifying informative and integrative biomarkers (e.g., shortened telomere length associated with cardiovascular disease, which is not specifically mentioned in this context) (Haycock et al., 2014). The evidence report could also be strengthened by incorporating a more comprehensive discussion on what is known about stressors influencing cardiovascular disease and degenerative tissue effects.

Does the Evidence Report Address Relevant Interactions Among Risks?

This evidence report introduces the concept of aging phenotypes and interactions among risks as being informative. Furthermore, potentially common biological mechanisms are involved in the development of cardiovascular effects and cataracts. Cerebrovascular disease involves degenerative aspects of both the central nervous system (CNS) and the cardiovascular system. There is also a combined cancer and circulatory disease risk associated with deep space mission ionizing radiation exposure. However, the committee appreciates that combining risks is currently preliminary, largely because the risk for space-relevant ionizing radiation-induced circulatory disease is associated with such large uncer-

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tainty due, for example, to the need for extrapolating from human populations exposed to acute, relatively high doses of low-LET radiation (NCRP, 2014). As noted above, these interactions are an important gap in current knowledge, and it will be important to reduce this uncertainty (i.e., relevant animal and human models and relevant space radiation exposures), to better inform astronauts of actual risks.

What Is the Overall Readability and Quality?

The evidence report's overall readability and quality is satisfactory.

Is the Breadth of the Cited Literature Sufficient?

The breadth of literature cited is sufficient with a few suggestions provided to improve the report. The statement that high-LET radiation has an enhanced ability to damage telomeres is not supported by the reference cited (p. 22 of the evidence report), as that study evaluated terminal deletions and was not specific for telomeres. As telomeres make up less than 1 percent of the total genomic DNA, it is highly unlikely that the effect of ionizing radiation on telomeres is the result of direct ionization during initial exposure. Rather, the report could be strengthened by noting that telomeres are extremely sensitive to reactive oxygen species, and that oxidative stress persists long after exposure and so may be of particular concern following high-LET long-term exposure; such a scenario is supportive of a non-targeted effect on telomere length regulation that could have important implications for late effects such as aging and age-associated degenerative diseases.

A recent report by Delp and colleagues (2016) and the subsequent commentary it sparked (Cucinotta et al., 2016) highlight the controversy associated with space-relevant ionizing radiation-induced cardiovascular disease. These relevant works also support the need for additional research to more precisely define the risk and provide more mechanistic insight in order to inform and improve mitigation strategies. A discussion of these recent reports and the issues involved would be of great value in the next edition of this evidence report.

Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk?

Is Input from Additional Disciplines Needed?

The expertise of the authors is sufficient and no additional disciplines need to be added. Experts in the field who made presentations at

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the committee's workshop (see Appendix A) also supported the evidence report.

Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?

The authors have responded to the 2008 report recommendations for this topic. Specifically, discussions of personal genetic variation and variable oxygen levels on radiosensitivity were called for, and both have been addressed in the current report; additionally other highlighted issues were also addressed: influence of genetic/individual susceptibility on degenerative radiation risk (p. 29), and synergistic effects with other spaceflight factors including various oxygen levels (p. 32).

RISK OF RADIATION CARCINOGENESIS

As previously noted, the radiation environment in space consists of a mixed field of high-energy protons, heavy ions, electrons, and helium ions. Missions to the ISS and any planned establishment of a moon base or manned missions to other planets, including Mars, implies radiation exposure to the crew. A major concern to space agencies is the cancer risk to astronauts caused by high-energy particles including galactic cosmic rays and solar particle events.

Does the Evidence Report Provide Sufficient Evidence, as Well as Sufficient Risk Context, That the Risk Is of Concern for Long-Term Space Missions?

In addressing the risk of radiation carcinogenesis, the evidence report *Risk of Radiation Carcinogenesis* (Huff et al., 2016) provides documented evidence that radiation is a potential risk of concern for long-term space missions within the effective dose range identified in the report. Based on the Japanese atomic-bomb survivors and other epidemiological data, there is sufficient evidence showing increased cancer risk from low-LET radiation exposure at doses relevant to those experienced by crew members during long-term space missions. Although the majority of these data are from short-duration high dose-rate exposure, there is evidence from studies of occupational radiation workers exposed to protracted long-term low-dose radiation that indicates a

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similar risk per unit of radiation dose between the two exposure rates (Richardson et al., 2015). Similarly, the evidence report notes that based on limited epidemiological data for high-LET radiation and from extensive laboratory studies, there is evidence that the cancer risk will be higher for high-LET radiation. For low orbital missions such as those on board the ISS, the evidence based on actual dose measurement suggests a relatively low cancer risk, but at durations of about 18 months (females) or 24 months (male) astronauts will exceed permissible exposure limits (Cucinotta, 2014). However, there are uncertainties and disagreements on the cancer risk from low dose and low dose rate of mixed-field LET radiation such as those present in the space environment. The risks are projected to be higher for deep space missions (beyond Earth's magnetosphere) as a result of the abundance of HZE ions (Zeitlin, 2013).

Does the Evidence Report Provide Evidence That the Named Gaps Are the Most Critical Presented?

The evidence report is comprehensive in describing and well documenting the 15 gaps in knowledge that are outlined. Radiation carcinogenesis is a complex process including both genetic and epigenetic changes in the targeted cells as well as associated changes in the surrounding tissues that serve to promote the neoplastic process over a protracted period. The contribution of each of these steps may vary with tissue types, which gives each tumor its unique characteristics. The evidence report recognizes the multitude of modulating factors, both physical and biological, that can dictate the final tumor outcome from space radiation exposure. The listed gaps are well conceived and cover the major areas where more information is needed for a better understanding of the mechanistic basis of radiation carcinogenesis. Of major concern is the cancer risk of galactic cosmic rays for which there are insufficient data.

Are There Any Additional Gaps in Knowledge or Aspects to Existing Gaps That Are Not Addressed for This Specific Risk?

Additional gaps in knowledge to be considered include

- Approaches in converting cancer incidence data obtained using animal models at low doses and with dose rates realistic to human cancer risk estimates.

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- Development and validation of early surrogate endpoint(s) for radiation carcinogenesis. The evidence report suggests that chromosome aberrations could be such an endpoint. However, the description is short on specifics on how this can be accomplished and validated. For example, correlation studies could be conducted on the radiosensitivities of the two endpoints at all major cancer sites in either human or animals.
- At low-dose and low dose–rate exposure conditions relevant to the space environment, there are several phenomena, including non-targeted response and adaptive protection that are known to play a role in radiation response. The evidence report describes these observations but further assessment of their impact on cancer risk should be considered.

Does the Evidence Report Address Relevant Interactions Among Risks?

Relevant interactions are addressed. Many confounding factors—such as microgravity, physiological stress, altered sleep and circadian rhythms, changes in immune functions, nutritional status and smoking history—are listed under gaps in knowledge. However, not much is known about how these confounding factors interact with radiation either singly or in combination to affect cancer incidence. For example, the possible effects of microgravity and radiation on the immune system, which could affect many other physiological endpoints, cancer included, are not known. Finally, how radiation interacts with these confounding factors, whether positively or negatively, is not known and should be studied once relevant model systems are developed and with a better understanding of the mechanisms of high-LET radiation carcinogenesis.

What Is the Overall Readability and Quality?

The evidence report on risk of radiation carcinogenesis is well written, comprehensive, and clearly focused. It provides an up-to-date overview on the state of knowledge in the field of space radiation carcinogenesis. One small point that might be worth clarifying is in the text on the parameters (p. 6 of the evidence report). The committee suggests the following edit:

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The scaling of mortality rates for space radiation risks to astronauts to the Atomic bomb survivors introduces many uncertainties (Cucinotta et al., 2001; Cucinotta and Durante, 2006) into risk estimates, and there are important questions with regard to the correctness of any scaling approach because of qualitative differences in the biological effects of HZE ions and gamma-rays. The two correction factors scaling parameters with the largest degrees of uncertainty are the radiation quality factor, which estimates the increased effectiveness of HZE nuclei compared to x-rays or gamma-rays for the same dose, and the dose and dose-rate effectiveness factor (DDREF), which reduces estimates of cancer risk when the at high dose and dose-rates when the dose and dose-rate are low (< 0.05 Gy/hr).

Is the Breadth of the Cited Literature Sufficient?

Although the evidence report includes an extensive bibliography, encompassing both NASA and external academic investigators, consideration could be given to adding the article by Mathews and colleagues (2013). In addition, several sources were cited in the text but were missing in the reference list: Cheema, 2004; Bennett et al., 2007; Bouville et al., 2015.

Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk?

Is Input from Additional Disciplines Needed?

Based on the quality of the evidence report, the authors are a team of experts who cover the various aspects of the report. No additional input appears to be needed.

Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?

In large part, the answer is yes. However, the previous IOM report highlighted the need to address relevant interactions among risk factors. The current evidence report merely listed many of the potential confounding risk factors without a substantive discussion of the interactions. It is important to note that while addressing interactions among the risk factors is appropriate for well understood risks, it may be premature to

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have in-depth discussions on interactions for poorly understood risks such as carcinogenesis.

RISK OF ACUTE RADIATION SYNDROMES DUE TO SOLAR PARTICLE EVENTS

Acute radiation syndrome is the response to intense exposure to high doses of radiation over short time periods. It refers to the disturbance of physiological processes of various cellular groups damaged by radiation and expressed within hours to weeks of exposure. NASA's focus is on the prodromal phase, typically manifest within the first 48 hours to 6 days after exposure. Symptoms include nausea, vomiting, anorexia, and fatigue.

The threshold for minimal hematopoietic effects, or mild prodromal, in the most at-risk populations is approximately 0.1 to 0.2 Gray (or 10 to 20 radiation absorbed dose [rad] in older units) (Carnell et al., 2016; HHS, 2016). Significant effects from acute radiation syndrome would most likely be induced by high doses (more than a Gray) of radiation from highly energetic particles produced by a solar storm (a solar particle event, or SPE). Solar particle events are intense periods of high rates of largely protons with energy between tens to a few hundreds of million electron volts (or megaelectron volts [MeV]). They last from a few hours to several days, with the possibility of recurring events prolonging the high exposure to a week or more. The probability of occurrence varies with the degree of solar activity, which in turn varies over a solar cycle of ten to twelve years. The intensity of a given event also varies significantly from one event to the next, with only a low probability of an event with significant intensity to cause substantial exposure (one to two per solar cycle).

An astronaut in a spacesuit could be exposed to a significant dose of radiation within a few hours of event onset during a modest to severe SPE. Relatively modest shielding, as would be provided by a nominal habitat or spacecraft, could substantially reduce SPE exposure to astronauts. Access to such shelter, along with an adequate alert and warning system, could mitigate the risk from all but the most powerful SPEs.

The committee reviewed the evidence report *Risk of Acute Radiation Syndromes Due to Solar Particle Events* (Carnell et al., 2016). The evidence report provides a thorough summary of the risk posed by acute radiation syndrome in response to a significant SPE. The report contains

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a review of the relevant data on SPEs from over the past 50 to 60 years, including distribution of occurrence, intensity, and duration. A summary of how these observations are compiled in a model of SPE intensity and event probability is also provided in the evidence book.

The discussion of acute radiation syndrome is based on extensive data on acute radiation response from a wide range of historic events, including exposure to atomic radiation following the use of atomic bombs in Hiroshima and Nagasaki, Japan; accidents at nuclear power plants, including Chernobyl, Ukraine, in 1986; and the 1999 criticality accident at the Tokai-mura, Japan, fuel cycle facility. The report also references scientific literature on medical exposures and research conducted within NASA's Space Biology Radiation Research Program.

**Does the Evidence Report Provide Sufficient Evidence,
as Well as Sufficient Risk Context, That the Risk Is of Concern
for Long-Term Space Missions?**

Possible acute effects from radiation exposure have been a concern to NASA since the Apollo program, and extensive research on the possibility of acute effects has been underway since the early 1960s, building on military concerns of radiation exposure in the tactical nuclear battlefield. Overall the report is a thorough documentation of the risk of acute effects of radiation exposure from SPEs. The fact that acute effects are a concern is well documented in the evidence report, which references studies of terrestrial radiation exposures including historical, medical, and laboratory studies.

Serious (life-threatening) prodromal events could occur under unusual (i.e., unlikely, but possible) space weather conditions, particularly during a spacewalk or surface excursion when rapid access to shielding would not be possible (e.g., if an astronaut or an extravehicular activity [EVA] vehicle was disabled). Preventing serious prodromal effects may be largely an operational issue, requiring adequate monitoring, warning, access to shelter, or other mitigation options.

Operational risk reduction could be enhanced with a better understanding of dose-latency, dose-response, and dose-rate dependence. In addition, better understanding is needed of the mechanism inducing prodromal effects, to help define where dose limits should be measured. The development of practical pharmaceutical countermeasures could also improve risk management, but such countermeasures would have to be shown to be effective in the operational space environment over time

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frames consistent with mission duration (up to 3 years). If approval by the U.S. Food and Drug Administration is needed for medications to ensure efficacy, the path to implementation may have additional complexity and longer development time. Finally, it will be essential to develop adequate radiation monitors appropriate for habitats, vehicles, and individual astronauts.

Does the Evidence Report Provide Evidence That the Named Gaps Are the Most Critical Presented?

The report provides evidence that acute risks are possible. The gaps are listed at the end of the report and are relevant. However, there is no accompanying justification that the gaps presented are the most critical (or even comprise a complete set of gaps).

Are There Any Additional Gaps in Knowledge or Aspects to Existing Gaps That Are Not Addressed for This Specific Risk?

While the threat posed by acute radiation syndrome is clear, many critical gaps in knowledge remain to be answered before there is enough evidence-based understanding of the risk of acute radiation exposure to implement successful countermeasures.

Several critical gaps exist in the risk assessment for prodromal effects. Gap 2 noted in the evidence report states: “What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict acute radiation risks in astronauts? How can human epidemiology data best support these procedures or models?” (Carnell et al., p. 49). Data for humans are based almost entirely on high dose-rate exposures, while the appropriateness of animal models is questionable. Where data are available, there are uncertainties in dose response, dose rate effects, dose latency and the relationship of these three factors. In addition, the role of additional stressors (chronic GCR, microgravity, infection, etc.) on acute radiation effects is not known.

Gap 5 (What are the optimal SPE alert and dosimetry technologies?) is listed as closed, with the explanation, “Technology maturation transferred to Advanced Exploration Systems” (Carnell et al., 2016, p. 49). But optimal dosimetry assumes an understanding of what aspects of the radiation environment are most effective at inducing acute radiation syn-

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drome (what should be measured and where from a biological efficacy perspective, particularly in regards to personal dosimeters). SPE alert and dosimetry are assumed to start with the onset of an SPE. There is no discussion of the knowledge gaps in forecasting SPEs, regarding either the physics of SPE generation or the necessary observational strategy to meet operational requirements.

Similarly, Gap 6 (What are the most effective shielding approaches to mitigate acute radiation risks, how do we know, and implement?) also assumes an understanding of what aspects of the radiation environment are most effective at inducing acute radiation syndrome. It may be adequate to say that shielding for a habitat to reduce the radiation environment below a certain threshold for a given event size is understood. However, it may be helpful to broaden the text of the gap to ensure that it covers optimal shielding of light-weight vehicles or for space suits, as well as other options.

Gap 7 asks: “What are the most effective biomedical or dietary countermeasures to mitigate acute radiation risks?” In spite of the extensive table addressing pharmaceutical countermeasures (13 pages long), the state of understanding of a pharmaceutical response to acute exposure for space-based applications is not clear. Practical agents still need development. Will those agents being developed for use against high-dose and largely gamma radiation or other low LET sources of injury be appropriate for use in acute radiation syndrome that is caused by high-dose, highly ionizing particles? The storage, use, and potential side effects of promising pharmaceuticals in an operational space environment also need to be considered.

Gap 8 asks: “How can probabilistic risk assessment be applied to SPE risk evaluations for EVA, and combined EVA+IVA [intravehicular activity] exposures?” However, there is no discussion of the need to identify a reasonable “worst-case” or “what-if” scenario and its impact during various phases of a mission. Instead, there is an over reliance on the statistical models averaged over several solar cycles to “demonstrate” that a large SPE is unlikely. There have been recent studies of extreme space weather events that could contribute to development of a worst-case/what-if scenario. For example, a 2012 National Research Council report notes:

Eventual movement to a total-system cancer risk model would require the development of scenario sets that include not only the quantification of the health effects but the details of the dynam-

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ics of the radiation source term and consideration of the “what can go wrong” scenarios associated with specific missions. Examples of such scenarios are unexpected solar particle events and a failure of radiation protection systems. (NRC, 2012, p. 47)

Such considerations are even more important when applied to the risk of acute effects.

The impact of prior radiation exposure on the healing of existing skin wounds or abrasions needs to be considered, as spacesuits can be very hard on the skin, and sufficient injury may make it difficult for an astronaut to participate in EVA or other surface excursions.

Finally, Gap 4, “What are the probabilities of hereditary, fertility, and sterility effects from space radiation?” is listed as “on hold pending evidence of risk at space relevant exposures” (Carnell et al., 2016, p. 49). First, it is not clear how this risk fits into the category of acute effects; fertility and sterility impacts may be more closely related to other degenerative tissue effects. However, it would appear that a lack of understanding of the risk is in itself a gap, and it is inappropriate to set it aside. For acute radiation syndrome in particular, it is important to address how individual susceptibility including hereditary pre-disposition alters an individual’s risk. Does individual susceptibility modify possible threshold doses for these risks in a significant way? Can genomics and epigenomics be included in assessing risks?

Does the Evidence Report Address Relevant Interactions Among Risks?

The report superficially addresses relevant interactions among risks. Acute Gap 1 notes: “Determine the dose response for acute effects induced by SPE-like radiation, including synergistic effects (focusing on effects that are evident at space-relevant doses) arising from other space-flight factors (microgravity, stress, immune status, bone loss, etc.) that modify and/or enhance the biological response.” These are significant potential issues which are not discussed in detail elsewhere in the report.

There is likely to be a continuum of radiation effects and interactions that could be manifest during a mission, including effects from acute radiation syndrome, central nervous system effects, and degenerative tissue effects, each of which is treated by a separate evidence book. A more focused effort in each of these evidence reports (Carnell et al., 2016; Huff et al., 2016; Nelson et al., 2016; Patel et al., 2016) to discuss the

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overlap and cross reference as appropriate is needed. Additionally, there should be a corresponding recognition or discussion of the relationship of mission-limiting radiation effects to the longer term (life-time) risk of radiation-induced cancer or other degenerative diseases (cardiovascular and CNS).

There may also be relationships between radiation effects and other spaceflight risks, particularly in the area of behavioral impacts in response to possible CNS effects. As noted above, greater cross-referencing among the radiation-focused evidence reports would be helpful.

What Is the Overall Readability and Quality?

The report's readability is good, and the committee provides a few suggested improvements. This evidence report provides a thorough articulation of the effects, however because it is one of four evidence books addressing radiation effects, there is overlap among reports and more cross-referencing would be an enhancement. For example, the discussion of NASA's permissible limits provides details on short-term and career limits for non-cancer effects, without putting them in the context of career limits for cancer. In addition, the short-term limits go beyond acute effects, and include limits intended to reduce risks to the circulatory system, central nervous system, and the lens of the eye. Several lengthy tables address the potential pharmaceutical countermeasures (13 pages long). However, it is not clear that this set of tables is the best way to communicate the state of understanding of a pharmaceutical response to acute exposure. The readability could also be improved by integrating the gaps into the text.

Is the Breadth of the Cited Literature Sufficient?

The evidence report includes extensive references and citations that cover the full range of concerns. However, the references do not include more recent research on the mechanisms for acute radiation effects or on recent studies of extreme space weather. For recent studies of acute radiation syndrome, see, for example, Dörr et al., 2014, and MacVittie et al., 2015. For recent reviews relevant to solar particle events see Lee et al., 2012; Baker et al., 2013; and Desai and Giacalone, 2016.

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**Is the Expertise of the Authors Sufficient to Fully Cover
the Scope of the Given Risk?
Is Input from Additional Disciplines Needed?**

The expertise of the authors is sufficient, but the report would benefit from additional perspectives. In particular, it would be helpful to include individuals more closely associated with research on the biological foundation of acute radiation effects; familiar with genetic and epigenetic contributions to susceptibility; and active in research on the physics of solar particle events.

The report largely addresses the range of disciplines that contribute to acute radiation effects. It could be improved by including input from genetic and epigenetic contributions to acute radiation susceptibility.

**Has the Evidence Report Addressed Previous Recommendations
Made by the IOM in the 2008 Letter Report?**

This evidence book meets the general recommendations of that review.

**RISK OF ACUTE AND LATE CENTRAL NERVOUS SYSTEM
EFFECTS FROM RADIATION EXPOSURE**

**Does the Evidence Report Provide Sufficient Evidence,
as Well as Sufficient Risk Context, That the Risk Is of Concern
for Long-Term Space Missions?**

This report, *Risk of Acute and Late Central Nervous System Effects from Radiation Exposure* (Nelson et al., 2016), does an admirable job of summarizing the evidence and risk context for both acute and chronic CNS effects from radiation. It describes in detail the evidence gained from work in cell culture and animal models that suggests a number of important alterations in neuronal and glial structure and CNS function that could create significant risks and decrements in performance for human crew members during exploration missions. The case for long-term cognitive deficits is also well presented. There is a dearth of human epidemiologic data, and information from the clinical arena generally involves much higher doses of radiation than anticipated during any projected space mission. Thus, assessment of this risk relies very heavily on the fidelity of the animal models used for modeling human responses.

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Even though these models and in vitro experiments yield a wealth of relevant data, there has been a significant lack of research conducted using non-human primates—perhaps the animal model best suited for assessing CNS effects and associated cognitive defects in humans.

Does the Evidence Report Provide Evidence That the Named Gaps Are the Most Critical Presented?

The long list of gaps is provided toward the end of this report. It would be useful to introduce the gaps near the beginning of the report to frame the reader's attention on the relevant gaps, as the evidence base is discussed in detail. The gaps listed are all justified as significant from the evidence presented. These gaps build directly and logically from observations in rodents regarding the effect on CNS integrity and function, and it is reasonable to presume that these effects will be of high relevance to human crew member health and in-flight performance. Due to the number of gaps, it might be useful to indicate those considered most critical in terms of frequency or severity of impairment, based on the best current understanding of those cognitive/structural changes after radiation exposure.

Are There Any Additional Gaps in Knowledge or Aspects to Existing Gaps That Are Not Addressed for This Specific Risk?

The functional cognitive impact of radiation in animal models raises concern about its impact on other aspects of CNS function, such as vestibular control (perhaps causing an increased susceptibility to space sickness), spatial perception, and hand-eye coordination. Unfortunately, rodent cognitive and motor function tests assess only gross motor skills. Another challenge in assessing additive or synergistic effects is the clear possibility that other stressors (e.g., sleep loss or circadian disruption) could mask smaller effects due to radiation exposure. Sufficient data to allow RBEs for these outcomes do not currently exist. The link between inflammation and CNS damage is well discussed, but one clear gap in our current knowledge base not mentioned in this report is whether endurance exercise (given its generally salutary impact on both inflammation and cognitive function) might be an effective countermeasure for the impact of radiation on the CNS.

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Does the Evidence Report Address Relevant Interactions Among Risks?

The report acknowledges the potential for interactions and notes that there are virtually no data on the impact of those interactions on CNS structure and function. These interactions seem quite likely, given that other space hazards (microgravity, isolation, closed environment) can independently contribute to psychological and physical stress. For example, might radiation impact the CNS by increasing susceptibility to depression during long-duration missions? In addition, sleep deficiency and disrupted circadian rhythms, hypercapnea, cephalic fluid shifts, altered nutrition intake, and perhaps even the high G-forces of launch can also impact the CNS (Nelson et al., 2016, p. 48). Because so many factors can affect CNS function acutely and might lead to early cognitive decline in retired astronauts, it might be reasonable to reword this risk as, “Acute and Late CNS Effects from Space Radiation and Other Elements in the Spaceflight Environment.”

What Is the Overall Readability and Quality?

The logical flow of this evidence report is good, and the report is well written. Some of the research review sections are quite detailed and will be most accessible to those who are expert in the discipline, though the writing is clear enough for the non-expert to appreciate the key points.

Is the Breadth of the Cited Literature Sufficient?

This is a well-documented report with an extensive reference list that includes a significant proportion of cited works published since 2008 (the date of the last IOM report on this risk).

Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk? Is Input from Additional Disciplines Needed?

The expertise of this writing team on the biological impacts of radiation exposure is excellent. Input from a behavioral specialist might be useful in future reports, given the possibility of radiation-induced CNS alterations' impact on behavior and psychological status.

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Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?

No specific recommendations were made in the 2008 Letter Report beyond highlighting the apparent need for a greatly expanded research program in this area. The many journal articles and research reports published since 2008 and cited in this evidence report (14-page bibliography) are evidence that this is an active area of research.

RISK OF ADVERSE COGNITIVE OR BEHAVIORAL CONDITIONS AND PSYCHIATRIC DISORDERS

The evidence report *Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders* (Slack et al., 2016) provides a broad overview of the evidence about the neuropsychiatric and psychological risks associated with long-duration and exploration spaceflight. The document extensively reviews the available literature relevant to the topic, which comes from analog environments and some of which is anecdotal. As an overall assessment, the report, for the most part, limits its interpretation of risk to those adverse conditions that have been seen during or in close temporal approximation to spaceflight missions. A rigorous evaluation of the long-term health effects of space travel on behavioral health is a goal, but little evidence exists so far about adverse mental health conditions that may have occurred months or years after a particular mission. Any available anecdotal descriptions of long-term impacts would be useful as a starting point, if available. The report also does not include a description of the risks and potential benefits of the use of psychotropic medication during missions. The committee's response to the key review questions are summarized below.

Does the Evidence Report Provide Sufficient Evidence, as Well as Sufficient Risk Context, That the Risk Is of Concern for Long-Term Space Missions?

The evidence report, which notes that most reports of behavioral health problems are either anecdotal, based on analog samples, or extrapolated from subclinical risks, clearly indicates that the risk is of concern for long-term space missions (e.g., to Mars, which would last approximately 3 years).

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The evidence report, however, does not mention situations where astronauts have had serious mental health problems later in their lives. Knowledge of these anecdotal data provides additional and important risk context. Consideration should be given to either adding a new gap or reformulating an existing gap to address the need to conduct surveillance on behavioral health of astronauts longitudinally and to view these risks from a career-long and lifelong perspective. The BMed9 gap now deals with post-mission behavioral health, and the need for longitudinal surveillance could be added there.

The utility of “resilience enhancing” programs is somewhat controversial, at least to the extent to which these have been studied in other contexts (e.g., military personnel). The report refers to such programs often, but does not provide a critical review of the evidence (if available) underlying their efficacy and safety.

Countermeasures are often measured in the report as if they are generic. They should be tied to the specific risks that are they intended to mitigate.

Does the Evidence Report Provide Evidence That the Named Gaps Are the Most Critical Presented?

The named gaps are extensive. Given the uncertainty about behavioral and cognitive effects of long-term exploration space missions, these gaps can all be considered critical.

Are There Any Additional Gaps in Knowledge or Aspects to Existing Gaps That Are Not Addressed for This Specific Risk?

As noted above, there is an under-emphasis—nearly a complete lack of discussion—of the possibility that psychotropic medications could be usefully administered during exploration-class space missions. The need to better determine under what circumstances they would be useful and a plan for how psychotropic medications could be administered and monitored, are gaps that are not addressed. Moreover, the distinct possible uses (and possible adverse effects) of various classes of psychotropic drugs (stimulants, hypnotics, anxiolytics, antipsychotics) are not discussed in the report.

The report highlights the fact that underreporting of behavioral health problems by astronauts is probably extensive. Underreporting may

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also extend to other health issues. The BMed 2 gap listed in the evidence report refers to the need to “identify and validate measures of behavioral health” (Slack et al., 2016, p. 14). It should probably be stipulated that such measures will necessitate striking a balance between individual privacy and operational mission needs. How to do this is not currently known and consideration should be given to adding this as a gap to BMed 2 or as a new gap in methodology. Knowing the extent of the potential risk of underreporting and how to deal with it while balancing individual and operational needs could be considered an unaddressed, new behavioral health risk.

The issue of remote communication with family, mental health professionals, and operational mission control over a long-duration mission is mentioned but insufficiently discussed and contextualized. The impossibility of real-time communication on a Mars mission could, and probably should, be identified as a specific and important knowledge gap.

Consideration should also be given to incorporation in the report of an overview of the current state of knowledge with respect to genetic or epigenetic influences on behavioral health.

Does the Evidence Report Address Relevant Interactions Among Risks?

Relevant interactions among risks are discussed to some extent, but there are some noteworthy missing elements. The interaction with radiation exposure risk is the best developed (although there is limited mention of potential impact of radiation exposure on cognitive function), as is the interaction between depression and sleep/circadian disturbance.

The interactions of the risks discussed in this evidence report with the risks discussed in the report on teams (Landon et al., 2016; see the next section of this report) are not adequately addressed. For example, how will a better understanding of the risks described in the teams evidence report help with identification and management of mental health problems in members of the team? Additionally, the issue of how trust is engendered is not discussed in this report (although it is discussed extensively in the evidence report on teams and could be cross-referenced).

What Is the Overall Readability and Quality?

The evidence report is well organized, readable, and generally of high quality.

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Is the Breadth of the Cited Literature Sufficient?

For the topics directly covered in this evidence report, the cited references were comprehensive. However, it is likely that the narrative and supporting references will need to be expanded to adequately address the above-mentioned knowledge gaps, particularly in the areas of longer term evidence of behavioral health problems (which may require a search beyond the traditional scientific literature sources, as some astronauts have written or talked about such problems in the popular press or in books), and in the use of psychotropic medications.

Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk? Is Input from Additional Disciplines Needed?

In general the expertise of the authors is sufficient to cover the scope of the risks detailed in the report. But in areas where there are gaps—notably in the possible uses of and risks associated with particular psychotropic medications—it is likely that additional input from psychiatrists and/or psychopharmacologists is warranted.

Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?

The current report addresses several issues that were raised in the 2008 IOM report, and one of the topics remains to be added. A discussion of the predictors and contributing factors has been added as recommended. Additionally, the 2008 report noted that “the extensive list of current countermeasures is tied neither to the published evidence base of psychological interventions nor to measures of effectiveness. A systematic evaluation of current and proposed countermeasures should be included in future iterations of the evidence book” (p. 9). This has been done in the current iteration. The section on countermeasures in the current evidence report is well referenced and responsive to the 2008 recommendations.

The 2008 report pointed to several issues that remain knowledge gaps and challenges in addressing this risk:

Behavioral and psychiatric problems have been viewed as operational medical issues that are held confidential, rather than as a health-related research agenda that deserves co-equal status with

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somatic health issues. The committee believes the potential seriousness of the psychological and behavioral health risks highlights the need for the evidence book to contain a review and any relevant data, including an analysis of newer instruments and scales for evaluating more subtle personality differences. Including this information will also point to potential associated research gaps. (p. 9)

The committee urges a continued commitment to clarifying the knowledge gaps and summarizing data on the behavioral health risks and the tools used in the evaluation of these risks.

**RISK OF PERFORMANCE AND BEHAVIORAL HEALTH
DECREMENTS DUE TO INADEQUATE COOPERATION,
COORDINATION, COMMUNICATION, AND PSYCHOSOCIAL
ADAPTATION WITHIN A TEAM**

The report focused on team-related issues, *Risk of Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication, and Psychosocial Adaptation within a Team* (Landon et al., 2016) is a relatively new risk to NASA's pathway to risk reduction (see Figure 1). This risk differs from the others discussed in the evidence reports in that it addresses team performance first; health is a secondary consideration. Research in this area does not mitigate typical human risks to human health; rather, it is focused on improving team functioning to optimize the performance of astronaut crews. Development of this risk area is consistent with the IOM's review of the Bioastronautics Roadmap, which recommended that "the Astronaut Office and representative flight surgeons be consulted regarding the crew selection process in order to place greater emphasis on the roles of crew compatibility and team performance in overall mission success" (IOM, 2006, p. 11). The risk was developed from the findings of an external review of space-flight medical operations conducted by NASA's Astronaut Health Care System Review Committee, and first appeared in the 2008 version of the evidence report as "Performance Errors Due to Poor Team Cohesion and Performance, Inadequate Selection/Team Composition, Inadequate Training, and Poor Psychosocial Adaptation" (IOM, 2008).

Research engendered by the Team risk represents a significant departure from earlier approaches to psychosocial development and function-

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ing of astronaut crews. Rather than promoting the historical approach based on a “select out” philosophy, Team emphasizes a “select in” approach that seeks to optimize crew performance beginning with astronaut selection.

The work on the Team risk is overseen by the Behavioral Health and Performance element of NASA's Human Research Program. At the time of review, eight research gaps were identified (see Box 2). They are numbered non-consecutively because one risk (Team Gap 7) was removed when it was deemed to be adequately mitigated.

BOX 2

Research Gaps Identified in the Team Report

Team Gap 1:

We need to understand the key threats, indicators, and evolution of the team throughout its life cycle for autonomous, long duration and/or distance exploration missions.

Team Gap 2:

We need to identify a set of validated measures, based on the key indicators of team function, to effectively monitor and measure team health and performance fluctuations during autonomous, long duration and/or distance exploration missions.

Team Gap 3:

We need to identify a set of countermeasures to support team function for all phases of autonomous, long duration and/or distance exploration missions.

Team Gap 4:

We need to identify psychological measures that can be used to select individuals most likely to maintain team function for autonomous, long duration and/or distance exploration missions.

Team Gap 5:

We need to identify validated ground-based training methods that can be both preparatory and continuing to maintain team function in autonomous, long duration, and/or distance exploration missions.

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Team Gap 6:

We need to identify methods to support and enable multiple distributed teams to manage shifting levels of autonomy during long duration and/or distance exploration missions.

Team Gap 8:

We need to identify psychological and psychosocial factors, measures, and combinations thereof that can be used to compose highly effective crews for autonomous, long duration and/or distance exploration missions.

Team Gap 9:

We need to identify spaceflight acceptable thresholds (or ranges) of team function, based on key indicators, for autonomous, long duration and/or distance exploration missions.

SOURCE: Landon et al., 2016, pp. 58–59.

This review considers the input from the committee and two expert reviewers who presented their analysis of the report at the workshop (see Appendix A). Additional insights offered by the Chief of the Astronaut Office at the committee's August web conference meeting (see Appendix A) helped refine the committee's views.

**Does the Evidence Report Provide Sufficient Evidence,
as Well as Sufficient Risk Context, That the Risk Is of Concern
for Long-Term Space Missions?**

This evidence report is an impressive compilation of the evidence from studies conducted in environments that are analogs to the space environment as well as from studies that are relevant to the basic issues of teamwork and team functioning. Research in this area is challenging because of the difficulty to quantify effects on teams, the small sample size, and the potential biases of team members, which might tend to minimize self-reporting. Nevertheless, the authors have done a remarkable job of synthesizing published data and reports from analog experiences such as Antarctic winter-overs. The evidence report identifies specific examples where weak team performance has affected spaceflight operations and where team functioning has been the focus of training for spaceflight operations. Astronaut journals of long-duration flyers reveal incidents of team disruption and interpersonal friction (Stuster, 2010). Strategies to improve team function include teamwork observation during astronaut

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selection and spaceflight resource management training for astronauts. Furthermore, the effectiveness of team dimensional training has been demonstrated for flight controllers.

Does the Evidence Report Provide Evidence That the Named Gaps Are the Most Critical Presented?

The authors appropriately assert that this risk addresses team performance, rather than crew health. Thus, the critical issue is team functioning; unfortunately, no validated measures of team function in isolated and confined environments exist. This gap is a focus of the ground-based research program.

The evidence report introduces the concept of a team life cycle; however, it is discussed only tangentially. This will be an important concept as teams function more autonomously at a greater distance from earth. The need is appropriately codified in a gap that seeks to identify a set of countermeasures to support team function for all phases of autonomous, long-duration and/or distance exploration missions.

Similarly, Gap 4 identifies the need for psychological measures that can be used to select individuals most likely to maintain team function on these types of exploration missions. The gap is well-framed to focus on crew selection, rather than astronaut selection. However, it is unlikely that such tools can be validated for all phases of an exploration-class mission, particularly when teams will develop greater amounts of trust and function over the course of mission training and execution. Workshop presenters noted the importance of tools such as team dynamics training, which can help improve team functioning even when the initial composition of the team is less than optimal.

The Team Gap 6 identifies the need to support and enable multiple distributed teams to manage shifting levels of autonomy during long-duration and/or distance exploration missions. This is likely to be an important gap during planetary missions; autonomy will need to increase as communication lags with increasing distance from Earth. The effects of greater independence on team functioning is likely to impact flight control teams and crews differently. Thus, this gap might be better addressed by decomposing it with separate foci written from the perspectives of the flight team, the ground team, and flight-ground interactions.

Similarly, the Team composition gap (Team 8) is quite vast and could be parsed. Like the rest of the gaps, it is written with a focus on flight teams; however, space missions operate as “teams of teams” that

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include, but are not limited to, flight crews, NASA Mission Control Center, NASA flight control teams, other (non-NASA) flight control organizations and flight control teams, other space agencies, etc. The gap could be rewritten to say, “We need better tools to compose long distance/exploration mission teams, balancing personalities, technical skills and other individual differences such as gender and nationality.”

**Are There Any Additional Gaps in Knowledge
or Aspects to Existing Gaps That Are Not Addressed for This
Specific Risk?**

The evidence report provides only limited consideration of individual support structures that exist outside the team (e.g., family and friends). The quality and quantity of these valuable exchanges is likely to erode as the distance from Earth increases. The committee believes that the evidence report could be improved by highlighting the linkages between individual performance and well-being and team performance and well-being.

How will cognition be shared among a network of teams (e.g., crew, mission control) as both teams become more autonomous during a long-duration mission? This gap is not well addressed, but there are probably appropriate analogs in polar exploration and remote military operations.

The Astronaut Journals project (Stuster, 2010, 2016) suggests that communication styles within crews and between crew and ground are quite different. This issue is likely to be magnified as communication lags grow. It is even conceivable that the composition of a flight control team could change considerably over the course of a 3-year mission to Mars. This observation recapitulates the point that team training may be of greater importance to team performance than team selection.

**Does the Evidence Report Address Relevant Interactions
Among Risks?**

This report clearly identifies interactions with the issues discussed in a number of the evidence reports on radiation, sleep, and biomedical risks. Missing is a likely interaction with the evidence report *Risk of Inadequate Critical Task Design* (Sandor et al., 2013). This interaction derives from operational experience that underspecified and mis-specified elements of critical tasks that involve multiple crew members incur a penalty of additional communication and unanticipated problem solving

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that impact overall team performance. Finally, coverage of the effects of emergent behavior problems on team functioning is lacking as is a discussion of the consequences of poor team performance and potential interactions with the cognitive and behavioral health risks discussed by Slack and colleagues (2016).

What Is the Overall Readability and Quality?

The overall readability and quality is very high. The authors are to be commended for their work.

Is the Breadth of the Cited Literature Sufficient?

The authors have provided an extensive review. The breadth of the cited literature is excellent.

Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk?

Is Input from Additional Disciplines Needed?

The authors are very experienced in this area. Additional input from discipline experts may be necessary when considering interactions among risks (e.g., sleep, radiation).

Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?

The 2008 report raised concerns about the overall readability of the report. These issues have been addressed completely in this revision. Again, the authors should be commended for an excellent revision. The 2008 review also made note that the issue of leadership is absent, including the interaction between leadership style and situational demands on the impact on a mission. This deficit has been addressed completely in the revised report, with an extensive discussion of leadership styles. Furthermore, the current report (Landon et al., 2016) incorporates the concept of situational followership—a skill that will likely be necessary as the phases of flight shift from launch/landing to transit to planetary exploration.

Not all aspects of the 2008 review have been addressed. The previous report stated that

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additional attention should also be given to the definition of teams and of cohesiveness, including potential impacts of the broader “mission team” that includes both astronauts and Earth-based support staff. A potential consideration is the distinction between group cohesion and individual morale and how personality, demographic, and situational variables influence the manner in which emotional reactions may affect the individual’s and the crew’s performance. (IOM, 2008, p. 65)

Although considerable progress has been made in team training and evaluation of ground personnel, interactions among teams and their shifting levels of authority and autonomy during exploration class missions has not been fully addressed.

RISK OF PERFORMANCE DECREMENTS AND ADVERSE HEALTH OUTCOMES RESULTING FROM SLEEP LOSS, CIRCADIAN DESYNCHRONIZATION, AND WORK OVERLOAD

The Behavioral Health and Performance element in NASA’s Human Research Program aims to further characterize the risk of performance decrements and adverse health outcomes resulting from sleep loss, circadian desynchronization, and work overload, which occur for ground and flight crews both before and during long distance and exploration spaceflight missions, in preparation for exploration missions beyond low earth orbit, including to Mars. Ground evidence indicates such risk factors may lead to performance decrements and adverse health outcomes, which could potentially compromise mission objectives.

Operationally relevant monitoring technologies that detect sleep quantity and quality and circadian rhythms as well as individualized countermeasures that prevent or mitigate the risk in long-duration isolated environments will prepare crews for optimal behavioral health and performance. Focused laboratory and ground analog studies as well as spaceflight studies can provide valuable insights into developing these technologies and countermeasures. Identification of the environmental and mission conditions that interfere with sleep and circadian alignment—as well as individual differences in vulnerability and resiliency to sleep loss and circadian desynchronization—are needed.

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The committee provides the following assessment of the NASA evidence report *Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload* (Flynn-Evans et al., 2016). Specifically, this report highlights a collection of new evidence to better characterize the risk, and it also reveals new gaps in this risk, including the following topical areas: sleep loss, sleep inertia, circadian desynchrony, work overload, performance metrics, individual variability and sex differences, countermeasures, and biomathematical models.

**Does the Evidence Report Provide Sufficient Evidence,
as Well as Sufficient Risk Context, That the Risk Is of Concern
for Long-Term Space Missions?**

The evidence report is very clear and provides strong evidence and sufficient risk context that the risk of performance decrements resulting from sleep loss, circadian desynchronization, and work overload is of concern for long-term (long-duration) space missions.

However, by contrast, the evidence report lacks a discussion of the evidence and risk context for how the physiological and behavioral health outcomes resulting from sleep loss, circadian desynchronization, and work overload are of concern for long-duration space missions. Such information is noticeably absent from the report, despite sufficient evidence available in this domain. Additionally, a discussion is needed of how these outcomes are of concern for long-duration space missions as is a discussion of the impact of individual chronotypes (e.g., “owls” and “larks”) on performance and team work.

**Does the Evidence Report Provide Evidence That the Named Gaps
Are the Most Critical Presented?**

The evidence report provides clear and strong evidence that the named gaps are the most critical presented in terms of prioritization. Laboratory data, clinical trial data, aviation and military data, mathematical modeling data, analog data, case reports, and anecdotal evidence from spaceflight all provide compelling evidence for the gaps. Overall, the report is excellent in providing such evidence.

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**Are There Any Additional Gaps in Knowledge
or Aspects to Existing Gaps That Are Not Addressed for This
Specific Risk?**

The gaps noted in the sleep loss, circadian desynchronization, and work overload report cover a broad range of topic areas. However, the committee identified additional significant research gaps that are not adequately addressed or are not currently addressed in the evidence report and warrant inclusion by modification of current gaps or the creation of additional gaps:

- Understanding of the physical adverse health outcomes (e.g., cardiovascular disease, diabetes, hypertension) resulting from long-term, chronic sleep loss, circadian desynchronization, and work overload;
- Characterization of the effects of repeated recovery or reversibility from sleep loss on performance and physiological (central and peripheral) measures;
- Understanding of the effects of long-term chronic circadian desynchronization and sleep loss on performance and physiological (central and peripheral) measures, including team performance;
- Understanding of the effects of sleep loss and circadian desynchronization on fine motor performance (beyond cognitive performance) and gross motor performance including balance, walking, and other operational outcomes. Both of these domains would affect EVAs as well as day-to-day activities;
- Understanding of the effects of microgravity on central and peripheral circadian oscillators, and on sleep homeostasis and sleep quality; and
- Knowledge of the effects of diet and nutrition on circadian rhythms and on sleep and investigate the timing of food as a countermeasure.

**Does the Evidence Report Address Relevant Interactions
Among Risks?**

The report appropriately addresses many of the relevant interactions with the risks described in the other behavioral health and performance element evidence reports (e.g., Landon et al., 2016; Slack et al., 2016). However, additional interactions that should be considered for inclusion

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in this report are those focused on how sleep, circadian rhythms and individual differences affect team performance and how they affect psychosocial stress.

The report would also be strengthened by more explicit links and emphasis with other elements and their risks such as radiation, vestibular/sensorimotor, nutrition and diet, pain, immune, the microbiome, cardiovascular, and microgravity. Sleep loss and circadian desynchronization are known to affect each of these other areas, and a more complete description of these interactions is warranted. Moreover, it is important to address such interactions because countermeasures will undoubtedly affect other risks beyond those directly related to behavioral health and performance.

What Is the Overall Readability and Quality?

Overall, the readability and quality of this report is excellent. This report is understandable to a nontechnical audience and serves as a valuable resource. The appendixes, figures, and tables are particularly helpful for such an audience. The addition of categories of evidence is commendable; however, in a number of places throughout the report, the specific category of evidence is not listed when discussing studies and/or results. This missing information should be added so readers can accurately assess the quality of the evidence. In addition, the references are inconsistent in style and in some cases, incomplete.

Is the Breadth of the Cited Literature Sufficient?

The breadth of the cited literature is outstanding for the performance area, derived from laboratory and analog settings, the International Space Station, military and aviation settings, mathematical modeling scenarios, case reports and anecdotal evidence. A few sections would benefit from updating with the most relevant and recent literature for the performance area. These include the following: laboratory evaluations describing the impact of sleep loss on human alertness, performance and wellness (including emotion); individual differences in response to sleep loss (both phenotype and genotype studies); work overload; and sex differences in response to sleep loss, circadian desynchronization, and work overload.

An emphasis on adverse health consequences is noticeably absent. There is an abundance of epidemiological and laboratory studies that highlight sleep loss and/or circadian desynchronization and their rela-

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tionships with and/or effects on cardiovascular disease, diabetes, hypertension, cancer, etc. This is an important body of literature that readily and importantly ties to other risks and gaps.

In several places, references are needed for statements made in the text. Examples of places where references would be helpful include in descriptions of specific models (e.g., FAST model described on page 55) and in definitions of specific terms (e.g., circadian misalignment, page 9). Moreover, some references are not easily accessible (e.g., those in technical reports, conference papers or abstracts, etc.). To resolve this issue, weblinks could be added to the evidence reports.

Examples of references that could be added include Bodenmann et al., 2009; Kuna et al., 2012; Lo et al., 2012; Minkel et al., 2012; Rupp et al., 2013; Goel et al., 2014; Maire et al., 2014; Pellegrino et al., 2014; Reichert et al., 2014; Patanaik et al., 2015; and Satterfield et al., 2015.

**Is the Expertise of the Authors Sufficient to Fully Cover
the Scope of the Given Risk?
Is Input from Additional Disciplines Needed?**

The authors are knowledge-domain experts in performance, sleep loss, circadian desynchronization, and work overload. Indeed, the report appropriately contains some of the research from these experts. Two authors are NASA employees and two authors are extramural reviewers. A number of the earlier authors are also experts in the fields of sleep, performance, circadian rhythms, and lighting.

The addition of one or two authors to add the necessary sections on adverse health consequences, as recommended above, would strengthen the report.

**Has the Evidence Report Addressed Previous Recommendations
Made by the IOM in the 2008 Letter Report?**

Some recommendations made by the IOM in the 2008 Letter Report have been adopted. Specifically, these include the following recommendations:

- Peer-reviewed literature has been added when available.
- Quality-of-evidence criteria (Category I–IV data) have been added in most places throughout the report.

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- The consistency and organization of the discussion on identified research gaps has been improved.
- A link to a summary of the current state of knowledge regarding countermeasures and the plan to mitigate risk has been added.
- Relevant literature and knowledge bases from in-flight data, ISS data, and data from polar environments have been added.
- Relevant literature from the military (Army, Navy, etc.) and other government entities has been added.

By contrast, other recommendations made by the IOM in the 2008 report have not been implemented. Specifically, these recommendations focused on additional data and areas of emphasis:

- Evidence for sleep loss and motor functioning has not been added (the committee has added this as a missing gap, above).
- Data from the NASA Life Sciences Data Archive and Longitudinal Study of Astronauts' Health have not been added.
- Data from other space agencies such as the European Space Agency, Japan Aerospace Exploration Agency, Roscosmos State Corporation for Space Activities, etc. have not been added.
- More emphasis on potential post-flight and long-term health outcomes is needed.

RISK OF IMPAIRED CONTROL OF SPACECRAFT/ASSOCIATED SYSTEMS AND DECREASED MOBILITY DUE TO VESTIBULAR/SENSORIMOTOR ALTERATIONS ASSOCIATED WITH SPACE FLIGHT

NASA's Human Research Program has identified that vestibular and sensorimotor alterations during spaceflight can increase risks related to the control of the spacecraft and other systems, as well as impair mobility following spaceflight. In the evidence report focused on this risk (Bloomberg et al., 2016, p. 7), the risk is described as follows:

Given that there is an alteration in vestibular/sensorimotor function during and immediately following gravitational transitions manifested as changes in eye-head-hand control, postural and/or locomotor ability, gaze function, and perception, there is a possibility that crew will experience impaired control of the space-

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craft during landing or decreased mobility following a landing on a planetary surface (Earth or other) after long-duration space flight. These changes have not specifically been correlated with real time performance decrements. The risk of impairment is greatest during and soon after G-transitions when performance decrements may have high operational impact (landing, immediate egress following landing). The possible alterations in sensorimotor performance are of interest for Mars missions due to the prolonged microgravity exposure during transit followed by landing tasks. This risk must be better defined and documented and vestibular/sensorimotor changes must be correlated with performance issues.

This evidence report provides a comprehensive synthesis of the information supporting the existence of this risk. This information includes anecdotal reports of human performance, as well as data from experiments conducted during and following spaceflight. The evidence report also evaluates countermeasures for the effects of microgravity on the vestibular and somatomotor systems, the prospect of modeling the effects of spaceflight in these systems, and potential scenarios in which the risk could have detrimental effects during a mission. The report concludes with a listing of knowledge and mitigation gaps.

**Does the Evidence Report Provide Sufficient Evidence,
as Well as Sufficient Risk Context, That the Risk Is of Concern
for Long-Term Space Missions?**

The report very convincingly shows that this risk is a serious concern for long-term space missions. It thoroughly describes evidence demonstrating that exposure to microgravity affects the processing of vestibular and somatosensory signals by the central nervous system, resulting in disrupted spatial orientation perception and motor responses. In addition, the report provides context for how this risk may impact crewed space missions. In particular, the appendixes are excellent and provide extensive documentation on the potential impact of sensorimotor impairment on crew performance during prior space missions.

While quite thorough, the report has several gaps. The effects of spaceflight on the vestibular and somatosensory systems can vary among individuals (e.g., some astronauts are highly susceptible to space motion sickness, while others are not). When relevant data exist, the report could

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go further in elaborating on the variability in individual susceptibility, and how this might affect crew selection and countermeasure development.

The report tends to focus on transitions from microgravity to Earth gravity, while transitions from microgravity to Mars gravity may result in a potentially less severe deterioration in performance. This point was not effectively considered. Limited rehabilitative support will be available for astronauts on Mars, but such support may not be required to the same extent on a planet with gravity 0.38 times that on Earth.

The evidence report touched on, but did not thoroughly consider, whether data collected in hyper-gravity (i.e., greater than 1 Earth G) environments provide insights about sensorimotor performance and adaptation, and countermeasure development for the effects of microgravity. Although not directly applicable, recent investigations using hypergravity (e.g., Nooij and Bos, 2007; Nooij et al., 2008; Clark et al., 2015a,b) may provide relevant insights into adaptation to the hypogravity environments of the moon or Mars.

The committee also notes that some sections (e.g., Section IV.3.6.2) reference only conference abstracts or proceedings, making it difficult for the reader to consider the quality of the data and assess the conclusions that are made. As these studies (e.g., Bloomberg et al., 2015) are fundamental, the committee does not recommend removing the citations or these portions of the evidence review. Instead, once formal, peer-reviewed publications become available, they should be included within the report.

Does the Evidence Report Provide Evidence That the Named Gaps Are the Most Critical Presented?

Broadly, the evidence report synthesized the literature thoroughly to arrive at the named gaps. Most are well supported by evidence as being the most critical. However, the committee provides some suggestions for improvement of the discussion of the gaps.

Gap SM 2.1 (*Determine the changes in sensorimotor function over the course of a mission and during recovery after landing*) is quite broad and does not provide sufficient direction for the research program. In fact, the evidence report thoroughly covers the information obtained over the past 40 years, which in some cases is quite extensive, regarding sensorimotor function over the course of a mission and during recovery after landing (e.g., most of Section IV). The committee suggests the evidence in this area directly addresses many aspects of this gap. However, the

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evidence report properly and effectively outlines the knowledge gap as well as the potentially most severe impacts of sensorimotor alterations on crew performance during (1) long-duration missions and (2) landing and the immediate post-landing period. Recommendations for further research directions to assess the performance deficits and generate effective countermeasures for these deficits are lacking. In addition, there should be some discussion added regarding the issue of whether landing on the moon or Mars would result in the same lapses in performance as landing on Earth, and whether the same countermeasures and transitional rehabilitative support would be optimal across gravitational environments. Adding these specifics to the SM 2.1 gap would help provide additional direction to the research program.

Gap SM 2.2 (*Determine the effects of long-duration spaceflight on sensorimotor function over a crewmember's lifetime*) seems unsupported by the evidence provided in Section IV. The potential consequences of sensorimotor alterations during long-duration spaceflight are thoroughly reviewed. However, little to no evidence is provided that sensorimotor effects from spaceflight have clinically relevant impacts longer than approximately one month after a gravity transition and thus not likely over a crewmember's lifetime. Although prolonged and repeated exposure to space flight has been shown to have some positive effects on vestibular adaptation (e.g., veteran astronauts experience less space motion sickness than first-time astronauts), little to no evidence is provided suggesting that sensorimotor effects from spaceflight have deleterious impacts that last longer than approximately one month after a gravity transition. It seems highly unlikely that such impacts would persist over a crewmember's lifetime. The report should explore the potential for permanent deleterious changes in sensorimotor function following a prolonged period of exposure to microgravity.

Finally, Gap SM 2.8 (*Develop a sensorimotor countermeasure system integrated with current exercise modalities to mitigate performance decrements during and after space flight*) may be overly constrained. Table 2 (pp. 81–82) provides a rigorous and thorough summary of the potential countermeasures for the various aspects of sensorimotor impairment during and after space flight. A large number of potential countermeasures are listed, some (but not all) of which are integrated with current exercise modalities. However, several other potentially promising sensorimotor countermeasures—including preflight adaptation training, sensorimotor adaptability training, load suits, tactile spatial awareness system, and vestibular stochastic resonance—are either unintegrated with

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or would have to be complementary to current exercise modalities. Certainly it would be unreasonable to use all of these countermeasures during a mission, but there is little effort to discuss which combination of countermeasures would be most effective. The report should go further in describing research directions needed to evaluate the plethora of sensorimotor countermeasures that have been proposed, how they can be most effectively combined, and whether different individuals would benefit the most from distinct countermeasures. Artificial gravity, the only countermeasure system that is listed as addressing each aspect of sensorimotor impairment, is not integrated with current exercise modalities and in fact would likely involve a replacement or substantial modification to current exercise protocols. The committee suggests that focusing on the countermeasure systems that are integrated with current exercise modalities substantially shortchanges other measures that could also be effective in addressing the effects of spaceflight on sensorimotor performance.

**Are There Any Additional Gaps in Knowledge
or Aspects to Existing Gaps That Are Not Addressed for This
Specific Risk?**

With the caveats provided above, the listed gaps are the most important to address. However, the committee proposes the addition of two additional gaps. First, the potential utility of animal models in developing countermeasures for sensorimotor deficits resulting from spaceflight is discounted. Use of animal models, particularly nonhuman primates, has provided great insights into sensorimotor integration by the nervous system. Animal models could also be helpful to evaluate countermeasures for sensorimotor changes during spaceflight, but this is not adequately explored in the report.

Section VI provides a literature review of computer-based modeling and simulation. The evidence report does a fine job in reviewing this literature and demonstrating the importance of numerical modeling approaches to evaluate risks and countermeasures. However, in several places the evidence report notes that future research is required to address a specific limitation. Based upon the evidence report's documentation of this research sub-field, it may be warranted to include a knowledge gap specifically related to computer-based models of sensorimotor function.

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Does the Evidence Report Address Relevant Interactions Among Risks?

Many sections of the evidence report do not address potentially important interactions among risks (e.g., interactions with risks of radiation exposure, cardiovascular deconditioning and orthostatic intolerance, etc.). The report briefly mentions a number of indirect factors that could impact spatial orientation perception and motor performance during and following spaceflight. These factors include sleep deprivation, anxiety, and muscle degeneration. These factors should be considered more deliberately in the report as they relate to the evidence reports, *Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload* (Flynn-Evans et al., 2016) and *Risk of Impaired Performance Due to Reduced Muscle Mass, Strength, and Endurance* (Ploutz-Snyder et al., 2015).

In addition, most studies have independently considered the effects of proprioceptive and vestibular system alterations during spaceflight on spatial orientation perception and motor performance. There has been limited consideration of interactions between these effects. This limitation should be better discussed in the evidence report, which may also be considered a gap in knowledge.

What Is the Overall Readability and Quality?

The overall readability and quality of the report are very good. The cited literature is quite extensive, it is generally well synthesized, and the report is well organized. With the caveats raised above, the evidence report provides a comprehensive understanding of the current data.

Is the Breadth of the Cited Literature Sufficient?

The breadth of the cited literature is generally sufficient. As detailed above, the only suggestions are to include additional literature reviews and citations regarding the effects of hyper-gravity on sensorimotor function and adaptation, and to replace citations to conference proceedings with peer-reviewed publications when they become available, allowing the reader to more readily assess the quality of the evidence.

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**Is the Expertise of the Authors Sufficient to Fully Cover
the Scope of the Given Risk?
Is Input from Additional Disciplines Needed?**

The authors have sufficient expertise to cover the scope of the given risk. No additional input from other disciplines is needed.

**Has the Evidence Report Addressed Previous Recommendations
Made by the IOM in the 2008 Letter Report?**

The topic area of this report was not explicitly covered in 2008.

SUMMARY

This is the fourth of five letter reports that will review the series of NASA's evidence reports on human health risks. This letter report reviewed eight evidence reports and provided the committee's responses to the questions detailed in the statement of task. The evidence reports are quite thorough in their review of the evidence of spaceflight risks, although they vary in format and in the consistency and quality of the writing.

Many of these reports cover broad fields of research, and the committee appreciates the challenges in identifying and summarizing the most salient literature. Challenges also arise in finding the best way to highlight the interactions among risks. Overall, the reports do an adequate job of discussing the interactions among those risks that are most directly related, but they struggle with establishing the connections and interactions among risks that are more tangentially related. As noted, in the introduction to the first of the radiation-related reports, improved cross-referencing (and hyperlinks) between the radiation reports would be useful to the readers. Other examples of the need to improve discussions among the risks are in regards to factors that affect performance such as sleep deprivation and anxiety, sensorimotor function, and team functioning. Given that this is the fourth in a series of five planned reports, the committee has noted throughout its reports that conveying the information on the interactions across risk domains is one of the biggest challenges for the evidence reports. The set of evidence reports could benefit from a more systematic approach to considering interactions with other risks. NASA should consider adding a standardized section or table in each report that shows the relationship of the risk described in the re-

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port to all other risks, noting whether and how each is related to the main topic of the report.

In a number of the evidence reports, the focus is on the acute health outcomes that potentially could result from exposures and risks of space travel. Other than radiation carcinogenesis, not enough attention is paid to longer-term outcomes of space health risks (including adverse behavioral health outcomes and cardiovascular events). The committee urges a greater focus on outcomes that may not be evident until after the astronaut's space career. As with most risks, individual phenotypic variability in response and in some cases differences between male and female astronauts are to be anticipated. It can reasonably be expected that the phenotypic response to space flight stressors will vary among astronauts, due to genetic, epigenetic, and other differences and attention needs to be paid to these variations as relevant to each risk.

For many of the health risks reviewed in this report the committee noted the current lack of relevant animal models. The committee urges NASA to characterize the fidelity and utility of various animal models for the behavioral, sensorimotor, and radiation-related health risks discussed in this report.

The committee greatly appreciates the opportunity to review the evidence reports and applauds NASA's commitment to improving the quality of its reports. The evidence reports provide the basis for the work of NASA's Human Research Program, and the in-depth review that they provide will contribute to improving the health and performance of future astronauts and enhancing future human spaceflights endeavors.

Sincerely,

Carol E. H. Scott-Conner, *Chair*
Daniel R. Masys, *Vice Chair*
Committee to Review NASA's Evidence Reports
on Human Health Risks

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A

Meeting Agendas

AGENDA

2016 Committee to Review NASA's Evidence Reports on Human Health Risks

Tuesday, May 17, 2016

Web Conference Call – Open Session (12:00 – 1:00 p.m. Eastern)

OPEN SESSION

- 12:00 – 12:05 p.m.** **Welcome and Opening Remarks**
Carol Scott-Conner, Committee Chair
- 12:05 – 1:00 p.m.** **Official Committee Charge and Discussion of
First and Second Letter Reports**
*John Charles, Chief Scientist, Human Research
Program, NASA*
- Discussion of Statement of Task and 2016
Reports with the Committee**
*Facilitator: Carol Scott-Conner, Committee
Chair*
- 1:00 p.m.** **ADJOURN**

AGENDA

**2016 Committee to Review NASA's Evidence Reports
on Human Health Risks**

Monday, July 25

**Keck Center of the National Academies
500 Fifth Street, NW
Washington, DC
Keck 101**

OPEN SESSION

- 9:00 – 9:15 a.m.** **Welcome and Opening Remarks**
Carol Scott-Conner, Committee Chair
- 9:15 – 10:15 a.m.** **Panel 1: Risk of Radiation Carcinogenesis**
Facilitator: Tom Hei
- 9:15 – 9:45 Presentations
*Eleanor A. Blakely, Lawrence
Berkeley National
Laboratory*
*Michael Weil, Colorado State
University*
- 9:45 – 10:15 Discussion with the Committee
- 10:15 – 11:15 a.m.** **Panel 2: Risk of Acute Radiation Syndromes
Due to Solar Particle Events**
Facilitator: Ron Turner
- 10:15 – 10:45 Presentations
*Jackie Williams, University of
Rochester*
*John Moulder, Medical College
of Wisconsin*
- 10:45 – 11:15 Discussion with the Committee

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- 11:15 a.m. –
12:15 p.m.** **Panel 3: Risk of Acute and Late Central Nervous System Effects from Radiation Exposure**
Facilitator: Susan Bloomfield
- 11:15 – 11:45 Presentations
Xiao Mao, Loma Linda University
Catherine Davis-Takacs, Johns Hopkins University
- 11:45 – 12:15 Discussion with the Committee
- 12:15 – 1:15 p.m.** **Lunch — Keck Atrium**
- 1:15 – 2:15 p.m.** **Panel 4: Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure**
Facilitator: Susan Bailey
- 1:15 – 1:45 Presentations
Marjan Boerma, University of Arkansas (via WebEx)
Dennis Kucik, University of Alabama at Birmingham
- 1:45 – 2:15 Discussion with the Committee
- 2:15 – 3:15 p.m.** **Panel 5: Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Space Flight**
Facilitators: Torin Clark and Bill Yates
- 2:15 – 2:45 Presentations
Dan Merfeld, Harvard University
Scott Wood, Azusa Pacific University
- 2:45 – 3:15 Discussion with the Committee

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3:15 – 3:30 p.m.	BREAK
3:30 – 4:15 p.m.	Discussion on Risk Interactions and Other Issues
4:15 – 4:45 p.m.	Public Comment
4:45 – 5:00 p.m.	Closing Remarks <i>Dan Masys, Committee Vice Chair</i>
5:00 p.m.	ADJOURN

AGENDA

2016 Committee to Review NASA's Evidence Reports on Human Health Risks

Tuesday, July 26

Keck Center of the National Academies
500 Fifth Street, NW
Washington, DC
Keck 101

OPEN SESSION

8:30 – 8:45 a.m.	Welcome and Opening Remarks <i>Carol Scott-Conner, Committee Chair</i>
8:45 – 9:45 a.m.	Panel 1: Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload <i>Facilitator: Namni Goel</i>
8:45 – 9:15	Presentations <i>Steven Hursh, Institutes for Behavioral Resources</i> <i>Frank Scheer, Harvard Medical School</i>
9:15 – 9:45	Discussion with the Committee

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- 9:45 – 10:45 a.m.** **Panel 2: Risk of Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication, and Psychosocial Adaptation with a Team**
Facilitator: Jim Pawelczyk
- 9:45 – 10:15 Presentations
Steve Kozlowski, Michigan State University
Jack Stuster, Anacapa Sciences (via WebEx)
- 10:15 – 10:45 Discussion with the Committee
- 10:45 – 11:00 a.m.** **BREAK**
- 11:00 a.m. – 12:00 p.m.** **Panel 3: Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders**
Facilitator: Murray Stein
- 11:00 – 11:30 Presentations
Charles Nemeroff, University of Miami
Marissa Shuffler, Clemson University (via WebEx)
- 11:30 – 12:00 Discussion with the Committee
- 12:00 – 12:30 p.m.** **Discussion on Risk Interactions and Other Issues**
- Closing Remarks**
- 12:30 p.m.** **ADJOURN**

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AGENDA

**2016 Committee to Review NASA's Evidence Reports
on Human Health Risks**

Monday, August 8, 2016

Web Conference Call – Open Session (3:00 – 4:00 p.m. Eastern)

OPEN SESSION

- | | |
|-------------------------|--|
| 3:00 – 3:05 p.m. | Welcome and Opening Remarks
<i>Carol Scott-Conner, Committee Chair</i> |
| 3:05 – 4:00 p.m. | Presentation from Captain Chris Cassidy

Discussion with Committee |
| 4:00 p.m. | ADJOURN |

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B

Committee Biographical Sketches

Carol E. H. Scott-Conner, M.D., Ph.D., M.B.A. (*Chair*), is a professor emerita in the Department of Surgery, University of Iowa, Iowa City. Dr. Scott-Conner received her undergraduate training in electrical engineering from the Massachusetts Institute of Technology and worked as an engineer before attending medical school at New York University (NYU). She received her M.D. from NYU, where she also completed a residency in surgery. After leaving NYU, she joined the faculty at Marshall University and then moved to the University of Mississippi. During her tenure there, she earned a Ph.D. in anatomy from the University of Kentucky and an M.B.A. In 1995, she became professor and head of surgery at the University of Iowa. Dr. Scott-Conner has been active on 22 editorial boards and has written more than 200 original papers, abstracts, reviews, and book chapters. She is certified by the National Board of Medical Examiners and the American Board of Surgery and has a certification of added qualifications in surgical critical care. Dr. Scott-Conner has served on a number of National Academies' committees, and she chairs the Standing Committee on Aerospace Medicine and the Medicine of Extreme Environments.

Daniel R. Masys, M.D. (*Vice Chair*), is an affiliate professor of biomedical and health informatics at the University of Washington School of Medicine, where he joined the Department of Biomedical Informatics and Medical Education in 2011. Previously, he served as a professor and chair of the Department of Biomedical Informatics and a professor of medicine at the Vanderbilt University School of Medicine. An honors graduate of Princeton University and the Ohio State University College of Medicine, he completed postgraduate training in internal medicine,

hematology, and medical oncology at the University of California, San Diego (UCSD), and the Naval Regional Medical Center, San Diego. He served as chief of the International Cancer Research Data Bank of the National Cancer Institute, the National Institutes of Health, and was director of the Lister Hill National Center for Biomedical Communications, which is a computer research and development division of the National Library of Medicine. He also served as director of Biomedical Informatics at the UCSD School of Medicine, director of the UCSD Human Research Protections Program, and professor of medicine. Dr. Masys is an elected member of the National Academy of Medicine. He is a diplomate of the American Board of Internal Medicine in medicine, hematology, and medical oncology. He is a fellow of the American College of Physicians and fellow and past president of the American College of Medical Informatics. Dr. Masys served as a member of the Institute of Medicine (IOM) Committee on Aerospace Medicine and Medicine of Extreme Environments and chaired the 2008 IOM review of NASA's Human Research Program evidence books.

Susan M. Bailey, Ph.D., is a professor and a cancer molecular biologist in the Department of Environmental & Radiological Health Sciences at Colorado State University. Dr. Bailey's current research focuses on the roles of chromosome aberrations and telomere length changes following exposure to ionizing radiations, including those experienced during spaceflight and in cancer and aging; implications for other age-associated degenerative diseases are also explored. She received her doctorate in Biomedical Sciences from the University of New Mexico School of Medicine.

Susan A. Bloomfield, Ph.D., earned her B.S. in biology at Oberlin College (Ohio) and her M.A. in physical education (exercise physiology) at The University of Iowa. After completing a Ph.D. (exercise physiology) at The Ohio State University, Dr. Bloomfield joined the faculty in the Department of Health and Kinesiology at Texas A&M University, where she currently holds the rank of professor and is director of the Bone Biology Laboratory. In addition, she serves as Associate Dean for Research in the College of Education & Human Development. Her research interests focus on the integrative physiology of bone, with specific reference to adaptations to disuse, microgravity, radiation, and caloric deficiency and how the sympathetic nervous system, altered blood flow, and endocrine factors modify those adaptations. Her more recent work has fo-

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cused on the independent and combined effects of simulated microgravity and space-relevant radiation on the integrity of bone and muscle, involving several experiments at Brookhaven National Laboratory. Collaborations with muscle biologists have enabled definition of concurrent changes in muscle-bone pairs with disuse and/or radiation exposure. She has served as principal investigator for a number of multidisciplinary teams of investigators, and is funded by the National Space Biomedical Research Institute (NSBRI), the Department of Defense, and NASA's Space Biology Program. From 2000 to 2012, Dr. Bloomfield served as the Associate Lead for the NSBRI Bone Loss (later, Musculoskeletal Alterations) Team, in addition to serving on numerous NASA and European Space Agency review panels over the past 16 years. Dr. Bloomfield is a Fellow of the American College of Sports Medicine, a member of the Texas A&M Department of Nutrition and Food Science graduate faculty, and associate member of the Texas A&M University Health Sciences Center School of Graduate Studies.

Torin K. Clark, Ph.D., received his doctorate in aeronautics and astronautics with a focus on humans in aerospace from the Massachusetts Institute of Technology in 2013. While there he studied the effect of altered gravity on human spatial orientation perception and control with a focus on the vestibular system. As part of this work, he extended a mathematical model of dynamic integration of semicircular canal and otolith signals to predict human orientation perception in altered gravity. Dr. Clark was a National Space Biomedical Research Institute First Award (post-doctoral) fellow in the Jenks Vestibular Physiology Laboratory at the Massachusetts Eye and Ear Infirmary and Harvard Medical School from 2013 to 2015. His research focused on understanding and predicting individual differences in sensorimotor adaptation to altered gravity environments. Specifically, he studied the relationship between sensory noise, such as in the vestibular system, and perceptual adaptation, as required for astronauts during space exploration missions. Dr. Clark is an assistant professor of aerospace engineering sciences at the University of Colorado, Boulder. He is a principal investigator in the Bioastronautics Laboratory and a faculty affiliate of BioServe Space Technologies. His current research focuses on vestibular adaptation relevant for astronauts and ground-based vestibular rehabilitation, spaceflight human factors, and artificial gravity.

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Andrew P. Feinberg, M.D., M.P.H., is a Bloomberg Distinguished Professor at the Johns Hopkins University School of Medicine, Whiting School of Engineering, and Bloomberg School of Public Health, where he is director of the Center for Epigenetics. Dr. Feinberg is considered the founder of the field of cancer epigenetics, having discovered altered DNA methylation in cancer as a postdoctoral fellow with Bert Vogelstein in the early 1980s. Over the decades since then, Dr. Feinberg and his colleagues have shaped the landscape of our understanding of DNA methylation and other epigenetic changes, and their applications to epidemiology and medicine, and have introduced groundbreaking statistical and laboratory methods to the study of the epigenome. He and his colleagues discovered human imprinted genes and loss of imprinting in cancer, and they proved the epigenetic hypothesis of cancer through their work on Beckwith-Wiedemann syndrome. Most recently, he pioneered genome-scale epigenetics (epigenomics), with the first National Institutes of Health (NIH)-funded Epigenome Center, pioneering methods that include the first comprehensive genome-scale methylation discovering the major target for epigenetic variation in humans, CpG island shores. Dr. Feinberg led the first whole-genome bisulfite sequencing analysis of human cancer, discovering large hypomethylated blocks that correspond to nuclear lamina-associated heterochromatin, as well as a mechanism for disruption of these blocks in epithelial-mesenchymal transition. He has also helped to create the field of epigenetic epidemiology, discovering epigenetic mediation of genetic variants in disease. He is a recipient of an NIH Director's Pioneer Award, is a member of the National Academy of Medicine, and has received honorary doctorates from the University of Uppsala, the Karolinska Institute, and the University of Amsterdam.

Namni Goel, Ph.D., is an associate professor of psychology in psychiatry in the Division of Sleep and Chronobiology, Department of Psychiatry, at the University of Pennsylvania Perelman School of Medicine. Dr. Goel received her B.A. in psychology and anthropology from the University of California, Berkeley, and her Ph.D. in biological psychology from the University of Michigan, Ann Arbor. She completed her postdoctoral training at Columbia University Medical Center and Cornell University Medical Center. Throughout her interdisciplinary career, as a broadly trained biological psychologist and behavioral neuroscientist, Dr. Goel has been investigating individual differences in how genetic, physiological, behavioral, hormonal and environmental factors relate to resilience and vulnerability in sleep-wake functions and circadian rhythm

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physiology, and regulate eating behavior (including night eating), energy balance, mood and cognitive performance in humans. She also has published a substantial number of papers on circadian rhythm physiology and sleep-wake functions in animal models. Dr. Goel is currently the principal investigator of a major 4-year grant from NASA investigating biomarkers as predictors of resiliency and susceptibility to stress and sleep loss in space flight. Dr. Goel has served as president of the Society for Light Treatment and Biological Rhythms and is on the board of directors of the Center for Environmental Therapeutics. Dr. Goel is an associate editor of *SLEEP*, an academic editor of *PLoS ONE*, and a review editor for *Frontiers in Behavioral and Psychiatric Genetics*. She also serves on the editorial boards of *Scientific Reports*, *Chronobiology International*, *Journal of Circadian Rhythms*, *Journal of Neurology Research*, and *Journal of Sleep Disorders: Treatment and Care*. She has been a grant reviewer for various NIH, NASA, and Department of Defense study sections and for many international granting organizations, including the Canadian Institutes of Health Research, the Wellcome Trust, the Royal Society and the Medical Research Council, among others. In 2014, she was awarded the prestigious NASA Johnson Space Center Group Achievement Award.

Tom K. Hei, Ph.D., is professor and vice-chair of radiation oncology, associate director of the Center for Radiological Research, and professor of environmental health sciences at Columbia University Medical Center in New York. Dr. Hei's research focuses on understanding the basic mechanisms of radiation and environmental cancer. Using a charged particle microbeam, his laboratory has made seminal contributions in our understanding of extranuclear and extracellular effects of ionizing radiation. The non-targeted response of radiation has resulted in a paradigm shift in our appreciation of the relevant targets of radiation. Dr. Hei was a committee member on the Institute of Medicine review of the National Institute for Occupational Safety and Health Roadmap for Research on Mineral Fibers and served on many NIH advisory panels over the years. Dr. Hei was elected an overseas expert by the Chinese Academy of Sciences and was elected Educator of the Year by the Association of Residents in Radiation Oncology in 2012. He is past president of the Radiation Research Society and has trained many graduate students, postdoctoral fellows, and resident physicians in radiological sciences, many of whom are now leaders in their fields. Dr. Hei is the chair of Sub-Commission F2 on radiation environment, biology and health of the

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International Council of Scientific Unions' Committee on Space Research (COSPAR). He is currently the editor-in-chief of *Life Sciences in Space Research*, one of the two flagship journals of COSPAR, and he is on the editorial board of the *Journal of Radiation Research and Translational Cancer Research*.

James A. Pawelczyk, Ph.D., is an associate professor of physiology, kinesiology, and medicine at Pennsylvania State University. Dr. Pawelczyk served as a payload specialist on STS-90 Neurolab (April 17 to May 3, 1998); the experiments on-board the space shuttle *Columbia* flight focused on the effects of microgravity on the brain and nervous system. Dr. Pawelczyk is a former member of the NASA Life Sciences Advisory Subcommittee in the Office of Biological and Physical Research, and he served as a member of NASA's ReMaP Task Force in 2002, which was charged with reprioritizing research on the space station. Dr. Pawelczyk's research areas include central neural control of the cardiovascular system and compensatory mechanisms to conditioning and deconditioning. He received his M.S. in physiology from Pennsylvania State University and his Ph.D. in biology (physiology) from the University of North Texas. He chaired the National Research Council (NRC) Decadal Survey on Biological and Physical Sciences in Space: Integrative and Translational Research for the Human System Panel. He also chaired an Institute of Medicine (IOM) report on NASA's directed research programs in 2012. He has served on several NRC and IOM committees and recently completed rotations on the IOM Committee on Aerospace Medicine and the Medicine of Extreme Environments and the National Academies' Space Studies Board.

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Hazards and the Vision for Space Exploration, Managing Space Radiation Risks in the New Era of Space Exploration, Technical Evaluation of the NASA Model for Cancer Risk (reviewer), and *NASA Space Technology Roadmaps and Priorities, Human Health and Exploration Systems* (panelist). Dr. Turner was on the Advisory Council to the National Space Biomedical Research Institute Center for Acute Radiation Research. He led a NASA Office of the Chief Engineer study to understand NASA's requirements for operational space weather support. He is a member of the International Academy of Astronautics, and also belongs to the American Geophysical Union and the American Institute of Aeronautics and Astronautics. Dr. Turner has a Ph.D. in nuclear/particle physics from The Ohio State University and a master's and bachelor's degree from the University of Florida.

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