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POLICY CONSIDERATIONS FOR PRECISION MEDICINE IN HUMAN SPACEFLIGHT

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INTRODUCTION

Over the 60-year history of human spaceflight, NASA has pushed the boundaries of human exploration, grappling with the challenge of understanding the risks faced by spacefaring crews and pushing the boundaries of technologies from many fields to help reduce those risks. After 20 years of constant human habitation in Low Earth Orbit ("LEO") aboard the International Space Station ("ISS"), NASA is poised to return to the Moon and eventually send humans to Mars. As NASA prepares to expand the reach of human exploration, it will benefit from leveraging advances in terrestrial health care to ensure that human explorers can travel longer and further than ever before, and safely return home to Earth.

Maintaining human health and performance in exploration missions is among NASA's most challenging technical problems.[2] This is due in part to the small number of people who have experienced those hazards. It is also a result of the daunting technical challenges of spaceflight itself, which have taken priority over understanding what long-term exposure to the spaceflight environment does to human explorers.[3] However, as NASA worked to solve the immense engineering challenges of exploration spaceflight, terrestrial advances in health care technology have changed the face of medicine. Clinical capabilities that seemed like science fiction 20 years ago—whole genome sequencing, tailored pharmaceutical and gene interventions for previously untreatable conditions, mail order genetic screenings, personalized medicine[4]—

2 INST. OF MED. ET AL., SAFE PASSAGE: ASTRONAUT CARE FOR EXPLORATION MISSIONS 3 (Wash., D.C.: The Nat'l Academies Press, 2001) [hereinafter SAFE PASSAGE] (Observing that "risks to human health of long-duration missions beyond Earth orbit, if not solved, represent the greatest challenge to human exploration of deep space. The development of solutions is complicated by lack of a full understanding of the nature of the risks and their fundamental causes.").

3 *Id.* at 18 ("Because of the engineering problems associated with early space endeavors, the historical approach to solving problems has been that of engineering. Long duration space travel will require a different approach, one requiring wider participation of those with expertise in divergent, emerging, and evolving fields.").

4 *See* NAT'L RESEARCH COUNCIL, TOWARD PRECISION MEDICINE: BUILDING A KNOWLEDGE NETWORK FOR BIOMEDICAL RESEARCH AND A NEW TAXONOMY OF DISEASE (Wash., D.C.: The Nat'l Academies Press 2011) [hereinafter TOWARD PRECISION MEDICINE]. The National Institute of Health (NIH) introduced the term "precision medicine" in this report. The NIH

are now becoming available to individual patients.[5] Advances in the fields of omics[6] and precision medicine provide an opportunity to gain a deeper understanding of the human body's response to space. However, the rate of technological change in medicine has outpaced the speed at which the federal government can develop appropriate policies and ethical frameworks to guide the adoption of new medical capabilities.[7] Faced with rapidly changing health care paradigms, NASA has the challenge of determining which advances are worthy of investment and investigation, and perhaps more critically, how to construct appropriate policy and ethical frameworks in advance that will allow the adoption of precision medicine technology as it becomes available. Exploring these issues may support NASA's work to mitigate the human health risks posed by exploration spaceflight.

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defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." Precision medicine allows the more accurate prediction of "which treatment and prevention strategies for a particular disease will work in which groups of people . . . in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are development for the average person, with less consideration for the differences between individuals." GENETICS HOME REFERENCE, *What is precision medicine?,* U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, lm.nih.gov/primer/precisionmedicine/definition (last visited Aug. 6, 2019).

5 *See* Geoffrey Ginsburg & Kathryn Phillips, *Precision Medicine: From Science to Value*, 37 HEALTH AFFAIRS 5 (May 2018), 694–701. *See also* Samuel Aronson & Heidi Rehm, *Building the Foundation for Genomics in Precision Medicine*, 526 NATURE 336 (Oct. 15, 2015).

6 "Omic" is a term intended to capture the information obtained in multiple domains including genomics, epigenomics, proteomics, metabolomics, and others. These include genetic information as well as the downstream effects of genetics within an individual.

7 *See e.g.*, Ginsburg & Phillips, *supra* note 5, at 3 ("Policy makers will need to address the return of results, privacy, confidentiality, and education while developing regulations and economic incentives that can align all stakeholders toward the same outcomes. Patients stand to benefit with optimized health outcomes in such a genomics and data enabled learning precision health system."); Benjamin Chin-Yee & Ian Chin-Yee, *Big Data, Precision Medicine, and Person-Centered Healthcare*, 6 EUR. J. FOR PERSON-CENTERED HEALTHCARE 513, 514 (2018) ("[T]he latest trend in precision medicine brings with it a focus on genomics, which has been criticized for downplaying the importance of other factors, such as social determinants of health. This is not to deny the importance of genes in human diseases, but simply to point out that if we understand disease solely in these terms we will inevitably constrain how we view problems and find solutions. As the common saying goes, if you only have a hammer, everything looks like a nail.").

Working with the Institute of Medicine ("IOM") (now known as the National Academy of Medicine)[8], NASA has spent several decades exploring the ethical and policy framework necessary to support human exploration and touched upon the need for an increased use of personalized medicine approaches. In its 2014 report, IOM observed that part of the ethics framework for exploration would include "identification of the astronauts health susceptibilities and personal risk factors (if known)" to inform decisions about mission participation.[9] The burgeoning field of precision medicine has the potential to help NASA develop this insight.

NASA has already made considerable strides to develop a policy framework that incorporates the IOM recommendations.[10] It has also begun building a framework for incorporating omics into NASA research.[11] For example, NASA's policy on genetic research was stimulated by work already being done in the NASA Twins Study.[12] This study was driven by the need ". . . to better understand the impact of prolonged spaceflight on human biology and health."[13] This study assessed longitudinal biomarkers including genomic, epigenomics, biochemical and physical changes that occurred during the one-year

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8 Throughout this paper, reference is made to the Institute of Medicine ("IOM"). In 2015, the IOM was renamed the National Academy of Medicine ("NAM"). Because this paper references studies published before the name change, the authors continue to reference the IOM.

9 INST. OF MED. ET AL., HEALTH STANDARDS FOR LONG DURATION AND EXPLORATION SPACEFLIGHT: ETHICS PRINCIPLES, RESPONSIBILITIES, & DECISION FRAMEWORK, 9 (Inst. of Med., National Academies Press, 2014) (hereinafter IOM HEALTH STANDARDS).

10 *See* IOM HEALTH STANDARDS, *supra* note 9. *See also* NAT'L AERONAUTICS & SPACE ADMIN., NASA PROCEDURAL REQUIREMENTS 8900.1B, NASA HEALTH AND MED. REQUIREMENTS FOR HUMAN SPACE EXPLORATION, APPENDIX F: ETHICAL PRINCIPLES AND RESPONSIBILITIES (Dec. 16, 2016), https://nodis3.gsfc.nasa.gov/npg_img/N_PR_8900_001B_/N_PR_8900_001B__Appendix F.pdf [hereinafter NPR 8900.1B APPENDIX F].

11 NAT'L AERONAUTICS & SPACE ADMIN., POLICY DIRECTIVE 7170.1, USE OF HUMAN RESEARCH GENETIC TESTING (Feb. 22, 2018), https://nodis3.gsfc.nasa.gov/npg_img/N_PD_7170_0001_/N_PD_7170_0001__main.pdf [hereinafter NPD 7170.1].

12 *See* NAT'L AERONAUTICS & SPACE ADMIN., FIREWORKS IN SPACE: NASA'S TWINS STUDY EXPLORES GENE EXPRESSION (Kelli Mars, ed., 2017), https://www.nasa.gov/feature/fireworks-in-space-nasa-s-twins-study-explores-gene-expression.

13 Francine E. Garrett-Bakelman et al., *The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight*, 364 SCIENCE 6436 (2019).

mission over 24 months in an effort to ". . . provide critical metrics for astronaut health that could aid in assessment of increased risks and guide potential personalized interventions."[14] Studies like these help gain insight into high value data and metrics that can guide monitoring and countermeasures selection for exploration missions of the future. However, the access to and use of those types of data must be carefully considered to ensure both legal and ethical compliance and the current research policy does not extend to operational and clinical collection or use of data.

This paper explores how NASA might enable exploration spaceflight by anticipating developments in precision medicine, monitoring the field for advances that map to spaceflight-specific needs, and prospectively positioning policies for the appropriate collection and use of omic information. Ultimately, this paper recommends that NASA consider developing additional anticipatory policies that enable adoption and deployment of precision medicine as it becomes available while providing appropriate boundaries and guidance regarding ethical dilemmas before they are encountered.

I. HAZARDS AND RISK IN SPACE

To understand how precision medicine can help address the risks to human health, we must first explore the nature of those risks and the hazards that drive them. There are five recognized hazards in human spaceflight: radiation; microgravity; hostile closed environments; isolation and confinement; and distance from the Earth.[15] NASA has derived from these hazards 30 Risks to human health and performance in exploration spaceflight.[16] These 30 risks represent the most critical human health challenges human explorers

14 *Id.*

15 *See 5 Hazards of Human Spaceflight*, NAT'L AERONAUTICS & SPACE ADMIN. https://www.nasa.gov/hrp/5-hazards-of-human-spaceflight (last visited May 5, 2019).

16 *See* NAT'L AERONAUTICS & SPACE ADMIN., JCS-66705, JSC HEALTH AND MEDICAL TECHNICAL AUTHORITY, HUMAN SYS. RISK MGMT. PLAN (May 2014) (providing a detailed discussion of the human health risks in spaceflight). The current state of each risk and NASA's progress on understanding and mitigating it can be found at *Human Research Roadmap: Human Research Program Evidence*, NAT'L AERONAUTICS & SPACE ADMIN., https://humanresearchroadmap.nasa.gov/evidence/ (last visited Aug. 6, 2019).

will face as they travel to the Moon and Mars.[17] These include risks related to exposure to radiation, challenges in providing medical care, food and pharmaceutical degradation, mental health in long term isolation, human system integration and design, and many others.[18]

Each mission has different risks, based on its duration and distance from Earth. NASA has several Mars Design Reference Missions ("DRM"); they range in duration from just over a year to nearly three years, depending on how long the mission will stay on or near Mars.[19] It will take a minimum of six months in the most optimistic assessments to travel to Mars—one way.[20]

Mars missions, because of their length and distance from earth will be much more challenging for human crews than anything NASA has done before. As mission duration and distance from earth increase, an increasing number of system challenges can threaten the ability of crews to remain sufficiently healthy to perform the jobs they need to do. Compounding these challenges, Mars missions will not have access to resupply, real time communication with mission control, or emergency medical evacuation capability. Mass and volume will be severely constrained, limiting the medical supplies and capabilities that will be available on the missions.

As a result of these complex technical challenges, NASA does not plan to fly a mission to Mars until the 2030s. Between now and then, NASA plans to return to the Moon, using the experience in the lunar vicinity to research and validate technologies that need to be developed to enable a Mars mission.[21] Precision medicine is one of the many technologies that will need to be evolved for application on a Mars mission. Precision medicine has the potential to help NASA better predict and treat human health and performance issues on a

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17 *See Human Research Roadmap: Human Research*, *supra* note 16.

18 The list of current human system risks can be found at *Human Research Roadmap: Risks*, NAT'L AERONAUTICS & SPACE ADMIN., https://humanresearchroadmap.nasa.gov/Risks/ (last visited Aug. 6, 2019).

19 NAT'L AERONAUTICS & SPACE ADMIN., HUMAN EXPLORATION OF MARS DESIGN REFERENCE ARCHITECTURE 5.0 ADDENDUM 57 (2009), https://www.nasa.gov/pdf/373667main_NASA-SP-2009-566-ADD.pdf [hereinafter Design Reference 5.0 Addendum].

20 *Id.*

21 *See Moon to Mars Overview*, NAT'L AERONAUTICS & SPACE ADMIN., https://www.nasa.gov/topics/moon-to-mars/overview (last visited Feb. 2, 2019).

Mars mission, tailoring the countermeasures and medical capabilities to the individuals on board, and better preparing those individuals for the rigors of spaceflight. As a result, NASA may wish to begin exploring the policy needed to support the use of precision medicine techniques in the near future.

The need for policy guidance in this area is due in part because of the challenges already being encountered in fields like precision medicine and genomics. For example, NASA, like most other employers in the United States, is subject to the Genetic Information Nondiscrimination Act ("GINA"). As a result, NASA must refrain from using genetic information for employment decisions, including things like astronaut selection and flight assignment. These limitations must be borne in mind as NASA determines how best to use precision medicine in the clinical and operational setting. In 2017, NASA instituted a policy on capturing and using genetic information in human subject research.[22] However, there are currently no policies that address the clinical or operational use of genomic data. This clinical and operational use is where the transition from collection of omic data to precision medicine (clinical use of omic data) would occur.[23] Even without the GINA restrictions, precision medicine has a strong potential to contribute to mission risk reduction and it would be advisable for NASA to consider adopting policies that ensure the continued ethical use of that data.

II. ROLE OF PRECISION MEDICINE IN SPACEFLIGHT

Precision medicine is a relatively new field. Less than a decade old, precision medicine is an approach to medical care designed to optimize efficiency or therapeutic benefit for particular a patient or group of patients, including by using genetic or molecular profiling.[24]

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22 *See* NPD 7170.1, *supra* note 11.

23 *See* Erik L. Antonsen & Rebekah D. Reed, *Should NASA Collect Astronaut's Genetic Information for Occupational Surveillance and Research?*, *20* AMA J. ETHICS 9 E849–56 (2018).

24 TOWARD PRECISION MEDICINE, *supra* note 4, at 125 ("'Precision medicine' refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their

In the past, genomics and precision medicine have been of limited value in the spaceflight arena for two reasons. First, the cost and maturity of technologies needed to characterize individual genomes and capture actionable information have not been sufficiently mature to seriously consider operational implementation. That is changing as advances in genomics have significantly reduced the costs and regulatory hurdles of gathering the relevant data. It has only been in the last two years that genomic testing has become affordable and widely available. In 2017, the cost of sequencing a single genome was just $1,000 (down from $100 million in 2001);[25] and, at the end of 2018, the FDA approved the first publicly available genomic testing technology targeting medication metabolism, ushering in a new era in direct-to-consumer testing.[26] Second, precision medicine has thus far been limited to discrete areas of medicine that were not immediately applicable to spaceflight, such as oncology.[27] The focus on oncology was in large part due to government initiatives that focused the short term work of NIH and other research institutions on cancer, leaving other areas for future investment.[28]

Despite these limitations, there is a general sense among those working in human spaceflight that genomics and precision medicine are likely to contribute significantly to our ability to understand and reduce the risks to individuals and crews involved in exploration missions. However, a general mapping of the risk-oriented needs to the areas in omics and precision medicine that are likely to yield benefits has not been done. As these fields mature, beneficial

response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.").

25 *See DNA Sequencing Costs: Data*, NAT'L HUMAN GENOME RESEARCH INST., https://www.genome.gov/sequencingcostsdata/ (last visited Feb. 2, 2018).

26 U.S. FOOD & DRUG ADMIN., *FDA Authorizes First Direct-to-Consumer Test for Detecting Genetic Variants that May be Associated with Medication Metabolism*, FDA NEWS RELEASE (Oct. 31, 2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm 624753.

27 *See* Francis Collins and Harold Varmus, *Perspective: A New Initiative on Precision Medicine*, 372 N. ENG. J. MED. 793 (Feb. 26, 2015).

28 *Id.* at 793 ("The proposed initiative has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease. Both components are now within our reach because of advances in basic research, including molecular biology, genomics, and bioinformatics.").

crossovers come into sharper focus and illuminate areas where NASA may want to explore developing policies to ensure the appropriate collection, analysis, access, interpretation, and usage of data. This was the case with the NASA Twins Study and the subsequent policy on research use of genomic information.[29]

The danger of not anticipating policy needs is that the methods of a maturing scientific and medical practice may be brought to bear without guidance from the agency on appropriate usage. Failing to develop a supportive policy framework in advance could result in delayed implementation of important research and clinical capabilities that can drive down risk in human spaceflight. The section below explores some of the challenges that precision medicine could help to address.

A. The Challenge of the Small "n"

One of the main reasons that Genomics and precision medicine are potentially important to NASA is that the agency is responsible for developing the scientific evidence base needed to understand how humans adapt to and function in the unique environment of space. In all other medical fields, characterizing the state of the human system is accomplished through the study of a large number of individuals pooled together for both statistical and clinical significance to build a reliable evidence base. There is no analogous pool of subjects in human spaceflight because of the small number of individuals who have experienced the spaceflight environment and were sufficiently monitored to add useful information to our understanding of the human response in this environment. This what is referred to as the challenge of the small "*n*".[30]

The small *n* problem is not unique to spaceflight. Other distinct research communities, such as members of small isolated communities or persons diagnosed with a very rare disease, also have a small *n* problem. [31] Although NASA is not alone in struggling with the

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[29] Garrett-Bakelman, *supra* note 13, at 1. *See also* NPD 7170.1, *supra* note 11.

[30] Small "*n*" refers to an inability to reach sufficient statistical power for a variety of reasons including rareness of a condition being studies or limited exposure of subjects to the environment of interest as in human spaceflight.

[31] *See e.g.*, COMM. ON STRATEGIES FOR SMALL-NUMBER-PARTICIPANT CLINICAL RESEARCH TRIALS,

problem of a small *n*, the challenge is particularly acute and the small number of human subjects in space has real scientific consequences for understanding the effects of space on the human body.[32]

For comparison, FDA guidance suggests that phase 3 clinical trials of a new medication should have between 300–3,000 volunteer participants who are studied for 1–4 years each, in a closely controlled protocol and set of conditions.[33] In the recorded history of the human species, there have been 559 individuals who have ever flown in space.[34] Using the FDA guidelines as a benchmark, NASA would have had to expose over half of the participants in human spaceflight to date to the exact same conditions and duration in space and monitored the same parameters to even start to meet the basic scientific requirements for approaching validity in population-based research studies.

While NASA has flown several hundred crew, those crew were exposed for different exposure times, and their physiological data where not collected in a consistent manner over the last 50 years. Today, medical data is collected in a consistent and rigorous way. However, the data capture challenges and limitations NASA faced prior to the ISS program were recognized by IOM in 2001:

> An effective health care system is founded on data that are accumulated, analyzed, and used to continuously improve health care for astronauts on future space missions. Inherent in an appropriate health care system

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SMALL CLINICAL TRIALS: ISSUES AND CHALLENGES 3 (Charles H. Evans, Jr. & Suzanne T. Ildstad eds., 2001) [hereinafter SMALL CLINICAL TRIALS] ("[E]ven though the size of the available research population does not allow a randomized clinical trial with adequate statistical power to be conducted, there might still be a need to design and perform the research (e.g., because treatments are unavailable for a rare disorder or a unique patient population or because studies require the participation of patients with terminal or severely debilitating or incapacitating disorders). In addition, some distinctive research populations—such as astronauts or members of a small, isolated community—may consist of less than five individuals. This research situation, in which large numbers of study participants cannot be obtained, is defined as a "small *n* clinical trial," where *n* refers to the sample size.").

32 *Id.* at 3 ("The sample size in small clinical trials might be very small, for example, a group of astronauts during a space mission, or could range upward to more than 100 individuals. This is in contrast to the sample sizes of some large clinical trials, where the number of participants is in the thousands.").

33 *The Drug Development Process, Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm (last visited Aug. 6, 2019).

34 Garrett-Bakelman, *supra* note 13, at 1.

> is a mechanism that can be used to gather and analyze data relevant to key variables. NASA could have collected and analyzed many more medical data had a comprehensive health care system focused on astronauts been in place and been given the priority and resources that it needed.[35]

While we have nearly twenty years of data on humans in LEO aboard the ISS, when missions beyond LEO are considered, our dearth of experience comes into even sharper focus. Only 12 people (all men) have walked on the surface of a celestial body other than the earth. No one has traveled beyond the Earth-Moon system.

NASA and the IOM both recognized the challenges posed by this small *n* problem. In 2001, at NASA's request, IOM reviewed NASA's approach to gathering and analyzing health information in preparation for exploration. The IOM observed that in addition to the challenge of having too few people to study, while clinical data was being collected that "data collection has not been done in a systematic way, nor have the data been fully analyzed."[36] This lack of health data was not the result of a failure on NASA's part to adequately plan or prepare, but a function of the engineering-centric approach to spaceflight that predominated in the pre-ISS era.[37] The IOM recognized that for NASA to successfully send humans on exploration missions beyond the Earth-Moon system, that approach would need adjustment.

While the small *n* problem has not been solved, NASA has been directed to use the International Space Station as a platform for biomedical research to understand the impacts of long duration missions.[38] Using this unique in-space platform, NASA has sought to

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35 SAFE PASSAGE, *supra* note 2, at 7.

36 *Id.* at 6.

37 *Id.* at 18 ("NASA, because of its mission and history, has tended to be an insular organization dominated by traditional engineering. Because of the engineering problems associated with early space endeavors, the historical approach to solving problems has been that of engineering. Long-duration space travel will require a different approach, one requiring wider participation of those with expertise in divergent, emerging, and evolving fields. NASA has only recently begun to recognize this insufficiency and to reach out to communities, both domestic and international, to gain expertise on how to remedy it.").

38 Nat'l Aeronautics & Space Admin. Authorization Act of 2005, Pub. L. 109-155 § 101(b)(2)(C), 119 Stat. 2895, 2898 ("Increasing knowledge of the impacts of long duration stays in space on the human body using the most appropriate facilities available, including the ISS.").

balance the challenges of small n research with the requirement that high quality and high value science be performed. One of the ways to address this challenge is by exploring the potential of omics research to improve longitudinal studies of individual crew to inform personalized risk profiles and countermeasures for exploration spaceflight.

B. Genetic Information and Research

Given the constraints on the number of humans we can fly in space, and the infeasibility of drawing on traditional clinical research approaches appropriate in a terrestrial setting, NASA should examine other ways to validly reduce risk.[39] Experts have recommended that NASA consider valid non-traditional approaches in the evaluation of research value where large-*n* studies are infeasible.[40] In the absence of traditional population-based studies, techniques for individual longitudinal studies called, *N*-of-1 studies, offer a promising pathway using precision medicine information.[41]

Omics is just one of many approaches to personalized medicine (as opposed to precision medicine which is focused on actionable, clinical data that is not omic-based). For example, Quantitative Computed Tomography ("QCT") has been researched to understand and model structural changes in bone that individual astronauts experience during spaceflight independent of omic information.[42]

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39 *See, e.g.* SMALL CLINICAL TRIALS, *supra* note 31, at 10 ("Studies of the use and effectiveness of various designs should be conducted and new methods should be developed. Evaluations of the utilities of individual and combined statistical analyses in a variety of small clinical trial designs will be necessary.").

40 Robert Ploutz-Snyder et al., *Justifying Small-*n *Research in Scientifically Amazing Settings: Challenging the Notion that only "Big-*n*" Studies are Worthwhile*, 116 J. APPL. PHYS. 1251, 1252 ("Such nontraditional approaches to communicating the value of small-*n* research are appropriate when large-*n* research is simply not feasible."). *See also*, SMALL CLINICAL TRIALS, *supra* note 31, at 10.

41 Nicholas J. Schork, *Time for One Person Trials*, 520 NATURE 609, 611 (2015) ("Key to making precision medicine mainstream is the ongoing shift in the relationship between patients and physicians. A major advantage of the *N*-of-1 approach over classical trials is that patients are no longer guinea pigs, whose involvement in a study may help only future generations. In *N*-of-1 trials, the effectiveness of different treatments are vetted for the actual participants.").

42 NAT'L AERONAUTICS & SPACE ADMIN., HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF EARLY ONSET OSTEOPOROSIS DUE TO SPACEFLIGHT 2 (2017), https://humanresearchroad

However, this is not predictive, but rather provides a post-flight measure of response. Empirical approaches such as ground testing have been used to personalize sleep medications for individual crew member use in spaceflight by testing for effectiveness and side-effects of different medications and doses prior to flight.[43] While effective, this method of ground testing is time consuming and expensive. However, as precision medicine advances in terrestrial applications, it is readily apparent that those same non-omic approaches used today could be correlated with omic information to identify relevant predictive biomarkers. Such an approach could eventually obviate the need for the more time-consuming and costly methods of assessing individual risk and response and yield more predictive information.[44]

Recognizing the potential value of omics in research, NASA implemented a genetic policy for research subjects in 2018;[45] however, the policy does not cover occupational surveillance of crews or applications of precision medicine to pre-flight and in-flight medical care and monitoring. In order to assess the utility of policies in operational and clinical care, it is important to understand the spaceflight specific challenges that may be approached through precision medical methods and the potential ethical difficulties that are likely to be encountered beyond the research domain.

map.nasa.gov/Evidence/reports/Osteo.pdf.

43 *See* David Dinges et al., *Effects of Zolpidem and Zaleplon on Cognitive Performance after Emergent Morning Awakenings at Tmax: A Randomized Placebo Controlled Trial*, 42 SLEEPJ, no. 3, 2019.

44 Schork, *supra* note 41, at 611 ("If done properly, claims about a person's response to an intervention could be just as well supported by a statistical analysis as by analyses designed to assess population-level responses on the basis of classical clinical trials.").

45 NPD 7170.1, *supra* note 11.

III. APPLYING PRECISION MEDICINE IN AN EXPLORATION CONTEXT

NASA and other Space Agencies have started to investigate the benefits of omics and precision medicine. The most notable human research so far was NASA's Human Research Program's Twins study in 2015.[46] The study compared astronaut Scott Kelly, who flew a one-year mission aboard the ISS, with his identical twin—also an astronaut—Mark Kelly being monitored on the ground. It was a unique opportunity to examine the changes that a year in space would cause to the human body. Twin Study researchers collected a Longitudinal Integrated Multi-omics analysis; biochemical profiles; immunologic assessments; cognitive assessments; and epigenetic and microbiome measurements in an effort to understand the changes induced by the spaceflight environment.[47]

NASA's GeneLab has been compiling omic data and metadata from experiments in space from 1995 on including Space Shuttle and ISS experiments.[48] More recently, the European Space Agency ("ESA") in 2015 published the results of a pharmacogenomics assessment of the ISS pharmaceutical formulary. The ESA study demonstrated that 30% of medications flown at that time may be metabolized differently by different individuals paving the way for pharmacogenomics matching for a spaceflight formulary.[49]

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46 For an overview of the Twins Study and the research released to date, *see NASA Twins Study Investigators to Release Integrated Paper in 2018*, NAT'L AERONAUTICS SPACE ADMIN. (Jan. 31, 2018), https://www.nasa.gov/feature/nasa-twins-study-investigators-to-release-integrated-paper-in-2018 (last visited Aug. 6, 2019). *See also* Christine Bear, *Twins in Space: How Space Travel Affects Gene Expression*, THE CONVERSATION (Jan. 19, 2019, 5:30 PM), http://theconversation.com/twins-in-space-how-space-travel-affects-gene-expression-107936. A complete description of the Twins study can be found at: *Human Research Program*, NAT'L AERONAUTICS & SPACE ADMIN., https://www.nasa.gov/twins-study (last visited Aug. 6, 2019).

47 Garrett-Bakelman, *supra* note 13, at 1.

48 *About Gene Lab*, NAT'L AERONAUTICS & SPACE ADMIN., GENELAB, https://genelab.nasa.gov/about (last visited Aug. 6, 2019) ("GeneLab's database is a collection of information from biological experiments that date as far back as 1995 through current studies conducted aboard the ISS and other platforms like the retired space shuttle program.").

49 Julia C. Stingl et al., *Where Failure is Not an Option – Personalized Medicine in Astronauts*, 10 PLOS ONE 10 (2015), https://journals.plos.org/plosone/article?id=10.1371/journal.

These studies suggest that clinical care informed by improved insight into genetic variability has the potential to significantly improve the safety and health of human space explorers in several areas. The potential gains that may be realized as the field matures fall into two overarching categories: (1) Improving NASA's ability to characterize the health risks faced by individual crew members and by extension mission risk due to performance decrements or Loss of Crew Life and (2) development of countermeasures to address those health and performance risks that are tailored to individual crew. This second part includes consideration of omic information to more precisely personalize countermeasures for individual crew members in a number of areas such as medication selection, food selection, sleep prescriptions, exercise prescriptions, and training modalities. Both the collection of the information needed to realize these benefits, and the real-world use of this information carries with it different legal and policy challenges. A short summary of potential mapping between precision medicine and possible application in spaceflight specific areas is reviewed in the following sections.

A. Radiation Hazard

For many years, the health effects of radiation during exploration missions have been regarded as one of the most challenging risks facing human explorers.[50] Radiation concerns historically have been broken up into two categories: in-flight concerns that radiation may affect a crew's ability to perform their mission and long-term health concerns for that radiation exposure during a mission would increase a crew member's lifetime risk of developing cancer and other diseases.

The in-flight issues can be broken into three major concerns for a long-duration exploration class mission:

1. Acute radiation sickness ("ARS") due to a large solar particle event;[51]

pone.0140764.

50 Jeffrey Chancellor et al., *Limitations in Predicting the Space Radiation Health Risk for Exploration Astronauts*, 4 NATURE PARTNER J.: MICROGRAVITY 1, 8 (2018).

51 *See* NAT'L AERONAUTICS & SPACE ADMIN., HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF ACUTE RADIATION SYNDROMES DUE TO SOLAR PARTICLE EVENTS, (2016), https://humanresearchroadmap.nasa.gov/Evidence/reports/Acute.pdf [hereinafter ARS EVIDENCE REPORT].

2. Subtle changes to central nervous system ("CNS") that may affect cognitive function and performance; and[52]
3. Degenerative effects on body tissues that will predispose to disease in mission.[53]

NASA has long been concerned that ARS would result if crews were exposed to large solar particle events ("SPEs").[54] ARS symptoms can have mission-ending consequences for the crew, including harm to the blood and circulatory system, the gastrointestinal system, skin, and neurovascular function. Crew performing EVAs during a SPE are also likely to experience severe symptoms within days after exposure, including nausea, vomiting, anorexia, skin injury, and fatigue.[55] Despite the potential seriousness of the ARS, the in-flight risk for ARS is now considered an "accepted" risk based on planned radiation shielding in exploration vehicles.[56]

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52 *See* NAT'L AERONAUTICS & SPACE ADMIN., HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF ACUTE AND LATE CENTRAL NERVOUS SYSTEM EFFECTS FROM RADIATION EXPOSURE (2016), https://humanresearchroadmap.nasa.gov/Evidence/reports/CNS.pdf [hereinafter CNS EVIDENT REPORT].

53 *See* NAT'L AERONAUTICS & SPACE ADMIN., HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF CARDIOVASCULAR DISEASE AND OTHER DEGENERATIVE TISSUE EFFECTS FROM RADIATION EXPOSURE (2016), https://humanresearchroadmap.nasa.gov/Evidence/reports/Degen.pdf [hereinafter DTE EVIDENCE REPORT].

54 *See generally* LYNDON B. JOHNSON SPACE CTR., NAT'L AERONAUTICS & SPACE ADMIN., HUMAN HEALTH AND PERFORMANCE RISKS OF SPACE EXPLORATION MISSIONS 171–190 (Jancy Mcphee & John Charles eds., 2009) (explaining in Chapter 5 ("Risk of Acute Radiation Syndromes Due to Solar Particle Events") the risk of acute radiation syndrome during the early human space program). *See also* NAT'L RESEARCH COUNCIL, RADIOBIOLOGICAL FACTORS IN MANNED SPACE FLIGHT 20–26 (Wash., D.C.: The Nat'l Academies Press, 1967); *What is Space Radiation?*, NAT'L AERONAUTICS & SPACE ADMIN. SPACE RADIATION ANALYSIS GROUP, https://srag.jsc.nasa.gov/SpaceRadiation/What/What.cfm (last visited Aug. 6, 2019) (describing space radiation and solar particle events).

55 *See* ARS EVIDENCE REPORT, *supra* note 51, at 4.

56 A full discussion of NASA's risk management process is beyond the scope of this paper. Under NASA's risk management guidelines, an "accepted" risk is one that has undergone the "formal process of justifying and documenting a decision not to mitigate a given risk associated with achieving given objectives or given performance requirements. Risk acceptance can take place when the consequences are tolerable should the risk occur, or when the risk cannot be reasonably mitigated with further action." NAT'L AERONAUTICS & SPACE ADMIN., DOCUMENT S3001: GUIDELINES FOR RISK MGMT. (Version G) 3 (Oct. 16, 2017), https://www.nasa.gov/sites/default/files/atoms/files/s3001_guidelines_for_risk_management_-_ver_g_-_10-25-2017.pdf.

The CNS and degenerative effects over long mission durations are less clear and in both cases NASA researchers see possible benefits to omic data for help in clarifying the clinical significance.[57,58]

The major long-term health concern from radiation exposure during an exploration mission is radiation carcinogenesis. This is most concerning for missions outside the Earth's magnetic sphere where crews are exposed to higher levels and different types of radiation than typically experienced on earth or in low earth orbit.[59] This is an area in which novel approaches using precision medicine are likely to play a larger role.

Currently NASA assesses individual risk for carcinogenesis base on a complicated algorithm that considers population-oriented statistics, but not individual response.[60] The current model incorporates sex and age at exposure to calculate excess risk from radiation induced cancers.[61] Susceptibility to radiation-induced cancer

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57 *See* CNS EVIDENCE REPORT, *supra* note 52, at 12 ("There are regional differences in tissues, and effects are sex-, age-, species-, and genetic background-dependent. Overall, the evidence points to persistent measureable [sic] changes in the functional status of the CNS similar to those seen during aging and in some neurological diseases, but we do not yet know if these changes rise to the level of operational or clinical significance in humans.").

58 *See* DTE EVIDENCE REPORT, *supra* note 53, at 29 ("[W]ith the recent advances in genomics research and "omics" data in general, it is likely that current and future research will provide an avenue to predict the risks of radiation based on genetic susceptibility.").

59 Chancellor, *supra* note 50, at 8 ("The health risks associated with exposures to space radiation will become more onerous as future manned spaceflight missions require extended transit outside of [low-Earth orbit] and beyond the protection of the Earth's magnetosphere.").

60 NAT'L AERONAUTICS & SPACE ADMIN., HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF RADIATION CARCINOGENESIS 12 (2016) [hereinafter CANCER EVIDENCE REPORT] ("as the models used currently at NASA to project space radiation risks are based on mortality data from population studies and do not include analysis of risk based on individual sensitivity, it is not currently recommended that genetic testing be performed on astronauts (NCRP 2010).").

61 *Id.* at 11 ("Because cancer is a genetic disease with important epigenetic factors, individual susceptibility issues are an important consideration for space radiation protection, and NASA's current cancer risk prediction model considers both sex dependence and how age at exposure effects the excess relative risks for radiation induced cancers (Cucinotta et al. 2013).").

is an area in which there is some level of known genetic variability.[62,63] Even very early studies of radiation victims showed evidence of individual susceptibility differences in radiation sickness and cancer.[64] As a result, individual genomic profiling may offer a more precise approach to defining individual health risks from radiation exposure than the current model which may over- or under-protect each individual crew member.[65]

When the National Council on Radiation Protection ("NCRP") approached this problem in 2010, precision medicine had not yet advanced to the point where there were identified genetic characteristics that could be linked to the "risk of radiation induced cancers or non-cancer health effects in humans."[66] Today, we are in a

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62 CANCER EVIDENCE REPORT, *supra* note 60, at 11 ("Genetic and environmental factors also impact risk of cancer from radiation exposure (NCRP 2010; Barcellos-Hoff et al. 2015). Studying the mechanisms of genetic sensitivity provides important insights into understanding the radiation risks to astronauts (Durante and Cucinotta 2008).").

63 *Id.* at 12 ("An important issue is how low penetrance genes impact sensitivity to radiation-induced cancer. A study on subjects exposed to high radiation doses… revealed a strong familial risk of radiation-induced meningioma (Flint-Ritcher and Sadetzki 2007), suggesting that radiation carcinogenesis might be an issue for a genetically predisposed subgroup of the general population, rather than a random event (Hall 2007; Sigurdson 2012). This is also supported by identification of genetic variants associated with increased occurrence of second cancers in survivors of childhood Hodgkin's lymphoma through the use of a genome wide association study (Best et al. 2011) and similarly, the identification of variants associated with radiation related papillary thyroid carcinoma in individuals exposed during the Chernobyl accident (Takahashi et al. 2010).").

64 *Id.* ("Studies of historical data sets such as the atomic-bomb survivors show that subsets of the exposed cohorts could have a higher than average radiation risk (Ponder 2001). A well-known example is *ataxia-telangiectasia* (AT) patients that dramatically demonstrated the importance of genetic susceptibility to radiation damage in cancer treatment. Other examples related to DNA repair genes include BRCA1&2, p53 (Ponder 2001), NBS (Pluth et al. 2008), Artemis (Wang et Risk of Radiation Carcinogenesis 12 al. 2005), and many other so-called high-penetrance genes involved in cancer susceptibility (Ponder 2001).").

65 *Id. ("*A predictive assay able to identify radiation hypersensitive, cancer-prone subjects could be useful in crew selection for long-term spaceflights. Alternatively, identifying resistant or reduced-risk individuals could substantially lower mission costs. However, as the models used currently at NASA to project space radiation risks are based on mortality data from population studies and do not include analysis of risk based on individual sensitivity, it is not currently recommended that genetic testing be performed on astronauts (NCRP 2010).").

66 NAT'L COUNCIL ON RADIATION PROTECTION, REPORT NO.167, POTENTIAL IMPACT OF INDIVIDUAL GENETIC SUSCEPTIBILITY AND PREVIOUS RADIATION EXPOSURE ON RADIATION RISK FOR ASTRONAUTS 4, 124 (Bethesda, Md., 2015).

different posture.[67] As mentioned above, genetic and environmental factors impact the risk of cancer from radiation exposure.[68] The Potomac Institute, in a recent report on a Projection of U.S. Cancer Mortality and Incidence Rates predicted that in the next several years, "[k]ey advancements in early detection and targeted treatment will allow cancer to be detected at its earliest and treated with precision, based on the unique genetic and epigenetic make-up of the individual and the cancer."[69] In 2017, the Human Research Program found that:

> Given the rapid advancement in genomics and personalized medicine, this type of assessment is likely scientifically achievable within the timeframe currently planned for a human deep space exploration mission. Ultimately, for a high risk and high cost endeavor such as a mission to Mars, screening astronauts for increased resistance to space radiation may be sought in order to reduce the costs of the missions or to support post mission disease surveillance.[70]

B. Ethical and Legal Implications

While GINA prevents NASA from using genetic information to make employment decisions, such as flight assignments, NASA can use genetic information to assess individual risk and to tailor countermeasures.[71] Of the four areas noted above, three (CNS, Degenerative Effects, and Cancer) appear to have the potential to use identification of individual sensitivities to radiation as a selection influencer. An example of this is the BRCA1 gene, which results in

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67 POTOMAC INST. FOR POLICY STUDIES, PROJECTION OF U.S. CANCER MORTALITY AND INCIDENCE RATES: FINAL REPORT 92 (2017) [hereinafter PIPS REPORT] (Noting that large advancements in DNA sequencing over the past decade has uncovered that more than 50% of human cancers conceal mutations in enzymes involved in chromatin organization. Cancerous tumor cells use epigenetic processes to ensure their survival. Thus, a growing field in cancer treatment research is the identification of drugs that target the epigenome.).

68 Cancer sensitivity in radiation therapy is an area where there are specific efforts to identify genomic markers for radiation sensitivity. Although spaceflight radiation is different, it is reasonable to assume there will be some crossover. *See* NCRP REPORT, *supra* note 65. *See also* Mary Barcellos-Hoff et al., *Concepts and Challenges in Cancer Risk Prediction for the Space Radiation Environment*, 6 LIFE SCIENCES IN SPACE RESEARCH 92 (2015); Brian Yard et al., *Radiotherapy in the Era of Precision Medicine*, 25 SEMINARS IN RADIATION ONCOLOGY 227 (2015).

69 PIPS REPORT, *supra* note 67, at 7.

70 CANCER EVIDENCE REPORT, *supra* note 60, 12–13.

71 *See* Antonsen & Reed, *supra* note 23.

increased likelihood of developing breast or ovarian cancer completely separate from radiation exposure. The incidence of breast cancer in individuals with the BRCA1 gene peaks in an age range of 41–50 years that is within the operational lifetime expected for career astronauts.[72] Cumulative estimates for breast cancer incidence in those with the BRCA1 gene is 40–87% by age 70; one study found that 72% of women with this genetic mutation developed breast cancer by age 80.[73] Additionally, this has implications for understanding whether individuals are at risk of increased incidence of cancer prior to their exposure to the spaceflight environment.

Genetic information may provide valuable insight into how the spaceflight environment, such as radiation, affects individuals and how to protect them. In 2010, NCRP noted that "it is generally not possible to predict an individual's inherent genetic susceptibility to the long-term risk of cancer or other diseases associated radiation."[74] Nearly 10 years later, it is worth revisiting that claim. Understanding an individual's predisposition for cancer or other illness is important not only to provide appropriate screening and countermeasures, but also to help guide determinations of the likelihood that a future incidence of disease is related to spaceflight, rather than just a part of normal aging. This will become increasingly important as NASA begins to implement the TREAT Astronauts Act. The TREAT Astronauts Act as written requires NASA to provide "monitoring, diagnosis, and treatment described in subsection (a) only for conditions the Administration considers unique to the training or exposure to the spaceflight environment"[75]

Beyond predicting the effects of radiation on an individual, precision medicine may help to inform countermeasures to counteract the effects of radiation. As above, three radiation considerations (ARS, CNS, and Degenerative Effects) may benefit from such personalized

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72 Karoline B. Kuchenbaeker et al., *Risks of Breast, Ovarian, & Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers*, 317 JAMA 23, 2405 (2017) (observing that "[t]he peak [breast cancer] incidence[s] occurred in the 41- to 50-year age group (28.3 [95% CI, 23.1–34.7] per 1000 person-years").

73 *Id.* at 2403.

74 *See* NCRP REPORT, *supra* note 65, at iii.

75 To Research, Evaluate, Assess, and Treat Astronauts Act ("TREAT Astronauts Act"), Pub. L. No. 115-10, § 442, 131 Stat. 18, 44-45 (2017).

countermeasures for an exploration crew. Although ARS is an accepted risk, there is still the potential for symptoms such as nausea and vomiting to occur as a result of an acute radiation exposure event. Common medications to treat radiation-induced nausea and vomiting include Ondansetron and Granisetron, both of which are metabolized differently in the liver.[76] Precision medicine may allow personalization of the pharmacy for each individual crew member to ensure that effective medications are provided. Such personalization has the potential to improve health outcomes and reduce the volume of the formulary by ensuring the drugs included are optimized for the crew.

C. Medical Conditions Susceptibility

Beyond the medical impacts of radiation, there are many other medical conditions related to spaceflight that may be responsive to a precision medicine approach. NASA developed a list of 100 concerning conditions that may be encountered in exploration, known as the Exploration Medical Condition List.[77] Among these conditions there are some that are impacted by genetic predispositions. For example, a medical condition like Cardiac Arrest can have an increased risk of occurrence based on many genetic factors.[78] These can include structural heart disease, dysrhythmias, and blood clots

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76 Rebecca S. Blue et al., *Challenges in Clinical Management of Radiation-Induced Illnesses During Exploration Spaceflight*, 90 AEROSPACE MED. & HUMAN PERFORMANCE 966, 970 (2019) ("Recent research has demonstrated a pharmacogenetic component in the response to different 5HT3 antagonists. As these medications are metabolized by the cytochrome-P450 enzymes, genetic variation in enzyme metabolism can affect individual response to each medication. For example, ondansetron is metabolized by the CYP2D6 enzyme; ultra-rapid metabolizers of the CYP2D6 pathway have a higher frequency of vomiting within 24 h of radiotherapy when treated by ondansetron compared to those who metabolize at a slower rate. In contrast, granisetron is metabolized by CYP3A and is more effective than ondansetron for rapid metabolizers of the CYP2D6 pathway. This suggests that therapies could be tailored based on genetic predispositions and that medications selected for an exploration mission could potentially be adjusted for individual crewmembers.") (internal citations omitted).

77 *See* SPACE & CLINICAL OPERATIONS DIV., LYNDON B. JOHNSON SPACE CTR., NAT'L AERONAUTICS & SPACE ADMIN., DOC. NO. JSC-65722, EXPLORATION MEDICAL CONDITION LIST (June 2013) [hereinafter EXPLORATION MEDICAL CONDITION LIST, JSC-65722].

78 *See* Matthew T. Bennett et al., *Review: Assessment of Genetic Causes of Cardiac Arrest*, 29 CAN. J. CARDIOLOGY 100 (2013).

that can lead to pulmonary embolism.[79] Structural heart diseases are likely to be caught during medical exams and through EKG. However, some known genetic causes of dysrhythmias such as Long QT syndrome, Brugada Syndrome, and ARVD are often identified through reviewing family history. Similarly, genetic factors such as Factor V Leiden or Protein C or S deficiencies are the important predisposing factor for blood clots in people younger than 50 years old.[80] These can cause a pulmonary embolus that precipitates cardiac arrest. Genetic testing is recommended for relatives of carriers of the Factor V Leiden mutation, as even a heterozygous carrier has a 4–7x increased risk to develop blood clots.[81] In the interest of compliance with GINA, NASA does not currently consider family history in astronaut selection evaluation, and these genetic risk factors are not part of the clinical screening performed on astronauts.

While omic risk factors for specific medical conditions may have impact on the risk that individuals and a program will ultimately take on a given mission, it is also likely that omic information can help to tailor mitigations to those same risks. Two areas, Systematic Molecular Phenotyping and Pharmacogenomics, appear to be making promising progress in this arena. These are discussed throughout the following sections.

D. Precision Medicine and Immune Function

Immune function and dysfunction, are potentially significant issues in exploration spaceflight.[82] Advances in the precision medicine world are beginning to elucidate the linkages between infectious disease, immune function, and genetic markers that in the future will likely help predict disease susceptibility on an individual basis. Systematic Molecular Phenotyping is a set of analysis techniques that seek to use information from genomics, transcriptomics, proteomics, and metabolomics to individualize diagnosis and treatment decisions

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79 EXPLORATION MEDICAL CONDITION LIST, JSC-65722, *supra* note 77, at 10.

80 *See* Cristina Hotoleanu, *Genetic Risk Factors in Venous Thromboembolism*, ADV. EXP. MED. & BIOL. 1 (2016).

81 EXPLORATION MEDICAL CONDITIONS LIST, JSC-65722, *supra* note 77, at 6.

82 Brian Crucian et al., *Immune System Dysregulation During Spaceflight: Potential Countermeasures for Deep Space Exploration Missions*, 9 FRONTIERS IN IMMUNOL. 1437, 1439 (2018).

in clinical medicine.[83] Limakeng et al. (2016) noted that "[i]n some cases, such research has identified disease subtypes that may respond differentially to existing treatments."[84] An example of this is recent work in Group A strep throat where immune-genetic markers help explain why some children have recurrent strep throat infections leading to tonsillectomy and others do not.[85] Advances in genetic immune-profiling like this are currently in the research pathway for the NIH to map our genetic factors that drive immune variability in response to infectious disease.[86]

In space, immune system changes have been observed in the six-month mission timeframe. These changes have been mostly subclinical, that is they don't seem to predispose crew members to increased likelihood of clinical disease within the current mission timeframes.[87] As Crucian et al. (2018) noted, the "human immune system is fundamentally 'shaped' by environmental exposures impacted by lifestyle choices (*i.e.*, diet, exercise, social habits, etc.) leading to epigenetic changes in gene expression in determining specific individual responses to various environmental antigen challenges."[88]

Some experiments suggest that the microgravity environment itself can affect genetic transcription of the immune cells required to fight disease.[89] While these immune changes have not significantly impacted crews in general during 6 month missions, it is known that there is "…increased incidence of infectious disease as well as

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83 *See* Alexander T. Limkakeng, Jr. et al., *Systemic Molecular Phenotyping: A Path Towards Precision Emergency Medicine*, 23 ACAD. EMERGENCY MED. 1097, 1098–1101 (2016).

84 *Id.* at 1098.

85 *See* Jennifer M. Dan et al., *Recurrent Group A Streptococcus Tonsillitis is an Immunosusceptibility Disease Involving Antibody Deficiency and Aberrant TFH Cells*, 11 Sci. Translational Med. 478 (Feb. 6, 2019).

86 *Immunoprofiling*, IMMUNE MATTERS 5 (2018) (observing "[t]hey are mapping out the genetic factors that drive the immune system's variability and finding out which kinds of cells control infections and which ones fail.").

87 *See* NAT'L AERONAUTICS & SPACE CENTER, HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF CREW ADVERSE HEALTH EVENT DUE TO ALTERED IMMUNE RESPONSE 9 (2015) [hereinafter ALTERED IMMUNE EVIDENCE REPORT].

88 Crucian, *supra* note 82, at 7.

89 *See* ALTERED IMMUNE EVIDENCE REPORT, *supra* note 87, at 17.

increased allergic symptoms and persistent skin hypersensitivity reactions in some crewmembers during orbital flight" despite the fact that crews have been isolated from terrestrial pathogens in the pre-flight domain.[90] It is a concern that subclinical immune changes will manifest to a level that impacts human health and performance in much longer missions.[91] If genomic, epigenomics, or transcriptomic markers are identified that predict individual variability to the spaceflight environment or susceptibility to specific medical conditions, then they would be useful in assessing individual risk and potentially for tailoring countermeasures.

E. Pharmacogenomics

Pharmacogenomics is the study of how a person's genes affect their response to medications.[92] While this is not widely used across all areas of medicine, the advances in this domain and applicability to spaceflight warrant consideration for future potential. A 2014 study of the medications on the ISS showed that as many as 30% are known to be differentially metabolized by individuals with polymorphisms in Cytochrome p450 enzymes. This insight suggests there may be more variation in medication effectiveness among the astronaut population than previously suspected.[93]

In the terrestrial population, the Mayo RIGHT study recently found that 99% of over 1,000 people tested had at least one actionable pharmacogenomic polymorphism of five reviewed.[94] Three of these

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90 Crucian, *supra* note 82, at 2.

91 ALTERED IMMUNE EVIDENCE REPORT, *supra* note 87, at 5 ("The specific cause of immune system dysregulation during flight remains unknown but it's likely associated with one or more of the following: physiological stress, disrupted circadian rhythms, microgravity, isolation, altered environment, altered nutrition, and radiation.").

92 *See* GENETICS HOME REFERENCE, *What is pharmacogenomics?*, U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics (last visited Aug. 6, 2019).

93 *See* Stingl, *supra* note 49.

94 Yuan Ji et al., *Preemptive Pharmacogenomic Testing for Precision Medicine: A Comprehensive Analysis of Five Actionable Pharmacogenomic Genes Using Next-Generational DNS Sequencing and a Customized CYP2D6 Genotypic Cascade*, 18 J. OF MOLECULAR DIAGNOSTICS 3, 443 (2016) ("Of the 1013 RIGHT patients, 99% carry at least one ACTIONABLE variant. Furthermore, 3% of participants carry actionable PGx variants in all of the five genes.").

same polymorphisms in the RIGHT study were also studied in Stingl's work. This suggests that it is both common for individuals to have some genetic predisposition to metabolizing medications differently and that a significant proportion of the medications that are already flown in space have the potential to be metabolized differently by different crew members in exploration missions.

It is not just possible—it is likely that genomics will impact the efficacy of treatment for medical conditions in exploration spaceflight. Of the 100 medical conditions that NASA lists in the Exploration Medical Conditions List,[95] 79 of them would indicate the use of at least one medication from the Stingl list known to have differential metabolizing properties in individuals. This list includes common medications for pain, fever, nausea, as well as some mediations that are definitive treatment for specific conditions such as phenytoin for seizures, and Bactrim for urinary tract infections.[96] Although these medications may not in every case be the terrestrial first-line medication, in an exploration mission where there is no possibility of resupply or adding new medications to a pharmacy, these medications would be drawn on heavily for treatment. The implication is that it may be common for individuals to have a variable response to the medications already flown in spaceflight as well as future medications likely to be considered for the formulary that are in part based on genetic indicators of metabolism. The deleterious effects of mismatched medications for a crew could be mitigated by one-time pharmacogenomics testing and personalizing pharmacies for exploration crews. Such a use of genetic information is consistent with GINA.[97]

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95 *See* NAT'L AERONAUTICS & SPACE CENTER, HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF ADVERSE HEALTH OUTCOMES AND DECREMENTS IN PERFORMANCE DUE TO IN-FLIGHT MEDICAL CONDITIONS (2017), https://humanresearchroadmap.nasa.gov/Evidence/reports/Medical.pdf. [hereinafter MEDICAL EVIDENCE REPORT]. *See also* EXPLORATION MEDICAL CONDITION LIST, JSC-65722.

96 *Id.*

97 *See* Antonsen & Reed, *supra* note 23.

F. Behavioral and Cognitive Factors

Personalized medicine may also improve Behavioral and Cognitive Health in exploration missions.[98] Current fitness for duty standards in Behavioral and Cognitive Health indicate that in-flight status shall be within clinically accepted values as judged by clinical psychological evaluation.[99] The maintenance of in-flight behavioral and cognitive function is expected to be more challenging in exploration missions than in low earth orbit. Increased distance from earth, time delays in communication, and extended isolation and confinement in smaller spaces are all expected to contribute to an increase in Behavioral Health and Cognitive needs.[100] NASA has already funded omic research that can inform Systematic Molecular Phenotyping approaches for Behavioral and Cognitive needs:

> NASA-funded research is currently assessing the predictive value of specific biomarkers, including catecholamines (such as dopamine), as potential biomarkers for sensitivity to central nervous system effects resulting from radiation exposure (Goel et al. 2015; St. Hilare et al. 2015);

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98 NAT'L AERONAUTICS & SPACE CENTER, HUMAN RESEARCH PROGRAM, EVIDENCE REPORT: RISK OF ADVERSE COGNITIVE AND BEHAVIORAL CONDITIONS AND PSYCHIATRIC DISORDERS 10 (2016), https://humanresearchroadmap.nasa.gov/Evidence/reports/BMed.pdf [hereinafter BMED EVIDENCE REPORT] ("The goal of the behavioral health component of the astronaut selection system is to identify individuals who, at the time of application, have diagnoses that are incompatible with the demands of space flight, and also to identify those who are believed to be best suited psychologically to be astronauts. Current BHP research efforts involving biomarkers may serve to inform the selection process for future exploration missions, as well as further enable a personalized approach to flight medicine.").

99 NAT'L AERONAUTICS & SPACE ADMIN., NASA-STD-3001 VOL. 1, REVISION 1 W/CHANGE 1, NASA SPACE FLIGHT HUMAN-SYSTEM STANDARD, VOL. 1 REV. A: CREW HEALTH 19 (Feb. 12, 2015), https://standards.nasa.gov/standard/nasa/nasa-std-3001-vol-1.

100 BMED EVIDENCE REPORT, *supra* note 98, at 11–12 (observing that "Not only might the missions be longer, but given their unprecedented distance from earth, there will also be other stressors not experienced on the Station. For example, depending upon the specific destination, exploration missions will be characterized by confinement in decreased habitable volume, decreased privacy, an inability to see Earth, a lack of resupply and care packages, anticipated periods of increased monotony and routine, limited medical care, no evacuation options, less social, physical, and sensory stimulation, danger from radiation exposure, and a delay in communication of up to 20 minutes one-way. These in turn are anticipated to affect both mission operations and crewmembers' perceptions of isolation and their limited ability to stay in touch with mission control and family and friends on the ground. Further, exploration missions will be marked with greater uncertainty as we move away from the known (the ISS) toward the unknown . . . .").

> metabolomics, as potential biomarkers of an increased stress response (see e.g., Cooksey et al. 2009) and epigenetic and genetic markers (e.g., Rokutan et al. 2005), such as single nucleotide polymorphisms of certain clock genes (e.g. PER3), as biomarkers for vulnerabilities to sleep loss (Goel 2015; Goel and Dinges 2011).[101]

Genomic markers of susceptibility to depression or anxiety might help to ensure the deployment of appropriate medications for in-flight countermeasures.[102] Genomic information would also help to ensure that the formulary for behavioral health and cognition are appropriate to the crew. As noted in the Stingl paper cited above, multiple medications relevant to behavioral health, cognitive performance, and sleep known to have variable metabolizing profiles based on the Cytochrome p450 system have already been flown in spaceflight.[103]

Sleep is an excellent example of a behavioral clinical issue with wide-ranging consequences that may be improved through genomics and precision medicine. Sleep interacts with many other health risks in spaceflight. For instance, animal studies have suggested that chronic moderate sleep restriction blunt the beneficial effects of exercise on immune function and carcinogenesis.[104] Crucian et al. (2018) note that "there is an established relationship between the immune system and psychological stress, circadian rhythms, and sleep."[105] Sleep issues in spaceflight are common, and a broad array of mitigation efforts have been brought to bear. Dinges and Goel note that there are genetic polymorphisms related to a variety of sleep parameters that impact individual variations observed in sleep that can impact performance as well as provide pathways for tailored countermeasures.[106]

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101 *Id.* at 10.

102 *Id.* at 60 ("An important consideration is future research on potential genetic biomarkers that will "personalize" the approach to help predict antidepressant and anxiety disorder treatment responses since both have effects on the serotonergic neurotransmitter system . . . .").

103 *See* Stingl, *supra* note 49.

104 Maria Moreno-Villanueva & Honglu Wu, *Radiation and Microgravity – Associated Stress Factors and Carcinogenesis*, 13 REACH: REVIEWS IN HUMAN SPACE EXPLORATION 9 (2019).

105 Crucian, *supra* note 82, at 12.

106 Namni Goel & David F. Dinges, *Predicting Risk in Space: Genetic Markers for Differential Vulnerability to Sleep Restriction*, 77 ACTA ASTRONAUTICA 207 (2012) ("In summary, a number

Approaches used to tailor countermeasures for sleep in spaceflight to date have been mostly empiric with little focus on genetic predispositions or pharmacogenomics impacts to countermeasures. These include scheduling accommodation, light spectral changes to affect circadian rhythm, and pharmaceuticals to help manage sleep and fatigue.[107,108] NASA currently employs individualized drug tolerance testing to manage challenges with sleep that are well known to occur in spaceflight.[109] This individualized drug tolerance testing requires overnight testing for individuals to try various medications at varying doses and measure parameters like sleep quality as well as post-sleep alertness. This is a time consuming and costly way to assess individual response to specific medications that likely have a genomic dependence for metabolism. Of the medications tested, Zolpidem is known to have a dependence on CYP3A polymorphisms[110] while Zalepon does not.[111] Pharmacogenomic testing may offer a simpler and cheaper way of reaching the same end goal of tailoring medication and dose to a crew member in order to optimize their performance while in-mission. By engaging in individual testing, NASA has already determined that the costs of doing this for crews on an empirical basis are worth the benefits realized in human performance in flight.

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of common genetic polymorphisms involved in circadian, sleepwake, and cognitive regulation appear to underlie inter-individual differences in basal (fully-rested) sleep parameters and homeostatic regulation of sleep in response to sleep loss (both chronic restriction and acute total sleep deprivation) in healthy adults.").

107 *See* George C. Brainard et al., *The Development of Lighting Countermeasures for Sleep Disruption and Circadian Misalignment During Spaceflight*, 22 CURRENT OPINION IN PULMONARY MED. 535 (2016).

108 *See* Erin Flynn-Evans et al., *Circadian Misalignment Affects Sleep and Medication Use Before and During Spaceflight*, 2 NATURE PARTNER J.: MICROGRAVITY 1 (2016).

109 MEDICAL EVIDENCE REPORT, *supra* note 95, at 27 ("In both the Space Shuttle and ISS Programs, NASA used personalized medicine, in the form of individualized drug tolerance testing, to personalize sleep and alertness interventions for crew . . . .").

110 Lisa L. von Moltke et al., *Zolpidem Metabolism* In Vitro*: Responsible Cytochromes, Chemical Inhibitors, and* In Vivo *Correlations*, 48 J. CLINICAL PHARMACOLOGY 89 (1999).

111 Stingl, *supra* note 49, at 6.

G. Bone Loss and Biologic Variability

A well-known example of concern in human spaceflight is bone loss associated with a prolonged exposure to the microgravity environment. A study of data from 45 long-duration astronauts and cosmonauts who were exposed to the spaceflight environment from 4–6 months in duration showed average bone mineral losses between 2–9% over a variety of bone sites recorded. The worst losses occurred in the hip bone (trochanter) and averaged around 7.8% with recovery times back to their pre-flight baseline estimated to take almost 3 years. This is remarkable because it suggests bone loss for the mostly white male cohort observed (there were 3 females included) averaging 43 years old responds to the spaceflight environment more like "*elderly*, post-menopausal white females."[112]

This only tells part of the story. Other studies that look at the internal structure of bone found significant losses beyond bone mineral density as well as significant individual variation. Research using different methods of looking at bone structure in 8 astronauts found average losses of 14% of hip bone trabecular bone mineral density lost; at least one individual showed much more rapid bone loss returning with a 24% decrease. [113]

The level of bone resorption and post-mission recovery varies dramatically among individuals. It is possible that genetic factors play a significant role in this variability for both loss and recovery of bone.[114] It is also thought that both psychological and physical stress

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112 Jean Sibonga et al., *Recovery of Spaceflight-induced Bone Loss: Bone Mineral Density after Long-Duration Missions as Fitted with an Exponential Function*, 41 BONE 973, 976 (2007).

113 Carpenter et al., *Long-term Changes in the Density and Structure of the Human Hip and Spine After Long-duration Spaceflight*, 67 ACTA ASTRONAUTICA 71, 79 (2010) ("In our study, crew members lost 14% of their femoral neck tBMD [Trabecular Bone Mineral Density] on average, or nearly 1/3 of the total expected lifetime loss, in only 4 to 6 months. One subject lost 24% of his femoral neck tBMD, or over 1/2 of the expected lifetime loss, in just over five months aboard the ISS. These results suggest that rapid changes in bone mineral distribution occur during spaceflight, and these changes affect bone structure for at least 4.5 years after returning to Earth.").

114 Sibonga, *supra* note 112, at 976 ("It is important, however, to note that skeletal recovery is highly variable among crew members . . . some crew members recover within the first year after return while others do not recover until much later. Factors that contribute to this variability in recovery are likely to include nutrition, skeletal muscle reconditioning, and genetics." (citations omitted)).

contribute to both immune function changes as well as changes in bone microarchitecture.[115] Other research has suggested that genetics accounts for as much as 60%–80% of bone remodeling in response to environmental loading and but that it may be the cumulative effects of many genes.[116] Researchers in this area have noted the potential benefit to understanding how genomic information affects bone metabolism.[117] In the case of bone loss, terrestrial research has long implicated genetic processes.[118] At least 24 genes and loci have identified genome-wide significant evidence for association with bone mineral density.[119]

If genetic or epigenetic markers are identified that can predict an individual astronauts' bone loss response to the spaceflight environment as well as likely metabolism rate of the medications under consideration, then that information could be used to provide improved individualized countermeasures to address bone loss. This offers potential in mission benefits including better characterization of the risk of fracture as the first crews plan to work on the surface of Mars as well as ways to personalize mitigation of the long-term health effects of multi-year missions in reduced gravity environments.

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115 Crucian, *supra* note 82, at 10.

116 Stefan Judex et al., *Genetic Loci that Control the Loss and Regain of Trabecular Bone During Unloading and Reambulation*, 28 J. BONE & MINERAL RESEARCH 1537, 1537–38 (2013) ("In spite of clear evidence that genetic variations influence bone's response to altered mechanical environments, little is known about the identity of the genes that harbor the responsible polymorphisms. For the acquisition of *peak bone mass*, it is assumed that 60% to 80% of the observed variability is due to genetic variables and that this trait is polygenic, with small cumulative effects of many genes.").

117 Sibonga, *supra* note 112, at 977 ("Collectively, future studies will not only need to evaluate how bone *metabolism* responds to changes in mechanical loading (at the molecular, cellular and tissue level) but how changes in skeletal mass and structure correlate with changes in muscle forces, with expression of skeletally relevant genes and with nutrient uptake in this crew member population.").

118 Stuart Ralston & Andr. . . Uitterlinden, *Genetics of Osteoporosis,* 31 ENDOCRINE REVIEWS 629, 630 ("Many factors influence the risk of osteoporosis, including diet, physical activity, medication use, and coexisting diseases, but one of the most important clinical risk factors is a positive family history, emphasizing the importance of genetics in the pathogenesis of the disease . . . .").

119 *See id*. at 641 (Table 4).

IV. POTENTIAL ETHICAL ISSUES IN PRECISION MEDICINE

While precision medicine has important applications to exploration, it introduces a number of ethical challenges. The challenges include balancing allowable uses of genetic information with mission risk and how to address incidental findings. Neither of these ethical challenges are unique to spaceflight. However, in the context of NASA's mixed role as both clinical care provider and employer, they take on particular significance.

A. Individual Variation and Mission Risk

In each of the examples discussed above—radiation risk, medical and immune response, behavioral and cognitive performance, and bone loss in space—there is reason to suspect that omic information about an individual crew member may help give insight into the risks that that individual will experience as well as the proportion of risk that they may bring to the larger mission. It may also inform and enable more effective countermeasures that are personalized for crew members, resulting ultimately in decreased individual and mission risks as exploration missions are undertaken.

Understanding the individual risk profile of crew members will also inform the risk profile for any mission that is undertaken. Using that information appropriately will require attention to the GINA restrictions. As an example, consider the Factor V Leiden mutation discussed above. Under GINA, it would be inappropriate to use that information in a flight assignment decision. However, there are appropriate and beneficial uses of that information that do not run afoul of GINA. While it is known that any individuals with a heterozygous mutation have a 4–7 fold increase in risk for blot clots, when oral contraceptives for control of menstruation are used by these individuals, the risk of blood clot increases 34 fold.[120] Female astronauts have long used oral contraceptive medications to suppress their menstrual cycle in spaceflight.[121] Flight surgeons could use this information to select personalized approaches that reduce risks to

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120 Hotoleanu, *supra* note 80, at 2.

121 Varsha Jain & Virginia Wotring, *Medically Induced Amenorrhea in Female Astronauts*, 2 NATURE PARTNER J.: MICROGRAVITY 1, 3 (2016).

individual crew members as well as the mission overall and remain in compliance with GINA. Such personalized approaches might include different methods of menstrual suppression or operational changes to account for avoiding suppressive therapy.

In cases where a crew member's individual risk predisposition increases mission risk overall without clear mitigation options, it becomes more challenging to use this information and continue to remain in compliance with GINA. Returning to the Cardiac Arrest example from above, Long QT syndrome is an important cause of sudden cardiac in young, previously healthy individuals including athletes.[122] It is estimated to be responsible for 7–23% of unexplained cardiac arrest, and up to half of the people who have this disorder have a normal resting EKG.[123] This acute risk is different from the lifetime risk of developing cancer as it may affect the safety and health of a crew while in space. To remain compliant with GINA, NASA policies would need to define how or whether this information is being collected and used. This presents an ethical dilemma in that not screening for it may be inconsistent with the responsibility that NASA has to "[f]ully inform astronauts about the risks of long-duration and exploration space flights and make certain that the informed decision-making process is adequate and appropriate."[124]

While this presents a dilemma, it also presents a possible path forward. NASA may wish to explore how to develop policies that balance the need to protect genetic information from misuse under GINA and the need to both inform astronauts of their own risk and appropriately manage overall mission risk.

Planning for precision medicine does not require a change in policy as much as it suggests the needs for additional policies that fills in areas in clinical and occupational use of information to establish appropriate use and boundaries. This would allow NASA to meet the ethical obligations for both understanding risk and mitigating risks it to the fullest extent possible. However, the benefits of precision medicine approaches must be balanced by considering the potential legal and ethical pitfalls.

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122 Bennett, *supra* note 78, at 101.

123 *Id.* at 102.

124 NPR 8900.1B APPENDIX F, *supra* note 10.

B. Incidental Findings

One of the most persistently perplexing challenges in genomics is the issue of incidental findings. An incidental finding is information that is unintentionally obtained in the course of research on or treatment for an unrelated condition.[125] In terrestrial medicine, incidental findings are a well understood ethical dilemma. As Berg et al. (2013) noted, "[a] central tension in the return of genomic IFs [Incidental Findings] is between the ethical principles of 'duty to warn' and 'do no harm' on the part of physicians" balanced against "the various choices of patients, some of whom wish to 'know everything' in their genome and others who will undoubtedly wish to exercise their preference 'not to know' certain findings."[126]

The sensitivities in this field are well illustrated by a real-life example. Dr. James Watson is notable for having received the Nobel Prize for his contribution to the discovery of the structure of DNA in 1963. In 2008, his full genome was sequenced and published with the exception of a single gene. That gene, ApoE, has been associated with an elevated risk of Late Onset Alzheimer's Disease. This disease, which is incurable, claimed one of his grandmothers.[127] Dr. Watson's ApoE results might have had implications for not only him, but his family, since it is heritable. Incidental findings may also reveal unwanted information about parentage, likelihood of developing disease, and other issues.

The problem of incidental findings is exacerbated by the disparity between what we can identify and what we can treat. Over 5,000 diseases can be identified through genetic testing, but only about 60 are considered actionable and therefore reportable from research results.[128] When the original recommendations for reporting

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125 *See* Shiri Shkedi-Rafid et al., *Defining and Managing Incidental Findings in Genetic and Genomic Practice*, 51 J. OF MED. GENETICS 715 (2014) (examining the challenge of incidental findings in genomic and genetics in several settings, including clinical care and research).

126 Jonathan S. Berg et al., *Processes and Preliminary Outputs for Identification of Actionable Genes as Incidental Findings in Genomic Sequence Data in the Clinical Sequencing Exploratory Research Consortium*, 15 GENETIC MED. 860, 861 (2013).

127 *See On Jim Watson's* APOE *Status: Genetic Information is Hard to Hide*, 17 EUROPEAN J. HUMAN GENETICS 147 (2009).

128 Sarah S. Kalia et al., *Recommendations for Reporting of Secondary Findings in Clinical Exome and*

incidental findings were released by the American College of Medical Genetics in 2012, there was community resistance based on the wording that suggested for any whole genome or whole exome testing 56 genes should be targeted and results provided to physicians to discuss with patients. [129] There was also a push to provide patients the opportunity to "opt out" of receiving information.[130] All of these issues are further complicated by the large uncertainty that still surrounds genomics: ". . . for most of the genes, we lack evidence about the predictive value of testing, genotype penetrance, spectrum of phenotypes, and efficacy of interventions in unselected populations."[131] These examples give credence to the need for a well-thought out policy approaches that anticipate issues before they arise in the clinic.

The potential for incidental findings creates an ethical challenge that NASA should consider addressing as it begins to collect genetic and genomic data. The recent Policy Governing Use of Human Research Genetic Testing[132] addresses these issues by making participation voluntary, restricting access to and use of data, requiring a separate database from the Electronic Medical Record, offering genetic counseling to all participants, and requiring monitoring for incidental findings such that the agency is aware of how often incidental findings occur.[133]

Beyond individual choice to know or not know about incidental findings, NASA may have an interest in clinically-significant findings. NASA's policy for the clinical and operational use of genetic information should engage with these difficult questions. Incidental findings could help NASA to characterize potential risks to mission success and the need for individualized countermeasures. Genetic

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Genome Sequencing, 2016 Update (ACMG SF v2.0): A Policy Statement of The American College of Medical Genetics and Genomics, 19 GENETICS IN MED. 249, 249 (2017).

129 Myra Roche & Jonathan Berg, *Incidental Findings with Genomic Testing: Implications for Genetic Counseling Practice*, 3 CURRENT GENETIC MED. REPORTS 166, 168 (2015).

130 *Id.* at 168.

131 Wylie Burke, *Recommendations for Returning Genomic Incidental Findings? We Need to Talk!* 15 GENETIC MED. 854, 854 (Nov. 2013).

132 NPD 7170.1, *supra* note 11.

133 *Id.*

markers for increased risk of heart disease or cancer could potentially alter mission risk profiles and call for enhanced screening and treatment capabilities during a mission. For instance, an incidental finding of a BRCA1 gene in a crew member would increase the likelihood of both breast and ovarian cancer. However, it is unknown if or when the disease might manifest and how it might progress. For a mission to Mars in which the training flow is at minimum two years and the mission itself three years, NASA policy would likely need to balance the interests of the astronaut with the interests of the crew and mission. Anticipating these issues will ensure a transparent and equitable process for addressing them.

Despite the GINA prohibitions on the use of genetic information for employment decisions, the IOM recommended that NASA consider doing just that as part of a larger strategy of risk reduction for Exploration Spaceflight:

The committee recommends that, wherever possible, NASA use actuarial data … as well as additional sources such a genomic data, where available to estimate and/or model the likelihood of intrinsic health alterations for crew who will be part of the Mars mission. Utilization of this information as part of the selection criteria for astronauts should be considered. After intrinsic health risks are estimated, NASA should then estimate and/or model the contribution of the space environment and life support system malfunction to increased risk.[134]

While it is unclear if there is a right answer in how to deal with these challenges, it is clear that the likelihood is increasing that NASA will have to deal with issues like this as genomic testing becomes more available, and potential application to characterizing and mitigating individual and mission risks matures.

CONCLUSION

NASA has adopted the ethical framework for Exploration set forward in the IOM report in 2014 and written it into agency policy.

134 INST. OF MED. ET AL., A RISK REDUCTION STRATEGY FOR HUMAN EXPLORATION OF SPACE: A REVIEW OF NASA'S BIOASTRONAUTICS ROADMAP 50 (Wash., D.C.: The Nat'l Academies Press, 2006).

This includes responsibilities to (1) create an adequate and appropriate risk informed decision-making process for exploration spaceflight; (2) adhere to a continuous learning strategy that draws from all relevant sources; and (3) provide comprehensive health care to protect their health, improve mission safety, and reduce risks for current and future astronauts.[135] Precision medicine as a field is making rapid advances that warrant the attention of NASA as it seeks to fulfill each of these responsibilities. On the timeframe for exploration missions to Mars, these fields are likely to have significant advances that will drive a desire for inclusion of these developing capabilities in clinical and operational areas such as astronaut selection, crew flight assignment, individual and mission risk assessment, fielded medical and pharmacologic capabilities in-mission, and health-care for crews post-mission.

By taking advantage of expected gains in these fields in the clinical and operational domains, NASA can position itself well through proactive development of enabling and bounding policies. Policies which enable the rapid application of advances in precision medicine as they mature will allow NASA to reduce the health risks inherent in human spaceflight in a number of ways. It will allow NASA to identify crew members at increased risk for medical conditions that may manifest during spaceflight and then support the development of tailored countermeasures to reduce the incidence and severity of those conditions. Systematic Molecular Phenotyping may allow improved understanding of crew responses to the spaceflight environment or medical conditions in-mission. Pharmacogenomic profiling may help to build personalized formularies for exploration, tailored to the unique metabolic profiles of a particular crew, minimizing waste and required mass and volume and improving outcomes. Increased insight into the Omic components of health risks associated with spaceflight are likely to aid NASA in assessing the long-term health consequences of exposure to the exploration environment.

The policies already put in place for Human Research on Genomic Information[136] can serve as a strong starting point for additional policy in the clinical and operational domain before NASA employees start

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135 NPR 8900.1B APPENDIX F, *supra* note 10.

136 NPD 7170.1, *supra* note 11.

grappling with the ethical questions that will inevitably arise. Identifying and addressing issues like incidental findings, operational use of precision medicine information, and appropriate use of genetic information in the operational context will help to ensure that policy does not lag too far behind technological advances.

NASA has an opportunity now, given the foreseeable trends in precision medicine and the potential benefits in human spaceflight, to enact anticipatory policies addressing clinical and operational challenges before they arise. This may include things such as appropriate collection of genomic information, how such data is stored and accessed, incidental findings, use of genetic information for occupational surveillance, development of personalized countermeasures, and the use of genomic information for individual and mission risk characterization. Policies that guide beneficial aspects of these fields into new standards and that help flight surgeons and others working in human spaceflight to deal with anticipated ethical challenges in the application of precision medicine and genomics will substantially improve our risk posture as we seek to explore outward into the solar system.