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Review article

Private Spaceflight: A New Landscape for Dealing with Medical Risk

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ABSTRACT

As NASA and other space agencies make plans to proceed with human exploration missions beyond low earth orbit (LEO), the private sector, including Space X, Virgin Galactic, Blue Origin, Space Adventures and others, echo these plans with initiatives of their own to send humans further into space. Development of more sub-orbital flight opportunities, orbital flight opportunities to LEO and even higher risk endeavors will certainly result in exposure to medical risks for an expanding and heterogeneous population of civilians. To date, a handful of "space tourists" have flown to the International Space Station (ISS), at their own expense, ushering in a new era in which anyone with reasonably good health and even those with physical disability may consider becoming space travelers. Indeed, medical and behavioral issues of healthy, professional astronauts, have not been problematic on short orbital flights. However, recent attempts to test the potential limitations in astronauts on extended duration orbital flights in preparation for future missions beyond LEO raise concern about individual differences in ability to tolerate the hazardous spaceflight environment. Given the rapid development of opportunities for non-professionals and the employees of private companies to travel into space, this is an appropriate time to consider the development of selection strategies for non-government space travelers, including the development of genomic and other modern tools to assess susceptibility to spaceflight risk.

1. A Growing Challenge—Space Tourism and Other Non-Government Space Travelers

With the expanding availability of civilian spaceflight opportunities and even discussion about the possibility of orbital spaceflight settlement in the future, there is growing consensus that increasing numbers of non-astronaut space travelers can be expected in the next few years (Krone 2006; Davidian 2020). The recent successful completion of the SpaceX *Inspiration 4* orbital spaceflight, with the first all-civilian "crew," has captured the imagination of the public and highlights the trend toward "citizen astronauts" in a compelling way (SpaceX n.d.). Clearly, the global space tourism industry is poised to grow (Courage 2014), with an increase in the value of the industry from $651M (2020) to $1.7B by 2027 expected by some market analysts (Businesswire 2021). Recently, Lockheed Martin announced that the company will be teaming up with partners to develop a commercial space station—StarLab—that will be a continuously crewed commercial platform, for research and industrial activity (Martin, 2021; SpaceX 2021). This announcement adds a new dimension to the topic, namely, the notion of a citizen-employee of a commercial space enterprise. While there is a natural hesitation to make quantitative predictions about the number of civilians who will go into space in the next few years, there is agreement across multiple stakeholder groups that those numbers will grow substantially (Davidian 2020). Non-government space travelers will include space tourists as well as the employees of commercial space enterprises. Private space enterprise will need to deal with medical issues, ranging from space traveler selection criteria, in-flight medical care and post-flight health monitoring, depending on the duration and complexity of the trip. The Federal Aviation Administration (FAA) in the United States has attempted to establish guidelines for some of these issues (Jennings et al. 2012), but, currently, no official guidelines exist.

2. Spaceflight Health Effects—Known and Unknown

Many of the physiological effects of space travel are well known, such as the headward redistribution of fluids that affects the cardiovascular system, fluid balance and even vision; the tendency toward bone loss and muscle atrophy; and changes in the vestibular system that result in impaired balance. All of these changes are direct consequences of reduced gravity (Fig. 1). Ionizing radiation poses concerns about hematopoietic progenitor cell effects that could lead to neutropenia; the possibility of leukemia or other forms of cancer developing during spaceflight or after return to Earth; and, the possibility of degenerative changes in the central nervous system and in other parts of the body. Many effects of the space environment, however, especially those due to space radiation, are not yet fully defined. Although, traditionally, NASA has studied the biological effects of reduced gravity and the biological effects of space radiation separately, the agency is now sponsoring

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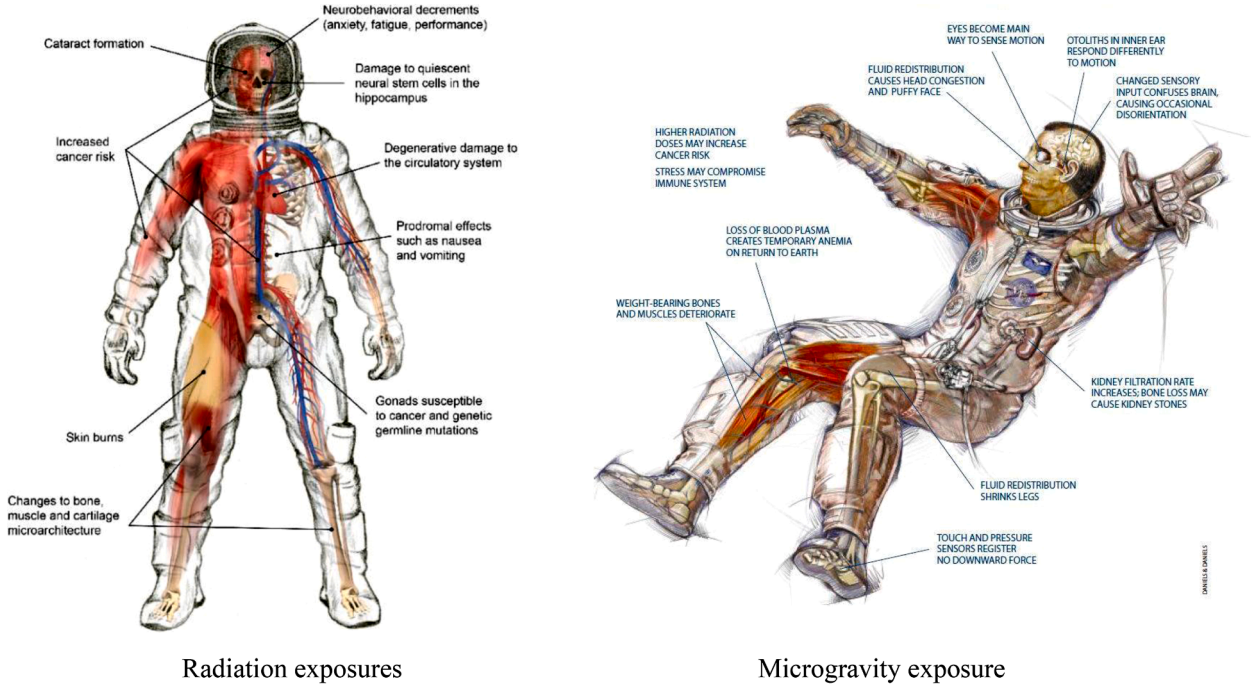

Fig. 1. The effect of spaceflight on human health. Reprinted from: (a) Chancellor et al., 2014; (b) Copyright ©Beaudaniels.com.

studies that examine combined effects of altered gravity and space radiation, to gain a fuller understanding of what might happen in space (Patel et al. 2020). Resources that help NASA to estimate risk include data from non-space-related radiation exposure of humans; analog environments or simulated space conditions for selected human studies; and, carefully conducted animal studies. Translation of the results of terrestrial radiation exposure or other human studies based on analog environments or simulated space conditions is a challenge, since terrestrial radiation exposure (primarily ionizing electromagnetic radiation) can never fully replicate the energetic particle radiation that occurs in space. Estimation of human radiation risk from the interpretation of animal experiments is certainly an even greater challenge because of the added uncertainty that is introduced by species differences (animal versus human). Until we learn the full spectrum of spaceflight effects from spaceflight experience, "risk uncertainty" will persist. Like NASA, private space enterprises will need to accept a substantial degree of risk as they send non-astronauts into space (Aerospace Medical Association Task Force on Space Travel 2001; Barratt 2006; Bogomolov et al. 2007; Courage 2014; Rayman et al. 2002; Tarzwell 2000; Yaqub 2015). In addition, these private enterprises will need to develop "crew member" selection practices that are appropriate to the spaceflight destination and trip duration, and they will need to be prepared to address in-flight medical conditions as well as post-flight medical conditions (Grenon et al. 2012). It is not clear who should bear the responsibility for monitoring the health of space travelers post-flight (commercial space companies themselves? perhaps governments?) but the development of the necessary tools for space traveler selection and post-flight health monitoring is of paramount importance.

3. Genetic Tools and Other Omics Technologies can Reveal Susceptibility to Spaceflight Risk

For non-government space travelers—tourists and employees of commercial space companies—the duration of the trip and the nature of the destination (LEO versus beyond LEO) will be important factors to consider in deciding the degree of scrutiny necessary to evaluate proposed space travelers. Short duration missions to LEO will require a minimal level of scrutiny, but long duration spaceflight in LEO or travel to the moon will require more in-depth evaluation. Medical history and family medical history should be considered for all travelers, to screen for risk of cardiovascular disease and other conditions that might lead to a medical emergency in space. With the recent development of a wide array of genomics analytical techniques and other omics tools that can shed light on human physiology, we will soon have the opportunity to use these advanced techniques to help select space travelers. A recent genome-wide association study (GWAS), for example, has identified variants in a centrosomal protein, CEP128, that predisposes radiation therapy patients to temporal lobe injury (Wang et al. 2019). Temporal lobe injury caused by radiation exposure is a serious complication of radiation therapy for nasopharyngeal carcinoma, and can affect memory, hearing and speech. This is an important finding because it shows that it is not just the dose of radiation that matters, but rather the individual genetic characteristics of the patient. Another carefully conducted genome-wide association study has identified 50 genomic risk loci and 64 candidate genes for risk of radiation-induced oral mucositis, another important complication of radiation therapy (Yang et al. 2020). These two studies are timely and may have important implications for understanding individual susceptibility to the risks of space radiation, even thogh doses of radiation in radiotherapy patients are significantly higher than the doses of radiation that are expected in the space environment. Additionally, genetic loci of susceptibility to loss of bone mineral density, osteoporosis and osteoporotic features have also been mapped in several studies (Karasik et al. 2010). Such genetic loci can be considered biomarkers for susceptibility to the spaceflight risk of microgravity. In addition to the genetic loci for radiation sensitivity and bone loss susceptibility, there are millions of additional spaceflight relevant single nucleotide polymorphisms (SNPs) in the human genome related to drug responsiveness, disease susceptibility, performance deterioration, physical and psychological tolerance (Table 1). Collectively, these studies highlight the importance of inter-individual variability in human physiology and susceptibility to disease. Commercial space enterprises have an extraordinary opportunity to apply these tools (and other omics technologies) (Schmidt and Goodwin 2013) to the challenge of selecting the most appropriate candidates for space travel.

Table 1
Planning for long-duration space flights requires consideration of complex disease prevention, behavioral health, and clinical treatment issues-issues resulting from the hazards of the space environment and from limitations to in-mission medical care (https://www.nap.edu/read/12261/chapter/4). A subset of defined human health and performance risks for future NASA exploration missions for which relevant genetic variations have been associated with a particular condition or disease based on genome wide association studies (GWAS) in populations.

Genetic loci for	GWAS link
spaceflight radiation risk	1
radiation susceptibility	2
varied individual response to radiation exposure	3
DNA damage response genes in radiosensitive individuals	4
spaceflight microgravity risk	5
susceptibility for bone mineral density	6
osteoporosis and osteoporotic features	7
performance risk	
endurance performance	8
cognitive impairment risk	9
dementia-like cognitive impairment	10
sleep quality	11
circadian rhythm variant	12
vestibular disbalance	13
inner ear infectious disease	14
cardiovascular risk	15
muscle susceptibility	16

GWAS link
1. https://www.ebi.ac.uk/gwas/publications/30299488
2. https://www.ebi.ac.uk/gwas/efotraits/GO_0009314
3. https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001911.v1.p1
4. https://www.ebi.ac.uk/gwas/efotraits/GO_0009314
5. https://www.ncbi.nlm.nih.gov/gap/advanced_search/?TERM=osteoporosis
6. https://www.ebi.ac.uk/gwas/publications/19079262
7. https://www.ebi.ac.uk/gwas/efotraits/EFO_0003882
8. https://www.ebi.ac.uk/gwas/publications/25729143
9. https://www.ebi.ac.uk/gwas/efotraits/HP_0100543
10. https://www.ncbi.nlm.nih.gov/gap/advanced_search/?TERM=cognitive%20impariment
11. https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001270.v1.p1
12. https://www.ebi.ac.uk/gwas/efotraits/EFO_0004354
13. https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001941.v1.p1
14. https://www.ebi.ac.uk/gwas/efotraits/EFO_0007537
15. https://www.ncbi.nlm.nih.gov/gap/advanced_search/?TERM=Cardiovascular
16. https://www.ncbi.nlm.nih.gov/gap/advanced_search/?TERM=Muscle

4. Pharmacological Considerations

Although NASA selects only the healthiest astronauts, virtually all crew members on the ISS use medicines to counteract the effects of spaceflight conditions (Blue et al., 2019). Pharmacological approaches, certainly, will be key for commercial space flight enterprises as well, for both space tourists and employees. Fig. 2 demonstrates the time-course of development of spaceflight conditions related to reduced gravity, with a gradual shift from acute conditions to chronic conditions. Longer trips will no doubt require increased reliance on *countermeasures* (specialized medicines designed to prevent sequelae of spaceflight stressors) to address these chronic conditions. Lengthy trips to more austere destinations will require more stringent selection criteria, and greater reliance on *pharmacogenomics* (selection of optimum pharmaceuticals based on an individual's unique genetic make-up) to predict countermeasure effectiveness. This is especially important in the context of future long-term space travel beyond LEO, where the combined effects of radiation and weightlessness will shape the spectrum of medical risk. Fig. 3 compares radiation doses received by astronauts for different types of space missions. For a mission to the ISS, within the protection of the Earth's magnetosphere, the effective radiation dose might be 80-160 milli-sieverts (mSv). In contrast, on a Mars mission, an astronaut may receive an effective dose of as much as 1,200 mSv. Non-astronaut space travelers will face the same risks. Fig. 4 shows that changes in bone and muscle strength are also dependent on mission duration. Indeed, on a trip to Mars, some of the changes to bone density can be quite substantial and may in, fact, be irreversible, in part (Carpenter et al. 2010).

A current review of NASA's Human Research Roadmap identifies medication use as the primary intervention for prevention or management of most conditions (NASA Human Research Roadmap, https://humanresearchroadmap.nasa.gov/). Application of on-board medications to mitigate clinical symptoms associated with certain medical conditions and illnesses is the first line of response to ensure sustainable health and performance of crew as well as to minimize long-term health consequences (Putcha et al., 1999). Technologies such as full genome sequencing to enable pharmacogenomics to predict an individual's response to treatment may seem futuristic, but these genetic tools are now economical (e.g. individual genome sequence costs less than $1000; https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data) and will likely be necessary to ensure the health of space travelers, especially as commercial ventures drive the development of more diverse populations of crew members. Previous spaceflights and simulated microgravity studies using animal models demonstrate that alteration in the activity of a number of drug metabolizing enzymes is an issue (Graebe et al. 2004; Groza, Bordeianu, and Boca 1987; Stingl et al. 2015). In a recent investigation funded by the European Space Agency, analysis showed that 31% of the 78 drugs carried aboard the ISS are affected by polymorphic enzymes of metabolism that are subject to alteration by the spaceflight environment (Stingl et al. 2015) (Fig. 5). Perturbation in CYP450 enzymes, which contribute to the hepatic metabolism of most drugs (Cozza 2007; Wynn and American Psychiatric Publishing 2009) would be expected to have a significant effect on drug levels. Furthermore, the genes encoding the CYP450 enzymes are highly variable in humans and have significant effects on therapeutic efficacy and treatment-related toxicity (Flockhart and Oesterheld 2000; Baba et al. 2008) in spaceflight. Additionally, the spaceflight environment as well as nutritional and physiological changes in astronauts may lead to significant epigenetic alterations, which could alter absorption, metabolism, clearance and even therapeutic targets (Kim et al. 2014). Collectively, these findings argue for the use of pharmacogenomics approaches to help manage medication strategies. Using individual space travelers' genetic information to guide pharmaceutical use could optimize therapeutic efficacy and minimize dangerous side effects.

5. Space Travelers as Medical Research Subjects

In the year 2000, the president of the United States signed Executive Order 13145 (Clinton 2000) which prohibited genetic discrimination in the federal workplace. Eight years later, the Genetic Information Non-discrimination Act (GINA) extended the protections of Executive Order 13145 by prohibiting genetic discrimination in the workplace for all Americans (Reed and Antonsen 2018), not just government workers. The executive order and GINA cover all U.S. astronauts. As of 2021, genetic screening or other forms of genetic sequencing cannot be used for astronaut selection or in any other employment-based decision

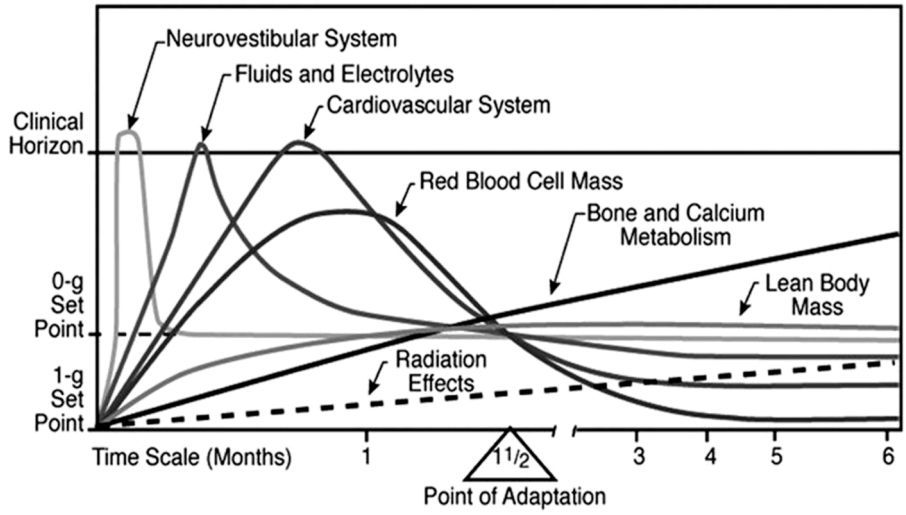

Fig. 2. Changes of various body systems during adaptation to weightlessness (Credit: NASA (National Aeronautics and Space Administration)).

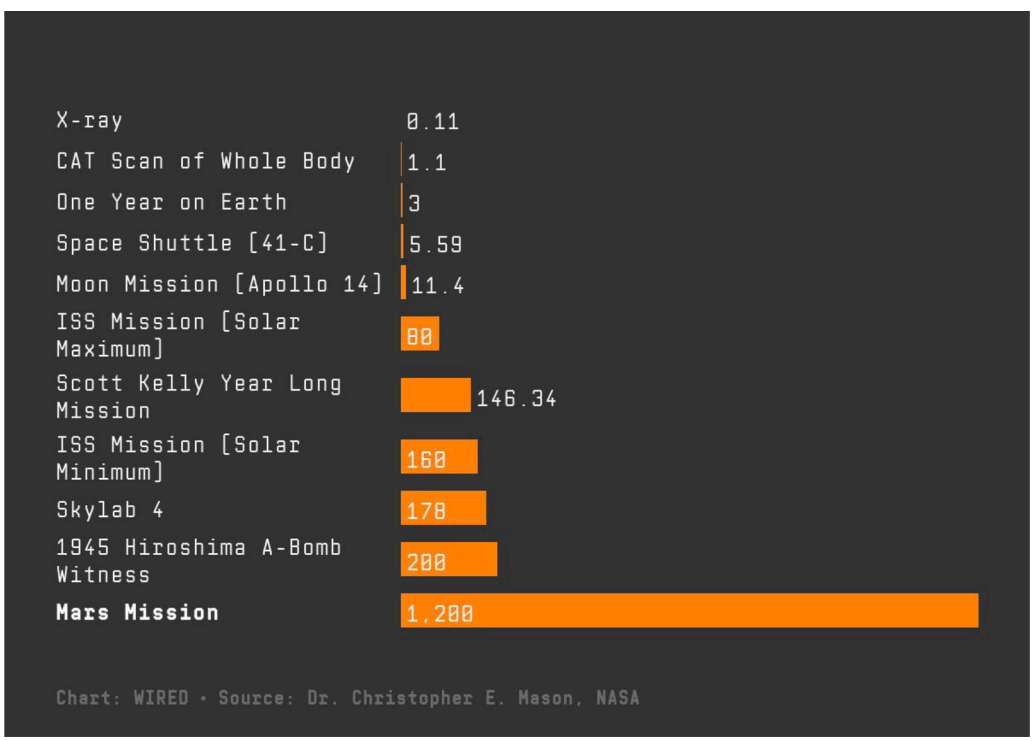

Fig. 3. Effective dose of estimated ionized radiation (mSv) received by astronauts during NASA's space missions. (Reprinted from: Chris Maison, NASA).

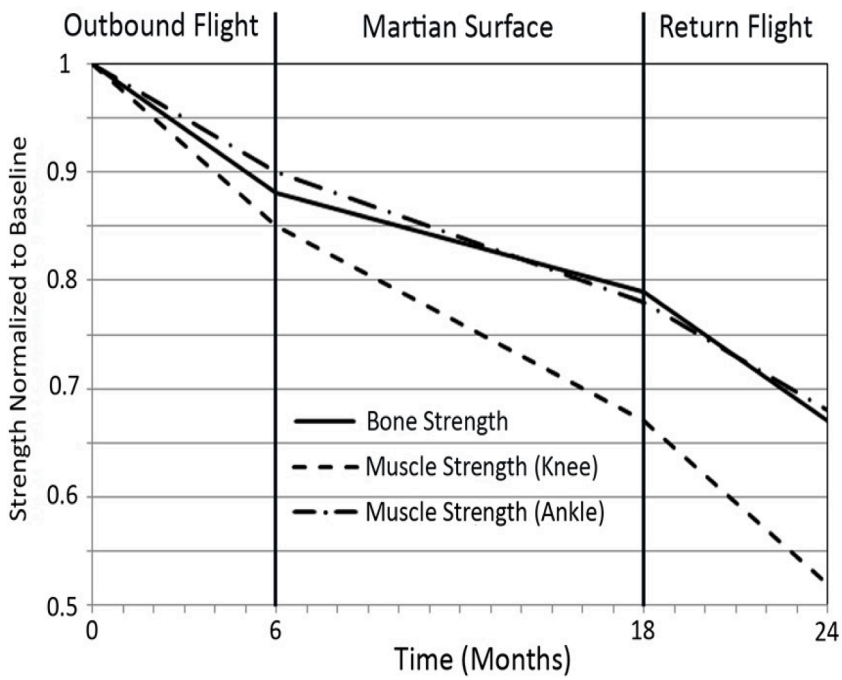

Fig. 4. Expected changes in bone and muscle strength that would occur on a manned mission to Mars. (Adopted from: Carpenter et al., *Journal of Cosmology, 2010, Vol 12, 3778-3780)*.

making. Although NASA is authorized to collect such information in the course of providing clinical care and doing research for development of medical and pharmaceutical countermeasures, the collection of genetic information is voluntary and must be consistent with all statutory requirements. The Privacy Act of 1974 (Privacy Act, 5 USC §552a, 1974), the Common Rule (45 CFR part 46, subpart A, 2017), as well as Occupational Safety and Health Administration (OSHA) guidelines (29 CFR part 1910, 2017) must all be followed, too.

But what about non-government space travelers as medical research subjects in space? The chance to participate in space medical research has been a strong motivating factor for space tourists for many years (Tarzwell 2000), and interest in serving as medical research participants is still a strong motivator for many (Chang 2021). The rapidly growing number of space tourists means that the pool of potential participants in space medical research is growing, too. Employees of private space companies should also be considered potential participants in space medical research. Like NASA astronauts, any employees of U.S.-based space companies are covered by GINA and other regulations governing medical research. Nonetheless, more people in space will undoubtedly translate to increased opportunities for human research. An added benefit is that the pool of available research subjects will be more diverse than the current astronaut pool, in terms of pre-existing conditions and overall level of health. Non-government astronauts are poised to have a profound impact on what we learn about the medical aspects of spaceflight in the coming years.

6. Summary

Commercial space enterprises, more than ever before, now share the spotlight with government space agencies when it comes to sending humans into space. Private space companies have demonstrated a commitment to orbital flight operations and even a sustained presence in LEO. Commercial space activities on the moon are expected to follow rapidly. Both space tourists and the employees of private companies will be traveling into space, and their numbers will likely eventually dwarf the numbers of professional astronauts. The scope of who needs medical care in space, therefore, is rapidly expanding outside the realm of the government-employed astronaut. The challenge of screening both space tourists and the employees of commercial space companies, to determine who is fit to fly, must be carefully addressed, especially as long duration spaceflights are undertaken. New technologies have become available to help gauge risk on an individual-by-individual basis, to facilitate the selection of space travelers, to guide pharmaceutical use and to monitor the health of space travelers when they return to Earth. The commercial spaceflight industry is the ideal setting for validating these new technologies and may help to encourage NASA and other government space agencies to adopt these approaches.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that cdocould have appeared to influence the work reported in this paper.

CYP2D6 substrates on ISS drug list	Indication	Information about polymorphic enzymes in the drug label	Dosing Guidelines: CPIC/ GWPG	References	Level of evidence*
Metoprolol	Heart failure, hypertension	FDA: warnings about pharmacogenetics and drug interactions	PM: 75% UM: up to 250%	[10, 11]	3
Diphenhydramine	Vomiting, allergic rhinitis	Warning about drug interactions with drugs metabolized by CYP2D6		[12]	3
Cetirizine	Vomiting, allergic rhinitis	Information about drug metabolism via CYP2D6		[13]	1
Loratadine	Vomiting, allergic rhinitis, urticaria	Information about drug metabolism via CYP2D6		[14]	1
Meclizine	Vomiting, allergic rhinitis	Information about drug metabolism via CYP2D6		[15]	1
Ondansetron	vomiting	Information about drug metabolism via CYP2D6		[16]	3
Promethazine	Rhinitis, urticarial, Sedation, vomiting	Information about drug metabolism via CYP2D6		[17]	3
Tamsulosin	Prostate hyperplasia	Information about drug metabolism, high exposure in PM as compared to EM		[18]	2
Acetaminophen	Pain, fever	Warning about interaction potential with CYP2D6 substrates		[19]	1
Hydrocodone	Pain	CYP2D6 involved in activation; PMs less efficacy		[20]	1
Venlafaxine	Depression	Metabolism of venlafaxine to the active metabolite, total active moiety not affected by polymorphism	80% in PMs 170% in UMs or select an alternative drug. Cardiotoxic risk higher in PMs	[21, 22]	3
Aripiprazole	Psychosis	Dose recommendations in FDA label, and interaction warning	Reduce dose in PMs to 67% UMs no recommendation	[23]	2
CYP2C19 substrates					
Diazepam	Sleep disturbances	Information about drug metabolism and interaction via CYP2C19		[24]	2
Sertraline	Depression	Information about drug metabolism via CYP2C19	Reduce PM dose to 50% UMs no recommendation	[6]	2
Omeprazole	Reflux	Drug interactions	UM dose 100–200% increased	[25]	3
CYP2C9 substrates					
Ibuprofen	Pain, Fever	CYP2C9 and CYP2C8 involved in metabolism	*CYP2C8 and 9 combined genotype involved in GI bleeding side effects*	[26]	3
Phenytoin	Epilepsia, seizures	PMs: enhanced risk of toxicity	PMs: 50%, higher risk for skin toxicity; IMs: 75% of dose	[27]	3
Ketamine	Anesthesia, pain	Minor enzyme involved in metabolism		[28]	1
Acetylsalicylic acid	Pain, fever, cardiovascular	Minor enzyme, Drug interactions	CYP2C9 PM higher risk for urticaria	[29]	1
Sulfamethoxazole	Antibiotic	Information about m via CYP2C9	Risk of hemolysis in Glucose 6 phosphatase dehydrogenase deficiency	[30]	1
Loperamide	Diarrhea	Interaction warning		[31]	1
CYP1A2					
Melatonin	Daytime sleep, insomnia	Metabolism, Interactions		[32]	3
Caffeine	Sleepiness	Metabolism, Interactions		[33]	3
Lidocaine	Anaesthetic	Interactions		[34]	3

* Level of evidence: 1: in vitro data only, 2: in vivo pk data, 3: clinical data on efficacy and/or side effects

doi:10.1371/journal.pone.0140764.t001

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Fig. 5. (a) Polymorphic CYP substrates within the ISS drug list; (b) The main enzymes or transporters involved in elimination of the drugs listed in the ISS drug repository. The retracted slices of the circle are enzymes with known genetic polymorphisms and empirical data for the formulation of therapeutic recommendations or dose adjustments. Credit: *Stingl, et al., PLoS One.* 2015;10(10):e0140764.

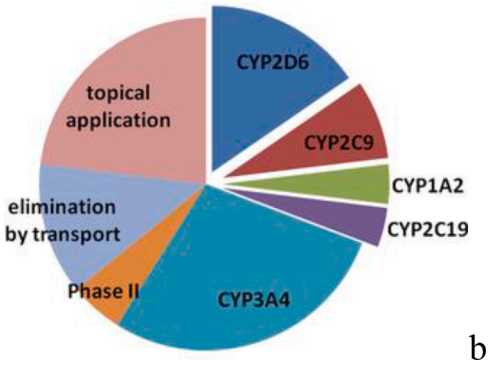

Fig. 5. (*continued*).

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