A Second Space Age Spanning Omics, Platforms, and Medicine Across Orbits

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Abstract

The recent acceleration of commercial, private, and multi-national spaceflight has created an unprecedented level of activity in low Earth orbit (LEO), concomitant with the highest-ever number of crewed missions entering space and preparations for exploration-class (>1 year) missions. Such rapid advancement into space from many new companies, countries, and space-related entities has enabled a“Second Space Age.” This new era is also poised to leverage, for the first time, modern tools and methods of molecular biology and precision medicine, thus enabling precision aerospace medicine for the crews. The applications of these biomedical technologies and algorithms are diverse, encompassing multi-omic, single-cell, and spatial biology tools to investigate human and microbial responses to spaceflight. Additionally, they extend to the development of new imaging techniques, real-time cognitive assessments, physiological monitoring, and personalized risk profiles tailored for astronauts. Furthermore, these technologies enable advancements in pharmacogenomics (PGx), as well as the identification of novel spaceflight biomarkers and the development of corresponding countermeasures. In this review, we highlight some of the recent biomedical research from the National Aeronautics and Space Administration (NASA), Japan Aerospace Exploration Agency (JAXA), European Space Agency (ESA), and other space agencies, and also detail the commercial spaceflight sector’s (e.g. SpaceX, Blue Origin, Axiom, Sierra Space) entrance into aerospace medicine and space biology, the first aerospace medicine biobank, and the myriad upcoming missions that will utilize these tools to ensure a permanent human presence beyond LEO, venturing out to other planets and moons.

Introduction

The launch of the Russian satellite, Sputnik, in 1957 and the establishment of the National Aeronautics and Space Administration (NASA) in 1958 marked the beginning of the first Space Age. This era not only changed humanity, but also reshaped our relationship with our Moon, solar system, and search for new stars. The Union of Soviet Socialist Republics (USSR) and the U.S.A. fiercely competed in space launches (**Fig. 1, inset**) during the Cold War, evolving from short missions to the first space stations (e.g., Salyut 1 by USSR

and Skylab by USA). Eventually, more countries created capacity for space exploration (**Fig. 1**), which introduced a wider range of genetic, medical, and ethnic backgrounds among the humans who have flown into space.

Moreover, while Russian cosmonaut Valentina Tereshkova was the first female in space in 1963[1], the first American female was not sent into space until 1983 (astronaut Sally Ride). Sex-specific differences in spaceflight's effects have gained attention as more females have entered space. Notably, females appear to be less affected by spaceflight-associated neuro-ocular syndrome (SANS), yet more affected in other modalities, such as vascular responses and possible cancer risk[2]. However, comprehensive studies on cell-specific and genetic changes in both sexes only began in 2021, revealing differences crucial for mission planning[3–5].

Astronaut selection, traditionally performed by government agencies like NASA, JAXA, and ESA, has expanded from the U.S. military's selection in 1959 to include scientists in 1962[6]. Current astronaut criteria typically involve citizenship, advanced degrees, and physical, cognitive, and stress testing. The private sector's involvement, starting with Orbital Sciences Corporation's Pegasus mission in 1990, has reshaped space exploration [1]. The private sector's contributions to spaceflight technology and crew health research expanded with the entry of companies like Blue Origin, Virgin Galactic, and SpaceX. In 2021, SpaceX's Inspiration4 marked the first fully private, crewed orbital mission, emphasizing the growing trend of civilian astronauts[7–9]. Then, 2022 and 2023 set records for the most launches into space by both commercial and government agencies (n=188, n=196, respectively)[10]. The SpaceX Starship, the largest rocket ever built, reached orbit in 2023, highlighting the accelerated pace of spaceflight technologies and new economies for space exploration[11].

These spaceflight developments are not just a difference of scale; they represent a substantive difference in the speed, type, and degree of access to space. For example, after more than 20 years of continuous human presence in space onboard the solitary International Space Station (ISS), there is now another orbiting space station (Tiangong) from the Chinese National Space Administration (CNSA) and five orbital platforms being planned by Axiom, Northrop Grumman, Sierra Space-Blue Origin, VAST, and Voyager-Nanoracks. Furthermore, additional research platforms are currently in development beyond LEO, including the NASA-led Lunar Gateway space station orbiting the Moon which will have Canadian Space Agency (CSA), ESA, Mohammed Bin Rashid Space Centre, and JAXA partners, and permanent Lunar habitats by NASA Artemis program, as well as Lunar habitats by the CNSA and ROSCOSMOS (led by Russian government). By the late 2030s, the Mars Base Camp orbital platform by an aerospace company

(Lockheed Martin) is planned for an orbit around Mars that can provide continual access to the surface[12] (**Table 1**).

These accelerating trends have arguably created a "Second Space Age" that features key differences from the first era. Specifically, (1) the commercial spaceflight sector is now leading many launches and missions instead of governmental agencies; (2) there is a log-level increase in the number of countries participating in space exploration (**Fig 1**); (3) the advanced cellular and molecular studies of the human body's spaceflight response has surpassed the number of publications from the prior missions like NASA's Twins Study[13] (4) the biomedical, behavioral, and omics data from the astronauts can now be accessed through a Biobank and Biorepository[8]; (5) there is increased crew heterogeneity across age, sex, and race; and (6) a continued human presence will extend beyond LEO, including lunar bases and planetary missions (**Table 1**).This Second Space Age enables "precision astronaut medicine" and thus, the chance to create personalized countermeasures for astronauts. In addition, accessible astronaut biomedical data in Biobanks benefits research in both space and Earth-based contexts[14,15], similar to the utility of the USA's AllofUs Program and the UK Biobank.

In this Perspective, we highlight research from the "Space Omics and Medical Atlas (SOMA) across orbits" package, which features data collected from SpaceX's Inspiration4 (I4) crew members, JAXA studies, NASA and ESA astronauts, and a comparison of these results with a large body of model organism data, cellular profiles, computational models, and countermeasures. The I4 mission, the first all-civilian spaceflight, provided unprecedented insights through multi-omics (RNA-seq, microbiomics, proteomics, etc.) and diverse medical assessments (neurobehavioral, cognitive, environmental). This mission generated nearly 3,000 samples and hundreds of terabytes of data, constituting the most extensive dataset for human space exploration to date, and the first mission with public access to paired astronaut data (SOMA portal) and samples (Biobank)[8,15] In addition, The SOMA package spans blood measurements from the 1960s Mercury missions up to recent commercial missions in 2024, and features a wide range of molecular and cellular assays across humans, model organisms, and ground-based simulations (e.g., NASA Space Radiation Laboratory)[16,17] performed by investigators across >100 institutions. These datasets show changes at the cellular, tissue, organismal and systematic levels (**Table 2**), and begin to map differences between populations (e.g. age, sex) and link specific countermeasures to each astronaut. We describe here the specific changes observed at each modality of biology, detail their significance, and link them to future missions and plans for the coming decades, with the aim to create a guide for potential countermeasures and tools essential for ensuring safe human space travel, particularly as mission durations, risks, and radiation levels escalate.

Cellular Adaptations in response to Spaceflight

Spaceflight introduces hazards that result in diverse cellular and molecular changes[18], primarily influenced by two factors: space radiation exposure and microgravity. Galactic cosmic radiation (GCR) is an unavoidable aspect of short- or long-term space missions, exposing astronauts to various atomic nuclei containing high linear energy transfer (LET) particles like ^{56}Fe and ^{28}Si, which pose significant health risks. The impact of radiation exposure includes distinct imprints on the human genome, transcriptome, and chromatin structure[19,20]. Understanding these effects is crucial for minimizing detrimental health outcomes[21].

Perdyan *et al.*[22] conducted a computational multi-omics analysis, investigating GCR's effects on epigenetic[23,24] and transcriptomic patterns using *in vitro* data from different bronchial epithelial cell lines exposed space radiation, *in vivo* data from mice exposed to whole body space radiation, and JAXA study astronauts' data[25] from NASA's Open Science Data Repository (OSDR)/GeneLab platform[26–28]. Results showed that ^{56}Fe induced DNA hypermethylation, while ^{28}Si and X-ray exposure led to global DNA hypomethylation. Differentially methylated sites primarily accumulated in nuclear periphery, with minor DNA methylation changes in euchromatic regions. Persistent epigenome and transcriptomic changes that lasted up to 4 months post-landing were induced by ^{56}Fe, but not by ^{28}Si, in model organisms exposed to simulated GCR and JAXA study astronauts. The possible mechanisms behind the distinct ^{56}Fe and ^{28}Si responses can be examined in future studies.

Spaceflight-induced changes also extend to telomeres, the nucleoprotein complexes essential for maintaining genome stability. Previous work showed telomere elongation in NASA astronauts[29–31], and recent studies shed light on the likely mechanisms behind this phenomenon[8,32]. Elevated levels of telomeric RNA (TERRA) in spaceflight samples suggest its role in facilitating telomeric recombination-mediated repair through the telomerase-independent ALT pathway[29], and TERRA may also form dipeptide-repeat signaling proteins. These findings have broad implications for scenarios involving persistent telomeric DNA damage, such as space radiation exposure.

Chromosomal and telomeric damage induced by the space environment also has a direct impact on immune-related dysfunction. Burke *et al.*[33] explored the effects of simulated GCR on murine models, revealing sexually dimorphic immune and endocrine responses. RNA sequencing also indicated sexually distinct sex-specific responses, with females showing more efficiently regulated inflammation profiles compared to males, which matches gene expression data from the I4 crew, and underscores the importance of personalized translational approaches for astronauts on exploration missions.

To further explore immune dysregulation in spaceflight, an extensive review by An *et al.* [5], highlighted the severe impact of the space environment on macrophages, central innate immune cells crucial for antigen removal and directing adaptive immune responses[13,34]. A single-cell multi-omics, and cytokine analysis of the I4 crews has identified 17 cytokines/chemokines related to inflammation and muscle homeostasis that increased after spaceflight and revealed changes in gene expression, chromatin accessibility, and TCR/BCR immune repertoire in response to spaceflight[3,8,9]. Differentially expressed genes (DEGs) were enriched for immune-metabolic pathways as well as chromatin modifications, and the immune cell types that were most impacted by spaceflight were CD14 and CD16 monocytes. Integrating with microbiome abundance data from the same crews has for the first time identified immune cell DEGs associated with microbiome shifts in taxonomy and viral activation[3].

In addition to space radiation, microgravity can also impact the entire human immune system[35]. Single-cell RNA-seq analysis of human peripheral blood mononuclear cells (PBMCs) exposed to short-term simulated microgravity revealed core features of immune impairment. Comparative transcriptomics identified conserved features of immune dysfunction across simulated microgravity and spaceflight, including changes in pathways linked to cytoskeleton dynamics, pyroptosis, temperature-shock, proteostasis, nuclear receptors, interferon, IL-6, and sirtuin cascades.

Liquid biopsies, an alternative to traditional biopsies, extract cell-free (cf) nucleic acids from the blood or urine[36,37], which emerge upon space-relevant stress[38], aging[39], metabolic disorders[40], inflammation[41], and DNA damage and clonal mutations[42,43]. These can detect changes earlier than protein biomarkers[44], providing enhanced molecular heterogeneity resolution compared to standard tissue biopsies[45]. “Full-body molecular profiling” using cfDNA and cfRNA from liquid biopsies, coupled with clonal hematopoiesis mutation scans[43,46], is a contemporary approach mapping spaceflight impact, ongoing in astronauts under the SOMA protocol (**Table 3**).

JAXA’s Cell-Free Epigenome (CFE) Study[47] conducted an 11-time point liquid biopsy study with six astronauts who resided on ISS for >120 days. The study showed that cfRNA in plasma can capture longitudinal gene expression profiles of stressed or lysed internal tissues. The cfRNA analysis before, during, and after spaceflight also revealed mitochondrial dysregulation in space[36], supporting previous studies[13,48,49]. The cfDNA analysis revealed a significant increase in relative mitochondrial DNA copy numbers during spaceflight, returning to baseline post-flight[36], replicating NASA’s Twins Study findings[13]. The association of the extracellular mitochondria (exMT)-enriched fraction with the CD36 scavenger receptor and the release of exMT-containing extracellular vesicles into the plasma during spaceflight indicated systemic metabolic stress responses to the space environment. These results suggest exMT as a potential biomarker to assess

tissue responses in spaceflight and to decipher tissues undergoing apoptosis, and reinforce theories that mitochondrial dysregulation is a central feature increasing spaceflight health risks.

Mitochondrial and immune function are interconnected, impacting insulin and estrogen signaling, and posing heightened health risks for the female reproductive system[50]. An integrated analysis of murine, JAXA cfRNA, and I4 scRNA-seq data revealed altered mRNA levels during and after spaceflight, affecting mitochondrial metabolic pathways, particularly lipid metabolism and oxidative stress[4]. These changes contribute to heightened health risks associated with reproductive hormone synthesis. Mitochondrial dysfunction in response to spaceflight was further supported by a comprehensive multi-omics analysis on I4 crew specimens[3, 32]. Distinct alterations in macrophages, neutrophils, and CD4+ T-cells, along with elevated interleukin-6 (IL-6) levels, were observed in scRNA-seq data, suggesting their potential impact on mitochondrial regulation, even in the relatively short I4 mission.

Organ and Tissue Responses in Spaceflight

The cellular changes that occur during spaceflight illustrate a consistent story of immune perturbation, DNA damage, and mitochondrial stress, evidenced across cellular, model organism, and astronaut models. Given the widespread cellular and molecular changes, studies have examined the combined impact of spaceflight at the organ and tissue levels. Here we will highlight the studies utilizing both existing data from model organism studies and astronaut data from the Twins, I4, and JAXA missions.

Muscle health is a crucial aspect of space research[18], given the abnormal changes it undergoes during extended space missions, involving microgravity and radiation exposure. These changes can result in muscle mass decline and bone density loss, posing challenges for astronauts' recovery upon returning to Earth and potentially accelerating biological decline or frailty[47]. These issues mirror the sarcopenia, characterized by muscle loss and frailty and often observed in older adults, and current countermeasures are relatively ineffective[51]. Castañeda *et al.*[52] identified key genes associated with sarcopenia and found these genes to be dysregulated when comparing human cells sent to ISS and astronaut data from JAXA and I4 missions. Interestingly, skin expression profiling in I4 astronauts revealed deregulation of genes related to muscle loss, suggesting that skin data could serve as informative indicators of muscle-related gene deregulation[53]. The study further predicted potential countermeasure drugs targeting sarcopenia-associated genes [52].

In an additional study addressing muscle loss, Kamal *et al.*[54] developed a new microgravity bioreactor using the StrexCell® system to release a daily bout of uniaxial

cyclic stretch, that elicits changes in tensile loading on skeletal muscle myotubes. They provided evidence of a new uniaxial bioreactor for skeletal muscle loading and unloading that could be used for the study of mechanotransduction in skeletal muscle during future spaceflight. The StrexCell bioreactor system could also be used to test new countermeasure strategies against the adverse effects of microgravity and also could help in studies of aging[55].

Skin-related issues, such as inflammation and discomfort during spaceflight, are well-known, but molecular insights and mitigation strategies are limited. Two manuscripts in this package enhance our understanding of skin changes during long- and short-duration spaceflight, featuring the first astronaut skin biopsies. Cope *et al.*[56] conducted a comprehensive analysis using transcriptomic skin data from OSDR, correlated rodent and astronaut data from various missions, and identified responsive pathways in cell cycle regulation, lipogenesis, DNA damage, and mitochondrial dysregulation. In a second study, Park *et al.*[57] analyzed 3mm human skin biopsies before and after spaceflight, revealing metabolic changes, DNA repair, cell cycle alterations, and immune system activation. Inflammatory responses and immune deregulation, driven by KRAS, were observed across skin tissue layers, consistent with cellular responses in previous studies.

Beyond muscle and skin, studies have delved into molecular changes affecting the central nervous system (CNS) and neuronal tissues, caused by exposure to GCR and microgravity. Desai *et al.*[58] simulated acute and chronic GCR exposure on murine models, and observed differences in psychomotor vigilance. The study highlighted potential adverse effects on attentional processes and reaction time, emphasizing the importance of cognitive and neurological metrics for in-flight mission decision-making. The investigation also explored the link between GCR exposure effects on neurocognitive performance and neurotransmitter abnormalities affecting circuit connectivity. Chronic GCR exposure was found to increase levels of neurotransmitters within the prefrontal cortex, indicating potential interventions targeting dopamine pathways to restore homeostatic signaling in the irradiated brain.

Masarapu *et al.*[59] and Houerbi *et al.*[60] examined brain alterations in ISS and ground control murine models using Spatial Transcriptomics and single-cell multiomics (RNA-seq and ATAC-seq). These studies provided evidence of spaceflight-induced disruptions in neurogenesis, neuronal development, synaptogenesis, and neurodegeneration, sharing similarities with changes observed in aging and neurodegenerative diseases. Spatial transcriptomic data suggested a disrupted blood-brain barrier (BBB) in rodents during flight, underscoring the importance of continued monitoring for brain health in future crews.

Cardiovascular tissues and related organs are also severely impacted by the space environment and subject to elevated health risks. Paar *et al.*[61] investigated the impact of space radiation on the heart, focusing on GCR-induced cardiac fibrosis. Activation of fibrosis-associated genes and pathways, including TGF-β1, was observed in blood samples from I4 Mission and JAXA CFE Study astronauts. Simulated GCR experiments in mice revealed time-dependent regulation of fibrotic processes, indicating the potential for developing novel countermeasures targeting various fibrotic markers related to spaceflight response. The study explored the influence of circulating microRNAs (miRNAs) linked to spaceflight-associated cardiovascular risks[61,62], and tested antagomirs targeting miR-16-5p, miR-125b-5p, and let-7a-5p to mitigate cardiac fibrosis. The treatment restored TGF-β1 and COL1 signaling to control levels, highlighting the potential for developing novel countermeasures (below section).

The kidney, often understudied in spaceflight, was the focus of a comprehensive study by Siew *et al.*[63]. The I4 crew members exhibited changes in urinary chemistry during spaceflight, associated with primary alterations in ion transporter regulation. Diverse approaches revealed functional and structural renal remodeling in spaceflight, including morphometry, imaging, and multi-omics on rodent kidneys from the ISS, simulated ground analog experiments, and the I4 data,. Acute GCR exposure demonstrated markers of mitochondrial distress and early proteinuria, suggesting glomerular and proximal tubule dysfunction. These findings suggest the possibility of transient, maladaptive nephron remodeling that might lead to progressive kidney damage during long-duration deep space missions, underscoring the importance of appropriate mitigation strategies.

Recognizing the varied radiosensitivity of each tissue/organ is crucial for targeted research and countermeasures. Radiosensitive organs, including hematopoietic-related organs, reproductive systems, gastrointestinal system, epidermis, and eyes, exhibit the greatest sensitivity (and risk from)to space radiation[64]. As deep space missions become more feasible, understanding and mitigating the risks posed by constant exposure to low-dose space radiation becomes imperative. Mitochondrial exhaustion due to inflammation and immune suppression[64] becomes a concern, particularly for organs less sensitive to radiation, like the brain and muscles, which also requires monitoring in spaceflight.

Systemic Effects of Spaceflight

With a better understanding of how the space environment impacts humans at both the cellular and organ/tissue levels, the overall biological response at the whole body, host-microbial, and systemic levels can be better understood and linked to prior work[18]. For example, understanding how spaceflight can advance aging and impact overall frailty can leverage the wide range of studies and indicate a systemic change. Camera et al.[51] focused on establishing a frailty index for humans during spaceflight, which also links to

well-defined hallmarks of aging[39,51,65], including: mitochondrial dysfunction, telomere alterations, genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication. Studies in this package link some aspects of spaceflight to the hallmarks of aging pathology, indicating signs of premature aging for some missions. The systemic impact of this can contribute to advanced muscle loss or sarcopenia, cardiovascular health risks (such as fibrosis), clonal hematopoiesis, immune dysfunction, CNS issues, and more. Camera et al.[51] created the "frailty index" using data from NASA's OSDR[27], from different mouse missions flown to the ISS, missions with cell culture flown to the ISS and simulated human microgravity experiments (i.e. bedrest studies[66]), and astronaut data from the JAXA study and I4 mission. Camera et al.[51] focuses mainly on the impacts of frailty on muscle tissue, which revealed a key set of genes associated with an early frailty phenotype. Specifically, they noticed key changes with interferon inflammatory response, metabolic disorders, hypoxia response, and increased cellular senescence.

The I4 mission provided a vast amount of both physiological and molecular data from the four civilian astronauts, spanning the six research projects, thousands of samples, and three mission phases (**Table 3**)[7]. Key measurements include multi-omics and virome analysis associated with spaceflight, organ ultrasound imaging, and comprehensive cardiovascular and neurocognitive assessments. Systemic alterations were evident post-flight, particularly in human PBMCs, showing thousands of DEGs at R+1. Notably, CD14+ and CD16+ monocytes displayed the most significant changes in gene expression , which were linked to regions of more open chromatin, including genes associated with DNA repair, immune activation, and nucleosome organization[8]. Physiological changes were recorded using handheld ultrasound devices for autonomous imaging of the urinary bladder, internal jugular vein, and eyes. Generally, short-duration spaceflight did not induce significant physiologic changes post-flight relative to pre-flight. However, crewmembers, even without space motion sickness, exhibited consistent vertical ocular misalignment post-flight, contrasting with pre-flight conditions. Cardiovascular function, activity levels, and energy expenditure were objectively measured using the Apple Watch Series 6, marking its inaugural use in spaceflight. Neurocognitive performance was assayed using a battery of ten cognitive tests developed for astronauts that has been deployed in both spaceflight and ground-based spaceflight analog studies.

Although the effects of short-duration spaceflight on cardiovascular function and neurocognitive performance were modest, there were marked interindividual differences in response to spaceflight, consistent with previous research[67,68]. Significant changes in heart rate, heart rate variability, energy expenditure, and activity levels occurred across mission phases. Furthermore, the spacecraft environment can impact crew physiology and neurobehavioral functions[68] and three out of the four I4 crew exhibited positive associations between CO_2 levels and heart rate variability in-flight. Moreover, cfRNA and

cfDNA profiles revealed that cells with the greatest lysis arose from the hematopoietic system[8,60], which mirrors the radiation risk of this system. Overall, the findings from the orbital mission demonstrate that the collection of high quality biomedical and behavioral data are feasible in a commercial crew with rapid training, and how systemic and whole-body level analysis from omics and biometrics data generates rich profiles on impact of spaceflight on the human body.

During spaceflight, alterations in host-microbial interactions have a systemic impact, particularly as microorganisms adapt to novel and extreme environments by incorporating new genetic material, particularly through bacteriophages[69]. Bacteriophages, upon inserting viral DNA into hosts, can become dormant (prophages), leading to modified host genotypes with gene disruption[70], silencing, and chromosomal rearrangement, thereby influencing host gene expression[8]. Prophages facilitate the transfer of bacterial genes, including virulence and antibiotic resistance genes, toxins, effector proteins, and regulatory proteins, among cells[71]. Irby *et al.*[72] investigated prophage presence and function in genomes of bacteria isolated from the ISS compared to terrestrial counterparts, exploring their contribution to microbial adaptation in the spaceflight-built environment. Analyzing ten bacterial species from five ISS sampling campaigns, they identified significant spaceflight-related differences in mobile genetic elements, particularly prophages. While transposes are common in terrestrial strains, they are notably absent in ISS strains. Instead, ISS strains exhibit an increased prevalence of Mu-like phages and unclassified phages. This variation implies that selective pressures unique to the space environment, such as limited nutrient availability and heightened genetic diversity, promote microbial survival under these conditions. Overall, the study indicated that prophage-encoded functions correlated with increased microbial persistence on the ISS, providing insights into potential mechanisms for microbial adaptation to this unique environment.

The I4 mission also created the largest astronaut microbiome study to date[73], spanning 750 samples across 10 time points, with shotgun metagenomics and metatranscriptomics performed for each sample. Data from Tierney *et al*. showed a microbiome architecture of spaceflight that was characterized by time-dependent and taxonomically-divergent microbiome alterations across both time and space (including strain exchange with the SpaceX Dragon spacecraft). They also observed pan-phyletic viral activation and signs of persistent changes that, in the oral microbiome, yielded plaque-associated species with strong associations to immune cell gene expression. Further, they found enrichments of microbial genes associated with antibiotic production, toxin antitoxin systems, and stress response enriched universally across the body sites, and were correlated with some of the T-cell and B-cell expression dynamics in the crew.

Countermeasure Development for Spaceflight

There are limited medical countermeasure options specifically designed to decrease the negative effects of radiation exposure in astronauts due to spaceflight. Currently, there are three FDA-approved medical countermeasures, Neupogen, Neulasta, and Leukine, which are intended to improve survival following exposure to an acute myelosuppressive radiation dose[74]. These countermeasures improve the likelihood of survival by mitigating neutropenia and thrombocytopenia associated with acute radiation sickness. However, their effectiveness has primarily been studied in the context of photon irradiation, with limited evaluations for proton or other radiation qualities experienced during spaceflight, such as GCR. Additionally, while the FDA-approved radioprotectant Ethyol (Amifostine) is available to reduce xerostomia post-radiotherapy for head and neck cancers, its utility in mitigating space radiation effects is limited due to its parenteral administration, short half-life, and side effects[18].

Addressing the challenges posed by space radiation and microgravity, Paar *et al.*[61] explored the potential of miRNA inhibitors as a countermeasure. Inhibitors targeting specific miRNAs (miR-16-5p, miR-125b-5p, let-7a-5p) were tested to alleviate cardiac fibrosis in mice exposed to simulated space radiation and microgravity. A complementary study by McDonald *et al.*[62] identified these miRNAs based on a previously established circulating miRNA signature associated with the space environment[75]. Using a 3D human model for microvessel physiology, inhibition of these miRNAs demonstrated significant preservation of the human microvessel structure, reducing DNA damage and stress after exposure to simulated Galactic Cosmic Rays (GCR). This approach, supported by observations in both 3D human microvasculature tissue model and astronaut data from missions like JAXA and Inspiration4, indicates the potential effectiveness of miRNA inhibitors in countering specific challenges encountered during spaceflight.

Expanding countermeasures to address skin-related issues observed in various datasets, including spatial transcriptomics from the I4 mission, JAXA CFE, and murine models[56], offers insights into potential interventions. Altered expression of *FLG* and *CASP14*, genes known to modulate skin permeability, during and after flight indicate that these genes may be involved in water loss and responses to irritants, allergens, and microbial products during spaceflight. FLG loss-of-function mutations are associated with conditions like atopic dermatitis. This can be treated by dupilumab, which inhibits interleukins 4 and 13, and thereby upregulates FLG expression and restores epidermal barrier function. This drug could be explored for in-flight and post-flight treatment to restore skin barrier function[76].

Interestingly, miRNA-based countermeasures offer innovative potential to mitigate space radiation damage; however, extensive pre-clinical and clinical trials are essential before

human implementation. Meanwhile, repurposed drugs are being explored as countermeasures for spaceflight-related damage, particularly addressing symptoms from solar particle events (SPE)[77]. Anti-nausea medications like Ondansetron, granisetron, palonosetron, Imodium®, Neupogen®, corticosteroid cream, and dolasetron are considered for mitigating SPE symptoms (e.g. nausea, vomiting, diarrhea, radiation dermatitis, neutropenia). Flavonoid supplements (e.g., apigenin[78]) and vitamin D[79], along with exercise[80], are also investigated as countermeasures to reduce inflammation[81] and mitigate spaceflight damage. Until specific miRNA-based treatments are developed, a combination of FDA-approved drugs, nutritional supplements, and microbial interventions[82] may be explored for comprehensive mitigation of spaceflight-induced damage.

Astronaut precision medicine (APM) emerges as an actionable countermeasure involving tailoring treatment and prevention to individual characteristics, encompassing molecular, physiological, morphological, and behavioral aspects[83,84]. Pharmacogenomics (PGx), a cornerstone of APM, examines gene variants influencing drug metabolism[85,86], optimizing drug safety and efficacy for individual astronauts. Developing PGx profiles of astronauts and crews could ensure personalized drug regimens, enhancing mission safety and effectiveness.

This principle can be applied to many of the drugs in a mission formulary. Importantly, these types of drug responses can be predicted and personalized. The application of PGx (drug-gene interaction) should also be accompanied by careful attention to drug-drug, drug-nutrient, drug-food, drug-microbe, and drug-herb interactions. These can be systematically assessed for individuals and crewsand can be implemented using large cohort databases and routine sequencing for the crews. Addressing these interactions removes another potential impediment to astronaut health, safety, and performance.

Applying APM/PGx to space missions involves molecular phenotyping to characterize functionally related molecular networks (FCN)[83]. By addressing dysregulations before space missions, APM aims to prevent their impact on health, safety, and performance in the space environment. Targeting specific gut microbe-produced substances, such as the elevated neurotoxin and nephrotoxin *p*-cresol observed in the NASA Twins Study[87], enables dietary countermeasures, including fiber and resistant starch, to lower *p*-cresol production. APM may also address challenges like space-associated neuro-ocular syndrome (SANS) by characterizing genotypes and metabolites related to the one-carbon molecular network.

Beyond the pharmacological and physical countermeasures, genetic and epigenetic tools have emerged as innovative approaches to mitigate spaceflight-associated risks. CRISPR technologies, utilizing Cas9 and other Cas systems, allows precise modification

of somatic cells to correct or replace disease-driving genes. Specifically, recent clinical trials have successfully treated conditions like beta-Thalassemia and sickle cell disease by deleting repressor genes for fetal hemoglobin[88]. Epigenetic modification systems, utilizing deactivated Cas9 (dCas9)[89], fused with histone or DNA modifiers, such as DNMT3A or TET1, enable targeted modification of gene expression, providing a means for permanent or transient genetic alterations related to spaceflight. These advancements may play a crucial role in addressing long-term challenges for human settlement on other planets[90].

Computational and omics Tools in Spaceflight Research

Advanced computational methods, omics platforms, and new algorithms play a crucial role in understanding factors related to spaceflight health. Casaletto *et al*.[91] utilized machine learning techniques, specifically the Causal Research and Inference Search Platform (CRISP), to predict features causally linked to a binary response variable, employing prediction invariance as a guiding principle. By applying CRISP to gene expression data from NASA's OSDR, they identified genes and molecular targets associated with lipid density phenotype in space-flown rodents. This approach unveiled novel insights not captured by traditional systems biology methods, particularly in addressing liver dysfunction. The SOMA Resource paper[8] also features four data portals and tutorials on data usage, to help discover more biology and replicate across missions. The study highlights the importance of a causal inference framework based on environment invariance for robust feature identification, emphasizing its applicability to various tissues, phenotypes, and omics data. Continued advancements in computational and biological tools are crucial for comprehending spaceflight's impact and developing effective countermeasures.

Limitations associated with space research

While the NASA's Twins Study[13] marked a significant stride in clinical genomics and multiomics analysis during spaceflight, limitations on crew size and follow-up were evident. The I4 and JAXA studies, with n = 4 for I4, n = 6 for JAXA, and n = 14 for an ISS astronaut study on bone marrow[92], have expanded the subject pool but still face constraints, especially when considering sex-specific analyses. The inherent challenges of limited human subjects in space experiments persist due to constrained flight opportunities, regulatory restrictions, and cost considerations.

Notwithstanding these challenges, meticulous planning, procedures, and analysis, coupled with a skilled team, have demonstrated the generation of valuable insights from I4 and JAXA studies. Ground-based studies and control cohorts, including those like HI-SEAS and analog astronauts in EXPAND, alongside collaborations with initiatives such

as the UK Biobank and commercial entities like Pheno.AI and the Human Phenome Project, continue to enhance our understanding despite the inherent limitations in human subject numbers for space research.

Outlook

While data from the various missions, computational tools, and model organisms provide valuable insights into the impacts of spaceflight, significant challenges persist. While some molecular signatures are consistent across both short and long-term missions (e.g. IL-6, IL-10 increases in plasma, telomere elongation, mitochondrial stress), others appear specific to extended exposure and chronic space radiation (e.g. CRP spikes). The increasing radiation burden observed in current missions like I4 and future missions (**Fig. 2**), highlights the necessity for precision medicine strategies tailored to individual astronauts, ensuring the right treatment at the right time for the specific mission.

Previous work has identified mitochondrial dysfunction as a key driver of systemic damages during spaceflight[48], including inflammation, immune suppression, cardiovascular dysfunction, muscle atrophy, bone loss, and circadian rhythm disruption. While these systemic stresses appear universal, individuals experience varying degrees of dysregulation, necessitating astronaut-specific precision medicine to ensure safe space travel for all. Data from I4 and JAXA missions reveal both universal changes (increased inflammation and mitochondrial stress), independent of sex and ethnicity, and sex-specific variations (insulin and estrogen changes in females)[4,8,33]. By aggregating these findings, we can annotate systemic changes and construct a molecular fingerprint for key alterations indicated that individualized astronaut healthcare is crucial.

While conventional countermeasures focus primarily on pharmacological interventions, emerging approaches utilizing RNA biology, omics-based methods, and gene therapies offer promising avenues for active defense[93–95]. These advancements, coupled with genomic tools and personalized activation of specific alleles[88], hold the potential to address individual health challenges encountered in space. However, careful consideration must be given to ethical concerns like informed consent[96], crew ownership of data[97–99], and adherence to full Institutional Review Board (IRB) protocols as research in this evolving landscape progresses, especially for long-duration missions (**Fig. 3**) and applies to ground studies as well.

Indeed, ground-based analog studies continue to complement spaceflight experiments[100–107], providing valuable insights into human responses to the space environment. As space research advances, integrating data from individuals of diverse ages, sexes, and lifestyles is essential to facilitate a comprehensive understanding of

genetic and epigenetic associations with space adaptation. Efficient subject stratification will be crucial for the successful evaluation of future medical interventions.

The data and new discoveries described above are exciting, but beg the question: How will we know when we've reached the end of the Second Space Age? Perhaps, it could happen within a matter of decades. China and the US have both announced plans for a crewed mission to Mars (no earlier than 2035 and 2039, respectively), as well as for active work to return samples from Mars (**Table 1**). New trajectories enabled by heavy-lift rockets like the Starship can enable missions that span longer lunar arcs (**Fig 3b**), or threeplanets in one trip (**Fig 3c**)[108] and future missions will be enabled by the current SpaceX Dragon parameters for crew and resources (**Fig. 3a**), enabling humans to travel farther than they have ever gone before. When successful, these events will signal the shift of humanity from a LEO-focused species to an interplanetary one, with instruments, missions, and crews moving around the planets of our first solar system. Indeed, by 2050, there should likely be: (1) orbital satellites around all planets in our solar system (**Table 1**); (2) a permanent presence of humans on the Moon; (3) the first crewed visit to another planet (e.g. Mars); (4) exchange of materials and samples between planets; and (5) plans to send probes to other stars. When that celestial stage is set, we will enter the next Space Age, when humans are permanent travelers and explorers in space.

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Competing interests

CEM is a co-Founder of Cosmica Biosciences. SMB is a co-founder and Scientific Advisory Board member of KromaTiD, Inc.

Ethics and inclusion statement

This manuscript has included authors from all backgrounds from the scientific international community and the results are held at the highest ethical standards.

Author contributions

Conceived and designed the review: CEM, AB. Reference check: all. All authors discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

Figure Captions

Figure 1. A historic overview of space launches. (inset) The launches that defined the first space age, from 1957 to 2022, broken down by the country of origin. (**Main)** The exponential increase in launches marks the Second Space Age, driven more by commercial launches. The number of launches (y-axis) per year (x-axis) is plotted with the color annotated as the United States (blue), Union of Soviet Socialist Republics (USSR)/Russia (purple), China (red), and other countries (green).

Figure 2. Radiation levels of Inspiration4 mission, NASA's Twins Study and other exposures. The effective accumulated radiation dose is provided in millisieverts (mSv). The low linear energy transfer (LET) radiation (or terrestrial radiation) is denoted by the green bars. The radiation levels experienced during the Inspiration4 mission and Scott Kelly year-long mission (NASA's Twins Study) are indicated by orange bars. The estimated radiation dose of a 3-year

future mission to Mars is depicted by a red bar. All other high LET radiation doses are indicated by the blue bars.

Figure 3. Long-duration missions enabled by heavy lift rockets. (a) The orbital trajectory and future missions enabled by the current Dragon capsule parameters. **(b)** Extra-lunar orbital trajectory that would approach the Lagrange point 1 (L1) closer to the sun and up to 1.54M km from the Earth (center blue diamond). The moon's orbit is shown in dotted lines around the Earth. **(c)** The orbital trajectory for a three-planet mission in 2033 that would flyby Mars twice and also Venus (flyby) within about 18 months. The launch dates and approximate orbital timings (left) are shown around the planetary orbits (dotted line circles) and the flight path (yellow line). The sun is shown in the middle of the figure.

Table 1. Upcoming LEO and interplanetary missions in the next decades. Current mission plans include those led by non-government actors (Non-Gov), NASA (GOV (US)), and non-US governments (Gov). The mission destinations are listed on the top of each category (Asteroids, exoplanets, Gas Giants, Low Earth Orbit, Mars, Moon, Venus and Mercury). Asteroids related missions will be conducted mainly by both NASA and European Space Agency (ESA) with the specific information found here[109–113]. The exoplanets missions will be conducted by Breakthrough Initiatives[114]. Gas giants missions will be conducted by NASA, ESA[115–117] and China National Space Administration (CNSA). Low Earth Orbit missions indicated in this figure will be done by Indian Crewed Spaceflight (ISRO)[118] and Virgin Galactic[119]. Several agencies are planning Mars missions which include: Lockheed Martin (LM)[120], United Arab Emirates (UAE) Space Agency[121], ISRO[122], NASA[123,124], CNSA[125], Japan Aerospace Exploration Agency (JAXA)[126], ESA[127], and SpaceX[128]. The Moon missions will be conducted by NASA Artemis program (with support from ESA)[129–131], China (CNSA)/ROSCOSMOS[132,133], and JAXA[134]. Both NASA[135,136] and ESA[137] are planning Venus missions. There is also a joint ESA/JAXA Mercury mission[138]. Abbreviations: DART, Double Asteroid Redirection Test; PERSEUS, Plasma Environment, Radiation, Structure, And Evolution Of The Uranian System; JUICE, Jupiter Ice moons explorer at Jupiter, Ganymede, Callisto, and Europa; MMX, Martian Moons Exploration; Rosalind Franklin, part of the ExoMars programme; ILRS, International Lunar Research Station; VIPER, Volatiles Investigating Polar Exploration Rover.

Destination	Mission name	Mission details	Agency	Agency type	Mission type	links
Asteroids / Kuiper Belt	DART	DART launch (2021); Asteroid Didymos impact (2022)	NASA	Gov (US)	Flyby	https://science.nasa.gov/mission/dart/
	DART/Hera	Hera launch to visit DART (2024); Hera arrives at Didymos site (2026)	ESA	Gov	Flyby	https://www.heramission.space
	Lucy	Launch (2021); Inner-Main Belt (2025); L4 Trojan Cloud (2027); L5 Trojan Cloud (2033)	NASA	Gov (US)	Flyby	https://science.nasa.gov/mission/lucy/
	Hayabusa2	Launch (2014); Asteroid Ryugu sample return (2020); Asteroid (98943)2001 CC21 (2026); Asteroid 1998 KY26 (2031).	JAXA	Gov	Flyby	https://science.nasa.gov/mission/haya

	New Horizons	Launch (2006); Pluto (2015); Arrakoth (2019); Kuiper belt (2023 onward)	NASA	Gov (US)	Flyby	https://science.nasa.gov/mission/new-
	OSIRIS-Rex	OSIRIS-Rex asteroid sample return: launch (2016); return (2023)	NASA	Gov (US)	Sample return mission	https://science.nasa.gov/mission/osiris
	Psyche	launch of Psyche asteroid probe (2023); arrival (2026); completion (2028)	NASA	Gov (US)	Orbiter	https://www.jpl.nasa.gov/missions/psy
Exoplanets	Starshot	launch of Breakthrough Starshot (2036); arrival (2061); signal returns (2065)	Breakthrough Initiatives	Non-Gov	Flyby	https://breakthroughinitiatives.org/initia
Gas Giants	Dragonfly	launch of Dragonfly lander (2027); arrival on Titan (2034)	NASA	Gov (US)	Lander	https://dragonfly.jhuapl.edu
	Europa Clipper	Launch (2024); Arrival (2028)	NASA	Gov (US)	Orbiter	https://europa.nasa.gov
	PERSEUS	Launch (2031); Arrival (2043)	NASA	Gov (US)	Orbiter	https://ntrs.nasa.gov/citations/471157
	JUICE	launch (2023); arrival (2030); orbit Ganymede (2034)	ESA	Gov	Orbiter	https://www.esa.int/Science_Explorati
	Tianwen-4	Launch (2029); Jupiter orbit (2035); Uranus flyby probe (2045)	CNSA		Orbiter and Flyby	
Low Earth Orbit	Gaganyaan	launch (2023)	ISRO	Gov	Crewed spacecraft	https://www.isro.gov.in/Gaganyaan.htr
	Space Tours	first tour (2023)	Virgin Galactic	Non-Gov	Crewed spacecraft	https://brochure.virgingalactic.com/spa
Mars	Mars BaseCamp	launch (2028); return (2031)	LM	Non-Gov	Deep space habitat	https://www.lockheedmartin.com/en-u
	Hope	Launch (2020); Arrival (2021); Completion (2024)	UAE	Gov	Orbiter	https://www.emiratesmarsmission.ae/h
	Mangalyaan 2 / Mars Orbiter Mission (MOM)	Launch (2024)	ISRO	Gov	Orbiter	https://www.youtube.com/w https://www.isro.gov.in/Mars nifies,the%20way%20for%20future%2
	Perseverance	Launch (2020); Arrival (2021); Collections (2021-2025).	NASA	Gov (US)	Rover	https://mars.nasa.gov/mars2020/
	Mars Sample Return (MSR)	Launch (2026); Arrival (2028); Return (2032)	NASA	Gov (US)	Retrieval	https://mars.nasa.gov/msr/
	Tianwen	Tianwen-1 Launch (2020); Arrival (2021); Tianwen-2 (2025); Tianwen-3 Sample Retrieval (2030)	CNSA	Gov	Rover	https://nssdc.gsfc.nasa.gov/nmc/space
	MMX	launch (2024); orbit (2025); return (2029)	JAXA	Gov	Orbiter	https://www.mmx.jaxa.jp/en/

	Rosalind Franklin	launch (2028); arrival (2030)	ESA	Gov	Rover	https://www.esa.int/Science_Explorati
	Starship - uncrewed lander	launch (2027)	SpaceX	Non-Gov	Uncrewed lander	https://www.spacex.com/vehicles/stars
	Starship - crewed lander	launch first crew (2027)	SpaceX	Non-Gov	Crewed lander	https://www.spacex.com/vehicles/stars
Moon	Argonaut	Argonaut 1 (2031); Argonaut 2 (2033); Argonaut 3 (2035)	ESA	Gov	Uncrewed spacecraft	https://www.esa.int/Science_Explorati
	Artemis	Artemis 1 (2022); Artemis 2 (2025); Gateway (2026); Artemis 3 (2027); Artemis 4 (2030); Artemis 5 (2031); Artemis 6 (2032)	NASA	Gov	Uncrewed spacecraft	https://www.nasa.gov/huma
	Moonlight	Moonlight (2024)	ESA	Gov	Uncrewed Satellites	https://www.esa.int/ESA_Multimedia/V
	Chandrayaan	Chandrayaan-3 (2023); Chandrayaan-4 (2028); Chandrayaan-5 (2030); Chandrayaan-6 (2032)	ISRO	Gov	South pole, drilling, and sample return missions	https://www.isro.gov.in/Chandrayaan3
	Chang'e	Chang'e 5 (2020)	CNSA	Gov	Sample return mission	https://nssdc.gsfc.nasa.gov/nmc/spac
	Chang'e	Chang'e 6 (2025)	CNSA	Gov	Lander	https://nssdc.gsfc.nasa.gov/planetary/
	Chang'e	Chang'e 7 / Rashid II (2026)	CNSA/MBRSC	Gov	Lander	https://nssdc.gsfc.nasa.gov/planetary/
	Chang'e	Chang'e 8 (2027)	CNSA	Gov	Lander	https://nssdc.gsfc.nasa.gov/planetary/
	ILRS	Launch (2026)	CNSA/ROSCOSMOS	Gov	Lander	https://www.cnsa.gov.cn/english/n646
	IM	IM-1 (2024); IM-2 (2025); IM-3 (2026)	Commercial	Non-Gov		
	Russia Lunar	launch test and lunar soil return (2027)	ROSCOSMOS	Gov	Lander	
	Russia Lunar	launch crew (2029)	ROSCOSMOS	Gov	Lander	
	SLIM	SLIM (2022)	JAXA	Gov	Lander	https://global.jaxa.jp/projects/sas/slim/
	VIPER	Launch (2024)	NASA	Gov (US)	Lander	https://science.nasa.gov/mission/viper
Venus	DAVINCI	Launch (2029)	NASA	Gov (US)	Flyby	https://ssed.gsfc.nasa.gov/davinci/
	Envision	Launch (2031)	ESA	Gov	Orbiter	https://www.esa.int/Science_Explorati
	Vertias	Launch (2031)	NASA	Gov (US)	Orbiter	https://www.jpl.nasa.gov/missions/veri
Mercury	BepiColombo	Launch (2018); Landing (2025)	ESA/JAXA	Gov (US)/Gov	Orbiter	https://www.esa.int/Science_Explorati

Table 2. The package of Space Omics and Space Omics and Medical Atlas (SOMA) across orbits. The research and papers discussed in this manuscript are highlighted and categorized by different biological components which are: cellular, organ and tissue, and whole body. In addition,

we categorize the countermeasures and computational research separately. Lastly, the annotation of astronaut data is included in the manuscripts.

	Main Assays	Key Cellular/Tissue Changes	Ref	Astronaut Data
Cellular				
Mitochondria	RNA-seq	Plasma cell free (cf) RNA maps indicating mitochondrial dysfunction	47	JAXA
	Whole-genome Sequencing (WGS)	Mitochondrial DNA in plasma; genome stability	32	JAXA; I4; NASA twin
Immune Cells	scRNA-seq	Immune dysfunction in space and simulated microgravity	35	JAXA; I4; NASA twin
	Single-cell multi-omics	Inflammation and chromatin changes in monocytes	3	I4
	Sex-specific immunomes	sexually dimorphic immune and endocrine kinetics	33	None
	Behavioral assays and flow cytometry-based immune cell profiling	Decreased monocyte driven changes over time	139	None
	RNA-seq	Haemoglobin dysregulation	140	JAXA; I4; NASA twin
Chromosomes / Telomeres	Whole Genomics Seq and RNA-seq	Elevated telomeric RNA	29, 32	I4, NASA twin
	Epigenetics & Transcriptomics	DNA methylation changes	8, 22	JAXA
Epigenetic changes	Epitranscriptomics	RNA methylation increases and shifts	141	I4, NASA twin
Endocrine Effects	Multi-Omics	Changes in insulin and estrogen signaling	4	JAXA; I4
Organs and tissues				
Heart	Multi-Omics & western blotting	Cardiac fibrosis and miRNA increases	61	JAXA; I4
	Clonal hematopoiesis of Indeterminate Potential (CHIP)	Increased CHIP Hazard Ratios	142	None
		CHIP changes from spaceflight	32	I4; NASA twin
Skin	Spatial Multi-Omics	Inflammatory skin changes	57	I4; NASA twin
	Transcriptomics	Skin health dysfunction	56	JAXA; I4; NASA twin
Skeletal Muscle	Bioreactor	Development of muscle countermeasures	54	None
	Transcriptomics	Sarcopenia	52	JAXA; I4
Brain	Spatial transcriptomics	Neurodegenerative disease	59	None
	Multi-omics and exosome profiling	Oxidative stress and blood-brain barrier disruption	60	I4, NASA twin
	Behavioral Assays	Psychomotor vigilance	58	None
Kidney	Multi-omics and spatial transcriptomics	Kidney dysfunction	63	JAXA; I4; NASA twin
Systemic, host–microbe, and whole-body impact				
	Biospecimen protocols	Blood, urine, and skin	9	I4; NASA twin

Artificial Intelligence (AI)	Biobank and data repository	Space omics & medical Atlas	8	I4, NASA twin; JAXA
	Physiological & molecular assays	Crew differences and I4 mobile imaging	7	I4, NASA twin
Microbiome	Metagenomics and Metatranscriptomics	Microbial exchange	74	I4, NASA twin
	Metagenomics	Microbial adaption to space	72	None
	Metagenomics	Microbial tracking on the ISS	143	None
Countermeasures				
Drugs	RNA-seq and treatments with miRNA inhibitors	Immune & mitochondrial activation	61, 62	JAXA; I4; NASA twin
Genes	WGS, RNA, CRISPRa/i	Protective Alleles and Data Modeling	97, 99	I4; NASA twin
Computational and omics Tools				
Artificial Intelligence (AI)	Multi-omics & Machine Learning (ML)	Calcium uptake in muscles	144	None
	ML & transcriptomics	Liver dysfunction	146	None
Omics Analysis	Transcriptomics	Muscle degradation	148	I4
	ML, CRISPR, Transcriptomics	Liver dysfunction	92	None
Perspective, reviews and ethics				
	Macrophage alterations in response to spaceflight		5	None
	AI-supported precision health in space		145	I4; NASA twin
	AI in space research		147	None
	Ethics for Commercial Spaceflight		98	I4
	Open science integration for space biology research		149	I4, NASA twin, JAXA
	Inspiration4 data availability on NASA's open science platform		150	I4
	Women's Health and Reproductive Systems		152	I4

Table 3. Study design and biospecimen collection schemes for current omics-based flight studies. A comparison of data generated as part of the NASA Human Research Program (HRP) Spaceflight Standard Measures and Omics Archive studies, Translational Research Institute for Space Health (TRISH) efforts, and the Cornell Space Omics and Medical Atlas (SOMA). Data generation protocols include Whole Genome Sequencing (WGS) in Clinical Laboratory Improvement Act (CLIA) labs, Pharmacogenomics (PGx), Whole Genome Bisulfite Sequencing (WGBS), Complete Blood Counts (CBC) with differential, Complete Metabolite Panel (CMP), biochemical assays with the Johnson Space Center (JSC) panel, extracellular vesicles and particles (EVPs), and B-cell receptor and T-cell receptor (BCR/TCR) repertoires. Some variations include Glycoproteomics (+Glyco) or poly-Adenylated (polyA) and ribosomal RNA-depleted (ribo-) RNA-sequencing (RNA-seq). Most samples are aliquoted and banked into long-term archives, including viably frozen cells in dimethyl sulfoxide (DMSO).

		Assays and Purpose		
	Protocol	HRP Core Measures / NASA	TRISH Omics	Space Omics and Medical Atlas
Blood	Whole Blood	-	CLIA WGS and PGx	CLIA WGS and PGx
		Blood cell count (CBC)	Blood cell count (CBC)	Blood cell count (CBC)
		Metabolic Panel (CMP)	Metabolic Panel (CMP)	Metabolic panel (CMP)
	Serum	Biochemistry (JSC panel)	Biochemistry (JSC panel)	Biochemistry (JSC panel)
	Plasma	Proteomics (+Glyc)	Proteomics	Proteomics (untargeted/targeted)
		Lipidomics	-	Lipidomics
		Metabolomics	Metabolomics	Metabolomics
		-	-	Exosome/EVPs Profiles and Proteins
	PBMCs	-	-	Viably Frozen Cells (DMSO)
		-	-	Telomere Length
		-	-	Clonal Hematopoiesis Panel
		-	Single-Cell RNA-seq	Single-Cell RNA-seq
		-	-	Single-Cell ATAC-seq
		Functional Immune Assessment	Immune profiling	Single-Cell (BCR/TCR)-seq
	cfDNA	-	-	Cell-free DNA sequencing
	cfRNA	-	-	Cell-free RNA sequencing
	PAXgene RNA	RNA-seq	RNA-seq	RNA-seq (polyA, ribo-)
		-	-	Direct RNA sequencing
Cheek Epithelia	Buccal Swab	WGS	-	Meta(Genome/Transcriptome)
		-	-	Metabolomics
Urine	24-hr-void	Proteomics	-	Proteomics
		Lipidomics	-	Lipidomics
		Metabolomics	-	Metabolomics
		Biochemistry (JSC panel)	-	Biochemistry (JSC panel)
	Morning void	-	Dipstick	Dipstick
		-	16S	Metagenomics
		-	-	Proteomics
		-	Metabolomics	Metabolomics
		-	-	Exosomes
		-	-	Cell-free DNA/RNA sequencing
		-	-	Biochemistry (JSC panel)
Saliva 1-day	Crude Saliva	Immune and qPCR viral panel	-	Immune and JSC qPCR viral panel
	Oragene	WGBS	16S	Meta(Genome/Transcriptome)
Microbiome	Body Swabs	Metagenome	16S	Meta(Genome/Transcriptome)
	Saliva	Metagenome	16S	Meta(Genome/Transcriptome)
	Fecal	Metagenome	16S	Meta(Genome/Transcriptome)
	Vaginal	-	-	Meta(Genome/Transcriptome)
Spacecraft	Swabs	-	-	Environmental data
		-	-	Meta(Genome/Transcriptome)
Hair Follicles	Hair	-	-	Telomere Length
		-	-	Nucleic Acid Banking
		-	-	Meta(Genome/Transcriptome)
Semen	Sperm	-	-	Concentration, Size, Count, Motility, Morphology
Skin Biopsy	3mm punch	-	-	Spatial transcriptome/proteome

		-	-	Histology & morphology

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