Situated Precision Health in the Smart Medical Home

Situated Precision Health in the Smart Medical Home: Insight and Innovation from NASA's Metascience

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ABSTRACT

Science Program Management in NASA's Human Research and Technology Development is relevant to a broader strategic transformation in research on healthcare. There is an opportunity and a challenge to harness the potential scientific knowledge transfer and associated technology transfer. In response to this challenge, I have engaged leaders in NASA's human research to address what it would mean for such scientific strategy, in and of itself, to be scientific. I consider two unique and essential attributes of the associated science of science (metascience): scientific method and scientific community. I argue that meta-scientific progress in any approach to translational research for human health and wellness requires participation of technical, operational and programmatic peers from outside a single community such as human health and performance research at NASA. I thus introduce specific meta-scientific constructs and evidence from NASA and business scholarship that are relevant to mega-trends in healthcare writ large.

The article is organized in three major sections: (a) making metascience matter in public-private collaboration, (b) need for NASA's demand-side innovation, and (c) combinatorial scientific and clinical paradigms. This provides a foundation for collaboration that can stimulate development of meta-scientific communities, defragment demand for solutions, and achieve a more coherent strategic approach to integration and development of a diversity of capabilities including but not limited to technology. I conclude with six meta-scientific principles from NASA that can transform research in healthcare through continual experimentation in a smart medical home. A companion article, *Bringing NASA's Metascience Down to Earth*, builds on this foundation to make recommendations for development of new scientific and clinical paradigms that aggregate heterogeneous sources of data for innovation in lifestyle interventions in a smart medical home as well as lifespan approaches to precision brain health.

KEYWORDS: aging; digital biomarkers; metascience; systems medicine; precision health

MAKING METASCIENCE MATTER IN PUBLIC-PRIVATE COLLABORATION

Toward a Metascience of Research on Human Health and Performance

Science Program Management in NASA's Human Research and Technology Development is relevant to a broader strategic transformation in research on healthcare. There is an opportunity and a challenge to harness the potential scientific knowledge transfer and associated technology transfer. In response to this challenge, I have engaged leaders in NASA's human research to address what it would mean for such scientific strategy, in and of itself, to be scientific. The intent of this broad approach is not to redirect attention away from the important issues at NASA in particular. Instead, the specific aims are to (a) reflect on fundamental assumptions about the value that medical research can deliver to stakeholders, (b) appreciate how disparate segments of the medical research community can share value and achieve outcomes beyond what they can achieve alone, and (c) identify how research and technology development outside the medical community can help medical research become better grounded in the life and work of individuals and thus can achieve more meaningful outcomes. This article focuses on the requisite generalization and abstraction motivated, in particular, by our interest in knowledge transfer between NASA and terrestrial medicine such as in research on diseases of aging [1]. The companion article [2] utilizes this broader foundation to reveal a path for a different kind of research to foster situated precision health.

At the highest level of abstraction, science has two unique and essential attributes on which the science of science (i.e., metascience) also must focus. One attribute is the scientific method in which systematic progress requires theories that can be falsified, in principle, by empirical data. That is, theories must be sufficiently specific to be differentiated from alternatives and for their predictions to be tested against reality in ways that can be reproduced by others and generalized to a broader range of phenomena. There should be persistence in some aspects of the results amid change in the conditions of replication. The more diverse the conditions, or the more complex the transformations among their descriptions, the more meaningful and powerful the invariants that describe (e.g., mathematically) those aspects of the results that are reproduced. This is perhaps the most well-known attribute of science both inside and outside of science [3, 4]. In the present context of metascience, the challenge reduces to identifying a range of scientific disciplines and applications beyond NASA research, from which theories and methods can generalize to NASA research, as well as the mathematical rigor that should attend such generalization.

An equally important attribute of science is diverse community in which there can be an opposition of ideas—a productive dialectic—that generates systematic progress both logically and through the scientific method [5, 6]. Such peer review is a central value of scientific communities. It is an implicit requirement of their decentralized activity and an explicit requirement of their formal governance. The value of peer review depends heavily on the extent to which it represents diversity within the community. Diversity of peer review speaks directly to the generalizability of theories and methods as well as reproducibility of the results they generate. The importance of dialectic in a diverse community seems to be taken for granted in scientific program management and evaluation, however, or at least it is not subject to the same scrutiny as various instantiations of the scientific method. Moreover, it is poorly understood outside scientific communities, most notably by stakeholders who can benefit from scientific progress [7, 8]. In the present context, a community of peers is required to address the science of science across a range of disciplines that can contribute to innovative research in NASA.

In our response, we give special emphasis to dialectic and diversity in a broader community of metascience from which NASA stakeholders can benefit to a substantially greater degree than in the past. The inquiry must start with a consideration of a diversity of stakeholders of relevance not only to NASA but more broadly to behavioral health and diseases of aging, if not to healthcare in general. We do this through the lens of clear trends in the healthcare industry for which there is an abundance of supporting literature. The verifiable assumptions and generalizable metascience in our inquiry motivate connections and conduits of knowledge transfer among disparate communities [9, 10] (Figure 1). In particular, we focus on connections between human research at NASA and research on diseases of aging that otherwise are not obvious and thus are a likely source of innovation for both communities.

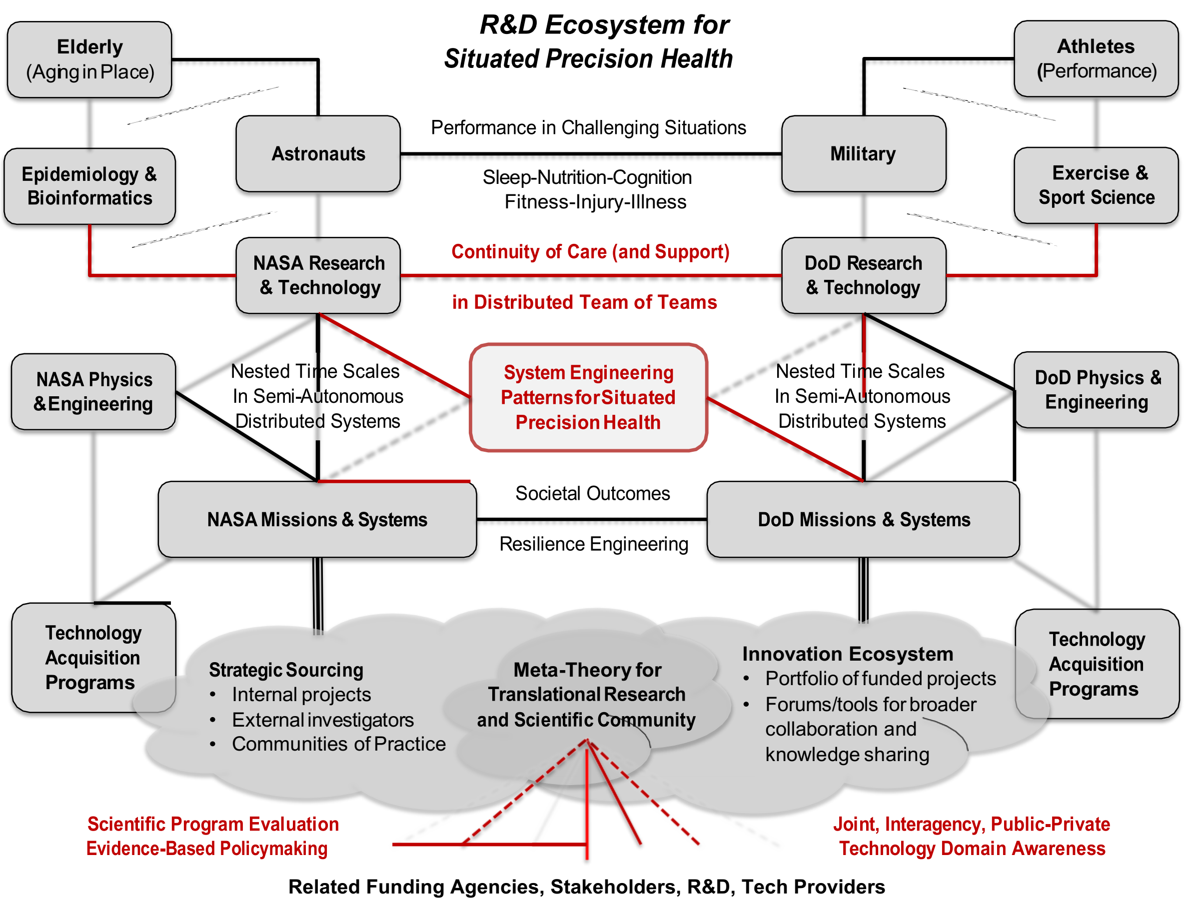

Figure 1. Framework for knowledge transfer among our disparate communities of research and practice. Annotations in the figure are addressed throughout the article. Our research in DoD and exercise & sport sectors are not discussed in this article but the meta-scientific framework generalizes to and benefits from work in those communities [11, cf. 10].

The reasons for knowledge transfer from NASA are systematically addressed in this article and in the companion article. In essence, the relevance of NASA's human research is that it has been forced for decades to address the delivery of healthcare by a distributed team of teams to a remote site where individuals are relatively isolated and must live and work under varying degrees of impairment to sensory, motor and cognitive function. Moreover, NASA has been on the cutting edge of planning and operation of a system-of-systems architecture that includes opportunities for increasingly comprehensive sensing of the built environment, human inputs and outputs, as well as physiological and medical status. This experience is important beyond NASA because future homes and workplaces will include a range of sensors and connectivity that the general population is only beginning to imagine. As discussed below, the business implications of such future technology are widely appreciated in the healthcare industry while the scientific and technological path toward an integrated system of systems is not. We argue that NASA provides a starting point and a map that is sufficiently specific for the private sector to progress systematically and potentially to surpass NASA in the near future.

Selective Pressures on the Supply-Side of the Healthcare Industry

Impediments to non-pharmacological alternatives

The specific challenge is to broaden the approach to healthcare far beyond the dominant paradigm of pharmacotherapy [1]. The challenge suggests deeper meta-scientific problems of paradigm perseveration and change that cannot be understood without considering the business models and economic assumptions that drive and constrain the research. These constraints are not unique to pharmacotherapy, nor to any specific set of medical conditions. Thus, there is much to be learned about the metascience of research on human health and performance from a broader diversity of healthcare consumer needs.

Resistance to change in healthcare is not simply due to potential problems of subjectivity such as cognitive bias that is characteristic of individuals as such and of organizations that lack of diversity [12, 13]. It also derives from objective manifestations of such bias in the highest priority clinical and business metrics such as those relating to near-term profitability and manageability [14]. The most convenient metrics are those that can be applied internally within the locus of control of a particular firm [15, 16]. Particular offerings come to dominate others with respect to such metrics through their influence on resource allocation. The most profitable and manageable offerings foster fragmentation into clinical practice subspecialties that ostensibly can stand alone with respect to return on investment. Business models inevitably become sub-optimized to the extent that value delivery to consumers becomes holistically incoherent [17, 18]. They also become fragile because of a lack of awareness of complementary or conflicting needs and because of adjacent offerings ostensibly outside the span of control of a particular subspecialty [19]. Value itself can come to be defined in terms of utilization of the subspecialty rather than holistic clinical outcomes that require a field of view beyond the subspecialty [15, 20].

The recent history of pharmacology provides a powerful example of how presumptions of success breed fragmentation and narrow conceptions of value [21, 22]. An alternative conception of value is required before economically viable bundles of treatments can be identified and assessed in a more holistic view of the value chain that captures what matters to a diversity of healthcare consumers as well as other stakeholders. Alternative economic models for the medical industry need not and probably should not be unique to the medical industry. Marianna Mazzucato and her colleagues have been addressing the gap between supply and demand, for example, through an insightful and influential economic framework [21, 23]. They view alternative directions for health innovation as “a contestable question among multiple actors [that takes] a normative view on how directions can be set by 'missions' that meet societal needs, such as healthy aging…" and with respect to which there is "a role of the public sector in making the necessary risk-taking investments to pursue those directions…" [21, p. 102]. This work recognizes NASA as a model of such a mission orientation in the space industry, for example, in which the public sector plays a critical role in initiation and ultimately in holistic guidance to innovators in the private sector. We address how NASA, more specifically, is providing a model for meta-scientific innovation in medical research for both pharmacotherapy and to non-pharmacological interventions that can be applied to research on AD.

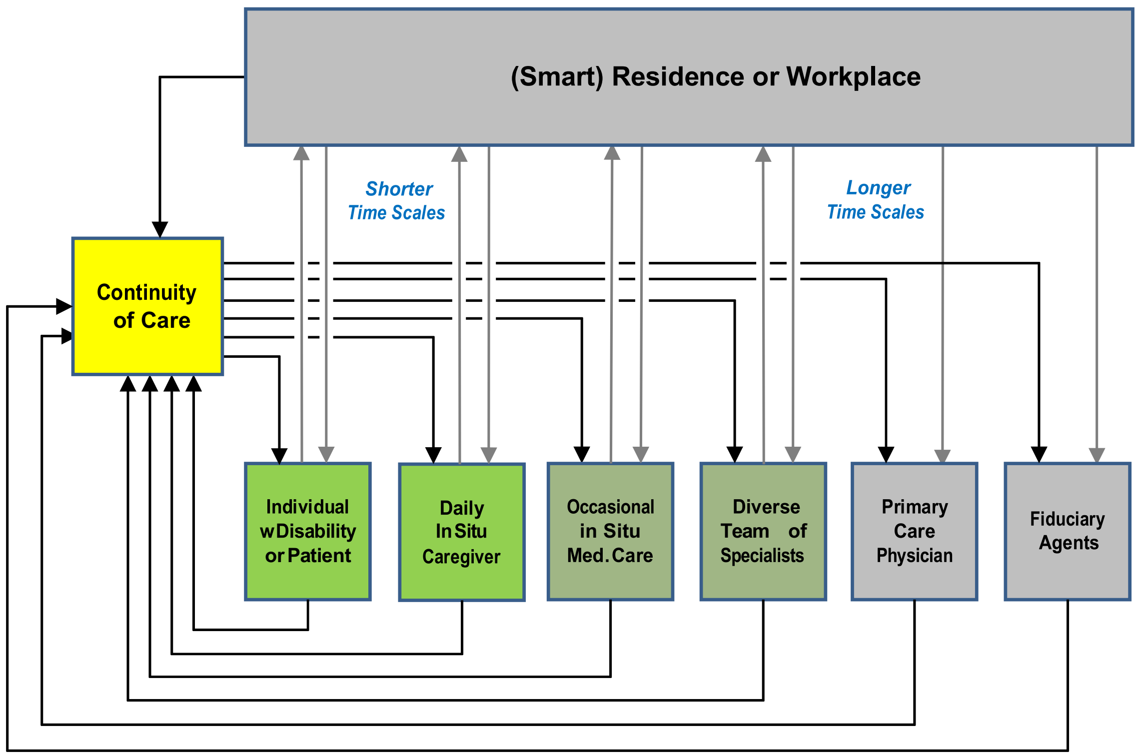

Figure 2. Continuity of care involves coordination among different kinds of stakeholders who typically are engaged intermittently over nested time scales that, as such, can be deconflicted and reciprocally influential by design. [29, cf. 30]

Continuity of care

Pharmacotherapy has been limited by a supply-side view in which such treatment is relatively attractive because it is low on continuing labor costs, such as in high-touch services, even though sunk costs in development are quite high [21]. The inevitable implication of reduced dependency on high-touch treatment alternatives, however, is *reduced capacity for observation* of well-being, self-care, adherence to treatment plans, external environment, behavioral patterns of life, and *reduced capacity for engagement* in collaborative activity and social interactions. This is not just a problem of lack of visibility into outcomes that matter to patients. It also misses opportunities in communication across the boundaries of medical specialties that often are utilized at different times and over different time scales (Figure 2). The opportunity lost is in helping healthcare providers think beyond processes in their direct control [13] and coordinate efforts of a multidisciplinary team [19, 24]. This is problematic because there are real and urgent needs to manage the entire value chain in healthcare [25, 26]. The outputs of the value chain to consumers, by definition, are what consumers experience. The experience of most healthcare consumers today arguably is anxiety due to volatility, uncertainty, complexity and ambiguity of both processes and outcomes; that is, about continuity of care.

Continuity of care is not a new consideration. It has long been a core value in healthcare, certainly in the practice of traditional primary care [27, 28]. Nevertheless, continuity of care has been steadily eroded by the fragmentation of medical service, the success of pharmacotherapy, and the dominant paradigm of healthcare coordination that relies increasingly on mega-hospitals and associated medical complexes in and around urban areas [24]. An important question for continual improvement in healthcare, if not transformation in it, is how to sustain the value provided by these developments in the healthcare industry while regaining what has been lost, and to potentially create and deliver entirely new kinds of value [16, 19].

Data-driven healthcare

A common assumption is that digitization of healthcare services is the most promising source of innovation to regain and improve continuity of care [19, 26, 31]. Such projections make two assumptions that impose hard constraints on development and deployment of healthcare technology: (a) information about services and patients can be obtained and retained in digital form without increasing labor costs that otherwise are an impediment to any healthcare innovation; and (b) information can be exchanged and delivered in the right amount and right form to the right person at the right time, also without increasing labor costs or burden on personnel. We address these assumptions by identifying meta-scientific frameworks in NASA, mostly over the last decade, that are sufficiently specific and generalizable to inform tradeoffs about continuity and transformation of services, products and associated business models in the healthcare industry.

Healthcare has had a long history of intertwined development with technology. The preoccupation with technology-driven transformation is common, but the expectations about emerging business models for digitization are at a different level. Why? One reason is that it is always difficult to predict the future of technology development while it is nevertheless it is important to do so [32, 33]. Levels of investment are a good guideline for technology forecasting especially when they are historically extraordinary and when the attendant rate of technological innovation is unprecedented [34]. Reliable facts and projections about the market for biosensors and biomarkers, for example, estimate that the market will be more than $30 billion and $70 billion (U.S. dollars), respectively, by 2024 with compounded annual growth rates (CAGR) of 8.4% and 13% [35]. This technology will vastly increase the capabilities for monitoring personal health and environmental hazards outside of the highly control environments and facilities of organizations with vast resources, that is, for use by individual consumers. These technologies are already finding their way into consumer markets.

The market for “smart home” technology was valued at USD 56 billion in 2016 and is projected to reach USD 174 billion by 2025, with 13.52% CAGR from 2017 to 2025 [35]. The combinatorial innovation of sensors and smart buildings will be accelerated by an even more impressive market for the Internet of

Things (IoT) valued at $2.1 trillion by 2023 from $679 billion during 2016 with 17.56% CAGR. This massive technological transformation in societal infrastructure will fuel the development of home health care, projected to reach $340 billion by 2024 with a 7% CAGR [35]. And finally, the most transformational technology on the horizon is the computational capability to analyze these massive amounts of heterogeneous data (e.g., "Artificial Intelligence"). The market for AI is valued at $24 billion in 2018 and expected to reach $208 billion by 2025 with the CAGR of 36.2% over the forecast period [35]. The healthcare industry must transform to accommodate these capabilities given that firms in adjacent marketspaces are likely to penetrate the healthcare market with an insurgency that cannot be resisted. [19, 25].

Clearly there is opportunity for the healthcare industry to leverage enormous investments in technology development in other industries [26, 31]. This requires a different mindset for R&D than what has come to dominate thinking in the industry given the unparalleled profitability of pharmacotherapy. The required kinds of expertise and investment for this new way of thinking are architectural, that is, organizing the system of systems and realizing combinatorial innovation that utilizes disparate resources such as biosensors, smart homes, IoT, and AI [36; 37]. The concept of a system of systems and its associated architecture are important because it transcends considerations of physical interface control. In such heterogeneous systems, functionality emerges from interdependencies inherent in concurrent or sequential use [29, 33]. There is considerable attention in the healthcare industry to architectural thinking that can defragment services in response to demand-side pressures (addressed below), mostly from the perspective of organizational design, but there is not a commensurate appreciation of the nuances of system-of-systems architecture that bundles and thus leverages technologies developed for other purposes. Where is this key ingredient to be found?

We agree with Mazzucato that (b) the mindset required for healthcare R&D to address large-scale societal challenges, such as diseases of aging, is best characterized by a mission orientation, and (b) exceptional niches in the public sector can be a model if not an accelerator for transformative missions [20, 23]. Finding peer leaders in the public sector, or in any different industry, requires a conceptualization of mission that can be generalized while being sufficiently specific to be implemented in different markets. Our thesis is that *situated precision health for continuity of care* is a mission that can connect leaders in the healthcare industry with peers in the public sector (see Figures 1, 2). In particular, we focus on lessons learned from NASA's preparation for human exploration of space that can be applied to collaborative innovation in the healthcare industry's pursuit of patient-centered care in a smart medical home.

NASA's Relevance to Combinatorial Innovation in Patient-Centered Healthcare

Toward the patient-centered medical home

One of the most important insights in our meta-scientific inquiry is the trend of reducing capacity for external observation of well-being, self-care, adherence to treatment plans, external environment, behavioral patterns of life, and reduced capacity for engagement in collaborative activity and social interactions. Continuity of care is in crisis. Without an alternative to isolated offerings, even the most basic calculus of medical practice—maximizing benefit while minimizing harm—is in peril. We agree with leaders in the healthcare industry, however, that the digital revolution and data-driven healthcare can be a way out and a way forward. As Mazzucato argues, without a mission orientation, the traditional private sector cannot deliver a solution that bundles different services to achieve outcomes beyond what can be addressed by any component service. The invisible hand has no vision in which the whole is greater than the sum of the parts, and it cannot see beyond the moment. This is where the public sector can complement the private sector. The primary point of the public sector is collective awareness and strategic action of which individual consumers and even entire market segments are incapable of initiating. Without a map and a head start from the public sector, holistic solutions for society will not be forthcoming [20, 23].

In the public sector, a high-profile mission that necessitates an interest in technological innovation for continuity of care is to ensure that astronauts are healthy and productive in deep space (e.g., Moon, Mars) as the "tether is broken" with Earth-based support systems that include but are not limited to medical support per se [38, 39]. Astronauts will experience prolonged periods of shared confinement with limited, indirect, and intermittent communication with a network of support from both people and technology. During a mission, this requires an operational capacity for collaboration between astronauts and a ground-support team of teams amid potentially problematic spatial and temporal isolation. Such a capacity includes decentralized healthcare that is directly relevant to the vision for patient-centered care in a smart medical home. For NASA, such care is not limited to medical support because it must address the activities of life and work that both influence and are influenced by a wide variety of medical conditions [29, 40]. The inescapable outcome-based context is instructive for the transformation in the healthcare industry. We address this below in the section on *demand-side innovation*.

At the level of a mission in *precision health for continuity of care*, where specifically in NASA should the medical industry look for such a map, that is, for a well-articulated strategy to address a system of systems that can inform development of a patient-centered medical home? In our view, science is the best place to look for technical details and assumptions that are open to outsiders and that can be reproduced, generalized, validated and verified by others. Metascience is the source of insight and dialectic about entire portfolios of research that serve the development of a system of systems [38, 39]. The assumption is that there are overarching meta-scientific principles of organization for enterprises to develop and employ such systems that apply across disparate communities of practice in the healthcare, space, military and sports industries [11, 40] (Figure 1). The opportunities to learn from each other are not lost on these communities, but there is not a general awareness of a strategic approach to cross-fertilization. We focus on NASA because our intent is to leverage the meta-scientific insights and challenges of NASA's Human Research Program [42, 43] to build such a strategy.

It may be surprising that astronauts in deep space and the well elderly who are aging in place share some of the same challenges. The similarity is to survive if not thrive at or near the limits of their physical, physiological and psychological capabilities. For maximum impact in any population, precision healthcare must be situated in the environments that challenge such individuals and in which the consequences of such challenges play out [44]. Their healthcare must have continuity across a variety of personal support systems that observe and intervene in different parts of their lives at different points in time. Research that can guide development of such situated precision health for continuity of care is as fragmented as the multiplicity of stakeholders for such care. The fragmentation in both supply and demand is a deep problem shared by communities of healthcare for the elderly and for astronauts (Figure

3). It is unreasonable to assume that passive market forces or individual organizations can solve this problem. The solution must be achieved by a community and, in our view, a scientific community.

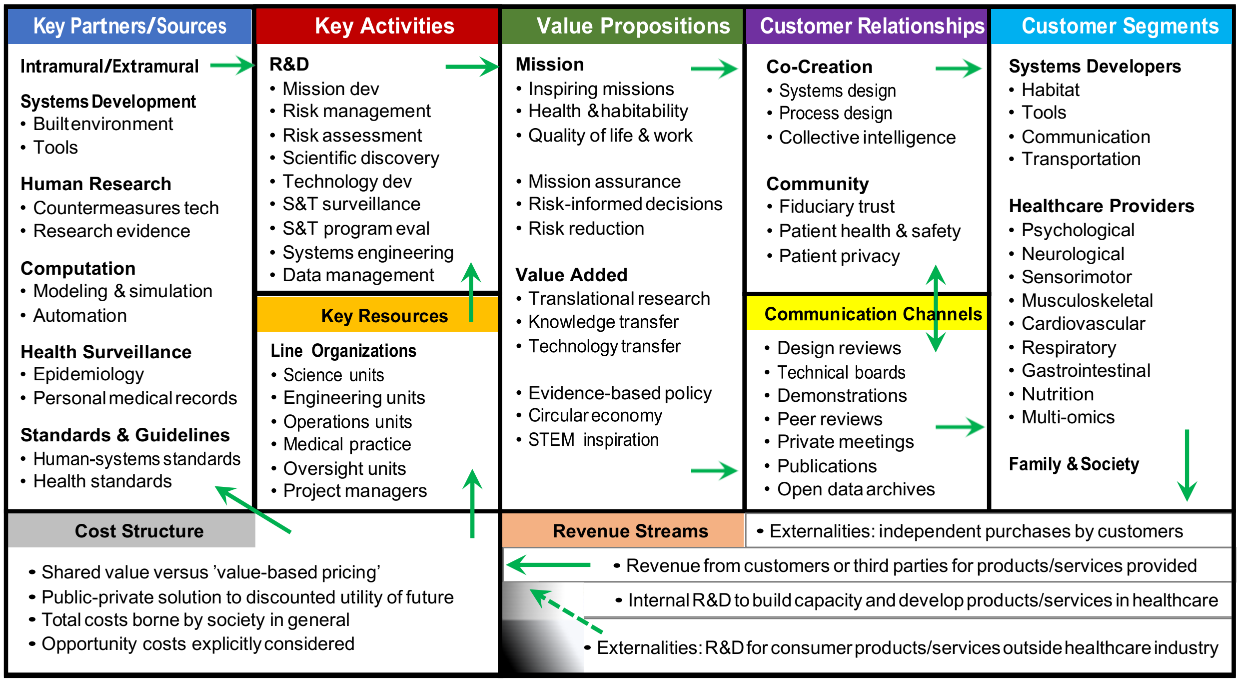

Figure 3. A business model canvas [45] that reveals fragmentation in both supply and demand for development of healthcare. The model is based on NASA organization and operations [41] but it is presented in a form that generalizes across sectors. Arrows show direction of value creation and imply falsifiable meta-scientific theories of proximate causality.

Programmatic defragmentation of the R&D ecosystem

Large organizations in the private sector or public sector can become more like an ecosystem of separate entities over time [46, 47]. One reason for this is that the relationship of organizational units to each other and to the whole tends to become more complicated in response to increasing complexity of their collective stakeholder relationships [48]. Transaction costs and difficulty of knowledge transfer across boundaries within an organization become increasingly problematic. At NASA, and in the medical industry more broadly, this is occurring at the same time the capability and necessity to leverage developments outside the span of control and responsibility are rapidly increasing [49, 50]. This changing constellation of boundary crossings is challenging the very definition and theory of the firm, and they are giving rise to what some scholars characterize as the "fourth industrial revolution" [51, 52]. The attendant opportunities and threats have concrete and urgent implications for strategy execution that has specific relevance to transformation of healthcare [25, 53]. Similar forces and trends are recognized by leaders in NASA who suggest that the agency must operate differently than it has in the past, especially because of the allure of that which was successful in different missions and capabilities of the past [54,55].

Open innovation across organizational boundaries has been a stretch goal for NASA in response to opportunity costs of strategy management in various line organizations that neglect the changing relevance of external sources and partnerships within and beyond NASA [56, 57]. The intent is similar to the initiatives in the DoD for technology domain awareness [50, 58]. Open innovation is a wicked problem, however, because knowledge transfer within many organizations is as difficult as it is beyond an organization [59, 60]. NASA's science, engineering and operations communities have long had intertwined interests in research and technology development to assure astronaut health and performance. Sharing information among these complementary communities, and their potential for reciprocal influence, appears to be a challenge that NASA shares with the development of high-tech high-touch systems medicine for the general population. The principal challenge for NASA has been to overcome the hegemony of selective pressures on the supply side that are not unlike the problem of 'value-based' pricing and other impediments to transformation in the medical industry [15, 16, 20]. Substantial R&D investments over long periods of time tend to narrow the field of view of healthcare to increasingly fragmented perspectives around which the investments build a critical mass of expertise and a maturity of associated interventions.

Our experience with NASA has led us to interpret the need for transformation in healthcare primarily as a problem of fragmentation of supply and demand or, in other words, a lack of coherence in multifaceted value creation and delivery. NASA also has shown us that organizational design is not the solution to fragmentation, at least not the sole solution, and it certainly is not the source of solutions. Nor, in isolation, are processes for open innovation the sole solution. A diverse community of public and private interests is required to conceptualize holistic business models that go beyond the business case for a pill, a device, or a service and, instead, recognize the broad span of activities and stakeholders that influence health and disease. The due diligence in such a community of interest must address the externalities beyond a particular healthcare offering. It must identify and come to understand the choices made by consumers and stakeholders not only with respect to adherence to treatment plans but also with respect to their self-care or self-neglect.

Consumers will engage in their own lifestyle interventions, and experience the effects of them, whether healthcare providers are aware of it or not, and whether providers approve of it or not. Consumer products and smart homes are providing the opportunity for naturalistic observation if not natural experiments that can provide visibility into such externalities. NASA has been on the leading edge of this potential for some time. A broader community of interest can accelerate the development and promulgation of a new capability for situated precision healthcare to which NASA is in a unique position to contribute. The generality of this collaboration does not lessen the potential applicability to continuity of care for diseases of aging. Rather, it increases the range of solutions that include but need not be limited to pharmacotherapy, solutions that improve the quality of life for those at risk from diseases of aging and who are challenged by it.

Toward collective intelligence on the demand side of healthcare

Meta-scientific reflection on NASA's human research provides a clear lesson. The combinatorics of integration among established lines of research and service are intractable. Initiatives in integration tend to be(come) an attempt to add value from a supply-side perspective. Such initiatives often are muddled by countless dead ends and nonoptimal pursuits because the outcomes are unclear, if considered at all, at the outset. Holistic innovation that can transform one's perspective on both needs and solutions, on the other hand, generally involves selectively forgetting the past [60, 61]. On this view, defragmentation provides an alternative to perseveration on assumptions from the past. It need not and should not provide a place for everything to which organizations or markets had become committed. But what is the organizing principle if it is not simply to identify a value added or emergent property among multiple prior commitments?

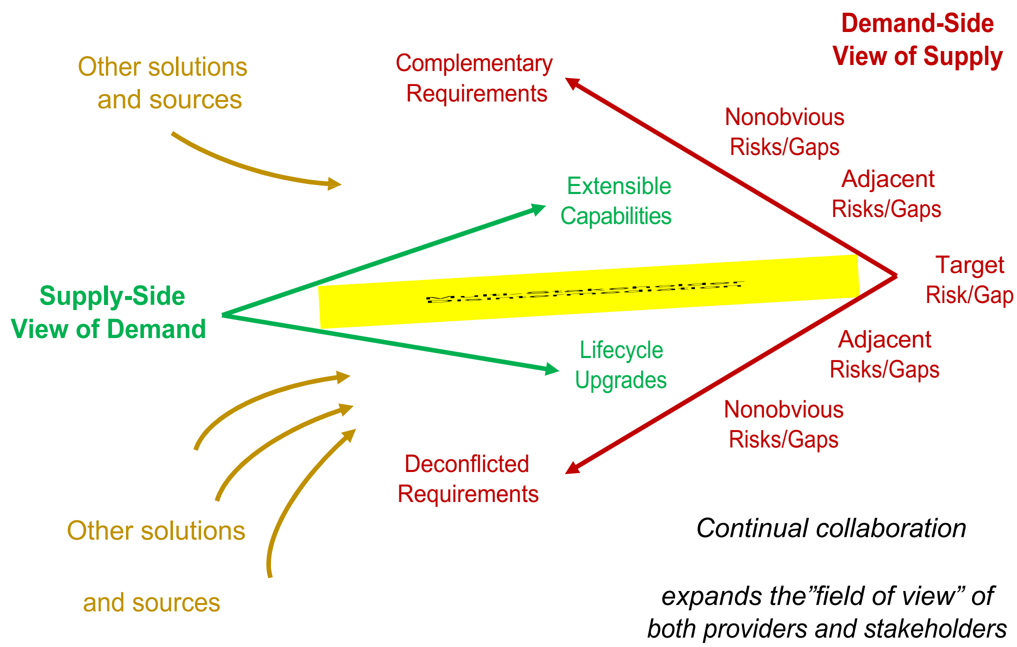

Figure 4. Concurrent development of capability solutions and gaps expands the view of participants on both the supply side and the demand side [29].

One must start with demand, as is always the case, but there must be an innovative look at demand in a holistic way that rarely is considered in the operation of passive market forces. Don't try to understand demand simply by asking consumers what they (think they) want, for example. Look beyond the needs that particular consumers and stakeholders can articulate. Look across the needs of a diversity of stakeholders. Deconflict the variety of factors affecting consumers and find synergies among them. Priorities will emerge that are different because of this holistic view. Different solutions will be sought. In a sense, the field of view of the demand side (e.g., customers and other stakeholders) will be broader and more diverse (Figure 4). Providers and stakeholders on the supply side will come to see demand in a different way. All of this implies an aggressive multifaceted communication between those on the supply side and those on the demand side. It also should imply an openness to be influenced by each other, to have assumptions challenged and commitments changed.

We know of no approach other than science, or at least no better approach, to meeting such requirements for holistic innovation. Because we are addressing the value creation and delivery through science itself, our approach is meta-scientific. How can scientific research and technology development be defragmented for continuity of care in a smart medical home in a way that is replicable, falsifiable, and generalizable? We will start by looking to trustworthy business scholarship about the variety of demands that are driving a healthcare transformation or that otherwise are currently unmet. Then we will look to lessons learned from NASA's Human Research Program about how to harness this more holistic view of the demand side of healthcare. We do not claim that NASA has all the answers, and we believe that NASA also needs help from outside its boundaries [40, 41]. At the same time, we claim that NASA provides the best initials conditions for an approach to situated precision medicine in a smart medical home [29, 44].

NEED FOR NASA'S DEMAND-SIDE INNOVATION

Selective Pressures on the Demand-Side of the Healthcare Industry

Personalized outcomes-based medicine

To start fresh, without any preconceptions about solutions, one must inquire into the outcomes desired by the consumers of healthcare. In a classic case study, Porter and Teisberg reviewed the experience of the Cleveland Clinic, for example, in the systematic development of outcomes-based medicine over more than ten years for 106 frequently treated patient conditions [15]. The evolution in their understanding of outcomes guided the development of new business models that could be tested in the marketplace. The Cleveland Clinic's business-model experimentation started small but accelerated as thinking about outcomes matured and the value of previously disparate services became clearer. It has had the historicity of a line of scientific investigation.

The lessons learned by the Cleveland Clinic reinforce the assumption and common observation that the predominant business models of medical care have become increasingly sub-optimized on processes and associated process measures valued by third parties (e.g., insurance companies) irrespective of the patient's experience or at least without re-examining assumptions about such value and long-term financial consequences. Such perseveration is precarious during times of change such as the rapidly increasingly differentiation of medical services and sub-specialties. In a sense, the imperative for integration has been increasing as models of integration have become more elusive. The bold move of the Cleveland Clinic was in returning to the basics of business (i.e., coupling of supply and demand) and investigating the aggregate value of its various services to patients over their journey through the system. This has direct implications for IT transformations in healthcare [31, 63].

The case study for the Cleveland Clinic redirects the definition and measurement of outcomes toward what matters to patients. A Knowledge Program was created to record observations of patients about their own "cognition, mood, social and functional outcome measures." The business model innovation of the Cleveland Clinic is representative of broader changes that are being considered and explored in the healthcare industry. For example, the shift from a transactional approach to an outcomes-based approach also was emphasized by the CEO of Novartis in an interview with McKinsey about the pharmaceutical industry [25]. An associated business model would view the transaction of "selling a pill" as part of a broader offering that may include remote monitoring of the consumer's vital signs to assess efficacy and the need for other kinds of treatments including admission to a hospital. For Novartis, investing in such health outcomes requires R&D that focuses on unmet medical needs. The strategic assumption is that "if we follow the science and we deliver on that unmet medical need, that the financial returns will happen" [p. 2]. Novartis recognizes that partnering and collaboration with nontraditional companies in healthcare, such as data management companies, will be required to assemble more comprehensive offerings [25, see also 31, 64].

At the same time the new leadership of the Cleveland Clinic was embarking on its outcomes-based healthcare initiative (ca. 2004), new leadership in human health & performance research at NASA were beginning to execute a very similar strategy [65, 66]. NASA's efforts to organize around outcomes instead of traditional scientific or medical specialties is described below in the section on *Demand-Side Innovation*, beginning with the "Integrated Medical Model" [67, 68] (Figure 5).

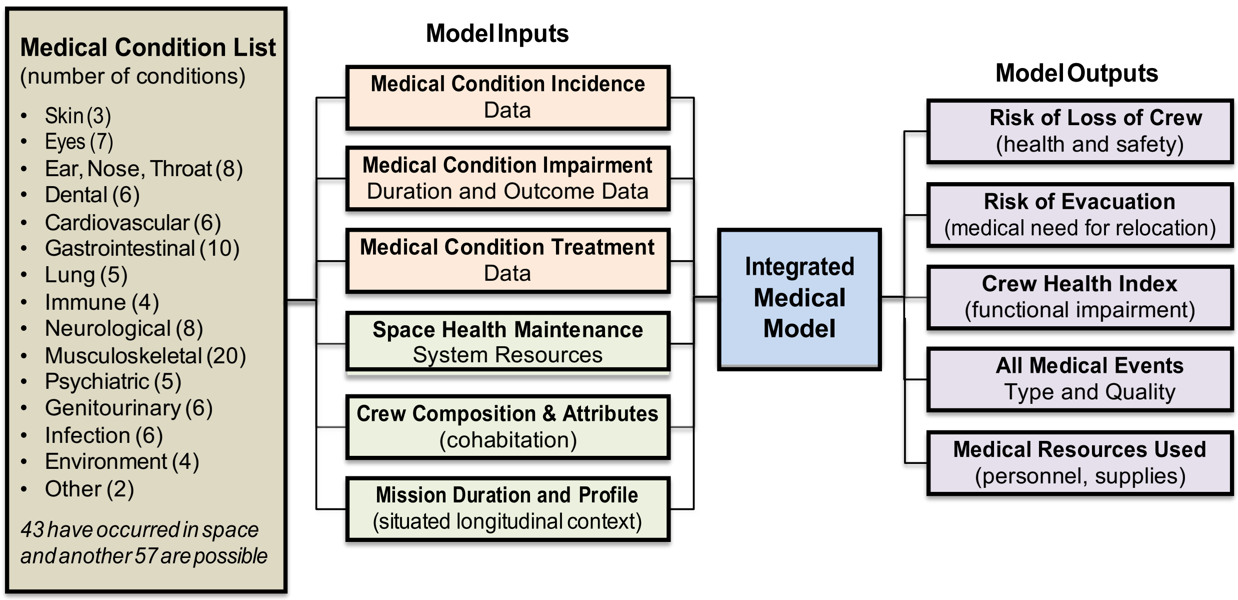

Figure 5. NASA's Integrated Medical Model [adapted from 67, 68].

Participatory healthcare and healthcare consumerism

There are interesting implications of listening to patients about the outcomes of their healthcare and their journey through treatment. One is the recognition that individual consumers compare and assess their healthcare experiences with other consumers [69]. This is noteworthy because such interactions influence decisions and actions of individuals largely outside the awareness and control of healthcare providers. The confounds this introduces into managing the healthcare of individuals derive from the possibility, if not the likelihood, that such consumerism does not respect the demographic population-based categories that, for better or worse, drive the healthcare decisions of providers and institutional influencers. Even if healthcare providers wish to minimize extra-procedural healthcare activity of consumers, they should allow for it, and be prepared to adjust to it, if not shape it. Amid the practical reality of autonomy currently outside the oversight of healthcare providers, patients should be incentivized to be responsible for their autonomy and to be informed accordingly [69]. In essence, for providers to put patients at the center of healthcare, they must first realize that individual healthcare consumers already view themselves at the center of their own healthcare challenges, but they aren't served in this way [70].

Siemens Healthineers recently had the Harvard Business Review Analytic Services survey 613 healthcare decision makers, influencers and managers for their opinions about trends that are shaping the future of healthcare [71]. 93% of respondents indicated that patient engagement should be increased to improve outcomes. Engagement has deep meaning existentially, certainly in any assessment of value that starts with the needs of an individual rather than presumptions about offerings to them. In a deep sense, engagement implies continuity of interaction and a trajectory of increased understanding if not development of a relationship [27, 28]. The latter is not an esoteric goal when one considers the practical and ethical demands to help consumers be responsible with respect to any autonomy in their healthcare decisions and actions. Such responsibility is as much about habits and the long-term consequences of them as it is about the momentary outcomes of the autonomous decisions and actions of consumers. In this context of continuity, Siemens expects “a shift from an acute-disease focus to a chronic-disease focus,” and they project that the “aging of the world’s population [will] push demand for lower-end services such as regular primary care” [p. 1].

Arguably, NASA flight surgeons and the broader ground support teams have been practicing such personalized medicine for decades given the frequency and richness of quantitative and qualitative information collected on astronauts [72]. At the same time, NASA researchers are monitoring the acceleration of capabilities in sensing and computing so that NASA's personalized medicine can be made increasingly precise and, more importantly, so that it can become situated in the hazardous space environments where astronauts work and live. NASA’s systematic approach to research that can support design and development of such a system of systems is described below in the section, for example, on *model-based systems engineering* for exploration medical capabilities [73, 74].

Paradigm breaking externalities of healthcare consumerism

Not surprisingly, leaders in healthcare recognize that consumer demand is changing. The findings of the Siemens-HBR survey are validated by McKinsey’s 2017 Consumer Health Insights (CHI) Survey [18]. The most revealing finding of the McKinsey survey is that consumers view healthcare more broadly than do insurers and traditional providers. The active participation of consumers in their own healthcare fills the gaps in continuity of care across providers and over time. In their impatience or urgency of need, they are looking to nontraditional services such as retail clinics and digital technology to replace unsatisfying engagements with traditional healthcare providers. This personal autonomy is almost certainly influenced by habits of engaging services and technology outside of healthcare that disrupts the doctor-patient social dynamics on which healthcare has relied for generations. Such healthcare consumerism brings uncharted risks and opportunities that must be understood and harnessed in a future dominated by a more holistic systems medicine that is predictive, preventive, personalized and participatory (P4) [75, 76]. R&D must help identify and mitigate such risks, and it should strive to realize opportunities to address unmet needs of healthcare consumers.

Metascience is the formal process by which R&D investments are made and evaluated across a portfolio. Peers in metascience for healthcare will not be limited to the traditional value network in healthcare because nontraditional services and technology already are having an impact on healthcare outcomes and because many of the lessons learned are not unique to the healthcare industry. New paradigms will emerge from this cross-industry collaboration. Consider, for example, the observations of Merck

Healthcare digital-transformation specialist in an interview with McKinsey: "integrated... Community care will be a key area for most pharma companies within the next five years. There are opportunities for digital health in the context of an aging society, for instance" [26, p. 1]. What scientific disciplines and paradigms will be required to understand this technology mediated self-organization? Clearly it will be transdisciplinary, translational and innovative [77-79].

Healthcare is a focus of leading business scholars on innovation [24, 80]. Reverse innovation, in particular, is instructive in the present context. By definition, this source of insight is found in situations where traditional solutions are either unavailable, impractical or otherwise deficient. Understanding such initiative, in a sense, requires an anthropological approach. How do individuals and organizations improvise when their needs are not being met? How do they do a kind of *in situ* resource utilization or repurposing of materials, devices and systems at hand with which they already are familiar albeit for some other use? Forward-looking companies are paying attention to how consumers use digital technology and how it can be adapted to provide healthcare services at much lower cost and greater accessibility [18, 19, 26]. But reverse innovation is not limited to technology.

Beyond technology, the case studies by Govindarajan [24] reveal how various services within an organization and within a community can be utilized for healthcare whether or not they had not been designed or implemented for that purpose. High-touch service locations such as schools provide opportunities for deep observation of the needs and habits of consumers. They not only provide the most direct way to discover unmet needs, they also reveal personnel and facilities that can be utilized in different ways. Such insights have led to similar innovations in healthcare in the U.S. Army [81, 82]. In Army behavioral health, a focus on outcomes and patients' care experiences helped defragment services worldwide into an order of magnitude fewer clinical "microsystems" that included nonclinical stakeholders such as command teams and family members, thus instantiating embedded healthcare in home and work locations. Moreover, care for soldiers has been aggregated with and informed by behavioral healthcare provided to family members, including in schools.

The generalizable lesson learned from reverse innovation and embedded healthcare is to provide coordination and continuity of care across a partially open team of teams; that is, a system of care that exploits the first-hand observations of people in established roles in the lives of patients beyond healthcare as well as reach back to facilities and experts as needed. Our companion article [2] addresses implications for research on *lifestyle interventions* that relate directly to the medical home model of care in the context of NASA's development of situated precision healthcare and autonomy given intermittent connectivity with institutional support for health and performance.

Demand-Side Innovation at NASA

We make a distinction between demand-side innovation and demand-driven innovation because characterizations of the latter often appear to be *post hoc* justifications for *a priori* commitments to particular lines of research and practice in various line organizations on the supply side. Demand-side innovation is more in the spirit of the "six paths framework" of Blue Ocean Strategy [83] in which unmet needs are identified as emergent properties across a combination of needs that are well-grounded in the buying patterns of a diversity of stakeholders and their use of associated products and services (Figure 2).

On this view, a variety of producers are pulled together, often in surprising ways, by the opportunities to cooperate in addressing a previously unrecognized mosaic of needs.

For science to participate in demand-side innovation, there must be programmatic commitment to look across a multiplicity of stakeholders whose interests may not be aligned and to represent those interests, collectively and dialectically, with theories of value that can be falsified, improved, and generalized. Scientific paradigms must be identified, utilized and continually assessed for their efficacy in aligning multiple stakeholders and in fostering systematic progress with respect to an architecture of stakeholder objectives [29, 40, 41] (Figure 6). The historicity of this meta-scientific process and progress at NASA is described here because it has unique relevance to the development of continuity of care in a smart medical home, that is, situated precision healthcare.

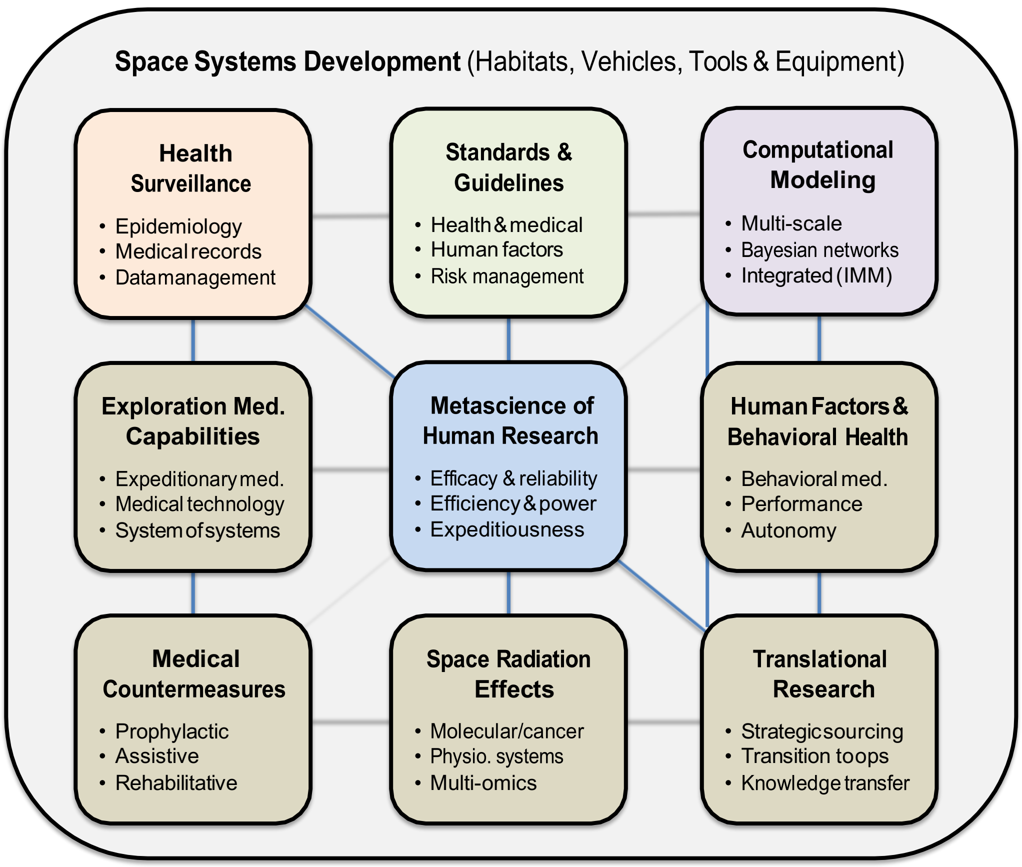

Figure 6. NASA's human health & performance research and stakeholder context, generalizable to the medical home model for situated precision medicine. [29].

NASA's integrated medical model

The work of Porter & Teisberg [15] is invaluable given the trustworthiness of their observations and conclusions. Given that such case studies are in the private sector, however, it is impossible to achieve a level of openness, about methods and data of the Cleveland Clinic for example, that is necessary for scientific reproducibility and generalizability. This is where research in the public sector can make an invaluable contribution [20, 43]. An instructive example is the strategic work of science programs and associated line organizations in NASA responsible for assuring health and performance of astronauts in future missions for human space exploration [66, 84, 85].

Analogous to the patients-first initiative of the Cleveland Clinic, at around the same time, NASA identified 100 medical conditions that can impair basic human functions in astronauts and that become impediments to completing space exploration missions. In reorienting to outcomes, research need not and generally should not be compartmentalized into traditional scientific disciplines or medical specialties suggested by particular medical conditions. Thus, the first lesson learned in moving toward outcomes-based medicine is how to structure deliberations of transdisciplinary teams and facilitate communication across terminological and conceptual boundaries [86]. NASA, for example, constructed boundary-crossing artifacts ("boundary objects" [87]) that provided a common lexicon and common objectives for research and decision-making teams. To this day, the most common and high-profile boundary objects at NASA are descriptions of human-system risks that are traceable to the original list of 100 medical conditions.

Since its formation in 2005, NASA's Human Research Program has been committed to a scientifically progressive path for deliberations and decisions about human-system risks. Boundary objects included much more than a list of medical conditions. Each medical condition has been developed into a theory of its likelihood and consequence that, at least in principle, can be falsified and refined through experimentation. The Integrated Medical Model (IMM) provided part of the prescientific foundation for this pursuit [67, 68]. As a computable theory (i.e., model), it describes cause-effect relationships grounded in observed incidents in the space program. Given the paucity of such data, the IMM also includes traceable extrapolations from the scientific and medical literature about incidence, factors affecting incidence, and treatments for each medical condition (Figure 5). Face-valid outputs of IMM that facilitate comparison across conditions include high-priority decision-making criteria such as the probability of evacuation (pEVAC) and loss of crew (pLOC) as well as required medical resources used and functional impairment.

Although the space exploration context for IMM is exotic, the outputs represent kinds of measures that can be applied to the development of continuity of care that includes a smart medical home [14, 63]. The relevance of pEVAC, for example, is that it involves multi-criteria decision making about whether a patient should be relocated to facilities outside the home, that is, away from the International Space Station (ISS) for astronauts, where a wider range of diagnoses and treatments are available. In some instances, patients also may need to be relocated to prevent exposure of others to the causes or effects of the patient's medical condition. In a workplace scenario (ISS also is a workplace), patients may need to be replaced by another person and, if that is not possible, pEVAC will be attended by multicriteria decision making about redistribution of workload to others and to machines [88, 89]. Decision making about EVAC and its implementation *require a scientific and technical understanding* of the capacity for continuity of care over time, across personnel with different kinds of expertise and across facilities with different kinds of technological capabilities (e.g., in-home, out-patient, in-patient) [29].

Consider also the nonobvious relevance of pLOC to development of the smart medical home. To date, the focus of pLOC in IMM has been the likelihood that a medical condition will result in death, with and without various kinds of treatment. There are interpretations and implications of pLOC that generalize to the home and the workplace. For example, a medical condition also can cause functional impairment of a kind and magnitude that, in turn, can lead to a fatal accident. Safety and mission assurance as well as health and medical care [90] *require a scientific and technical understanding* of the potential for such cascading effects. This requires more than the failure analysis that would be applied to passive physical systems. Adaptive systems, including but not limited to human beings, can wander into the unknown with activity for which the risks have not been managed or even considered [30, 91]. They also can display poor judgment even without adaptation. A functionally impaired person can perseverate, for example on skills developed or mastered in prior states of better health. Or, if impairment is not detected, a person can be expected to perform under externally imposed objectives and timelines that are unrealistic and unsafe. Another common problem, especially with highly motivated and talented people, is that they can neglect or misjudge their state of recovery or rehabilitation from a functional impairment. They can take on too much, too soon, or otherwise put themselves in unsafe if not lethal situations.

Implicit in the discussion above is the importance of maintaining constant awareness about states of functional impairment in potentially hazardous or otherwise extreme situations. The stressors that risk health, safety and mission can derive from functional impairments due to a current medical condition, prior medical condition, subacute conditions, variable environmental effects, poor task design or even medical treatments [92, 93]. Population data that are inputs to IMM generally will not and cannot have the level of detail needed to address such a chain of causality. Scientific investigations are needed to understand constraints on human performance *in extremis*. NASA's Human Research Program thus includes various lines of inquiry into human behavior and performance as well as inquiry into medical diagnosis and treatment in current missions on orbit and future missions beyond low-Earth orbit [43, 94].

Given that data from spaceflight are very limited, research must be conducted in analogous situations for which there are meta-scientifically falsifiable theories of relevance to spaceflight (see section below on *experimental analogs*). Results of research outside NASA also must be adapted and utilized in ways that are meta-scientifically falsifiable and improvable. Models such as IMM provide a rigorous way to utilize such data sources and to make the theories of relevance more transparent (see section below on *computational modeling*). Absent models that are computable, conceptual frameworks are required to synthesize heterogenous findings across multiple scales of analysis (see section below on *assessment of human-system risk)*. Both computational models and conceptual frameworks must take into account levels of confidence in the quality and relevance of the evidence they integrate (Figure 6) [95]. Ultimately, quality and relevance of evidence is a meta-scientific issue that must be addressed rigorously, analytically and empirically with suitable peer review [e.g., 96].

Progressive scientific assessment of human-system risk

Even without scientific investigations to test the theories implicit in the IMM and the veracity of its outputs, there was sufficient confidence by 2011 to winnow down the list to around 30 high-priority risks [43, 84]. This list or risks is discussed in the next section. Deliberation about the risks has steadily increased in formality and sophistication partially because the most senior programmatic representatives and decision makers regularly participate in one forum or another that address the risks [84; 99]. Other stakeholders and relevant experts in the workforce attend in person or remotely. While the list of risks has been largely unchanged over the last ten years, there have been some important changes such as (a) spaceflight associated neuroocular syndrome due to headward fluid shift, based on experience with long-duration missions on the International Space Station; and (b) aggregation of inextricably interrelated risks related to human interaction with physical systems, based on meta-scientific reflection on research to assess and mitigate such risks. There are generalizable lessons learned from NASA's development and use of such boundary objects for R&D portfolio planning and decision making. The first lesson is that there is value to utilizing expert deliberation that is traceable to scientific and medical literature even before scientific hypothesis testing can begin. It can immediately create a new vector for progress and then accelerate it. Precarious assumptions can be tolerated in the near term to the extent there is the potential to translate expert opinion into empirically testable theories. Computational models facilitate this translation.

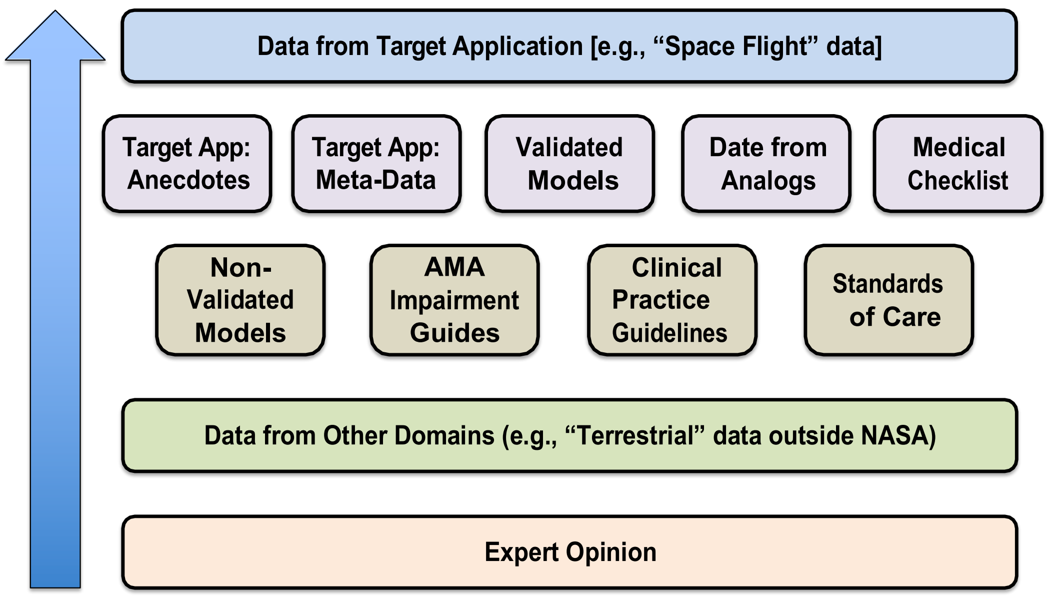

Figure 7. Kinds of evidence and levels of confidence in their quality and relevance [96] not to be confused with the more common levels of evidence in evidence-based medicine [see e.g., 97].

Another important meta-scientific lesson from NASA is that there are tradeoffs between stability of a framework, such as the list of human-system risks, and empirically driven modifications of it. A stable framework makes it possible to evaluate progress of the research program over time as well as the relative fruitfulness of investments in alternative lines of research. It also allows program planners to set notional timelines and milestones that are relevant to external stakeholders who can benefit from the research findings [100]. A simple example is the timeline for progress on research that informs a milestone decision about how much weight and volume to allow for a medical kit in a spacecraft. Such decisions have design implications far beyond medical care [67]. At the same time, assessing scientific progress is not the same as assessing progress in technology development. Scientific research is a process of discovery that pointedly challenges assumptions such as those on which a list of human-system risks is based. Changes in the risk list should be expected because of such systematic exploration, although they should be judicious and sufficiently stable so that progress can be assessed. The rate of change in boundary objects such as the human-systems risk list will be limited by the rate at which the research provides evidence about its use, utility and value to stakeholders. Continual improvement in the list can be viewed as a meta-scientific measure of the impact of research it motivates.

Again, while the space exploration context for the list of human-systems risks is exotic, they are uniquely relevant to diseases of aging and continuity of care for the well elderly who are aging in place. Most of the risks address functional biological attributes such as breathing, eating, sleeping, sensing and moving; and much of the associated research has general applicability beyond spaceflight. Even with the radiation risk, most of the likely applications of the research will be in early detection of molecular changes and potential medical interventions to minimize damage and long-term health consequences [101]. What is most unique about NASA's human-system risk framework is that it is holistic. Its special relevance to diseases of aging is that it allows for a coherent approach to co-morbidity in general and, in the present context, specific kinds of co-morbidity often experienced during aging [102, 103]. The various manifestations of Neuropsychiatric Symptoms (NPS), for example, present some of the most significant if not defining challenges of dementia, for example [104, 105]. Behavioral health, more broadly, is becoming an increasing concern for NASA given the challenges of prolonged shared confinement that will be experienced during future missions to deep space [94]. The associated research portfolio is leading the way in defragmentation of risks at the molecular, physiological, and behavioral levels [106].

There are two broad categories of stakeholders for healthcare that is predictive, preventive, personalized and participatory. One is the group involved with the provision of medical care to a patient. The other group is involved in the life and work of a current or potential patient. They are represented in the Human Research Program by the Exploration Medical Capabilities (ExMC) element and the Human Factors and Behavioral Performance (HFBP) element, respectively, albeit without an immutable division of responsibilities between these two sets of interests (Figure 6). The portfolio of ExMC has direct relevance to the architectural design and implementation details of an enterprise that can deliver continuity of care to patients as well as their cohabitants and coworkers who can be isolated from primary care facilities for significant periods of time. Because of these architectural exigencies, ExMC has been on the vanguard of model-based systems engineering for the Human Research Program [73, 74]. That work will be addressed briefly below because its evolution in NASA is instructive for development of the smart medical home.

The most meaningful way to defragment various lines of healthcare research and practice is to start with what matters most to patients and to those with whom the patient's life and work is intertwined. HFBP tackles these issues, and it increasingly strives to provide the holistic vision for an outcomes-based healthcare for NASA [107]. Thinking beyond the individual, for example, teamwork during prolonged shared confinement in space has been one of the most extensive lines of research in HFBP [108]. As missions of unprecedented duration are considered (e.g., a three-year mission to Mars), risks pertaining to social interactions must move beyond the traditional domain of teamwork per se to issues that approach existential significance (i.e., the meaning of life and work in space) [109, 110]. Accordingly, this element of NASA's Human Research Program must address risks associated with (a) adverse cognitive or behavioral conditions and psychiatric disorders; (b) performance and behavioral health decrements due to inadequate cooperation, coordination, communication, and psychosocial adaptation within a team; (c) risk of performance decrements and adverse health outcomes resulting from sleep loss, circadian desynchronization, and work overload; among others [43]. In essence, HFBP must address the totality of life and work of astronauts during periods of prolonged isolation and shared confinement required by exploration missions.

As in other elements of NASA's human research portfolio, HFBP also must address interventions to prevent, mitigate, or otherwise plan and prepare for the effects of human-systems risks such as (a) incompatible vehicle or habitat design; (b) inadequate design of human and automation or robotic integration; (c) inadequate human-computer interaction; and (d) inadequate mission, process and task design [43]. All of these issues generalize in straightforward ways to development of the built environment and wearable electronics that will be part of the smart medical home. Moreover, they relate directly to the experiences, lifestyles and consumer products of most patients outside of institutional settings today, including those affected by diseases of aging such as AD. Wearables and smart home technologies are a rapidly growing market that is being leveraged for continuity of care by medical professionals and families of individuals who are aging in place [111]. There does not, however, appear to be a system-of-systems architecture for this medical market that starts with a holistic understanding of needs to guide product development and ad hoc consumer choices about use, let alone to identify gaps that require R&D. This is where NASA provides an otherwise improbable source of insight and common interest.

The concept of a *smart medical* home cannot be limited to traditional medical treatment. It must address a broad span of activities in which in-home patients commonly are engaged (i.e., lifestyle). The design of a smart medical home must recognize that common daily activities can have an impact on health and well-being, including the impact of lifestyle on the efficacy of traditional medical treatment. It also must consider the impact that medical conditions have on lifestyle through intervening physical, physiological, psychological and social impairments. The reciprocal interactions between medical conditions and lifestyle provide a clear source of demand-side innovation (see section below on *Lifestyle Interventions*). This must be the starting point for outcomes-based medicine. Our claim is that the degree of experimental control in NASA's development of self-contained microenvironments for human occupants will reveal the art of possible for a smart medical home even amid hazards and stressors of aging in place that, at least superficially, seem incommensurate with those encountered in space exploration.

Human-system risk board and multi-criteria decision making

The development of new capabilities for healthcare unavoidably involves an intersection of science and business that is often unfamiliar and sometimes uncomfortable for participants in the respective communities. Characteristics commonly associated with business—profit, free markets, or competition narrowly conceived—seem incompatible with scientific values. As addressed in the introductory sections above, however, a more important and clear area of convergence is in business model generation (e.g., Figure 3); that is, development of falsifiable theory of value delivery to multiple stakeholders whose independent interests may not be aligned [42, 43]. Multi-stakeholder theory [112, 113] and the closely allied insights from fiduciary law [114, 115] and mega-project management [116, 117], in particular, are large bodies of scholarship and contemporary innovation that are relevant to mission-oriented science program managers [42].

The convergence of scholarship in science and business indicates that decisions in large programs are best made by groups that represent a relevant diversity of stakeholders whose respective interests may to some extent be in conflict, that is by groups designed for multi-criteria decision making. Various methods have been developed to aid multi-criteria decision analysis (MCDA) ranging from highly esoteric to highly applied. The Analytic Hierarchy Process (AHP), for example, has enjoyed decades of scientific and technical development as well as a wide range of applications. Notably, the AHP has been adapted over the years to support programmatic decision making at NASA [118-120]. In NASA's maturity model approach to risk management [121, cf. 122], the Human Research Program and its stakeholders have not yet reached the stage where it can utilize a methodology like AHP [123, 124], but it is getting close. At the same time, MCDA is gaining traction in deliberations in the medical industry [125-127]. More generally, multi-criteria decision making implicit in evidence-based policymaking is enjoying rare bipartisan support in the United States Congress [128, 129] as well as in relevant segments of the medical science community [86, 130].

In NASA's human research, a key entity that removes intermediates from knowledge transfer among multiple stakeholders is the Human Systems Risk Board. This group meets periodically to juxtapose perspectives of various scientific and technical subject matters experts with physicians and other healthcare providers as well as engineers who are responsible for developing tools, devices and systems. The primary objective of each meeting is to iterate on the dispositions of particular risks in the human-systems risk list. The risk list, as discussed above, and the associated format for individual risk dispositions provide boundary objects to bridge the gaps among domains of expertise that have a stake in risk management at NASA [98] (Figure 8). Color coded categories for likelihood and consequences of each risk are the most recognizable boundary objectives across NASA. More nuanced boundary objects include risk dispositions that address various factors contributing to a particular risk and, to varying degrees, their interrelationships. These artifacts are as useful to researchers and science program management as they are to healthcare providers and technology developers [84, 99], thus they facilitate deliberation across domains of expertise and responsibility. Critical path uncertainties in the understanding of risks are a focus of such deliberations. Research is continually reviewed that can resolve the uncertainties or reveal ways the uncertainty can be reduced. A trajectory of uncertainty reduction results from research that progressively improves with respect to levels of evidence [95, 131].

The deliberations of the HSRB have the character of medical decision-making boards in which the social dynamics of collective intelligence are as important as the evidence [132, 133] and in which "big data" at multiple levels, from biochemistry to behavior, are attended by nontrivial issues of privacy and data management [134, 135]. Unlike the metascience and findings of the allied Human Research Program, the deliberations and products of the HSRB are not open to the public. This may change as the HSRB continues to innovate with respect to its boundary objects and the collaborative processes utilized to refine them. The outlet for such open science about the HSRB could, for example, be meta-scientific research conducted by the Human Research Program. This will become more important as the needs increase to analyze risk factors across ostensibly incommensurate medical conditions and to comparatively evaluate associated lines of research. As argued above, outcomes are the most meaningful and expeditious way to evaluate such a transdisciplinary portfolio of research.

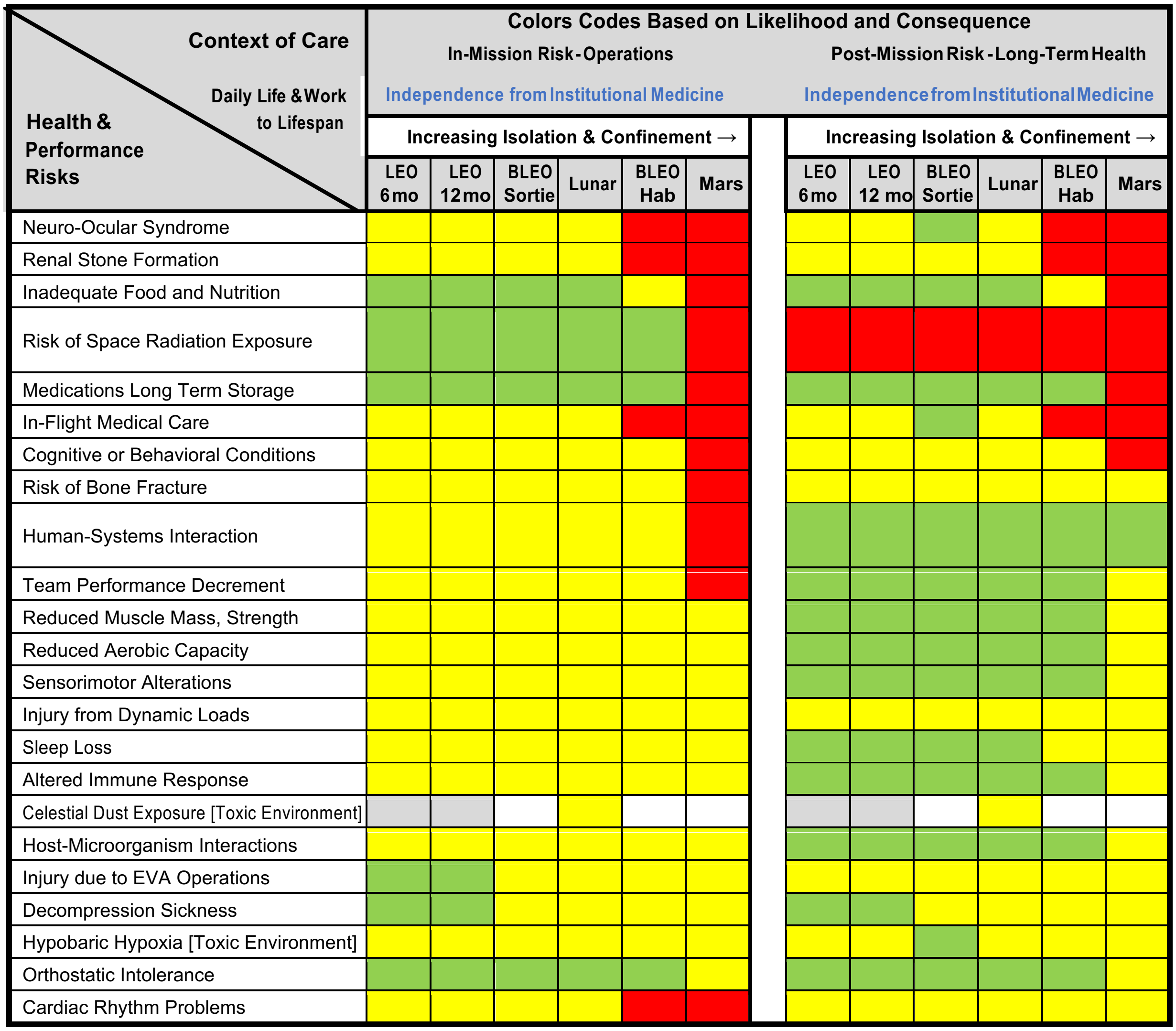

Figure 8. NASA's human health and performance risks for design reference missions (DRM) in low-Earth Orbit (LEO) and beyond (BLEO). Color codes ultimately reflect priorities for R&D based on likelihood and consequences of the risk [adapted from 98]. Annotations in blue suggest generalization of the meta-scientific framework for R&D in terrestrial healthcare [2].

Enterprise risk management in loosely organized coalitions

NASA's risk management guidelines and practices provide a rigorous way to identify and analyze outcomes throughout an enterprise (Figure 9) [123, 136]. Objectives hierarchies are an important part of this. Hierarchies can be constructed by making explicit the relationships among the respective objectives of a variety of organization units. The relationships are illuminating even if they do not constitute a strict hierarchy and even if the enterprise is not organized as a simple hierarchy. The important point is that different kinds of objectives will apply to different enterprise layers responsible for phenomena and systems of different inclusiveness and complexity (i.e., levels of decomposition). They will be correlated loosely with levels of abstraction [137, 138] that, as with the considerations of different levels of management, may seem incommensurate. Measures to assess progress and impediments must be identified for all objectives. In enterprise risk management, measures collectively must enable empirical evaluation of causal relations across levels of abstraction and decomposition. The measures become boundary objects that facilitate communication and coordination across layers of the enterprise [139, 140]. Uncertainties or gaps in the collaborative management of risk with respect to extant measures may require re-evaluation of objectives and their interrelationships. Enterprise risk management is inherently a meta-scientific activity in a diverse community of stakeholders. Failure to recognize this is a likely source of common failures in enterprise risk management [141, 142].

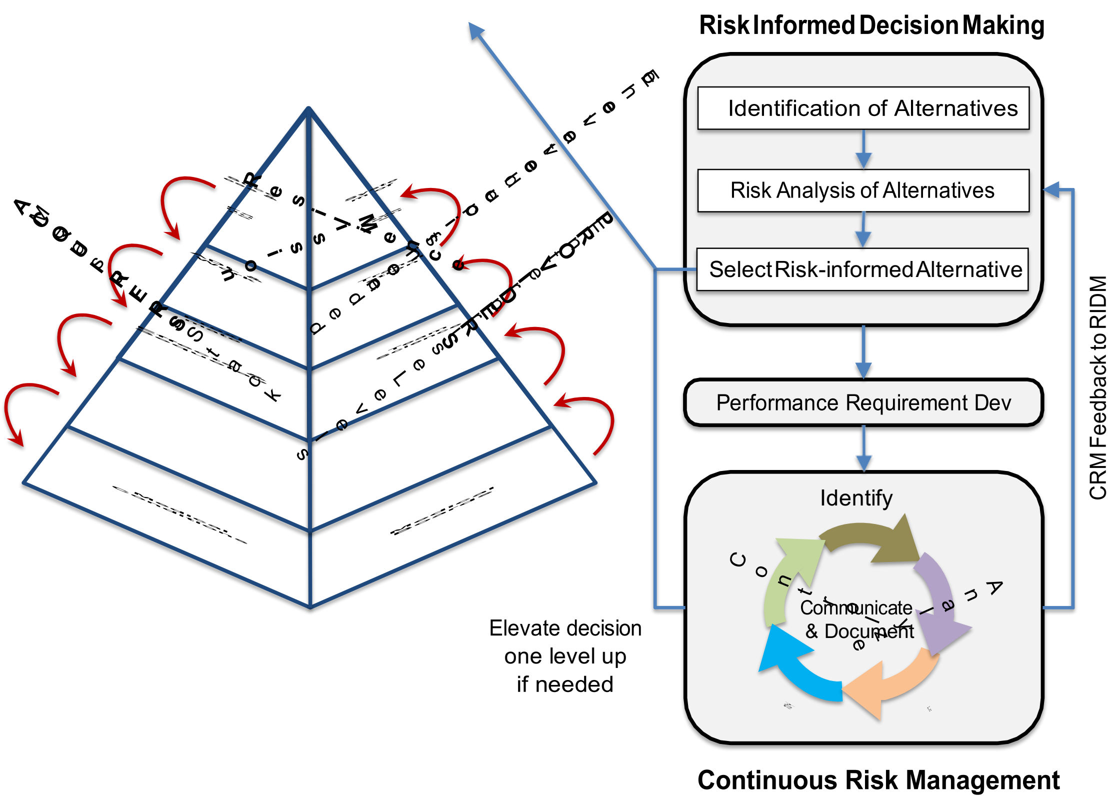

Figure 9. Risk management in an enterprise [adapted from 136]. CRM tends to focus on deliberations and decision making in a particular layer of the risk management pyramid, while RIDM focuses more on objective hierarchies that cross layers of the pyramid and provide theories of causal connections among them (ADL refers to activities of daily living).

At the most general level, impediments identified in NASA's objectives hierarchies typically refer to factors affecting safety (e.g., avoidance of injury, fatality, or destruction of key assets), technical capabilities (e.g., amount of observational data acquired), cost (e.g., execution within allocated cost), and schedule (e.g., meeting milestones). More nuanced analyses of objectives reveal process constraints and networks of interaction that can be either impediments or enablers to mission success [143, 144]. Consistent with NASA's maturity model approach, the HSRB currently is working on a hierarchy of objectives that will capture important interrelationships among the human-systems risks listed in Figure 6. The notional hierarchy attempts to organize risks and their interrelationships in a stack ranging from space system needs and basic human needs through intervening effects on human health and performance up to capabilities for long duration spaceflight and sustained presence in deep space [145]. This trajectory of human-systems risk management has paradigm-breaking implications that are addressed below in the section on *lifestyle interventions* for healthcare in our companion article [2].

While the relevance of NASA's lines of human research to diseases of aging is more or less obvious, why should researchers in geriatric medicine pay attention to the maturity model machinations of risk informed decision making in NASA or enterprise risk management in general? A central premise of this article is that there is a critical gap in this kind of holistic view of demand that can harnesses a system of systems to achieve healthcare that is predictive, preventive, personalized and participatory (P4). As highlighted above in our interpretation of the challenge, the market for systems that can be leveraged for continuity of care in a smart medical home is vast. The home care market in the United States alone, for example, is expected to grow from $100 billion in 2016 to $225 billion by 2024 [146]. Moreover, the U.S. Census bureau estimates that, by 2050, the population of Americans older than 65 years of age will double to over 88 million while the general population is expected to increase by 44% to 439 million. Within this older population, the percentage of people over 85 of age is expected to increase to more than 21 percent by 2050 [147]. Clearly, solutions will have to be systemic. Early entrants into the market—such as A Place for Mom, HomeCare.com, Home Instead Senior Care, and Seniors Home Care—surely will evolve into offerings that are more digital and more inclusive both of people and systems.

Achieving P4 medicine and continuity of care in the smart medical home does not depend on the emergence of a comprehensive offering by a single firm. It is more likely to evolve as a vision of how a diversity of offerings can achieve a whole that is greater than the sum of the parts. The burden need not be entirely on the consumer to organize the available offerings in their lives. Firms can develop and promulgate a holistic vision by striving for an awareness of influences beyond their span of control and beyond their primary value propositions. With the help of the public sector, they can internalize externalities [148], and they can do so intertemporally [14, 149]. A diversity of firms can coordinate in a loosely organized mosaic of independent firms if they share and converge on a holistic vision. To do this, they will need boundaries objects, objectives and measures that can communicated across their respective cultures. NASA's HSRB reveals that meta-scientific frameworks can be utilized by a relatively small number of catalysts in a broader community of interest to negotiate coherent development and use of a diversity of offerings by a much larger number of stakeholders. The influence of groups such as the HSRB is due to the power of such frameworks and the communication they facilitate rather than any statutory power. The HSRB resides in the white spaces between largely autonomous organizations rather than at the top of an overarching command structure. Constructs and practices for negotiation of such white spaces will be a defining characteristic of decentralization and coordination of innovation in the fourth industrial revolution [51, 52].

The most important takeaway from the broad portfolio of NASA's Human Research Program and the multi-stakeholder disintermediation of the allied Human Systems Risk Board is that a holistic systems approach to personalized healthcare is feasible even if it seems to ask too much of individual subject matter experts [84, 98, 99]. Such programmatic deliberations and their boundary objects raise well-established practices of medical decision-making boards to the level of science program management, and it infuses the latter with the considerations of engineering design and management (e.g., mindset of a chief engineer) in a technology development program for a "system of systems" [150, 151]. In our view, the most meaningful distinction between a system of systems and a system is the diversity of functions it performs and the multifaceted value it delivers to a diversity of stakeholders whose interests may not be aligned [92, 93]. Approaches that enable communication, coordination and deconfliction among a such diversity of stakeholders (i.e., demand-side innovation) will play a critical role in the development of a system of systems that instantiates a smart medical home just as they do in development of analogous capabilities for human exploration of space [152, 153].

COMBINATORIAL SCIENTIFIC AND CLINICAL PARADIGMS

Model-Based Systems Engineering and Transdisciplinary Team Science

The network of strategic groups in which NASA's human research program is embedded show that multi-criteria decision analysis and associated decision making is practical and efficacious if and only if there is a representative diversity of stakeholders who can achieve a collective intelligence that is relevant to real-world outcomes. Moreover, the HSRB shows that there can be continual improvement in the organization, operation and outputs of such deliberative bodies as empirical lessons are learned about the influence and implications of their decisions for various stakeholders. The iterative deliberations and their influences have the character of a scientific paradigm. They are the foundation for an approach that is more rigorous than what the HSRB has been resourced to develop; an approach that is capable of addressing far greater complexity. Model-based systems engineering (MBSE) provides that next step in maturity in the design and development of complex systems [154, 155], and it is being utilized aggressively in NASA's development of exploration medical capabilities [73, 156].

The deliberations in a multi-stakeholder decision making board such as the HSRB reveals who should be talking with whom about what, as well as how and when to do so, and why it is necessary. The responsibilities of interdependent stakeholders for a smart medical home are depicted in Figure 10 based on NASA's initial systems engineering analyses for distributed semi-autonomous medical capabilities to support space exploration [74, 157]. Interviews, observation of operational systems, and experimentation with prototypes helps systems engineers work with scientists to articulate the essential functions and systems for which various stakeholders are responsible. This enables the systems engineering team to describe the information and energy that must be transferred between stakeholders to ensure coordination among their respective systems, and they must do this with sufficient specificity to be verified and validated empirically. MBSE takes systems engineering to the next level. It reduces the ambiguity of language (e.g., requirements documents) by providing boundary objects that facilitate communication among a diversity of subject matter experts [158, 159]. The artifacts utilized in NASA's MBSE for exploration medical capabilities include concepts of operation, block diagrams, activity diagrams, sequence diagrams, scenarios, architecture, and trade studies [73, 156].

Systems engineering diagrams for a system of systems can be quite large and complex but, in MBSE, they become computable elements that can be manipulated collaboratively by members of the systems engineering team. As model elements, these artifacts reveal functional interdependencies among subsystems. Manipulation of the model elements reveals design alternatives and consequences that can be evaluated and replicated. The functional consequences of model structure thus become a fruitful topic for deliberation and shared experience in the systems engineering team with or on behalf of the relevant stakeholders [143, 157]. This allows for very specific conjectures that can be examined with prototypes of varying degrees of fidelity in test beds of varying degrees of fidelity. MBSE thus allows systems engineering to be more fully evidence based. It enables systems engineering to be complementary and essential to programmatic management of a diverse portfolio of transdisciplinary team science, for example, and it illuminates the path for transitioning such science to operations. It will be essential to translational research for continuity of care in the smart medical home.

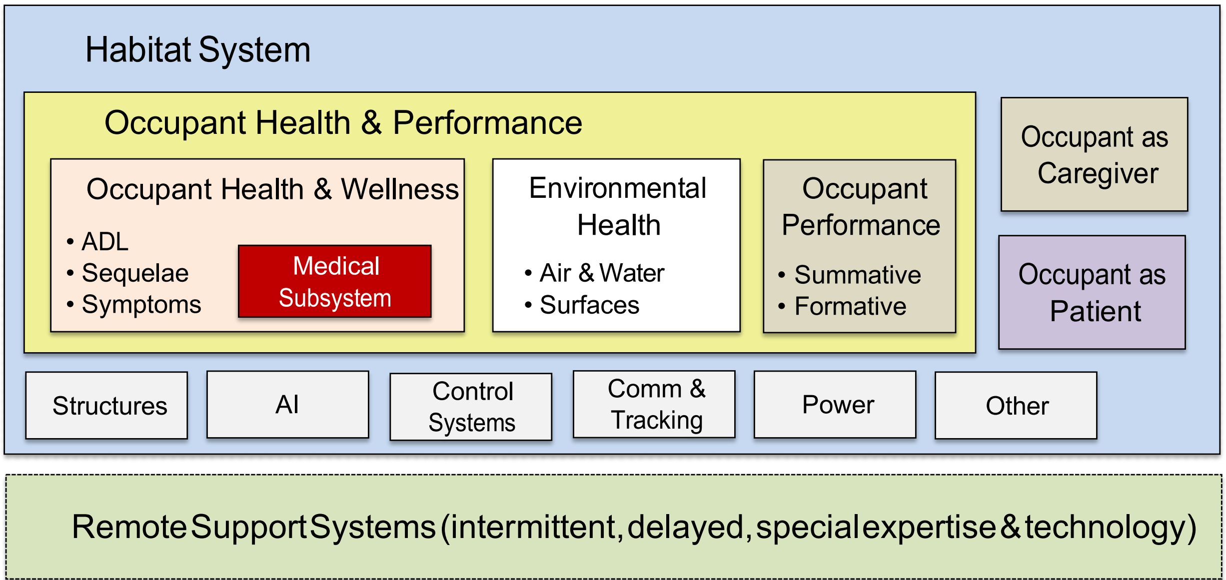

Figure 10. Situating subsystem design and development in a nested system of systems for deep space exploration or a smart medical home [adapted from 74; see also 157].

Essential Role of Experimental Analogs

Varieties of fidelity in research methods

Another benefit of MBSE is that it allows for rigorous definition and measurement of the fidelity of prototypes and testbeds ("analogs"). This is important not only for decisions about adequacy and appropriateness for testing and experimentation, it also is instrumental in designing an ecosystem of complementary analogs for which the meta-scientific whole is greater than the sum of the parts. Such specificity and differentiation is invaluable in understanding the maturity of a capability and the trajectory of its development and integration with other capabilities. In the DoD and NASA, for example, stages or levels of maturity (e.g., Technology Readiness Levels in NASA) correspond to differences between models, components demonstrated in a laboratory, components demonstrated in a relevant (simulated operational) environment, systems demonstrated in a relevant environment, and systems demonstrated in an operational environment [160, 161]. Beyond analogs for verification and validation of technology under development, understanding fidelity of research methods and associated artifacts (e.g., models, simulation, laboratory apparatus) is critical in science program management and translational research in particular. It enables meta-scientific assessment of the explanatory power and range of particular scientific paradigms, and it provides the basis for levels of evidence used in NASA's risk management (e.g., Figure 7). Rigorousness in definition and measurement of fidelity also stimulates meta-scientific innovation in design and use of an ecosystem of complementary analogs.

NASA has another meta-scientific practice that can be useful in thinking fidelity of research methods, its design reference missions (Figure 8) [42]. The DRM vary in terms of the challenges they impose, such as 6-month missions, 12-month missions, and missions to Mars that can be up to 3 years in duration. They also vary with respect to the kinds of habitats and environmental hazards. Beyond low-Earth orbit, for example, radiation hazards will be different and greater outside the protection provided by "the Van Allen radiation belt." Habitats won't be as large as the on International Space Station, and they will be even smaller during transits to Mars. Important factors influencing fidelity and differentiation across DRM include: duration of confinement to a habitat, size of the habitat, time delay between need for care and provision of care, update rate in provision of care, in-person versus remote care, distribution and makeup of the team of teams that provides support, technology available for monitoring and intervention, and availability of consumable medical supplies and drugs. All these factors affecting the architecture of care and its concept of operations for specific DRM.

How can R&D strategy be organized around missions [22, 23] if we can't be sure about the mission nor about technological or organizational constraints the future will bring to execution of those mission? NASA's meta-scientific solution is to take the best guess about a variety of missions so they can "tile the space" of possibilities amid the unknowns. The level of detail in a mission should allow generalization of meta-scientific assumptions and scientific findings to plausible variants of the mission in the future. Such missions can vary because of national will, budgets and the unknown consequences of trying to construct an unprecedented system of systems as in any mega-project [116, 117]. A portfolio based on multiple missions of different kinds makes the tradeoff between detail and generalizability considerably easier and less arbitrary. The concept of operation and the envisioned system of systems for each mission become a point of departure for research and technology development. The missions provide a design reference, hence the name. Design reference missions are exceedingly useful in establishing the fidelity of an experimental analog and, collectively, for decisions about the necessary portfolio of testbeds. In other words, design reference missions are as useful in design of testbeds as they are in design of systems that will support future missions that actually send astronauts into deep space for periods of weeks to years.

Fidelity of research methods relative to a particular application also can be evaluated with respect to various criteria pertaining to the look, feel, and function of the artifacts with which participants interact [159]. The look of an experimental setting, for example, is generally the most important determinant of its face validity. A good example of this, albeit to a fault, has been the development of virtual reality from its inception [162]. Perhaps more importantly, the "feel" of an artificial situation represents constraints on interaction with the setting and immediate consequences of a participant's actions in it. A good example of its importance is in the development of flight simulation [163] and surgical simulation [164]. The right balance of face validity and realistic constraints on action can provide an extraordinarily productive setting for collaboration, about functional fidelity, among innovators and stakeholders whose expertise is so different they may have had no prior experience with each other and perhaps little or no prior knowledge of each other [165, 166]. The objective should be to represent functional outcomes without the burden of recreating incidental details that have little or no influence on outcomes. Research settings with the right kind of fidelity (individually or collectively) can bridge the gaps not only between research and practice but also between near-term and far-term considerations [167, 168].

NASA's experimental analogs

MBSE has unparalleled potential to make the meta-scientific assessment of fidelity more objective and outcomes based. It enables programmatic utilization of a diversity of test beds to be more strategic and coordinated. NASA's human research utilizes a variety of research settings [169]. The "analogs" enable NASA to study the physiological, psychological and social effects of prolonged shared confinement and the associated continuity of care in remote settings (Figure 11). The NEK facility in Russia provides an infrastructure that enables researchers to assess small teams (e.g., four people) isolated for up to a year in a habitat that is comparable to plausible deep space habitats. The Concordia facility in Antarctica provides a psychologically realistic environment in that it is inaccessible for months (e.g., "winter over"), as in space, even there is an emergency. Through prolonged bedrest (months), the :envihab facility in Germany enables researchers to study conditions that can lead to cardiovascular, respiratory and musculoskeletal problems as well as fluid shifts. The HERA facility at NASA's Johnson Space Center (JSC) is a highly accessible laboratory for a continual sequence of experiments with crews confined, to date, up to 45 days. The HESTIA facility at JSC provides a rapid reconfigurable habitat to assess the impact of design alternatives on occupants. The relevance of utilizing analogs in research on the diseases of aging is discussed in our companion article [2].

Figure 11. Use of research facilities on Earth that are analogous to space habitats in various ways and that collectively enable experimental manipulation of hazards and observation of the experiential effects during prolonged isolation and confinement in future missions beyond low Earth orbit [adapted from 169].

The most important feature of NASA's analogs is the experimental capacity to observe and manipulate, in principle, almost anything about the built environment and activity of the occupants. We do not argue that NASA's analogs should be used to study the diseases of aging. Rather, a central point of this article is that there is no better place than NASA's human research to learn about the potential for coherent multifaceted programs of transdisciplinary translational research that can guide development of systems and practices for continuity of care in a smart medical home. Design and use of experimental analogs are an important part of that potential. An important lesson learned from NASA is that is that value of an ecosystem of complementary analogs is meta-scientifically greater than that of the individual analogs, thus, they should be designed and used as a whole.

The use of analogs in NASA and the DoD is ubiquitous for both training and R&D. These sectors are adept in fine tuning the scope and level of detail to meet practical constraints on implementation and priorities for discovery [170], however, this cultural capacity resides almost entirely in tacit knowledge. Meta-scientific initiatives are needed to make such experience and expertise in the public sector explicit and to help the private sector benefit from it [22, 171]. In our view, NASA's human research program provides the best foundation for such initiatives [42, 43]. Their frameworks for outcomes-based management of human-systems risk and associated research are useful beyond their own portfolios by (a) identifying and situating research funded by other organizations in a common context for a broader ecosystem of research communities, and (b) aggregating research across communities of interest to achieve a wholeness of understanding and potential that is greater than the sum of parts. An interesting recent example is the BASALT research program funded by the Planetary Science and Technology Through Analog Research Program of NASA's Science Mission Directorate [172].

The Science Mission Directorate doesn't typically fund human research. The intent of the BASALT research program was to identify immediate priorities for research given long-term projections about development of a wide variety of technology needed to execute geological science tasks during human exploration on the surface of Mars. The program utilized several testbeds to simulate different aspects of communication and coordination in a team of teams. The challenge is that this kind of teamwork is distributed over distances and time in ways that necessitate degrees of decentralized autonomy that vary somewhat unpredictably. Operational and technical capabilities must be resilient and adaptive given situations that will be volatile, unknown, complex, and ambiguous. The fact that the project focused on geological science objectives does not detract from its relevance to medical objectives that also are a priority in human exploration of Mars [109].

Many of the considerations and innovations explored in the BASALT program are directly relevant to the medical home [29], including practices and procedures for: (a) coordination between two or more people involved in a task at hand with delayed, intermittent, and unreliable connections to support from subject matter experts; (b) coordination between humans and intelligent machines; (c) communication with support systems nearby but not on site; (d) communication with remote support systems for feedback from experts that may take from hours to weeks; and (e) division of labor and communication within remote support systems with respect to medical and nonmedical issues.

Many technical issues and constraints in the BASALT program also are directly relevant to the smart medical home, including: (a) limits on data storage and processing at the point of care; (b) connectivity and bandwidth of alternative media for communication between point of care and nearby or remote support systems; (c) robustness and reliability of communications; (d) interfaces to maintain shared situation awareness and commensurate calendars of activity given intermittency of communication with point of care and remoteness from it, and (e) artificial intelligence to augment decision making at the point of care.

Situating research on team of teams in a system of systems

All of the analogs utilized by NASA's Human Research Program for studying quality of work and life during prolonged periods of shared isolation and confinement require support of a team of teams in a system of systems that is at least as complex as that created in the BASALT project. The support systems for these analogs generally has been not described in terms of falsifiable theories of fidelity that is similar to the research conducted in those analogs, nor in such ways that the BASALT testbed is described. Meta-scientifically, what is needed is a level of detail sufficient to replicate a testbed and, for the present purposes, sufficient to generalize it for research into the quality of life and work for the well elderly. BASALT, in many ways, shows the art of the possible. Implicit in this claim, however, is the concept of generalization through levels of abstraction that are not unique to specific tasks and objectives such as those in a mission to Mars [110]. The artifacts generated in MBSE for NASA's exploration medical capabilities can be an important guide in this respect. They help separate the essential from the incidental for continuity of care in a remote habitat. Our research strives to identify such constructs and methods that can be generalized to research on the diseases of aging.

MBSE for exploration medical capabilities articulates an architecture for people, processes and technology—who should be talking with whom about what, as well as how and when to do so, and why it is necessary—but at a high level with respect to what and why. MBSE products thus provide a template for description of methods sufficient for replication and generalization [173, 174], as in common descriptions more specifically of *participants*, *materials* and *data gathering procedures* in quantitative research [175] or *researcher-participant relationships*, *situatedness*, *data collection strategy* in qualitative research [176]. At the level of metascience, MBSE describes what makes a research setting an analog of an operational application. It does not necessarily address analyses of data and the meaning made of them by stakeholders beyond recognition of objectives hierarchies such as those being developed by the HSRB (Figure 9). It is not typically concerned with hypothesis testing about causal factors that influence the associated measures and relationships among them. For that, other meta-scientific paradigms and tools are needed for knowledge transfer among stakeholders, across investigations and across domains of application.

Continual improvement and impact of high-fidelity experimental analogs

NASA has both observational and experimental data on life and work in space because of continuous occupation of the International Space Station (ISS) for almost 20 years. The ISS is one of humanity's most impressive engineering accomplishments and one of the few structures and megaprojects that have involved a sustained collaborative effort of many governments around the globe. The ISS is the size of an American football field, with living and working space larger than a six-bedroom house, and it has been sustainably falling over the edge of the Earth at a tangential velocity of five miles per second (i.e., on orbit) for twenty years! To date, it has been occupied by 239 individuals from 19 countries [177], typically six at a time. While it is an operational facility for life and work in space, it also is an experimental analog for long-duration missions (i.e., greater than a few weeks to over a year) of a different kind, specifically beyond low-Earth orbit. Thus, it has been an invaluable source of both observational and experimental data for planning future missions as well as for design and development of deep space vehicles and habitats.

The International Space Station is a model for development of a smart medical home even if it is not the NASA analog from which terrestrial medicine can learn most. Its special value as a model for research and technology development is that it has been continually evolving as a somewhat isolated habitat for twenty years, and its upgrades have been continually improving the health and performance of its crews. Research in terrestrial analogs and ISS has led, for example, to development of technology for exercise and prescriptions for its use along with pharmaceuticals on ISS that have mitigated problems of bone loss and muscle weakness [178]. Other research is leading to changes in lighting on ISS that, also bundled with pharmaceutical interventions, address problems of sleep disorders that can have cascading impact on human health and performance [179]. Moreover, practices in telemedicine for ISS are systematically maturing based on research and technology development inside NASA and in the broader scientific and medical community [74]. These are just a few of the ways that research has led to lifecycle upgrades of ISS [43] that have could not have been fully anticipated at the outset [65]. NASA's research and technology development for ISS provides important technical, operational and programmatic lessons learned for development of a smart medical home.

Need for analyses that are commensurate with high-fidelity analogs

Terrestrial analogs and the ISS are exceedingly valuable as a bridge between naturalistic inquiry in an application environment and highly controlled laboratory experiments that are ubiquitous in the broader scientific community [131, 180]. One kind of naturalistic inquiry is retrospective epidemiological analyses of incidents and collaborative problem-solving that have addressed issues in health and performance of personnel who have been occupants in various space vehicles and habitats [181, 182]. Such data inevitably span the wide range of medical conditions captured in the Integrated Medical Model. From the beginning, the IMM was part of a broader effort to assess medical conditions that otherwise are difficult to compare and contrast. As discussed above, the broader meta-scientific strategy has been to develop frameworks to facilitate planning and preparation for various health and medical risks that otherwise seem incommensurable, collectively intractable and beyond the reach of programmatic decision making about unprecedented missions and the system of systems they require. The programmatic objective is to have a process for setting priorities and making investments in R&D that enable risk informed decision making across all risks and with all stakeholders (Figure 9).

As in NASA's HSRB, logical frameworks ("logic models") enable researchers and stakeholders to trace any and all potential risks to outcomes in ways that are transparent, auditable and improvable. An approach to modeling a chain of risk consequences that is meta-scientifically generalizable makes it possible to compare and contrast lines of research on a variety of risks. A programmatic commitment to computational modeling builds on this foundation by providing the capability for collective assessment of end-to-end credibility of the entire causal chain from data, constraints and assumptions to predictions about outcomes (Figure 12) [94]. Computational models become laboratories in and of themselves that allow rapid assessment of variation in context and interactions among elements in the model. As such, they are an invaluable complement to retrospective epidemiological studies and experimental investigations that are challenged by small sample sizes and a multiplicity of confounds in NASA and in any plausible instantiation of research for situated precision healthcare. Moreover, the intelligible transparency of computational models enables their developers (e.g., in NASA) to participate in the dialectic—about model credibility, generalizability and alternatives—of a broader scientific community that transcends particular application domains. A promising example of such a community is the Interagency Modeling and Analysis Group initiated in 2003 by the National Institutes of Health and the National Science Foundation [184].

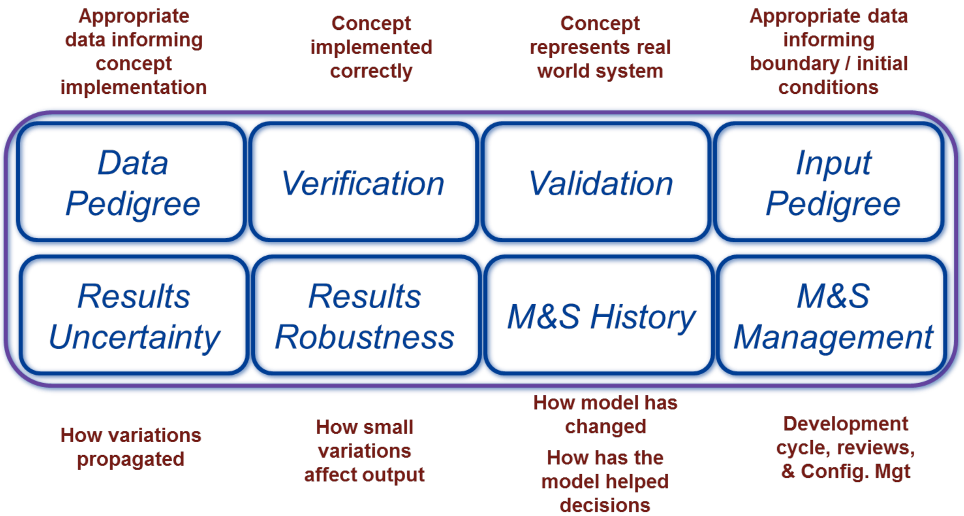

Figure 12. Credibility of models and simulation [88; 173]

NASA's Cross-Cutting Computational Modeling

Model as falsifiable theories of complexity

NASA's cross-cutting computational modeling project (CCMP) is engaged in the broader scientific community of IMAG [96] while it is also intimately intertwined with NASA's model-based systems engineering teams for development of exploration medical capabilities [185]. This multi-faceted multi-layered approach to collaboration recognizes models as falsifiable scientific theories that can develop reciprocally with the accumulation of evidence from interactions with a diversity of stakeholders (see section on *use, utility and value* in companion article [2]. It is a meta-scientifically valid, if not essential, methodology that transcends particular models and methods. The value of such computational modeling is not only that it makes the assessments of various medical conditions and associated human-systems risks more commensurable, for example with respect to outcomes. Beyond this source of insight, as with the Integrated Medical Model in particular, CCMP's models incorporate hypotheses and findings about the downstream consequences of risks, individually and collectively, as well as factors influencing both the risk likelihoods and consequences [186].

NASA's early work with the Integrated Medical Model began a commitment to Bayesian constraint-based modeling. The approach is orthogonal to point estimates from experimental research that attempts to generalize from small numbers of participants in spaceflight analogs to future astronauts and situations.

The latter have been extraordinary efforts of collaborative design and decision making involving many tradeoffs and compromises that, nevertheless, have yielded important design guidance and efficacious medical countermeasures [187]. Significance testing in such experimental scenarios suffers, however, from some of the same challenges as clinical trials conducted in somewhat naturalistic or putatively generalizable conditions. This notionally ideal level of evidence often is characterized by extrinsic factors influencing the results that are beyond the control of investigators and that presumably are the primary reason for failures to reproduce results [188, 189]. The lack of observation and documentation about such factors also leads to misinterpretation of reproducibility and, in particular, its meta-scientific conflation with generalizability (i.e., recognizing invariance and transformation, as such, as opposed to signal and noise or treatment effects and sources of random error). Awareness of factors that are beyond one's span of control and accounting for such sources of variation requires a different kind of paradigm, such as the kind of modeling and simulation being developed and promulgated by NASA's computational modeling teams and by broader communities such as the IMAG. They do not preclude experimental manipulation, multiple comparisons and significance testing. They can be synergistic with it.

Bayesian paradigm shift

Bayesian modeling takes advantage of the contextual nature of phenomena; that is, the likelihood of a particular context will influence the likelihood of observing some phenomenon in the context on which it partially depends. Such contingent estimates of likelihood are challenged by some of the same inferential error-rate problems of point estimates that have been well-recognized since the early days of experimental design [190, 191]. A potential advantage of a Bayesian approach is that it can aggregate knowledge about multiple co-occurring or otherwise related phenomena. It has some conceptual similarity and overlap with meta-analysis in that it assesses the likelihood estimates of findings across situations (patterns) as well as the sources of error and alternative explanations [192]. The trustworthiness of such aggregation is entirely dependent on confidence about the comparability of the situations that are aggregated [193]. Thus, a particularly powerful utilization of Bayesian methods is in the longitudinal analysis of sequential and coincidental events (i.e., network of events) involving the same group of participants and investigators. This essentially is the approach being pursued by NASA's CCMP in its use of Bayesian network modeling.

Consider, for example, observation of a sequence of events that starts with a broken exercise device on ISS [96]. Lack of exercise combined with lack of load bearing in weightlessness (as with prolonged bedrest on Earth) leads to loss of bone mass with increased calcium spilling into the blood. Hypercalcemia, in turn, increases the risk of kidney stones. If such a painful and debilitating condition occurs, workload will have to be distributed to other members of the crew. Overwork of another astronaut (e.g., physically demanding activities in a 'space suit' outside the vehicle) could lead to a hip fracture because of osteopenia that results from her lack of exercise. If the work that had to be done by astronauts outside the vehicle was necessary either to make a critical repair or for construction that was the purpose of the mission, the potential result is that the mission becomes a partial or complete failure. Bayesian modeling allows planning for such contingencies to be more objective, auditable and improvable.

Again, even though the context of spaceflight is exotic, the network of causal connections is not substantially different from the occurrences that must be considered in providing continuity of care for the well elderly who are aging in place and for the increasing populations who will be situated in a smart medical home. The noteworthy difference in NASA is that such issues are being addressed holistically and systematically by a few cross-cutting groups with the kind of mission orientation emphasized by Mazzucato in her call for a different kind of relationship between the public and private sectors [22, 23]. Cross-cutting computational modeling, and Bayesian network modeling in particular, is a holistic analytical approach that has great potential for knowledge transfer and reciprocal influence between communities of interest in government and industry that are focused on development and implementation of digital medicine [146, 184]. Its utility in each sector and intelligibility between sectors, however, depends heavily on meta-scientific frameworks that can accommodate a diversity of risks and guide exploration of relationships among them.

Necessity of multiscale modeling

NASA's CCMP also is leveraging other methods that are on the leading edge of science and technology development across sectors. Among them is multiscale modeling that can accelerate the exploration of relationships across multiple spatial and temporal scales including heterogeneous measurements (i.e., *kinds* of observation). Their initial multi-scale modeling focuses on a problem that has become apparent in long-duration exposure to weightlessness: headward fluid shifts leading to increased intracranial pressure (ICP) and intraocular pressure (IOP) that can be a source of visual impairments [194]. The five-compartment lumped-parameter model concatenates blood and aqueous humor dynamics, ICP, and IOP-dependent ocular compliance [195]. As is often the case with multi-scale models, different temporal and spatial scales of change were revealed for the concurrent dynamical processes. More generally, this helps isolate mechanical constraints and causes of changes observed in the nested systems. Ultimately, the lumped-parameter approach will span spatial scales from systemic pressures in the whole-body cardiovascular system and an intermediate scale of ICP to the small structures in the eye. This will help researchers determine whether exercise modality, for example, influences ICP, IOP [196, 197] and changes in the volume and shape of associated anatomical compartments.

Fluctuations on different time scales in nested systems also can provide insight into the reversibility of changes and hysteresis in them. Such issues are not unique to spaceflight. ICP decreases with age, and fluctuations in ICP may be a risk factor for glaucoma, but this may be due to physiological or mechanical factors. Cerebrospinal fluid production and turnover is decreased in some diseases such as AD. Impairments in perivascular transport may lead to a buildup of waste products that can damage the optic nerve [198]. Multiscale modeling of ICP and IOP can differentiate among causes as well as among potential effects. This can motivate the development and use of sensor systems that can differentiate and detect early markers of problematic medical conditions [194, 199]. Such models and associated diagnostic devices also can stimulate broader communities of interest that connect research on medical conditions in spaceflight with research on diseases of aging to the extent they give a diversity of investigators commensurate artifacts through which they can communicate and transfer knowledge. The potential of multiscale modeling is not limited to physiological processes and interventions, nor is it limited to a lumped-parameter approach [184]. Machine learning, for example, will be an important capability in the further development of multiscale modeling and its employment in situated precision health [200, 201]. The advantage of using machine learning in this context is that it enables the data to inform components of the model that are not yet completely formulated. These models are abstract and can map a set of inputs to an observed output. The challenge is then transformed from the generation of a predictive model to one that seeks to extract biological insight from the components of the machine learning model.

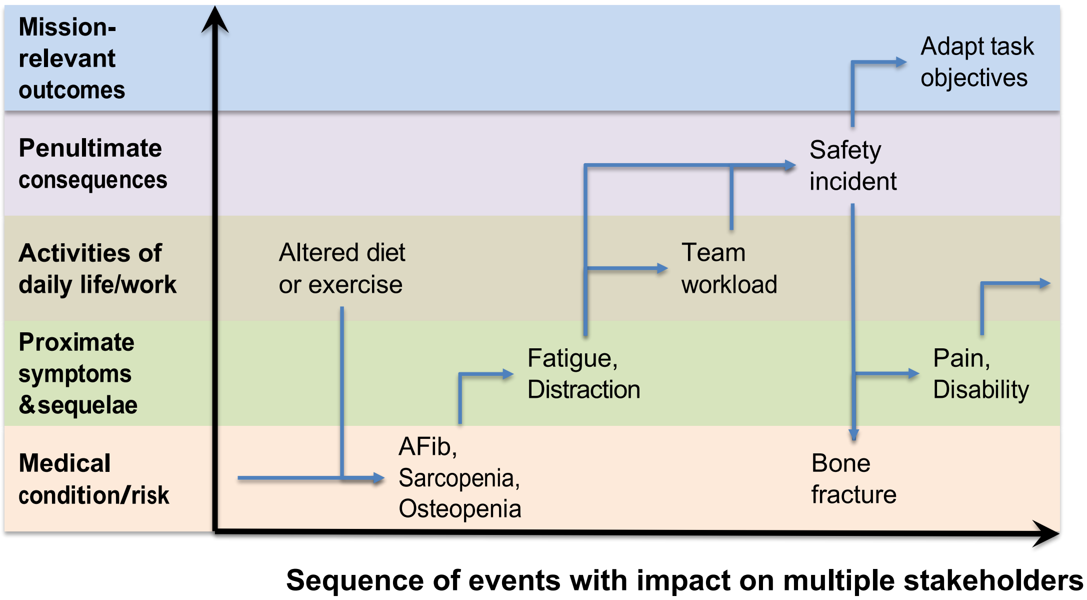

Figure 13. Notional adaptation of NASA's event-driven Bayesian network modeling and simulation combined with its multiscale modeling [96; 29]. Compare with Figure 9.

The CCMP's Bayesian network modeling is extensible to causal influences across multiple scales as well as across sequences of events. There will be opportunities to explore relationships across molecular, physiological, biomechanical, behavioral, and interpersonal levels and kinds of measures. We believe it will be more useful to conceptualize these levels in terms of objectives hierarchies (e.g., levels of abstraction) than in terms of the more or less arbitrary boundaries between scientific disciplines. Figure 13 depicts a variant of the event sequence described above [96] that utilizes levels of abstraction for a cascade of consequences similar to those described by other NASA investigators over the years [202, 203]. The practical relevance of such a means-end hierarchy in a Bayesian analysis of event sequences suggests opportunities for observation of early indicators as well as early interventions and adaptation that can help assure mission success [29]. The implications of this approach for resilience engineering in situated precision healthcare are addressed in the section on a *lifespan approach to precision brain health* in our companion article [2].

Simplicity in Focus on Use, Utility and Value

Complexity and Complicatedness

Experimental analogs allow research and technology development to be more holistic and to be more similar to the ultimate domain of application. Cross-cutting computational modeling provides the capability to formulate theories of a more inclusive system, in principle to falsify holistic theories empirically, and to identity alternatives with respect to which holistic theories can be compared and contrasted (i.e., analysis of alternatives). But is it practical to analyze phenomena in naturalistic or more operationally relevant situations? A common fallacy is that holistic approaches, such as systems medicine, can quickly become intractably complex and that they are otherwise impractical. This view is predicated on assumptions of linearity and additivity that may or may not be obvious or intentional. On such assumptions, a more inclusive view of needs or solutions implies interactions among the elements that increase the dimensionality of associated research and development. Moreover, this typically implies that elements of a more holistic view must be retained and receive the same level of attention (e.g., priority, resources) if they ostensibly have been valuable in the past.

Another approach is to assume that a system is nonlinear, especially if it includes elements such as biological entities at any level of analysis that are adaptive or not specifically fabricated to behave linearly [204, 205]. Changing relationships may affect the global dynamics (e.g., stable vs. unstable states related to the health of the individual) and persistence of and transitions between states. In this case, relationships among elements may be the most fundamental and productive level of analysis. The elements themselves may simply be remnants of prior ways of thinking, and some of them may become marginal or entirely irrelevant to the behavior and performance of the system at hand [92, 206]. Holistic systems thinking can be a method of simplification through selective loss of detail in observation and intervention [207, 208]. On a programmatic level, this is important because NASA can't do everything, nor can any other R&D organization. Some lines of research and development are always neglected because of a lower priority. Even important lines of research may have to be sacrificed. It is inevitable that systems thinking will replace some prior commitments, and this will continue to be an impediment to its adoption. Experimental analogs and multi-scale modeling are exceedingly valuable in making the case for the priority of lines of research and development that are more holistic in the sense of means-end hierarchies and event sequences discussed above.

The premise of this article on situated precision health in the smart medical home is that NASA's human research is a peer community from which the broader medical industry can learn, specifically with respect to situated precision healthcare in a smart medical home. It is always the case, however, that both positive and negative lessons are learned from peers in the scientific community. It could be argued that the NASA enterprise for human exploration has become unintelligibly complicated in response to the complexity of health and performance issues describe above. This problem is not unique to NASA [48, 209]. Innovators in the medical industry should not try to replicate the complicatedness of NASA that has evolved for reasons peculiar to NASA as in many other important institutions in the public sector. For this reason, many aspects of NASA's organization and operations have been avoided herein. Catalysts for transformation must "selectively forget the past" as they "create the future" because the latter often requires the former [61, 62]. For a scientific and technical organization, this selectivity requires explicit meta-scientific frameworks that enable it to be auditable, intelligible and improvable [40].

Risk informed decision-making and model-based systems engineering suggest a path to simplicity, in particular, through a focus on outcomes and associated hierarchies of objectives [1]. They are processes that can inform the implementation of Morieux's "six rules of simplicity," and the processes can be informed by these rules: (a) understand what your people do, (b) increase the total quantity of power, (c) increase reciprocity, (d) reinforce integrators, (e) extend the shadow of the future, and (f) reward those who cooperate [48, 209]. As such efforts mature, they increasingly reveal an expeditious and effective set of trajectories to objectives, as well as trajectories that are objectives in and of themselves, rather than a comprehensive accounting of activities. From a meta-scientific perspective, even when stakeholders are involved in deliberations, objectives hierarchies should be viewed as theories that are only as good as the ability to test them empirically. In a multilayered mission-oriented enterprise such as NASA [1], the test of such theories is to observe the way the results of research and technology development are used, the utility they have with respect to functions for which various stakeholders are responsible, and ultimately the value they deliver with respect to mission outcomes (Figure 14).

Use of Results from Research and Technology Development

NASA does have systems and procedures to assess the use of deliverables from research and technology development. There are human-systems standards, for example, that address crew health [211] as well as human-factors, habitability and environmental health [212]. NASA research informs these standards that are intended for use in decisions about design and development of space systems. NASA also has requirements for the kinds of stakeholders that should be involved in communication about their various standards, collaborative interpretation of them and when they should do so, such as in the context of design review milestones as well as in continual updates of requirements documentation [139, 212]. The high-priority processes—in which numerous personnel are involved from across the NASA enterprise—do not include the kind of hypothetico-deductive activity that is characteristic of a scientific community, however, nor is that the intent. This is an opportunity for any research and technology development community that seeks to build on NASA's foundation by adding scientific inquiry into the methods and outcomes of science itself. What would such meta-scientific inquiry look like?

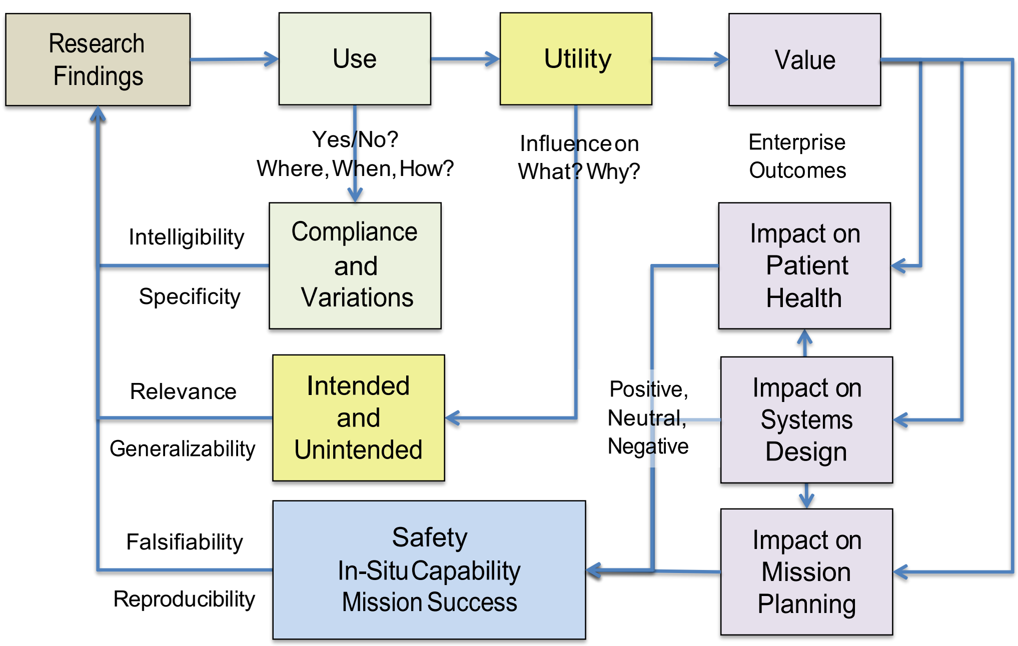

Figure 14. Meta-scientific evaluation of attempts to influence naturally occurring events [21].

Figure 14 is a high-level logic diagram for meta-scientific inquiry into efficacy (impact), efficiency (affordability), and expeditiousness (timeliness) of research that has clear stakeholders such as in outcome-based medicine. Consider, for example, the prescription for exercise to mitigate osteopenia and sarcopenia among other physiological and psychological conditions. If facilities and equipment allow for exercise in the habitat (home), the first question to ask is whether the healthcare consumers actually engage in the prescribed exercise. If they don't, then the explicit theory of *use* is falsified or otherwise demonstrated to be incomplete. One must identify the assumptions that are vitiated and those that can be retained in a revised theory. Such lessons learned rarely are binary. Users may engage in more or different kinds of exercise as a result of the prescription but deviate from the prescription. The lack of compliance may simply be due to a lack of intelligibility in the way the prescription is communicated through the value chain and ultimately to the consumer, or it may be due to a lack of diligence or skill. In either case, the prescription should be revised, and further research may be needed.

Utility of Results from Research and Technology Development

Lack of compliance also may reflect extra-procedural activity of the consumer that reveals equivalence classes of activity previously not considered in the research that led to the prescription. Consumers may actually come up with a variant of the prescription that is superior because of idiosyncratic or common conditions that had not been considered in the research. For example, consumers may utilize different equipment or ranges of motion that require less volume. The time savings or accommodation of other activities may be important to consumers but not something that exercise researchers would have considered to be in their span of expertise, responsibility or control. Such information nevertheless would be useful for new directions of research that would have clear implications for designers of equipment and the habitat. Such meta-scientific inquiry may even require organizational changes or collaboration among previously independent units to engage in a new kind of transdisciplinary research that responds to the cross-cutting needs of consumers. In general, there is no reason to believe that consumer needs map in any simple way to technical disciplines or organizational units that developed under a different set of selective pressures often dominated by supply-side considerations. This is only a tiny sample of the kinds of actionable information that can be gained by observing use of research products *in situ*.

As use of research products is verified, the next level of inquiry should address their *utility*. As with use, there can be surprises and, at the very least, there almost always is further clarification of the consequences of use. Consider again, for example, an exercise prescription. Is the effect on bone loss and muscle strength what was observed in a different environment (e.g., laboratory) or otherwise different from what was predicted? In any case, some variations in the effects may be influenced by externalities from the perspective of research that delivered the exercise prescription. Perhaps consumers didn't comply with a synergistic prescription for bisphosphonates. The reasons for this may lead to modifications of the exercise prescription if compliance cannot be guaranteed in the future. Collateral effects of exercise on sleep and nutrition also may become more refined in the application environment (home), and confidence about them increases. While not surprising, evidence about such complementary activity can lead to changes in the exercise prescription. It may necessitate additional research that could not have been anticipated, and the new line of research that may be a higher priority that what had been planned.

Value of Results from Research and Technology Development

It also is possible that the utility of a research product, such as an exercise prescription, is not entirely positive and in ways that could have been anticipated. Perhaps the exercise necessitates changes in activities of daily living that involve hygiene and clothing because of perspiration and comfort. Exercise in the application environment may give rise to altered patterns of breathing and co-contraction that compensate for instability when more common skills of balance are ineffective. Old skills may be degraded due to medical conditions, or they may be inappropriate because of different mechanical constraints in the application environment. Modification in the exercise prescription would be needed if these differences were to have an undesirable impact on blood pressure, cardiac rhythm, and fluid shifts. This probably would require different kinds of transdisciplinary research and changes in the priority of various lines of research in the portfolio.

Constraints on exercise also may be imposed to accommodate cohabitation because of noise, respiration, perspiration or utilization of common space. This could necessitate modifications to the exercise modality, the exercise devices and the habitat in which the exercise is situated. Alternative designs and associated lines of research always should be considered in a portfolio, and some should be retained even after deselection, because of such unexpected results from inquiry into the utility of a research product. Consider the need to adjust to a smaller habitat because of new missions in deep space for which the luxury of space on the International Space Station is not possible. In deep space, NASA probably will not be able to utilize the exercise devices and prescriptions it has developed for station because of more draconian constraints on mass, volume, and perhaps power. A lifecycle upgrade plan for research on exercise can include meta-scientific inquiry that can gather evidence from the unanticipated utility of larger devices that, at least to some extent, can be generalized to smaller devices and thus accelerate their development. These considerations are not unique to NASA. An analogous need for alternatives is salient in the terrestrial case of a medical home because it is common for patients to move from independent living to generally smaller spaces in facilities with increasingly more skilled care givers, more sophisticated technology, and a broader range of each.

As the examples above reveal, there is a logical progression from inquiry about use, through utility, to the ultimate *value* of research products. The holistic impact on patient health obviously is the most important criterion of value. The patient or consumer is the primary and most important stakeholder. There are other stakeholders, however, whose contributions are essential to the patient's health and well-being. The engineers who design and develop the habitat as well as the technology that makes it smart also are critical stakeholders. They must think holistically, in terms of a system-of-systems architecture, if they are to minimize undesirable unintended consequences and to maximize synergy of capabilities that can be utilized by patients, caregivers and healthcare providers. This cannot be done without a holistic systems science that is commensurate with the system of systems to which its research products will be translated and transitioned, that is, through which it delivers value (see Figures 1 and 3). Meta-scientific inquiry into use, utility and value of research is necessary for this linkage. Finally, research must deliver value to healthcare provider organizations and the sociotechnical ecosystem in which they can survive if not thrive. In their ecosystem of revenue and cost constraints, providers must have a mission orientation for health and well-being supported by resilient systems (see sections above on *selective pressures on the* *supply side…* and *demand side of the healthcare industry*). Meta-scientific inquiry into use, utility and value of research is necessary for assurance of mission success.

Six Meta-Scientific Principles from NASA's Human Research

Our working assumption is that the translational research objective that is common to NASA and communities of interest in the diseases of aging is situated precision healthcare that is predictive, preventive, personalized and participatory. The most important take-away points from the NASA's human research correspond to six meta-scientific values around which scientific and technical innovation as well as associated organizational change initiatives can be organized.

1. Meta-scientific frameworks and forums for multi-stakeholder disintermediation
2. Managing scope and detail of research through design reference missions
3. Diversity of experimental analogs for holistic translational research
4. Assessment of consequences of medical status for life and work
5. Multi-scale computational modeling, simulation, and analysis
6. Scientific focus on use, utility and value at the point of care

Interestingly, these organizing themes correspond nicely, even if not in a one-to-one mapping, to Ivankova's taxonomy for methodologies that have been valuable in the development of translational research [213, 214]. Our points about meta-scientific frameworks for disintermediation correspond primarily to considerations she emphasizes in "community-based participatory research." Design reference missions are especially valuable in "dissemination and implementation." Assessment of consequences, arguably the most important emphasis in our meta-scientific review, has its most powerful precedents in "action research." We argue that multi-scale modeling is the most promising approach to aggregating diverse sources of evidence for improvement of outcomes in "evidence-based practice." Continual experimentation with interventions is most relevant to continual "adaptation" in the process of implementation and diffusion of innovations. The most unique practice that NASA adds to Ivankova's taxonomy is utilization of a diversity of analogs as settings in which all these methodologies can be utilized from the concept stage to the operational stage of capabilities integration and development.

In response to Au [1], the companion article [2] applies NASA's six meta-scientific principles to (a) aggregation of translational medical research; (b) lifestyle interventions in the medical home; and (c) lifespan approach to precision brain health.

CONCLUSION

In a time of unprecedented acceleration in technology innovation and development, it is easy to assume that technology is the solution for everything. Scientists and engineers are especially susceptible to this trap because of societal expectations and organizational incentives to deliver this kind of value. While program managers, scientists and engineers involved in capabilities integration and development generally are aware of this bias, it often dominates their strategic decision making. The proverbial "shiny object" is not an apocryphal trap. Fragmented investment in a blinding diversity of technology and the science that supports it will not lead to systems-level solutions. A different strategic approach is required for development of a smart medical home that can deliver continuity of situated precision healthcare to individuals with various diseases of aging.

In this article, strong claims were made about the centrality of demand-side innovation in translational research and about the metascience that can support it. Our specific aims were to (a) reflect on fundamental assumptions about the value that medical research can deliver to stakeholders, (b) appreciate how disparate segments of the medical research community can share value and achieve outcomes beyond what they can achieve alone, and (c) identify how research and technology development outside the medical community can help medical research become better grounded in the life and work of individuals and thus can achieve more meaningful outcomes. Numerous examples from NASA were provided in a comprehensive meta-scientific framework and approach to translational research for a smart medical home and for its concept of operation. The hope is that this kind of collaboration can stimulate development of meta-scientific communities, defragment demand for solutions, and achieve a more coherent strategic approach to integration and development of a diversity of capabilities including but not limited to technology.

AUTHOR CONTRIBUTIONS

The content of the paper was envisioned for a panel entitled *Situated Precision Health in Extraordinarily Closed Environments* organized by GR for a workshop, *Spaces in Space: Optimizing Behavioral Health & Cognitive Performance in Confined Environments*, offered by the Translational Research Institute for Space Health (TRISH) and the MIT Media Laboratory's Space Exploration Initiative, February 7, 2019.

CONFLICTS OF INTEREST

The author spent the majority of his time between 2015 and 2018 advising leaders in NASA's Human Research Program and in its provider ecosystem about the need for demand-side innovation, multi-stakeholder fiduciary intelligibility, the critical role of metascience research and peer review beyond NASA in optimizing its research portfolio for long-during missions beyond low-Earth orbit. The author declares that he otherwise has no conflicts of interest.

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