Function Begets Function and Resilience in Old Age: Is Precision Gerontology Possible?

The Precision Medicine Initiative (PMI) was created to accelerate the development of new approaches to diseases that currently cannot be prevented or adequately treated, and toward this end, its primary focus has been on emphasizing variability between individuals in terms of genes, lifestyle, and environment.[1] As part of this effort, the National Institutes of Health is spearheading the establishment of a large-scale national research enterprise, with more than 1 million volunteers recruited and the stated goal of extending precision medicine to all diseases.[1] Aging and chronic diseases of aging have not emerged as a defined focus within this broad and ambitious initiative, but recently renamed the "All of Us" Research Program, this effort is committed to reflecting the diversity of the broad U.S. population, enrolling not only participants from diverse social, racial, ethnic, ancestral, geographic, economic, and health status backgrounds, but also those of varying ages, such as elderly adults.

In spite of such promising developments, the long-range future of this effort remains unclear with a new administration in Washington. Furthermore, such investments will not succeed in improving health care for vast numbers of typical older adults unless efforts are made to reconcile the reductionist, simplistic, and at times even naïve foundational assumptions behind such laudable efforts with the remarkable complexity, interindividual variability, and overall "messiness" of real-world geriatric concerns.[2,3]

An earlier emphasis on personalized medicine presented even greater challenges in terms of its applicability to a geriatric context. It was often misconstrued as implying that unique treatments could be designed for each individual.[1,4] Also, its emphasis on genetics and traditional pathophysiological approaches failed to provide a coherent framework in the context of aging in which individual inherited[5] and other[2] risk factors generally provide only a modest contribution to the remarkable variance seen in old age. The term "precision medicine" was coined more recently to emphasize the need and ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or condition, in the underlying biology, or in the response to a specific treatment.[6] With such knowledge, preventive or therapeutic interventions could then be offered to those who will most likely benefit, sparing expense and side effects for those who will not.[6]

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In seeking to explore the importance and suitability of such approaches to older adults, it is important first to recognize the tremendous variability in terms of aging trajectories from the perspective of physical and cognitive function, frailty, disability, and measures of successful aging that has now been demonstrated across multitudes of populations and settings.[7–10] To that end, any effort to begin developing a conceptual framework for precision medicine for older adults must begin by first recognizing the existence of the remarkable and multifaceted complexity that contributes to variable trajectories in aging, followed by strategies to identify and target defined clusters of individuals with similar trajectories, especially when this helps to classify older adults into subpopulations that differ in their susceptibility to a particular combination of diseases or conditions, their underlying biology, or their response to specific treatments.[6]

Efforts to begin unravelling such complexity may seem overwhelming at first but will succeed as long as relevant disciplines are engaged and overarching clinical concepts behind such variability are reconciled with the final vision (Table 1). First, not only are underlying chronic disease and geriatric syndromes common, their numbers and specific combinations vary tremendously in old age between older adults with multimorbidity.[3,11] Second, individual chronic diseases and geriatric syndromes are highly multifactorial, involving complex clusters of risk factors that vary not only between different conditions, but also to some extent between individuals experiencing the same condition or cluster of conditions.[2] Third, although genetic factors remain important,[5] they have a far less-important role in aging than inherited diseases such as cystic fibrosis or some cancers in which PMI-guided therapies can promote the use of defined therapies targeting germline variants known to result in defined disease subcategories.[4] Fourth, functional measures such as gait velocity are robust predictors of future frailty, disability, and death,[12–14] perhaps in part because they provide an integrated assessment of performance involving muscle, neural circuits, nutrition, cardiovascular fitness, volitional considerations, and others. Fifth, whether conceptualized as a phenotype[15] or deficit accumulation,[16] frailty helps predict variability in the risk of future disability or death and offer insights into processes involved in disablement. Sixth, may also older adults vary greatly in their capacities to respond to defined stressors as diverse as infection, changes in ambient temperature, dehydration, bedrest, surgery, and anesthesia.[17] Seventh,

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Table 1. Some Overarching Clinical Observations and Geriatric Concepts Pertaining to Increasing Interindividual Variability with Aging That Must Be Encompassed within Precision Gerontology to Make the Precision Medicine Initiative (PMI) or Similar Efforts Relevant to Needs of Real-World Older Adults

Clinical Observations and Geriatric Concepts	Relevance to Precision Gerontology
Multimorbidity	Numbers and specific combinations of chronic diseases and geriatric syndromes vary tremendously in older adults with multimorbidity[3,11]
Multifactorial complexity	Individual chronic diseases and geriatric syndromes are highly multifactorial, involving complex clusters of risk factors that vary not only between different conditions, but also to some extent between individuals experiencing the same condition[2]
Inherited versus acquired factors	Genetic factors have a less-important role in aging than inherited diseases such as cystic fibrosis or some cancers in which PMI-guided therapies in help select therapies targeting specific germline variants, resulting in specific disease subcategories[1,4,14]
Functional performance measures	Functional measures such as gait velocity are robust predictors of future frailty, disability, and death,[12,13] perhaps in part because they provide an integrated assessment of performance involving muscle, neural circuits, nutrition, cardiovascular fitness, volitional considerations, and others
Frailty	Whether conceptualized as a phenotype[15] or deficit accumulation,[16] frailty helps predict variability in the risk of future disability or death and may offer insights into processes involved in disablement
Resilience	Older adults vary greatly in their capacities to respond effectively to defined stressors as diverse as infection, changes in ambient temperature, dehydration, bedrest, surgery, and anesthesia[17]
Aging is a major shared risk factor for geriatric syndromes and chronic diseases of aging	As stated in the Geroscience Hypothesis, efforts to target shared biological pathways may help delay the onset and progression of such conditions[18,19]
Personal preferences	Not only do treatment goals and preferences tend to change with aging, but increasingly they also vary based on differences in individual health considerations and cultural, social, and economic factors[3,20]

because aging is a major shared risk factor for geriatric syndromes and chronic diseases of aging, efforts to target shared biological pathways, such as the proposed TAME (Taming Aging with Metformin) trial may help delay the onset and progression of such conditions.[18,19] Finally, it is impossible to speak of more-individualized health care for elderly adults without also considering individual treatment goals and preferences. Not only do these tend to change with aging, but differences in individual health considerations and preferences and cultural, social and economic factors have a great influence on personal preferences and treatment goals.[3,20]

With all of the above considerations in mind, elderly adults have the most to lose from "one size fits all" approaches to health care and the most to gain from successful efforts to transform elements of the PMI into precision gerontology. Moreover, in the context of caring for older adults with complex and highly variable multimorbidities, precision medicine must ultimately be transformed into precision care, carefully considering the applicability of each healthcare decision to an individual's unique profile of chronic and subacute conditions, health and functional status, goals, and stated preferences.[3,20]

As noted above, the roles of mobility performance measures as strong predictors of future frailty, disability, and mortality have been well established,[13] but two reports published in the Journal[21,22] highlight the importance of considering functional measures involving distinct cognitive domains when seeking to identify subsets of older adults with definable risk profiles for future disabilities and diseases. In evaluating relationships between these various functional constructs and how these may be applied to precision gerontology, it is helpful to consider the findings of such studies within the framework of the Nagi Model of Disablement, first described more than half a century ago[23] (Table 2).

Davis and colleagues[21] used principal component analysis to identify slowed processing speed and executive functioning (PS-EF) as the most consistent predictor of future falls, including injurious falls, in 288 community-dwelling older adults seen in a falls prevention clinic. As discussed in the accompanying editorial by Manning and Wolfson,[24] active pathology with microvascular disease involving vulnerable white matter tracts in the periventricular and prefrontal regions is associated with functional impairments involving PS-EF. Functional limitations in terms of declines in mobility performance,[24] affect,[24] and bladder control[25] often follow, ultimately predisposing an individual to falls, depression, and urinary incontinence through lack of resilience (ability to maintain normal function or return rapidly to baseline) when confronted by a stressor that is sufficiently potent, prolonged, or sometimes poorly timed occurring concurrently with or soon after other stressors.[17,26] Thus, in this manner, interventions such as intensive cognitive training and improved blood pressure control, as Manning and Wolfson[24] discuss, may assist in helping to prevent, slow, and possibly mitigate this pathway to disability.

The report in this issue, by Farias and colleagues[22], presents another distinct, yet related issue. Self- and informant-based changes involving the Everyday Cognition scale, an instrument designed to measure everyday function in six cognitive domains, were associated with a significantly greater risk of diagnostic conversion to mild cognitive impairment (MCI) after controlling for objective cognitive test performance in 324 members of a

Table 2. Results of Findings from Davis and Colleagues[21] and Farias and Colleagues[22] Framed within the Conceptual Framework of the Nagi Disablement Process As Modified by Jette[23]

	Active Pathology	Impairment	Functional Limitation	Disability
Definition	Intrinsic pathology or disorder	Anatomic, physiological, mental, or emotional abnormality	Limitation of performance at level of whole person	Limitation in performance of socially defined tasks within sociocultural and physical environment
Frame of reference	Cell(s)	Tissue, organ, or body system	Whole person	Whole person in context of external environment, culture and society
Example 1 (Davis et al.[21])	Microvascular disease with pathology of vulnerable prefrontal white matter tracts (anterior periventricular regions, corona radiata)	Slowed processing speed and executive functioning	Declines in mobility performance, affect, bladder control	Injurious falls, depression, urinary incontinence
Example 2 (Farias et al.[22])	Neurodegenerative cellular processes associated with Alzheimer's disease and vascular dementia	Declines and slowing of cognitive processes	Conversion to mild cognitive impairment or early dementia	Measure of Everyday Cognition evaluating function across 6 cognitive domains

longitudinal research cohort defined as being cognitively normal at baseline.[22] At first it may not seem that evidence of disability would be observable on self- and informant-based reports long before an expert clinician could diagnose an accepted functional limitation or disease in the form of MCI. Nevertheless, in the case of clinical trials targeting cognition, observers sometimes report functional improvements while objective improvements in formal cognitive testing may not be evident. These observations illustrate several important points. First, when evaluating resilience and the transition from functional limitation to disability, one must consider the environment in the form of the stressor and the ability of the individual to respond to that stressor.[17] Thus, an individual who performs adequately (e.g., within the average range) when undergoing cognitive testing in a usual structured one-on-one environment may experience subtle functional changes when confronted by the rigors and stressors of daily life that are not captured on the objective examination.

These observations also highlight the fact that disablement pathways are not always strictly linear in nature, proceeding all the way to disability independently from other risk factors and pathways.[2,27] Rather, intervening acute, subacute, and chronic events may influence the bidirectional nature of these disablement pathways, as may various interventions such as those involving intensive cognitive training and improved blood pressure control.[24]

Many unanswered questions remain regarding the manner through which investments in efforts such as the PMI may lead to better care of typical real-world older adults. For example, geriatrics still struggles with defining a coherent approach to translating well-established measurements of physical performance from the domain of research into everyday clinical care.[28] Also, it remains to be seen to what extent advances in Next-Generation Sequencing[4] and single-cell genomics[29] may help facilitate the pathway to precision gerontology, because functional genomics and epigenomics are likely to be of far greater importance in aging than germline genetic variants and phenotypes. Finally, the importance of making all such approaches relevant to each individual's unique combination of multimorbidity, social and environmental considerations, and personal preferences cannot be overrstated.[3] This journal and its readers—all committed to improving the lives of older adults through clinical care, education, and research—must be active participants in this process because the cost of failure would be exceedingly high for our patients, our field, and all of us.

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