Carpenter Christopher (Orcid ID: 0000-0002-2603-7157)

Models and Studies of Aging: Executive Summary of a Report from the U13 Conference Series

Arti Hurria, M.D.[1], Christopher R. Carpenter, M.D.[2¥], M.Sc., Frances McFarland, M.A., Ph.D.[3], Nancy E. Lundebjerg, MPA[4], Rafael DeCabo, Ph.D.[5], Luigi Ferrucci, M.D., Ph.D.[5], Stephanie Studenski, M.D., MPH.[5], Nir Barzilai, M.D.[6], Josephine Briggs, M.D.[7], Joachim Ix, M.D., MAS.[8], Dalane Kitzman, M.D.[9], George A. Kuchel, M.D.[10], Nicolas Musi, M.D.[11,12], John C. Newman, M.D., Ph.D.[13,14], Thomas A. Rando, M.D., Ph.D.[15], Alexander K. Smith, M.D., MS, MPH[14], Jeremy Walston, M.D.[16], James L. Kirkland*, M.D.. Ph.D.[17], Raymond Yung*, M.D.[18]

[1] City of Hope National Medical Center, Duarte, CA

[2] Washington University School of Medicine, St. Louis, WA

[3] Science/Medical Writer, Independent Consultant, Annapolis, MD

[4] American Geriatrics Society

[5] National Institute on Aging, Bethesda, MD

[6] Albert Einstein College of Medicine, Bronx, NY

[7] National Center for Complementary and Integrative Health, Bethesda, MD

[8] University of California, San Diego School of Medicine, San Diego, CA

[9] Wake Forest Baptist Medical Center, Winston-Salem, NC

[10] UConn Center on Aging, UConn Health, Farmington, CT

[11] San Antonio Geriatric Research, Education and Clinical Center

[12] Barshop Institute for Longevity and Aging Studies, San Antonio, TX

[13] Buck Institute for Research on Aging, Novato, CA

[14] University of California, San Francisco School of Medicine, San Francisco, CA

[15] Stanford University, Palo Alto, CA

[16] Johns Hopkins School of Medicine, Baltimore, MD

[17] Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, MN

[18] University of Michigan, Ann Arbor, MI

[*] Drs. James L. Kirkland and Raymond Yung are dual senior authors of this report.

[¥] Corresponding Author:

Christopher R. Carpenter, M.D., M.Sc.

Division of Emergency Medicine & Evidence Based Medicine

Washington University

1 Barnes-Jewish Hospital Plaza

St. Louis, MO 63110

Office Phone: 314-758-6787

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ABSTRACT

The American Geriatrics Society (AGS) convened a conference in Bethesda, Maryland, to explore models and studies of aging. This was the second of three conferences, supported by a U13 grant from the National Institute on Aging (NIA), to aid recipients of Grants for Early Medical/Surgical Specialists Transition to Aging Research (GEMSSTAR) awardees in integrating geriatrics into their specialties. Recognizing that aging is the largest risk factor for multiple chronic diseases and age-related loss of resilience, the conference organizers focused scientific sessions on how targeting age-related mechanisms can delay, prevent, or reverse geriatric syndromes, age-related chronic diseases, and loss of resilience. The rationale for studying models of aging as well as study designs, strategies, and challenges of studying human aging were reviewed. This article provides a summary of the full conference report, Models and Studies of Aging: Report from the U13 Conference Series and summarizes key take home

messages that were designed to support GEMSSTAR in developing their research careers focused on aging research (see supplemental text – FULL REPORT).

Key Words: Aging, Geriatrics, Biology, Research

Introduction

On September 21-23, 2016, the American Geriatrics Society (AGS) convened a conference in Bethesda, Maryland, to explore models and studies of aging. This was the second of three conferences, supported by a U13 grant from the National Institute on Aging (NIA) that focuses on assisting recipients of Grants for Early Medical/Surgical Specialists Transition to Aging Research (GEMSSTAR) to integrate geriatrics into their subspecialties. The GEMSSTAR program builds upon the success of two programs that were funded by the Atlantic Philanthropies and the John A. Hartford Foundation, Inc. (the T. Franklin Williams and Dennis W. Jahnigen Scholars Awards) [1-3]. The goals for each of the U13 conferences were two-fold. The first goal is to introduce participants to key concepts and approaches that are important to understand when undertaking research on aging. The second goal is to help GEMSSTAR awardees to prepare for the next stage of their research careers and to build the GEMSSTAR collaborative network. Drs. James Kirkland, of the Mayo Clinic, and Raymond Yung, of the University of Michigan, served as co-Chairs for this conference.[4] A total of 110 people representing 19 specialties attended the meeting (Table 1). This article provides a high level

overview of the full conference report, Models and Studies of Aging: Report from the U13 Conference Series (see supplemental text – FULL REPORT) and offered thoughts on contributions that the GEMSSTARs could make to future research progress.

The Rationale for Studying Models of Aging: The Geroscience Hypothesis

The rationale for studying models of aging is based on the geroscience hypothesis, which is that targeting fundamental aging processes will delay, prevent, alleviate, or reverse multiple geriatric syndromes, chronic diseases, and loss of resilience. Despite the complexity and variability in aging, it is hypothesized that aging is driven by interconnected biological mechanisms called the hallmarks or pillars of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication[5]. Disruptions in one or several of these hallmarks of aging will contribute to the development of chronic diseases and/or frailty. At present, geriatric medicine focuses on tertiary prevention, managing complications of chronic diseases, and geriatric syndromes. However, interventions that target fundamental aging processes will likely be most useful if they are administered before the beginning of disability. With this approach, advances in the biology of aging could lead to interventions that compress morbidity and delay chronic diseases and geriatric syndromes.

Several interventions that target these hallmarks of aging are making their way from basic biology studies in animals through early translation studies. Throughout the U13 conference

specific considerations in the development of intervention studies targeting aging processes or age-associated diseases was discussed (see Table 2). First, preclinical models should include aged or frail animals, those fed high-fat diets, models of resilience, and other models exposed to clinically relevant insults. Likewise, toxicity testing requires age-appropriate models and should address short- and long-term toxicity and be acceptable to the FDA for inclusion in Investigational New Drug applications (INDs). When moving interventions from preclinical testing to clinical trials, investigators should test effects on measurable, clinically relevant outcomes that are appropriate for older populations. Studies of agents targeting aging processes should assess effects on panels of mechanistic biomarkers related to the hallmarks of aging. Finally, trials testing agents that target aging processes might be served better by enrolling older participants, particularly those with multiple comorbidities. However, emerging evidence from cohort studies are suggesting the need for intervention at earlier time points in the disease process, but the best time for evaluation and effective intervention remains unclear.

In addition to standard, phase I, II, and III clinical trials, the concept of pragmatic clinical trials was discussed as an attractive option for studying older adults. They are designed to inform health care decision-makers, which can include patients, clinicians, and policymakers. They compare clinically relevant alternatives, enroll diverse study populations from the real world, recruit from several practice settings, and measure a broad range of relevant health outcomes or streamline data collection to ensure adequate power[6]. Pragmatic clinical trials differ from

explanatory trials by offering broader eligibility, flexible interventions, typical practitioners, no follow-up visits, and usual adherence[7].

Strategies and Challenges in Clinical Trials Targeting Human Aging

Strategies, challenges, and frameworks for proof-of-concept and clinical trials of interventions derived from studies in aging biology had been discussed at an R24 geroscience retreat that brought together members of the NIH funded Geroscience Network[8]. Major themes that emerged from these discussions were summarized for the GEMMSTAR scholars (see Table 2):

Target big picture outcomes. Not only is aging the primary non-modifiable risk factor for several chronic diseases, it is also the prism or processor that determines how diseases manifest in people's lives. Thus, clinical studies in aging should focus on integrative, big-picture outcomes that are important to people's lives, such as functional outcomes and independence, geriatric syndromes, and mortality. The workshops recommended extending the health span as one framework, where targeting the mechanisms underlying aging could prevent or delay the losses and declines associated with aging, and studies would assess global outcomes such as multimorbidity or daily function. Enhancing resilience was also recommended as a framework. At every level, from the cellular and molecular level to the whole person, aging presents universally as a weakened ability to cope with new stresses and stimuli. Within this framework,

interventions that target the mechanisms of aging could reduce the period of decline or enhance the period of recovery following stress, again at various levels.

Study an aging population. The majority of clinical studies still look for ideal participants, for example patients with no comorbidities.[9] Although there is some mechanistic value to studying interventions in the ideal population, these agents also should be studied in populations that will actually be treated. Clinical trials should include older people, particularly those who are frail or have multiple morbidities, and embrace heterogeneity. The choice of study population will depend on the intervention under study, the presence and severity of illness and how that affects outcomes of interest, and the window of opportunity for intervention. Small pilot studies should be conducted to determine the best time and approach for applying interventions. In addition, clinical studies should be considered within the overall context of aging: how is the disease of interest affected by the hallmarks of aging, their biochemical markers, and the interactions among them; how is the disease of interest influenced by other chronic diseases, and what markers should be used to measure them, and which global outcomes should be measured?

New tools for helping older adults. Studies in aging biology could yield new interventional tools that clinicians can use to affect their disease of interest. Among potential interventions emerging from basic and clinical studies are those, such as metformin, acarbose, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors, that are already approved by

the FDA but could play broader roles in aging. However, many agents have not been tested specifically in frail or older adults. Existing clinical programs targeting older adults can be leveraged to provide infrastructure and comparisons in clinical studies. These tools and clinical studies can also contribute to an evidence base to support aging as an indication on which the FDA could base approvals of interventions. Composites of existing outcomes, for example multiple diseases, could also be used.

Accelerating translation. Workshop discussions also focused on how to facilitate the incorporation of aging into clinical studies. Suggestions included the development of cognitive and physical infrastructure to accelerate research; subspecialists' integration of aging concepts into their studies; a shared library of templates for trial designs, INDs, IRB proposals, and data safety monitoring board reports adapted to older adults and aging-related outcomes; a standardized, modular outcome toolkit; and a national geroscience biobank that is diverse and enriched for multimorbidity and frailty.

Future of Aging Research: Opportunities for GEMSSTAR to Contribute to Progress

Over the next decades, as the U.S. population ages, specialty clinician investigators will contribute to an evolution of progress in several areas. Discussions throughout this meeting emphasized the value of inter-specialty collaboration in aging research (see Table 2). Stimulating

inter-specialty collaboration could prove powerful and lead the nation in revolutionizing care, particularly because of the pleiotropic nature of aging-related mechanisms.

In the closing plenary, Dr. Evan Hadley, National Institute of Aging highlighted some of the areas where he believes specialty clinician investigators are particularly well positioned to contribute to future progress (see Table 3). He emphasized that inter-specialty collaborations will be particularly important to future progress and encouraged GEMSSTAR Awardees to think broadly about collaboration and how best to promote it. He advised GEMSSTAR awardees to embrace flexibility, leverage unexpected developments, and envision how research can evolve beyond the next short-term study – emphasizing key points that had emerged from prior presentations. He noted that clinician investigators bring a particular value to aging research, including:

- their experience in technology and technology development for assessing human biology and function *in vivo*;
- experience in and ability to collaborate with preclinical researchers, ongoing disease-focused research on the mechanisms underlying aging;
- knowledge of real-world constraints on the feasibility of translating an intervention; and
- their ability to assess the whole patient as opposed to a target organ.

Finally, the scholars were reminded that the translation of a discovery from the bench to the bedside rarely follows a linear pattern and conference participants were encouraged to

embrace this winding path with unexpected turns that can potentially be the path to breakthroughs to improve the quality of care for an aging population.

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Authors JB, NB, RD, LF, AH, JI, DK, JLK, NM, JN, TR, AS, SS, JW and RY worked on concept and design of this manuscript. Authors AH, JI, DK worked on analysis and interpretation of data of the manuscript. Authors JB, CC, RD, LF, AH, DK, GK, JLK, FM, NM, TR, AS, SS, JW and RY worked on the preparation of the manuscript.

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This report has been reviewed by all workshop speakers.

Dedication:

We humbly dedicate this mentorship essay to our co-author, GEMSSTAR U13 principle investigator, friend, and hero Arti Hurria who lost her life on November 7, 2018.

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Supplemental Text. Full Report from the U13 Conference Series

Table 1: Represented Specialties

Anesthesiology	Nephrology
Cardiology	Obstetrics and Gynecology
Emergency Medicine	Ophthalmology
Endocrinology	Palliative Medicine
Gastroenterology	Physical Medicine and Rehabilitation
General Internal Medicine	Psychiatry
General Surgery	Pulmonary and Critical Care
Geriatrics and Gerontology	Urology
Hematology/Oncology	Vascular Surgery
Infectious Diseases	

Table 2: Topics, Speakers and Take Away Themes

Topic	Speaker	Key Take Away Theme
Biology of Aging		
Pillars of Aging	Luigi Ferrucci, MD, PhD, National Institute on Aging	• Importance of studying resilience, as well as decline • Variability and complexity among older adults • Need for the FDA to specify aging mechanisms and multimorbidities as indications for treatment and endpoints for clinical studies
Inflammation	Jeremy Walston, MD, Johns Hopkins University School of Medicine	
Metabolism	Nick Musi, MD, Barshop Institute	
Resilience	George Kuchel, MD, UConn Health	
Interventions		
Translation: Bench to Bedside	Thomas Rando, MD, PhD, Stanford University	• Need for flexibility and taking advantage of unexpected developments
Trials: Phase I and II	James Kirkland, MD, PhD, Mayo Clinic	
Trials: Phase III	Nir Barzilai, MD, Albert Einstein College of Medicine	
Geroscience R24: Research Strategies, Barriers, Opportunities		
Pre-Clinical: Developing therapeutics targeting aging mechanisms	James Kirkland, MD, PhD, Mayo Clinic	• Target big picture outcomes. • Clinical trials should include older people, particularly those who are frail or have multiple morbidities, and embrace heterogeneity. • Need for infrastructure, including assistance with preparing investigational new drug applications, to facilitate translation of basic science discoveries to the clinic

Research Methods and Strategies		
Pragmatic Trials	Marcel Salive, MD, MPH, NIA Division of Geriatrics and Clinical Gerontology	• Prioritizes comparing clinically relevant alternatives in diverse study populations from real-world practice settings • Increasing opportunities for pragmatic trial designs in frailty, disability, and multiple chronic co-morbidities since <15% of guidelines are based on high-quality evidence
Finding Research Questions	Josie Briggs, MD, NIA Aging Research for the Specialties	• Focus questions on conventional wisdom and the supporting evidence • Incomplete knowledge stems from inadequate biological understanding, inappropriate outcome measures, insufficient high-quality data, or efficacy data with limited external validity or heterogeneous effects, as well as failure to weigh potential harms with benefits • The Precision Medicine Initiative® offers opportunity to inform a broad variety of research studies and a transformational approach to diversity
The Continuing Value of Clinician Investigators	Evan Hadley, MD, Director of the National Institute on Aging	• Specialty clinical investigators remain essential to better understanding the role of aging mechanisms in age-related conditions, the bidirectional interactions of multimorbidities, earlier targeting of chronic disease or risk factors as prevention, and development of appropriate performance and outcome measures to inform payment reform

Junior Investigator Resources		
Large Databases: Pros/Cons/Limitations	Joachim Ix, MD, MAS, University of California-San Diego	• Existing dataset projects can increase collaborative research productivity with potential for ancillary studies • Large epidemiological studies often have topic-oriented working groups and statistical support to provide advice on ideas, manuscripts, and career • Disadvantages include administrative complexities, limited data and sub-samples, and intellectual property rights – how investigators are approached is key
Baltimore Study of Longitudinal Aging	Stephanie Studenski, MD, PhD, National Institute on Aging	• Established as a lifelong cohort study of normative aging in 1958 with updates in 2004 and 2011 to characterize various aspects of the aging process and interactions through biannual (ages 60-79) or annual assessment of core and advanced measures • Endpoints include life expectancy, health longevity, mobility, cognitive impairment, and frailty • Aims to be responsive to emerging research questions in aging with opportunities for translational studies
Health and Retirement Study (HRS)	Alex Smith, MD, University of California-San Francisco	• HRS includes biennial surveys since 1992, ~20,000 participants • Provide focus on the relationship of financial and social status with health • Access to functional status and cognition, health services

		use, geographic data, and mortality
Career Development		
Getting Started: Large Project	Dalane Kitzman, MD	• Anticipate a path filled with challenges rather than a straight path of early and sustained success • Select an important question and the answers will matter regardless of the results • "Mistakes" offer best clues from which to adapt in relentless pursuit of truth • Enjoy the journey of discovery
After the R03: Scaling Up Your Research Program	Robin Barr, D. Phil	• Contemplate three paths simultaneously: career development, research, and organizing a field. • These three paths are not necessarily independent • NIA career development awards include K08, K23, and Beeson K76 • Early stage investigators have a 10-point advantage in the R01 funding line provide
Career Development: Do's and Don'ts	Stephanie Studenski, MD, PhD, National Institute on Aging	• Develop a graphic illustration of the conceptual framework of your science to orient "consumers" of your proposal. • Seek critical feedback on gaps in your rationale • Focus communication on the take-home message • Harness expertise of seasoned administrators to navigate

		your organization's human resources game • Develop winning negotiation strategies by illustrating the value of your request for the organization and providing a clear plan for resources

Table 3: Future Specialty Clinician Investigators' Contributions to Progress

Topic	Specialty Clinician Educator Future Contributions
Role of aging mechanisms in age-	• Development of mechanism-proximal markers and targets and relating them to multiple

related conditions	aging phenotypes • Knowledge about favorable and unfavorable clinical effects of interventions targeting particular aging mechanisms and pleiotropy in the effects of aging mechanisms on multiple outcomes • Application of new technologies, such as imaging and other noninvasive measures
Multimorbidity	• Knowledge about the bidirectional interactions between aging mechanisms and age-related conditions • How one age-related morbidity might influence the progression of others through effects on aging mechanisms • The interactions among specific disease combinations and their treatments • The trade-offs between the potential benefits and harms of interventions
Prevention	• Knowledge about the implications of research participant selection; the development of screening methods • The potential for expanding the role of tests that might detect early stages of aging pathology • The sensitivity, specificity, and clinical impact of new screening or diagnostic tests in patients of differing ages and comorbidities • The value of linking with epidemiological studies, and integrating information from clinical encounters with data from longitudinal studies to improve understanding of modifiable risk factors for aging outcomes.
Healthcare quality measures and evidentiary bases for payment	• Development of appropriate performance and outcome measures for patients with multimorbidities and integrate them with disease-specific measures • Assess the relative clinical value of new diagnostic tests of interventions, compared with alternatives, and evidence-based indications for which patients should receive them