

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

Arti Hurria, MD,* Christopher R. Carpenter, MD, MSc,[†]  Frances McFarland, MA, PhD,[‡] Nancy E. Lundebjerg, MPA,[§] Rafael de Cabo, PhD,[¶] Luigi Ferrucci, MD, PhD,[¶] Stephanie A. Studenski, MD, MPH,[¶] Nir Barzilai, MD,^{||} Josephine P. Briggs, MD,^{**} Joachim H. Ix, MD, MAS,^{††} Dalane W. Kitzman, MD,^{‡‡} George A. Kuchel, MD,^{§§} Nicolas Musi, MD,^{¶¶|||} John C. Newman, MD, PhD,^{***†††} Thomas A. Rando, MD, PhD,^{‡‡‡} Alexander K. Smith, MD, MS, MPH,^{†††} Jeremy D. Walston, MD,^{§§§} James L. Kirkland, MD, PhD,^{¶¶¶¶¶} and Raymond Yung, MD^{|||||a}

The American Geriatrics Society 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, to aid recipients of Grants for Early Medical/Surgical Specialists Transition to Aging Research (GEMSSTAR) 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,

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 awardees in developing their research careers focused on aging research (see supplementary text for the full report). *J Am Geriatr Soc* 67:428–433, 2019.

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From the *City of Hope National Medical Center, Duarte, California; [†]Washington University School of Medicine, St. Louis, Missouri; [‡]Science/Medical Writer, Independent Consultant, Annapolis, Maryland; [§]American Geriatrics Society, New York, New York; [¶]National Institute on Aging, Bethesda, Maryland; ^{||}Albert Einstein College of Medicine, Bronx, New York; ^{**}National Center for Complementary and Integrative Health, Bethesda, Maryland; ^{††}School of Medicine, University of California, San Diego, California; ^{‡‡}Wake Forest Baptist Medical Center, Winston-Salem, North Carolina; ^{§§}UConn Center on Aging, UConn Health, Farmington, Connecticut; ^{¶¶}San Antonio Geriatric Research, Education and Clinical Center, San Antonio, Texas; ^{|||}Barshop Institute for Longevity and Aging Studies, San Antonio, Texas; ^{***}Buck Institute for Research on Aging, Novato, California; ^{†††}School of Medicine, University of California, San Francisco, California; ^{‡‡‡}Stanford University, Palo Alto, California; ^{§§§}Johns Hopkins School of Medicine, Baltimore, Maryland; ^{¶¶¶}Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota; and the ^{|||||}University of Michigan, Ann Arbor, Michigan.

Address correspondence to Christopher R. Carpenter, MD, MSc, Division of Emergency Medicine Emergency Care Research Core, Washington University in St. Louis School of Medicine, Campus Box 8072, 660 S. Euclid Avenue, St. Louis, MO 63110; E-mail: carpenterc@wustl.edu

^aJames L. Kirkland and Raymond Yung are dual senior authors of this report.

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On September 21–23, 2016, the American Geriatrics Society 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 on 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 twofold. The first goal was to introduce participants to key concepts and approaches that are important to understand when undertaking research on aging. The second goal was to help GEMSSTAR awardees 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 supplementary text for the full report), and it offers thoughts on contributions that the GEMSTARs could make to future research progress.

RATIONALE FOR STUDYING MODELS OF AGING: THE GEROSCIENCE HYPOTHESIS

The rationale for studying models of aging is based on the geroscience hypothesis: 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 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 were discussed (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 Food and Drug Administration (FDA) for inclusion in investigational new drug (IND) applications. 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 suggests 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 healthcare decision makers that 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 were discussed at an R24 geroscience retreat that brought together members of the Geroscience Network funded by the National Institutes of Health.⁸ Major themes that emerged from these discussions were summarized for the GEMSTAR scholars (Table 2).

Target Big-Picture Outcomes

Not only is aging the primary nonmodifiable 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

Most 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

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 | <ul style="list-style-type: none"> • 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 end points 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 | <ul style="list-style-type: none"> • 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 | | |
| Preclinical: Developing therapeutics targeting aging mechanisms | James Kirkland, MD, PhD, Mayo Clinic | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 comorbidities because <15% of guidelines are based on high-quality evidence • 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 an opportunity to inform a broad variety of research studies and a transformational approach to diversity |
| Finding Research Questions | Josie Briggs, MD, NIA Aging Research for the Specialties | |
| The Continuing Value of Clinician Investigators | Evan Hadley, MD, Director of the National Institute on Aging | |
| Junior investigator resources | | |
| Large Databases: Pros/Cons/Limitations | Joachim Ix, MD, MAS, University of California, San Diego | <ul style="list-style-type: none"> • Existing data set 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 subsamples, and intellectual property rights—how investigators are approached is key |
| Baltimore Study of Longitudinal Aging | Stephanie Studenski, MD, PhD, National Institute on Aging | |
| | | <ul style="list-style-type: none"> • 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 • End points 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 |

Table 2 (Contd.)

| Topic | Speaker | Key take-away theme |
|---|---|--|
| Health and Retirement Study (HRS) | Alex Smith, MD, University of California, San Francisco | <ul style="list-style-type: none"> • HRS includes biennial surveys since 1992, about 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 |
| Career Development: Do’s and Don’ts | Stephanie Studenski, MD, PhD, National Institute on Aging | <ul style="list-style-type: none"> • 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-related conditions | <ul style="list-style-type: none"> • Development of mechanism-proximal markers and targets and relating them to multiple 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 |
| Multimorbidity | <ul style="list-style-type: none"> • Application of new technologies, such as imaging and other noninvasive measures • 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • Development of appropriate performance and outcome measures for patients with multimorbidities and integrating them with disease-specific measures • Assess the relative clinical value of new diagnostic tests or interventions, compared with alternatives, and evidence-based indications for which patients should receive them |

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 the disease of interest is affected by the hallmarks of aging, their biochemical markers, and the interactions among them; how the disease of interest is 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, institutional review board 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 US population ages, specialty clinician investigators will contribute to an evolution of progress in several areas. Discussions throughout this meeting emphasized the value of interspecialty collaboration in aging research (Table 2). Stimulating interspecialty 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, NIA's Dr. Evan Hadley highlighted some of the areas where he believes specialty clinician investigators are particularly well positioned to contribute to future progress (Table 3). He emphasized that interspecialty 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 the following:

- 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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DEDICATION

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

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Text: Full Report from the U13 Conference Series.