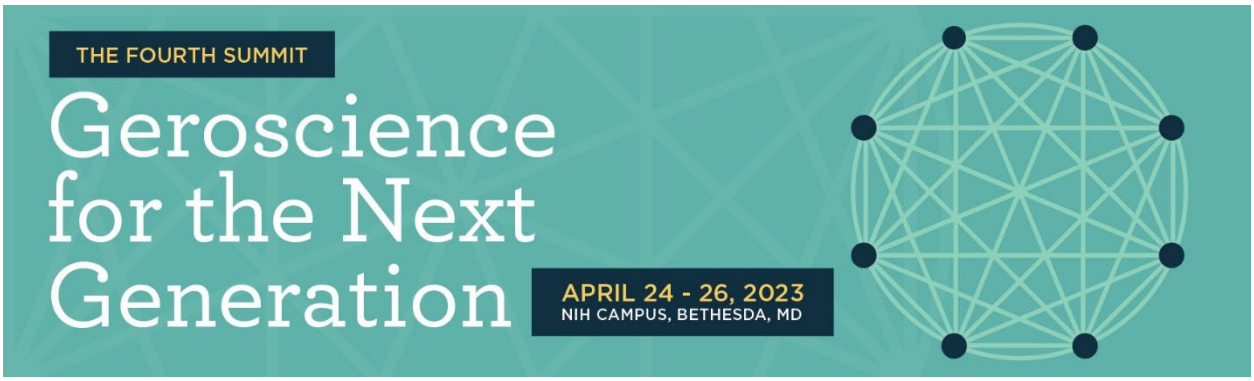

BRIEFING BOOK

The Fourth Summit:
Geroscience for the Next Generation

April 24-26, 2023

NIH Campus
Bethesda, MD

Table of Contents

Welcome from the Organizers

Dear Summit Speakers, Panelists, and Participants,

We are delighted to welcome you to the NIH's ***Fourth Summit: Geroscience for the Next Generation***. This landmark event brings together an outstanding group of researchers and clinicians from across disciplines and career stages, to discuss advances in our understanding of the processes of aging and potential interventions that may slow down or reduce the disease and functional burdens often associated with older age. We are especially pleased to have this opportunity to gather in-person after the COVID-19 hiatus.

The goal of this summit is to explore topics at the forefront of the geroscience field and consider novel ways to advance this rapidly evolving area of research. We especially want to highlight the need to further develop this field in an equitable and inclusive way. Over the course of the next three days we will cover many topics including health disparities in aging, multimorbidities, mathematical modeling of aging, clinical trials in geroscience, and incorporating geroscience advances in the clinic.

The NIH Geroscience Interest Group (GSIG) was instrumental in developing this event, and we would like to thank members from across the NIH who contributed their ideas, time, and effort into making this event a reality. We encourage everyone to visit the GSIG website for important resources and alerts about upcoming events as they become available.

We would like to extend our deepest gratitude to the speakers, panelists, and session facilitators who are taking time from their busy schedules to join us for this event. Lastly, we would like to thank the summit participants, both in-person and virtual, for joining this important conversation. We look forward to gathering your ideas and input on future directions for this field.

All the best,

Ronald Kohanski
Director, Division of Aging Biology
National Institute on Aging (NIA)
National Institutes of Health (NIH)

Luigi Ferrucci
Scientific Director
National Institute on Aging (NIA)
National Institutes of Health (NIH)

Summit Agenda

DAY ONE: Monday, April 24

9:00 a.m. **Framing the Summit: Welcome and Introduction**

Richard J. Hodes
Director
National Institute on Aging
National Institutes of Health

Ronald A. Kohanski
Director, Division of Aging Biology
National Institute on Aging
National Institutes of Health

SESSION I: Biological Determinants of Health and Disparities in Aging

Session Motivation:

Health disparities related to aging are the result of complex biological, environmental, sociocultural, and behavioral factors. Many open questions and gaps in knowledge remain with regard to how these factors impact an individual's health over their life course. The overarching goal of this session is to consider ways in which research on geroscience and the biology of aging can provide important new information about disparities in aging, and ultimately improve the health status of older adults in diverse populations. This session will provide an introduction and overview of health disparity frameworks for research which identify key domains of influence over the life course and how those domains impact individuals and communities at different levels. The session will also include a presentation on the impacts of structural disadvantages on aging related health outcomes, an overview of basic and translational cancer biology research for understanding and reducing cancer health disparities, and perspectives on framing fundamental biological research to expand progress in addressing health disparities of aging.

Session Chair: Roland Thorpe, Jr. Johns Hopkins Bloomberg School of Public Health
Session Facilitator: Jessica Smith, National Institute on Aging

9:30 a.m. **Introduction – Health Disparities Frameworks**

Eliseo J. Pérez-Stable
Director
National Institute on Minority Health and Health Disparities (NIMHD)
National Institutes of Health

10:00 a.m. **Structural Disadvantages and Health Disparities**

Shannon Zenk
Director
National Institute of Nursing Research (NINR)
National Institutes of Health

10:30 a.m. **Health Disparities and Cancers**

Tiffany Wallace
Program Director
Center to Reduce Health Disparities (CRCHD)
National Cancer Institute (NCI)
National Institutes of Health

11:00 a.m. **Addressing Health Disparities in the Biology of Aging**

Stacy Carrington Lawrence
Deputy Director
Division of Aging Biology
National Institute on Aging

11:30 a.m. **Panel Discussion**

Jamaine Davis
Assistant Professor of Biochemistry and Cancer Biology
Meharry Medical College
Vanderbilt University

Roland Thorpe, Jr.
Co-Director DRPH Concentration in Health, Equity, and Social Justice
Professor of Medicine
Johns Hopkins Bloomberg School of Public Health

12:00 p.m. **Lunch Break** ***(on your own)***

SESSION II: Populations for Geroscience: High and Low Burdens of Functional Deficits and Morbidities

Session Motivation:

Populations may be selected to participate in studies based on some special characteristics, such as familial lifespan, early disease or chronic infection, or as a birth cohort independent of other features. These studies reveal differences related to those characteristics, and within-population heterogeneity in apparent rates of aging. Reports of major findings from these well-studied populations will be presented during this session, to emphasize what has been

learned about rates of aging and explore how these might inform biological research on health disparities.

Session Chair: VJ Periyakoil, Stanford University
Session Facilitator: De'Larrian Knight, National Institute on Aging

12:45 p.m. Centenarians - Exceptional Aging

Sofiya Milman
Associate Professor, Department of Medicine
Albert Einstein College of Medicine

1:00 p.m. Aging in Non-Industrialized Contexts: Lessons from Indigenous Populations

Michael Gurven
Professor, Department of Anthropology
Co-Director, Tsimane Life History and Health Project
University of California Santa Barbara (UCSB)

1:15 p.m. HIV and Accelerated Aging

Kristine Erlandson
Associate Professor, Medicine-Infectious Disease
University of Colorado Anschutz Medical Campus

1:30 p.m. Cancer and Accelerated Aging

Mina Sedrak
Associate Professor, Medical Oncology
Deputy Director, Center for Cancer & Aging
City of Hope Comprehensive Cancer Center

1:45 p.m. ICU Survivors and Accelerated Aging

Nathan Brummel
Clinical Associate Professor of Internal Medicine
Physician, Pulmonary Disease
The Ohio State University

2:00 p.m. Panel Discussion

Leon McDougle
Past President
National Medical Association

VJ Periyakoil
Professor of Medicine (Primary Care and Population Health)

Stanford University

2:45 p.m. **Break**

SESSION III: Multimorbidities and Geriatric Syndromes

Session Motivation:

Although geroscience is rooted in the discovery of the biological mechanisms of aging, this emerging field is also intently focused on translation, with the goal of improving health and quality of life for older individuals. Multimorbidity (the co-occurrence of two or more chronic conditions in the same individual) and geriatric syndromes (common health issues observed in older individuals that do not fall into discrete disease categories) are two pressing issues facing geriatricians and their patients. Over the past several years, the identification of the molecular causes and regulatory networks associated with "interesting biological phenomena" (e.g., development) have led to a better understanding of the molecular basis of human physiologic and pathologic conditions – and suggested new strategies to ameliorate deleterious conditions (e.g., diseases, infections, depression, etc.).

This session will explore the idea that both multimorbidity and geriatric syndromes are emergent properties of underlying global instability intrinsically connected with the biology of aging. Thus, multimorbidity and geriatric syndromes should be considered as fundamental and guiding outcomes when developing a "geroscience toolbox" for geriatricians and their patients. The ideal geroscience toolbox would contain ways to quantify aging and methods to improve health and quality of life for older people. Although most basic research with laboratory animals has focused on specific diseases or individual conditions, the geroscience hypothesis postulates that the biology of aging causes multiple diseases and conditions. Thus, a critical question to be addressed in this session is "How can we use other mammals for geroscience research on multimorbidities and geriatric syndromes?" For basic and translational research, is it helpful to model experimental approaches using naturally occurring multimorbidities in other mammals, or do we need common (overlapping) multimorbidities to advance the geroscience concept beyond single diseases of aging?

Session Chair: Alessandro Bartolomucci, University of Minnesota
Session Facilitator: Richard Oppong, National Institute on Aging

3:15 p.m. **Multimorbidities and Geriatric Syndromes in Humans**

Luigi Ferrucci
Scientific Director
National Institute on Aging
National Institutes of Health

3:30 p.m. **Multimorbidities and Geriatric Syndromes in Non-Human Primates**

Ellen Quillen
Assistant Professor, Molecular Medicine

Wake Forest University School of Medicine

3:45 p.m. **Multimorbidities and Geriatric Syndromes in Companion Dogs**

Natasha Olby
The Dr. Kady M. Gjessing and Rahna M. Davidson Distinguished Chair in Gerontology
Professor, Neurology and Neurosurgery
NC State University

4:00 p.m. **Morbidities in Diverse Species**

Caroline Zeiss
Professor of Comparative Medicine and Ophthalmology and Visual Science
Chief of Pathology, Comparative Medicine
Yale University

4:15 p.m. **Panel Discussion**

Noah Snyder-Mackler
Assistant Professor, Center for Evolution & Medicine
Arizona State University

Alessandro Bartolomucci
Professor and Ancel Keys Biomedical Scholar in Physiology and Metabolism
University of Minnesota

5:00 p.m. **End of Summit Day One**

DAY TWO: Tuesday, April 25

9:00 a.m. **Welcome and Opening Remarks – Summit Day Two**

Luigi Ferrucci
Scientific Director
National Institute on Aging
National Institutes of Health

SESSION IV: Methods for Measuring Health

Session Motivation:

This session proposes to explore different methods for "measuring health" across the lifespan. The identification of independent variables for aging and health other than years-since-

birth would represent a major advance for the field of geroscience. Ideally, such measures would serve as quantitative measures of aging (and health) as a dynamic process, and their diagnostic utility would allow people, or other animals, to be grouped by physiological and/or biochemical characteristics. Furthermore, this type of measure should be predictive of changes in response to deleterious or beneficial changes in circumstances (e.g., stressors or therapies).

Session Chair: Lolita Sai Nidadavolu, Johns Hopkins University
Session Facilitator: Michael Duggan, National Institute on Aging

9:15 a.m. **Deficit Accumulation Index**

Susan Howlett
Professor, Department of Pharmacology
Division of Geriatric Medicine
Dalhousie University

9:35 a.m. **Geriatric Assessment with Focus on Mobility**

Thomas Gill
Professor of Medicine, Epidemiology, and Investigative Medicine
Director, Yale Program on Aging
Yale University

9:55 a.m. **Frailty and Resilience**

Jeremy Walston
Raymond and Anna Lublin Professor of Geriatric Medicine & Gerontology
Johns Hopkins University

10:15 a.m. **Multisystem/Multilevel Biomarker Associations with Human Aging**

Eileen Crimmins
AARP Chair in Gerontology
Director, USC/UCLA Center on Biodemography and Population Health
USC Leonard Davis School of Gerontology

10:35 a.m. **The Aging Intervention Pipeline**

Gordon Lithgow
Professor and Vice President, Academic Affairs
Buck Institute for Research on Aging

10:55 a.m. **Panel Discussion**

Lolita Sai Nidadavolu
Assistant Professor of Medicine

Johns Hopkins University

12:00 p.m. **Lunch Break** ***(on your own)***

SESSION V: Mathematical Modeling of Aging and Health for Geroscience

Session Motivation:

A major ongoing challenge for the field of geroscience is how to measure overall health and rates of aging. It is important to know whether conditions in life or interventions slow or accelerate aging, especially in the context of clinical outcomes. Mathematical modeling of aging could inform which parameters to measure to achieve useful information on rates of aging and may indicate which interventions – targeted to specific hallmarks of aging or molecular pathways – may be most effective to change the rate of aging. Modeling aging should illuminate causal connections between environments or therapies and aging outcomes. To date, molecular clocks (e.g., methylation clocks) have been put forward as key metrics for the rate of aging. This session will explore the current state-of-the-science in this area and consider the importance of modeling for basic and translational research.

Session Chair: Chia-Ling Kuo, Senior Biostatistician, UConn Center on Aging
Session Facilitator: Zhaoyuan Gong, National Institute on Aging

1:00 p.m. **Modeling Multiple Aspects of Aging**

Trey Ideker
Division Chief, Medical Genetics
Professor of Bioengineering and Medicine
UC San Diego School of Medicine

1:20 p.m. **Input Parameters to Model Aging**

Dan Ehninger
Group Leader and Professor
German Center for Neurodegenerative Diseases (DZNE)

1:40 p.m. **Selecting and Extracting Features Relevant to Aging**

Alex Zhavoronkov
Founder and CEO
Insilico Medicine

2:00 p.m. **Rejuvenation to Model Aging**

Irina Conboy
Professor of Bioengineering
UC Berkeley

2:20 p.m. **Panel Discussion**

Brian Chen
Chief Science Officer
FOXO Technologies

Alan Cohen
Associate Professor and Chair in Biological Complexity and Healthy Longevity
Department of Environmental Health Sciences
Butler Columbia Aging Center
Mailman School of Public Health
Columbia University

Chia-Ling Kuo
Senior Biostatistician, Connecticut Convergence Institute for Translation in Regenerative Engineering
UConn Center on Aging
University of Connecticut

3:00 p.m. **Break**

SESSION VI: Biomarkers for Geroscience

Session Motivation:

The development of biomarkers for aging and geroscience faces several challenging issues, which include wide variation in any health metric when measured against age; variation in organ and tissue function compared between individuals, and variations in life histories that impact health (at any age) in ways that may be adaptive or maladaptive. The underlying biology of aging studied in other animals will share some important common features with humans, but important species- and strain-specific differences need to be addressed. For example, the identification of biomarkers may be influenced by conditions of accelerated aging – notably in human progeroid syndromes and in laboratory animals genetically engineered to accumulate deficits at accelerated rates. Conversely, interventions that yield improved health are expected to be reported in biomarkers of aging. Biomarkers are important research tools for geroscience, but ultimately need to have clinical utility; their complexity should be handled to be on par or close to biomarkers for other clinical conditions encountered by geriatricians.

Session Chair: Jamie Justice, Wake Forest University
Session Facilitator: Dimitrios Tsitsipatis, National Institute on Aging

3:15 p.m. **Fundamental Considerations for Biomarkers of Aging**

Stephen Kritchevsky
Professor, Gerontology and Geriatric Medicine
Wake Forest University

3:30 p.m. **Biomarkers from the Dunedin Study**

Daniel Belsky
Associate Professor, Epidemiology
Columbia University

3:45 p.m. **Organ System-Specific Biomarkers of Aging**

Albert Higgins-Chen
Assistant Professor, Department of Psychiatry
Yale University

4:00 p.m. **Bridging Biomarkers of Aging from Model Organisms to Humans**

Martin Picard
Associate Professor of Behavioral Medicine
Columbia University

4:15 p.m. **Mouse Models to Study Biomarkers for Geroscience**

Alice Kane
Assistant Professor
Institute for Systems Biology

4:30 p.m. **Panel Discussion**

Nathan Basisty
Investigator and Head of the Translational Geroproteomics Unit
National Institute on Aging
National Institutes of Health

Jamie Justice
Assistant Professor, Gerontology and Geriatric Medicine
Wake Forest University School of Medicine

Lauren Gaydosh
Assistant Professor of Sociology
The University of Texas at Austin

5:15 p.m. **End of Summit Day Two**

DAY THREE: Wednesday, April 26

9:00 a.m. **Welcome and Opening Remarks – Summit Day Three**

Ronald A. Kohanski
Director, Division of Aging Biology
National Institute on Aging
National Institutes of Health

SESSION VII: Geroscience as Medicine in the Clinic and Community

Session Motivation:

The goal of this session is to advance the tenets of geroscience by improving crosstalk among biologists, clinicians, patients and caregivers, as a way to positively impact the care of older adults. Currently, there is not a universally accepted meaning of the concept of 'geroscience' by clinicians, which likely adds to underuse and misinterpretation of the term. Accordingly, clinicians and patients have yet to incorporate geroscience as a clinically helpful tool for predicting health outcomes, attempting strategies for prevention, enhancing resilience, and treating disease and/or geriatric syndromes. Speakers will highlight four areas in which geroscience could advance care of older adults, with the goals to facilitate communication among researchers and providers and their patients, and to improve understanding and integration of geroscience in their clinical practice or patient care.

Session Chair: Debra Whitman, EVP and Chief Public Policy Officer, AARP
Session Facilitator: Vernon Kennedy, National Institute on Aging

9:20 a.m. **Geroscience in Prediction**

Heather Whitson
Professor of Medicine
Duke University

9:40 a.m. **Geroscience in Treatment**

Robert Pignolo
Professor of Medicine
Mayo Clinic

10:00 a.m. **Geroscience in Management**

Daniel Forman
Chair, Section of Geriatric Cardiology
University of Pittsburgh School of Medicine

10:20 a.m. **Training Translational Geroscientists and Geroscience-Savvy Clinicians**

George Kuchel
Travelers Chair in Geriatrics and Gerontology
Professor of Medicine
Director, UConn Center on Aging and UConn Pepper Center
University of Connecticut

10:40 a.m. **Panel Discussion**

Iman Al-Naggar
Assistant Professor
University of Connecticut

Daniel Parker
Assistant Professor, Medicine and Neurology
Senior Fellow of the Center for the Study of Aging and Human Development
Duke University

Erwin Tan
Director of Thought Leadership
AARP

11:45 a.m. **Lunch Break *(on your own)***

SESSION VIII: Geroscience Clinical Trials

Session Motivation:

Geroscience clinical trials are based on the geroscience hypothesis – interventions against again affect multiple conditions of aging. To test anti-aging therapeutics, there appear to be at least two routes: (1) Test one therapeutic (or combination) against multiple conditions in a series of trials, or (2) Test for effects against multiple geriatric conditions and diseases but remain agnostic as to which those are. It is important to structure trials to be inclusive and incorporate social determinants of health among the parameters. This session aims to explore the challenges associated with developing and carrying out a geroscience-based clinical trial, and speakers will highlight potential paths forward.

Session Chair: Jennifer Ailshire, USC
Session Facilitator: Daisy Zamora, National Institute on Aging

12:45 p.m. **Translational Geroscience Network: Considerations of Parameters and Populations for Geroscience Clinical Trials**

James Kirkland
Professor, General Internal Medicine
Geriatrician and Internist

Mayo Clinic

1:00 p.m. **Primary and Secondary Outcomes of a Geroscience Trial**

Sara Espinoza
Associate Professor of Medicine
Director, San Antonio Geriatric Research, Education, and Clinical Center
UT Health San Antonio

1:15 p.m. **Geroscience Trial Desgn for Multimorbidity and Frailty**

Ilaria Bellantono
Professor of Musculoskeletal Aging
Department of Oncology and Metabolism
The University of Sheffield

1:30 p.m. **Geroscience Trial Design for Health Disparities**

Heather Allore
Professor of Medicine (Geriatrics) and of Biostatistics
Leader, Data Management and Statistics Core
Yale University School of Medicine

1:45 p.m. **Panel Discussion**

Jennifer Ailshire
Associate Professor of Gerontology and Sociology
Assistant Dean of International Programs and Global Initiatives
USC

2:30 p.m. **Break**

SESSION IX: Looking Forward: Where Do We Go from Here?

Session Motivation:

The goal of this session will be to explore what is needed to form productive new collaborations to advance geroscience. Session facilitators will provide brief summaries of each session along with the key takeaways, and their ideas for next steps to move the field forward.

Session Chair: Ronald Kohanski, National Institute on Aging

3:00 p.m. **Summaries and Key Takeaways by Session (7 minutes each)**

Session 1 Facilitator: Jessica Smith, National Institute on Aging

Session 2 Facilitator: De'Larrian Knight, National Institute on Aging

Session 3 Facilitator: Richard Oppong, National Institute on Aging

Session 4 Facilitator: Michael Duggan, National Institute on Aging

Session 5 Facilitator: Zhaoyuan Gong, National Institute on Aging

Session 6 Facilitator: Dimitrios Tsitsipatis, National Institute on Aging

Session 7 Facilitator: Vernon Kennedy, National Institute on Aging

Session 8 Facilitator: Daisy Zamora, National Institute on Aging

4:00 p.m. **Final Comments and Wrap-Up**

Ronald A. Kohanski
Director, Division of Aging Biology
National Institute on Aging
National Institutes of Health

4:15 p.m. **Summit Adjourns**

Abstracts

Listed in alphabetical order by speaker's last name.

Heather Allore

Geroscience Trial Design for Health Disparities (Session VIII)

This presentation will overview key elements of clinical trial design embedding health equity into the design and analysis. We introduce the deleterious effects of age discrimination and negative stereotypes, equipoise, health equity, key elements of randomization, and steps to build health equity into the design of a clinical trial as developed by the National Institute on Aging (NIA) IMbedded Pragmatic Alzheimer's Disease (AD) and AD-Related Dementias (AD/ADRD) Clinical Trials (IMPACT) Collaboratory grant (U54AG063546).

Daniel Belsky

Biomarkers from the Dunedin Study (Session VI)

Development of biomarkers to track the pace and progress of biological aging is a priority for geroscience. Current state-of-the-art biomarkers are derived from data-mining methods that integrate dozens to hundreds of molecular measurements into algorithms that predict healthspan and lifespan. Initial efforts focused on modeling biological differences between older and younger individuals. A second generation of methods focus on prediction of differences in survival. Here, we introduce a third approach, focused on modeling the rate of decline in system integrity within individuals as they age, what we call the Pace of Aging. A DNA methylation biomarker of Pace of Aging, DunedinPACE, can be computed from a single blood test. DunedinPACE is predictive of disease, disability, and mortality, is accelerated by early-life adversity, and is slowed by calorie restriction. Pace of Aging and DunedinPACE represent a new approach to aging biomarker development to accelerate intervention testing at the frontiers of geroscience.

Nathan Brummel

ICU Survivors and Accelerated Aging (Session II)

The number of survivors of critical illness has doubled over the past 20 years. This good news regarding survivorship from once fatal critical illness is tempered by knowledge that many survivors suffer with newly acquired or worsened disability in activities of daily living and impairments in cognitive, physical, and mental health function. Collectively, these syndromes are referred to as the Post-Intensive Care Syndrome. Because 2 out of every 3 patients admitted to an ICU is over the age of 65 years, older adults bear the brunt of these outcomes. Nevertheless, younger survivors of critical illness demonstrate higher rates of classical syndromes of aging than would be anticipated by age alone. This talk will review age-related syndromes in both older and younger survivors of critical illness that suggest critical illness may lead to accelerated aging, describe methodological issues related to the study of the aging-related syndromes in emergent critical illness, and explore early data that could link critical illness with alterations in pathways of biological aging.

Eileen Crimmins and Eric Klopack

Multisystem/Multilevel Biomarker Associations with Human Aging (Session IV)

Geroscience research suggests aging is a coordinated physiological decline occurring in multiple systems and at multiple biological levels. However, it is largely unknown how molecular and cellular biological aging and specific systemic aging co-occur and influence one another to affect

mortality and other age-related health outcomes. There is also emerging interest in understanding how social exposures may differentially accelerate decline in individual systems. We utilize data from the Health and Retirement Study, a nationally representative sample of about 4000 US adults over age 55. We used a machine learning approach - eXtreme Gradient Boosting (xgboost) - in a training subsample to create estimates of mortality risk based on sets of biomarkers representing biological systems (e.g., brain and nervous system, adaptive immune system, cardiovascular system, renal system etc.) as well as cellular aging (using epigenetic clocks and telomere length). These models were used to generate scores for mortality risk based on biomarkers of each system (e.g., renal functioning using BUN, creatinine, and cystatin C). Mortality was regressed on these scores in a testing subsample to assess the relative impact of each system on mortality risk. Results suggest cellular aging, cardiovascular aging, and respiratory poor function contribute significantly to mortality risk. Aging of these systems also partially mediates the mortality risk associated with age, race/ethnicity, sex, and education. These results suggest aging of specific systems may be differentially affected by sociodemographic exposures and may differentially contribute to mortality risk. This research may help guide interventions focused on reducing inequalities in mortality risk by identifying health risks that would have the greatest impact on mortality at the population level.

Dan Ehninger

Input Parameters to Model Aging (Session V)

Studies focused on identifying factors that regulate natural lifespan heavily inform current concepts on the biology of aging. However, using lifespan as the sole measure to represent aging may have limited value as it could be restricted by specific sets of pathologies, rather than general physiological decline. We used deep phenotyping to define, on a large scale, age-sensitive phenotypes (ASPs), including their lifetime trajectories, across tissues and organ systems in mice. Collectively, these ASPs define a multi-dimensional representation of aging that can be used to test putative anti-aging interventions (PAAIs) against. We used this approach to assess key pro-longevity interventions for their potential to counter aging in mice. Unlike many previous studies, we incorporated young treated groups of animals in our study design that were subjected to PAAIs before the onset of detectable age-dependent change in ASPs. Many PAAI effects influenced phenotypes long before the onset of detectable age-dependent change in ASPs. Hence, these PAAIs did not alter the rate of aging-associated phenotypic change, indicating limited effects on aging. These observations highlight the importance of establishing lifetime ASP trajectories and excluding age-independent treatment effects when evaluating PAAIs for the potential to counter aging.

Kristine Erlandson

HIV and Accelerated Aging (Session II)

A majority of people with HIV (PWH) in the US and Europe are now aged 50 and older, with a rapid increase in the number of older adults in low and middle-income countries expected over the next decade. PWH have experienced a drastic improvement in life expectancy, but with a concomitant increase in comorbidity burden and development of geriatric syndromes. These comorbidities and syndromes appear to develop at an accelerated or accentuated rate (or both), and are likely the result of numerous underlying factors including the hallmarks or pillars of aging. As such, a geroscience approach to therapeutic considerations may have particular relevance among

PWH: an intervention targeting multiple aging pathways may have a greater impact on shifting the "normal" aging curve than among the general population.

Luigi Ferrucci

Multimorbidities and Geriatric Syndromes in Humans (Session III)

The population is aging steadily around the world with no sign of this process slowing down. The extension of life occurs both in the part of life in good health and of the life lived with chronic diseases and functional limitations. Paradoxically, the length of ill life is progressively longer in the country that invest more in health care and in those with high income. At younger age, both black men and women have more severe multimorbidity than white men while at older age, older black men and women have less multimorbidity than their counterparts. These data suggest that the quality of care and socio-economic status are important factors that affect multimorbidity in olde age. The progressive reduction of mortality that occurred in the older part of the population over the last decades was mostly due to the decline of CVD and, to a less extent, cancer mortality. However, the diseases that typically affect older persons with multimorbidity and disability, such as chronic pulmonary or kidney diseases, are not declining and, in fact, tends to increase. The percentage of people with multiple concurring causes of death in the death certificate is increasing. Recent data suggest that at the end of disease-free life, disease tend to accumulate in cluster, meaning that given the same demographics, those individuals who have one disease are more likely to develop a second compared to those who have no diseases. In general the more severe the multimorbidity the higher the risk of developing further diseases. A substantial role on the health of the individuals only occurs with the emergence sign and symptom of the first disease. Therefore, the quality of health care only expands the period of life characterized by diseases and disability. This is in part why those are privileged live longer when ill and/or disabled and develop a more severe multimorbidity. The Geroscience hypothesis by postulating that the biology of aging is the root cause of most diseases and functional limitations in older age offers an alternative approach that may reconciliate health care with public health. If the pace of biological aging can be modulated, then most diseases and disability can be prevented or delayed at a time when they are not clinically manifest, therefore expanding the period of life free of disease and realizing the dream of compression of morbidity. Deranged resilience mechanisms lead to accelerated aging, which based on the specific genetic susceptibility and the previous exposures emerge clinically as specific diseases and, when the damage accumulation is even higher, as geriatric syndromes and frailty. Evidence is accumulating that this hypothesis is correct. For example, there is already evidence that mitochondrial function affect mobility loss with aging, and this association is explained by the negative effect of mitochondrial impairment on sarcopenia. Also, muscle mitochondrial function assessed by P31 spectroscopy is associated with accumulation of beta-amyloid assessed by PET, blood biomarkers of neurodegenerative diseases as well as mild cognitive impairment and dementia.

Daniel Forman

Geroscience in Management (Session VII)

Contemporary healthcare is largely oriented to disease-specific pathophysiologic challenges, with comprehensive organization oriented to diagnosis, prognosis, and management focused on each disease. Many stakeholders (e.g., industry leaders, administrators and providers) are invested in this paradigm of care. In contrast, Geroscience shifts emphasis to healthspan, wherein diseases and age-related impairments (e.g., frailty, disability) can be largely eliminated or pared down if

aging hallmarks are mitigated. Yet, rather than anticipating a complete transformation of the current models of care, it seems more likely that Geroscience will enrich existing healthcare approaches. In this talk, I will focus particularly on cardiovascular disease, and the evolving enrichment of cardiovascular pathophysiological understandings and management with Geroscientific perspectives. In particular, the value of prevention is elevated by Geroscience, as rationale for exercise, diet, and other dimensions of basic self-care are reframed as Gerotherapeutics, with key value to augment resilience to Aging Hallmarks over a lifetime.

Thomas Gill

Geriatric Assessment with Focus on Mobility (Session IV)

Mobility is a central element of geriatric assessment. Disability in mobility is a highly prevalent public health problem that profoundly affects how a person "lives, functions and feels". Mobility disability that is attributable to aging and chronic diseases meets the United States Food and Drug Administration's (FDA) definition of an indication and, hence, is an important focus for the development and testing of gerotherapeutic agents. Mobility can be assessed reliably by valid self-reported and performance-based measures. These measures of disability and functional limitations, respectively, are being reverse translated to comparable measures in rodents and nonhuman primates, allowing geroscience discoveries to be translated across species.

Michael Gurven

Aging in Non-Industrialized Contexts: Lessons from Indigenous Populations (Session II)

The majority of aging studies target urban citizens of the Global North. While indigenous populations living in adverse, resource-poor conditions show worse health than their non-indigenous counterparts, indigenous groups still practicing traditional lifeways (but outside of the Global North) offer a rare opportunity to study healthy aging. To this end, I present several lessons from the Tsimane Health and Life History Project, a longitudinal study of aging among Bolivian forager-horticulturalists. The Tsimane show little evidence of heart disease or dementia, and lack several other common chronic diseases of aging. Broader sampling that includes diverse populations spanning distinct environments and lifestyles not only addresses concerns about health equity, but will improve our understanding of physiological aging and its clinical manifestations.

Albert Higgins-Chen

Organ System-Specific Biomarkers of Aging (Session VI)

A variety of aging biomarkers have been proposed that summarize age-related changes, are associated with risk factors for pathological aging, and can predict the incidence of future age-related disease. Most commonly, aging biomarkers are trained to predict chronological age, mortality (time-to-death), or the longitudinal pace of phenotypic aging. However, these biomarkers summarize aging in a single “biological age” number, effectively treating aging as a single unidimensional process. Multiple recent studies have introduced organ system-specific aging biomarkers, where many biological age values corresponding to different organ systems are reported for any given individual. However, these studies vary markedly in their approaches to incorporating organ system-specificity in their biomarkers. Here, we describe how each of these approaches modifies the typical process of training aging biomarkers and then discuss important considerations for defining system specificity. We also discuss Systems Age, a novel set of epigenetic clocks that utilize only blood DNA methylation data to predict aging in 11 organ systems with high system specificity. Ultimately, the clinical and scientific utility of organ system-

specific biomarkers will depend on whether they add value over traditional clinical risk models or unidimensional aging biomarkers, whether they are practical and cost-effective, and whether they can serve as surrogate biomarkers in geroscience-based interventions.

Susan Howlett

Deficit Accumulation Index (Session IV)

The concept of frailty captures variability in risk of adverse health outcomes in people of the same chronological age. Frailty can be quantified clinically with different instruments including the commonly used frailty index (FI). An FI considers many health deficits (>30) across diverse bodily systems and counts the number of deficits present in an individual as a fraction of the total number considered. Frailty is then scored between 0 and 1, where higher scores denote greater frailty. Importantly, this instrument has been reverse-translated to quantify frailty in aging animals. The FI has signature features that have been demonstrated in both humans and animal models including: a) deficits accumulate at a rate of approximately 3% per year; b) there is a limit to frailty (FI score ≈0.6) beyond which additional deficits are not survivable; c) females have higher FI scores than males; and d) high FI scores predict mortality. The preclinical FI tool has many different applications in a research setting. For example, it has been used to demonstrate that interventions can attenuate (e.g. geroprotectors, exercise) or exacerbate (e.g. radiation exposure, polypharmacy) frailty in aging mouse models. In addition, studies in aging mice provided proof-of-concept that an FI based solely on routinely collected clinical laboratory data (known as the FI-Lab) can be used to quantify the degree of frailty in people. The development of an FI that can quantify frailty in humans and mouse models is an important advance to facilitate a molecular understanding of frailty and how interventions can modify frailty to affect healthspan.

Alice Kane

Mouse Models to Study Biomarkers for Geroscience (Session VI)

Biomarkers, or 'clocks', to predict age based on molecular measures including DNA methylation and metabolomics have been developed for both mice and humans. The difference between predicted age with these clocks and actual age is assumed to provide information about health status, or biological age. More recently, there has been a focus on the development of clocks that directly predict biological age by training models to predict composite health measures such as mortality risk or blood test results, rather than chronological age alone. I will present data on the first of such clocks for mice, trained to predict either frailty index, or phenotypic age (chronological age adjusted for frailty and mortality risk). We longitudinally tracked a large cohort of male and female C57BL/6 mice until death, regularly collecting blood for DNA methylation analysis, plasma for metabolomics and conducting frailty assessments with the mouse clinical frailty index. Using elastic net regression with leave-one-out cross validation, we developed clocks based on either DNA methylation data, metabolomics or the combination of both, that accurately predict frailty index and phenotypic age. The correlation coefficients, standard errors and p values are comparable to previous mouse clocks for the prediction of age. We also explored the specific CpG sites and metabolites that are most associated with each of our outcomes, and found both overlapping and distinct features. These clocks will be valuable tools for aging and intervention studies in mice.

James Kirkland

Translational Geroscience Network: Considerations of Parameters and Populations for Geroscience Clinical Trials (Session VIII)

The Hypothesis of the Translational Geroscience Network (TGN; R33AG 61456) is that clinical interventions targeting fundamental mechanisms of aging can delay, prevent, or treat age- related diseases and disabilities as a group, instead of one at a time. The TGN provides advice/ support for over 40 clinical trials of agents and lifestyle interventions targeting fundamental aging processes across the lifespan that are underway, with more planned. The trials range from testing interventions targeting aging processes (senolytics, metformin, rapamycin, NAD precursors, anti-inflammatories, lifestyle interventions, and others) for such conditions as the accelerated aging-like state that can occur in survivors of childhood or adult cancers, Alzheimer's disease, mild cognitive impairment, acute complications of COVID-19, Longhauler and chronic HIV syndromes, frailty in the elderly, osteoarthritis, are-related osteoporosis, eye diseases, diabetes/ obesity, enhancing function of organs from older donors to allow use in transplantation, complications of space travel, and others. The TGH is developing Gerodiagnostics (composites of "biomarkers" of fundamental aging processes for predicting or diagnosing conditions contributed to by these processes that can predict which intervention or combinations of interventions to use and when, monitor responses to these interventions, act as surrogate endpoints for clinical trials, and eventually be translatable to clinical practice), discover further mechanisms that can be targeted to prevent or treat multiple disorders and diseases, and speed translation of interventions from bench to bedside.

The TGN provides: 1) administrative and regulatory support (consent templates, IRB and FDA documentation, investigator brochures/ interinstitutional agreements, sources for manufacturing, stability testing, etc.) for NIH-funded and other observational and Phase 0, 1, and 2 trials; 2) data analysis support; 3) analysis of body fluids and other biospecimens from across TGN clinical trials through the Facility for Geroscience Analysis (>150 assays of multiple fundamental aging processes); and 4) biobanking of annotated samples from across the trials to allow reverse translation from bedside to bench. The founding institutions of the TGN include the University of Texas Health Sciences Center at San Antonio, Mayo Clinic, Wake Forest University, and the Universities of Connecticut, Michigan, Minnesota, Harvard, and Johns Hopkins Universities. Additional institutions with investigators working through the TGN include St. Jude Children's Cancer Hospital, Northwestern University, City of Hope, and the Steadman-Phillipon Orthopedic Center, among others, including partners in Europe.

Stephen Kritchevsky

Fundamental Considerations for Biomarkers of Aging (Session VI)

A goal of geroscience is to increase health span. Clinical trials of interventions targeting health span outcomes such as advancing multi-morbidity or disability-free survival are lengthy and expensive. Thus, there is a strong interest in identifying biomarkers that change over a short period of time to guide intervention development. There are number of criteria that must be met for biomarkers to fulfill this role, and so far, only a handful of markers meet even minimal criteria. Ultimately, trials of interventions that successfully improve health span are needed to serve as anchors to fully validate biomarkers as surrogate measures of health span.

George Kuchel

Training Translational Geroscientists and Geroscience-Savvy Clinicians (Session VII)

Aging is by far the main risk factor for chronic conditions that jointly account for most morbidity, mortality, and health care costs. Geroscience-guided therapies seeking to alleviate such disorders as a group by targeting basic aging processes are now entering early stage clinical trials. The discovery, validation, and implementation into routine clinical care of such transformational therapies will require the creation of a robust and diverse geroscience workforce and training pipeline, together with the training of clinicians skilled in the appropriate use of such therapies.

Education and training in geroscience must closely accompany rapid research progress in the field, while also respecting significant differences in needs amongst learners from varied backgrounds. For example, individuals wishing to pursue research careers focused on translational geroscience must complete training which will ensure that they gain selected additional competencies in four different content domains (general clinical research, geriatric medicine, geriatric clinical research, and geroscience) to help complement their existing skills. Conversely, efforts to provide a first introduction in geroscience to early stage research trainees will require a significantly different emphasis in terms of educational content and format. Finally, clinicians likely to prescribe such therapies in the future will require training in geroscience therapeutics, which will become especially urgent once specific treatment strategies are approved by the FDA.

This presentation will also provide an update on the NIA Geroscience Education and Training (GET) Network (R25AG073119), and its efforts to create a training pipeline in translational geroscience research through the establishment of a Certificate in Geroscience Research Program, together with work to develop shared geroscience curricula and educational materials for early stage PhD students, first year medical students, and geriatric fellows. Finally, efforts to more broadly disseminate high quality geroscience information to practicing clinicians, as well as the broader public will also be discussed.

Leon McDougle

Holistic Geroscience Approaches and Intersectional Dimensions of Health and Wellbeing (Session II)

The COVID-19 pandemic served as a stress test that was failed by many communities made vulnerable by geography, disability, racism, bias, and socioeconomic status. Developing holistic geroscience approaches to address intersectional dimensions of health and wellbeing may lower burdens of functional deficits and morbidities of aging.

Objectives:

1. Describe importance of the 5 A's of ACCESS (availability, accessibility, accommodation, affordability, and acceptability) in fulfilling the promise of translational research for older persons.
2. Describe Whole Health and Whole PERSON Health Score and potential benefits for aging and wellbeing.
3. Describe weathering and its impact on minoritized and marginalized communities.

Sofiya Milman

Centenarians - Exceptional Aging (Session II)

Aging is a major risk factor for most chronic diseases that afflict older adults, including cancer, diabetes, cardiovascular disease and Alzheimer's disease. Yet centenarians, despite their advanced age, delay the onset of these conditions by several decades and often escape from them altogether. This feature makes centenarians an ideal cohort for the study of biological mechanisms that delay aging. Centenarian cohorts have contributed to discoveries of genetic and biochemical factors that contribute to healthy longevity. Moreover, discoveries made directly in human cohorts with exceptional longevity have the potential to accelerate the development of gerotherapeutics.

Mina Sendrak

Cancer and Accelerated Aging (Session II)

Advances in cancer treatment have led to a significant decline in cancer-related mortality and a dramatic rise in the number of cancer survivors. More and more survivors are now living 10-15+ years after their cancer diagnosis. However, for many of these survivors, the burden of other chronic conditions that they had prior to their cancer diagnosis doesn't go away after cancer and its treatment. This disease burden, in fact, increases in intensity and frequency in cancer survivors as compared to individuals without cancer. One thought is that cancer and cancer treatment disrupt fundamental aging processes. Disruption of fundamental aging processes in the context of cancer and cancer treatment may drive increased premature or accelerated morbidity and mortality of cancer survivors. Hence, to reduce the evolving burden of morbidity and mortality in cancer survivors, there is a need to understand the dynamic relationship between cancer and aging. Understanding the dynamic interplay between aging and cancer is critical to set the stage for precision medicine – the right treatment, for the right patient, at the right time - across the entire cancer care continuum, from prevention to survivorship. In this talk, Dr. Mina Sedrak will discuss research at the interface of aging and cancer, highlighting his work to improve patient-centered outcomes in oncology by targeting the biology and heterogeneity of aging.

Caroline Zeiss

Morbidities in Diverse Species (Session III)

Animals provide a rich source of mechanistic insight into aging biology that could be harnessed to expand healthspan. How best we can use animals to translate these fundamental discoveries to the clinic? The purpose of this talk is to provide a comparative overview of key animal models used in geroscience – mice, non-human primates, dogs and unusual species such as the naked mole rat. The overall goal is to explore how these could be used in preclinical studies that ultimately translate to humans. Key concepts include 1. developing a shared vocabulary of measurable components of healthspan across species that can be used to assess efficacy, 2. identifying reproducible mechanistic relationships that translate across species, and 3. developing validated biomarkers across species that permit longitudinal assessment of interventions in vivo.

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Additional Resources

NIH Geroscience Interest Group Website:
https://www.nia.nih.gov/gsig

Past NIH Geroscience Summit Publications/Reports:

- 2013 Geroscience Summit
- 2016 Geroscience Summit
- 2019 Geroscience Summit

Preview Editorial of 2023 Summit:
Gustavo Duque, PhD, FGSA, Lewis Lipsitz, MD, FGSA, Luigi Ferrucci, MD,PhD, Siobhan Addie, PhD, Stacy Carrington-Lawrence, PhD, Ronald Kohanski, PhD, Geroscience for the Next Chapter of Medicine, *The Journals of Gerontology: Series A*, 2023;, glad083, https://doi.org/10.1093/gerona/glad083.