

Workshop on the Role of the Behavioral and Social Sciences in the Geroscience Agenda

Bridging Biological and Social Hallmarks of Aging

National Institute on Aging

Division of Aging Biology

Division of Behavioral and Social Research

October 31, 2022

Virtual Meeting

Revised February 8, 2023



This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the National Institute on Aging (NIA). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of NIA. Contributions to this meeting summary by the following individuals is gratefully acknowledged: Amy Kiefer, Dana Carluccio, Irina M. Conboy, Eileen M. Crimmins, Ana Maria Cuervo, Jessica Faul, Vadim N. Gladyshev, Chandra Keller, Tom Kirkwood, Ron Kohanski, George Kuchel, Nathan K. Le Brasseur, Anna Marsland, Terrie Moffitt, Lis Nielsen, Daniel Promislow, Marissa Schafer, Nancy Tuveson

Acronym Definitions

BLSA	Baltimore Longitudinal Study of Aging
BSR	Division of Behavioral and Social Research
CALERIE	Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy
CMA	chaperone-mediated autophagy
DAB	Division of Aging Biology
DEA	Division of Extramural Activities
DN	Division of Neuroscience
DunedinPACE	Dunedin Pace of Aging Calculated from the Epigenome
LSS	Longitudinal Studies Section
mtDNAcn	mitochondrial DNA copy number
NIA	National Institute on Aging
NIH	National Institutes of Health
SASP	Senescence-Associated Secretory Phenotype
SES	socioeconomic status
WHO	World Health Organization

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Executive Summary

On October 31, 2022, the National Institute on Aging (NIA) Division of Behavioral and Social Research (BSR) and Division of Aging Biology (DAB) convened the first in a series of three workshops on Geroscience and the social hallmarks of aging. Geroscience is the study of ways to impact health at older ages, based on discoveries in the basic biological mechanisms of aging. The long-term goal of this workshop series is to identify research gaps and opportunities to facilitate and incorporate a life course perspective on behavioral and social drivers of aging processes in Geroscience. This effort would meld research on behavioral and social processes (including social determinants of health) with the biological mechanisms and hallmarks of aging and advance the discovery and validation of biomarkers of aging. The goals of this first workshop were to set the stage for future discussions, to develop shared understanding and terminology, and to review existing research on the biological and social hallmarks of aging as potential guides and impetus for collaborations.

The long-term goal of this series is to bring together researchers studying the hallmarks of aging from biological or social perspectives to consider several foundational questions: (1) differences in terminology across these perspectives; (2) mutual research needs and potential cross-field contributions; (3) their field's dominant causal frameworks and methods; and (4) potential convergence of causal models of resilience and reversibility/plasticity/compensation in biology and behavioral and social science. The workshop identified several key areas for an expanded Geroscience agenda.

Emerging Themes

Address Health Disparities in Aging

Key goals for behavioral and social research are to understand the structural, social, and behavioral drivers of health disparities at older ages and to determine how these factors influence the aging-related biological processes presumed to underly these disparities. By illuminating how social and biological processes interact to affect aging trajectories throughout the life course, this research will help inform interventions to slow aging and mitigate disparities in healthspan and life expectancy.

Research Gaps and Opportunities

1. Validate existing measures of biological aging in additional racial and ethnic groups.
2. Employ validated measures of biological aging in humans to assess the impact of multiple social determinants of health, including structural racism and discrimination, on aging trajectories throughout the life course.
3. Consider historical cohort effects on health disparities in aging, such as exposure to segregation and redlining.
4. Assess how potential mediators of the impact of social factors, including psychological, physiological, and behavioral mechanisms, affect biological aging.

Incorporate a Life Course Approach

Numerous studies demonstrate that early life adversity can have profound effects on rates of aging and longevity. Longitudinal biosocial surveys offer opportunities to study how social and behavioral processes impact biological processes related to aging and chronic diseases of aging over the life span.

Research Gaps and Opportunities

1. Build bridges between Geroscience and research on developmental origins of health and disease to understand how factors in early life contribute to variation in when the aging process begins. Such efforts may involve following up on cohorts assessed before adulthood and dialogue between Developmental Origins of Health and Disease (DOHaD) and aging researchers to consider what developmental predictors and trajectories should be assessed to inform studies of individual and group differences in aging processes.
2. Incorporate measures of biological aging into studies of large epidemiological human cohorts to determine potential to influence aging acutely or prospectively, and to help inform the timing of interventions.
3. Examine how measures of resilience can help discriminate between adaptive and maladaptive changes.

Expand and Refine Biological Measures of Aging and Stress Resilience

Numerous aging biomarkers assessing multiple physiological systems exist, and more are in development. Some of these biomarkers have been suggested to predict age-related outcomes such as multimorbidity and mortality in humans. In addition, human aging is known to be nonlinear and have healthy plateaus, as well as exponential curves. Lastly, correspondence with aging and health outcomes does not necessarily imply a causal relationship: changes in biomarkers can lack functional significance or represent adaptive responses to accumulating age-related damage.

The breakdown of resilience may be an indicator of aging. Measures of biological and functional resilience may therefore provide a way to assess changes in the rate of aging and, assuming such measures assess causal drivers of aging, may provide appropriate targets for intervention research. Important additional considerations are that bodily systems do not age at the same rate within an individual, individuals in populations do not age at the same rate, diverse populations have not been adequately incorporated in the development and validation of biomarkers of aging, and many age-related biomarkers do not correlate strongly with one another.

Research Gaps and Opportunities

1. Conduct longitudinal research to help elucidate how different aspects of human biological aging relate to one another and to functional and health outcomes.
2. Identify which measures of biological aging are appropriate for large-scale population-based longitudinal studies and which are more appropriate for smaller scale longitudinal human biobehavioral studies.

3. Develop a battery of measures of human aging and biological or functional resilience that assesses a range of bodily systems and aspects of biological resilience, that is, how these systems alter in response to stress and whether they return to homeostasis.
4. Study how biological resilience changes with age and varies among aging individuals.
5. Determine how physiological and psychological resilience to stress corresponds to measures of biological resilience over time.
6. Determine the effects of macro-level exposures such as climate change on biological resilience to age-imposed changes (in demographically and socioeconomically diverse regions).

Conduct Intervention Studies to Determine the Causal Impact of Social Factors

Numerous past and ongoing behavioral and social intervention studies provide opportunities to assess the impacts of these interventions on measures of biological age and to determine whether changes in biomarkers correspond to observed changes in health.

Research Gaps and Opportunities

1. Include measures of biological aging in recent and upcoming social and behavioral interventions to determine whether these measures are malleable and potential mediators of social determinants of aging.
2. Using evidence from longitudinal studies, identify biological and functional signatures of both adaptive and maladaptive responses to behavioral, structural, and social exposures and stressors, including early-life adverse events.

Meeting Summary

Opening Remarks

Lis Nielsen, PhD, NIA

This workshop series aims to integrate social research on aging-related health disparities with biological frameworks and measures related to Geroscience—the study of how to slow aging to prevent or forestall the onset of many chronic diseases and extend the healthspan. As the first of at least three formal conversations, this workshop focused on initiating a transdisciplinary dialogue with a shared vocabulary and understanding of conceptual frameworks, guiding hypotheses, and measurement approaches. An overarching goal of these formal conversations is the creation of an informal network of scholars who are motivated to more closely align social and biological frameworks and approaches for studying the drivers of aging.

Behavioral and social research on aging focuses on understanding how biological, behavioral, social, and environmental processes interact to shape health and to inform interventions. A core component of this research is the study of social determinants of health and structural drivers of health inequities. To understand and potentially ameliorate stark disparities in healthspan and longevity, BSR takes a life course perspective that considers the early origins of disease. To this end, BSR has invested in numerous deeply phenotyped longitudinal studies and longitudinal biosocial surveys that span the full life course and assess a wide range of social, environmental, biological, and clinical aspects of health and aging. These studies may provide avenues for understanding the aging trajectory throughout the life course and determining when interventions might have the largest impact on aging.

Session 1: Geriatric and Life Course Perspectives on Aging

Moderator: George Kuchel, MD, University of Connecticut

Geriatric Syndromes and Hallmarks of Aging

Luigi Ferrucci, MD, PhD, Scientific Director, National Institute on Aging, NIH

Dr. Ferrucci conceptualizes aging as the gradual failure of organismal resilience mechanisms that help prevent and repair damage from entropy and stress. Humans use several mechanisms of resilience to deal with stress, including particularly the integrated stress response. This response converges in a series of kinases that phosphorylate the protein EIRF2 α , which halts protein synthesis and activates activating transcription factor 4 (ATF4). Depending on cellular resilience and on the intensity and duration of the stress, ATF4 activation either increases cellular repair mechanisms, such as autophagy and inflammation, or triggers apoptosis. Stress can therefore be beneficial, insofar as it unleashes cellular defense mechanisms; however, when stress exceeds these mechanisms' repair capacities, it induces substantial damage.

Successful cellular defense requires energy. Cells can address macromolecular and cellular damage and organelle degradation through repair and recycling and replacement, but only with healthy, functional mitochondria to supply energy. Mitochondria are also hubs of multiple

inflammatory mechanisms, including the NLRP3 inflammasome, cGAS/STING pathway, and NF- κ B. Stressed, but not healthy, mitochondria activate beneficial alternative splicing transcripts, which increase energy production and decrease energy utilization in response to acute stress. Thus, stressed mitochondria can exert global effects on cellular metabolism, which can result in damage accumulation and aging. The mitochondrial DNA copy number in whole blood (mtDNAcn) predicts longevity in the Baltimore Longitudinal Study of Aging (BLSA) and the SardiNIA cohorts.

A Life Course Approach to Understanding Behavioral and Social Drivers of Biological Aging

Terrie Moffitt, PhD, Duke University and King's College London

Socioeconomically disadvantaged individuals develop heart disease, lung disease, and other disease at relatively young ages. The Geroscience hypothesis posits that these diseases arise from whole body aging, which implies that deprivation may accelerate aging. To test this hypothesis, Dr. Moffitt has measured whole body aging in the Dunedin Multidisciplinary Health and Development Study. The Dunedin study has followed 2,000 individuals born in 1972, collecting data on 19 biomarkers at ages 26, 32, 38, and 45. Virtually all these biomarkers show a gradual worsening of physical integrity with age. Using a composite of these biomarkers, researchers created personalized slopes that reflect individualized rates of biological aging (DunedinPACE). Individuals varied from 0.8 to 2.0 years of DunedinPACE aging per chronological year. DunedinPACE predicts functional decline, mortality, and dementia risk in the Framingham heart study, and correlates with dementia status in the Alzheimer's Disease Neuroimaging Initiative (ADNI). The BLSA measure, which assesses aging phenotypes across multiple domains, similarly predicts mortality, cognitive decline, and physical function.

With these validated measures of aging, researchers have identified several correlates of accelerated biological aging: low socioeconomic status (SES), family-level and neighborhood-level disadvantage, adverse childhood experiences, poor childhood health, low IQ, low self-control, poor relationship quality, and smoking. In contrast, familial longevity, high IQ and education, physical activity, and a Mediterranean diet are linked with a slower pace of aging. Studies have shown that several behavioral and environmental changes affect the pace of aging during the life course, such as climbing the socioeconomic ladder, quitting smoking, experiencing trauma or COVID-19 infection, or adopting a Mediterranean diet. However, early life social and behavioral risk factors are the ideal intervention targets. The optimal timing to slow aging is before the fifth decade of life.

To mature this work, researchers need to validate additional longitudinal measures of whole body aging in a wider range of racial and ethnic groups. These measures can then be incorporated into existing large epidemiological human cohorts to determine the potential timing of specific social and behavioral effects on aging and to inform when to intervene. Researchers will need to determine whether these effects are causal. Many social and behavioral risk factors, like rate of biological aging, are under genetic influence. If causal, researchers will need to determine what factors (e.g., stress biology, health behaviors) mediate

these relationships. Ultimately, randomized controlled trials (RCTs) are needed to test causality and to assess the impact of social and behavioral interventions.

Panel Discussion: Integration of the Geriatric and the Life Course Perspectives

Moderator George Kuchel, MD, University of Connecticut

Stacy Drury, PhD, Tulane University School of Medicine

Early life experiences predict later health outcomes, particularly those associated with aging. Understanding early-life interactions among biomarkers may thus help illuminate the underlying mechanisms involved in aging. In addition, the rate of growth and development in early life may correspond to rate of decline later in life. For example, individual differences in telomere length adjusted for age remain largely consistent across the lifespan, with the largest changes in telomere length appearing primarily in the first 5-10 years of life; however, these conclusions are based on very limited data on individuals under the age of 20.

Daniel Promislow, PhD, University of Washington

Studies of resilience to date have focused almost exclusively on social and psychological stress and neurological degeneration. These studies could be expanded using a systems biological perspective to understand how the epigenome, microbiome, and metabolome alter in response to stress and how they return to homeostasis, how these processes change as we age, and how these processes vary among aging individuals.

Tony Wyss-Coray, PhD, Stanford University

Cells, organs, and individuals age asynchronously. Thus, to test interventions targeting underlying aging processes, researchers need the ability to measure tissue aging within the individual. Such measurements of transcriptional aging in mice show dramatic variation across different brain regions. These findings also suggest that multiple brain regions, including those not typically studied in neurodegenerative disease, may contribute to the risk for these diseases.

Cliff Rosen, PhD, Tufts University

Impaired stem cell recruitment during aging leads to bone loss and marrow adipogenesis. Importantly, not all physiological and biological changes represent adverse phenomena. For example, marrow adipogenesis was once thought to indicate bone deterioration, but we now know that it is a healthy compensatory mechanism; adipose cells in the bone provide additional energy to the failing bone. Other age-related biological changes may also be healthy compensatory mechanisms.

Vadim Gladyshev, PhD, Harvard Medical School

There is no consensus on the nature of aging, nor whether it should principally be defined in terms of increased risk of mortality, functional decline, aging phenotypes, or damage

accumulation—or viewed as a continuation of development. Distinguishing social and behavioral factors from biological aspects is also difficult; some social and behavioral factors may be viewed as high-level manifestations of biology. The true nature of aging, and which biomarkers we use to assess it, will be especially critical questions in intervention development. Many biomarkers and clinical signs of age are not causal determinants of aging (e.g., doctor visits). Researchers need a better framework for establishing causality.

Biomarker Meaning and Interpretation

Not all age-related changes in biomarkers are pathological or reflective of negative age-related processes. Some changes in biomarkers may result from normal developmental process and lack functional significance. Other changes in biomarkers, including those that predict functional outcomes, may be adaptive responses to underlying structural damage, such as adipogenesis in aging bone. Both types of biomarkers are causal, but they have opposing effects and implications. Dr. Gladyshev noted that in epigenetic clocks, for example, changes are somewhat evenly split between the maladaptive and adaptive. As researchers develop interventions that aim to alter the rate of aging, they need to ensure that the targeted biomarkers are causally related to aging. Additional measurement challenges come from variation across cell and tissue types and bodily systems, which can all age at different rates and may manifest damage in a variety of ways. Researchers may therefore need to examine patterns and signatures across multiple biomarkers that predict health status or ability to respond to a health insult.

Using Biomarkers to Assess the Exposome

NIA uses *the exposome* as an umbrella term that captures the full range of social, behavioral, interpersonal, and environmental exposures (including pollutants and other toxic chemicals) that an individual encounters over the life course. The exposome is difficult to assess comprehensively. Moreover, many social, behavioral, and toxic environmental effects interact in complex ways, and their impact on aging and disease is poorly understood. For example, baby boomers who were exposed to high levels of aerosolized lead from leaded gasoline are now re-releasing lead into their bloodstreams as bones start to break down, leading to re-exposure decades later. However, these complex relationships between early exposures and biomarkers might enable researchers to use biomarkers to determine exposures retrospectively. Many systems biological tools now available to assess the epigenome, transcriptome, metabolome, microbiome, and lipidome may enable integrated measurement of environmental and genetic variation. For example, the National Institute of Environmental Health Sciences is working to understand how the exposome and the toxic built environment affect aging.

Social and Biological Resilience

A broad definition of resilience—one that reflects the capacity of various biological, psychosocial, and behavioral systems to respond to perturbations—could provide a unifying conceptual framework for aging across multiple systems. Several research groups are working to refine such operational definitions. The NIA-funded Research Definitions of Reserve and Resilience in Neurobiology of Aging recently published [its conceptual framework](#) of reserve and

resilience in the context of cognitive aging. A number of NIH Institutes and Centers, including the [Trans-NIH Resilience Working Group](#), are also working to develop an overarching definition of resilience.

If resilience is defined broadly, then it might be assessed with a common, dynamic, analytical framework that involves a stressor acting on a system and the psychological, functional, or biological recovery from that stressor. By measuring biological resilience, researchers may be able to assess the combined impact of social and biological factors on downstream morbidity and mortality. One approach for advancing research on resilience, suggested at the NIA-supported “Overview of the Resilience World—State of Science” workshop held in October 2022, is to add further measures of resilience to ongoing studies—for example, measures of physiological and functional resilience to studies of cognitive resilience. The ecological perspective on resilience further implies the importance of “tipping points”: at certain ages, a stressor that an organism might once have recovered from now pushes it into a more frail or morbid state. Assessing resilience might help identify such tipping points in humans.

However, to develop a unifying definition of resilience, researchers must overcome several challenges:

- Defining recovery to a baseline is a nontrivial task, because organisms can intentionally shift their physiological state and may have multiple healthy, physiologically normal states.
- A gold standard for assessing biological resilience in humans has yet to be identified.
- Resilience may manifest differently in response to intermittent or chronic stress versus acute stress, and relatively little research has been done on biological resilience to chronic stress.

An additional consideration is that the notion of social resilience has acquired problematic implications: the term is sometimes used to refer to disadvantaged individuals’ ability to surmount inequities and structural failures, potentially implying that social disadvantage is a function of failures in individual capacity. Hence, researchers may wish to focus on biological resilience or use a different term to describe psychological, social, and behavioral resilience.

Dr. David Furman suggested that *intrinsic capacity* might offer an alternative to resilience. A decline in intrinsic capacity is listed in the *International Classification of Diseases 11th Revision* and is accepted by the World Health Organization (WHO) as a condition. An intrinsic capacity framework could therefore help elucidate the links between social and biological aging. WHO defines intrinsic capacity as the composite of all physical and mental capacities that a person can draw on, including biological reserve. For example, a recent [paper](#) assessed intrinsic capacity by screening for abnormalities in locomotion, cognition, psychology, vitality, hearing, and vision.

Timing of Aging-related Impacts

Panelists generally agreed that early life events, including prenatal impacts, appear to have substantial impact on aging trajectories. This pattern may be related to energy levels: resilience

is the ability to resist entropy, which requires energy. Energy expenditure is highest between ages 5-10. An energetic framework may therefore help illuminate critical periods of development.

Notably, energetic costs early in life may have hidden or long-term health tradeoffs. For example, glucocorticoids given to hasten the terminal differentiation of lung progenitor cells in premature infants improve their survival, but the resulting loss of physiological reserve can cause lung problems in midlife.

Despite the recognized importance of early life events, it is unclear what specific measures in developing children would be most informative for future aging studies, and only a few studies have assessed biological aging in young adults. The National Institute of Mental Health intramural program has studied normative brain development early in life, and a few studies have shown that children living in poorer, more disadvantaged families and neighborhoods exhibit a faster pace of aging in early adulthood (e.g., [Belsky et al., 2017](#); [Raffington et al., 2021](#)). Some forthcoming research has shown that early-life exposure to the Great Depression is linked with a faster pace of aging in mid-life ([Schmitz and Duque, 2022](#)). Dr. Moffitt noted that although the DNA-methylation Predictor of Pace-of-Aging (DunedinPoAm) can be used at any age, it has not been used in infants or young children, because of the difficulty of collecting blood from minors. Buccal DNA measures are being developed that may facilitate studying younger populations.

Assessing development-related biomarkers in children and young adults also presents statistical challenges, because biological differences can be quite subtle at these ages. Dr. Promislow noted that in fruit flies, differences in aging rates manifest within the first few weeks of life but are so subtle that they require very large samples to detect. A related concern is that many aging biomarkers assess damage after it has occurred and may not accurately assess aging-related changes in younger individuals. For example, blood levels of mtDNAcn reflect damage from free oxygen radicals. However, researchers cannot currently measure directly the production of free oxygen radicals, only its long-term consequences. More generally, stress can cause gradual, cumulative damage with effects that are evident only decades later, and timing of when these effects become apparent can differ widely.

Further discussion between developmental scientists and aging researchers on addressing the impact of early-life exposures on aging could be of value. One possibility would be to connect with the ECHO program, a consortium of studies measuring biomarkers and environmental exposures in infants and adolescents.

Timing of Interventions to Slow Aging

Panelists generally agreed that interventions to extend the healthy lifespan will need to target people before the onset of age-related diseases, that is, before the fifth decade of life. They noted the possibility of tipping points, including very early in life, when interventions would have the greatest impact.

Session 2: Integrating the Social and Biological Hallmarks of Aging

Generating Hypotheses Using the Biological Hallmarks of Aging

Ana Maria Cuervo, MD, PhD, Albert Einstein College of Medicine

Dr. Cuervo defines biological hallmarks of aging as cellular and organism systems whose malfunction drives the aging process. To be a driver of aging, a biological hallmark must (1) be associated with functional outcomes, (2) change with age, and (3) have a direct relation to functional decline or onset of disease, such that reversal or reduction of the biological process delays these outcomes. One such hallmark is proteostasis, a process by which cells control the quality of cellular components. Dr. Cuervo studies a component of the cellular proteostasis network known as chaperone-mediated autophagy (CMA), which involves chaperones identifying proteins and bringing them to the lysosome for degradation. CMA is a constitutive process present in all cells and inducible by a variety of stressors (e.g., oxidative stress, hypoxia, and starvation). CMA degrades misfolded/damaged proteins, contributes to energetics by producing free amino acids, and helps regulate cellular processes by degrading functional proteins to terminate their function. To measure CMA in vivo, researchers have developed animal models in which lysosomes fluoresce when they contain proteins delivered by CMA. CMA activity declines with age in most organs, but the cause of the decline is different in males and females. For example, with age, neuronal lysosomes become less active for CMA in females, whereas the overall number of lysosomes declines in neurons in males.

Dr. Cuervo has conducted studies targeting a key lysosome receptor for the CMA process: lysosome-associated membrane protein type 2A (LAMP-2A). She has developed a LAMP2A $-/-$ animal that shows multiple signs of aging, including neurodegeneration, metabolic syndrome, loss of stemness, disruption of circadian rhythms, and higher propensity to cancer. She has also developed genetically modified animals that allow researchers to activate an extra copy of LAMP2A at the age when declines in expression are usually seen. These animals have increased mean and maximum lifespan and healthspan, reduced frailty, and improved organ resilience and function; they also respond better to stress. Dr. Cuervo is now studying novel activators of CMA. These drugs appear to improve pathology associated to diseases of aging such as neurodegeneration or retinal degeneration and also improve cellular metabolism and stem cell function. To study CMA in humans, Dr. Cuervo is building computational models to create a CMA index based on expression of network components. She and others are studying autophagy directly in human peripheral T cells to characterize how changes in autophagy activity with age correspond to immune function. Additional research is needed on how drivers such as CMA interact with other hallmarks of aging.

Generating Hypotheses Using the Social Hallmarks of Aging

Eileen Crimmins, PhD, University of Southern California

The social hallmarks of aging are social factors that influence the rate of aging, including minority status, low SES, adverse life events, adverse psychological status, and adverse behaviors; all can have substantial impacts on health. Dr. Crimmins and other social science

researchers have generated and tested several overarching hypotheses about the role of these hallmarks in the aging process: (1) Social hallmarks are fundamental causes of almost all aspects of age-related poor health (e.g., physiological dysregulation, physical disability, cognitive loss, etc.); (2) Many “social” pathways (e.g., access to social and economic resources and health care and living and environmental circumstances) over the life course link social factors to health; (3) The size of these social effects varies with the health outcome; (4) Social factors get “under the skin” through biological mechanisms; (5) These biological mechanisms also differ by health outcome; and (6) When biology is completely and accurately measured, it will account for observed social differences; that is, biological changes will fully mediate the effects of social hallmarks on health.

This set of generative hypotheses is incorporated in an evolving multidisciplinary social science model of health and aging. The model posits that demographic factors, genetic endowment, and SES affect health behaviors (e.g., smoking, obesity, and heavy drinking), psychological states, and risk for adverse experiences, all of which in turn affect the molecular and cellular hallmarks of aging (e.g., telomere length, epigenetic changes, proteomics), leading to physiological dysregulation and ultimately driving health outcomes such as cognitive dysfunction, multimorbidity, and early mortality.

Dr. Crimmins and others have begun to study physiological dysregulation and molecular and cellular hallmarks of aging to determine whether these biological and physiological factors mediate the health impacts of social factors. For example, in the Health and Retirement Study, a nationally representative longitudinal panel study, social factors explain 10-30 percent of observed variance in mortality, multimorbidity, difficulties with activities of daily living, and cognitive dysfunction, with SES and race showing relatively strong associations with cognitive dysfunction. Dr. Crimmins has also measured physiological dysregulation using 22 markers of expanded biological age (such as markers of inflammation, blood glucose, blood pressure, and cholesterol), as well as a set of molecular and cellular measures (telomere length, mitochondrial DNA copy number, DNA methylation (epigenetic age with GrimAge), and RNAseq measures of conserved transcriptional response to adversity (CTRA), senescence-associated secretory phenotype (SASP), and DNA damage response (DDR). Including these biological factors modestly improves the amount of variance explained in aging outcomes. Controlling for these biological factors, however, does not significantly reduce the impact of the social factors; that is, these biological factors do not mediate the social effects. Adding genetic effects to the statistical model had a negligible effect on the amount of variance explained. Together, these findings imply that researchers are not adequately capturing the biological mechanisms.

Future research needs to develop more nuanced interpretations of social and biological pathways in aging that consider pathway interactions and variability by outcome. Social scientists must expand and refine their repertoire of measures of aging biology to improve understanding of mechanisms, the timing of their impacts, and how they interact. Additional attention to the social mechanisms that underly social effects is needed, while biological scientists can help social scientists implement novel biological measures in large human studies.

Additional biological research on how different biological aspects of aging interact to affect health would help inform large human studies of aging.

Panel Discussion: Integrating the Social and Biological Hallmarks of Aging

Moderator: Terri Moffitt, PhD, Duke University and King's College London

Tené Lewis, PhD, Emory University

Dr. Lewis studies Black White disparities in aging-related health conditions. Numerous historical conditions and policies may influence aging in Black individuals and result in cohort effects. For example, in early life, aging Black individuals may have experienced segregation and Jim Crow, busing in the 1970s, and White flight in the 1970s and 1980s. These early life stressors may have led to accelerated aging and weathering.

Tom Kirkwood, PhD, Newcastle University and University of Copenhagen

Dr. Kirkwood emphasized the importance of acknowledging the complex causality of the changes that occur through the life course. Complexity arises within both the biological and social domains, separately and together. To make concrete progress in exploring this complexity requires explicit recognition of networks, hierarchies, and interactions. Dr. Kirkwood's experience was that building dynamic, quantitative models of these processes and their interactions could be very revealing. He suggested that reflecting on past examples, such as the classic Whitehall study of socioeconomic disparities in health among British government employees, might also throw light on the added value that could be generated by integrating social and biological hallmarks.

Steve Cole, PhD, University of California, Los Angeles

In humans and in animal models, adverse life events are associated with increased expression of inflammatory genes in white blood cells, a reduction in transcriptional activity in genes involved in innate antiviral responses, and changes to hematopoiesis (a shifting of white blood cell production away from lymphoid cells and toward more pro-inflammatory myeloid lineages)—all of which are mediated by the stress response. These changes could be called *inflammaging* and resemble the aging signatures derived from black box machine learning algorithms. Arguably these changes illustrate the ability of social threat to drive aging in the white blood cell population. Although inflammation increases with age, it also increases temporarily in response to infection and sympathetic nervous system signaling. These findings raise the broader questions of how to distinguish “aging” from health, and how to distinguish temporary dynamic changes from longer-term changes that drive aging.

Marissa Schafer, PhD, Mayo Clinic

Dr. Schafer's lab is studying how senescent cells in the central nervous system and periphery affect brain microenvironments and cognitive function. The researchers are also starting to investigate how social and behavioral parameters such as stress and diet influence cellular senescence in the brain and systemic tissues, and how these effects differ by sex.

David Furman, PhD, Buck Institute

Dr. Furman has developed a metric of systemic chronic inflammation that predicts chronological age, multimorbidity, mortality, and frailty seven years before onset. This measure also correlates with social and emotional characteristics such as reduced interest in sex and motivation to work, chronic stress, and feelings of guilt.

Martin Picard, PhD, Columbia University

Mitochondria are a genetically related family of organelles that perform dozens of functions and specialize as cell type- and tissue-specific mitotypes. Researchers thus need cell type- and tissue-specific measures of mitochondrial biology. Mitochondria sense and integrate numerous cellular inputs and transduce these signals to affect genetic regulation, thereby acting as information processors within the cell. They also provide the energy for the transfer of information. As critical transducers of information, mitochondria likely play important roles in how physiological stressors affect transcription and age-related epigenetic changes.

Ron Simons, PhD, University of Georgia

Dr. Simons and colleagues have collected longitudinal prospective data from several hundred large African American families. They have found that cumulative exposure to class- and race-related stressors in these families has led to accelerated aging (as assessed by epigenetic measures) throughout the life course. He has also found that exposure to adverse social and behavioral experiences during the 5th decade of life are linked with accelerated aging; conversely, positive social experiences in this decade are linked with declines in the rate of aging. In the coming years, Dr. Simons will explore peripheral measures of neuronal degeneration in this cohort.

Irina Conboy, PhD, University of California, Berkeley

When old blood and young blood are mixed, the effects of old blood on biomarkers of aging predominate. Dr. Conboy has shown that dilution of old blood—by replacing plasma with a mixture of saline and albumin—leads to organ rejuvenation, enhanced neurogenesis in the hippocampus, reduced DNA damage, and restoration of a youthful proteome. These effects are conserved between mice and people and are not simply the result of diluting SASP. In humans, multiple rounds of plasmapheresis rejuvenate humoral and cellular blood compartments.

Stability of Biomarkers of Aging

Highly malleable or dynamic biomarkers may not clearly capture aging-related processes or distinguish aging-related changes from temporary illness-related changes. The epigenome and proteome, for example, are highly dynamic; and some related biomarkers fluctuate regularly or in response to short-term stimuli. In the past, aging and ill health were distinguished mainly by temporality: aging was taken to be monotonically increasing or at least nondecreasing. (Age is validated as probability of death, but this definition is also an operationalization of health). However, Geroscience is changing this notion of aging by revealing that the aging process is reversible, and healthspan and lifespan can be extended. Thus, malleability is no longer a reason to exclude potential biomarkers as indicators of aging. Instead, highly dynamic

biomarkers may be useful indicators of aging processes, provided they can be linked to more stable markers known to influence clinical outcomes, such as arteriosclerosis.

Session 3: Planning Next Steps

Moderator Elissa Epel, PhD, University of California, San Francisco

Dr. Epel noted that key questions regarding biological measures of aging remain: How reliable are these measures? Are they predictive of aging-related outcomes? What critical periods influence them, and do we have information on normative development? How malleable are they? What are the right targets for interventions?

Nathan K. LeBrasseur, PhD, MS, Mayo Clinic

“Reverse” translational research enables the study of the interplay between the biology of resilience to physical, social, and psychological challenges and the biology of aging at the tissue and cellular level. For example, do more resilient mice at older ages exhibit less evidence of age-related molecular or cellular damage? Do mice exposed to such challenges exhibit accelerated accumulation of damage? Many physical, social, and psychological challenges experienced by humans can be modeled in rodents. For example, physical challenges such as infection or chemotherapy, social challenges such as isolation, and psychological challenges such as bullying. The use of animal models to study how physical, social, and psychological challenges influence biological mechanisms of aging at specific ages or across the life course may help illuminate aging processes in humans. These models may also provide insight into accessible biological indicators, or biomarkers, of aging that are informative of the impact of various challenges on biological age and health risks in humans.

Alan Cohen, PhD, Columbia University

To integrate social and behavioral research perspectives with research on aging biology, researchers need a proper ontological framework. Emergent effects arise at every level of biological and social and behavioral analysis, from atoms to tissues to ecosystem-level effects. Researchers need a better understanding of how these levels interact and of which social and biological effects are context-dependent and which are universal. Research in this area may benefit from exploration of dynamic responses to physical insults or stressors as indicators of resilience.

Anna Marsland, PhD, University of Pittsburgh

Prenatal and early life biological embedding may be adaptive for health in the short term, but maladaptive in the long term and across generations. For example, many social factors predict elements of an accelerated life course, such as early puberty. Researchers need prospective investigations early in life to determine early critical periods and identify interventions that slow aging. However, many biomarkers do not correlate with one another, which makes interpretation of results challenging.

Duygu Ucar, PhD, Jackson Laboratory for Genomic Medicine

Dr. Ucar studies heterogeneity in immune system aging, particularly in response to vaccination, which varies by age, sex, and comorbidities. For example, gene expression on natural killer (NK) cells can predict response to a bacterial pneumonia vaccine. Such findings may enable doctors to tailor vaccines and treatments to individual needs. Dr. Ucar also emphasized that large diverse cohorts are required to analyze heterogeneity in social aging, including its co-factors and mediators, and to determine its health impacts.

Rozalyn Anderson, PhD, University of Wisconsin, Madison

Dr. Anderson suggested that clinical studies of physiology could help connect social factors of aging with molecular and cellular mechanisms. Researchers are now gathering the necessary physiological data in longitudinal clinical studies and by leveraging electronic health records. Dr. Anderson also noted that many biological measures remain in development. Thus, researchers may wish to consider what biomarkers they will want to assess in the future to determine the types of samples to collect.

Dan Belsky, PhD, Columbia University

Dr. Belsky noted that studies of the Dutch Hunger Winter and the Great Depression have demonstrated accelerated aging in later life of those exposed to hardship in utero. He suggested that the next research challenge is to conduct interventions to slow aging. Adding biomarkers to existing intervention studies will help researchers study whether aging biomarkers shift in response to interventions, and whether those shifts are predictive of aging-related outcomes. He noted several trials that might be well suited for such research: NIA CALERIE trial, the Paycheck Plus study, and MyGoals for Employment Success study.

Jessica Faul, PhD, MPH, University of Michigan

Dr. Faul noted that biomarkers do not predict aging equally well across groups. Studies of human aging needs more diverse, representative samples to ensure that the biomarkers used are applicable across racial and ethnic groups.

Moving Toward a Standardized Battery of Biological Aging

A standardized battery of measures for prospective Geroscience studies of aging might include biological, social, and behavioral factors, as well as measures of biological and functional resilience. Panelists described several biomarkers in development. Dr. Conboy noted that the UCSF Memory and Aging Center has identified blood markers of mild cognitive impairment. Dr. Conboy expressed interest in collaborating with other researchers on studies involving these markers to see how they correspond with social and behavioral factors. Dr. Ferrucci noted that IL-6 captures rapid changes in biological responses, while TNF α and IL1RA may be the best choices for more stable indicators of inflammaging. Longitudinal proteomics analyses are now also available. Dr. Moffitt added that soluble urokinase Plasminogen Activator Receptor (suPAR) levels reflect inflammation, with less acute fluctuation than CRP or IL-6. Oxytocin is another potentially useful biomarker of longevity: it is elevated in seniors living in loving environments and linked with metabolic function and with regeneration of muscle, liver, and bone. Measuring energetics tradeoffs may also enable researchers to assess allostatic load. In an avian model,

food insecurity led to enhanced energy storage at the cost of physiological repair ([Bobba-Alves et al., 2022](#)).

However, because biological measures are evolving rapidly, it is too soon to codify a standard set. Instead, researchers can test available measures in ongoing interventions and consider priority measures for current use in longitudinal studies, while retaining samples for later biomarker analysis. In gathering and storing these samples, researchers should envision what biomarkers might be useful in the next 5-10 years.

Calibrating Biomarkers

Chronological age may not be the best way to calibrate markers of biological age. Appearance of disease onset is exponential, which implies that multiple, nonexponential predictors interact to cause disease. The most predictive epigenetic clocks in use today, for example, are not trained purely on chronological age, but on various factors that predict health. DunedinPACE, for example, is trained on the rate of physiological deterioration in a same-age birth cohort, and GrimAge is trained on mortality risk. At the same time, most predictors continue to show high correlations with chronological age.

Determining Causal Changes in Rates of Aging

Research in animal models has shown that aging is malleable. Measuring reversals in the aging process, however, presents considerable challenges. Indeed, measuring stress response and resilience remains the largest barrier to progress in Geroscience from a biological perspective. Gene expression changes within minutes, but these changes may not have functional significance. At the population level, epigenetic age may help indicate causal changes in the rate of aging, because epigenetic clocks are highly predictive of health outcomes and mortality. Moreover, testing epigenetic clocks and other aging biomarkers in natural and actual experiments could help determine whether they are malleable, and whether changes in these biomarkers predict changes in the healthspan. However, because epigenetic age alone does not provide any information about underlying biological mechanisms, it should be used in conjunction with other biomarkers. In addition, because several stress response pathways inhibit protein synthesis, a narrow focus on the genome or transcriptome can miss the impact of stress.

Assessing Resilience to Stress

A broad framework for studying resilience, defined as the capacity (of a cell, system, organism, etc.) to resist, adapt to, recover, or improve in function in response to a stressor or challenge, has parallels across disciplines and may provide a way to harmonize social and biological frameworks. Behavioral and social researchers have studied resilience across multiple levels of analysis in experimental psychobiology and in biosocial surveys, incorporating physiological measures of, for example, inflammation, glucocorticoid sensitivity, norepinephrine and epinephrine, cortisol, peripheral physiology, alongside measures of psychological function (e.g., emotions, cognition), health, and behavior in response to a range social, environmental, and physical stressors. Some of this research assesses responses to lab-based stress challenges,

which enables assessment of dynamic stress responses in real time, with strong design parallels to work conducted in biological studies of resilience in animal models.

Assessing Individual Differences in Rates of Aging

To understand the social factors that affect rates of aging, researchers should assess not only group- and population-level shifts, but also individual dynamics. Broad population-based models do not necessarily shed light on individual rates of aging. Instead, researchers may want to focus on the molecular signatures and social characteristics of resilient individuals who experience severe life events, such as the Dutch Hunger Winter. Bringing together researchers who study individual-level social and biopsychological resilience may provide a methodological bridge from social science research to aging biology studies of resilience. NIA has already supported successful efforts to bridge approaches in population-based survey biology with lab-based psychobiological approaches to studying stress and resilience (e.g., through the Stress Measurement Network, the Telomere Research Network, and the Biomarker Network). As future meetings seek to bridge conceptual frameworks and approaches across population-level social science research and basic biology of aging, these initiatives may provide a guide to what has worked well in the past.

Appendix 1. Agenda

Monday, October 31, 2022		
11:30 (15)	Welcome and Meeting Charge	Lis Nielsen , BSR Ron Kohanski , DAB
Session 1: Geriatric and Life Course Perspectives on Aging Informed by the “Motivating Questions” above, each speaker will: Share terminology used within their overall research framework or orientation to the study of aging, address gaps that might be filled by incorporating information from other frameworks, articulate the causal model(s) and hypotheses being tested, and articulating how the framework/orientation helps us think about the malleability of aging.		
11:45 (20)	Geriatric Syndromes and Hallmarks of Aging	Presenter: Luigi Ferrucci
12:05 (20)	A Life Course Approach to Understanding Behavioral and Social Drivers of Biological Aging	Presenter: Terrie Moffitt
12:25 (65)	Panel Discussion: Integration of the Geriatric and the Life Course Perspectives Discussant Remarks (3 minutes each): Perspectives from scientists addressing aging and the emergence of chronic disease from a life-span developmental framework • Sonia Entringer • Stacy Drury • Laura Niedernhofer • Daniel Promislow • Cliff Rosen • Tony Wyss-Coray • Vadim Gladyshev • Rose Anne Kenny Open Discussion and Q&A	Moderator: George Kuchel
1:30 (15)	BREAK	

Session 2: Integrating the Social and Biological Hallmarks of Aging

Informed by the “Motivating Questions” above, each speaker will:

Share terminology used within their overall research framework for studying causal drivers of aging, address gaps that might be filled by incorporating information from other frameworks, articulate the causal model(s) and hypotheses being tested, and articulating how the framework helps us think about the malleability of aging.

1:45 (20)	<i>Generating Hypotheses using the Biological Hallmarks of Aging</i>	Presenter: Ana Maria Cuervo
2:05 (20)	<i>Generating Hypotheses using the Social Hallmarks of Aging</i>	Presenter: Eileen Crimmins
2:25 (65)	<i>Panel Discussion: Integrating the Social and Biological Hallmarks of Aging</i> <i>Discussant Remarks (3 minutes each):</i> Perspectives from scientists working at the intersection of social determinants of health and biological aging. • Tené Lewis • Tom Kirkwood • Steve Cole • Marissa Schafer • David Furman • Martin Picard • Ron Simons • Irina Conboy <i>Open Discussion and Q&A</i>	Moderator: Terrie Moffitt

Session 3: Planning Next Steps

3:30 (60)	<i>Discussant Remarks (3 minutes each):</i> • Nathan LeBrasseur • Alan Cohen • Anna Marsland • Dyugu Ucar • Rozalyn Anderson • Dan Belsky • Jessica Faul	Moderator: Elissa Epel
4:30	ADJOURN	

Appendix 2. Participants

Invited Speakers and Moderators

Rozalyn Anderson, PhD, University of Wisconsin
Dan Belsky, PhD, Columbia University
Alan Cohen, PhD, Columbia University
Steve Cole, PhD, University of California, Los Angeles
Irina Conboy, PhD, University of California, Berkeley
Eileen Crimmins, PhD, University of Southern California
Ana Maria Cuervo, MD, PhD, Albert Einstein College of Medicine
Stacy Drury, PhD, Tulane University School of Medicine
Elissa Epel, PhD, University of California, San Francisco
Jessica Faul, PhD, MPH, University of Michigan
Luigi Ferrucci, MD, PhD, NIA Office of the Scientific Director (OSD)
David Furman, PhD, Buck Institute
Vadim Gladyshev, PhD, Harvard Medical School
Tom Kirkwood, PhD, Newcastle University and University of Copenhagen
George Kuchel, MD, University of Connecticut
Nathan LeBrasseur, PhD, MS, Mayo Clinic
Tené Lewis, PhD, Emory University
Anna Marsland, PhD, University of Pittsburgh
Terri Moffitt, PhD, Duke University and King's College London
Martin Picard, PhD, Columbia University
Daniel Promislow, PhD, University of Washington
Cliff Rosen, PhD, Tufts University
Marisa Schafer, PhD, Mayo Clinic
Ron Simons, PhD, University of Georgia
Dyugu Ucar, PhD, Jackson Laboratory for Genomic Medicine
Tony Wyss-Coray, PhD, Stanford University

Workshop Organizers

Ronald Kohanski, PhD, Director, Division of Aging Biology (DAB)
Lis Nielsen, PhD, Director, NIA Division of Behavioral and Social Research (BSR)
Chandra Keller, EdD, NIA Division of Behavioral and Social Research (BSR)

Other Attendees

Siobhan Addie (NIA/DAB)	Christy Carter (NIA/DAB)
Steven Beach	Ruijia Chen
Amanda Boyce (NIA/DAB)	Tiziana Cogliati (NIA/DAB)
David Braudt	Jennifer Fox (NIA/DAB)
Grace Brennan	Yih-Woei Fridell (NIA/DAB)
Ryan Brown	Yi-Ping Fu (NIA/DAB)
Stacy Carrington-Lawrence (NIA/DAB)	Hongwei Gao (NIA/DAB)

Melissa Gerald (NIA/BSR)
Brian Gray (NIA/OD)
Max Guo (NIA/DAB)
Richard Hodes (NIA/OD)
Jennifer Isaacs (NIA/DN)
Petra Jacobs (NIA/BSR)
Dinesh John (NIA/BSR)
Amelia Karraker (NIA/BSR)
Pragati Katiyar (NIA/DAB)
Amy Kelley (NIA/OD)
Theresa Kim (NIA/BSR)
Jon King (NIA/DBSR)
Rebecca Krupenevich (NIA/BSR)
Man Kit Lei
Meital Mashash
Manuel Moro (NIA/DAB)
Liz Necka (NIA/BSR)

Rose Li and Associates

Amy Kiefer
Scotia Morris
Sabira Mohamed

Georgeanne Patmios (NIA/BSR)
Viviana Perez Montes (NIA)
Dana Plude (NIA/BSR)
Aric Prather
Rebecca Ricklis (NIA/BSR)
Kenneth Santora (NIA/DEA)
Janine Simmons (NIA/BSR)
Eleanor Simonsick (NIA/LSS)
Raquel Sitcheran (NIA/DAB)
Chelsea Siwik
Alexandra Sullivan
Toshiko Tanaka (NIA/LSS)
Melissa Trevino (NIH)
Leonid Tsap (NIA/DAB)
Allie Walker (NIA/BSR)
Linda Yang (NIA/OD)
Sue Zieman (NIA/DGCG)