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Special Issue: Heterogeneity and Successful Aging: Perspective

Workshop Report—Heterogeneity and Successful Aging Part I: Heterogeneity in Aging—Challenges and Opportunities

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Abstract

Historically, aging research has focused primarily on the study of differences in means of varied measures obtained at different ages. However, growing evidence has shown that for many parameters, variability in measurements obtained both between- and within-age groups increases with aging. Moreover, growing heterogeneity may become especially apparent when examined via longitudinal as opposed to cross-sectional aging data. Efforts to deconvolute and better understand such heterogeneity present remarkable translational opportunities for developing targeted and more effective interventions into aging. Here, we present Part I, a summary of the NIA *Heterogeneity and Successful Aging* workshop virtually held in May 2023.

Keywords: Variability, Trajectories, Diversity, Biology, Physiology

Aging is a complex process, in part due to remarkable variation in rates and manifestations, both between and within individuals. Heterogeneity can be attributed to genetics as well as lifestyle, environmental, and socioeconomic factors; and it can manifest disparities in mortality, biomarkers, and therapeutic responses. General principles governing the biology of aging have been challenging to establish due to this heterogeneous complexity, so increased comprehension of heterogeneity could improve targeting efforts to enhance the healthspan of older adults.

Historically, aging research has predominantly focused on cross-sectional efforts to identify aging-related differences between young and old groups, including characterization on the cellular, organ, systemic, individual, and population levels. Two important concepts add complexity to that approach. First, many individuals develop complex multimorbidities; yet even amongst those who experience what could be considered healthy aging, few experience exceptionally successful aging (1,2). Second, conclusions regarding the impact of aging on specific trait outcomes can differ when individuals are followed longitudinally versus cross-sectionally (3,4). The challenges that heterogeneity poses to the study of aging in humans also apply to model organisms, even genetically identical nematodes, mice, yeast, and bacteria (5), even when maintained under identical, controlled conditions (6,7).

Because of advancing technology, our current understanding of heterogeneity of aging extends beyond a whole organism perspective, to within organism tissue and cell aging mosaicism (8). Also, aging has become increasingly defined by organismal resilience. For example, the ability to respond to stressors as varied as ingestion of an oral glucose meal (9) or reprogramming growth factors (10) and resolution of inflammatory signaling (10) demonstrates increased heterogeneity of magnitude and temporal responsiveness. Because aging is the greatest common factor underpinning chronic disease risk but reflects a diverse constellation of integrated biological phenomena and complex trait outcomes, it is imperative that we reframe the limiting notion of aging heterogeneity and instead leverage biological variability for scientific innovation and therapeutic opportunity. To this end, we will need to develop strategies to investigate heterogeneity in phenotypes associated with or predictive of successful or unsuccessful aging, including prolonged healthy lifespan. We will need to define the challenges and opportunities posed by heterogeneity in

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aging cohorts, and how heterogeneity in aging cohorts can be harnessed to understand the factors that determine successful aging and prolonged health, such as organ and tissue integrity and functionality.

To this end, in May 2023, the Division of Aging Biology of the National Institute on Aging (NIA) convened the virtual workshop *Heterogeneity and Successful Aging* to gather background knowledge on variation in biological aging and to discuss how heterogeneity can be harnessed to advance aging research. This is Part I of the report that summarizes the salient points from the workshop. The interested reader can refer to the transcript found on the dedicated event page on the NIA website LINK (https://www.nia.nih.gov/research/dab/workshops/workshop-heterogeneity-and-successful-aging) (11).

Here, we discuss how different types of assays—including epigenetics, frailty measures, and tissue multiomic analyses—reveal facets of aging heterogeneity in animal studies, both at baseline and in response to interventions aimed at delaying aging (eg, controlled feeding and exercise). We also discuss the pervasiveness of phenotypic heterogeneity in aging as chronicled by research in centenarian humans and the female reproductive system. We summarize in Box 1 the areas of research opportunities identified by the workshop.

Heterogeneity and Measures of Aging (Lots of Word/Concept Redundancy)

While the time since birth determines chronological age, the parallel concept of biological age attempts to summarize the physiological changes that occur through time, potentially at individual-specific rates, and associated with disease risk. Determination and contextualization of biological age remains a challenge in the field and these concepts were the focus of talks by Dr. Alice Kane and Dr. Trey Ideker.

Epigenetic clocks predict age at the molecular level via quantification of the extent of DNA methylation across the CpG islands found near many gene promoters (12). As presented by Dr. Ideker, methylation clocks built from human leukocytes (13) predict both chronological age and all-cause mortality. Projection of this model onto homologous genomic sites in dogs also predicted chronical age (14), suggesting evolutionary conservation of epigenetic aging mechanisms.

Frailty indexes (FIs) quantitatively summarize the accumulation of diverse phenotypic deficits with age, capturing "a multiply determined, age-related state of increased risk for adverse health outcomes" (15). Dr. Kane observed that both the mean and variance of FI scores increased with age in mouse populations, and thus captured an additional heterogeneic feature of age. Frailty-based clocks can be used to predict both chronological age (eg, Frailty Inferred Geriatric Health Timeline or FRIGHT age) and remaining lifespan (eg, Analysis of Frailty and Death or AFRAID clock) (16,17).

The power and potential of mechanistic insight from combining FI and epigenetic analyses with multiomic data was emphasized. Dr. Kane highlighted that individual frailty scores can be predicted in aged mice using DNA methylation and/or metabolomic analysis of blood samples. She further highlighted individual CpG's that both contribute to mouse methylation clocks and genes with known roles in aging biology (eg, Ercc5 and Elol2). Dr. Ideker remarked that mutations in CpG methylation sites exert a broad impact, affecting methylation tens of kilobases away, which expands the set of genes directly impacted by methylome and can potentially unify the mutational and epigenetic theories of aging.

Heterogeneous Responses to Perturbations in Animal Models

Responsiveness to perturbations that impact healthspan and lifespan can reveal underlying molecular determinants of accelerated aging and frailty. The workshop focused on heterogeneous responses to healthy interventions in animal models, including different methods of caloric restriction (CR) and physical activity.

Dr. Isabel Beerman presented her research on periodic restricted feeding (PRF) from the Aging Intervention Studies in rhesus macaques (18). In contrast to mice, nonhuman primates show greater variation in metabolic profile at baseline, indicating species-specific heterogeneity. Important methodological issues can contribute to heterogeneous responsiveness to feeding intervention, for example, the type, level, and timing of restriction; as well as sex bias, for example, lower baseline consumption in females that remains depressed after resuming ad libitum feeding (18). Importantly, in a 2-year follow-up after PRF cessation, male monkeys maintained lower body weight versus ad libitum fed, implying the conservation of "metabolic memory" observed in mice. Also persistent were PRF-induced improvements to physical performance in mice, metabolic signatures in both models (19) and microbiome diversity/abundance in primates. Given the consistent experimental results across 2 evolutionarily distant animal models, including a diverse nonhuman primate population, they propose that this intervention would likely promote healthy aging even in the very heterogeneous human population.

Box 1. Challenges and opportunities to investigating heterogeneity in aging

- Need for development of consensus definitions and methods for the study of heterogeneity in aging.
- Decrease reliance on cross-sectional studies with greater emphasis on longitudinal follow-up.
- Increase interindividual diversity of animal models selected for study (eg, use of genetically diverse versus inbred mice).
- Increase the diversity of human subjects studies in terms of age, sex, self-reported race, genetic diversity, socioeconomic status, and health to better reflect that of our communities.
- Need for more multi-omics and integrative modeling to understand pathways to pathology as well as health improvement.
- Importance of continued interrogation of sex- and genetic-biased responses to aging and systems-level perturbations/interventions.
- Sex and genetic differences in lifespan and health should be considered when attempting to explain heterogeneity, in developing better models, and in understanding the underlying biological mechanisms.
- Improved understanding of life-phase changes in women (puberty, pregnancy, and menopause) that underlie change in healthspan and lifespan.
- Determination of robust predictive biomarkers of aging and disease risk.

Dr. Rozalyn M. Anderson described heterogeneous aging in rhesus macaques from the Aging and CR study (20). Although CR improves health and survival in monkeys, there is considerable heterogeneity among individuals for typical clinical indices such as lipoprotein profiles, glucoregulatory indices, and circulating lipids. Heterogeneity among individuals increases with age, especially for the control group of monkeys. CR delays the onset of sarcopenia and is associated with maintained muscle quality. Despite heterogeneity among individuals, integrative approaches can identify links among parameters such as muscle mass retention and insulin sensitivity, or physical function and metabolic cost of movement (21). Shifts in body composition induced by CR include reduction in visceral and subcutaneous adiposity and are concomitant with reduced metabolic disease risk; however, the impact of CR at the molecular level is adipose depot-dependent, pointing to differences in the function of adipose depending on where it is in the body. Heterogeneity among individuals presents a challenge for more traditional statistical approaches. One solution is to take a multiomic approach to seek corroborative evidence among different molecular platforms, a strategy that identifies CR-induced hepatic metabolic reprogramming (22). Integrative analysis that identifies patterns among molecules can inform about the underlying biology of diseases, such as insulin resistance, where lipid homeostasis is disrupted well in advance of loss of glycemic control (23).

Dr. Andrea L. Hevener discussed leveraging heterogeneity as a driver of innovation in the field of metabolic health research across the lifespan (24–27). The Hevener laboratory studies a 100-strain mouse panel (Hybrid Mouse Diversity Panel, HMDP) to identify important relationships between genes, traits, and key drivers of metabolic outcomes (24–27). Due to female-biased protection against metabolic-related diseases prior to menopause, the Hevener laboratory pays attention to sex hormone receptors, leveraging both transgenics and the genetic variance of the mouse diversity panel to probe gene action.

To translate their observations from rodents to humans, they have successfully compared findings from multiple HMDP and genetically engineered rodent studies to human—Genotype-Tissue Expression, Metabolic Syndrome in Men, Comprehensive Assessment of Long Term Effects of Reducing Intake of Energy, Stockholm-Tartu Atherosclerosis Reverse Network Engineering Task, and Skeletal Muscles, Myokines and Glucose Metabolism (24–27). These translational studies, where genetic heterogeneity is leveraged as a scientific method for discovery, have uncovered significant gene–trait relationships, driven estrogen receptorα target gene identification, and revealed novel trait-loci and species-conserved mechanisms underpinning health-benefitting adaptations to exercise training.

Heterogeneity in Humans from Population Studies to Extreme Longevity Cohorts

Social and economic factors are known to influence health outcomes, which suggests a contribution to the heterogeneity of human biology. Dr. Michal Engelman explored the biological embodiments of social stratification in studies of heterogeneous human populations. Research on Epigenetics, Weathering, Aging, and Residential Disadvantage and Survey of the Health of Wisconsin studies (28) show heterogeneity in aging phenotypes across time, geographies, and demographics (eg, gender, race, ethnicity, nativity, education, income). She introduced a common measure of population health—life expectancy or average age of death—which is calculated based on a cohort's cumulative age-specific mortality. Results show that when individual characteristics are considered, neighborhood-level exposure to disadvantage matters for the pace of epigenetic aging, from 1.08 to 1.9 times faster for those living in the highest quintile of neighborhood-level disadvantage. Dr. Engelman posited that this may inform policy interventions at the community level to improve health outcomes with the goal of reducing morbidity and mortality in the United States.

Dr. Paola Sebastiani emphasized the heterogeneity of extreme human longevity and suggested that the many paths to extreme old age can offer insight into factors that promote resilience and resistance to aging-related diseases (29,30). She presented findings from studies of centenarians including: New England Centenarian Study (30), Long-Life Family Study (31), and Integrative Longevity Omics (32), which highlighted the heterogeneity of healthy aging (https://elite-portal.synapse.org/). Comprehensive phenotypic, genetic, and multiomic data from these studies enabled cluster-based analysis to determine differential patterns of cognitive decline in the Long Life Family Study. Individuals with high cognitive performance and slow decline were defined as "superagers" and those with long lifespans in spite of rapid decline were defined as "super resilient" (33). Cognitive decline manifested heterogeneously in the study population, and Dr. Sebastiani suggested that genetics may contribute to heterogeneous cognitive aging patterns. She also presented examples of extreme metabolomic heterogeneity correlating with patterns of aging—highlighting the potential for extreme cohorts to provide insight into patterns promoting longevity.

Heterogeneity in Ovarian Aging

Female reproductive aging is associated with an increased prevalence of age-related diseases after menopause. It is well established that ovaries influence overall health and lifespan, not just reproductive function. Dr. Yousin Suh's laboratory focuses on functional genetics in humans to understand the mechanisms underlying ovarian aging and the relation to overall health and lifespan. Targeting ovarian aging to achieve geroprotection in women is a new area of exploration that has recently garnered increased attention from the White House, including specific funding opportunities. There is substantial genetic heterogeneity in ovarian aging as substantiated by 290 GWAS variants associated with the timing of menopause (34). Single-nuclei and multiomic analyses of ovaries from young and old rodents have allowed the Suh Lab to connect these variants to mechanisms of ovarian aging. CRISPR-based mutagenesis in human pluripotent stem cells validated functionality of the DEPTOR locus, associated with mTOR signaling. Validating Benefits of Rapamycin for Reproductive Aging Treatment, a prospective double-blind classical control clinical trial, is currently being performed to evaluate the effectiveness of rapamycin (an mTOR inhibitor) to extend female reproductive lifespan.

A challenge in studying reproductive aging is the failure of rodents to mimic human ovarian aging and heterogeneity of estropause. Dr. Minhoo Kim presented her research from the laboratory of Dr. Bérénice A. Benayoun on modeling of ovarian aging in mice using 4-vinylcyclohexene diepoxide

(VCD) at various ages up to middle age to model the heterogeneity of human age-at-menopause (Kim and Benayoun, Personal Communication). VCD exposure has been used in young animals to induce atresia of immature follicles driving premature ovarian failure, thus provoking endocrine changes phenocopying human menopause (35). Modeling confirmed ovarian age acceleration based on endocrine markers following VCD administration in rodents at all ages of initiation. Single-cell transcriptomics provided details on the cell-specific changes occurring during ovarian failure. Of the 8 cell types characterized, granulosa and theca cells contributed substantively to VCD-induced transcriptional changes. Upon single-cell interrogation, pathway analysis, and additional modeling the group achieved enhanced ovarian aging modeling and prediction accuracy with the future goal of providing greater insight into menopausal-associated disease risk.

Challenges and Opportunities to Investigate Heterogeneity in Aging

Box 1 lists the main challenges and opportunities identified by the speakers at the workshop. The panel concluded with a call for the development of consensus definitions and approaches to the study of heterogeneity of aging across disciplines. Moreover, efforts to define the heterogeneity of process toward disease and mortality must be undertaken. Death is a generally useful research endpoint due to its uniform definition. However, that convergence to a similar endpoint masks the vast heterogeneity of paths to it, and comprehension of those early, diverse mechanisms will be crucial for progress to be made against the latest-stage consequences. The panel discussed epigenetic DNA methylation clocks as an exemplar "omic" biomarker of aging, which can provide early-stage mechanistic insight while capturing the multidimensional heterogeneity of the aging process.

Sex differences in lifespan and health must be considered when attempting to explain heterogeneity of aging. Because of sex differences in life phases (eg, pregnancy and menopause), longitudinal observations in women over the lifespan as opposed to continued reliance on cross-sectional studies are required. To capture the full diversity and heterogeneity of human, aging recruitment of research participants based upon age, sex, race, socioeconomic status, and health must accurately reflect that of our communities. The challenges involved in multidimensional studies of heterogeneity necessitate the formulation of interdisciplinary teams with basic science to translational reach expertise. The goal is to leverage novel analytic, computational, and machine learning approaches to advance discoveries, as well as more accurately model and predict biological aging and disease risk in humans.

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Conflict of Interest

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the United States Government.

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Author Contributions

G.A.K. prepared the initial draft of the manuscript. A.L.H., J.G.R., P.S., V.K. substantively edited the initial draft. All authors contributed to the content and reviewed or edited the manuscript.

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