

NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE ON AGING

Summary Minutes

The 149th Meeting
NATIONAL ADVISORY COUNCIL ON AGING
May 16-17, 2023

National Institutes of Health
Hybrid Meeting
Bethesda, MD 20892

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Department of Health and Human Services
Public Health Service
National Institutes of Health
National Institute on Aging
NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
May 17, 2023

The 149th meeting of the National Advisory Council on Aging (NACA) was convened on Wednesday, May 17, 2023, at 9 a.m. in person and by videoconference. Dr. Richard Hodes, Director, National Institute on Aging (NIA), presided.

In accordance with the provisions of Public Law 92–463, the meeting was closed to the public on Tuesday, May 16, from 2 p.m. to 5 p.m. for the review, discussion, and evaluation of grant applications in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of Public Law 92–463.¹ The meeting was open to the public on Wednesday, May 17, from 9:00 a.m. to 12:40 p.m.

Council Participants:

Dr. Sanjay Asthana
Dr. Darren Baker
Dr. Anne Case
Dr. Maritza Ciliberto
Dr. Yanira Cruz
Dr. Susan L. Greenspan
Dr. Yadong Huang (not in attendance)
Dr. Rev. Cynthia Huling Hummel
Dr. Sharon Inouye
Dr. Sohail Khan
Dr. Frank Longo
Ms. Nancy Lundebjerg
Dr. Jennifer Jaie Manly
Dr. Charlotte Peterson
Dr. David B. Reuben
Dr. Julie A. Schneider
Dr. Linda J. Van Eldik
Dr. David R. Weir (joined via teleconference)

Executive Secretary:

Dr. Kenneth Santora, NIA

Ex Officio Participants:

Dr. Radha Holavanahalli, Administration for Community Living (ACL) (not in attendance)

¹ For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure only applied to applications that were discussed individually, not to “en bloc” actions.

Dr. Anne Ordway, National Institute on Disability, Independent Living, and Rehabilitation, ACL
(not in attendance)

In Addition to NIA Staff, Other Federal Employees Present:
Dr. Rick Woychik, National Institute of Environmental Health Sciences

Members of the Public Present:
Dr. Stephen Kritchevsky, University of North Carolina at Chapel Hill
Dr. Hong-Wen Deng, Tulane University School of Medicine
363 live views via NIH videocast.

I. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).²

A total of 2,249 applications requesting \$5,365,422,257 for all years underwent initial review. The Council recommended 1,261 awards for a total of \$3,294,307,351 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

II. CALL TO ORDER

Dr. Kenneth Santora welcomed members to the open session of the 149th NACA meeting. Dr. Hodes called the meeting to order at 9:00 a.m. on Wednesday, May 17, 2023.

A. Director's Status Report

Fiscal Year 2023 Pay Lines

Dr. Hodes announced the current fiscal year (FY) 2023 grant pay lines. For general applications reviewed by the Center for Scientific Review (CSR) and requesting less than \$500,000 (direct costs) in any one year, pay lines are 15% for most regular research applications, 18% for new investigator applications, and 20% for early-stage investigator applications. For CSR-reviewed applications seeking \$500,000 or more, pay lines are 12% for most regular research applications, 15% for new investigator applications, and 17% for early-stage investigator applications. Pay lines are higher for applications focused on Alzheimer's disease and Alzheimer's disease-Related Dementias (AD/ADRD): 25% for most regular research applications, 28% for new investigator applications, and 30% for early-stage investigator applications.

For NIA-reviewed applications, the impact scores for general pay lines are 24 for program projects, 24 for other NIA-reviewed research, 24 for career development awards, and 30 for fellowship awards. The corresponding AD/ADRD pay lines are 35, 35, 35, and 40, respectively.

² For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to "en bloc" actions.

NIA AD/ADRD Funding

Dr. Hodes emphasized NIA's commitment to accelerating AD/ADRD research by growing the AD/ADRD research workforce. During FYs 2015-2022, NIA awarded approximately one-third of its AD/ADRD research funding to new or early-stage investigators and one-fifth to investigators who were new to the field. Furthermore, in FY 2022, NIA distributed \$339,039,351 to 23 sister Institutes within the National Institutes of Health (NIH), with the National Institute of Neurological Disorders and Stroke receiving \$267,369,231. One mechanism by which NIA has successfully recruited the perspectives of other sister Institutes to AD/ADRD research is by funding grant supplements that are relevant to AD/ADRD. Dr. Hodes reported that many of the researchers who have received these supplemental funds have proceeded to incorporate AD/ADRD into primary research proposals.

NIA AD/ADRD Real-World Data Platform

Dr. Hodes introduced the AD/ADRD Real-World Data Platform, which aims to leverage public-private partnerships to establish a robust AD/ADRD research infrastructure with longitudinal data from pharmacy chains, health organizations, electronic health records, insurance claims, and wearable sensors, as well as data pertaining to social determinants of health (SDOH). With these data, the Platform seeks to capture 80% of the AD/ADRD population. The Platform will help researchers screen and recruit participants for clinical trials, evaluate drugs for repurposing, conduct long-term follow-ups, surveil the outcomes of participants from diverse communities, and develop innovative clinical trial designs. The overarching goals of the Platform are to (1) improve the applicability and generalizability of findings in AD/ADRD research by providing larger and more diverse datasets, (2) capture more complete information by linking data from multiple sources, (3) increase the speed at which specific research questions can be answered, (4) enhance researchers' ability to answer questions not readily answerable via clinical trial, and (5) facilitate higher clinical trial recruitment and participation.

[Applications](#) to the Platform, which is a U54 cooperative agreement, are due by July 31, 2023. NIA staff will work closely with awardees, who are expected to stay up to date on the data science landscape and research regulations. At minimum, the Platform will include the following eight cores: (1) Vision, Planning, and Administration; (2) Clinical Research Networks; (3) Business Case and Translation; (4) Stakeholder, Data Privacy, and Ethics; (5) Health Disparities Research and Recruitment Innovation; (6) Trial Innovation; (7) Data Quality, Integration, and Access; and (8) Incubator. Applicants are encouraged to address the objectives of all eight cores, described in the Request for Applications (RFA), but may also propose up to two investigator-initiated optional cores relevant to AD/ADRD research.

NIA Start-Up Challenge and Accelerator

Only a small fraction of graduate students in the behavioral, social, and biological sciences pursue academic careers, and students from diverse backgrounds can provide valuable contributions to the development of health-promoting and life-prolonging interventions. To increase the representation of women and individuals from racial/ethnic minority groups in science entrepreneurship, NIA launched a [Start-Up Challenge and Accelerator](#). In 2022, the first year of the Challenge, more than 200 applicants submitted proposals for innovative science-driven technologies with the potential to improve the health and quality of life of older adults. The 5 winners, selected from 20 finalists, each received a \$60,000 prize. Winning proposals included an aging clock-based drug discovery platform for neurodegenerative disorders; a

machine learning platform for connecting senior homeowners and renters to vetted home remodeling companies for aging in place; a digital health app for African American older adults to self-manage hypertension; a hormone-free vaginal suppository for vulva-vaginal atrophy in post-menopausal women; and an online system that simplifies and streamlines the licensing and renewal process for certified nursing assistants, home health aides, and other medical professionals.

NIA Events and Communications

The [2023 National Research Summit on Care, Services, and Supports for Persons Living with Dementia and Their Care Partners/Caregivers](#) occurred on March 20-22, 2023, and featured eight sessions: (1) The what matters most framework and living well with AD/ADRD; (2) the impact of detection and diagnosis on individuals and their care partners; (3) dementia care models and coordination of care; (4) disparities in health care access, utilization, and quality; (5) support for care partners and caregivers; (6) the dementia care workforce; (7) economic impacts, implications, and approaches; and (8) approaches to participatory research and diverse recruitment and retention in dementia care research. The plenary talk focused on challenges and best practices for dissemination and implementation of interventions for persons living with dementia and their care partners.

The [Fourth Summit: Geroscience for the Next Generation](#) occurred on April 24-26, 2023, and featured eight sessions focused on (1) biological determinants of health and health disparities in aging, (2) populations for Geroscience research, (3) multimorbidities and geriatric syndromes, (4) methods for measuring age-related health outcomes, (5) mathematical modeling of aging and health, (6) Geroscience biomarkers, (7) Geroscience applications in medicine, and (8) considerations for Geroscience clinical trials.

Since January 2023, NIA has released 19 research highlights, each featuring at least one NIA-supported publication, 16 blog posts, and 4 news announcements. In addition, Dr. Hodes, Dr. Kelley, and other senior NIA staff have participated in 12 stakeholder and advocacy group meetings and 6 Congressional briefings and hearings. Active [funding opportunities](#), recently [approved concepts](#), and [blog posts](#) are publicly accessible on the NIA website.

NIH SenNet Consortium Underrepresented Student Program

The [NIH Common Fund Cellular Senescence Network \(SenNet\)](#) seeks to identify and characterize differences in senescent cells across the body, states of health, and the lifespan by developing technologies that build upon previous advances in single cell analysis. SenNet recently launched the [Comprehensive Underrepresented Summer Internship Program \(CUSP\)](#) for undergraduate students from populations historically underrepresented in science. From June 5 to August 18, 2023, participating students will conduct research in a SenNet host lab and will have the opportunity to present a virtual poster at the SenNet annual meeting.

NIH UNITE Initiative

NIH is committed to developing and implementing new methods for supporting diversity, equity, and inclusion in biomedical research. As part of this commitment, NIH established the UNITE initiative, which aims to promote *understanding* of stakeholder experiences through listening and learning; facilitate *new* research on health disparities, minority health, and health equities; *improve* NIH culture and structure for equity, inclusion, and excellence; foster *transparency*,

communication, and accountability with stakeholders; and construct a robust *extramural* research ecosystem that encourages workforce diversity. NIA staff involved in UNITE leadership include Ms. Melissa Espinoza, Dr. Frank Bandiera, and Dr. Patricia Jones.

NIH recently published the [2021-2022 UNITE Progress Report](#), which describes NIH's efforts to identify and address structural racism within NIH and in the broader biomedical and behavioral research community. Two key achievements highlighted in the report include (1) NIH's support of funding opportunities for research on health disparities and the impact of structural racism on minority health and (2) the launch of the Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program through the NIH Common Fund to enhance and maintain inclusive scientific environments.

NIH Strategic Plan for Diversity, Equity, Inclusion, and Accessibility

NIH released the [FY 2023-2027 NIH-Wide Strategic Plan for Diversity, Equity, Inclusion, and Accessibility \(DEIA\)](#), which articulates NIH's commitment to embracing, strengthening, and integrating DEIA across all agency activities. The plan outlines the ways in which NIH will address DEIA in its operations, workforce, and research activities—emphasizing the need to foster sustainable change; harness data; and promote transparency, communication, and engagement.

New NIH Director

On May 15, 2023, President Biden [announced](#) his intent to nominate Dr. Monica Bertagnolli as Director of NIH. Dr. Bertagnolli currently serves as Director of the National Cancer Institute (NCI) and will be the first woman to hold the position. Dr. Bertagnolli's appointment will require Senate approval, and NCI is in the process of identifying a new Director.

Discussion

Dr. Frank Longo asked how NIH ensures that its various AD/ADRD initiatives are comprehensive yet not duplicative. Dr. Hodes responded that NIH annually submits to Congress a Bypass Budget for AD/ADRD research that estimates the additional funds needed to prevent and effectively treat AD/ADRD by 2025. To create this budget, NIH develops milestones based on AD/ADRD research gaps and opportunities identified during NIA summits. NIA also hosts an annual planning retreat that serve as a forum for discussing opportunities and priorities for advancing aging research, including AD/ADRD research. Through these processes, NIH is able to examine where AD/ADRD initiatives coalesce or are lacking.

Dr. Sohail Khan suggested that NIA expand its diversity efforts to include initiatives that directly engage first-generation college graduates, who could potentially serve as powerful role models in their communities. He noted that low socioeconomic status (SES) and underrepresented students who do not complete college often lack resources, mentorship, and role models.

Referring to the extensive data that NIA has collected over the past few decades, Dr. Sanjay Asthana suggested that NIA develop a centralized informational resource for investigators interested in leveraging artificial intelligence (AI) for data analysis. He noted that such a resource should include information on the risks and benefits of AI. Dr. Hodes responded that several NIA working groups are discussing AI methods in aging research and could potentially report on their discussions at future Council meetings.

B. Staff Introductions

NIA division directors introduced new NIA staff members from the Divisions of Aging Biology (DAB), Behavioral and Social Research (BSR), Neuroscience (DN), and Extramural Activities (DEA); the Office of Administrative Management (OAM)'s Workforce and Administrative Management Branch (WAMB) and Information Technology Branch (ITB); the Office of the Director (OD); the Office of Legislation, Policy, and International Activities (OLPIA); the Office of Communications and Public Liaison (OCPL); and the Intramural Research Program (IRP).

C. Future Meeting Dates

September 19-20, 2023 (Tuesday and Wednesday), Building 31
January 23-24, 2024 (Tuesday and Wednesday), Virtual
May 21-22, 2024 (Tuesday and Wednesday), Building 45
September 18-19, 2024 (Wednesday and Thursday), Building 31

D. Consideration of Minutes of the Last Meeting

The minutes of the January 2023 Council meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. Yanira Cruz summarized presentations by Dr. Robin Green, Dr. Nathan Stinson Jr., and Ms. Joy Toliver to the Task Force on Minority Aging Research. Dr. Jennifer Manly emphasized that these presentations showcased the potential for intentional investment in diverse communities to affect change in research, health care, and entrepreneurship.

Dr. Green presented on lessons learned from the [Study of Women's Health Across the Nation \(SWAN\)](#) regarding strategies for effectively engaging women of color in clinical trials. SWAN is a longitudinal cohort study designed to examine the natural progression of menopause and decline in ovarian function among women from diverse racial/ethnic groups, geographic regions, and SES. The study has enrolled 3,302 African American, Chinese, Japanese, Hispanic, and non-Hispanic Caucasian women across seven clinical sites in the United States.

Dr. Green highlighted several strategies she believes were instrumental to engaging and retaining this diverse study cohort. She recommended leveraging multiple sources (e.g., census, voter registration records, insurance records, telephone directories, membership lists for racial/ethnic organizations) and recruitment techniques (e.g., asking recruited participants to recommend other potential participants). Dr. Green also emphasized that researchers should consider the needs and challenges of the populations from which they seek to recruit. She highlighted, for example, the importance of focusing on health issues that most concern the communities being studied, making study sites accessible and providing transportation, allowing flexible scheduling for study sessions, translating study materials into multiple languages, and sharing study findings with participants. For research on older adults, in particular, Dr. Green noted that accommodations such as providing materials with larger font sizes are essential for optimizing participants' experiences. Lastly, Dr. Green discussed ways to incorporate cultural competence into clinical trial procedures. She noted that clinical trial staff should be recruited from diverse

racial and ethnic groups and speak multiple languages, consider participants' beliefs and cultural norms, and acknowledge the importance of family to certain cultures by allowing relatives to accompany participants to study sessions.

Dr. Stinson's presentation focused on the efforts of the [NIH Community Engagement Alliance \(CEAL\) Against COVID-19 Disparities](#), which works closely with underserved and racial and ethnic minority communities disproportionately affected by COVID-19. CEAL conducts community-engaged research and outreach focused on COVID-19 awareness and education to address widespread misinformation and distrust and to promote evidence-based responses to both COVID-19 and future pandemics. CEAL also promotes and facilitates the inclusion of diverse racial and ethnic populations in clinical trials for disease prevention and the development of vaccines and therapeutics. Dr. Stinson shared lessons learned from CEAL activities, including the importance of disaggregating existing data to uncover potentially hidden racial and ethnic disparities, disseminating outreach materials in multiple languages, and frequently communicating with local leaders, community organizations, and government officials who understand the needs of their communities. He also emphasized that, when conducted correctly, community-engaged research generates findings and interventions that best resonate with diverse populations and is thus a critical tool for addressing health disparities.

Ms. Toliver's presentation provided an overview of the [NIA Small Business Programs](#) and NIA's efforts to increase the representation of women and racial and ethnic minorities in science entrepreneurship. NIA provides more than \$140 million annually in research and development grants to small businesses through its Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, which aim to support the development of interventions that prevent or treat age-related diseases. To increase the participation of underrepresented populations in SBIR and STTR, NIH offers several programs and resources such as the [NIH Applicant Assistance Program \(AAP\) for Small Businesses](#) and the previously described NIA Start-Up Challenge and Accelerator. The AAP is a 10-week coaching program that aims to prepare small businesses for Phase 1 SBIR and STTR program applications and increase the number of applications submitted by underrepresented small businesses compliant with SBIR and STTR review criteria. Through the AAP, small businesses can receive free one-on-one coaching, needs assessment and mentoring, assistance with required registrations, and application review.

Discussion

Dr. Nancy Lundeberg asked whether NIA has attempted to capture a comprehensive assessment of successful recruitment strategies across studies. She noted that for AD/ADRD research, in particular, additional challenges exist for recruiting individuals with advanced dementia who either live alone or whose caregivers do not have the time or resources to accompany them to study visits. Dr. Manly responded that NIA researchers are increasingly working to develop means of engaging participants such as by conducting studies remotely and providing participants with smartphones and wearable devices. Dr. Susan Greenspan added that electronic study equipment could also be brought to participants' homes and assisted living communities or provided in accessible community locations such as recreational centers and churches.

Regarding recruitment of caregivers to studies, Dr. Cruz stated that more efforts are needed to understand the challenges they face and identify the best means to engage them. She commented

that caregivers belonging to certain communities, such as Hispanic caregivers, often do not self-identify as caregivers, which creates a barrier for outreach and recruitment. Dr. Sharon Inoue added that institutional review boards frequently fail to consider the need to pay additional incentives for dementia patients and caregivers, including to cover transportation and childcare costs. Dr. Santora emphasized that these topics are of high priority for NIA and were discussed during the 2023 National Research Summit on Care, Services, and Supports for Persons Living with Dementia and Their Care Partners/Caregivers. Dr. Santora added that NIA's Clinical Research Operations and Management System (CROMS) also enables NIA staff and grantees to track their clinical research enrollment data in real time and collect information that may help inform future recruitment strategies.

Multiple Council members noted a need to increase public awareness of AD/ADRD research and suggested that researchers collaborate with community leaders to conduct outreach efforts and examine the recruitment strategies utilized in large studies such as the Health and Retirement Study. Dr. Asthana noted that studies that provide services to participants, such as long-term exercise classes, have been shown to increase participant retention.

IV. REPORT: WORKING GROUP ON PROGRAM

Dr. Greenspan, Chair of the Working Group on Program (WGOP), led the updates.

A. Notice of Funding Opportunity Concept Clearance

Dr. Greenspan invited Dr. Longo, the primary reviewer of the proposed concept for DEA and the Office of Strategic Extramural Programs (OSEP), to present the concept to the Council. The Council members unanimously and enthusiastically concurred with approval of the concept, summarized below.

Technology to Facilitate Characterization of the Exposome in Under-Resourced Populations for AD/ADRD Studies

The exposome, which consists of the comprehensive set of exposures people experience in their physical, chemical, social, psychological, and economic environments, plays a significant role in the development of age-related diseases. To fully characterize the exposome, researchers must collect both environmental and biological samples; however, the under-resourced populations that carry the highest burden of age-related diseases are often difficult to collect samples from and are thus excluded from critical research. The short-term goal of this concept is to develop technologies for remote- or self-sampling of exposome measures that would enable researchers to capture a broader range of participants in exposome characterization research. In addition to facilitating the inclusion of under-resourced populations in this research, the technologies proposed by this concept may also reduce research costs. The long-term goal of this concept is to promote the widespread adoption of these technologies by under-resourced communities.

B. Division of Geriatrics and Clinical Gerontology Review Final Report

Dr. Greenspan introduced Dr. Stephen Kritchevsky, who oversees efforts to review the progress of the Division of Geriatrics and Clinical Gerontology (DGCG). The DGCG Review Committee, led by Dr. Kritchevsky and consisting of current and former Council members and other experts, was tasked in 2022 with evaluating the research goals and strategies of the DGCG. Dr.

Kritchevsky provided an overview of the DGCG and reported on the outcomes of the Committee's review. A final report of the Committee's review will be submitted to Dr. Hodes by May 31, 2023.

DGCG Research Goals and Areas of Interest

The DGCG consists of three branches: Geriatrics Branch, Clinical Gerontology Branch, and Clinical Trials Branch. The goal of the Geriatrics Branch is to characterize factors in older individuals that influence their risk for and the severity of morbidities, disabilities, and vulnerability to stressors. The goal of the Clinical Gerontology Branch is to examine factors that influence changes over the lifespan affecting health and longevity. The goal of the Clinical Trials Branch is to develop and test interventions to prevent or treat age-related conditions and extend the healthspan. Overall, the DGCG is interested in improving the pipeline for developing new interventions that merit testing in clinical trials and achieving sufficient diversity in research study populations to address the underlying mechanisms and effects of outcome disparities.

DGCG Funding Allocations

In FY 2021, the DGCG allocated \$24 million (8.9% of its total budget) to funding T32 awards, K awards, and fellowships. The DGCG allocated \$488,631 to funding diversity supplements. Most DGCG-funded awards supported geriatrics research, with far fewer awards focusing on clinical trials and gerontology.

Initial Remarks and Broad Recommendations

Dr. Kritchevsky congratulated the DGCG for the progress made since its last evaluation in 2015 and thanked DGCG staff for providing materials for review. He noted that the Review Committee was impressed by the urgency and scope of the DGCG mission, recognizing that the number of older adults in the United States will continue to increase substantially. Dr. Kritchevsky also thanked DGCG Review Committee members for their efforts, which culminated in nearly 50 recommendations for the DGCG. Broadly, these recommendations centered on conducting health system and implementation-focused research, developing a clinical trials network as a platform to accelerate testing of interventions, applying insights from the biology of aging to clinical research, examining social and structural determinants of health, and collaborating with other NIA divisions and NIH Institutes, as well as external organizations such as the Patient-Centered Outcomes Research Institute, Food and Drug Administration, and the Centers for Medicare & Medicaid Services (CMS).

Recommendations for the Geriatrics Branch

The DGCG Review Committee recommended that the Geriatrics Branch consider creation of two sub-branches (either structurally or conceptually), focusing on (1) basic, clinical, and translational research and (2) health care research pertaining to diagnostics, appropriate use of pharmacological and nonpharmacological interventions, innovations in health care settings, and the care provided at sites where older adults live or receive health care. The Review Committee also recommended that the Geriatrics Branch collaborate with DN to support research related to the medical management of patients with AD/ABRD. The Review Committee lauded the work of the Claude D. Pepper Older Americans Independence Centers (OAICs), overseen by the Geriatrics Branch, and recommended that the Geriatrics Branch fund additional OAICs and increase funding for existing OAICs.

Recommendations for the Clinical Gerontology Branch

The DGCG Review Committee emphasized the importance of conducting longitudinal studies and evaluating a diverse cohort of individuals as they age versus conducting cross-sectional studies and examining different cohorts of individuals at different life stages. The Review Committee recommended that the Clinical Gerontology Branch both facilitate the creation of new longitudinal studies and review the existing longitudinal studies that it supports—taking into consideration research population diversity, coverage across the lifespan, requirements for new assays, and the effectiveness and appropriateness of study designs and analytical methods. For omics research, in particular, the Review Committee cautioned that proper scale is also necessary to achieve strong signals.

To facilitate the development of multimodal interventions targeting the biology of aging, the Review Committee recommended that the Clinical Gerontology Branch support Phase 2 and 3 clinical trials; participate in pre-competitive programs with the pharmaceutical industry to investigate assay harmonization, identify surrogate endpoints, and explore various trial designs; and partner with other NIA divisions and NIH Institutes to jointly support RFAs for early drug screening and assay development.

The Review Committee remarked that the Aging Research Biobank, overseen by the Clinical Gerontology Branch, promises to become an important resource for researchers nationwide. It encouraged the Clinical Gerontology Branch to further its development and better communicate to the broader research community its purpose and utility.

Lastly, the Review Committee highlighted several topics in need of additional research by the Clinical Gerontology Branch, including dietary patterns and obesity, induced pluripotent stem cells (iPSC) and lab-on-a-chip technologies, aging biomarkers, and the role of the immune system in the biology of aging.

Recommendations for the Clinical Trials Branch

The DGCG Review Committee recommended that the Clinical Trials Branch increase its pool of investigators and recruit talent with more diverse areas of expertise. The Review Committee also noted the need for the Clinical Trials Branch to address demotivators for developing clinical trials, such as non-standardized peer review processes and high fixed costs, and to collaborate with other NIA divisions, NIH Institutes, CMS, and pharmaceutical companies to identify which interventions merit testing. In addition to newly developed interventions, many existing compounds intended for a variety of different uses may merit re-evaluation through the lens of aging biology.

The Review Committee encouraged the development of a clinical trials network consisting of a coordinating center to provide standardized data management and regulatory support and multiple clinical centers that each submit grants to fund network trials. The Review Committee noted that the ability for individual clinical centers to respond to targeted RFAs could enable the DGCG to more efficiently address its priorities.

Recommendations for Achieving Participant and Workforce Diversity

The DGCG Review Committee emphasized the importance of bidirectional, trust-based relationships to recruit diverse populations to research studies. The Review Committee recommended examining disparities that affect participants who are older, homebound, and live

in rural areas and exploring collaborative opportunities with the Resource Centers for Minority Aging Research to develop best practices for recruiting and analyzing data from participants in underrepresented communities.

To promote workforce diversity, the Review Committee recommended that the DGCG provide resources to involve high school and college students in funded grants, facilitate cross-institutional mentorships of early-career investigators in institutions with high proportions of trainees underrepresented in clinical aging research, integrate community-engaged research principles into research training, and promote the uptake of diversity supplements through strategic partnerships between historically black colleges and universities and OAICs.

C. Center for Scientific Review Initiative to Strengthen the Peer Review Process

Dr. Greenspan invited Dr. Santora to summarize a presentation by Dr. Delia Olufokunbi Sam to the Council.

Dr. Olufokunbi Sam's presentation included an overview of the scope of grant applications reviewed by CSR and methods by which CSR aims to strengthen the NIH peer review process. NIH receives approximately 79,000 grant applications each year, with CSR reviewing approximately 60,000 (76%) of those applications. CSR staff consists of 275 senior research officials who conduct 1,200 meetings a year, utilizing 19,000 reviewers. In 2022, 45% of reviewers were women, and 18% were underrepresented minorities.

To ensure that study sections evolve with science, CSR developed the Evaluating Panel Quality in Review (ENQUIRE) program, which integrates data from multiple stakeholders to determine whether changes in study section focus or scope are needed. CSR clusters study sections for review via ENQUIRE by scientific topics and implements an iterative, systematic review process to evaluate approximately 20% of CSR study sections per year. Any proposed changes to study sections require final approval by the CSR Advisory Council, and all study sections are reviewed approximately every five years.

To simplify the peer review process, CSR is also in the process of revising NIH funding opportunity review criteria, which currently include significance, investigators, innovation, approach, and environment. CSR proposes changing these criteria to the importance of research, rigor and feasibility, and expertise and resources, with the latter category incorporated into the overall impact score of the grant application rather than scored separately.

To address the fact that only a small subset of institutions has been represented in NIH National Research Service Award (NRSA) fellowships, CSR is closely examining the application and review processes for NRSA fellowships. Across all funding opportunities, CSR aims to increase fairness in the review process by instituting bias awareness and integrity training modules based on real-life cases that have been presented to NIH. The bias awareness training module has already been tested in 20,000 reviewers and has been well received. Both modules are expected to be fully available for use in May 2024.

V. PROGRAM HIGHLIGHTS (DAB)

Multi-Omics Integrative Studies for Complex Diseases

Dr. Hong-Wen Deng, Professor and Chair; Director, Center for Biomedical Informatics and Genomics, Tulane University School of Medicine

Clinical outcomes of disease are determined by the interaction of multiple levels of omics and environmental factors, including SES and SDOH. In the past, most research efforts have focused on individual aspects of these factors (i.e., genomic, epigenomic, transcriptomic, proteomic, or metabolomic changes) and have revealed many novel loci for complex human conditions. However, for many diseases, these identified loci account for only a small fraction of genetic risk, the specific functional genomic or epigenomic variants and causal genes are largely unknown, and their molecular mechanisms are even less well elucidated. For example, the more than 500 known osteoporosis-associated loci account for only 20% of the disease's total heritability. To address this research gap, integrative trans-omics analysis of multi-omics data can be leveraged to not only identify disease risk-associated genes, variants, and molecules but also better understand their functions in humans.

Osteoporosis is a progressive, age-related metabolic bone disease characterized primarily by low bone mineral density (BMD) and microstructural deterioration of bone tissues, which increases bone fragility and risk for fractures. Dr. Deng's trans-omics studies of osteoporosis include two cohorts of 7,352 and 5,100 Caucasian participants from the Omaha Osteoporosis Study and Kansas City Osteoporosis Study (KCOS), respectively, as well as a cohort of more than 17,000 racially diverse participants in the Louisiana Osteoporosis Study (LOST). These participants have been surveyed for bone and body composition via dual X-ray absorptiometry (DEXA) and quantitative computed tomography as well as for diverse epidemiological and lifestyle data through questionnaires. DNA, plasma, and stool samples have been collected from most participants, and some participants have also been assayed for COVID-19.

Dr. Deng's research group focuses on the use of multi-omics analysis to identify factors associated with low BMD, a major characteristic of osteoporosis. In a four-phase study of 119 Caucasian women with either high or low BMD, his research team integrated genomics, transcriptomics, methylomics, and metabolomics to identify osteoporosis biomarkers. The first phase included single-omics analysis to identify differentially expressed genes (DEGs), differentially methylated CpG sites (DMCs), and differential metabolic products (DMPs) associated with osteoporosis risk. The second phase involved integrating identified DEGs, DMCs, and DMPs via a novel, sparse multiple discriminative canonical correlation analysis (SMDCCA) to isolate the most prominent osteoporosis biomarkers. Once prominent biomarkers were identified, the third phase involved conducting targeted quantitative trait locus (QTL), interaction network, functional annotation, and classification analyses to examine the relationship between those biomarkers and single nucleotide polymorphisms. Lastly, Mendelian randomization (MR) was used in the fourth phase to assess the potential causal effects of the prominent biomarkers on BMD variation.

Phase 1 single-omics analyses uncovered 1,594 DEGs, 1,219 DMCs, and 204 DMPs that were subsequently input into multi-omics analyses leveraging SMDCCA. Advantages of SMDCCA include its relaxed assumptions about data distribution and flexibility to answer questions across

biological disciplines, computational capacity to handle large datasets, and implementation of dimension reduction to illuminate the largest sources of variation in data. The disadvantage of SMDCCA, however, is its inability to capture correlations within a single-omics dataset. Phase 2 multi-omics analyses identified 74 DEGs, 75 DMCs, and 23 DMPs as prominent osteoporosis biomarkers. Phase 3 analyses revealed that a substantial proportion of these biomarkers not only interact with each other but also contribute to multiple well-known signaling pathways critical to osteoblastogenesis and osteoclastogenesis, such as the Wnt/ β -catenin, RANK/RANKL, and MAPK/TGF- β signaling pathways. Lastly, phase 4 MR illustrated that gene expression of fatty acid desaturase 2 (FADS2) may have a robust causal effect on BMD variation, providing novel insight into the pathogenesis of osteoporosis.

Another recent study, provisionally accepted in *Nature Communications*, involved a systematic, multi-omics analysis of the human genome, gut microbiome, and targeted metabolome in 517 peri- and post-menopausal women. Linear regression analyses testing the association between individual gut microbiota species, BMD, and short-chain fatty acids revealed that *Bacteroides vulgatus* in the human gut microbiome was negatively correlated with both lumbar spine BMD and serum valeric acid, which were positively correlated with each other. MR revealed that *B. vulgatus* may causally suppress valeric acid levels, presumably through its negative association with other probiotic gut bacterial species.

To evaluate the potential impact of *B. vulgatus* on bone metabolism, Dr. Deng's research group performed oral gavage experiments in ovariectomized female mice (models for post-menopausal status). *B. vulgatus*-treated mice exhibited significantly lower trabecular thickness and bone volume fraction, higher trabecular separation, lower percentages of mineralized bone volume, increased osteoclasts in the lumbar vertebral body, and increased bone resorption. They also exhibited lower serum valeric acid levels and decreased relative abundance of valeric acid-producing microbes such as *Megasphaera elsdenii* and *Oscillibacter valericigenes*.

To investigate whether down-regulation of valeric acid mediates the impact of *B. vulgatus* on bone metabolism, Dr. Deng's research group also evaluated the direct effects of valeric acid on bone metabolism in ovariectomized mice. Mice treated with valeric acid exhibited higher trabecular thickness, bone volume fraction, and percentages of mineralized bone volume. They also exhibited significantly fewer osteoclasts and lower bone resorption levels.

Further analyses conducted in vitro demonstrated that treatment of murine macrophages and pre-osteoblasts with valeric acid for 5 days significantly decreased the proportion of mature osteoclast-like cells. Treatment with valeric acid for 14 days significantly increased differentiation of the pre-osteoblasts into osteoblasts and mineralization of the extracellular matrix. In addition, treatment of cultured osteoclast-like cells and osteoblasts with valeric acid resulted in increased expression of the anti-inflammatory cytokine, IL-10, and NFKBIA and decreased protein levels of NF-kB P65. Taken together, these findings indicate that *B. vulgatus* inhibits valeric acid-producing gut microbiota, reducing serum valeric acid levels and triggering increased osteoclast and osteoblast inflammation. In turn, this inflammation promotes osteoclast activity and bone resorption but reduces osteoblast differentiation and activity, leading to reduced BMD and poor bone microstructure.

In addition to studying osteoporosis, Dr. Deng's research group recently started to investigate AD genetic risk mechanisms in diverse populations. The aims of this research include (1) generating a new multi-omics dataset to be used in the Alzheimer's Disease Sequencing Project – Follow Up Study (ADSP-FUS) and (2) constructing single-cell and spatial multi-omics tissue maps in brain tissues from AD patients and controls to identify differences in transcriptomes and cell compositions. Leveraging known relationships between different omics data, Dr. Deng and his colleagues are using trans-omics imputation to fill gaps in multi-omics data and generate more comprehensive datasets that provide insight into complex biological systems. Preliminary results demonstrate slightly differential performance of trans-omics imputation for Caucasian and African American participants, but integrating local ancestry data into the trans-omics imputation method may mitigate this differential.

To more comprehensively study AD/ADRD by incorporating neuropsychological and functional clinical data collection into multi-omics studies, Dr. Deng's research group is also collaborating on a pilot study with Dr. Pericak Vance's ADSP-FUS research group at the University of Miami. The pilot study has recruited more than 110 African American patients to date and will help the Tulane Center for Bioinformatics and Genomics to develop the infrastructure needed to develop a larger scale AD/ADRD study in the future.

Discussion

Dr. Linda Van Eldik asked whether Dr. Deng plans to include proteomics in future studies given that protein levels do not always correspond with RNA levels. Dr. Deng responded that the Tulane Center for Bioinformatics and Genomics recently recruited a professor who specializes in proteomics. With this professor's expertise and with recent technological innovations in analyzing the proteome, Dr. Deng intends to conduct additional proteomic studies.

Dr. Manly asked whether Dr. Deng intends to apply techniques such as machine learning to research in Hispanic and non-White individuals. Dr. Deng noted that although previous studies were limited by funding, resources and population accessibility, his research group's goal is to expand research to as many ethnic groups as possible.

Dr. Asthana asked whether Dr. Deng will collect clinical data, such as from positron emission tomography scans and cognitive measures, to correlate with multi-omics data. Dr. Deng noted that his pilot study with the ADSP-FUS research group will involve analysis of serum and plasma samples to identify biomarkers for AD and for cardiovascular disease, which is a risk factor for AD.

VI. COUNCIL GUEST SPEAKER

Environmental Health and Older Adults: Research Priorities of the National Institute of Environmental Health Sciences

Dr. Rick Woychik, Director, National Institute of Environmental Health Sciences

The National Institute of Environmental Health Sciences (NIEHS) seeks to investigate the impact of the environment on health and provide global leadership for innovative research that improves public health by preventing disease and disability. NIEHS' strategic plan consists of three overarching themes: (1) environmental health sciences, (2) data knowledge to action, and (3) stewardship and support. NIEHS studies how environmental exposures impact the biological pathways that drive human health, applies research findings to benefit public health, and supports the next generation of environmental health scientists through training and the development of collaborative data networks. NIEHS is updating its strategic plan, taking into account several emerging scientific priority areas including the exposome and the relationship between climate change and health.

Many different aspects of the environment can impact human health, and the exposome refers to the totality of exposures people experience over the life course. Techniques and tools such as mass spectrometry, sensors, and bioinformatics can be leveraged to measure the exposome, but a robust operational definition of exposome is needed to develop new technologies to study it. In 2022, NIEHS hosted five virtual workshops aimed at operationalizing the exposome that featured discussions on what types of data to measure as well as methods and approaches for data harmonization, analysis, interpretation, sharing, and translation to impact health and disease.

Exposome research requires a coordinated effort among researchers. An upcoming NIEHS RFA centers on the need for a commonly agreed upon framework for exposome research that promotes best practices for data collection and sharing and facilitates the development of a global exposome research community. In addition, NIEHS sponsors the Human Health Exposure Analysis Resource (HHEAR) created at Mount Sinai. HHEAR provides an infrastructure for NIH-funded researchers to access exposure-assessment services, expertise on exposome research study design and data analysis, and a public data repository of de-identified epidemiologic and biomarker data. HHEAR exposure-assessment services include both traditional biomonitoring for targeted, hypothesis-driven research and hypothesis-free exploratory analyses utilizing advanced technologies.

To address the variability in individuals' responses to environmental exposures, precision environmental health can not only complement precision medicine but also help identify gene-environment interactions that may contribute to processes such as aging. Precision environmental health integrates genetics, epigenetics, and omics data to understand individual disease risk. Because no single gene predisposes a differential response to a particular exposure, global collaborative efforts such as those of the International Common Disease Alliance (ICDA) are needed to implement precision environmental health and link complex traits with environmental exposures. The environmental health science community should engage with the ICDA in order to incorporate exposome and epigenetics research into ICDA patient phenotyping efforts.

To help integrate environmental data into patient phenotyping, NIEHS plans to collaborate with the *All of Us* Research Program, which aims to accelerate medical breakthroughs by gathering

health data from at least one million people living in the United States. By contributing environmental data, NIEHS will enhance the *All of Us* Research Program's diverse dataset of genomic, biospecimen, wearable, electronic health record, behavioral, survey, and physical measurement data. NIEHS proposes to integrate geospatial environmental exposures into *All of Us* through three interrelated phases that can be developed, in part, in parallel: (1) integration of location information through a decentralized address geocoding tool; (2) development of an infrastructure for integrating information on geospatial, environmental, and social determinants of health; and (3) assessment of assay exposures in biospecimens and study of combined genomic, environmental, and social determinants of health. Potential geospatial exposure data types include air quality measures, daily weather metrics, and the Centers for Disease Control and Prevention (CDC) Social Vulnerability Index.

Studies at the intersection of environmental health science and aging have linked environmental factors such as toxin exposures to the development of AD/ADRD. An exposome-integrated approach can support aging research by identifying mixtures of chemicals or other environmental factors and their associations with hallmarks of aging. For example, telomere length appears to be a molecular marker of stress and resilience that merits probing. Shorter telomeres are associated with increased hypoxia, psychosocial stress, exposure to calcium, hyperoxia, and cancer risk. Meanwhile, longer telomeres are associated with increased risk for other types of cancers, increased protection against cardiovascular disease, exposure to arsenic, and exposure to polychlorinated biphenyls. The Telomere Research Network sponsored by NIEHS and NIA aims to facilitate collaboration between basic telomere biologists, population and exposome researchers, and other scientists to compare existing and novel methods of telomere measurement applicable to population studies and to elucidate the relationship between telomeres and environmental exposures, psychosocial stress, and disease susceptibility.

Beyond genetic predispositions, multiple windows of susceptibility occur throughout development, during which environmental exposures have the greatest impact on the aging trajectory. For example, research has shown that exposure to the pesticide rotenone during pregnancy in mice alters patterns of liver DNA methylation in offspring. Another study revealed that neonatal rats exposed to low doses of bisphenol A (BPA) experience accelerated epigenetic aging. To elucidate the molecular mechanisms of such changes, Phase II of the NIEHS Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET) Program is characterizing epigenetic changes induced by environmental exposures in a variety of tissue and cell types such as the brain, lung, liver, skin, and blood. TaRGET Phase II is also investigating whether factors such as the timing of exposure and sex of the organism that influence those epigenetic changes are conserved across tissue and cell types. In 2021, NIA provided \$3 million in co-funding to TaRGET to support the generation of multi-omics, exposure-induced signatures and gene expression profiles from the cortices of 10-month-old animals and surrogate tissues and analyses from 5- and 10-month-old animals.

The collaborative efforts of NIEHS and NIA reflect their strong partnership and combined interests in environmental factors that contribute to age-related disease, the development of aging biomarkers sensitive to environmental exposures, and gene-environment interactions implicated in age-related health outcomes. Future areas of opportunity for NIEHS include developing comprehensive exposomic tools that incorporate multiple sources of exposure information, genetics, and age-related outcomes; creating a data repository framework to facilitate data

sharing; and continuing to provide joint support for climate- and health-related activities such as disaster response research.

Discussion

Dr. Longo and Dr. Hodes asked about the possibility of combining exposome and omics research to comprehensively examine aging trajectories. Dr. Woychik responded that exposomics should be an additional domain of omics studies in addition to transcriptomics, genomics, and proteomics. He noted that high-resolution mass spectrometry applied to just one milliliter of blood can uncover more than 600 different metabolites that are indicators of different environmental exposures. NIEHS aims to lead the development of tools and technologies that can be leveraged by researchers to incorporate exposomics into their omics studies. Dr. Woychik emphasized the need to raise awareness of the large impact of the environment on health and methods for studying environmental factors.

Dr. Manly asked how geocoded exposures can be linked to the early childhood experiences of older individuals and also noted that factors such as racism and sexism are often at the root of harmful exposure patterns. Dr. Woychik emphasized the importance of conducting longitudinal studies that allow researchers to examine the effects of exposures over extended periods of time and of developing robust biomarkers beyond exposure-induced epigenetic changes. He also noted that, in addition to chemicals, NIEHS researchers are investigating psychosocial and lifestyle factors such as sleep and diet that may vary across different communities and lead to differential aging and health outcomes.

VII. ADJOURNMENT

The open session of the 149th meeting of the National Advisory Council on Aging adjourned at 12:40 p.m. on May 17. The next National Advisory Council on Aging meeting is scheduled for September 19-20, 2023.

VIII. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.³



Richard J. Hodes, M.D.
Chairman, National Advisory Council on Aging
Director, National Institute on Aging

Prepared by Kenneth Santora, Ph.D.
With assistance by Rose Li and Associates, Inc.

³ These minutes will be approved formally by Council at the next meeting on September 18-19, 2023, and corrections or notations will be stated in the minutes of that meeting.