

NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE ON AGING

Summary Minutes

The 153rd Meeting
NATIONAL ADVISORY COUNCIL ON AGING
September 18-19, 2024

National Institutes of Health
Hybrid Meeting

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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
September 19, 2024

The 153rd meeting of the National Advisory Council on Aging (NACA) was convened on Thursday, September 19, 2024, at 9:00 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 Wednesday, September 18, from 3:00 p.m. to 5:00 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 Thursday, September 19, from 9:00 a.m. to 1:00 p.m.

Council Participants:

Dr. Sanjay Asthana
Dr. Anne Case
Dr. Yanira Cruz
Dr. Susan L. Greenspan
Dr. Yadong Huang
Dr. Rev. Cynthia Huling Hummel
Dr. Sharon K. Inouye
Dr. Sohail Khan
Dr. Frank Longo
Ms. Nancy E. Lundebjerg
Dr. David B. Reuben
Dr. Julie A. Schneider
Dr. Linda J. Van Eldik

Executive Secretary:

Dr. Kenneth Santora, NIA

Ad Hoc Participants:

Dr. Robert Hummer, Carolina Population Center, University of North Carolina at Chapel Hill

In Addition to NIA Staff, Other Federal Employees Present:

Dr. Radha Holavanahalli, Rehabilitation Program Specialist, National Institute on Disability, Independent Living and Rehabilitation Research, Administration for Community Living, U.S. Department of Health and Human Services (HHS)

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. Janine Clayton, Director, Office of Research on Women's Health (ORWH), National Institutes of Health (NIH)

Members of the Public Present:

Dr. Holly Ingraham, Professor, University of California, San Francisco

326 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 2,636 applications requesting \$6,537,718,902 for all years underwent initial review. The Council recommended 1,399 awards for a total of \$3,730,016,850 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 153rd NACA meeting. Dr. Hodes called the meeting to order at 9:00 a.m. on Thursday, September 19, 2024.

A. Director's Status Report

In Memoriam: Leonard Hayflick, Ph.D.

Dr. Hodes recalled the significant contributions of Dr. Leonard Hayflick to NIA and the scientific community. Dr. Hayflick was a pioneer in the study of cell biology and aging processes, demonstrating the mortality of in vitro human cells. He was an emeritus professor of anatomy at the University of California, San Francisco and held multiple leadership roles, including as President of the Gerontological Society of America, Chairman of the Scientific Review Board of the American Federation of Aging Research, and Editor-in-Chief of *Experimental Gerontology*. Dr. Hayflick was a founding member of NACA and served as a consultant to the National Cancer Institute.

Appropriations Status for the National Institute on Aging

On July 10, 2024, the House Labor-Department of Health and Human Services (HHS) Fiscal Year (FY) 2025 appropriations bill advanced out of the full House Appropriations Committee. If enacted, the bill would implement structural changes across NIH, including consolidating the 27 current Institutes and Centers (ICs) into 15 institutes, including a new National Institute on Dementia. NIH would receive \$48.5 billion as flat funding relative to FY24, and the National

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Institute on Dementia would receive \$4.6 billion, a slight increase from the \$4.51 billion allocated to NIA in FY24.

On August 1, 2024, the Senate Labor-HHS appropriations bill advanced out of the Senate Appropriations Committee. If enacted, NIH would receive \$50.224 billion, an increase of \$2.05 billion from FY24, and NIA would receive \$4.6 billion, an increase of more than \$137.5 million from FY24. The bill proposes an additional \$275 million for research on Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) (divided equally between NIA and the National Institute of Neurological Disorders and Stroke (NINDS)) and an additional \$12.5 million for research on palliative care. These appropriations depend on the avoidance of a government shutdown, passage by the full Senate, as well as signature from the President.

Fiscal Year 2024 Allocations for Competing Research Grant Awards

For current NIH FY24 allocations for applications under \$500,000 in direct costs reviewed by the NIH Center for Scientific Review (CSR), the NIA pay line is the 16th percentile (19th and 25th percentiles for new investigator (NI) and early-stage investigator (ESI) R01s, respectively). For applications over \$500,000 in direct costs reviewed by CSR, the pay line is the 13th percentile (16th and 23rd percentiles for NI and ESI R01s, respectively). For AD/ADRD applications under \$5 million in direct costs reviewed by CSR, the pay line is the 17th percentile (20th and 25th percentiles for NI and ESI R01s, respectively). For AD/ADRD applications over \$5 million in direct costs reviewed by CSR, the pay line is the 14th percentile (17th and 23rd percentiles for NI and ESI R01s, respectively). For NIA-reviewed applications, the general pay lines are associated with priority scores of 25 for program projects, other NIA-reviewed research, or career development awards, and 30 for fellowship awards. NIA-reviewed AD/ADRD application pay lines are associated with priority scores of 25 for program projects and other NIA-reviewed research, 30 for career development awards, and 35 for fellowship awards.

2026 Professional Judgment Budget for Alzheimer's Disease and Alzheimer's Disease-Related Dementias

Each fiscal year through 2025, the NIH Director is required to submit directly to the President a professional judgment budget for the NIH initiatives pursuant to the National Plan to Address Alzheimer's Disease.³ This budget reflects input from NIH, academia, industry, other federal agencies, nongovernmental organizations, and advocates. The budget outlines priorities, gaps, and opportunities in AD/ADRD research; identifies milestones toward the Plan's goals; and proposes funding specific to achieving each milestone. [The FY26 Professional Judgment Budget Proposal](#) estimates \$3.98 billion total FY26 resources needed for AD/ADRD research, which is the total of \$3.87 billion in FY24 enacted dollars and \$113.49 million for additional research. The project cost of resources needed for new and evolving research to meet the research goals of the National Plan to Address Alzheimer's Disease is \$445 million. These funds are divided into the eight Common Alzheimer's Disease Research Ontology (CADRO) categories as follows: epidemiology and population studies (\$60 million); disease mechanisms (\$20 million); diagnosis, assessment, and disease monitoring (\$82 million); translational research and clinical interventions (\$148 million); dementia care and impact of disease (\$26 million); research resources (\$59 million); ADRD (\$40 million); and staffing needs and administrative support (\$10 million).

³ As required under section 2(d)(2) of Public Law 111-375.

2024 Alzheimer's and Related Dementias Progress Report

The [2024 NIH Alzheimer's and Related Dementias Research Progress Report](#) summarizes significant NIH-funded dementia research advances over the past year. These accomplishments include (1) advancing understanding of the risk and protective factors, genetics, and mechanisms of dementia; (2) expanding large and complex datasets in accessible platforms to accelerate translational research on therapeutic candidates; (3) diversifying and de-risking the therapeutic pipeline for disease-modifying drugs; (4) accelerating drug repurposing and combination therapy development; (5) developing tools to detect, diagnose, and monitor dementia; (6) advancing clinical research on lifestyle interventions; (7) increasing understanding of how social and environmental factors affect dementia risk and disparities; (8) expanding research on dementia care and care partner interventions; and (9) enhancing diversity and inclusion in clinical trials.

National Institute on Aging Updates

Dr. Hodes summarized NIA updates. NIA is supporting 461 AD/ADRD clinical trials, classified as dementia care and caregiving trials (201); non-pharmacological (152); pharmacological (67); understanding disease processes (21); diagnostic tools, assessments, and imaging studies (17); and treatments for neuropsychiatric symptoms (3). The majority of the 201 dementia care and caregiving trials focus on formal care settings (44); improving caregiver health and well-being (38); and caregiver assessments, tools, training, and education (23). Most of the 152 non-pharmacological studies are testing exercise (39), neurostimulation (26), and cognitive training (19), as well as other modalities including sleep (15), diet/supplements (6), stress reduction/mindfulness (5), and social engagement (3). Current pharmacological clinical trials target a variety of disease processes, including inflammation, amyloid, metabolism/bioenergetics, receptors, vasculature, circadian rhythm, and tau. The neuropsychiatric trials consist of non-pharmacological (2) and pharmacological (1) interventions.

At the request of Congress in FY22 appropriations language, NIA and NINDS entered into an agreement with the National Academies of Sciences, Engineering, and Medicine (NASEM) to identify research priorities for preventing and treating AD/ADRD. NASEM established an ad hoc committee on September 20, 2023, which held three public meetings and four closed sessions between October 2023 and February 2024. The committee is currently drafting a final report with release anticipated in the first quarter of 2025.

On September 16, 2024, Dr. Hodes participated in a public conversation with Dr. Atul Gawande, Assistant Administrator for Global Health at the U.S. Agency for International Development (USAID), on “International Perspectives on Health, Aging, and Longevity.” A recording of the exchange, moderated by Dr. Kathleen Neuzil, Director, NIH Fogarty International Center, can be found on [the NIH website](#).

A Request for Information (RFI) on NIA Strategic Directions closed on September 13, 2024. NIA sought input on topics to consider when formulating its *Strategic Directions for Research* for 2026-2030. This document serves as a statement of NIA's scientific priority areas and provides a framework for systematic analysis of NIA's scientific portfolio. The document both complements and forms a foundation for more targeted and specific planning tools, including the National Alzheimer's Project Act plan and milestones and NIA's forthcoming strategic plan for diversity, equity, inclusion, and accessibility.

Since May 2024, NIA has released 25 research highlights of NIA-supported publications, 14 blog posts, and 3 news announcements. In addition, senior NIA leadership has participated in 14 meetings with interest and advocacy groups as well as 5 Congressional briefings or hearings.

NIA is hosting a third iteration of the Healthy Aging Start-Up Challenge in 2025 to support efforts that foster diversity in aging research and innovation. Winners will receive a \$60,000 prize and continued coaching and mentorship with NIA entrepreneurs-in-residence. NIA will accept submissions from September 3 to December 9, 2024, and will host a pre-submission webinar on October 9, 2024, at 1 pm ET.

NIA will also host the Falls Prevention and Older Adults expert question-and-answer session on September 23, 2024, at 3:30 p.m. ET. In addition, the [2024 NIH Alzheimer's Research Summit: Building a Precision Medicine Research Enterprise](#) will be held September 23-25, 2024.

NIA is celebrating its [50th anniversary](#) by conducting a series of activities to highlight progress over the past 50 years and to inspire future generations of aging researchers.

National Institutes of Health Updates

NIH has established [a centralized website](#) for information about pending changes to NIH grant applications and peer review in 2025. For application due dates on or after January 25, 2025, the following changes will be in effect:

- [Simplified Review Framework for Most Research Project Grants](#)
- [Revisions to the NIH Fellowship Application and Review Process](#)
- [Updates to Institutional Training Grant Applications](#)
- [Updates to Reference Letter Instructions for Referees](#) (published in November 2024)
- [Updated Application Forms and Instructions](#)

For due dates on or after May 25, 2025, the following change will be in effect: [Common Forms for Biographical Sketch and Current and Pending \(Other\) Support](#).

Discussion

Dr. Hodes explained that the proposed reorganization would consolidate the 27 ICs to 15 and NIA would be replaced by the National Institute on Dementia. In response to a question about the origins of the reorganization proposal, Ms. Lundeborg shared that the proposal has been led by Rep. Cathy McMorris-Rodgers (R-WA), chair of the House Energy and Commerce Committee, who is not seeking re-election in 2024. Further, the authorizing language is buried in the House appropriations bill, which is not expected to pass under the current Congress. Although the proposed reorganization could reappear in the next Congress, there has been strong support for the current structure. The authorizing language includes a provision that any reorganization should be informed by a report from an external organization such as NASEM, but the proposal does not reflect input from the scientific community and NIH leadership. Dr. Longo asked about any existing concerns, forces, or perspectives that might advance the proposed NIH reorganization. Ms. Lundeborg responded that the proposal is likely driven by a desire to shift indirect costs from NIH to universities because the second half of the proposal focuses on reducing government support for indirect costs.

Dr. Longo commended the ongoing diversity of pharmacological clinical trial targets and

reflected on the influx of new staff as a reminder of the multidisciplinary nature of aging research that is strengthened by a workforce with different backgrounds and experiences.

B. Staff Introductions

NIA leadership introduced 45 new NIA staff members from the Divisions of Behavioral and Social Research (BSR), Geriatrics and Clinical Gerontology (DGCG), and Neuroscience (DN); the Office of Strategic Extramural Programs (OSEP); the Grants and Contracts Management Branch (GCMB); the Scientific Review Branch (SRB); the Financial Management Branch (FMB); the Information Technology Branch (ITB); the Workforce and Administrative Management Branch (WAMB); the Office of Communications and Public Liaison (OCPL); the Office of Legislation, Policy, and International Activities (OLPIA); and the Intramural Research Program (IRP) Administrative Office, Center for Alzheimer's and Related Dementias (CARD), Translational Gerontology Branch (TGB), Laboratory of Epidemiology and Population Science (LEPS), Laboratory of Clinical Investigation (LCI), Laboratory of Cardiovascular Science (LCS), and Office of the Scientific Director (OSD).

C. Future Meeting Dates

January 28-29, 2025 (Tuesday and Wednesday), Virtual
May 13-14, 2025 (Tuesday and Wednesday), Building 45 – Natcher
September 17-18, 2025 (Wednesday and Thursday), Building 45 – Natcher
January 27-28, 2026 (Tuesday and Wednesday), Virtual
May 12-13, 2026 (Tuesday and Wednesday), Building 45 – Natcher
September 15-16, 2026 (Tuesday and Wednesday), Building 45 – Natcher

D. Consideration of Minutes of the Last Meeting

The minutes of the May 2024 Council meeting were considered. A motion to approve the minutes was made, seconded, and passed unanimously.

III. CERTIFICATE OF RECOGNITION TO 2024 RETIRED MEMBERS

Dr. Hodes presented certificates of recognition to retired NACA members, Drs. Yadong Huang, David Reuben, and Julie Schneider as well as Rev. Dr. Cynthia Huling-Hummel. Recipients all expressed appreciation and gratitude for the opportunity to serve on NACA.

IV. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Drs. Cruz and Schneider summarized presentations to the Task Force on Minority Aging Research by Drs. Kenneth Goodman, Lakshman Tamil, Krystal Tsosie, and Jason Flatt.

During his presentation, Dr. Goodman spoke about his work at the University of Miami on the intersection of data, diversity, and aging. He emphasized the existence of systemic racism throughout the scientific enterprise and society at large, including existing data and datasets. Acknowledging the racism imprinted in these datasets is critical, particularly because they underlie the research needed to advance health policy. These data are also used in the rapidly advancing fields of artificial intelligence (AI) and machine learning (ML). Dr. Goodman urged the biomedical and scientific community to understand the limitations and utility of these

computational tools, and to assume the responsibility of fixing data corrupted by racism. He concluded by emphasizing that the pursuit of diversity, equity, and inclusion (DEI) is a civic duty, and that DEI efforts are most likely to succeed when they are interdisciplinary.

Dr. Tamil from the University of Texas at Dallas focused his presentation on addressing racial bias in AI and ML as they increasingly influence health research, and specifically for aging populations. Dr. Tamil emphasized the importance of acknowledging the bias in current datasets and ensuring diverse data representation. Addressing racial bias will require both innovative technological and policy solutions. Finally, Dr. Tamil discussed ML, machine reasoning, and the existential threat of AI as it progresses from narrow to general to sentient.

Dr. Tsosie (Diné/Navajo Nation) from Arizona State University and co-founder of the Native BioData Consortium, discussed her work on Indigenous genetics and genomic data sovereignty through tribal data repositories for health equity. She shared challenges that researchers face when pursuing community engagement, such as a lack of training, variable local infrastructure, difficulty identifying and connecting with key community leaders, and often conflicting institutional and community policies. Dr. Tsosie also noted the lack of adequate grant funding for engagement strategies and of conversations about the role of community engagement throughout the research life cycle. She emphasized that researchers should ensure that subsequent generations will benefit from genomic research findings. Finally, she discussed her work engaging Indigenous communities in genomic research, many of whom have enacted data access restrictions to ensure data sovereignty.

Dr. Flatt shared methods for recruitment of sexual and gender minority (SGM) older adults that he utilizes in his research at the University of Nevada, Las Vegas. He explained that SGM is the scientific term used to describe the LGBTQIA+ community, but researchers must learn and utilize an individual's preferred terms when working within the community. Dr. Flatt recruits SGM adults with memory loss and their care partners to the Research Inclusion Supports Equity (RISE) Registry and leads the Rainbows of Caring Study, which characterizes the experiences of SGM adults living with AD/ABD and SGM care partners. He emphasized the central role of an extended network of caregiving in the SGM community, where individuals may not be supported by immediate family.

V. REPORT: WORKING GROUP ON PROGRAM

Dr. Greenspan, Chair of the Working Group on Program (WGOP), led the updates on 21 concept clearances. The Council members unanimously and enthusiastically concurred with approval of all concepts, summarized below.

A. Notice of Funding Opportunity Concept Clearances: Division of Aging Biology

Dr. Greenspan invited Dr. Huang to present to the Council as primary reviewer on three DAB concepts.

RNA Metabolism in Aging and Aging-related Diseases

In collaboration with DN, this R01 concept aims to solicit studies that would identify and characterize changes in RNA editing, alternative splicing, and modification that are associated with aging processes and aging-related diseases. Researchers' understanding of how changes in

RNA metabolism contribute to aging and disease were limited by costs and technology. However, recent advances in sequencing and other technologies have revolutionized the field, making this a timely and important proposal.

Bats and Healthy Aging

As the human lifespan has increased, so has the number of chronically ill patients suffering from aging-related diseases, resulting in a toll on individuals and society. Traditional animal models for aging research include rodents, whose lifespans are much shorter than humans, and non-human primates, who are expensive and difficult to maintain. Alternatively, bats can live up to 40 years in laboratory settings, and their colonies are easier and more affordable to maintain than non-human primates. This concept originates from a 2024 NIA workshop that identified bats as a new complementary model system for aging research of relevance to NIA's four research divisions and will focus on the characterization and validation of wild and captive bats as aging models.

Aging Mammalian Tissues in Vitro

Recent discussions about animal research have highlighted the need for human-centered models. The broad availability of induced pluripotent stem cells (iPSCs) and organoids paired with the Food and Drug Administration (FDA) Modernization Act has provided new opportunities to develop and utilize in vitro human-relevant models of aging that can serve as an alternative to animal models for drug testing. This concept, which involves collaboration with DN and DGCG and follows a recent NIA workshop, proposes use of the R21 mechanism to support the development of 3D in vitro models derived from mammalian tissue that can recapitulate the aging process.

B. Notice of Funding Opportunity Concept Clearances: Division of Behavioral and Social Research

Dr. Greenspan invited primary reviewers to present their respective BSR concepts to the Council. Primary reviewers were Drs. Case, Cruz, and Reuben, and Ms. Lundebjerg.

National Longitudinal Study of Adolescent to Adult Health (Add Health) Wave VII (Renewal)

Initiated in 1994, the National Longitudinal Study of Adolescent to Adult Health (Add Health) is a nationally representative, racially and ethnically diverse study that began when participants were aged 12-20 years and has continued across six waves of data collection into midlife. This concept proposes a seventh wave that includes an unprecedented special focus on AD/ABDR risk beginning in midlife, including collecting assessments of physical, cognitive, and sensory function assessments in addition to blood-based biomarker assays.

Advance Aging Research through Centers for Medicare & Medicaid Services (CMS) Data Linkage

NIA established the Data Linkage Program in 2021 to link NIA-funded study data with CMS claims data and storage of these data in a cloud-based environment (enclave) for investigator use. This concept, which BSR advanced in collaboration with DN and DGCG, seeks to reduce administrative and financial burdens associated with data linkage by awarding administrative supplements to investigators to support linkage of study data with CMS data. The concept prompted a Council discussion on how NIA can continue to encourage CMS to release data in a more timely fashion.

Artificial Intelligence and Technology Collaboratory (Renewal)

The renewal request for the Artificial Intelligence and Technology Collaboratory (AITC) seeks to continue and expand its services and resources, including an additional P30 grant (for a total of four) and U24 coordinating center. AITC P30 centers support cross-disciplinary, collaborative projects that use AI and technology to improve the health of older adults, including people living with AD/ADRD and their care partners. The AITC program team continues to support research projects aligned with the priorities of each NIA division.

Dementia Care and Caregiver Support Intervention Research—Stage I Only (Renewal)

This concept would serve as an incubator for Stage I research on dementia care and caregiving, encompassing the preliminary data collection and methodological development necessary to establish an intervention's feasibility. The concept aims to stimulate rigorous research with the expectation that not all projects will advance to Stage II. Later stage trials would be supported by a separate, companion concept.

Dementia Care and Caregiver Support Intervention Research—Stages II through V (Renewal)

This companion to the preceding Stage I concept would focus on determining an intervention's effectiveness and, if it is found to be successful, disseminating the intervention to stakeholders. The concept includes a milestone-based process that aims to increase the number of well-designed clinical studies of behavioral interventions.

Social, Behavioral, and Economic COVID Coordinating Center (Renewal)

The Social, Behavioral, and Economic (SBE) COVID Coordinating Center supports the activities and research of the NIH SBE Research on COVID-19 Consortium. The Consortium funds research activities related to the health and economic outcomes of the COVID-19 pandemic, including projects focused on racial inequities in COVID mortality rates as well as the creation and continued support of a COVID data archive and common data elements. This renewal concept would fund the continued coordination of Consortium-supported research and shift its focus toward rapid response workshops, pilot research, and data needs.

Interdisciplinary Research Network on Housing and Health

Cross-disciplinary coordination and collaboration is one of the key challenges facing researchers interested in understanding and mitigating the effects of housing on health outcomes. To address this gap, the concept proposes to establish an Interdisciplinary Research Network on Housing and Health consisting of federal partners that will convene housing, public health, and aging researchers in an ongoing series of meetings and trainings. The Network would also encourage the formation of multidisciplinary teams that will plan and execute pilot projects.

C. Notice of Funding Opportunity Concept Clearances: Division of Geriatrics and Clinical Gerontology

Dr. Greenspan invited primary reviewers to present their respective DGCG concepts to the Council. Primary reviewers were Dr. Asthana and Ms. Lundebjerg.

Clinician-Scientist Transdisciplinary Aging Research (Clin-STAR) Coordinating Center (Renewal)

First funded in 2019, this concept supports the continuation and expansion of a program that has successfully trained many clinician-scientists to be leaders in aging research, with support from all NIA divisions. The renewal would allow Clin-STAR to accommodate expanding interest in the aging research field; facilitate the integration of expertise and approaches from a wide range of clinical specialties; and provide training, support, and resources to early-stage clinicians.

Caring for Complex Older Adults Through Electronic health record Dashboards (COATED)

This new U24 concept, which involves collaboration by BSR and DN, is focused on facilitating partnerships between electronic health record (EHR) vendors, researchers, clinicians, and health care systems to foster research and development of EHR dashboards and infrastructure. Council discussion focused on experiences working with EHR vendors and recommended that the project team address the challenges that will arise when working across vendors. Council members also recommended that the cooperative establish partner advisory groups that include people living with dementia and their care partners.

D. Notice of Funding Opportunity Concept Clearances: Division of Neuroscience

Dr. Greenspan invited primary reviewers to present their respective DN concepts to the Council. Primary reviewers were Rev. Dr. Huling-Hummel, and Drs. Huang, Inouye, Longo, and Schneider.

National Alzheimer's Coordinating Center (NACC) (Renewal)

The NACC is critical for NIA-funded AD/ADRD research, supporting a database of longitudinal data from more than 50,000 participants and 35 Alzheimer's Disease Research Centers (ADRCs). The concept renewal would support NACC's plans to upgrade, modernize, and harmonize its database infrastructure and technology; expand participant diversity data; upgrade data sharing capabilities in accordance with findable, accessible, interoperable, and reusable (FAIR) principles; integrate existing and emerging data streams; and make all ADRC data searchable and accessible.

National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) (Renewal)

The NCRAD is a centralized infrastructure for NIA-funded AD/ADRD research, serving as a biorepository of 2 million samples from 126,000 individuals. The concept will support the continuation of this critical biospecimen repository, facilitate sample sharing, and advance biomarker research. NCRAD also proposes to serve as a bridge between clinical and basic science research.

Interdisciplinary Research to Understand the Complex Biology of Resilience to Alzheimer's and Related Dementias Disease Risk (Renewal)

In coordination with DGCG, this concept builds upon the prior work of the Resilience-AD program in advancing understanding of the molecular determinants of resilience, which has identified several novel candidate drug targets. The proposed renewal will further advance the development of genomic and mechanistic resilience-based therapeutics by integrating epidemiological, genomic, and mechanistic research with computational resources and AI. The Council suggested that the proposal incorporate social determinants of health, include clinical gerontology expertise, and expand the medical contributions to resilience; the program has agreed to incorporate these changes.

Institutional Research Training Award for AD/ADRD and Aging Research in Low- and Middle-Income Countries (LMICs)

This proposed concept is for an international training grant that addresses the trans-NIA need for research, workforce training, and infrastructure in LMICs to support research on aging populations. The concept leverages current NIA investment in LMICs to build capacity, support collaborations between the United States and LMICs, and strengthen LMIC institutions' research contributions and training programs. The proposed program aims to increase training in aging research, research collaborations, training exchanges, and joint research projects and networks through eight awards, five of which are AD/ADRD-specific and three of which are general. The program would also include a pre-application webinar and an annual meeting to present trainee research.

Data Coordinating Center for the Aging and Alzheimer's Disease Mouse Brain Atlas (AD-MBA)

The progression of AD often follows a specific temporal and spatial pattern in which specific brain regions are affected at different disease stages. However, why specific regions or cell types within these regions are particularly vulnerable to AD is unknown. NIA supports multiple projects using mouse models to better understand the mechanisms and impact of AD progression in the brain through generating comprehensive atlases of vulnerable brain regions and cell subpopulations. This concept seeks to address the critical need to centralize data sharing, integration, infrastructure, and dissemination across these atlases through establishment of the Aging and AD-MBA. The AD-MBA would include a data coordinating center to facilitate collaborations across research groups, analyze multiscale datasets, and manage data dissemination.

Translational Center for Accelerating the Use of Digital Technologies in Alzheimer's Disease and Related Dementias (AD/ADRD) Research

Recent advances in digital health technologies (DHTs) such as wearable and environmental devices and sensors may provide opportunities to support risk assessment, early detection, and functional monitoring in AD/ADRD research. This concept, with participation by BSR, proposes the creation of a centralized data center for digital biomarker data to enable the secure storage, distribution and sharing, and harmonization of DHT data. The concept would further facilitate remote collection of DHT data and thereby improve recruitment of diverse participants and reduce participant burden. The data center could also facilitate integrating DHT biomarker data with imaging and other biomarker data.

E. Notice of Funding Opportunity Concept Clearances: Division of Extramural Activities (DEA)

Dr. Greenspan invited primary reviewers to present their respective DEA concepts to the Council. Primary reviewers were Drs. Asthana, Greenspan, and Van Eldik.

Advancing Diversity in Aging Research (ADAR) Through Undergraduate Education Programs Coordinating Center

The ADAR Through Undergraduate Education program has been very successful at providing intensive research experiences for undergraduate students from diverse backgrounds with the goal of transitioning them into advanced degree-programs or private-sector research careers in aging-related disciplines. ADAR programs funded in FY13-22 (n=26) have supported nearly 700 undergraduate participants to date, 71% of whom are from underrepresented racial and ethnic groups and 50% of whom are women. This concept, in collaboration with BSR and DN, would establish a coordinating center that would coordinate communication across the 36 existing ADAR programs; support sites in developing and sustaining new partnerships; and facilitate common metrics, uniform evaluation strategies, and harmonized reporting to better track participants and outcomes.

Transition to Aging Research for Predoctoral Students (Renewal)

NIA's Transition to Aging Research Award (F99/K00) was launched in 2020 to support advanced graduate students in their doctoral studies and their transition to postdoctoral training in aging research. Between FY20 and FY23, NIA received 136 applications for this award, 37 of which were funded; 26 awardees have completed their doctoral training and 23 have pursued postdoctoral aging research. This concept would adjust the program to increase its success and reduce barriers to prospective applicants, including expanding to two application cycles per year, increasing stipends for awardees, and increasing support for career development.

New General Aging Institutional Training Programs for Aging Research

T32 Institutional Research Training Grants are the cornerstone of NIA's training and career development programming. T32s support institutions providing select pre- and postdoctoral scholars with training, coursework, mentored research experiences, and technical and professional skill development. However, applications for new T32 programs are scored lower (median = 34) than renewal applications (median = 19); renewal applications also request more training slots than new applications, resulting in higher costs. These factors have resulted in a 13% success rate for new T32 applications, compared to a 62% success rate for renewals. This concept would set aside funds to specifically support three new general aging T32 applications each year; these applications would not compete against renewals and would encourage applications from institutions that have previously held an NIA-funded T32.

VI. COUNCIL SPEAKER

Women's Health Trajectories and Inflection Points

Dr. Janine Clayton, MD, FARVO, Director, NIH Office of Research on Women's Health

The Office of Research on Women's Health (ORWH) was founded in 1990 to ensure the inclusion of women in NIH-supported clinical trials, enhance and expand women's health research, and promote career advancement for women in health research careers. The 1993 NIH Revitalization Act required researchers to include women in clinical studies. The 21st Century Cures Act expanded this requirement to include individuals of all ages, created a path for clinical studies to include pregnant and lactating women, and required applied Phase III clinical trials to report results into ClinicalTrials.gov disaggregated by sex, race, and ethnicity. NIH-supported research plays a critical role in women's health; for example, NIH supported the basic science

that led to the development of the human papilloma virus and Janus kinase (JAK) inhibitors. Most recently, Executive Order 14120 to Advance Women's Health Research & Key Innovation Points was announced in March 2024 and directs federal agencies to prioritize investments in women's health research, integrate women's health across the federal research portfolio, galvanize research on women's midlife health, and assess unmet needs to support women's health research.

Dr. Janine Clayton focused her presentation on NIH and ORWH work that considers women's health as a trajectory across the lifespan, particularly studies that investigate specific transition and inflection points such as menopause. NIH has funded menopause research for more than 30 years and across ICs. Dr. Clayton highlighted the Study of Women's Health Across the Nation (SWAN), a multi-site, longitudinal epidemiological study that began in 1994 and examines the effects of the menopause transition (MT) on women's health and functioning in early old age (ages 66-75). SWAN is diverse by design and led to the discovery of MT differences across women of different races and ethnicities.

The NIH-Wide Strategic Plan for Research on the Health of Women reflects the collaborative nature of women's health research at NIH, centering a multidimensional framework that considers women's health across the lifespan. The framework highlights social and environmental exposures in combination with biological factors that affect women's health outcomes from preconception to old age. For example, a study of 1,700 SWAN participants found that women who experienced physical intimate partner violence showed a decline in working memory as menopause stage advances.

MT is a critical junction point where chronological, biological, and reproductive aging intersect, resulting in a significant increase in risk for chronic diseases such as metabolic syndrome and cardiovascular disease (CVD). For example, a SWAN study found that frequent and persistent vasomotor menopause symptoms are associated with increased risk of CVD events later in life. Women are also more likely than men to experience two or more chronic conditions, and these multi-morbidities are more likely to involve different organ systems. The decrease in estrogen and increase in follicle-stimulating hormone during menopause is associated with many cardiometabolic changes, including increased adiposity, changes in sleep patterns, altered glucose metabolism in the brain, bone loss, and increased immune activation.

ORWH leads the Specialized Centers of Research Excellence (SCORE) on Sex Differences program, which is disease agnostic and includes basic science, translational, clinical, and career enhancement cores. Six of the 12 SCORE programs are supported by NIA, including the Microvascular Aging and Eicosanoids–Women's Evaluation of Systemic Aging Tenacity (MAE-WEST) SCORE at Cedars Sinai Medical Center. A recent MAE-WEST study found that the threshold for hypertension and its associated cardiovascular consequences in women occurs at lower systolic blood pressure levels than for men; this finding may alter how clinicians identify and treat hypertension in women.

Future research should address critical gaps in menopause knowledge, including biomarkers predictive of menopause duration and symptoms, the ideal timing for hormone and other therapies, development of new hormonal and non-hormonal treatments to improve quality of life during the MT, and equitable improvement of education and access to care for all women

seeking intervention for menopause symptoms. ORWH has collected links to menopause resources and research on [its website](#).

Discussion

Ms. Lundebjerg asked whether the recent executive order could serve as a vehicle for increasing investment in women's health research across all ICs. Dr. Clayton shared that a recent analysis of funding opportunities across ICs found that women's health research funding opportunities have dramatically increased between 2019 and 2023. Although each IC addresses women's health as related to its scientific area, the Coordinating Committee for Research on Women's Health is planning an Interdisciplinary Women's Health Research program that would facilitate increased collaboration across the ICs and answer integrative research questions. Dr. Hodes added that increased women's health research will be driven as much by the scientific questions as the executive order; Dr. Clayton echoed this comment, adding that rigorous research and consideration of sex as a biological variable (SABV) have revealed new research questions and opportunities.

Dr. Ingraham asked how to increase the scientific workforce's knowledge of women's health and SABV. Dr. Clayton explained that ORWH collaborates with FDA to provide SABV primer courses and train-the-trainer modules. ORWH also has six modules in the Bench to Bedside course that highlight how sex and gender affect health and disease.

Dr. Inouye asked whether the requirement to report Phase III clinical trials data stratified by sex could be extended to all studies, noting that doing so could provide the basis for a rich SABV database. Dr. Clayton responded that the SABV policy requires accounting for SABV in research design, analysis, and reporting, including the project report. Although investigators are not required to include SABV data in their progress reports, clinical trial investigators are asked to include information on any sex or gender differences in their final progress report. She added that the lack of SABV data is an ongoing issue for the broader scientific ecosystem and that ORWH is working with journal editors and publishers to encourage the use of sex and gender equity in research guidelines.

VII. PROGRAM HIGHLIGHTS (DAB)

Unlocking the Secrets of Female Physiology

Dr. Holly Ingraham, University of California, San Francisco

Females live longer than males in almost all species, including humans. Men have higher prevalence and mortality rates for five of the six most prevalent diseases in humans; however, women suffer from more chronic diseases and experience higher disease severity than men. Dr. Ingraham proposed that this mortality–morbidity paradox is driven by the estrogen cycle; many of the most common and debilitating chronic illnesses in women are associated with the reproductive and menopausal periods. However, very little is understood about the basic mechanisms underlying these diseases and how they affect women throughout the lifespan. Dr. Ingraham highlighted a NASEM report on funding and scientific gaps in women's health showing that funding for breast cancer, which affects 4 million women in the United States, is several orders of magnitude higher than for endometriosis and polycystic ovarian syndrome, which combined affect 12 million women.

Dr. Ingraham's research leverages the peaks and valleys of the estrogen cycle to understand female physiology. The medial basal hypothalamus is a key brain region for estrogen signaling in addition to its involvement in homeostatic responses and reproductive behavior. Medial basal hypothalamic neurons are enriched in estrogen receptor alpha, particularly in the ventromedial hypothalamus (VMH) and arcuate nucleus (ARC). Dr. Ingraham's research group originally chose ARC to use as a control region for its VMH study, but instead discovered that ARC neurons control bone density through brain-derived osteoanabolic factor (BDOF). Elimination of estrogen signaling in the ARC of female mice resulted in highly dense and strong trabecular bone, the bone type affected by osteoporosis. The research group later found that the increases in bone density are mediated by kisspeptin 1 (KISS1) neurons.

To determine how this female-specific bone phenotype arises, Dr. Ingraham used parabiosis, a technique in which a mutant and a wild type mouse are stitched together so that their circulation becomes joined, to establish that BDOF is a circulatory factor that results in increased skeletal stem cells. A subsequent experiment showed that injection of these skeletal stem cells into the hypothalamus resulted in ossicle formation within the brain. Dr. Ingraham then encountered challenges identifying the molecular type and source of BDOF, largely due to an assumption that BDOF was a neuropeptide originating in the pituitary. Instead, the answer arose from a study that discovered that high-fat diet eliminated bone density gains in KISS1 knockout mice. A subsequent tissue profile found that cellular communication network factor 3 (CCN3) ARC expression is suppressed when animals are fed a high fat diet and increased concurrent with bone remodeling.

Dr. Ingraham found that although a CCN3 global knockout does not affect bone mass, expressing mutated CCN3 (mCCN3) in the liver leads to increased bone volume, strength, and formation in both male and female mice. Further, recombinant mCCN3 accelerated callus formation at fracture sites and reversed the aging repair process; repaired fractures in 2-year-old mice resembled repairs in a 2-month-old mouse. These results suggest CCN3 as a novel target for repairing and improving bone in a variety of skeletal diseases and conditions, including osteoporosis, hip fractures, and dental implants.

Finally, Dr. Ingraham investigated whether CCN3 expression is present only in mutant female brains, finding that CCN3 is expressed only during lactation. Knockdown of CCN3 in the ARC of mice prior to pregnancy resulted in bone loss when lactating and, if this knockdown was paired with a low-calcium diet, mice are unable to sustain their progeny. Mice normally lose 30% of their bone volume during lactation, primarily in trabecular bone. Dr. Ingraham hypothesized that low estrogen during lactation activates expression of CCN3, which increases bone remodeling to ensure that mice have sufficient bone and calcium to sustain progeny. She finished by emphasizing that this work is a key example of the importance of studying female animals and brain-body connections.

Discussion

When asked about future experiments, Dr. Ingraham explained that the next steps of her work are to detect BDOF and CCN3, identify the CCN3 receptor, and understand how CCN3 is activated during lactation. She is working with a company to translate these results into human clinical studies.

Asked whether CCN3 interacts with a growth hormone such as insulin-like growth factor, Dr. Ingraham explained that CCN3 has four domains that have to date been studied independently in a two-dimensional view; she believes that in a three-dimensional view, the protein may fold to bind to a discrete set of receptors.

Dr. Van Eldik asked whether the group has tried knocking down or overexpressing CCN3 in an osteoporosis model. Dr. Ingraham clarified that the group has conducted experiments in mice whose ovaries have been removed and found that overexpression of CCN3 leads to an increase in bone. She added that the fracture repair results suggest promise as a translational bridge toward a clinical treatment.

Asked whether CCN3 is targeting osteoclasts or osteoblasts, Dr. Ingraham explained that the bone formation is affecting osteoblasts with no effect on osteoclasts.

VIII. ADJOURNMENT

The open session of the 153rd meeting of the National Advisory Council on Aging adjourned at 1:00 p.m. on September 19. The next meeting is scheduled for January 28-29, 2025.

IX. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.⁴

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.

⁴ These minutes will be approved formally by Council at the next meeting on January 28-29, 2025, and corrections or notations will be stated in the minutes of that meeting.