

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 139th Meeting

NATIONAL ADVISORY COUNCIL ON AGING

January 21–22, 2020

**National Institutes of Health
Building 45, Conference Room E1/E2
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
January 21–22, 2020**

The 139th meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, January 21, 2020, at 3 p.m. in Building 45, Conference Room E1/E2, National Institutes of Health (NIH), Bethesda, Maryland. 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, January 21, from 3 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 the Public Law 92–463.¹ The meeting was open to the public on Wednesday, May 22, from 8 a.m. to 1:15 p.m.

Council Participants:

Mr. James Appleby
Dr. David A. Bennett
Dr. Shalender Bhasin
Ms. Meryl Comer
Dr. Eileen M. Crimmins
Dr. Monica A. Driscoll
Dr. Terry T. Fulmer
Dr. Alison M. Goate
Dr. Margaret A. Goodell
Dr. J Taylor Harden
Dr. David M. Holtzman
Dr. Stephen B. Kritchevsky
Dr. Eric Michael Reiman
Dr. Clifford James Rosen
Dr. Amy Jo Wagers

Ad Hoc Participants:

Dr. Jennifer Manly
Dr. David Weir

Ex Officio Participants:

Dr. Sarah Ruiz, Administration for Community Living

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.

The Council Roster, which gives titles, affiliations, and terms of appointment, is appended to these minutes as attachment A.

In Addition to NIA Staff, Other Federal Employees Present:

Dr. Susan Gregurick, Office of Data Science Strategy, NIH

Members of the Public Present:

Dr. Bérénice Benayoun, University of Southern California

Dr. John Haaga, Maryland Commission on Aging

Catherine Kebs, Physicians Committee for Responsible Medicine

Dr. Rose Maria Li, Rose Li and Associates, Inc.

Dr. Rachel Lazarus, American Association of Retired Persons

Dr. Frank Longo, Stanford University School of Medicine

Dr. Mara Mather, University of Southern California

Dr. Bradley Willcox, University of Hawaii

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 1,826 applications requesting \$3,998,158,377 for all years underwent initial review. The Council recommended 978 awards for a total of \$2,512,670,483 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. Hodes welcomed members to the open session of the 139th NACA meeting and called the meeting to order at 8 a.m. on Wednesday, January 22, 2020.

A. Director's Status Report

Dr. Hodes reported that Congress has increased its appropriation for NIH to \$41.7 billion. This includes targeted funding increases of \$500 million for All of Us, \$500 million for the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN), \$60 million for Down syndrome research, and \$350 million for research on Alzheimer's disease (AD) and related dementias (ADRD). The appropriation for NIA has increased to \$3.54 billion. In addition to the increase in targeted funding for AD/ADRD, the appropriation includes an increase of \$110

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million for non-targeted research. Dr. Hodes noted that appropriations for NIA have essentially tripled since 2015, and he thanked the Council for its guidance in investing these funds.

NIA has established interim paylines. For general applications reviewed by the Center for Scientific Review (CSR) and costing less than \$500,000, interim paylines are 11% for most applications, 14% for new investigators, and 16% for early-stage investigators. For CSR-reviewed applications costing \$500,000 or more, paylines are 8% for most applications, 11% for new investigators, and 13% for early-stage applications. Paylines are higher for AD/ADRD-targeted applications: 28% for most, 31% for new investigators, and 33% for early-stage investigators. Dr. Hodes noted that interim paylines scores for NIA-reviewed applications were 20 to 21 for general applications and 28 to 40 for AD/ADRD-targeted applications. NIA will revisit and adjust all paylines as it receives more applications.

In response to questions from the Council, Dr. Hodes highlighted the wide range in paylines across all NIH Institutes and Centers (ICs), noting that NIA's paylines fall in the middle. He and Dr. Robin Barr also explained that half of ICs do not publish paylines. However, they suggested that, later in the year, NIA could provide an informal report on how NIA compares with other ICs that do publish paylines. Dr. Hodes emphasized that NIA would have a more definitive idea of paylines by the May Council meeting. He also acknowledged that although investigators often assume that these interim paylines are final, NIA revisits them as it receives more applications, and strives for transparency in reporting its paylines as they emerge.

Dr. Hodes then highlighted recent NIA-supported research findings, including the following:

- An October 10, 2019 publication showing that a blood test may predict amyloid deposits in the brain and potentially identify AD.
- An October 28, 2019 report based on an analysis of the Whitehall II study, indicating that social contact in midlife could reduce dementia risk.
- A December 17, 2019 publication showing that a person's blood protein profiles indicate their age.

Dr. Hodes also noted that two NIA-supported studies were included in *JAMA*'s list of top articles of the decade and that one was included in *Discover Magazine*'s top science stories of 2019. The articles included in *JAMA*'s list of top articles are: "The Association Between Income and Life Expectancy in the United States, 2001-2014" (Raj, C., Stepner, M., Abraham, S. et al, April 26, 2016), and "Intensive vs. Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥ 75 Years: A Randomized Clinical Trial" (Williamson, J., Supiano, M., Applegate, W., et al, June 28, 2016). The article honored by *Discover Magazine* is "A New Kind of Dementia Strikes the 'Oldest Old'" (Marsa, L., December 23, 2019).

In other updates, Dr. Hodes reported that NIA has established a new collaboratory, NIA-IMPACT, to spur innovation for improving dementia care. He also reported that NIH's first Eureka Challenge offered a total prize purse of \$400,000 and focused on development of technology-based applications to improve coordination and/or navigation of dementia care. The Challenge attracted 33 applications, with winners announced in October 2019. MapHabit, a mobile app that prompts persons with dementia to accomplish activities of daily living, won first

place. Second-place went to the University of California, Los Angeles' Dementia Care Software System, a case management software that integrates with electronic health records (EHRs). Third place went to Caregiver411, a mobile app developed by North Carolina Agricultural and Technical State University to help caregivers obtain tailored resources for their patients. Dr. Hodes also noted the TREAT-AD Centers for Discovery of New Medicines, another component of the infrastructure to provide open-source tools, reagents, and methods integrating enabled targets into drug-discovery campaigns.

Dr. Hodes announced that registration is open for the second Dementia Care, Caregiving, and Services Summit, scheduled for March 24–25, 2020 at the Natcher Conference Center. He also announced that NIH's second Inclusion Across the Lifespan Workshop will occur on September 2–3, 2020.

Dr. Hodes concluded his report by acknowledging Dr. John Haaga, former Director of the Division of Behavioral and Social Research (DBSR), who retired at the end of 2019. Dr. Lisbeth Nielsen will be the new DBSR Director. Dr. Hodes also acknowledged the deaths of Drs. Marcelle Morrison-Bogorad, Director of the Division of Neuroscience (DN) from 1997 to 2011, and Huber Richard Warner, Director of the Biology of Aging program from 2000 through 2005. Finally, Dr. Hodes announced that Dr. Ned Sharpless is returning to NIH as the Director of the National Cancer Institute.

B. Future Meeting Dates

May 26–27, 2020 (Tuesday and Wednesday, Building 31)
September 8–9, 2020 (Tuesday and Wednesday, Building 45)
January 12–13, 2021 (Tuesday and Wednesday, Building 31)
May 11–12, 2021 (Tuesday and Wednesday, Building 31)
September 14–15, 2021 (Tuesday and Wednesday, Building 45)

C. Consideration of Minutes of the Last Meeting

The minutes from the September 2019 Council meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes.

D. A Word from Dr. Robin Barr on His Retirement

Dr. Barr, Director of Extramural Activities and Executive Secretary for NACA, will retire on January 31, 2020. As this was his final Council meeting, he acknowledged the staff and contractors who have helped him manage the Council. He also noted that Dr. Kenneth Santora, the incoming Director of Extramural Activities, will be supported by the same team, providing continuity. Dr. Santora had previously served as director of the Office of Extramural Research Policy and Operations, Division of Extramural Activities, National Institute of Allergy and Infectious Diseases.

Dr. Barr described the Council as an organic whole that changes over time, particularly in response to environmental circumstances. He also noted Council's ability to respond to growing demands resulting from the growth in funding that the NIA has experienced over the past 4 years. This has led to the establishment of procedures that are more efficient. Dr. Barr closed by

describing his time at NIA, and as Executive Secretary of the Council, as “extended postdoctoral training”, and thanked everyone present.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. David Bennett, Task Force Co-Chair, began by reviewing presentations from past Task Force meetings to provide background, and reported that the Task Force had heard two presentations.

The first presentation, by Ms. Dawn Corbett, reviewed NIH implementation of and requirements related to inclusion of women, minorities, and individuals across the lifespan in NIH-funded research. NIH first established policies in 1986 to encourage the inclusion of women in clinical research. These policies expanded to include minorities in 1993, and to include children in 1998. In response to the 21st Century Cures Act of 2017, NIH added further requirements. NIH now requires Phase 3 clinical trials to report on ClinicalTrials.gov the results of inclusion analyses, and most recently, NIH established a new policy requiring inclusion across the lifespan (i.e., removing age caps from study eligibility criteria and including adults in their ninth and tenth decades when possible). Ms. Corbett presented data enrollment data for NIH-supported clinical research, noting that data from certain years might be skewed by the nature of the studies. For example, the large increase in Asian participants in 2017 reflected a large ongoing study in Asia.

The second presentation, by Dr. Crystal Glover of the Rush Alzheimer’s Disease Center, described the Health Equity through Aging Research and Discussion (HEARD) study. Brain donation allows researchers to learn more about AD/ADRD among diverse populations, discover better treatments for, and discover how to prevent, ADRD. However, despite persistent efforts, few minorities agree to brain donation, and among those who do, rates of completed autopsies are low; thus, tissue from older individuals from minority groups is limited. The HEARD study employs a mixed-methods approach to identify barriers and facilitators of brain donation. Phase 1 uses qualitative methods to understand participants’ perspectives, and Phase 2 leverages these perspectives to develop a quantitative instrument for a larger survey across diverse communities. Current data show that patient uncertainty regarding the donation and autopsy process is the most significant barrier among white participants of low socioeconomic status, whereas lack of family support for the role of research and brain donation in AD is the most significant barrier among African American and Latino participants. Council members discussed approaches for gaining consents to brain donation, including consideration of what works well in the organ donation process, and ways to engage family members and funeral homes.

Dr. Bennett concluded his report by conveying the following updates from Drs. Mia Lowden and Jaron Lockett:

- Two women of color, Drs. Melody Goodman and Gilda Barabina, recently spoke at the NIH Wednesday Afternoon Lecture Series.
- The Butler-Williams Scholars Program will occur July 6–10, 2020 at the Natcher Conference Center. The application deadline is February 14. NIA has increased the number of slots from 50 to 55.

In response to questions from Dr. Eileen Crimmins, Dr. Bennett reported that more women than men currently participate in NIA-supported Phase 3 clinical trials.

IV. REPORT: WORKING GROUP ON PROGRAM

A. Recommendations from Past Meetings – None

B. Clinical Trials Advisory Panel (CTAP) Report – None

C. RFA/RFP Concept Clearances

Dr. Stephen Kritchevsky reported that the Working Group reviewed three concepts for clearance.

Development of Cost-Effective and Customizable Training and Educational Platforms for AD/ADRD Caregivers That Focus on Financial Management and Legal Planning

The proposed concept will support research to create and integrate web-based and mobile platforms to address financial management decisions related to topics such as estate planning, power of attorney, living wills, financial directives, and insurance coverage. The Working Group recommended approving the concept, noting that it improves knowledge of the availability and accessibility of AD/ADRD supports and services. The Council seconded the Working Group's recommendation, and unanimously approved the concept.

Advancing Research for Prevention of Multiple Chronic Conditions and Their Consequences

The presence of multiple chronic conditions contributes to excess morbidity, mortality, and health care costs. The proposed concept will support the development of innovative interventions to prevent and treat multiple chronic conditions and their consequences, as well as research to improve measures and methods. The concept encourages inclusion of children, younger adults, and older adults. It also encourages community studies to address the complex health-related social and behavioral issues. In response to questions from the Working Group, program staff clarified that the intent of the funding opportunity is to encourage diversity among studies and development of new approaches to integrate data from diverse sources. The concept does not call for set-aside funding, but it will establish special mechanisms for the receipt, referral, and review of applications. Aside from suggesting that NIA incorporate two funding announcements into one, the Working Group recommended approving the concept. The Council accepted the recommendation and unanimously approved the concept.

Late-Onset of AD (LOAD) Family-Based Study (FBS)

This concept will continue and extend the NIA LOAD FBS, which began during 2003 with assembly and follow-up of multiple and diverse families with three or more affected members. The study has become an important resource in using genomic approaches to identify new target pathways for AD prevention. It has supported several initiatives, including the AD Sequencing Project, the AD Genetics Consortium, and the Consortium for AD Research. The extension will support recruitment of additional family members, including offspring of initial participants, and allow for collection of additional sample types, including peripheral blood mononuclear cells, plasma, and brains for autopsy. The Working Group agreed that the LOAD FBS provides crucial infrastructure and deserves continued support, and recommended approval. The Council seconded the recommendation, which passed with two abstentions.

D. Review of the Division of Behavioral and Social Research (DBSR)

Dr. Crimmins, Co-Chair of the DBSR Review Committee, presented the Committee's final report. The DBSR Review aimed to assess the state of the DBSR-funded research portfolio and resulting advances, provide specific recommendations to NIA on useful scientific directions for future BSR funding, and evaluate the ability of DBSR, with current resources and mechanisms, to develop its research and training portfolio as recommended. The Committee assessed several inputs, including the 2013 Review Report, the NIA Strategic Plan, the DBSR Data Infrastructure Review Report, scientific advances, funding opportunity announcements and current awards, workshops and meetings, and publications. The Committee also considered memos on cross-cutting themes (i.e., health disparities, AD/ADRD, basic behavioral and social research, interventions and translational research, centers and networks, and training and career development) as well as short portfolio reviews.

Overall, the Review Committee's impression of DBSR was outstanding. The Committee was impressed with both the breadth and depth of science supported by DBSR and the dedication of the DBSR staff and administration. The Committee offered 10 recommendations:

- Improve understanding of health disparities in aging.
- Increase understanding of how macro-social trends influence aging.
- Incorporate and integrate a range of approaches to understanding behavioral, psychological, social, and geroscience explanations for aging health, happiness and wellbeing, and other positive aspects of aging such as wisdom, compassion, and emotion regulation.
- Encourage research that examines the lifespan.
- Support research on behavior change in individuals and organizations.
- Enhance research on cognitive aging.
- Support research to improve care for persons with dementia and caregivers.
- Enhance research into technology and aging.
- Emphasize multidisciplinary training, including policy relevance that might require new training methods.
- Reduce barriers to accessing data for research.

The Committee concluded that DBSR has excelled during the past five years in developing its portfolio, advancing science, and integrating AD research. They emphasized that the poor health overall in America and the growing disparities in some parts of the population and country require increased attention. The Committee recommended not only documenting disparities, but also identifying approaches to prevention and intervention. Dr. Crimmins ended her report by thanking the DBSR staff and leadership, and contractor support provided by Rose Li and Associates, Inc., for their assistance with the review.

In response to questions from the Council, Dr. Crimmins noted that DBSR's portfolio seems to balance its focus between individual aging and societal/environmental aging. Council members

commended NIA staff and leadership in general for their dedication, responsiveness to rapidly emerging challenges, proactiveness in identifying and seizing opportunities, and thoughtfulness in comprehensively addressing key challenges.

V. GUEST SPEAKER: EMERGING DRAFT DATA-SHARING POLICY

Dr. Susan Gregurick, Associate Director for Data Science at NIH, began her presentation with three vignettes. She noted first that osteoporosis is associated with many genetic loci, but that identifying genes and associated phenotypes is challenging, although integrating epigenetic data with other relevant molecular measurements could facilitate identification of genes associated with osteoporosis. Secondly, Dr. Gregurick noted that although researchers understand the Findable, Accessible, Interoperable, and Reusable (FAIR) principles, they often need guidance to apply them. Particularly challenging are dataset annotation and curation, metadata selection, and secure and long-term data storage. Thirdly, Dr. Gregurick noted that making data available to citizen scientists (i.e., community members who want to contribute their time and expertise to biomedical research and discovery) is challenging. The NIH Strategic Plan for Data Science, aiming to address these and other challenges, focuses on five goals underlying the FAIR principles: data infrastructure; data ecosystem modernization; data management, analytics, and tools; workforce development; and stewardship and sustainability of a FAIR data ecosystem.

The Strategic Plan aligns with NIH's longstanding commitment to publicize research results and achievements, which is reflected in established policies on data sharing (2003), public access (2008), genome-wide association study (GWAS) and genomics sharing (2015), and public dissemination of information from NIH-funded clinical trials (2017). Most recently, NIH drafted a policy on data management and sharing, which will require NIH-funded investigators to submit a plan for managing and sharing their data. The final version of this policy will likely be released during summer 2020, and it will go into effect during 2021. Investigators can apply for funds to support data curation and management.

Dr. Gregurick shared ways investigators can make their data FAIR, noting that preferences will vary among investigators:

- Use open-access data-sharing repositories. NIH strongly encourages investigators to consider this as a first choice.
- Use PubMed Central to share data related to publications. Supplemental materials will receive a Digital Object Identifier (DOI) and be indexed, but no metadata will be associated.
- Use a generalist repository, such as NIH Figshare. Investigator data will receive a DOI, and some metadata will be applied and checked. NIH Figshare supports data citation, usage and citation statistics, and other metrics, and can be exported to other systems through an application programming interface (API). Investigators can add their grant information to this system, although it does not support sharing of Patient and Public Information (PPI) data.

- Enter data into Google or Amazon Web Services (AWS) through the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability Initiative (STRIDES). NIH-supported investigators can receive discounted pricing for computing, storage, and related cloud services. They also will receive professional services, technical support, and training for both data owners and researchers. NIH is also exploring other collaborations, and it has moved several of its large platforms to cloud-based platforms.

Dr. Gregurick noted that interoperability is more challenging, because investigators usually collect data without considering how others might use it. However, lessons can be learned from the health care and information technology industries. Fast Healthcare Interoperability Resources® (FHIR) allows patients, providers, and payers to access information on mobile, web-based, or cloud platforms. Each hospital is connected to a FHIR server that holds data in a structured way. FHIR offers more than 100 foundational, supporting, administrative, health care, and clinical reasoning resources that package information into searchable, sharable units. Several ongoing pilot projects at NIH aim to understand how to use FHIR standards and methodology for data interoperability. These projects include development and testing of tools to allow clinical investigators to extract information from EHRs, development of an API to retrieve phenotypic data from large cohort studies, and a FHIR-based schema for returning structured genetic results from a clinical report.

In closing, Dr. Gregurick announced the NIH Data and Technology Advancement (DATA) National Service Scholar Program, which will place data science and technology experts on one- to two-year sabbaticals in high-impact programs. Sample projects include the use of artificial intelligence to analyze AD Sequencing Project data. The program will begin this summer with an expected five or more scholars to work on the first cohort.

In response to questions from the Council, Dr. Gregurick noted that FHIR standards could be enhanced to include data on functional outcomes, which are typically excluded from medical records. She also acknowledged that the FAIR concept might be new to review panels and that NIH wants the community to have enough time to consider what constitutes a good data-management and sharing plan. One way to accommodate this learning curve is to require that data management plans be submitted to Just in Time (JIT), then evaluate whether it should be considered by the Center for Scientific Review (CSR). Dr. Gregurick reiterated that every principal investigator (PI), regardless of grant mechanism, is required to submit a data management and sharing plan.

Dr. Gregurick reported that NIH is beginning to work with partners to determine how to retain EHR data in a way that preserves privacy, and how best to store and manage data in a cloud environment. She acknowledged that institutions often discard EHR data after 10 to 20 years. The NIH Office of Data Science Strategy is also working with the State Department, as well as the Department of Health and Human Services (HHS) and NIH leadership to identify best practices for data management and sharing to help overcome institutions' reluctance to sign data-sharing agreements. NIH is also considering how best to accommodate established resources where consent might not have been given for data-sharing. In response to questions about what happens to data after investigators leave the field, Dr. Gregurick suggested that investigators consider depositing data into community or generalist repositories if they feel the data should be

shared in perpetuity. She and Council members also noted that sharing all data would be impossible; thus, the research community should consider which data to prioritize for sharing.

VI. PROGRAM HIGHLIGHTS

A. Division of Behavioral and Social Research: Emotion and Cognition in the Aging Brain

Dr. Mara Mather, of the University of Southern California, presented recent work on the positivity effect among older adults. While working with Drs. Susan Charles and Laura Carstensen, Dr. Mather observed positivity effects in both memory and attention: older adults tended to recall mostly positive information from pictures, and they tended to focus primarily on positive aspects of those pictures. The investigators hypothesized that the positivity effect arises from changes in time perspectives; as time appears to become more limited, people tend to focus more on emotional goals, leading them increasingly to attend to positive stimuli. This suggests that older adults use prefrontal cognitive control resources to implement those goals. Indeed, the positivity effect is eliminated among older adults under a working memory load, indicating that older adults deploy cognitive resources at the rapid attention level. However, prefrontal cognitive control processes, compared to other brain processes, undergo precipitous decline during normal aging. Thus, the positivity effect is an age-related effect that does not depend on age-related decline in the brain.

Dr. Mather and her colleagues are now examining the effects of arousal. In a series of “oddball” experiments, the ability of participants to remember pictures immediately preceding or following an emotional oddball photo is impaired, compared with their memory for pictures surrounding a neutral one. This result suggests that arousal enhances processing of high-priority stimuli while impairing processing of low-priority stimuli. Priority is given to mental representations that are enhanced versus suppressed by the process of selective attention. Additional work suggests the involvement of the locus coeruleus-norepinephrine system in both impaired and enhanced processing of high-arousal events. Dr. Mather and her colleagues have shown that coordinated activity between the locus coeruleus and the place image is highest during arousal and at salient places, both in younger and older adults. However, neural activity becomes more selective under arousal among younger adults, yet not among older adults. The dynamics that appear to be disrupted in older adults are related to the frontoparietal areas involved in attention. These findings are of interest because the locus coeruleus-norepinephrine system is among the first areas where AD pathology manifests.

Council questions and discussion focused on other conditions or manipulations that Dr. Mather and her colleagues might consider in their experiments. Suggestions included exploring the positivity effect in younger adults with lesions in the dorso- or mediolateral prefrontal cortex, or in older adults with different perceived time horizons. Dr. Mather also observed that depression is known to shorten perceived time horizons. Council members also discussed insights from this research that could potentially be applied to the loneliness epidemic.

B. Division of Neuroscience: A New Therapeutic Approach for Alzheimer's: From Mechanism Discovery to Creation of a Novel Therapeutic Class to Human Trials

Dr. Frank Longo, of the Stanford University School of Medicine, described a drug-discovery approach leveraging basic mechanisms associated with neuron degeneration. He credited the wide spectrum of NIA funding mechanisms for helping him and his colleagues cross “the valley of death” (i.e., preclinical, Phase 1 and Phase 2a studies) in drug discovery and development.

AD pathology, which involves a complex milieu of A β , tau, and microglia all interacting with age, begins long before clinical manifestations are apparent. It appears to trigger a network of degenerative signaling. Decreases in protein kinase A lead to declines in phosphorylated CREB, increases in RhoA lead to declines in phosphorylated cofilin, and increases in several stress hormones lead to tau pathologies and changes in fyn and NR2B. These changes lead to increased synaptic dysfunction, spine loss, and neurite degeneration. If emergence of pathology is tied to this entire network, attempting to target therapeutics to network components could prove futile.

Dr. Longo and his colleagues have found that the p75 receptor modulates the neurodegeneration pathway based on its interactions with neurodegeneration adaptors or survival adaptors. They have generated a novel class of small molecules, including the lead molecule LM11A-31, that function as p75 ligands, downregulate degeneration signaling, and upregulate survival signaling. These small molecules block various points across the neurodegeneration signaling network in preclinical models. LM11A-31 also appears to reverse spine degeneration, inhibit formation of toxic tau species, reverse synaptic impairment, and reduce microglial activation. Work in preclinical models has also shown that LM11A-31 reverses age-related neuronal atrophy. Dr. Longo and his colleagues have founded a company to conduct Phase 2A clinical trials assessing this small molecule in individuals with mild to moderate cognitive impairment in Europe.

In response to questions from Council members, Dr. Longo noted that these clinical trials will be conducted in Europe because cerebrospinal fluid (CSF) samples are more readily available there. He suggested increased education on the importance of CSF samples and the importance of an effective person overseeing CSF sample collection as important for increasing CSF donation in the United States. Dr. Longo also noted that, in the normal brain, p75 is expressed predominantly in regions affected by AD.

C. Division of Geriatrics and Clinical Gerontology: From Polygenics to Omnigenics: A FOXO3-Driven Gene Resilience Network on Chromosome 6

The Honolulu Heart Program is part of an international study examining patterns of cardiovascular disease among Japanese nationals and immigrants. The program includes a biorepository of nearly 500 thousand blood and tissue samples, a wealth of phenotypic data, ongoing autopsy studies, and genetics and lifespan studies. Dr. Bradley Willcox of the University of Hawaii and the Honolulu Heart Program discussed current knowledge of FOXO3, which was identified by the Hawaii Lifespan Study as a gene associated with longevity.

The association of FOXO3 with extended lifespan has been replicated by more than 20 studies. The gene is also associated with extended health span. FOXO3 is involved in several biological processes that protect against aging. Although it tends to be deactivated in many cancers,

epidemiologic studies have not shown a protective effect of FOXO3 on cancer or stroke. However, FOXO3 expression is associated with reductions in both overall mortality and mortality associated with coronary heart disease.

Whereas most studies in model organisms adopt a polygenic approach, which focuses on the importance of a signaling pathway to a given phenotype, Dr. Willcox and his colleagues have employed an “omnigenic” approach, focusing on FOXO3 as a master regulator of a network contributing to longevity. They have identified a longevity haplotype with 13 single nucleotide polymorphisms and found that FOXO3 relates to at least 46 other genes over a large region of chromosome 6. Using lymphoblastic cell lines from individuals with the protective “G” FOXO3 allele, Dr. Willcox and colleagues have found that these genes migrate together in response to stress. Chromatin looping brings the *cis*-regulatory elements of these genes into coregulated islands, and multiple coregulated islands are brought together into a functional neighborhood surrounded by gene deserts. The genes associated with FOXO3 are associated with several aging-related systems, including autophagy and energy-sensing. Evidence also suggests that long, noncoding RNAs participate in the network. The Honolulu Heart Program has recently received funding for translational studies to explore this network further.

Council members discussed possible relationships between FOXO3 and dementia. Dr. Felipe Sierra, Director of the Division of Aging Biology, clarified that longevity studies aim to identify genes that help an individual withstand stress, which in turn might extend their lifespan.

D. Division of Aging Biology: Genomic and Epigenomic Regulation of Vertebrate Aging

Much aging research has been conducted in short-lived organisms, such as *C. elegans*, fruit flies, and yeast. These model organisms offer the advantages of being inexpensive and having well-understood genetics. However, because they are invertebrates, they are ill-suited for comparative studies of human aging. Vertebrate models such as rodents and zebrafish offer promise but are not easily used for longitudinal experiments.

Dr. Bérénice Benayoun, of the University of Southern California, presented work assessing how genomes, epigenomes, and transcriptomes reconfigure with age. She first described work in the African turquoise killifish, a vertebrate organism with the lifespan of a fruit fly. The killifish shows aging-associated phenotypes such as cognitive decline, decreased fertility, muscle wasting, color declines, and increased burden from neoplastic lesions. As with other organisms, dietary restriction increases the killifish’s longevity and health span. Researchers can obtain genetically diverse killifish from the wild as well as an inbred laboratory strain, making it feasible to study and manipulate the organism’s genetics.

Dr. Benayoun’s laboratory is using the killifish to study the impact of transposable elements on vertebrate aging. Approximately 60% of the killifish genome is repetitive, and most of it derives from transposons. The laboratory has leveraged repeat-specific assemblers and data from public databases to discover that age induces most transposons, suggesting that loss of control of these elements is a hallmark of aging. Dr. Benayoun’s laboratory is now investigating age-, sex-, and tissue-specific regulation of transposases in the inbred killifish strain.

Dr. Benayoun also described work using mouse models to investigate sex-specific differences in mechanisms of immune aging. Humans exhibit sexual dimorphism in effects of longevity interventions, in -omics profiles, and in incidence rates of autoimmune diseases, which are higher among females than males. Leveraging the NIA Aging Mouse Colony, Dr. Benayoun and colleagues have discovered high sexual dimorphism in the aging macrophage transcriptome. They also have found an increased reliance on glycolysis in aging females and in younger males, identified genes that are not expressed in aging females, and observed substantial reductions in transcription among older females (but not among older males). These observations suggest that trajectories in the genomic and functional landscape differ between aging males and females. Dr. Benayoun and her colleagues also have found evidence that sex hormones and Ahr signaling could be a driver of female immune aging.

Council discussion focused on technical aspects of Dr. Benayoun's work.

VII. INTRAMURAL PROGRAM REPORT

A. Laboratory of Neurogenetics

Dr. Andrew Singleton, Chief of the Laboratory of Neurogenetics (LNG), provided an overview and progress report. LNG aims to understand the genetic basis and etiology of age-related neurological disorders; help intramural and extramural colleagues develop critical methods and projects; publish data and other resources quickly and without restrictions; and recruit, train, and develop first-class scientists. The Laboratory comprises six PI-led groups, along with an investigator from the National Institute of Neurological Disorders and Stroke and three supporting groups focused on data sciences, genomic technologies, and computational biology. LNG has engaged in multiple collaborations, increasingly with industry. Fourteen percent of LNG's publications are within the top 1% of cited publications, and 28% are within the top 10%. LNG has used a traditional reductionist approach—identify the locus and the gene, understand the pathobiology, and identify therapeutic targets—but is now shifting toward more system-wide omics approaches.

Dr. Singleton highlighted several successes, including the following:

- A recently published GWAS and functional inference, doubling the number of Parkinson's disease (PD)-associated risk loci to 1000, involving roughly 40,000 patients.
- Creation of a mouse model for auxilin, which contains rare mutations associated with younger-onset PD. Using this model, LNG has shown that synapses in dopaminergic neurons lack vesicles in PD, and it has shown a functional connection between auxilin and Lrrk2.
- A report that depletion of a particular population of dopaminergic neurons affects the ability to learn adaptive motor learning.

LNG is also leading the Global Parkinson's Genetics Program (GP2), a consortium connecting PD researchers from around the world to genetically characterize 150,000 patients. GP2 has created a hub to facilitate gene identification in monogenic PD and is increasing emphasis on

patients of non-northern European ancestry. The consortium is also focusing on deployment and support of a data sharing platform.

Council questions and discussion focused on the technical aspects of the successes Dr. Singleton highlighted.

B. Intramural Program Review

This portion of the meeting was closed to the public in accordance with the provisions set forth in section 552b(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).

VIII. ADJOURNMENT

The open session of the 139th meeting of the National Advisory Council on Aging adjourned at 1:35 p.m. on January 22, 2020. The next meeting is scheduled for May 26–27, 2020.

IX. 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 May 26-27, 2020, and corrections or notations will be stated in the minutes of that meeting.