

**NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE ON AGING**

Summary Minutes

The 136th Meeting

NATIONAL ADVISORY COUNCIL ON AGING

January 29–30, 2019

**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 29–30, 2019**

The 136th meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, January 29, 2019, 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 29, 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 Public Law 92–463.¹ The meeting was open to the public on Wednesday, January 30, from 8:00 a.m. to 2:15 p.m.

Council Participants:

Mr. James Appleby
Dr. David A. Bennett
Ms. Meryl Comer
Dr. Eileen M. Crimmins
Dr. Alison M. Goate
Dr. Margaret Goodell
Dr. J. Taylor Harden
Dr. David M. Holtzman
Dr. Stephen B. Kritchevsky
Dr. Terrie E. Moffitt
Ms. Susan K. Peschin
Dr. Eric Michael Reiman
Dr. Clifford James Rosen
Dr. Amy Jo Wagers

Ex Officio Participants:

Dr. Vijeth Iyengar, Administration for Community Living
Dr. Jane Tilly, Administration for Community Living

Absent Ex Officio Participants:

Dr. Alex Azar II, Department of Health and Human Services
Dr. Francis S. Collins, National Institutes of Health

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:

Members of the Public Present:

- Dr. Shalender Bhasin, Harvard Medical School*
- Ms. Trish D’Antonio, Gerontological Society of America/Friends of NIA
- Dr. Monica Driscoll, Rutgers University*
- Dr. Terry Fulmer, John A. Hartford Foundation*
- Dr. Rose Maria Li, Rose Li and Associates, Inc.
- Dr. Samuel H. Preston, University of Pennsylvania
- Dr. Michael A. Province, Washington University School of Medicine
- Dr. Adam Salmon, University of Texas Health Science Center at San Antonio
- Dr. Julie Ann Schneider, Rush University Medical Center
- Dr. Reisa Sperling, Harvard Medical School
- Ms. Yana Vierboom, University of Pennsylvania

*New Council members pending final approval

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 1707 applications requesting \$ 3,308,337,588.95 for all years underwent initial review. The Council recommended 852 awards for a total of \$ 2,111,105,336.92 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. Richard Hodes welcomed members to the open session of the 136th NACA meeting and called the meeting to order at 8:00 a.m. on Wednesday, January 30, 2019.

A. Director’s Status Report

Dr. Hodes reminded the Council that FY2019 was the first year in some time that a Federal budget was in place for the Department of Health and Human Services (DHHS) and NIH before the beginning of the year. This budget includes \$39 billion for NIH, an increase of approximately \$2 billion. Within that amount is \$40 million for universal flu vaccine research, \$29 million for the BRAIN initiative, \$86 million for All of Us, and \$425 million to NIA specifically for

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research on Alzheimer's disease (AD) and related dementias (ADRD). In addition to these targeted monies is an increase of \$84 million across all NIA Divisions, bringing the Institute's total budget to \$3.1 billion. Dr. Hodes also reported that the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs have increased more rapidly in obligations, compared with other NIA funding mechanisms. These obligations are projected to increase to \$105 million in FY2019.

Having a budget set before the beginning of the fiscal year has allowed NIA to announce initial paylines. For general applications, the initial paylines are 15% for those requesting less than \$500,000 (direct costs in any year), and 12% for those requesting more than \$500,000. For AD/ADRD-targeted research, the paylines among applications scored by the NIH Center for Scientific Review are 28% for applications requesting less than \$500,000 and 25% for those requesting more than \$500,000. The paylines for program projects and other NIA-reviewed applications are 20 for general applications and 38 for AD/ADRD-targeted applications. Paylines for training awards range from 21 to 28 for general applications and 28 to 35 for AD/ADRD applications. NIA continues to give preference to new and early-stage investigators. Dr. Hodes cautioned that these paylines could change, depending on the number of applications received. He also noted that, as NIA is able to fund more applications, it will continue to pay close attention to individual reviews, comments, and consultations.

Dr. Hodes noted that NIA has used some of its increase in AD/ADRD-targeted funding to recruit new investigators to the field. In our recent years of substantial growth, more than one-third of total awards have been made to investigators who have never applied for AD/ADRD-targeted research funding in the past. Following a brief pilot program in collaboration with the National Institute of Biomedical Imaging and Bioengineering, NIA has invited other Institutes and Centers to solicit investigators and recommend applications with enough relevance to AD to justify administrative supplements related to AD/ADRD to grants which themselves were not previously focused on AD/ADRD. NIA has funded 300 such supplements. Dr. Hodes expressed excitement at the diversity of applications that received administrative supplements. The 2019 deadline to apply for such administrative supplements is February 26.

Dr. Hodes then provided several updates:

- The results of the Systolic Blood Pressure Intervention Trial-Memory and Cognition in Decreased Hypertension (SPRINT-MIND) have been published. SPRINT, the parent study, was stopped early because it showed a clear benefit, with respect to deaths associated with cardiovascular disease, from intensive blood pressure control. Although SPRINT-MIND showed only a trend toward a reduction in dementia, the primary outcome, it showed that more intensive blood pressure control led to a statistically significant reduction in the secondary outcomes of mild cognitive impairment (MCI, 19%) and combined MCI/dementia (15%). SPRINT-MIND also showed that more intensive blood pressure control affected white-matter density as measured by imaging.
- The NIH Policy on Inclusion Across the Lifespan, which was implemented on January 25, 2019, requires new grant applications to justify the age of inclusion for their study populations. Applicants must explain the reasons for exclusion of older adults or children. Scientific review committees must consider inclusion in its deliberations. Grantees are

required to provide anonymized data about sex, age, and race/ethnicity in their progress reports. Drs. Marie Bernard, Michael Lauer, and Janine Clayton published this policy, along with an analysis of the underrepresentation of older adults in past studies without justification, in the *Journal of the American Geriatric Society*.

- The National Strategy for Recruitment and Participation in AD and ADRD Research aims to engage broad segments of the public in this research, with a focus on underrepresented communities. In response, NIA has intensified efforts among existing staff and is recruiting new staff with expertise in the science of recruitment.
- The Agency for Healthcare Research and Quality (AHRQ) and the National Academies of Sciences, Engineering, and Medicine (NASEM) are developing a report on dementia care interventions. AHRQ is conducting a literature review and will report on the level of evidence for several interventions. NASEM will appoint an expert panel to review the AHRQ assessment and to conduct its own analysis to make recommendations about the quality of evidence and research gaps. The draft report is expected to be released before the Dementia Care Summit in 2020.
- The iCARE-AD/ADRD Challenge is offering a prize for technological approaches to enhance the ability of individuals to track and navigate support and care for dementia patients and their caregivers. The Challenge is accepting submissions from October 1, 2018 through June 30, 2019, and will make up to \$400,000 in cash prizes to teams or individuals that participate in the competition.
- The Building Our Largest Dementia (BOLD) Infrastructure for AD Act was signed into law on December 31, 2018. The BOLD Act establishes AD public health centers of excellence; provides cooperative agreements to public health departments; increases data collection, analysis, and timely reporting by the Centers for Disease Control and Prevention; and requires coordination across HHS to avoid unnecessary duplication of effort.
- NIH is mourning the loss of Dr. Steve Katz, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Dr. Katz died suddenly on December 20, 2018.

Dr. Hodes noted that the application deadline for this summer's Butler-Williams Scholars Program is March 22. He asked Council members and attendees to save the dates for the ADRD Summit (March 14–15, 2019), the third Geroscience Summit (November 4–5, 2019), and the Dementia Care Summit (March 24–25, 2020).

One Council member questioned the initial payline for program projects, which is 10 points higher than that for K awards. Dr. Hodes acknowledged the continued importance of career development and noted that NIA provides its best service by allowing funding without delay. He added that the payline for K awards will likely be higher, but NIA will make that decision in the context of the reviews and the issues raised. Dr. Barr also noted that the number of applications for K awards has doubled over the past 3 years.

In response to questions about the AHRQ/NASEM report, Dr. Hodes noted that the NASEM Committee will interact with the Minnesota evidence-based practice center (EPC) and NIA before releasing the final review questions and preliminary study design.

Dr. Hodes referenced the press clippings assembled by NIA's Public Information Office that are available online to Council members, and encouraged members to stay informed and connected between Council sessions by visiting <https://www.nia.nih.gov/research/funding> for active NIA funding opportunities, and subscribing to the NIA blog, <https://www.nia.nih.gov/research/blog>.

B. Future Meeting Dates

May 21–22, 2019 (Tuesday and Wednesday), Building 60

September 10–11, 2019 (Tuesday and Wednesday), Neuroscience Building, Executive Boulevard

January 21–22, 2020 (Tuesday and Wednesday), Building 31

May 26–27, 2020 (Tuesday and Wednesday), Building 31

September 8–9, 2020 (Tuesday and Wednesday), Building 45

C. Consideration of Minutes of the Last Meeting

The minutes of the September 2018 meeting were considered. A motion to approve the minutes was made, seconded, and passed unanimously.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. J. Taylor Harden began her report by acknowledging Dr. David A. Bennett, Co-Chair of the Task Force, who won the 2018 Potamkin Prize for Research in Pick's, Alzheimer's, and Related Diseases, which she described as the Nobel Prize of Alzheimer's Research. She then reported on the Task Force discussion about the NIA Inclusion Report. The NIH Revitalization Act of 1993 mandates reporting on the inclusion of women, minorities, and other underrepresented groups in NIH-supported research. The 2019 Triennial Advisory Council Reports cover FY2016 through FY2018. On the basis of the aggregate data, NIA has consistently met its goals for the recruitment of white participants, but its success with underrepresented groups has varied. Thus, NIA should intensify its efforts. Dr. Harden explained that most of the inclusion enrollees in the reports were derived from epidemiologic studies and that one report from a large, prospective study could sway the results widely. She added that there are some redundancies because the reports contain both prospective recruitment data and secondary data analyses. Because it is not required by law, data on retention are not collected.

Task Force members noted that the tables in the inclusion report were insufficient and suggested that NIH better identify what it wants to know about recruitment and how to ask for that information. They also noted the absence of statistical analysis and reporting of inclusion data (e.g., via publication) from diverse groups. The Task Force offered to work with the NIA Office of Planning, Analysis, and Evaluation (OPAE) to survey publications and identify the extent to which diverse groups have been included in statistical analyses. Dr. Hodes and Dr. Robin Barr responded that the tables were constructed to reflect the legislative mandate, but that NIA could add different and more detailed studies on its progress on recruitment and retention. Dr. Bernard added that because the new NIH inclusion policy allows for anonymized, individual-level data, opportunities exist for more specific reporting. A motion was forwarded and seconded to accept the NIA Inclusion Report. The motion passed unanimously.

Dr. Harden reported that the Task Force heard a presentation from Dr. Shahrooz Vahedi, of the NIA Division of Extramural Activities, and Dr. Jaron Lockett (OPAE), on how NIA implements the NIH-wide program that awards research supplements to existing grants to promote diversity in health research. These supplements provide flexible salary and training-related support for a maximum of 2 years to a wide range of trainees from the high school to the faculty levels. Representation of diverse groups in the program is similar to that across NIH. Drs. Vahedi and Lockett noted that it is impossible to establish a direct link between participation in this program and career outcomes, but these supplements likely represent a significant step toward an independent research career and therefore should be continued. They also noted that many supplement awardees have applied for, and received additional funding, from not only NIA, but also other funding agencies.

Dr. Harden reported that the Task Force heard a presentation from Dr. David R. Wilson, Director of the NIH Tribal Health Research Office. Established in 2015, this Office plans initiatives and strategic directions to increase Native American representation in research and to build an American Indian/Alaska Native research community. It works with career development programs and other program initiatives and has engaged 573 American Indian tribes across the United States to review research-related policies and outcomes. The Office will soon release its first NIH Strategic Plan for Tribal Health. Future plans include building a research portfolio, convening a summit on traditional medicine, consulting on intellectual property, and partnering with other research programs to provide technical assistance in Indian Country.

Dr. Harden concluded her report with information updates:

- During the annual NIA Director's Regional Meeting on Aging Research, the NIA Director, together with the Division Directors, meet with communities, particularly those that are underrepresented in NIA-supported research.
- The NIA Health Disparities Research Administrative Supplements program offers supplements to existing grants to explore the science of health disparities.
- The Gerontological Society of America (GSA) Scientific Meeting will be held on November 13–17, 2019, in Austin, Texas.
- The American Public Health Association (APHA) conference will be held on November 2–6, 2019, in Philadelphia, Pennsylvania.
- Council is reminded about the NIH Women of Color Research Network, which brings together extramural and intramural scientists to share their experiences and support each other as they advance their careers.
- Applications for the 2019 Butler-Williams Scholars program are due March 22.

IV. REPORT: WORKING GROUP ON PROGRAM

A. CTAP Report

A motion to accept the Clinical Trials Advisory Report that was presented on the previous day was forwarded, seconded, and passed unanimously.

B. Review of the Division of Neuroscience (DN)

Dr. Reisa Sperling gave her final report on the DN review. She noted that overall, the review committee was impressed with DN's progress and accomplishments. DN has been flexible and responsive to milestones set by the National Alzheimer's Project Act (NAPA) and several summits, and it has issued more than 100 new funding opportunity announcements in response to the unprecedented growth in AD research funding. As a result, the number of grant awards managed by DN has more than doubled.

The review committee recognized several strengths:

- The appointment of Dr. Eliezer Masliah as Division Director.
- Improved interactions, both within DN and between DN and other NIA Divisions.
- The empowerment of senior staff to develop and implement highly impactful new initiatives spanning basic/discovery science, clinical trials, and clinical care.
- The leading role that DN plays in setting research priorities, organizing research summits, preparing Congressional bypass budgets for AD/ADRD, and supporting other NIA initiatives.
- Multiple collaborative initiatives between DN and NIH Institutes and sectors.

The review committee also recognized several issues:

- DN lacks a comprehensive communication strategy to publicize successes and increase public awareness of DN and NIA's role as a driver of inventive research within NIH.
- The level of growth experienced by DN is not sustainable without additional personnel.
- The number of training, fellowship, and career development awards to train the next generation of investigators has not kept pace with DN's growth.
- The diversity of investigators and study participants, with respect to race/ethnicity, sex, and scientific discipline, should be improved.
- More can be done to improve data sharing.
- Continued support of basic/discovery science research is needed to further understand the fundamental mechanisms of aging and disease and how they influence neurodegenerative disease.

Dr. Sperling reported that the review committee generated 163 recommendations, which it distilled into 10.

- Develop more scalable, lower-cost, and less-invasive biomarkers for AD, as well as for comorbidities and other conditions, and develop the infrastructure to support such efforts.

- Dramatically improve the value of existing longitudinal study cohorts and other studies, for example by identifying ways to embed more AD-association biomarkers, improving the diversity of participants, and ensuring that the data are widely accessible.
- Support the development of next-generation approaches to clinical assessment, for example new digital tools for monitoring and for functional and cognitive assessments. DN should consider partnerships with the technology industry.
- Create processes to support robust data-sharing and incentivize investigators to share their unique data broadly.
- Identify additional opportunities to attract and retain trainees, other new investigators, and senior investigators from other fields. Enhance processes to increase first-time funding, support mentors, and consider building “farm teams” that support trainees from the K/R01 transition through their establishment in leadership positions.
- Emphasize data science by recruiting more computational and data neuroscientists.
- Minimize the false dichotomy between aging and AD research, by supporting integral research that explores aging and AD as a continuum.
- Consider ways to expand the research portfolio and integrate DN programs to improve the pipeline for therapeutics development and diversity.
- Enhance partnerships and stakeholder communication strategies.
- Bring in as many qualified staff as possible to support program sustainability and growth.

Dr. Sperling acknowledged the DN staff, particularly Dr. Cerise Elliott, for their diligent work in preparing materials for review.

Noting the growth in funding targeted to AD funding, Council members agreed on the need for continued advocacy for aging research in general. When paylines were lower, some priorities fell by the wayside; now, in this time of plenty, these priorities should be restored. They also supported the notion of a dedicated communications professional to report to Congress on the use of AD and other research funding dollars and other ways to support this research. Some Council members noted that such a professional could serve as a “translator” to explain the relevance of NIA-supported research to the advocacy community and the community at large.

Dr. Hodes and others noted that the number of career development awards in AD has increased, but that the number of Alzheimer’s-focused training grant applications has not kept pace. Likewise, DN has received insufficient applications from individuals with appropriate expertise for open positions in the Division. Dr. Hodes asked Council to spread the word about these positions and to encourage prospective applicants to contact NIA leadership. Regarding communications, Dr. Hodes suggested that the Communications Office make a presentation during a future Council meeting, so that Council members can provide feedback.

Dr. Masliah thanked the Council members, review committee, and staff for its work with the review. He echoed Dr. Hodes’ comments about efforts to recruit additional staff.

A motion to accept the DN review was forwarded, seconded, and passed unanimously.

C. RFA/RFP Concept Clearances

Dr. Eileen Crimmins reported that the Working Group on Program had considered 29 concepts at its earlier meeting and is recommending 27 of them for consideration by Council. The Council made and seconded a motion to approve these 27 concepts en bloc. The motion passed unanimously.

Basic Biology of Aging in Reproductive Tissues

The bidirectional interplay between the reproductive system and the aging soma is well appreciated, but the underlying mechanisms are poorly understood. An increased understanding of these mechanisms might offer a point of intervention in the entire aging process. This concept proposes to support research on mechanistic factors and cellular interactions in the aging reproductive system. It will encourage partnerships between reproductive biologists and researchers focused on aging, and it will support the development of models and methodologies.

Renewal of the Nathan Shock Centers of Excellence in the Biology of Aging

The Nathan Shock Centers of Excellence program began in 1996 and has since funded six centers committed to aging biology research. Since the last renewal, the Centers have developed a more robust approach to core development, and a new Coordinating Center, sponsored by the American Federation for Aging Research, has increased the Centers' visibility. Working Group members noted that this is a strong program. They also suggested that the program promote a greater presence around other NIA-supported programs, because many pilot projects have been awarded to individuals outside the Centers. The Working Group recommended that the program be renewed in its current form, with a significant consolidation of the Centers as a single unit.

Aging, Driving, and Early Detection of Dementia

A properly equipped automobile can provide data about driving performance, and these data could be used to determine whether a driver is becoming unsafe. Such data also might reveal early signs of dementia before cognitive decline becomes apparent. The proposed concept will support research using automobile technology to collect data. The Working Group noted that the concept focuses more on the technology than on the driver and his or her possible impairments. However, the Working Group suggested that researchers keep the end user in mind as they develop and evaluate their technologies. For example, the technology could provide the driver's doctor with hard data that could aid in discussions with older patients about driving.

Dementia Care: Home- and Community-based Services

It has been established in the literature that delaying the placement of an individual with dementia in a nursing home or other institution can yield significant savings for family members and funding agencies. In addition, home is a place of comfort, routine, and personalized attention for most individuals with dementia. Thus, home-based dementia care should be considered the nexus of long-term care. The proposed concept will support research that aims to improve outcomes for patients and their families by identifying barriers to home and community-based services and the degree to which these barriers affect the use of nonresidential services. Target research will comprise observational studies with primary and secondary data collection.

Increasing Research Capacity in Behavioral and Social Science Research on AD and ADRD

The proposed concept aims to improve multidisciplinary, interdisciplinary, and disease-specific knowledge among behavioral and social scientists working in AD and ADRD. Supported activities will include short educational courses, NIA Pioneer Awards, and M.D./Ph.D. training programs and will focus on topics such as projections of dementia incidence and prevalence, analyses of health care systems and financing, and analyses of dementia care. Working Group members suggested inclusion of Ph.D. programs with other clinical scientists.

Innovations to Foster Healthy Longevity in Low-Income Settings

For this concept, “low income” includes individuals in low- and middle-income countries as well as those who are low income, disabled, or isolated in high-income countries. The concept aims to support research to improve function and quality of life through the development of innovative products, devices, environmental modifications, and service delivery. Small research projects will be conducted in collaboration with the National Academy of Medicine’s Grand Challenge in Health Longevity.

Interpersonal Processes in AD/ADRD Clinical Settings

This concept emerges from an awareness that dementia care is delivered with a family medicine approach: there is usually a triad of doctor, patient, and one or more family members or caregivers, rather than the traditional confidential doctor-patient dyad. The proposed concept will support research applying methodologies from communications or family systems research toward the clinical encounter in geriatric visits. The Working Group noted that greater than 20% of older Americans, even those with adult children, are aging alone. They therefore suggested that funded research be responsive to modern population realities. Working Group members also noted that advanced directives are often overlooked, and they therefore recommended an increased emphasis on listening to the voice and wishes of the older patient.

Science of Behavior Change (SOBC) Resource and Coordinating Center Renewal

The proposed concept aims to continue support of the Coordinating Center for SOBC, a trans-NIH initiative that began as a Common Fund project. The Coordinating Center has operated for 4 years and has made significant progress in producing a coalition of scientists spanning health outcomes and multiple approaches. It has been highly productive in terms of producing publications and providing materials on measurement and approach.

Tailoring Interventions to Improve Preventive Health Service Use

The surge in electronic health records (EHRs) has allowed for the expansion of access to clinical data and assessments of preventive strategies. The proposed concept aims to support data analytics and techniques to improve the way that clinicians partner with patients to accelerate the use of preventive health services. EHR and administrative data will be used as sources to identify approaches and to address health disparities. Working Group members discussed how the annual Medicare Wellness Visit would be included.

NRSA Short-Term Institutional Research Training Grant

This concept proposes to continue support for the National Research Service Award (NRSA) training grant, which will expire in July 2019. The grant supports up to 10 institutions in providing short-term research training experiences, such as summer internships. It has helped several physicians and other health professionals interested in aging research to receive training, research, and loan-repayment grants. The NRSA Short-Term Institutional Research Training Grant program complements other later-stage research programs. Working Group members suggested that the program consider a larger number of qualified applicants. Program staff noted that they could measure the long-term impact of this grant on students as they pursue careers in aging research.

Transition to Aging Research Award for Postdoctoral Students

The proposed concept is an aging-focused training grant that will support the latter stages of predoctoral and early stages of postdoctoral research. Similar to the K99/R00 program, this concept would support scientists at a critical transition point in their careers. It would be a non-overlapping grant and therefore increase the pool of NIA-supported predoctoral and postdoctoral trainees.

Early-Stage T1 Translational Aging Research (Bench to Bedside)

The proposed concept renews an early-stage, T1, bench-to-bedside initiative that began in 2012. The initiative has supported 26 awards, through the R21 mechanism, and brought basic discoveries closer to the bedside. Some of these discoveries have moved on to successful SBIR/STTR awards. The new concept will support phase I and phase II awards and has been extended to 5 years; thus, there are opportunities to support more individuals in early-stage translational research.

Expansion of the Claude D. Pepper Older American Independence Centers

The Claude D. Pepper Older American Independence Center (OAIC) program is a P30 award mechanism that promotes the development of infrastructure to increase research in preserving and restoring independence among older Americans. It has been instrumental in expanding the research workforce and developing leaders in geriatric research. The current concept proposes to expand the number of funded OAICs from 12 to 15 and to increase the amount of funding for each Center. The Working Group noted growing interest from medical centers and the opportunity to bring more people into this network. They also believed that the increased allotment is justified in light of the increasing expense of clinical trial development.

Investigation of the Effects of Complex Botanical Products on Human Resilience

An October 2017 study reported that 70% of older Americans use at least one supplement and that 29% use four or more supplements daily. The proposed concept will support a trans-NIH initiative led by the NIH Office of Dietary Supplements and the National Center for Complementary and Integrative Health. It will offer the opportunity for NIA to collaborate with Botanical Supplements Research Centers to identify age-related changes in resilience. Working Group members discussed the number of botanical products that would be studied, whether they would meet prespecified criteria, how manufacturing of Good Laboratory Practice-grade

material would be standardized, and whether NIA funding would be limited to the Centers themselves or be disbursed to the wider community,

Lucidity in Dementia

This concept proposes a modest initiative to begin to develop the science focused on episodes of lucidity in individuals with dementia. At present, most data about these episodes are anecdotal or found in case reports. A recent workshop recommended surveys and observational studies in this area.

Renewal of the Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) Program

The GEMSSTAR program targets clinician-scientists in the medical, surgical, and dental specialties during the early stage of faculty appointments and helps them establish a track record in aging and geriatric science. It includes a career-development component supported by applicants' home institutions. The program has funded 127 awards so far and has been effective in training early-career scientists and clinicians from many backgrounds. The proposed concept aims to renew this program.

Cognitive Systems Analysis of AD Genetic and Clinical Data

The proposed concept aims to support the development of methods and analytical approaches to analyze large amounts of genomic data to generate insight into causal mechanisms. The data, which are housed at the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) at the University of Pennsylvania, include whole-genome sequencing data from several cohorts. The Working Group noted that this concept aligns with the NIA Strategic Plan. It recommended that funds for the required infrastructure at NIAGADS be included in data analysis and methods development applications, rather than in a separate application, so that infrastructure requests would match the needs of data analysis applications.

Early-Career Physician-Scientist Award for Mentored Research in AD/ADRD

This concept proposes to support a collaboration between NIA and the U.S. Department of Veterans Affairs (VA). The VA will support early-stage investigators in working with R01-funded investigators. Although the VA initially required that applicants be physician-scientists out of their residencies within the past 5 years, the Working Group recommended that NIA work with the VA to extend that time period to 10 years.

Genome Center for AD

The AD Sequencing Project began in 2012 in response to NAPA, with the overarching goals to identify new genes and gene variants contributing to the risk for, or protection from, AD and to identify avenues for therapeutic prevention. NIAGADS assembles, analyzes, and performs quality control on data from the sequencing project and provides that data to other investigator groups. The proposed concept aims to renew funding for this Center for another 5 years. Working Group members noted that continuation of funding would permit the development of well-designed pipelines and collaborative teams. They also emphasized the importance of

allowing the Center to work uninterrupted, particularly with additional sequencing data coming from underrepresented groups.

Increasing Competitiveness Around Potential AD Centers

The proposed concept would help institutions interested in becoming AD Centers (ADCs) to begin to develop infrastructure and make them more competitive for the P30 AD Centers program. The Working Group agreed that increased competitiveness among prospective Centers would benefit the entire program.

Infectious Etiology of AD

Recent data note the prevalence of infectious agents in patients with AD. For example, recent studies have reported an overrepresentation of herpes simplex virus and viral response pathways, and other studies have shown that the injection of bacteria or viruses in the brain can seed amyloid deposition. The proposed concept will support research to increase understanding of how infectious agents might contribute to AD.

Noninvasive Neurostimulation in AD and ADRD

Transcranial magnetic stimulation has been approved by the U.S. Food and Drug Administration for depression and obsessive-compulsive disorder. However, other neurostimulators are used widely without a scientific basis. The proposed concept will support research on these methods. The Working Group suggested expansion of this concept to include other devices.

Oscillatory Pattern of Gene Expression in AD

Increasing evidence suggests that circadian rhythms are not only disrupted in AD, but also might play a role in AD biology. The proposed concept will support research using datasets obtained at specific times of the day to assess the role and influence of circadian rhythms in AD. The Working Group suggested that the funding opportunity include support for projects that obtain data from and analyze samples that have already been collected.

Regulation of Brain Regional and Cell Type Specific Proteome Dynamics in Normal Brain Aging and AD

Studies that assess AD-related proteins in single cells or regional interactions could provide additional insight into synaptic and regional vulnerability in aging and neurodegeneration. In addition, newly available labeling techniques have not been applied toward the study of the nervous system in aging and disease. The proposed concept will fund new applications in this area.

Standardization of AD and ADRD Neuroimaging Biomarkers

The proposed concept will support the harmonization of positron emission tomography and magnetic resonance imaging data from 30 ADCs, the shared use of data from various sites, and the relationship of findings to those from the AD Neuroimaging Initiative and other cohorts. The concept will aid in standardizing image-acquisition protocols, developing centralized processes

to upload and analyze images, and sharing information with the research community. The ADC Neuroimaging Steering Committee will oversee this effort. The Working Group noted that this concept would improve the value of longitudinally assessed individuals from ADCs and yield more information on both impaired and unimpaired individuals. The Group also noted that this initiative could subject less-expensive, noninvasive biomarkers to more rigorous tests. They suggested that the initiative value centers that are acquiring and using images in a unique way.

Stimulating Multidisciplinary Programs for AD and ADRD

The goal of this concept is to develop and implement multidisciplinary curricula and programs to help institutions develop and strengthen their own programs related to goals and milestones from various research summits. The funding opportunity would support time for senior investigators to develop programs addressing complex problems associated with prevention and novel therapeutic strategies.

Understanding Senescence in Brain Aging and AD

Although the role of senescence in aging has been established, few studies have investigated senescence in the brain or in brain disease. In addition, few aging and AD/ADRD researchers have backgrounds in this area. The proposed concept would support new collaborative studies to increase understanding of the role of senescence in the aging brain and AD.

V. PROGRAM HIGHLIGHTS

A. Division of Aging Biology (DAB): Moving Towards Translation of Interventions To Biological Aging Using the Common Marmoset

Dr. Adam Salmon, of the University of Texas Health Science Center at San Antonio (UTH-SA), described studies using the marmoset as a bridge between mouse studies and clinical translation.

Evidence has clearly shown that aging is a malleable process. Studies in mice have shown that approaches such as caloric restriction, genetic mutation, and pharmacologic intervention can extend lifespan and slow the pathology underlying age-related diseases. Although mice serve as a good model for the laboratory, the ability to translate findings from mouse models into human studies is limited. Mice die primarily of cancer and do not naturally develop many of the diseases that are top killers in humans. Moreover, basic physiology differs between mice and humans.

One approach to address these challenges is the use of alternative mammalian species. Non-human primates are particularly attractive as models because of their close evolutionary relationship to humans. The common marmoset is particularly advantageous because it has the shortest lifespan of the anthropoid primate species, it is small and has a small laboratory footprint, and the cost of maintenance for these animals is low. In addition, the range of age-related diseases in marmoset more closely replicates what occurs with human aging.

Dr. Salmon and his colleagues are focusing on mammalian target of rapamycin (mTOR) signaling inhibition, which has been shown consistently to extend lifespan. An ongoing study at UTH-SA has enrolled 64 middle-aged marmosets, with a goal of 80, and treats these animals daily with control or rapamycin. Dr. Salmon and his colleagues established a rapamycin dosing

range in marmosets and found that the trough concentration is effective in inhibiting mTOR signaling similar to what is seen in mouse models. However, there is wide variability, similar to what might be expected in humans. The first cohort of animals is now in year 3, and some marmosets have died. However, it is too early to interpret the data with respect to effects of mTOR inhibition on lifespan.

Another goal of these studies is to assess the health implications of long-term, chronic rapamycin treatment. Mouse data indicate that chronic rapamycin treatment causes glucose intolerance. Although marmosets tend to have high blood glucose levels, there is no strong evidence that rapamycin causes glucose intolerance in these animals. Likewise, the marmosets in Dr. Salmon's cohort show no evidence of hyperlipidemia or gross immunosuppression after 3 years of rapamycin. However, the data do suggest that chronic rapamycin treatment can protect against kidney dysfunction and cognitive decline. Dr. Salmon and his colleagues are still assessing the effects of mTOR signaling inhibition on longevity and age-related changes in physiologic function. They are also exploring the use of marmosets as a model for reverse translation. Studies on osteoarthritis and changes in oral health are under way.

Council discussion focused on technical challenges in Dr. Salmon's work.

B. Division of Geriatrics and Clinical Gerontology (DGCG): Evidence for Rare Protective Variants for Healthy Aging and Longevity in the Long-Life Family Study (LLFS)

Dr. Michael A. Province, of the Washington University School of Medicine, described the LLFS as a longitudinal pedigree study that aims to identify the causes of longevity and healthy aging in humans. It has enrolled approximately 5,000 participants representing 539 two-generational families, each of which has at least a living sibling pair in the top generation. The study population offers considerable phenotypic and familial history. LLFS conducts longitudinal measurements through two home visits 8 to 10 years apart. Each visit includes a medical history; tests of physical function; pulmonary testing; cognitive testing; and assessments of personality, depression, dementia, and social habits. LLFS has stored blood samples for each participant. It has also conducted genome-wide association studies (GWAS), exome sequencing, and low-pass regional sequencing, as well as metabolomic and transcriptomic analyses on a subset of participants.

LLFS has generated several publications demonstrating that LLFS families are healthier for their age and sex than the average family. For example, compared with the Framingham Heart Study population, LLFS families exhibit higher high-density lipoprotein levels, better pulmonary function, less hypertension, better gait speed, and better cognitive testing. Although the distribution of obesity is identical between the two groups, the prevalence of diabetes is lower among LLFS families. These healthy aging phenotypes are heritable. Dr. Province and his colleagues have found, particularly with the Danish families in the cohort, that the protective familial effects seen in LLFS families diminish with each generation but persist into the third generation. They have also found that the protection level is heterogeneous across families in the LLFS cohort.

These phenotypes are likely driven by multiple rare protective gene variants, which are missed in GWAS. Dr. Province and his colleagues have developed a linkage screening procedure that adjusts for the common gene variants detected by GWAS. They have also conducted whole-genome sequencing on selected pedigrees. They have identified 12 single nucleotide polymorphisms (SNPs) that are associated significantly with telomere length. All of these SNPs cluster around *ANKRD30A*, which has been associated with breast cancer and epigenetic age acceleration.

Questions from Council members focused on how LLFS incentivized families to participate, socioeconomic characteristics of participants, and how Dr. Province and colleagues addressed the challenge of statistical and biologic validation for rare variants. Dr. Province indicated that the study has very stringent entry rules. It does not pay participants.

C. Division of Behavioral and Social Research (DBSR): Exceptionally Slow Mortality Improvement in the United States: The Role of Obesity

Dr. Samuel H. Preston, of the University of Pennsylvania, presented the results of an analysis on the consequences of the changing pattern of obesity in the United States that he coauthored with Yana Vierboom and Andrew Stokes, published in the *Proceedings of the National Academies of Science* in 2018.

The annual rate of adult mortality has improved slowly in the United States, compared with other wealthy countries. At the same time, according to data from the National Health and Nutrition Examination Survey (NHANES), obesity prevalence in the United States has risen substantially, from 15% in 1980 to 40% in 2016. In addition, if estimates include individuals who are formerly obese, approximately 52% of the U.S. population and 57% of those older than 60 years are obese or were formerly obese. Yet it has been difficult to determine whether the rising prevalence of obesity is a direct cause of the slow improvement in adult mortality, because the relationship between obesity and longevity is complicated by individual history of body mass. For example, individuals who have reached lower weight categories because of illnesses such as cancer, diabetes, or heart disease still die more quickly.

Dr. Preston, with Yana Vierboom and Andrew Stokes, used the Cox proportional hazards model and NHANES data from 1988 to 2011 to explore the contribution of changes in body mass index (BMI) to trends in adult mortality. The analysis was restricted to NHANES participants who were ages 40 to 79 years at baseline. On the basis of this analysis, Dr. Preston and his colleagues estimated that increasing BMI slowed the annual rate of decline in adult mortality by 0.54%. They also calculated that increasing obesity decreased life expectancy at age 40 by 0.9 years, and they estimated that increased BMI accounted for an additional 186,000 deaths, or 11.7% of all deaths at ages 40 to 84, in 2011. The effect of increasing BMI on the annual rate of decline in adult mortality was consistent even when factors such as smoking, education, race, sex, or various combinations were introduced into their model. In addition, the effect of smoking on the annual rate of decline was only half that of increasing BMI.

Dr. Preston closed his presentation by sharing results from a study on regional patterns of mortality change. Council members discussed how the availability of health services might affect

those patterns. Dr. Preston also noted that, although the relative health risks associated with obesity decline with age, an individual's lifetime history of obesity may be more important.

D. Division of Neuroscience (DN): The Complex and Evolving Landscape of Brain Diseases Underlying Alzheimer's Dementia

Dr. Julie Ann Schneider, of the Rush University Medical Center, discussed data from the Religious Orders Study and the Rush Memory Aging Project. Both are longitudinal studies in which participants agree to annual cognitive testing and brain donation. Follow-up rates in these studies are higher than 90%, and autopsy rates are higher than 80%. Data from these studies have revealed pathologies other than amyloid tangles and tau in the aging brain. Among participants who died with a diagnosis of probable AD, the diagnosis was almost always confirmed pathologically. However, in approximately half of these participants, the presence of AD pathology was combined with Lewy body, infarcts, or both. Similarly, among participants with MCI, half showed evidence of mixed pathologies. Moreover, all individuals who died at age 90 showed evidence of amyloid and tau pathologies, but they also showed other pathologies. Dr. Schneider and her colleagues further found that the presence of an additional pathology, such as Lewy bodies, vascular disease, or TDP-43, substantially increased the risk for developing dementia.

TDP-43 is a DNA- and RNA-binding protein involved in transcription. First recognized as a player in frontotemporal lobar degeneration and amyotrophic lateral sclerosis, TDP-43 is now recognized as a common abnormal protein in the brains of older adults. It is independently related to amnesic dementia, which mimics AD, it commonly occurs with AD, and it has been associated with cognitive decline and hippocampal sclerosis. Abnormalities in TDP-43 have a strong effect and account for an amount of cognitive decline similar to that seen with AD-related tangles. Dr. Schneider and her colleagues found a relationship between age and abnormalities in TDP-43 leading to dementia. They also found that neurodegenerative pathways, and primarily TDP-43-associated hippocampal sclerosis, accounted for 68% of dementia cases.

On the basis of brain pathologies, Dr. Schneider and her colleagues have found that the proportion of individuals with mixed pathologies increased with age, whereas the proportion of individuals with single pathologies remained constant. Approximately 75% of individuals with dementia showed evidence of mixed pathologies, regardless of age. TDP-43 and vascular pathologies accounted for more mixed pathologies with increasing age. However, the association of mixed pathologies was attenuated with age.

A framework emphasizing amyloid and tau biomarkers has been published. This framework also emphasizes neurodegeneration, but that component is nonspecific. The presence of mixed pathologies among individuals with MCI and dementia suggests the need for biomarkers related to vascular disease and TDP-43. Dr. Schneider concluded her presentation by showing preliminary data on such biomarkers, which could open the way for more personalized approaches to dementia.

Council discussion focused on possible implications of Dr. Schneider's findings for risk prediction and treatment.

VI. INTRAMURAL PROGRAM REPORT

A. Laboratory of Genetics and Genomics

Dr. Myriam Gorospe provided an update on the Laboratory of Genetics and Genomics (LGG), which investigates the gene expression programs that modulate and dictate age-associated decline and disease. At the time of the Board of Scientific Counselors (BSC) review in 2017, LGG consisted of three sections and three core facilities. The BSC determined that LGG was highly productive and collaborative, and it recommended recruitment at the senior level once the Federal hiring freeze was lifted. Since the review, LGG has published an additional 75 papers. LGG now consists of three sections and two core facilities. Dr. David Schlessinger, head of the Human Genetics Section, retired from LGG and is now a Scientist Emeritus. Dr. Jun Ding, head of the Human Statistical Genetics Core, transferred to the Translational Gerontology Branch. Dr. Norman Sharpless joined LGG as a senior investigator and head of the Aging Biology and Cancer Section, and Dr. Payel Sharpless was recruited as a Stadtman Tenure-Track Investigator and head of the Functional Epigenomics Unit.

Dr. Gorospe provided brief updates on the three sections. In the Human Genetics Section, Dr. Schlessinger's primary focus is the SardiNIA Project, which has published 201 articles and has an increasing focus on longitudinal and age-related studies. The Genome Instability and Chromatin Remodeling Section, headed by Dr. Weidong Wang, has published a paper reporting that topoisomerase 3-beta interacts with the interfering RNA machinery to promote heterochromatin formation and transcriptional silencing in *Drosophila*. The RNA Regulation Section, headed by Dr. Gorospe, has identified DPP4 and SCAMP4, which are expressed on the surface of senescent cells, as important proteins in elimination of these cells and the secretion of factors associated with the senescence-associated secretory phenotype. The Section has also observed overexpression of APP/PS1 in amyloid plaques and found senescent cells embedded in these plaques. This work has been accepted for publication.

B. Laboratory of Molecular Biology and Immunology

Dr. Ranjan Sen noted that the Laboratory of Molecular Biology and Immunology (LMBI) comprises five principal investigators who share common goals in elucidating the molecular and cellular mechanisms that regulate immunity and the age-associated declines in immune responses. These investigators include Dr. Mia Sung, who recently joined LMBI.

Dr. Sen highlighted two ongoing projects. The first investigates NF- κ B dynamics as a mediator of pathogen-specific transcriptional responses. Dr. Sung established a system that images fluorescent derivatives of NF- κ B family members, relates the dynamics of NF- κ B induction, and uses mathematical modeling to correlate those dynamics with output from macrophages and fibroblasts. The second project has focused on innate B1a cells, which are highly inflammatory and contribute to age-related insulin resistance. This work has received a large amount of publicity, including a Research Highlight in *Nature Reviews Immunology*.

Dr. Sen also reported on LMBI participation in the Intramural Research Program-wide Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT) project. The goal of the immune GESTALT project is to identify changes in human immunity associated with

vulnerability among older adults. Phase 1 focused on analyzing cell-intrinsic changes in immune components. Phases 2 and 3 focus on chromatin structure and functional changes associated with human aging. Dr. Sen reported that the project has identified DNA methylation patterns that provide insight into lineage specificity within the transcriptome and epigenome, among others. Dr. Sen closed his presentation by noting that first-level analyses provide insights into basic human immunology and set the foundation for assessing age-associated changes.

VII. REVIEW OF INTRAMURAL RESEARCH PROGRAM

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 136th meeting of the National Advisory Council on Aging adjourned at 1:15 p.m. on January 30, 2019. The next meeting is scheduled for May 21–22, 2019.

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 Robin Barr, D. Phil
With assistance by Rose Li and Associates, Inc.

³ These minutes will be approved formally by Council at the next meeting on May 21–22, 2019, and corrections or notations will be stated in the minutes of that meeting.