

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 127th Meeting

NATIONAL ADVISORY COUNCIL ON AGING

January 19–20, 2016

**National Institutes of Health
Building 31, C Wing, 6th Floor, Conference Room 10
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 19–20, 2016**

The 127th meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, January 19, 2016, at 3 p.m. in Building 31, Conference Room 10, National Institutes of Health (NIH), Bethesda, Maryland. Dr. Richard J. 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 19, 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, January 20, from 8:00 a.m. to 1:15 p.m.

Council Participants:

Dr. Kimberly Acquaviva
Dr. Maria Carrillo
Dr. Steven R. Cummings
Ms. Jennie C. Hansen
Dr. Kevin P. High
Dr. Bradley T. Hyman
Dr. James L. Kirkland
Dr. Eliezer Masliah
Dr. Richard Mayeux
Dr. Charles P. Mouton
Dr. Anne B. Newman
Dr. Thomas A. Rando
Dr. Reisa A. Sperling
Dr. Debra Bailey Whitman

Ad Hoc Council Participants:

Dr. Eileen M. Crimmins
Dr. Raynard S. Kington
Dr. Terrie E. Moffitt
Dr. Norman E. Sharpless

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.

Ex Officio Participants:

Dr. Richard M. Allman, Veterans Health Administration
Dr. Jane Tilly, Administration for Community Living/Administration on Aging

Absent Ex Officio Participants:

Dr. Kenneth G. Pugh, National Naval Medical Center
Mr. Edwin Walker, Administration on Aging

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. Bruce Reed, Center for Scientific Review, NIH

Members of the Public Present:

Mr. James Appleby, Gerontological Society of America
Dr. Malaz A. Boustani, Indiana University
Dr. Anne Case, Princeton University
Dr. Laura Claxton, Purdue University
Dr. Jeff Haddad, Purdue University
Dr. Ryan Grant, Purdue University
Dr. Perry Kirkheim, Purdue University
Dr. Dalane Kitzman, Wake Forest University
Ms. Ann Lam, The Physicians Committee for Responsible Medicine
Dr. Frances McFarland Horne, Rose Li and Associates, Inc.
Dr. Laura Niedernhofer, Scripps Research Institute
Dr. Monika Schneider, The American Association of Immunologists

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 1148 applications requesting \$1,885,307,768 for all years underwent initial review. The Council recommended 626 awards for a total of \$1,226,520,390 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

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

II. CALL TO ORDER

Dr. Hodes welcomed members to the open session of the 127th NACA meeting and called the meeting to order at 8:00 a.m. on Wednesday, January 20, 2016.

A. Director's Status Report

Dr. Hodes reported that for FY 2016, NIH had received an appropriation of \$32 billion, an increase of approximately \$2 billion from the previous year. This increase is the largest since the time of doubling budgets for NIH. Dr. Hodes noted that the increase included specific earmarks for the Personalized Medicine Initiative (\$200 million), the Brain Research through Advancing Innovative Neurotechnologies (BRAIN, \$85 million) Initiative, and research on Alzheimer's disease (AD, \$350 million). Of this appropriation, NIA received \$1.6 billion, representing an increase of 4.2%, in addition to the set-aside for AD research. This increase is in line with an average increase of 4% across NIH.

The table below shows paylines for FY 2015. Paylines for research on Alzheimer's disease were considerably more generous than the general payline. Thus, not all highly meritorious research received funding. Dr. Hodes noted that NIA expects the payline for AD research to be much higher in 2016, depending on the responses to funding opportunity announcements (FOAs).

	<500 K		>500 K	
	General	AD	General	AD
Payline	8	17	5	14
New Investigators (R01)	12	21	9	18
Early Stage Investigators (R01)	14	23	11	20

Dr. Hodes reported that NIA released 10 FOAs focusing on Alzheimer's disease research in October 2015. Approximately 200 applications were received by the first submission date. Dr. Hodes noted that these investigators submitted applications without knowing whether funding would be available. He indicated that an upcoming submission deadline in February allows for another round of applications from these FOAs. Some of these may also be paid in 2016. He reminded the Council about several new AD initiatives approved for FY 2017 and reported that the National Institute of Neurological Diseases and Stroke (NINDS) will release several FOAs focused on AD-related dementias. The NIH Research, Condition, and Disease Categorization (RCDC) system will report on the FY 2015 dollars spent on AD and related dementias, along with other individual categories, in early 2016. Dr. Hodes noted changes in categorizations with a new parent category of Alzheimer's disease and Alzheimer's

disease related dementias. This new category will be reported by RCDC and will serve as the new baseline for tracking Alzheimer's research. The International AD Research Portfolio will continue to track initiatives and awards with respect to AD research milestones.

In the context of new funding, NIA and NIH will revise its plans for FY 2017. Dr. Hodes noted that the FY 2017 bypass budget, a congressionally mandated estimate of the funding needed to accelerate progress in the National AD Plan, was developed based on budgetary assumptions in FY 2016. The increase in funding in the 2016 appropriation will allow NIH to accelerate some FY 2017 milestones to FY 2016. Dr. Hodes reported that the FY 2018 bypass budget will be based on current knowledge of FY 2016 funding and the assumption that funding in FY17 will be flat relative to FY16.

Dr. Hodes highlighted several examples of NIA research from the past year, including:

- A study showing that mortality rates have increased from 1970 to 2013 for white, non-Hispanic adults in the United States aged 45-54 years, even as rates have decreased by 44% for this age group overall **in comparable European countries**.
- A study showing that age-related changes in multiple proteins are tissue specific.
- A study associating the circulating factor Klotho with age and risk for declines in knee strength and cognition.
- The Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS), a joint effort between NIA and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development to support longitudinal studies assessing dementia progression in individuals with Down syndrome.
- The Molecular Mechanisms of the Vascular Etiology of AD (M²OVE-AD), an initiative to understand the degree to which vascular etiology contributes to AD. NINDS will contribute funding to this initiative.
- Findings from the Baltimore Longitudinal Study on Aging regarding interactions between ApoE4 and amyloid.

Dr. Hodes also noted the following updates regarding NIH and the Department for Health and Human Services:

- The Precision Medicine Initiative, on which the National Center for Complementary and Integrative Health Director, Josephine Briggs, M.D., has served as temporary Program Director, concluded its search and will soon announce a permanent Director. Six award/FOA announcements will be issued this year, and three additional FOAs are under development.
- An NIH-wide strategic plan was released on December 16, 2015, and is now online. Required by Congress, this plan articulates principles, processes, and priorities without addressing specific areas of research, thus providing a broad view of how NIH decides its priorities.

- NIH has evaluated its HIV/AIDS portfolio and updated its priorities, which include reduced incidence, new therapeutics, research toward a cure, and HIV-associated comorbidities. Research projects of low priority will not receive HIV/AIDS set-aside funding in FY 2016. Instead, these funds will go into a pool to support higher-priority research. NIA has submitted a project proposal to be supported from these funds.
- In October 2015, NIH held a workshop focused on approaches to understanding and preventing elder abuse. This workshop represented a collaboration between NIA, the NIH Office of Research on Women's Health, and the NIH Office of the Director.
- In September 2015, Dr. Michael Lauer, former Director of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute (NHLBI), was named the NIH Deputy Director for Extramural Research. He succeeds Dr. Sally Rockey.
- NIH issued a notice on November 25, 2015, to clarify priorities for research in health economics.

Dr. Hodes also announced that the NIA Strategic Directions update is now available and that a subcommittee of the Council will review operations across NIA. He also reminded the Council about the Butler-Williams Scholars Program, which will be held on July 25–29, 2016. He noted that NIA will continue to find ways to support this program, even as other supporting agencies are reevaluating their priorities. Dr. Hodes concluded by reporting that Dr. Eliezer Masliah has been selected as the new Director of the NIA Division of Neuroscience (DN) and, thus, will leave the Council.

In response to questions from Dr. Masliah, Dr. Robin Barr pointed out that NIA and the Center for Scientific Review had arranged for the first submission date for the AD program announcements to fall outside the regular R01 application submission date. Subsequent submission dates will coincide with the regular submission dates. The next round of applications will be reviewed at the September Council meeting. Dr. Hodes added that the FOAs, while identifying targeted research areas, were designed to be broad enough to allow for investigator-initiated applications. NIH and NIA will continue to pay attention to the balance between targeted initiatives and investigator-initiated research.

Dr. Maria Carrillo asked about the NIA applications submitted for HIV/AIDS funds. Dr. Hodes clarified that NIA already had applications that had been submitted for FY2016 but that these applications, while meritorious, had fallen outside the NIA funding payline. Thus, in the immediate future, NIA would seek HIV/AIDS set-aside funds for these applications. However, NIA will identify targeted areas and review potential requests for applications (RFAs) with the NIH Office of AIDS Research going forward.

B. Future Meeting Dates

September 27-28, 2016 (Wednesday and Thursday, Building 31)

January 17-18, 2017 (Tuesday and Wednesday, Building 31)

May 16-17, 2017 (Tuesday and Wednesday, Building 31)

September 26-27, 2017 (Tuesday and Wednesday, Building 31)

C. Consideration of Minutes of the Last Meeting

The minutes of the September 2015 meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. Charles Mouton began his presentation by reiterating Dr. Hodes' reminder about the Butler-Williams Scholars Program and by noting the release of the RFA for aging research on stress and resilience to address health disparities in the United States (R01). He then reported that the Task Force had heard two presentations.

The first presentation, given by Dr. Erica Boone, summarized the NIH Loan Repayment Program, which aims to increase the number of biomedical and biobehavioral researchers committed to scientific research by assisting them with their educational debt. Twenty-two Institutes and Center (ICs) participate in this program, which pays up to \$70,000 per year toward loans in return for a 2-year commitment to research. Since its inception, the NIH Loan Repayment Program has disbursed more than \$800 million across more than 17,000 recipients. The average debt is approximately \$90,000, with a range of \$7,000 to \$424,000. The average amount of time in the program is 36 months. The vast majority of awards have gone to clinical and pediatric researchers. The gender breakdown has been fairly even across research categories except for health disparities, contraception, and infertility, where women have received more awards. Approximately 11% of awardees are Asian, 4% black, 2% more than one race, and 6% Hispanic.

The second presentation, given by Dr. Julene Johnson, described the Community of Voices project, which explored the health-promoting effects of community choirs among 390 diverse older adults. The study, which involved 12 centers in the San Francisco area, employed a cluster randomization design. The intervention group immediately participated in community choirs, whereas participation in the control group was delayed for 6 months. Cognitive, physical, and psychosocial engagement was assessed. Although he did not discuss the findings from this project, Dr. Mouton noted that Community of Voices has received additional support from partners such as the Google Impact Challenge and the University of California, San Francisco Philanthropy Program for Accelerated Arts. He also pointed out that this study had a high retention rate and was the only study that had a waitlist for participation.

During discussion, Ms. Jennie Hansen commented that the enrollment and retention success of this study can provide lessons on successful recruitment for future studies.

IV. REPORT: WORKING GROUP ON PROGRAM

The Working Group on Program considered one report and 12 concept clearances.

A. CTAP Report

Dr. Kevin High reported that Dr. Sergei Romashkin provided a report from the Clinical Trials Advisory Panel (CTAP) in September 2015. This report noted that CTAP reviewed three concept proposals. One, Effectiveness of Discontinuing bisphosphonates (EDGE), was recommended by CTAP with high enthusiasm. CTAP also reviewed the other two concept proposals, a project for translating the LIFE study program into diverse community-based partners (“implementation of LIFE” or iLIFE) and the Targeting Aging with Metformin (TAME) study, but noted issues that still must be addressed.

B. RFA/RFP Concept Clearances

A motion was forwarded and seconded to approve these concepts en bloc. The motion passed unanimously.

Nathan Shock Centers Coordinating Center

This concept proposes to establish a center to facilitate interactions among the Shock Centers.

Systems Biology of Aging

This concept proposes an RFA to support research to create data networks examining lifespan in invertebrate models. The working group discussed the possible inclusion of single-cell systems.

Data Archiving and Dissemination

This concept proposes to establish a group that would improve the ability to archive and distribute existing data for secondary analysis. This group would also help investigators develop data for distribution.

Adult Maturation Changes and Dysfunction in Emotion Regulation

The proposed RFA, representing a joint effort by NIA and the National Institute of Mental Health, would build on research showing that while cognitive function declines from mid- to late life, emotional well-being improves. The RFA would support research exploring the social and brain mechanisms used by older adults to reduce negative emotion.

Encouraging Appropriate Care Using Behavioral Economics

This proposed concept will support research that adopts technology from behavioral economics and explores ways to encourage physicians and caregivers to adopt community-vetted recommendations. The initiative would include both a pilot and an implementation phase.

Alzheimer’s Disease Clinical Trials Consortium

The proposed concept would employ a two-part strategy, to re-envision the clinical trial infrastructure supported by NIA. The new infrastructure would include a coordinating center and aim to improve efficiency by decreasing trial start-up time, then work with R01-supported investigators to implement new trials.

Impact of Aging in Human Cell Models of AD

This concept would support research that takes advantage of technology to transform skin cells into neurons and related cells, and explores the impact of aging on these cells.

Neurodegenerative Disease Biorepository

This concept proposes a program to establish a biorepository that would accept samples from projects that have been discontinued. This repository, which would be available to researchers across the country, would be linked to a database with phenotypic information.

From Association to Function in the AD Post-Genomics Era

The proposed concept would support research characterizing the functions of AD-associated genes, representing the next step after identification of these genes.

Mobile Consent

This concept proposes to evaluate the utility and acceptability of including mobile consent, defined as interactive informed consent on mobile devices, in new studies involving older adults. The concept is of particular interest as a way to enhance recruitment and increase diversity in studies.

Technology to Assess Everyday Functions

The proposed concept aims to advance research that builds on work using continuous monitoring technology to assess everyday function, which has not been captured in existing longitudinal AD research. Inclusion of these technologies in clinical and epidemiological studies will be emphasized.

Predictors and Determinants of Age-Related Changes in Physiological Resiliencies

This concept, which builds on a similar RFA on aging and resilience in animal models, was generated from a state-of-the-science meeting on physiological resiliencies in humans. The concept will include two linked phases: (1) an exploratory phase to identify specific resilience phenotypes and mechanisms and to design measures and assays and (2) an optimization and evaluation phase to validate measures and assays, identify mechanistic factors shared across resiliencies, generate predictive models, and identify potential therapeutic targets. Investigators will be asked to submit applications for both phases. The Working Group discussed the use of hospitalizations as a key event to identify individuals for these studies.

V. COUNCIL SPEAKER: EVIDENCE-BASED FUNDING: APPLYING THE SCIENTIFIC METHOD TO OURSELVES

Dr. Michael Lauer, the NIH Deputy Director for Extramural Research, described NIH efforts to evaluate funding policies and programs for clinical research. He began by noting an editorial in which, Dr. Michael Rosbash noted the difficult funding climate and called for NIH to evaluate its funding policies and programs, particularly for large and expensive clinical and epidemiological research. This editorial was followed in 2012 by a *BMJ* study showing that half of completed clinical trials had not published their results 2.5 years after trial completion, as well as by communications from both Congress and NHLBI expressing concern about the implementation of the study. Dr. Lauer described a *New England Journal of Medicine* study by Dr. David Gordon, himself, and colleagues analyzing data on 244 NHLBI-supported trials conducted over 10 years. This study found that, from the time data were cleaned and locked, two-thirds of trials that focused on clinical endpoints had published their main findings within 1 year, compared with 10% of trials focused on surrogate endpoints. By 2 to 2.5 years, all trials focused on clinical endpoints had published their main findings, whereas less than half of those focused on surrogate endpoints had done so. Yet only 45 of the 244 trials were focused on clinical endpoints. In response to this study, an editorial by Devereaux and Yusuf suggested that clinical trials failure to yield a sufficient return on investment, were primarily because there were not enough large trials focused on clinical endpoints. Devereaux and Yusuf suggested possible solutions that included avoiding inefficient and unimportant aspects of trial design, improving the appreciation of review panels for such studies, and changing funders' priorities. This was consistent with another editorial in the *Proceedings of the National Academy of Sciences*, which suggested that the conversation around research and the measures of success should change. Rather than celebrate the amount of funding received, institutions should highlight the impact of their research. However, in a *JAMA* editorial, Ioannidis and Khoury proposed an appraisal system focused on productivity (i.e., published trial results, highly cited papers), quality, replication, sharing of data and resources, and translation when applicable.

Dr. Lauer also reported on a new analysis he is conducting of NIA grants. A preliminary analysis finds that, from 1985 through 2011, 5,664 NIA-funded research project grants yielded 55,504 unique publications. Of these, 15,612 were published in the top 10% of journals in their fields and, in the year they were published, were among the top 10% of most cited studies. Thus 28% of NIA-funded studies were in the top 10% of the most cited publications, having been cited three times more than expected. In a comparison of mechanisms, the analysis found that P01-funded grants outperformed R01s, P01 projects lasted longer and were more likely to be renewed than R01s. P01 grants also yielded a higher number of publications, a higher proportion that were highly cited, and a higher number of highly cited papers per million spent. Thus P01-supported projects appear to be more productive, producing a large body of highly cited papers, compared with a large body of R01-funded grants producing relatively little. Dr. Lauer speculated that the P01 mechanism was the workhorse of research project grants while the R01 mechanism supported more high-risk, high-reward studies. He also cautioned that the

distribution is skewed, this analysis is preliminary, and NIH is considering analyses that account for differences between mechanisms.

Dr. Lauer closed his presentation by noting that the most recent NIH strategic plan, which was well received by Congress, emphasized the issue of accountability and enhancing stewardship. NIH and others acknowledged the need to better understand the ultimate impact of the billions of dollars spent on research each year and that NIH and the research community will need to develop the “science of science,” applying the scientific method to themselves.

Questions were raised on whether funding positive or negative results or breaking into a new area influenced timing of publications and on whether breaking into new fields may be seen as a measure of success. Dr. Lauer indicated that there is a weak positive association between positive results and publication publications but that most of the highly cited trials reported negative results. He discussed new methodology to measure when research moves into new fields, and programs to encourage research that breaks new ground.

VI. PROGRAM HIGHLIGHTS

A. Division of Aging Biology (DAB): Novel Mouse Models for Dissecting Mechanisms and Therapeutic Targets of Aging

Dr. Laura Niedernhofer, of The Scripps Research Institute, described work in a mouse model of the XPE progeroid syndrome. She began by providing background on progeroid syndrome. Although diverse, all progeroid syndromes, defined clinically as accelerated aging, are associated with changes in DNA maintenance or in tolerance of DNA damage. XFE progeroid syndrome, which manifests as a degenerative process after a child meets developmental milestones, has been associated with reduced expression of XPF/ERCC1, a nuclease that protects the nuclear genome from damage and is involved in several DNA repair pathways. The nuclease comprises the XPF and ERCC1 proteins, which stabilize each other and are both important for enzymatic activity.

At histopathologic, molecular, metabolic, and functional levels, mice deficient in XPF/ERCC1 show signs of accelerated aging. Treatment of these mice with senolytics, muscle-derived stem cells, mitochondria-targeted radical scavengers, or NF- κ B inhibitors extend their lifespan, consistent with similar work in normally aged mice. Thus interventions against progeroid syndromes can be applied to normal aging. Dr. Niedernhofer also described work in which knocking out XPF/ERCC1 in specific tissue types led to models of age-related diseases, supporting a role for endogenous DNA damage in these diseases.

These findings suggest a model in which aging primarily involves a cell-autonomous mechanism, where accumulation of endogenous DNA damage drives cells to die or senesce. However, these results also suggest that accumulation of DNA damage somehow triggers non-autonomous events leading to protective mitochondrial changes,

increased production of reactive oxygen species, and cell autonomous events. Once these protective changes are overwhelmed, however, mitochondrial changes become irreversible. These non-autonomous changes suggest several molecular targets for therapeutic intervention. Discovery work comparing proteomics in younger versus aged mice is under way.

In responses to questions from Dr. Richard Mayeux, Dr. Niedernhofer noted that mice deficient in XPF/ERCC1 in the forebrain showed neuronal loss, reactive gliosis, and degeneration. Discussion focused on possible comparisons between this model and AD models, the varying degrees of severity in tissue-specific XPF/ERCC1-associated pathology, and potential strategies to advance these ideas into human testing.

B. Division of Neuroscience (DN): From Brain Care Discovery to Brain Care Delivery in Less Than a Decade

Dr. Malaz Boustani, of Indiana University, described the Indiana University Aging Brain Care model (ABC), an initiative to shorten the amount of time needed to translate brain care discoveries into brain care delivery.

The large proportion of older adults with cognitive impairment presents a challenge to primary care practices and hospitals. Despite decades of research, however, up to 80% of cases are not recognized. The majority of unrecognized patients with cognitive impairment show symptoms that would warrant intervention. Moreover, patients with severe cognitive impairment account for high utilization of health services. Yet, they often receive no treatment or inappropriate medications with adverse cognitive effects. In many cases the treatment they receive has not been approved by the U.S. Food and Drug Administration. Potential interventions often take 17 years to develop, and only a tenth of these potential interventions reach the market.

In the Indiana University aging brain care model, university researchers work with primary care clinicians to manage delirium, depression, and psychiatric symptoms in patients with AD. Developed and evaluated from 2001 to 2006, ABC has been translated to a local model (ABC 1.0) serving 1,000 patients in Indianapolis and a scaled-up model (ABC 2.0) serving 5,000 patients across Indiana. In each of its iterations, ABC has improved care for patients, reduced health resource utilization, and improved caregiver burden. Whereas ABC 1.0 was driven primarily by physicians, registered nurses, and social workers, development of ABC 2.0 has relied more heavily on care coordinators and assistants without affecting the quality of care. An advanced scalable version, ABC 3.0, is under development. In this version, the workforce will be significantly expanded to include patients and caregivers with technological support. This should help bring down per member costs while providing 24/7 care.

Dr. Boustani noted that in developing and evaluating ABC, he and his colleagues had to learn much about implementing change outside the sphere of publishing papers, in a complex, adaptive human network. They saw the need for proactive surveillance and confirmation of clinical opportunities, finding appropriate solutions, having a clear view of how to stop if the model did not work, and developing minimum standard operating

procedures if the model did work. Moreover, Dr. Boustani and his colleagues had to localize content, develop feedback loops, and monitor the impact of outcomes across the entire system.

In response to questions from Dr. Mouton about working with Medicare Advantage programs and moving ABC beyond AD, Dr. Boustani noted that many health plans had reached out to Indiana University. He also noted that the model could be applied to any patients with complex conditions, not just those with AD, and that ABC 3.0 would move to patients with schizophrenia, bipolar disorder, and other chronic conditions. In response to questions from Dr. Marie Bernard, NIA Deputy Director, Dr. Boustani pointed out that the major barriers to moving forward were not financial. Instead, messaging and engaging physicians to collect data and participate in the care feedback loop were more likely challenges. Dr. Boustani also noted that he and his colleagues spent a considerable amount of time trying to find ways to reduce the number of prescriptions for anti-cholinergic drugs. He and his colleagues have worked directly with consumers, their caregivers and families, and primary care clinicians, and are considering ways to employ behavioral economic principles to change prescription patterns.

C. Division of Geriatrics and Clinical Gerontology (DGCG): A Novel Approach to Improving Exercise Intolerance in Older Patients with Heart Failure with Preserved Ejection Fraction

Dr. Dalane Kitzman of Wake Forest University reported the results of a study examining ways to improve quality of life in patients with Heart failure with preserved ejection fraction (HFPEF). This Condition is the fastest-growing form of heart disease in the United States and the most common form of heart failure among older persons living in the community. It is a major cause of morbidity and mortality and is associated with worsening outcomes and high health care expenditures. However, there are no effective treatments for HFPEF. Exertional dyspnea and fatigue are primary symptoms of HFPEF, and exercise intolerance is inherent in the definition of this disease. Dr. Dalane Kitzman, of Wake Forest University, and his colleagues found that the exercise intolerance caused by HFPEF is as severe as that seen with the classic form of heart failure. Severe arterial stiffness contributes to exercise intolerance, and exercise training improves HFPEF by improving skeletal muscle function rather than by improving cardiac or vascular function. Dr. Kitzman and colleagues also observed increased intramuscular fat and a lower capillary to fiber ratio in type 1 oxidative fibers in HFPEF. In addition, obesity is the third strongest risk factor for HFPEF: 85% of patients with HFPEF are overweight or obese. Thus, sarcopenic obesity and exercise intolerance may play a role in older persons with HFPEF.

Dr. Kitzman described the Study Evaluating Caloric Restriction and Exercise Training (SECRET), a trial examining peak oxygen consumption (VO₂) during exercise and quality of life in 100 patients aged 60 years or older randomized to attention control, caloric restriction, aerobic exercise training, or both. Although peak VO₂ improved the most when caloric restriction was combined with exercise, quality of life improved only with caloric restriction. However, dietary weight loss was associated with reductions in

body mass, fat mass, and markers of inflammation and with increased lean and mitochondrial mass. Dietary weight loss was also associated with modest improvements in cardiac function. Thus, caloric restriction appears to improve exercise capacity and quality of life, primarily as the result of improvements in extra-cardiac factors.

Dr. Kitzman noted, however, that one-third of the weight loss seen in SECRET was in skeletal muscle. This loss was not prevented by aerobic exercise and was not reversed by weight gain. Thus, body composition could worsen in the long run. Resistance training is being added to SECRET-2, which was recently launched. Other future directions include translating SECRET findings to younger patients with the classic form of heart failure; implementing exercise training and dietary weight loss in a community-based setting; and examining long-term outcomes, weight maintenance, and impacts on clinical outcomes and survival.

Council members' questions focused on whether the composition of cardiac muscle changed after the interventions. Dr. Kitzman indicated that he lacked the tool needed to measure change there.

D. Division of Behavioral and Social Research (DBSR): Changes in Mortality in Midlife Americans

Dr. Ann Case reported the results of a study reported by Dr. Case and Angus Deaton in the proceedings of the National Academies of Science. Mortality and morbidity rates in middle-aged and older adults have declined markedly over the long term, and the gap in life expectancy between white and black individuals is closing. These trends are welcome and are accounted for in calculations for Social Security and Medicare. However, the Case and Deaton paper reported that, since 1999, all-cause mortality among adults aged 45 to 54 years has increased by half a percentage point per year for white, non-Hispanic Americans. On the basis of data from the Centers for Disease Control and Prevention (CDC), this trend could be attributed to a rise in external causes, which includes suicide, injuries, and poisonings. An increasing number of deaths in this group were also attributable to chronic liver disease and cirrhosis. Dr. Case called these "deaths of despair."

Dr. Case noted that the rate of deaths of despair had increased for all age subgroups among white, non-Hispanic adults aged 45 to 54 years. However, these deaths increased primarily among those with a high school education or less. Dr. Case also noted that the proportion of individuals reporting good or excellent physical or mental health fell among this age group but rose among older individuals. White, non-Hispanic individuals in the younger age group who reported chronic pain also reported social difficulties at a later date, and the fraction of individuals reporting an inability to work rose dramatically. Among a group that should have been in its prime earning years, approximately 10% to 12% reported that they were unable to work.

Dr. Case suggested that the increase in midlife morbidity might be associated with increased prescriptions for opioid pain medications, because physicians began to prescribe these drugs more widely for pain in the late 1990s. Many, but not all, regard

the widespread prescription of opioid pain medications as a mistake, because these drugs do not relieve pain over the long term and can have negative consequences. In *Health, United States 2013*, CDC noted that opioid analgesics play an important role in appropriate pain management, but their misuse is a growing public health concern. For instance, poisoning deaths from opioid analgesics more than tripled between 2000 and 2010. In response, some states have begun to restrict prescriptions for opioid drugs. However, early research suggests that such restrictions are not effective. Instead, an increasing number of individuals have switched to high-grade heroin, and the number of deaths attributed to heroin overdose has increased markedly. Dr. Case also noted a systematic review suggesting that proper management of opioid painkillers in patients with no history of substance addiction or abuse can lead to long-term pain relief.

Thus, Dr. Case cautioned that the cause underlying the rising rate of deaths of despair among white, middle-aged Americans is still not clear. Although drugs and alcohol appear to be proximate causes, Dr. Case also noted the disappearance of well-paying jobs for high school graduates as a potential factor. In addition, why these causes have not affected black Americans similarly remains unclear.

Some questions from the Council focused on ways to examine the opioid/heroin hypothesis more closely and the proportion of the white, middle-aged population that might be veterans or obese. Council members also noted the need to rethink *Healthy People* goals, approaches to health care, and possible changes to public policy such as raising the retirement age. One Council member also noted that among adults aged 55 to 74 years, black Americans are at a significantly higher risk for drug overdose.

VII. INTRAMURAL PROGRAM REPORT: LABORATORY OF GENETICS

Dr. Myriam Gorospe provided an overview of the Laboratory of Genetics (LG), which aims to understand the genes and genetics that govern processes underlying aging physiology. LG comprises the Human Genetics Section, the Genome Instability and Chromatin Remodeling Section, the RNA Regulation Section, and supporting units in statistics, gene recovery and analysis, gene expression and genomics, and image informatics and computational biology. In its May 2014 review, LG received supportive comments from NACA and top ratings from the NIH Board of Scientific Counselors (BSC). Since then, the Laboratory has published 114 articles. Although LG has also undergone changes in structure and leadership, productivity has remained strong.

Dr. Gorospe highlighted the following projects or findings:

- The SardiNIA Project, a collaboration between NIA and Italy, published more than 150 articles since it began. The Human Genetics Section used the SardiNIA dataset to estimate mitochondrial DNA (mtDNA) copy number and find decreasing mtDNA copy number and increasing mtDNA mutations with older age.
- Work from the Image Informatics and Computational Biology Unit showed that age can be predicted accurately from physiologic data. In addition, genome-wide association studies (GWAS) showed the heritability of aging rates and yielded significant hits related to telomere metabolism.

- Work from the Genome Instability and Chromatin Remodeling Section showed that Fanconi and Bloom syndrome complexes work together to bypass DNA interstrand crosslinks.
- Work from the RNA Regulation Section defined AUF1, the phenotypic effects of modulating its activity, and interaction between AUF1 and Let-7. In addition, the Section identified noncoding, regulatory RNAs involved in aging.
- The Gene Expression and Genomics Unit acquired the HiSeq 2500 Illumina sequencing system, which has enabled a wide range of sequencing projects at greater depth and lower cost.

VIII. INTRAMURAL PROGRAM REPORT: LABORATORY OF NEUROGENETICS

The Laboratory of Neurogenetics (LNG) aims to understand the genetic basis and etiology of neurological disorders; provide collaborative infrastructure for both intramural and extramural colleagues; make data and resources publicly available as soon as possible; and recruit, train, and develop first-class scientists. The Molecular Genetics Section is the hub for most LNG work, and the Laboratory also includes the Cell Biology and Gene Expression Section, Transgenics Section, Neurodegenerative Disease Research Unit, Computational Biology Core (CBC), and Statistical Genetics Group. The Genomic Technologies Group, which is supported by NINDS, also resides within the LNG space. Since the last BSC review, Dr. J. Raphael Gibbs has become head of the CBC, Dr. Mike Nalls has become head of the Statistical Genetics Group, Dr. Bryan Traynor has earned tenure, and Dr. Sonja Scholz has joined LNG as an Assistant Clinical Investigator.

Dr. Andrew Singleton noted that LNG has engaged in several collaborations within the NIA Intramural Research Program and around the world. Significant effort has been devoted to Parkinson's disease (PD) and other neurodegenerative diseases, protein kinases or protein genetics, GWAS, and genetic predisposition to disease. Through 2013, LNG has published approximately 110 to 120 papers per year. Of these, 12% were among the top 1% of cited articles, and 46% were among the top 10%. Dr. Singleton highlighted the following successes:

- Identification of 28 risk loci associated with PD and TREM2 as a rare risk factor in AD.
- Work showing the contribution of C9ORF72 mutations to the genetic architecture of amyotrophic lateral sclerosis.
- Work using high-throughput screening to examine protein-protein interactions and understand which GWAS peaks contained functionally relevant genes.
- Work showing that neurons positive for ALDH1A1 are particularly affected in PD.

Dr. Singleton also emphasized that collaboration and sharing have driven the majority of LNG successes. He noted that, although the field of genetics is becoming more

complex, LNG employs an integrated approach that allows it to undertake long-term and high-risk projects, train interdisciplinary scientists, and remain quick and flexible.

IX. INTRAMURAL PROGRAM REPORT: LABORATORY OF NEUROSCIENCES

The Laboratory of Neurosciences (LN) focuses on neurodegenerative diseases leading to dementia, disease-specific processes leading to misfolded proteins, the interplay between mechanisms underlying cellular housekeeping and bioenergetics, and adaptive stress responses and neurotrophic support. One project focused on the critical role of PGC1-alpha in maintaining hippocampal synapsis and BDNF-induced synaptogenesis. LN also showed that mice deficient in the mitochondrial deacetylase Sirt3 exhibit hyperacetylation in the mitochondrial enzymes cyclin D and SOD2. In addition, these mice are also more vulnerable to oxidative damage and cell death from glutamate challenges. Further work supports a protective role for Sirt3 and enhancement of this protection by exercise.

A separate LN project focused on the discovery of novel biomarkers by identifying plasma exosomes enriched for neuronal origin. This approach provides a snapshot into the cytoplasm of neurons in the brain, allowing access to biomarkers that might otherwise be inaccessible. Using this approach, LN has identified IRS-1 as a biomarker of brain insulin resistance. The Laboratory has also shown that amyloid oligomers in the brain promote serine phosphorylation of IRS-1 and inhibit tyrosine phosphorylation of IRS-1. Consistent with this finding, patients with AD show a marked decrease in tyrosine phosphorylation of IRS-1 and an increase in serine phosphorylation of IRS-1. Thus the phosphorylation state of IRS-1 may provide a means to separate patients with diabetes from those with progressing dementia.

Dr. Dimitrios Kapogiannis concluded his presentation by noting that LN also focuses on translating its mechanistic and biomarker discoveries into clinical studies and intervention. The Laboratory is particularly interested in factors that might improve energy metabolism, stress responses, and plasticity. For example, LN is conducting a phase II clinical trial examining exenatide in patients with early AD and the brain effects of caloric restriction in middle-aged individuals with insulin resistance.

X. ADJOURNMENT

The open session of the 127th meeting of the National Advisory Council on Aging adjourned at 1:00 p.m. on January 20, 2016. The next meeting is scheduled for May 10–11, 2016.

XI. REVIEW OF INTRAMURAL RESEARCH PROGRAM

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).³

XII. CERTIFICATION

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



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

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

³ For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to "en bloc" actions.

⁴ These minutes will be approved formally by Council at the next meeting on May 10-11, 2016, and corrections or notations will be stated in the minutes of that meeting.

MEETING ROSTER
National Advisory Council on Aging

NATIONAL INSTITUTE ON AGING

NACA
Agenda Seq Num - 00298180
January 19, 2016 - January 20, 2016

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