

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

Summary Minutes

The 123rd Meeting

NATIONAL ADVISORY COUNCIL ON AGING

September 16–17, 2014

**National Institutes of Health
Building 45, P2 Level, Conference Room E1/E2
Bethesda, MD 20892**

CONTENTS

I.	REVIEW OF APPLICATIONS.....	4
II.	CALL TO ORDER.....	4
III.	REPORT: Task Force on Minority Aging Research	7
IV.	REPORT: Council of Councils	9
V.	COUNCIL SPEAKER: Open Science in Clinical Research: The Time is Now .	11
VI.	REPORT: Working Group on Program	13
VII.	COUNCIL SPEAKER: Update on NIH Big Data to Knowledge (BD2K): Towards the Biomedical Digital Enterprise	15
VIII.	PROGRAM HIGHLIGHTS	17
IX.	ADJOURNMENT	20
X.	CERTIFICATION	20

Attachment A: Roster of the National Advisory Council on Aging

Attachment B: Director’s Status Report to Council

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Institute on Aging

**NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
September 16–17, 2014**

The 123rd meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, September 16, 2014, at 3 p.m. in Building 45, Conference Room E1/E2, 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, September 16, 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, September 17, from 8:00 a.m. to 12:45 p.m.

Council Participants:

Dr. Kimberly Acquaviva
Dr. Norman Anderson
Dr. Laura Carstensen
Dr. Ana M. Cuervo
Dr. Steven R. Cummings
Dr. Kevin P. High
Dr. Bradley T. Hyman
Dr. Richard Mayeux
Dr. Richard Morimoto
Dr. Charles P. Mouton
Dr. Eliseo Perez-Stable
Dr. Thomas A. Rando
Dr. Jonathan Skinner
Dr. Reisa A. Sperling
Dr. Debra Bailey Whitman

Absent Council Participants:

Jennie C. Hansen

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

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. Vera Charkasova, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
Dr. Jennie Larkin, Office of the Associate Director for Data Science, Office of the Director (OD), NIH

Members of the Public Present:

Dr. Vera Gorbunova, University of Rochester
Dr. Harlan Krumholz, Yale University
Linda Harootyan, Gerontological Society of America
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Dr. Frances McFarland Horne, Rose Li and Associates, Inc.
Dr. Marco Pahor, University of Florida
Dr. Arthur Stone, University of Southern California

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 **1075** applications requesting \$**1,784,147,772** for all years underwent initial review. The Council recommended **588** awards for a total of \$**1,081,283,023** for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

II. CALL TO ORDER

Dr. Hodes welcomed members to the open session of the 123rd NACA meeting and called the meeting to order at 8:00 a.m. on Wednesday, September 17, 2014.

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.

A. Director's Status Report

Budget Update

Dr. Hodes reported that both the House and the Senate are working on a continuing resolution that will continue funding at FY 2014 levels through December 11, 2014. In June 2014, the Senate Appropriations Subcommittee presented a draft FY 2015 budget that recommends more than \$30 billion for NIH, an increase of \$605 million. The recommended appropriation includes \$1.27 billion, an increase of approximately \$100 million, for NIA, primarily to support research on Alzheimer's disease (AD). The recommended appropriation would bring the NIH/NIA budget back to pre-sequestration levels, but Dr. Hodes noted that it would still represent an erosion in constant dollar value. He also cautioned that the attitudes of both houses of Congress would depend on the 2014 election results.

The 2014 paylines for established investigators is the 11th percentile for grants lower than \$500,000 and the 8th percentile for grants of \$500,000 and higher. For new investigators, the paylines are the 22nd and 13th percentile, respectively. Dr. Hodes reminded the Council that NIA supported these levels in FY 2013 by reducing non-competing awards and that in FY 2014, with some relief of the sequester, NIA could sustain these paylines without cutting non-competing awards. He also reported that the number of unsolicited applications reviewed at the January 2015 Council meeting increased across several categories, largely because the guidelines for A1 submissions have changed. Although it was not clear whether this increase will be sustained, Dr. Hodes cautioned that it could affect application success rates.

Legislative Update

Dr. Hodes noted the introduction of several pieces of legislation:

- The Conference Accountability Act of 2013, which will further restrict the attendance of Federal employees at international conferences. Specifically, the bill would prohibit agencies from paying travel expenses for more than 50 employees at such conferences unless the Secretary of State says that such attendance would be in the national interest. Dr. Hodes noted the potential detrimental effect of such legislation on scientists in the Intramural Research Program.
- The Accelerating Biomedical Research Act, which would provide additional authority for NIH funding for FY 2015 through FY 2021, so long as the Appropriations Committee maintains funding at more than \$29.9 billion.
- The Research for All Act of 2014, which would provide for expedited review of drugs and biologics to enhance the safety and effectiveness of treatment for males and females and the consideration of sex differences in basic and clinical research.

Dr. Hodes also reported on several other activities with the legislative branch. These include testimony by Dr. Francis Collins, NIH Director, and others on using Federal

investment to drive innovation NIA participation in House and Senate hearings on aging research a meeting between NIA leadership and Representative Mark Amodei (R-NV), and a briefing by NIH leadership to a bipartisan staff of the House Labor-HHS Subcommittee on gender and sex inclusion in NIH research. The briefing highlighted the NIA Interventions Testing Program as a model for inclusion. Dr. Hodes also noted that planning is under way for a White House Conference on Aging, which will focus on retirement security, healthy aging, long-term services and supports, and elder justice.

NIH and NIA Update

NIH has announced a new policy on genomic data sharing, expanding the current policy on sharing of data from genome-wide associations studies. The new policy is intended to increase the volume and kinds of data available for sharing. In addition, NIH has made three awards through its Multiple Chronic Condition program, which is supported by the Common Fund. NIA is co-managing one award, which will evaluate video education as a tool for decision-making. Dr. Hodes further reported that registration is now open for the next AD research summit, which will take place on February 9–10, 2015, and that the World Health Organization will hold a conference in March 2015 to review progress in international collaborations on AD and dementia.

Dr. Hodes noted that in June 2014, NIA announced awards supported by its Falls-Injury Prevention request for applications (RFA), which will be funded by the Patient Centered Outcomes Research Institute and administered by NIA. This initiative will support a large clinical trial on the prevention of fall-related injuries in non-institutionalized older adults. Dr. Hodes also noted that NIA will celebrate its 40th anniversary in a symposium at the Gerontological Society of America (GSA) conference in November. This symposium will be open even to individuals who do not register for the GSA conference.

A notebook of press clippings was circulated, documenting the record-setting number of references to NIA-supported research over the past several months.

B. Future Meeting Dates

January 27–28, 2015 (Tuesday and Wednesday, Natcher Building)

May 12–13, 2015 (Tuesday and Wednesday, Natcher Building)

September 16-17, 2015 (Wednesday and Thursday, Building 31)

C. Consideration of Minutes of the Last Meeting

The minutes of the May 2014 meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes with one correction: Dr. James Burris is no longer representing the Department of Veterans Affairs on Council so his name will be removed from the minutes roster.

D. Comments from Retiring Council Members

Dr. Hodes recognized Drs. Norman Anderson, Richard Morimoto, and Eliseo Perez-Stable for their service to the Council.

Dr. Anderson described his many relationships with NIH overall and pointed out that, through these experiences, he has come to see NIA as a model Institute that never shies away from addressing the true complexity of health and illness. He cited the minority health disparities model in a way, reflecting a NIA model, because NIA emphasizes several levels of analysis and addresses each level seriously. Dr. Anderson also expressed his admiration for the NIA leadership and staff and particularly acknowledged their willingness to take Council's suggestions seriously. He expressed a sense of honor at being part of the Council during NIA's celebration of Dr. Richard Suzman and at an Institute of Medicine symposium highlighting the contributions of the Institute.

Dr. Morimoto noted that he had enjoyed the Council experience of reviewing grants, sharing opinions, and working together to determine what is good at NIA, what should be better, and what should be delayed. He added that his time on Council has shown him a dimension of biomedical research to which he had not been exposed. He also noted the passion of the NIA leadership and staff. Dr. Morimoto reminded Council members that they function as ambassadors with a deep understanding of how the NIA functions, and he called upon Council members to continue sharing that knowledge and insight with their colleagues, particularly young investigators.

Dr. Perez-Stable noted the phenomenal intellectual stimulation from Council meetings, and he noted getting to know fellow Council members and sharing academic and research experiences as a highlight of his time on the Council. He also acknowledged the NIA staff for their dedication and hard work, and he emphasized the need to continue to spread the word about the value of the NIA. He thanked the NIA for the opportunity to serve on Council and offered his service in the future.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. Perez-Stable reported that the Task Force had heard two presentations. The first, by Lisa Evans, J.D., continued the Task Force's ongoing discussions about the inclusion of diverse populations in research, with a focus on the duality of diversity. The main point centers on the duality of the two categories: diversity and workforce diversity. The first category relates to the extramural program and involves legislative mandates to increase education and training opportunities for and recruitment of study participants from underrepresented populations, including racial and ethnic minorities, persons with disabilities, and persons from disadvantaged backgrounds. This mandate also emphasizes the recruitment of women at the levels of faculty and above. On the other side of this duality is diversity in the workforce, which is voluntary and follows a business management model to include individuals regardless of race, color, national origin, religion, age, disability, sex, parental status, genetic information, and even political affiliation. Thus duality of diversity is inherent in a conceptual model presented by Dr. Hannah Valentine, Chief Officer for Scientific Workforce Diversity, NIH.

The second presentation, given by Dr. David Chae, an emerging scholar, focused on the Bay Area Heart Health Study, which explores the hypothesis that stress related to actual or perceived discrimination leads to a physiologic response that affects health

positively or negatively. The study enrolled 95 African American men aged 30 to 50 years and employed standard measures of perceived racial discrimination, the Implicit Bias Test, and measures of telomere length. Dr. Chae found that a significant proportion of the study sample exhibited an anti-black bias on the Implicit Bias test, that telomere length increased or remained stable among individuals with a pro-black bias who faced racial discrimination, and that telomere length shortened among individuals who faced racial discrimination and had an anti-black bias. These results suggest that 1) anti-black bias along with external discrimination represents threats to self and group identification, 2) that negative in-group bias renders individuals more vulnerable to internalizing racially stigmatizing experiences, and 3) that positive in-group bias might serve as a buffer and build resilience. The study results further suggest that personally mediated and internalized forms of racism may be risk factors for poor health.

Dr. Perez-Stable also presented a research framework integrating environmental, sociocultural, behavioral, and biological factors of health disparities over the life course. This framework was developed by Dr. Carl Hill, Director of the NIA Office of Special Populations, and refined by the Task Force. The framework is not intended to show every area of interest with respect to health disparities; instead, it will provide a fairly large sample of specific examples of NIA research. The Task Force recommends that this framework be endorsed by the Council and placed on the NIA website, with links to publications and NIA grants related to each example area of interest. Once posted, the framework should be a living document. The Task Force also suggested publishing a paper on the framework, with the inclusion of salient examples.

Dr. Perez-Stable closed his presentation by reporting that 50 scholars attended the Butler-Williams program, which was held on August 8, 2014 at NIH. As a retiring Council member, he also summarized the accomplishments of the Task Force and noted that accomplishments in health disparities research, as well as in training researchers from underrepresented populations, were still fairly unique to NIA. He cited the continued discussion of accountability in the inclusion of minorities in clinical studies as unfinished business for the Task Force.

In response to questions from Dr. Laura Carstensen regarding guidance for recruiting individuals from underrepresented populations into clinical studies, Dr. Perez-Stable noted a series of articles published by Dr. James Jackson as well as information provided by the Resource Centers for Minority Aging Research during their early years. He pointed out that there is little science with respect to minority recruitment, but that a reasonable amount of experience indicates the importance of language, face-to-face meetings or phone calls, and including investigators from those populations. Dr. Carstensen suggested that compiling success stories or case studies could help investigators who see such recruitment as too difficult. Studies presented recently by Dr. Richard Mayeux, as well as an African American cohort recruited by the University of Chicago, were cited as success stories.

Dr. Reisa Sperling suggested that incentives be provided for investigators to show progress in recruiting, as well as supplements to hire research assistants that would go to communities to recruit participants. The Task Force has discussed a carrot-and-stick

approach to bolster accountability in minority inclusion. Dr. Marie Bernard, NIA Deputy Director, described administrative supplements to enhance the health disparities component of projects as a small effort in this direction.

A motion to endorse the Task Force's recommendation to post the framework on the NIA website, with links to examples of research grants and publications related to those topics, was forwarded and seconded by the Task Force. During discussion, Council members called for a modification of the framework title, per the previous day's discussion by the Task Force, and they encouraged NIA to consider a publication, even a brief one, to help the research community see how one would think about the factors in the framework. The motion passed unanimously. Dr. Mouton encouraged NIA to include studies of abuse and violence in the framework.

Dr. Robin Barr noted that, during discussion at the May Council meeting, the Council raised questions about incorporating age into the legislative mandate for inclusion. He and Dr. Bernard reported that NIA has taken these concerns to a subcommittee of the Extramural Activities Working Group, and the subcommittee has committed to considering the inclusion of older adults in clinical studies. Dr. Bernard noted that, although this would not carry the weight of a legislative mandate, it could offer opportunities to develop guidelines in the near future. Dr. Bernard also reported that the NIA Office of Planning, Analysis, and Evaluation is developing a trans-NIH pilot approach to assess the representation of older adults in the existing portfolio.

Discussion closed with Dr. Bernard thanking the Hartford Center for Nursing Excellence, the Alliance for Academic Internal Medicine, and the American Federation for Aging Research for supporting the Butler-Williams Scholars Program by supplementing the attendance of additional trainees. She pointed out that the program had had a record number of applicants and participants.

IV. REPORT: COUNCIL OF COUNCILS

Dr. Ana M. Cuervo's summary of the September Council of Councils (CoC) meeting focused on the Common Fund, laboratory practices and research, and funding initiatives. She began by discussing the Single Cell Analysis Challenge: Follow That Cell, in which the Common Fund's Single Cell Analysis Program is challenging scientists to identify new methods to follow changes in the behavior and function of a single cell over time. During Phase I, applicants will develop proposals describing the methodologies they intend to develop. Up to six awards will be made during Phase I. Phase II of the challenge will provide one or two awards to develop the proposed methodology and generate time course measurements from a single cell. Dr. Cuervo noted that methodologies to track single cells would be particularly useful for aging research, as tissues age at different rates. She also noted the challenge as an example of ways to engage the public, industry, and academia to solve problems of importance to the NIH mission.

The CoC also heard a Common Fund report on the Knockout Mouse Production and Phenotyping (KOMP) initiative, an international, high-throughput effort to produce

knockout models for all mouse genes and to make these models available to the public. This initiative, launched in 2006, has aimed to generate stem cell lines containing null mutations for 8,500 mouse genes. It has received 1,250 orders for vectors and 980 orders for cells, and it is ahead of its target for the number of genes knocked out. Phase II of the initiative (KOMP2) will focus on producing and characterizing knockout mouse lines and placing these mice, data, and information in the public domain. KOMP2 can benefit the research community by offering sex-balanced cohorts, generating findings for follow-up, creating an infrastructure for the testing of preclinical models, and pushing real-time, public dissemination of products and data. Future plans include completing the generation of mouse lines, metabolomic profiling of select lines, the development of new phenotyping platforms, and the adoption of the CRISPR/Cas9 genome editing technology. Although there are no plans to age the animals at present, Dr. Cuervo suggested that KOMP2 might still offer opportunities for NIA and geroscience.

With respect to laboratory practice and research, Dr. Cuervo noted that analysis of sex differences has garnered much interest, with several studies arising after a *Nature* article stating that sex is a fundamental biological variable. She cited several examples of Common Fund supplements, which have provided approximately \$4 million to support the analysis of sex differences. Dr. Cuervo also reported that CoC discussed trans-NIH activities to enhance reproducibility in research. These include workshops to engage journal editors, the pharmaceutical industry, academia, and reagent suppliers; training modules, such as an online course on experimental design; and a series of talks for the Intramural Research Program on data interpretation. Dr. Cuervo noted several examples, including the NIA Interventions Testing Program, an assessment of reproducibility in cell culture studies (National Institute of General Medical Sciences [NIGMS]), the development of a checklist for journal publications (National Institute of Environmental Health Sciences), validation studies (National Human Genome Research Institute), and the Mouse Metabolic Phenotypic Centers (National Institute of Diabetes and Digestive and Kidney Diseases).

Dr. Cuervo also reported that the CoC discussed a review and consolidation of NIH-supported cores. This activity addressed a perception discussed at the last NACA meeting that many institutions apparently have redundant NIH-supported cores; e.g., several histology cores or several genomics-related cores. On a pilot basis, institutions were asked to consolidate some of the cores. On the basis of before-and-after data, the majority of 14 participating institutions have consolidated two or more cores, with successful centralization of billing, purchasing, scheduling, and tracking. This consolidation has led to an increase in the number of users and services, and it has ultimately led to an increase in income.

With respect to funding initiatives, the CoC discussed a process evaluation for the Early Independence Award (EIA), which was designed to train exceptional investigators to move directly into an independent role without a postdoctoral fellowship. Although the evaluation is not complete, it has found that only 50% of applicants came from the intended applicant pool. The evaluation also has found that among awardees, only 25% to 30% have reached independence. CoC discussion focused on confusion about

candidate eligibility, as well as confusion among review panels. The evaluation will collect data for 1 more year and present it to the CoC.

Dr. Cuervo reported that the CoC also discussed ways to enhance extramural research without increasing costs. The CoC agreed that mid-career is a critical time for strong support, and suggested building on the success of the Pioneer Awards, which focus more on an investigator's track record and less on project details and provide more stable support for a longer duration. The Pioneer Awards have enhanced flexibility, promoted risk-taking, and reduced the hypercompetitive atmosphere investigators face. Following this model, the National Cancer Institute has implemented the Outstanding Investigator Award, which provides up to \$600,000 per year for 7 years to investigators with an outstanding record in cancer research. NIGMS has issued a request for information on a potential Maximizing Investigators Research Award, which would provide \$150,000 to \$750,000 per year for 5 years.

V. COUNCIL SPEAKER: OPEN SCIENCE IN CLINICAL RESEARCH: THE TIME IS NOW

Dr. Harlan Krumholz, of Yale University, described his experience with the Vioxx case to discuss aspects of the research infrastructure that present a threat to biomedical and particularly clinical research. He noted, for example, instances in which academics simply lent their names to publications written by the manufacturer through medical education companies. Of particular concern, however, was the number of experimental studies that were done on humans but never reported. For example, several meta-analyses found no differences in cardiovascular thrombotic events among Vioxx, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), and placebo. These analyses missed osteoarthritis studies showing a relative risk of 1.9 (compared with the published relative risk of 0.94), but no one knew these studies were missing because they were never reported.

Dr. Krumholz and his colleagues have found that only 46% of trials registered on ClinicalTrials.gov are published, even years after the trials are completed. Even among NIH studies, only 50% are published 3 years after completion. The National Heart, Lung, and Blood Institute repeated this analysis for the studies it supported and found similar results. In another analysis, Dr. Krumholz and his colleagues found that 97% of studies with positive results are published, versus approximately half of studies with mixed results. Two-thirds of studies with negative results are never published. Dr. Krumholz noted that reporting or sharing results is touted as part of the scientific method as early as elementary school. However, in reality, results are shared only if they confirm a hypothesis.

The Food and Drug Administration Amendments Act has mandated the reporting of the results of certain studies on ClinicalTrials.gov, without precluding publication in a journal. However, this mandate is not enforced, and many studies, for example those that do not focus on drugs, are not covered by the legislation. In addition, Dr. Krumholz and his colleagues have been unable to convince academic institutions to support a requirement for all investigators to report results. Dr. Krumholz noted that there is no

record of whether investigators have published the results of their studies that future study sections could take into account when considering grant applications. He called for all studies to be published in the true spirit of institutional review boards (IRBs) and the science itself, and particularly to honor individuals' participation in these studies.

Dr. Krumholz noted that the requirement for registration has been successful because it allows for auditing; however, in many cases, clinical trials are registered after they have already begun. Furthermore, members of the research community have pointed to increased registration as a reason for the increased negative results seen by the NIH during the past decade, and smaller journals see the requirement for registration as a self-inflicted handicap if larger journals do not require it. Many do not see registration as effective or worth the effort.

As a result of the Vioxx litigation, evidence emerged of discordance between published data and actual trial data. For example, study investigators stopped adjudicating heart attacks much sooner than they stopped adjudicating gastrointestinal events, which favored the drug. The heart data was not included in the publication. More recently, a study looking at 110 phase III or IV clinical trials registered on ClinicalTrials.gov found that 20% reported the primary outcome inconsistently between ClinicalTrials.gov and subsequent journal publications. This analysis also found that 35% of the trials reported serious adverse events inconsistently, and of the 29 studies that reported deaths, 28% reported those deaths inconsistently. These findings were consistent with another analysis of 96 trials that were registered on ClinicalTrials.gov and published in high-impact journals. Likewise, discrepancies have been found between trial information reviewed by the Food and Drug Administration (FDA) and the information presented in publications. As a result, true replication is impossible for clinical research.

Dr. Krumholz pointed out that it is not enough simply to report the results of a trial. Data sharing is essential, particularly because the size and expense of clinical trials preclude a replication cohort. He suggested that lessons could be learned from physicists and astronomers, who regularly share data, and he suggested that lead investigators should have time to generate their first publication before making their data available to others. Dr. Krumholz described recent efforts among industry to share their data with independent expert analysts. Almost all major pharmaceutical companies now have plans or processes for releasing their datasets, but academia is lagging behind. In the clinical research enterprise, investigators are hesitant to share their data because of a sense that only they can understand it. This implies that the investigators have knowledge about a topic that is never documented or shared.

Dr. Krumholz emphasized that the investigators involved in the Vioxx litigation had no intent to harm; instead, they were misled by confirmation bias, which is a risk for all investigators. He described himself as “pro-informed choice” and “pro-shared decision-making” when it comes to using a drug such as Vioxx, but he expressed concerns about the amount of information available and the degree to which individuals could make decisions. He closed by calling on NIA and the NIH to aid in changing the culture by assessing how they promote the responsible conduct of science, how they actively manage their portfolio and ensure that results are published, how they track scientists'

reporting history, and how they support meta-analyses. He closed by calling for NIH to fund replication studies and establish rewards for investigators who do report and share their data.

In response to questions from Dr. Hodes, Dr. Krumholz suggested that notices of awards, as well as IRB expectations, should promote the principles of the scientific method and the responsible conduct of research. Investigators should be required to submit a plan for data-sharing, and reviews should consider investigators' track record for sharing data and reporting study results. Dr. Krumholz suggested that investigators should be required to report their results as soon as possible, but no later than 12 months after study completion.

Dr. Steven Cummings cited lack of staffing, time, and resources as one barrier to data analysis. Investment that fosters an international community of scientists who could analyze datasets was suggested as one way to address this barrier. Dr. Krumholz acknowledged that some bad science would be done, but he also suggested that this type of science could be filtered out by peer review.

Dr. Debra Bailey Whitman echoed Dr. Krumholz's call for sharing the results of taxpayer-funded research. However, she also noted proposals that go even further to make all research, not just clinical trials, more transparent.

VI. REPORT: WORKING GROUP ON PROGRAM

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

A. Recommendations from Past Meetings: Clinical Trials Advisory Panel Report

Dr. Sergei Romashkan, of the Division of Geriatrics and Clinical Gerontology (DGCG), reported that the Clinical Trials Advisory Panel (CTAP) reviewed two clinical trial concepts at its Spring 2014 meeting.

The Statin Therapy for Reducing Events in the Elderly (STAREE) trial proposes to examine the risks and benefits of statin therapy for primary prevention in older adults who do not have major clinical diseases. The primary endpoint for this trial would be disability-free survival, a composite endpoint. CTAP agreed that the proposed trial addresses an issue of clinical importance, as there are no recommendations for this population. However, the Panel recommended that NIA reconsider the study design, with particular attention to the proposed primary outcome and potential approaches for interpreting study results.

The second concept proposes a randomized clinical trial examining the effect of testosterone therapy in female patients with hip fractures and persistent mobility impairment. Specifically, the trial would assess whether such therapy, with or without exercise, would improve muscle strength and function. CTAP did not express much enthusiasm for this proposal, noting that its concerns outweighed the potential benefits of such a trial.

Dr. Romashkan also discussed a CTAP white paper on interactions among translational aging research activities. This white paper focused on the limitations of existing activities focused on increasing longevity and health span and the need to increase integration of different research approaches to inform translational decisions. The Panel emphasized that the translation of findings from the clinic to animal models is just as important as the translation from animal models to the clinic. The Panel also recommended that DGCG ensure expert review for translational applications.

Dr. Romashkan closed his presentation by noting that CTAP recommended several changes to procedures for developing and accepting clinical trials. Recommendations include requirements for pre-applications and the establishment of a dedicated review panel.

B. Request for Applications/Request for Proposals Concept Clearances

Lifespan Human Connectome Project

An existing NIH Blueprint initiative, the Human Connectome Project, is mapping the connectivity between brain structure and function among younger adults, and there is a limited pilot project looking at such connectivity across the lifespan. The Division of Neuroscience (DN) has proposed extending this pilot project, with the overall goals of capturing connectivity data from both younger and older adults; providing a reference dataset for the normative trajectory of connectivity over the full lifespan; and understanding how the brain is organized, how that organization changes over time, and how that organization changes with disease. The Working Group on Program expressed enthusiasm for this proposal. Working Group members suggested exploring ways to deepen phenotyping (in addition to imaging work), fostering cross-talk between Human Connectome Project investigators and the aging research community to ensure the inclusion of important outcomes, and ensuring that results are made available to the public.

The Working Group on Program forwarded and seconded the motion that this concept be approved. The motion passed unanimously.

Contract for the Development and Maintenance of a Multigenotypic Aged Rat Colony

This colony is an essential resource for the research community focused on the basic biology of aging. The Working Group on Program noted that the colony had been run flawlessly and acknowledged the tremendous effort of the leadership to ensure service continuity during a time of transition. Working Group members felt that this colony would continue to be important, because the rat model offers some advantages in comparison to the mouse model. The Working Group on Program forwarded and seconded the motion that this renewal of this contract be approved. The motion passed unanimously.

Renewal of Aged Rodent Tissue Bank Contract

The Aged Rodent Tissue Bank has been in place since 2001. The Working Group on Program noted that this resource has been successful and highly productive, making

the use of aged animals more efficient than previously maximizing their use. The Working Group forwarded and seconded the motion that this contract be renewed. The motion passed unanimously.

C. Division of Aging Biology (DAB) Review

Dr. Morimoto reported on the progress of the DAB review and thanked Division staff for their work and participation in the process. The DAB review group has considered critical areas of basic science and the importance of integrating these areas into a systems biology approach. The group also has highlighted the Interventions Testing Program as a model for success, as well as ways in which this program can contribute to mechanistic understanding. The Nathan Shock Centers, NIA efforts to integrate activities across Divisions when appropriate, and NIA efforts to integrate with other Institutes and Centers were also discussed. The review group also discussed concerns about funding and recommended creative strategies to address these concerns. The final review will be completed and presented at the January 2015 Council meeting.

VII. COUNCIL SPEAKER: UPDATE ON NIH BIG DATA TO KNOWLEDGE (BD2K): TOWARDS THE BIOMEDICAL DIGITAL ENTERPRISE

Dr. Jennie Larkin, of the Office of the Associate Director for Data Science, discussed the BD2K program, which represents a partnership between NIH and the biomedical research community that aims to build a sustainable digital enterprise. The biomedical research enterprise is constantly finding new and better ways to conduct research, and the number of digital assets, including data, software, analytical tools, and publications, is increasing rapidly. However, these assets are distributed across the nation and the world and can be difficult to find, use, and integrate. In addition, the rewards, incentives, and metrics used to review investigators' performance are still based primarily on a record of publications. Moreover, even as digital assets are increasing, research budgets remain flat. Thus, while publication remains important, new approaches are needed to drive innovation, recognize and reward other important contributions, and ensure the availability of digital assets to the research community. The need for cultural changes and the risk that NIH may fail to capitalize on digital advances were emphasized in 2012 in a report by the NIH Data/Informatics Working Group (DIWG), which had been established by the NIH Director.

Governance for BD2K comprises an executive committee with representation from each NIH Institute or Center, a multi-Council working group, and a Scientific Data Council. However, Dr. Larkin emphasized that collaboration between NIH and the community extends beyond the extramural research community to other government agencies and even to other sectors in the community. BD2K is funded at \$30 million for FY 2014 and is expected to increase to \$80 million in FY 2015 and \$100 million in later years. Dr. Larkin noted that the first round of BD2K awards would soon be announced.

BD2K is addressing five major problems noted by DIWG:

- Locating and citing digital assets with data and software indices.

- Ensuring assets are useful and usable by leveraging existing standards.
- Extending policies and practices for data sharing, for example by working across NIH to provide incentives.
- Developing new methods to analyze and manage biomedical Big Data.
- Training researchers to develop a strong group of researchers skilled in Big Data and to elevate competition among biomedical scientists in general.

Programmatic themes within BD2K include sustainability, education, innovation, process, and collaboration, and specific deliverables have been established for each of these themes. One BD2K activity involves a Commons for Sustainability, which is intended to support data sharing, accessibility, and discoverability of biomedical data and tools. The Commons is also expected to enable innovation by co-locating data with advanced computing resources. Innovation activities, driven largely by the extramural community, include a Data Discovery Index, BD2K Centers of Excellence, and the development of standards for data and meta-data. Process and collaboration activities include harmonization of clinical data, data citation, and machine-readable data-sharing plans.

NIH anticipates that within 5 to 7 years, BD2K will:

- Create a new digital enterprise including researchers, clinicians, computer scientists, and others who work with digitally rich assets.
- Recognize and support the importance of publications, data, software, and analytical tools.
- Ensure that the knowledge and resources generated by the biomedical research community will be more informative and reusable.
- Promote cultural changes both within NIH and in the broader scientific community.

Discussion focused on the need to educate IRBs on consent issues and patient protection with Big Data, the problem of access to data when industry takes over cohorts that were initially funded by the Federal government, and ways to help investigators who will want to work with Big Data but do not know how. Dr. Larkin noted that NIH is working with its partners on IRB issues, that more public-private partnerships are needed to overcome blocks to data-sharing, and that local expertise should be promoted to provide assistance for investigators. Organizations such as Public Responsibility in Medicine & Research (PRIM&R) were suggested as potential partners in developing practices for patient protection. Dr. Larkin also noted that NIH is talking not only with U.S. Department of Health and Human Services agencies, but also with other agencies to overcome data silos and ensure that data from various sources are accessible and interoperable.

In response to questions from Council about screening researchers who will access such data and peer review for research projects using Big Data, Dr. Larkin clarified that NIH will not ask that all data be openly available to all people at all times. She

acknowledged the need to identify data that must be secured and to allow access only to authorized researchers, but in a way that fosters the sharing of knowledge. Dr. Larkin also acknowledged that the traditional publication process can take at least 1 year and that peer review processes are needed to facilitate sharing more quickly. One approach involves earlier publication, with a review of the publication by the larger community.

VIII. PROGRAM HIGHLIGHTS

A. Division of Geriatrics and Clinical Gerontology (DGCG): Physical Activity to Prevent Major Mobility Disability: The Primary Results of the Lifestyle Interventions and Independence for Elders (LIFE) Study

Lower mobility, as demonstrated by a slower walking speed over 400 m, is associated with a 5-year risk for mobility limitation, mortality, hospitalizations, and cardiovascular events. It is also associated with higher health care costs; data from a survey of Medicare beneficiaries found that costs for individuals who were unable to walk were approximately 50% higher than those for individuals with no difficulties. Disability is therefore a primary outcome of interest in geriatrics. However, until recently, there has been no phase III evidence that this outcome could be prevented.

Dr. Marco Pahor, of the University of Florida, presented results of the LIFE study, the largest study examining physical activity in older persons. This study randomized older adults (aged 70 to 89 years) who were sedentary and at high risk for limited mobility to a moderate-intensity physical activity intervention or a health education intervention. In a pilot study, both interventions were associated with increased physical performance, but physical activity appeared to be superior. In the main study, 32.5% of participants developed major mobility disability over 3 years of follow-up, and 17.2% developed persistent mobility disability. The proportion of patients with major mobility disability was lower in the physical activity group than in the health education group, 30.1% versus 35.5%. The proportion of patients with the more severe outcome was also lower in the physical activity group, 14.7% versus 19.8%. A subgroup analysis revealed that most of the benefit accrued to the most disabled or highest-risk group. Thus, structured moderate-intensity physical activity reduces both major mobility disability and persistent mobility disability. Surprisingly, the rate of hospitalizations was higher in the physical activity group than in the health education group. However, this higher rate did not appear to be associated with lowered homeostatic reserve.

Dr. Pahor concluded his presentation by noting that the LIFE study group has a resource-sharing policy and has received more than 20 requests from investigators seeking to replicate the study results. He also announced plans for European trials.

When questioned on whether the trial included muscle biopsy samples, Dr. Pahor pointed to the difficulty of accomplishing ancillary studies to an ongoing clinical trial. Time lost in review and award means the trial is over before the ancillary study can begin.

B. Division of Behavioral and Social Research (DBSR): Update on Progress and Challenges in Subjective Wellbeing

Dr. Arthur Stone, of the University of Southern California, provided an overview on subjective wellbeing. A component of overall wellbeing, subjective wellbeing accounts for how individuals see the quality of our lives. It comprises a eudemonic component, which focuses on how one feels about the meaning of activities; a hedonic component, also known as affective or experiential, which focuses on how one feels day to day; and life satisfaction. Dr. Stone cautioned that the term “happiness” is confusing, because it could relate to life satisfaction, an evaluative term, or the hedonic component, an affective one.

Subjective wellbeing is increasingly important in policy, particularly in economic circles. For example, measures of subjective wellbeing could supplement the gross domestic product, which is becoming an unsatisfactory indicator of a population’s economic welfare. Subjective wellbeing is already used in cost-benefit analyses to find pockets of misery, track quality of life, or track health, unemployment, or taxation policies.

As quality of life studied in the United Kingdom, subjective wellbeing also can be used to gain insight into different lives or different jobs. In 2009, the President of France established a commission on the Measurement of Economic Performance and Social Progress, which advocated for the inclusion of subjective wellbeing in policy. The World Health Organization defines health as encompassing mental, physical, and social wellbeing. The Kingdom of Bhutan has developed a measure, Gross National Happiness. The Gallup Organization, the U.K. Office of National Statistics, and the Organisation for Economic Co-operation and Development all measure or monitor wellbeing. NIA has supported the inclusion of subjective wellbeing measures in several major surveys, including the Health and Retirement Study.

Dr. Stone highlighted conclusions and recommendations from a report developed by a National Academies panel on measuring subjective wellbeing in a policy-relevant, national accounting framework. This panel was asked to assess whether the research on measuring hedonic (experienced) wellbeing has progressed to a point where these measures should become national statistics. The panel also was asked to recommend strategies for collecting data on hedonic wellbeing and on wellbeing in general. Dr. Stone noted the following conclusions or recommendations:

- Experiences are important and multifaceted, and several dimensions, including affective and evaluative, should be measured together.
- There should be a stronger emphasis on suffering and misery, which are not the inverse of happiness. Measures of subjective wellbeing have not included the concept of pain.
- Measures of subjective wellbeing should look more deeply at meaning and purpose in life.
- Cultural aspects of subjective wellbeing need to be understood.

Because the National Academies panel concluded that a number of aspects of subjective wellbeing needed for this study, the panel recommended against modeling these measures in national indices at this time.

Dr. Stone also described ongoing work by his group to examine how individuals self-report subjective wellbeing. He closed his presentation by noting upcoming publications on subjective wellbeing.

Discussion focused on work to link measures of subjective wellbeing with economic and long-term health outcomes. Dr. Jonathan Skinner noted his work showing that simple, self-reported measures can predict outcomes, and he pointed out that many health systems are now using these measures. Analyses within the English Longitudinal Study of Aging have linked wellbeing to future morbidity or mortality, and the City of Santa Monica has engaged in a comprehensive evaluation of the wellbeing of its residents. Dr. Stone noted that the Santa Monica government has asked all its stakeholders, such as police or urban planners, what they need to know about residents' wellbeing.

Dr. Perez-Stable asked about data on wellbeing among diverse populations in the United States. Dr. Stone suggested that more qualitative work was needed to get at these types of questions.

C. Division of Aging Biology (DAB): Longevity Mechanisms in the Naked Mole Rat: Lessons from the Longest-Lived Rodent

Dr. Vera Gorbunova, of the University of Rochester, described her work with the naked mole rat. Since the advent of molecular biology tools, comparative biology has not been as popular as it once was. However, it can be particularly useful for aging biology, for example by comparing genetically and physiologically similar species with different lifespans to identify mechanisms associated with longevity. Among rodents, lifespans generally increase with size; mice and rats are relatively short-lived, whereas porcupines and beavers live much longer.

The naked mole rat is the longest-lived rodent, with a lifespan of about 30 years, despite its small size. The naked mole rat also shows resistance to many age-related diseases, including cancer. Dr. Gorbunova's group has found that, compared with cultured mouse fibroblasts, which stop proliferating once they fill a plate, cultured fibroblasts from naked mole rat stop proliferating much sooner, showing a hypersensitivity to contact inhibition. This hypersensitivity arises from the production of high molecular weight hyaluronan (HA); the HA chain produced by naked mole rat is six to ten times longer than that produced by humans or mice. High molecular weight HA has shown both anti-proliferative and anti-inflammatory effects. Other data from Dr. Gorbunova's laboratory suggest that high molecular weight HA also confers longevity by mediating stress resistance.

Dr. Gorbunova's laboratory has also found alterations in ribosomal structure in the naked mole rat. Whereas ribosomal RNA normally shows a 28S and 18S band on a gel, the 28S band has split in half in the naked mole rat. Using a firefly luciferase reporter

assay, Dr. Gorbunova's laboratory has shown that ribosomes from the naked mole rat make fewer translation errors during protein synthesis, compared with ribosomes from mice. Thus the cellular accumulation of aberrant proteins, which has been associated with many pathologies, is less likely to occur in the naked mole rat. Dr. Gorbunova and her colleagues also have found that the blind mole rat, which is also long-lived and resistant to cancer, makes even more HA than the naked mole rat does. However, its anti-cancer mechanisms appear to be different.

Dr. Gorbunova concluded her presentation by noting that many long-lived species from different ecological niches have developed various mechanisms for longevity. Once mechanisms from other species are understood, investigators can look for conserved mechanisms and find ways to apply adaptations to human health. Dr. Gorbunova and her colleagues are creating a mouse model that expresses the naked mole rat gene for HA to determine whether these mice will live longer.

Questions concerned a possible link between resistance to cancer and longevity and the possible relation between fewer errors in protein synthesis and proteostasis.

D. Division of Neuroscience (DN): Tau Propagation and Alzheimer Progression

The DN program highlight, which was to be presented by Dr. Bradley Hyman, will be given at the January 2015 Council Meeting.

IX. ADJOURNMENT

The open session of the 123rd meeting of the National Advisory Council on Aging adjourned at 1:30 p.m. on September 17, 2014. The next meeting is scheduled for January 27–28, 2015.

X. 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 January 27-28, 2015, and corrections or notations will be stated in the minutes of that meeting.