NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 144th Meeting

NATIONAL ADVISORY COUNCIL ON AGING

September 14-15, 2021

National Institutes of Health
Virtual Meeting
Bethesda, MD 20892

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 14-15, 2021

The 144th meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, September 14, 2021, at 3 p.m. by videoconference. Dr. Richard Hodes, Director, National Institute on Aging (NIA), presided.

In accordance with the provisions of Public Law 92–463, the meeting was closed to the public on Tuesday, September 14, from 3 p.m. to 5 p.m. for the review, discussion, and evaluation of grant applications in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of Public Law 92–463.[1] The meeting was open to the public on Wednesday, September 15, from 10:00 a.m. to 1:11 p.m.

Council Participants:
Mr. James Appleby
Dr. Shalender Bhasin
Ms. Meryl Comer
Dr. Monica A. Driscoll
Dr. Terry T. Fulmer
Dr. Alison M. Goate
Dr. Margaret A. Goodell
Dr. Yadong Huang
Dr. Rev. Cynthia Huling Hummel
Dr. Jennifer J. Manly
Dr. Eric Michael Reiman
Dr. David B. Reuben
Dr. Clifford James Rosen
Dr. Julie A. Schneider
Dr. Amy Jo Wagers
Dr. David Weir
Dr. Keith E. Whitfield

In Addition to NIA Staff, Other Federal Employees Present:
Dr. James Anderson, Director, Division of Program Coordination, Planning, and Strategic Initiatives, NIH

Members of the Public Present:
Dr. Kaare Christensen, University of Southern Denmark

[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 applicatious that were discussed individually, not to "en bloc" actions.

Ms. Rebecca Lazeration, Rose Li and Associates, Inc.
Dr. Rose Maria Li, Rose Li and Associates, Inc.
256 live views via NIH videocast

I. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[2]

A total of 2,092 applications requesting $4,945,446,344 for all years underwent initial review. The Council recommended 1,094 awards for a total of $2,789,550,926 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 144th NACA meeting and called the meeting to order at 10:00 a.m. on Wednesday, September 15, 2021.

A. Director's Status Report

NIH/NIA Budget Status

Dr. Hodes reported that the President's budget for fiscal year (FY) 2022 was released on May 28 and called for a proposed $51 billion appropriation for NIH, a $9 billion increase from FY 2021. The additional funds include $6.5 billion to establish the Advanced Research Projects Agency for Health (ARPA-H), which will initially focus on cancer and other diseases such as diabetes and Alzheimer's disease (AD). The House appropriations bill called for $49.4 billion for NIH, a $7 billion increase from FY 2021. The Senate has not released its FY 2022 appropriations bill. The federal government, including NIH, is currently funded through September 30, 2021.

For general applications reviewed by the Center for Scientific Review (CSR) and requesting less than $500,000 (direct costs) in any one year, paylines are 10% for most regular research (R01) applications, 13% for new investigator applications, and 15% for early-stage investigator applications. For CSR-reviewed applications seeking $500,000 or more, paylines are 7% for most, 10% for new investigator, and 12% for early-stage investigator applications. Paylines are higher for applications focused on AD and AD-related dementias (AD/ADRD): 28% for most, 31% for new investigator, and 33% for early-stage investigator R01 applications. Dr. Hodes noted that current FY 2021 interim paylines for NIA-reviewed applications (e.g., program project, career development, and fellowship awards) were 15% to 21% for general applications and 35% to 40% for AD/ADRD-targeted applications.

Dr. Hodes presented on the FY 2023 Alzheimer's Disease Bypass Budget, which was released in July 2021. Budget language states that in each fiscal year through FY 2025, the NIH Director

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shall prepare and submit directly to the President for review and transmittal to Congress an annual budget estimate (including an estimate of the number and type of personnel needs) for NIH initiatives pursuant to the National Alzheimer's Plan. The budget is framed by the eight Common Alzheimer's Disease Research Ontology (CADRO) categories. Using the FY 2021 enacted level for AD/ADRD research as the baseline estimate, the total FY 2023 budget totals $3.4 billion, including $226 million additional resources to support new AD/ADRD research. The budget narrative includes many examples of recent science advances across multiple research topics. NIA will track awards under the CADRO categories, as well as funding initiatives aimed at addressing the research milestones associated with the National Alzheimer's Project Act.

COVID-19 Updates
Dr. Hodes mentioned that NIA released two Notices of Special Interest to address the COVID-19 epidemic:

- NOT-AG-21-016 focuses on Neurological and Neurocognitive Sequelae from SARS-CoV-2 Infection and COVID-19 in Aging and Age-Related Neurodegeneration with expiration date May 8, 2023
- NOT-AG-21-015 focuses on Aging-Relevant Behavioral and Social Research on Coronavirus Disease 2019 (COVID-19) with expiration date September 10, 2021

NIH Updates
Dr. Hodes reported that NIH issued a Request for Information (NOT-OD-21-131) on Developing Consent Language for Future Use of Data and Biospecimens, seeking input on the utility and usability of sample language developed for use in informed consent documents for data and biospecimen sharing, with the aim of upholding the principles of autonomy and trust in biomedical research.

Dr. Hodes announced that the NIH-Wide Strategic Plan for Fiscal Years 2021-2025 is available. The Plan's framework has three key objectives: (1) advancing biomedical and behavioral sciences; (2) developing, maintaining, and renewing scientific research capacity; and (3) exemplifying and promoting the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

NIA Updates
Dr. Hodes reported that with the addition of two new research hubs in North Carolina and Texas, NIA expanded the Alzheimer's Disease and Related Dementias Centers (ADRC) Research Network to 33 centers. In addition, 4 exploratory centers opened in Alabama, Nevada, New Mexico, and Tennessee that will focus on representation of minority populations. The ADRCs conduct clinical, neuropathology, imaging, biomarkers, genetics, pathogenesis, and therapeutics research, serving as a backbone for ADRD research since the network's establishment in 1984.

Dr. Hodes noted that NIA supports two resources for recruitment of diverse participants in clinical trials: (1) the Alzheimer's and Dementia Outreach, Recruitment, and Engagement (ADORE) online, a searchable database of resources for engagement, recruitment, and retention of study participants into clinical trials and studies on AD/ADRD; and (2) Outreach Pro, the recently launched tool to enable health care professionals to more easily produce and brand

tailored clinical trial recruitment materials and strategies to help reach multiple cultures and those who do not speak English.

Dr. Hodes announced NIA staffing updates since the May 2021 NACA meeting. Also, since that meeting, NIA has released 27 research highlights, 15 blog posts, 5 news announcements, and 5 press releases. Further, since May 2021, Dr. Hodes, Dr. Melinda Kelley (acting NIA Deputy Director), and/or senior NIA staff participated in 4 stakeholder or advocacy group meetings, 4 Congressional briefings, and 1 Congressional hearing.

Dr. Hodes concluded by reminding the meeting participants to remain connected between the NACA meetings through online NIA resources.

B. Future Meeting Dates
January 25-26, 2022 (Tuesday and Wednesday), Virtual
May 10-11, 2022 (Tuesday and Wednesday), Building 45
September 7-8, 2022 (Wednesday and Thursday), Building 45
January 18-19, 2023 (Wednesday and Thursday), Building 45
May 16-17, 2023 (Tuesday and Wednesday), Building 45
September 19-20, 2023 (Tuesday and Wednesday), Building 45

C. Consideration of Minutes of the Last Meeting
The minutes of the May 2021 Council meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Co-chairs Drs. Cliff Rosen and Keith Whitfield presented an update on the Task Force meeting of September 14, 2021. First, Dr. Whitfield summarized Dr. Kathleen Mullen Harris' presentation on the role of social and economic factors influencing health outcomes among older adults using examples from the National Longitudinal Study of Adolescent to Adult Health (Add Health). This presentation, focused on midlife social and behavioral factors and how they impact health outcomes among older adults, offered the following takeaways: (1) three drivers of working age mortality that vary with race and gender are drug poisoning and alcohol-induced mortality, suicide, and cardiometabolic disease; (2) social and economic factors at the macro and individual levels create disparities among working age adults; and (3) later life health disparities can originate in midlife and are embedded in biological, behavioral, psychological, and social precursors.

Next, Dr. Rosen summarized Dr. Kind's presentation on the role of contextual factors in aging and brain health research leveraging the Neighborhood Atlas, including development of a deprivation index, validation of the index to census block groups, and innovation of the Neighborhood Atlas. Living in a disadvantaged neighborhood is linked to several negative health outcomes, including higher rates of diabetes and cardiovascular disease, higher utilization of health care services, and earlier death. The Neighborhood Atlas freely shares measures of neighborhood disadvantage with the public and has been utilized by various educational institutions, health systems, nonprofit organizations, and government agencies. The Atlas has also been applied in the Neighborhoods Study project, which studies the exposome's relation to

AD/ADRD and involves 22 ADRD centers and a national cross-section of dementia patients. Dr. Rosen commented that this work has provided the field with a novel window into the sociobiological mechanisms that underlie neighborhood disadvantage.

IV. REPORT: WORKING GROUP ON PROGRAM

Dr. Monica Driscoll, Chair of the Working Group on Program (WGOP), led the updates.

A. CTAP Report

Dr. Driscoll reported that NIA's Division of Geriatrics and Clinical Gerontology (DGCG)'s Clinical Trials Advisory Panel (CTAP) met on March 20, 2021. During the meeting, CTAP reviewed the amended concept for the REHAB Heart Failure with Preserved Ejection Fraction (HFpEF) clinical trial submitted by Dr. Kitzman of Wake Forest University. REHAB HFpEF is a randomized, single-blind, controlled trial testing the efficacy of multidomain transitional physical rehabilitation interventions in adults aged 60 or older with the HFpEF phenotype. CTAP was highly enthusiastic about the study concept because it addresses an area of importance and unmet need. If successful, the study results will provide the evidence needed for payers to cover the costs of this enhanced multicomponent rehabilitation intervention for geriatric patients.

B. FOA Concept Clearances

Dr. Driscoll invited the primary reviewers to summarize the 15 concepts submitted from four NIA units: Division of Aging Biology (DAB), Division of Behavioral and Social Research (DBSR), Division of Geriatrics and Clinical Gerontology (DGCG), and Division of Neuroscience (DN). Although the WGOP suggested minor changes to some concepts, it approved most concepts for full Council consideration. One DGCG concept was deferred pending more significant edits. The Council members unanimously concurred with approval of the 14 concepts and deferral of the one concept seeking clearance.

Division of Aging Biology

DAB proposed three interconnected concepts focused on the interactions of aging hallmarks as a framework for innovative research on aging biology. Each concept can stand on its own but the value of the three together is increased sharing of resources and expertise.

Cytosolic DNA Sensing as an Integrating Point of the Aging Hallmarks

This proposed concept would advance the understanding of cytosolic DNA as an integrator of interactions among the aging hallmarks and as an instigator of the downstream cascade of events leading to cellular senescence and inflammation. The concept encourages researchers to collaborate for needed expertise, especially in the areas of new or advanced technologies that could transform their ability to address critical mechanistic questions.

Mapping Interconnectivity Among Hallmarks of Aging under Lifespan Modifications

This proposed concept would solicit research projects that increase understanding of the interactions among hallmarks of aging and their regulation in five key areas: (1) providing information about timing and priority of hallmarks of aging; (2) identifying whether hallmarks are an adaptive response to maintain health at different life stages; (3) determining whether a threshold mechanism exists that leads to specific aging phenotypes; (4) determining whether interactions among hallmarks are necessary and sufficient to change aging trajectory; and (5)

uncovering interactions from the onset of interventions started at different times over the life course

Inter-organelle Communication as a Platform to Interrogate the Interactions of Hallmarks of Aging
This concept addresses the complexity and scope of the studies needed to address inter-organelle communication. This concept would encourage comprehensive, multi-disciplinary research projects focused on (1) identification and characterization of novel organelle communication impacting aging hallmarks; (2) evaluation of pro-longevity interventions in the context of organelle communication; (3) investigation of genetic and environmental factors involved in "re-wiring" inter-organelle communication; (4) characterization of regulatory roles of inter-organelle communication influencing the aging process; and (5) development of systems-level imaging and microscopic technology to map organelle communication in aging relevant models.

The other 12 concepts are as follows:

Division of Behavioral and Social Research
Resources to Promote Coordination and Collaboration across Deeply Phenotyped Longitudinal Behavioral and Social Studies of Aging
BSR supports many deeply phenotyped small- to mid-size longitudinal studies that collectively span the full lifecourse. The proposed concept would establish a Resource Development Network focused on the infrastructure needed to promote and support coordination and collaboration across psychologically rich, deeply phenotyped longitudinal behavioral and social studies of aging.

Health Equity and the Cost of Novel Treatments for Alzheimer's Disease and Related Dementias
The population of individuals with AD/ADRD is projected to reach 16 million Americans by the year 2050. The proposed concept contemplates the health equity implications of access to novel pharmacological treatments. It will support projects to conduct simulation modeling to clarify the costs and health outcomes of new therapeutics for a diverse population using methods that account for known racial and ethnic disparities in AD/ADRD treatment.

Understanding Place-Based Health Inequalities in Mid-Life
The National Academies of Sciences, Engineering, and Medicine recently released the Consensus Study Report *High and Rising Mortality Rates Among Working Age Adults*, which examines the reasons for declining life expectancy in the United States. The proposed concept would support studies that aim to clarify social, economic, behavioral, and policy explanations for place-based health disparities; examine intersections between place and sociodemographic characteristics to better understand and address processes driving health disparities; and include data collection and data enhancements to support these endeavors.

SCREENing for Cognitive Impairment: Decision-Making (SCREEN CID)
The proposed concept would focus on the development of a taxonomy of higher-level skills that support autonomy in daily life as well as a more detailed mapping between those skills and daily life activities to screen for individuals impacted by cognitive impairment. The work will support

the design and validation of reliable and valid instruments to measure those skills, enabling future work to ascertain which skills are most amenable to intervention.

Division of Geriatrics and Clinical Gerontology

Coordinating Center for the Claude D. Pepper Older Americans Independence Centers

The Claude D. Pepper Older Americans Independence Center (OAIC) program supports centers of research excellence and research training that aim to improve or maintain functional independence in older adults. The proposed concept would support a coordinating center to support the programmatic activities of current and future centers within the OAIC network and to play a crucial role in fostering collaborations across OAICs in a way that no single site could achieve.

Optimization and Personalization of Diagnostic Tests for AD/ADRD in Older Adults with Multiple Chronic Conditions (MCCs)

People newly diagnosed with AD/ADRD typically have three to four other chronic conditions or geriatric syndromes that can confound interpretation of traditional disease assessments. The proposed concept would support the initial formation of a transdisciplinary aging AD/ADRD diagnostic biomarker and imaging research center to develop resources, assemble and analyze existing and available data and biobank resources, support pilot studies, conduct collaborative research, and integrate expertise. MCC may affect diagnosis of AD, particularly among those who are frail or who have functional impairment due to other conditions. Although the importance of MCC is clearly stated, the rationale for research on diagnostic testing in MCC at the diagnoses stage was less convincing. The proposed concept seems to emphasize biomarkers. It also covers multiple topics that could each command its own R24, for example: psychometrics and accuracy of biomarkers (including blood, imaging); decision making and diagnostic setting, including following a positive screen; tools for clinician-patient communications about benefits, harms, preferences; and relationship between biomarkers and clinical diagnostics or syndromes such as dementia or mild cognitive impairment. This concept was therefore not approved, and DGCG was encouraged to revise and resubmit this concept with a better-defined focus for further consideration.

Pharmacokinetic and Pharmacodynamic (PK/PD) Studies of mTOR Inhibitors on Aging-Related Indications

Although rapamycin was recently shown to prolong lifespan in model organisms, including mammals, there are limited preclinical and clinical data on the effects of other mTOR inhibitors on aging-related indications. The proposed concept would seek to address critical gaps in PK/PD data for mTOR inhibitor studies. During the first year, researchers will focus on improving and validating measurement techniques. Thereafter, they will conduct three-year studies to develop harmonized measures and pool data to facilitate comprehensive assessment of the PK/PK of mTOR inhibitors in older adults.

Division of Neuroscience

Noncoding RNAs in Alzheimer's Disease and Related Dementia

The proposed concept would stimulate research in noncoding RNAs to investigate the causality, directionality, mechanisms, and therapeutic potential of ncRNAs implicated in AD/ADRD. The initiative will support investigators to discover novel mechanisms mediated by ncRNA and

elucidate molecular and cellular functions involved in the pathogenesis and progression of AD/ADRD.

Cell Specific Impact of Liquid-Liquid Phase Separation in Aging and Neurodegenerative Disease (RFA-AG-23-002)
Protein aggregation has been a long-standing hallmark of neurodegenerative diseases, with a wide variety of proteins implicated in aggregation and disease. A common link between these proteins is that they all undergo liquid-liquid phase transitions (LLPS) to form biomolecular condensates (BMCs) under normal biological conditions to function properly. The proposed concept will provide two years of funding to allow researchers to collect preliminary data on cell-specific BMC differences, particularly using emerging tools and techniques.

Lipids in Brain Aging and AD/ADRD
The research field requires additional, high-quality evidence of the important roles of lipids in brain aging and AD/ADRD. The proposed concept aims to promote investigation of the following topics: whether lipids, lipid droplets, or lipoproteins could act as readouts of brain aging and disease; APOE- and lipid-mediated changes in the hallmarks of aging; mechanistic studies of lipid droplet function, composition, and modulation; relationship of APOE isoforms and brain lipid metabolism, bioenergetics, and inflammation in brain aging and diseases of aging; and contributions of lipid-rich myelin and myelinating oligodendrocytes.

Mechanisms of Brain Hypoperfusion in AD/ADRD
The proposed concept would seek to understand the molecular and cellular mechanisms underlying the cerebral blood flow reduction in AD/ADRD. The FOA will build upon recent observations that β-amyloid leads to constriction of pericytes, that under physiological condition pericytes exert substantial influence on blood flow, and that stalled capillary flow are caused by neutrophil adhering to capillary walls. The FOA will seek to leverage existing tools and technologies, such as advanced in vivo imaging, which uniquely enables the studies of blood flow in capillaries and accumulation of pathological protein aggregates in small vessels.

Understanding the Role of Bilingualism in Cognitive Reserve/Resilience in Aging and AD/ADRD
The proposed concept aims to promote studies that can address several areas where research in bilingual effects on cognitive reserve and resilience in aging and AD/ADRD needs further development. Areas of focus include better measurement and contextualization of environmental and sociocultural factors; strategic use of ongoing longitudinal studies of aging; identification of critical aspects of second language learning (e.g., proficiency, duration, age of exposure, literacy); multimodal approaches that can clarify neural mechanisms; computational modeling approaches to test and refine potential theories; studies of structural and functional connectivity changes in the aging bilingual brain; and epigenetic changes induced by second language learning that may drive cognitive reserve and resilience.

V. A WORD FROM RETIRING MEMBERS

Dr. Hodes introduced the retiring NACA members and invited them to make remarks. Dr. Patricia Jones (NIA Director of the Office of Special Populations) expressed gratitude to retiring member Dr. Rosen for his work as co-chair of the Task Force on Minority Aging Research and

his commitment to addressing important topic areas. She also acknowledged Dr. James Appleby and the Gerontological Society of America's (GSA) partnership with the Butler-Williams Scholars program, which promotes early career scientists in the aging research field.

Dr. Appleby commented that he felt honored to serve on NACA. He considered his work alongside passionate colleagues to support NIA's research portfolio to be very rewarding. He suggested, and Dr. Hodes concurred, that the NACA orientation document titled "Advice to Council Members" be revised periodically to incorporate changes in policies and operations. Dr. Appleby concluded by expressing appreciation on behalf of GSA members for NIA's work as the backbone for aging research infrastructure.

Dr. Meryl Comer thanked the NIA leadership for the privilege of serving on NACA and her fellow NACA members for their willingness to work alongside a non-clinician. She highlighted three impressive aspects of NACA: (1) the integrity and discipline in grant application review and grant administration; (2) the long-standing commitment to issues of disparity, mentoring, and management of input from patients and the advocacy community; and (3) the humility of the members, and their openness to different perspectives in the pursuit of improving the health and quality of aging for all.

Dr. Alison Goate echoed the gratitude expressed by her colleagues and their good fortune to have been involved in the expansion of the AD/ADRD budget within NIA, adding that the fast pace of this expansion required significant effort from NACA members and NIA staff. During her tenure, she learned much about the diverse scientific topics covered by NIA, and noted that NIA's attention to diversity, health disparities, and training of early career researchers is admirable and commendable.

Dr. Eric Reiman expressed his deep appreciation to the NIA team, noting the comprehensive way that NIA enables researchers to advance AD/ADRD and aging research. He highlighted NIA's highly collaborative and successful team-based model for aging research. He added that NIA will take risks when warranted, but always in a transparent and accountable way. He concluded by stating it was an honor to serve on NACA among his distinguished colleagues.

Dr. Rosen expressed his gratitude to Dr. Hodes and NACA for emphasizing the importance of collaboration between the biology and psychosocial sciences to better understand the broader picture of aging science. He commended NIA for leading the way to explore science from a broader societal perspective.

Dr. Amy Wagers thanked the NIA team and her fellow NACA members. She noted that NIA responded rapidly to changes in the aging research field and in the world, particularly during the past two years as business and clinical practices have changed. She expressed interest in continued interactions with NACA and NIA, whose commitment to aging research is inspiring.

Dr. Kenneth Santora concluded by noting that, if approval of the next slate of NACA members is delayed, then some retiring members may be asked to serve additional time in their position. He will contact members individually to determine their interest in extending their service on Council.

VI. PROGRAM HIGHLIGHTS (DGCG)

Kaare Christensen, DMSc, Professor, Head of Research Unit, Epidemiology, Biostatistics and Biodemography, University of Southern Denmark

The Long Life Family Study (LLFS) began as an NIA U01 and transitioned to a U19. The study sites include one data management coordinating center, one demography center, and three field centers in the United States and one in Denmark. The LLFS aims to study the pedigree of individuals with extreme familial longevity, calculated using the Family Longevity Selection Score (FLoSS). This score accounts for the exceptionality of ages at death and of expected ages at death and provides a bonus score for living siblings.

Prior to transitioning to the U19, the study followed two generations (Generation 1 and their offspring, Generation 2) for a total of 4,953 subjects, including offspring spouses as controls. Showcase (i.e., pedigreed) families include 539 two-generational families with at least one living sibling pair in Generation 1 (the probands) and a FLoSS score of greater than or equal to 7 (for comparison, less than 1% of Framingham Heart Study families would meet these criteria). With the U19, the study team has added Generation 3, composed of select grandchildren of the proband generation with exceptional pedigrees according to genetic analyses of the first two generations. Launched in March 2020, the U19 portion is following 382 remaining members of the proband generation, 1,941 remaining offspring, and 826 grandchildren.

Dr. Christensen concentrated his presentation on a spin-off project involving long-lived siblings in Denmark. The study team identified 650 families with exceptional longevity and are following 10% of them in person and 90% of them via Danish national registries (e.g., Danish Cancer Registry, Cause of Death Register, Danish National Patient Register). In addition, the study team has collected a random sample of background population controls.

The researchers analyzed large families in the proband generation, positing that large family sizes equate to socioeconomic advantage and therefore a "good start to life." However, they found modest differences in socioeconomic status between the pedigreed Generation 0 (parents of the probands) with Generation 0 of the offspring spousal controls (spouses' grandparents), with the pedigreed families having a slight socioeconomic advantage.

Researchers also examined the difference in "robustness" and "resilience" (health and survival) between the pedigreed families and control families. To illustrate robustness, researchers examined the rates of disease occurrence in the proband and offspring generations. In the proband, researchers found significantly lower risk of 23 common diseases (e.g., depression, cerebrovascular diseases, hypertensive diseases) in pedigreed female siblings compared to controls. Differences between long-lived males and control males could not be reliably calculated because of a lack of male controls. Similarly, the offspring generation was shown to have 22% reduced cancer incidence, particularly for lung and tobacco-related cancers. To illustrate the resiliency of the offspring generation, the researchers compared those individuals who were diagnosed with cancer to matched controls from the background population to observe survival rate. Researchers found that the pedigreed offspring were more likely to survive individual cancer diagnoses than their control counterparts.

Based on these results, the LLFS researchers expanded their research to well-pedigreed grandchildren to observe whether robustness and resilience trends continued. The grandchildren demonstrated continued robustness against disease compared to the control population; however, the effect size of the difference in diagnosis rates was reduced compared to the effect size in the offspring generation. Researchers also demonstrated resiliency in the grandchildren, noting that the cause-specific mortality for grandchildren is reduced compared to the control population; however, at a quarter less of the effect size compared to the offspring generation.

The in-person portion of the LLFS seeks to determine whether the differences between the pedigreed families and background controls are from genetic, epigenetic, and/or environmentally influenced advantages. Planned and ongoing Danish register research to further support these findings include updating the register linkages, performing end-of-life and cause-of-death comparisons, studying dementia in long-lived siblings, determining mechanisms of lower infant mortality in long-lived families, and tracking SARS-CoV-2 and COVID-19 testing and treatment in long-lived families to determine whether infection or death rates differ compared to the population control.

In response to questions from Council members, Dr. Christensen explained that the gradient of socioeconomic variability is larger in the United States than in Denmark; however, there are still measurable differences in Danish population life expectancy between the least educated and most educated individuals. The study is collecting biological samples in both Americans and Danes to investigate the genetic component of longevity through genome-wide association studies and a variety of omics.

NACA members asked Dr. Christensen about potential sources of bias, such as inclusion of only living siblings in long-lived families and not including smaller or infertile families. Dr. Christensen explained that the study team considered data from both interviewed and non-interviewed siblings. He added that studies of smaller families or infertile families are challenged by the small numbers of offspring and grandchildren to ascertain whether longevity is genetically carried through generations. He welcomed feedback from Council members on reducing the impact of bias in the study.

VII. COUNCIL SPEAKER

Introduction to the NIH Common Fund

James Anderson, MD, PhD, Director, Division of Program Coordination, Planning and Strategic Initiatives, NIH

In 2004, the NIH Roadmap for Medical Research was established to provide NIH with a formal set of guidelines to allow Institutes, Centers, and Offices (ICOs) to coordinate on cross-cutting, trans-NIH programs. Signed by Congress in 2006, the NIH Reform Act created the NIH Common Fund as a separate appropriation inspired by the Roadmap. The Act combined multiple ICOs that previously coordinated trans-NIH work into the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the NIH Office of the Director.

In FY 2021, the NIH Common Fund received an appropriation of $649 million. Programs funded by the Common Fund are milestone-driven, limited to 10 years, and must engage two or more NIH ICOs. Typically, the Common Fund supports 25 projects simultaneously, with disease-

agnostic goals that target a transformative deliverable to accelerate research across NIH through generating data, developing technology, developing the workforce, or identifying a new knowledge paradigm.

Approximately 30% of the Common Fund budget is devoted to investigator-initiated High-Risk, High-Reward Research Programs that do not allow preliminary data and include multiple potential award categories with various funding budgets (e.g., Pioneer, New Innovator, Transformative, Early Independence). The remaining budget is devoted to goal-driven, time-limited Common Fund projects. These projects are often inspired by meetings with external scientific experts, solicitation of ideas from ICOs, discussions with NIH leadership and advisory committees, and engagement with the broader scientific community. Programs are selected based on input and interest from ICO directors, DPCPSI Council of Councils review, and the NIH Director. While the Common Fund Programs are not limited on their subject matter, most fall into one or more of four main categories: transformational discoveries and tools, catalytic data resources, re-engineering clinical and translational research processes, and innovative approaches to workforce development.

NIA has led numerous Common Fund programs in the past, including the Health Care Systems Research Collaboratory; Molecular Transducers of Physical Activity Consortium (MoTrPAC); Cellular Senescence Network (SenNet); Building Blocks, Biological Pathways, and Networks (BBPN); Science of Behavior Change (SOBC); and Health Economics. Successful programs change the way that researchers understand human biology and prevent or treat disease, enable sustained changes in the way research is conducted, and/or stimulate investigator-initiated research by catalytic data or tools.

Dr. Anderson presented on the successes and challenges of the Health Care Systems Research Collaboratory; MoTrPAC; SenNet; and Protein Capture Reagents Program. The Health Care Systems Research Collaboratory aimed to strengthen the national capacity to implement cost-effective, large-scale research studies that engage health care delivery organizations as research partners. The Collaboratory succeeded in established a coordinating Collaboratory Coordinating Center to lead pragmatic clinical trials. After the award ends, the Center will receive continued funding from various ICOs positively impacted by its creation. MoTrPAC sought to uncover at the molecular level how exercise improves and preserves the health of the body's tissues and organs. This ongoing program seeks to complete studies in both mice and humans that will collect various omics-level data from individuals following specific exercise regimens and make the data publicly available. Launched this year, SenNet seeks to comprehensively identify and characterize the differences in senescent cells across the body, across various states of human health, and across the lifespan. The Protein Capture Reagents Program sought to create renewable and cost-effective protein capture reagents for the human proteome. Despite risk mitigation through a pilot phase, the program was not feasible because the mature technologies were difficult to scale, and the new technologies did not succeed as reliable or scalable reagents. Shifting focus, the program has instead produced antibodies to match hundreds of human transcription factors and made them publicly available.

In response to questions from Council members, Dr. Anderson observed that the lack of diversity in the pool of Common Fund researchers is a troubling issue that NIH has sought to address. For

example, women are less likely to apply for awards but are more successful in winning awards. The Common Fund continues to conduct outreach to groups with diverse community members to increase the application rates for diverse researchers. Council members noted that the two-phase review may contribute to the bias and suggested initiating blind written reviews to diversify the pool of individuals that advance to the interview stage.

Council members also suggested that an important focus area for future Common Fund research includes restoring the public faith in science and increasing public participation in clinical trials. They noted that dis-/misinformation during the past 18 months has influenced public trust and therefore clinical trial participation rates. Dr. Anderson agreed, noting that many groups have expressed interest in research to increase the public's understanding of the importance of science and value of scientific research.

VIII. ADJOURNMENT

The open session of the 144th meeting of the National Advisory Council on Aging adjourned at 1:11 p.m. on September 15, 2021. The next meeting is scheduled for January 25-26, 2022.

IX. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.[3]

Richard J. Hodes -S

Digitally signed by Richard J. Hodes -S
Date: 2022.02.07 10:56:00 -05'00'

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

Prepared by Kenneth Santora, Ph.D.
With assistance by Rose Li and Associates, Inc.

[3] These minutes will be approved formally by Council at the next meeting on January 25-26, 2022, and corrections or notations will be stated in the minutes of that meeting.