NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 145th Meeting

NATIONAL ADVISORY COUNCIL ON AGING

January 25-26, 2022

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
January 25-26, 2022

The 145th meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, January 25, 2022, 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, January 25, 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 Section 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of Public Law 92–463.[1] The meeting was open to the public on Wednesday, January 26, from 10:00 a.m. to 2:15 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 Jaie Manly
Dr. Eric Michael Reiman
Dr. David B. Reuben
Dr. Clifford James Rosen
Dr. Julie A. Schneider
Dr. Amy Jo Wagers
Dr. David R. Weir
Dr. Keith E. Whitfield

Ad Hoc Participants:
Dr. Darren Baker, Mayo Clinic
Dr. Anne Case, Princeton University
Dr. Yanira Cruz, National Hispanic Council on Aging
Dr. Susan Lynn Greenspan, University of Pittsburgh
Dr. Frank Longo, Stanford University

[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.

Dr. Charlotte A. Peterson, University of Kentucky

Ex Officio Participants:
Dr. Radha Holavanahalli, Administration for Community Living
Dr. Anne Ordway, Administration for Community Living

In Addition to NIA Staff, Other Federal Employees Present:
Dr. Clinton Wright, National Institute of Neurological Disorders and Stroke

Members of the Public Present:
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Mr. Alexander Sagona, Rose Li and Associates, Inc.
Dr. Kenneth Walsh, University of Virginia School of Medicine
261 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 Section 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 2,223 applications requesting $5,129,390,198 for all years underwent initial review. The Council recommended 1,148 awards for a total of $2,937,339,221 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 145th NACA meeting and called the meeting to order at 10:00 a.m. on Wednesday, January 26, 2022.

A. Director's Status Report

NIH/NIA Budget Status

Dr. Hodes reported that the House and Senate have not yet reached agreement on an appropriation for fiscal year (FY) 2022. On July 29, 2021, the House passed its FY 2022 Labor-HHS appropriations bill, which provides $49.4 billion for NIH overall (an increase of $7 billion over the FY 2021 enacted level), including $3 billion for the Advanced Research Projects Agency for Health (ARPA-H), and $4.3 billion for NIA. The NIA appropriation includes an additional $200 million for AD/ADRD research and $29 million for research related to opioids, pain, and pain management. On October 18, 2021, the Senate released its draft FY 2022 Labor-HHS appropriations bill, which provides $47.9 billion for NIH overall (an increase of $5 billion over the FY 2021 enacted level), including $2.4 billion for ARPA-H, and $4.2 billion for NIA (including an additional $235 million for AD/ADRD research and $29 million for research

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related to opioids, pain, and pain management). Dr. Hodes added that ARPA-H has not yet been authorized. The federal government, including NIH, is currently funded through February 18, 2022, via a continuing resolution.

For general applications reviewed by the Center for Scientific Review (CSR) and requesting less than $500,000 (direct costs) in any one year, pay lines are 8% for most regular research (R01) applications, 11% for new investigator applications, and 13% for early-stage investigator applications. For CSR-reviewed applications seeking $500,000 or more, pay lines are 5% for most, 8% for new investigator, and 10% for early-stage investigator applications. Pay lines are higher for applications focused on AD/ADRD: 25% for most, 28% for new investigator, and 30% for early-stage investigator R01 applications. For NIA-reviewed applications, the general pay lines for program projects (priority score: 13), other NIA-reviewed research (priority score: 13), career development awards (priority score: 18), and fellowship awards (priority score: 25) are lower than the corresponding AD/ADRD pay lines (priority score: 37, 37, 28, and 28, respectively).

NIA Updates

Dr. Hodes reported that 365 NIA AD/ADRD clinical trials were active as of October 2021, including 72 pharmacological interventions, 120 non-pharmacological interventions, and 155 dementia care and caregiving interventions, and 18 other trials.

NIA supported a consensus study of the National Academies of Sciences, Engineering, and Medicine, which released *Reducing the Impact of Dementia in America: A Decadal Survey of the Behavioral and Social Sciences* in July 2021. This report highlights opportunities for behavioral and social science research in AD/ADRD over the next decade. The report calls for research that addresses the causes of and solutions for disparities in developing dementia and receiving adequate treatment, as well as research that sets meaningful goals for researchers and people living with dementia and their caregivers.

Dr. Hodes noted the continued collaboration between NIA's Alzheimer's Disease Research Centers (ADRCs) and the Department of Veterans Affairs (VA) to increase the participation of veterans in AD/ADRD research. To date, the ADRCs have conducted more than 15 outreach events, communicated with more than 300 veterans, and recruited more than 60 veterans into AD/ADRD research.

The Butler-Williams Scholars Program for junior faculty and researchers new to the field of aging will be held virtually August 23-25, 2022. The multi-day program is intended to bring together early-stage researchers to discuss the breadth of aging research with a strong emphasis on health disparities research. The deadline for applications is April 15, 2022.

Dr. Hodes announced that Alzheimers.gov is now fully available in Spanish. Other languages will be added soon (future release dates to be determined). Visit www.Alzheimers.gov/es

The NIA leadership team announced NIA staffing updates (31 new hires) since the September 2021 NACA meeting. Also since that meeting, NIA has released 31 research highlights, 16 blog posts, six news announcements, and three press releases. In the same timeframe, Dr. Hodes, NIA

Acting Deputy Director Dr. Melinda Kelley, and/or senior NIA staff have participated in six stakeholder/advocacy group meetings and three Congressional briefings.

COVID-19 Updates
Dr. Hodes noted that NIA and other NIH Institutes and Centers released two Notices of Special Interest related to the COVID-19 pandemic:

- 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 an expiration date of May 8, 2023.
- NOT-MH-21-330 focuses on the Social, Behavioral, and Economic Impact of COVID-19 in Underserved and Vulnerable Populations with an expiration date of September 8, 2024.

NIH Updates
Dr. Hodes shared a number of NIH updates:

- The NIH Common Fund launched the Cellular Senescence Network (SenNet), a program that will comprehensively identify and characterize the differences in senescent cells across the body, various states of human health, and the lifespan.
- The 2022 ADRD Summit will be held March 22-23, 2022, with Dr. Natalia Rost as the Scientific Chair and Dr. Roderick Corriveau as the NIH Lead.
- Dr. Francis Collins stepped down as NIH Director after serving three U.S. presidents over more than 12 years. Dr. Lawrence A. Tabak is serving as Acting NIH Director, and Dr. Tara A. Schwetz will serve as Acting NIH Principal Deputy Director. President Joe Biden has not yet nominated a new NIH Director.

Discussion
In response to questions from Dr. Terry Fulmer, Dr. Hodes explained that the numbers of Congressional briefings and constituent meetings have remained steady during the COVID-19 pandemic and that NIA staffing has been increasing to meet the extent and diversity of its research portfolio. Dr. Shalender Bhasin voiced concern about the paperwork required to satisfy administrative assurance requirements in grant applications, especially for junior investigators. Dr. Kenneth Santora replied that NIA regularly seeks ways to reduce the administrative burden and implement efficiencies, to the extent allowed by regulation.

B. Future Meeting Dates
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 September 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

Dr. Keith Whitfield, Task Force Co-chair, began his report on the January 25, 2022, Task Force meeting by announcing that Dr. Jennifer Manly will replace Dr. Clifford Rosen as a Task Force Co-chair. He then summarized his presentation on contrasting within and between group analyses in the pursuit of understanding racial differences in aging populations. He explained that culture impacts every step of the scientific process: questions, models, measurement, analysis, and interpretation. Models of cultural differences consider cultural deviance, cultural equivalence, and cultural variance. The larger the difference in size between two groups, the larger the sample needed to achieve sufficient statistical power to reliably detect differences. The study of minority populations offers unique opportunities that many researchers do not fully appreciate, for both basic science and applied issues about phenomena impacted by social and psychological factors. Alternative strategies to study minority populations (between and within) will advance understanding of cognitive function and dysfunction in both minority populations and the general population.

Dr. Manly provided an overview of Dr. Donna L. Washington's presentation on "Selected Findings from the 2021 National Veteran Health Equity Report: Disparities by Veteran Race/Ethnicity and Socio-Economic Status." This report discusses the status of health equity within the VA health system and is grounded in the belief that systemic change comes from measurable results. Dr. Washington used the World Health Organization definition of "health equity," that is, the absence of unfair and avoidable (or remediable) differences in health among social groups. A demographic analysis of Veterans Health Administration (VHA) patients revealed that racial and ethnic diversity is greatest among patients younger than age 65 and that 58% of patients had a service-connected disability. To provide an example of the type of data analysis contained in the report, Dr. Washington described two findings from a survey of VHA users. First, in the middle (45-64 years) and older (65 years and older) age ranges, racial and ethnic minorities reported that, within the past 6 months, their provider did not spend enough time with them. Second, across age ranges, VHA users of low socioeconomic status (SES) reported a lower frequency of being asked by their provider, within the past 6 months, whether they experienced feelings of sadness, emptiness, or depression. Overall, the report revealed disparities in person-centered care and access to care and coordination in the VA health system, particularly by race and ethnicity, SES, sex/gender, and service-connected disability. The report's purpose is to raise awareness of disparate care or outcomes among veterans and to implement changes to improve their lives. During their discussion, Task Force members commented that the report also highlights data collection needed for analysis, design, and generation of tools and interventions to narrow disparities.

IV. REPORT: WORKING GROUP ON PROGRAM

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

A. RFA/RFP Concept Clearance

Dr. Driscoll invited the primary reviewers to summarize the 11 concepts submitted for clearance from three NIA units: Division of Behavioral and Social Research (DBSR), Division of Geriatrics and Clinical Gerontology (DGCG), and Division of Neuroscience (DN). The Council members unanimously concurred with approval of 10 concepts and voted to defer one concept.

Division of Behavioral and Social Research (DBSR)

Policy and AD/ADRD Healthcare Disparities: Access, Utilization, and Quality
The proposed concept will support research that capitalizes on policy variations to address gaps in knowledge of the processes that drive inequalities in health care access, utilization, and quality for people living with AD/ADRD in communities, assisted living facilities, and nursing homes. Policies broadly include official national or federal laws and regulations as well as state, local, or institutional- and facility-level policies and procedures. This concept could expand beyond the R01 mechanism to include the R03 or R24 mechanisms.

Understanding the Supply of Professional Dementia Care Providers and Their Decisions
Global diagnoses of ADRD are expected to triple in the next 30 years. There was robust enthusiasm for better understanding of how dementia care is supplied by professional providers and how that care affects people living with dementia (PLWD) and the overall health care system. The proposed concept calls for an internet survey of health care providers to enable researchers to explore the composition, qualities, and actions of this workforce to ensure that challenges such as barriers to entry, retention, and an aging physician workforce can be addressed to meet the needs of the growing population of PLWD.

More Mobile Monitoring of Cognitive Change, Continued (M3C3)
The proposed concept would extend work previously funded under RFA-AG-18-012, "Mobile Monitoring of Cognitive Change (U2C)," by addressing the need to assess noncognitive and behavioral factors that may modify cognitive performance. It also seeks to extend previously funded work in the Mobile Toolbox Project and support the continued development of the platform with expanded content including noncognitive measures and behavioral assessments, wider dissemination of instruments to allow studies to customize apps, and incorporation of electronic consent for mobile monitoring. This exciting work generated great enthusiasm.

Measures and Methods for Research on Family Caregivers for People Living with AD/ADRD
The proposed concept acknowledges changes in family structure and composition over the past several decades, which may have altered the role that families play in caring for PLWD. Little is known about family members' expectations and senses of obligation regarding caregiving—and what factors (including barriers and facilitators) predict whether a sense of obligation translates into actual care given and received. This initiative addresses the pressing need to develop measures and methods to better capture the picture of more broadly refined notions of family and what AD/ADRD caregiving tasks are expected or provided by family.

Broadening the Scope and Reach of NIA's AD/ADRD Resource Centers for Minority Aging Research (RCMAR) Program
The proposed concept aims to support new or renewal applications proposing RCMARs that focus on behavioral and social science research in a key area related to aging, health disparities in older adults, and/or ADRD. The RCMAR Program has been a very successful mechanism for mentoring diverse scientists in aging research since its inception in 1997. AD/ADRD RCMARs were added in 2018. There is also a single RCMAR Coordinating Center funded as a U24 cooperative agreement. New strategies and infrastructure are needed to support expansion and to

foster the inclusion of researchers at Historically Black Colleges and Universities, Hispanic-Serving Institutions, Tribal Colleges and Universities, and other Minority-Serving Institutions, with expectations for leadership and career management, support for additional interactions/connections beyond annual meetings, and creation of online content and networking that could be supported by the RCMAR Coordinating Center.

Predicting Early Alzheimer's Disease and Related Dementia (AD/ADRD) in Diverse Populations

The proposed concept is a grand challenge that capitalizes on a prize competition created by the America Competes Act to incentivize a collaborative approach to research on detecting subtle changes in preclinical AD/ADRD in diverse populations. The competition would provide three sequential challenges that aim to (1) provide cognitive/clinical electronic health record (EHR) claims, biomarkers, and other types of data among diverse populations; (2) help understand and address potential biases; and (3) make the data widely available through trusted repositories. Council members expressed enthusiasm for this proposal but questioned whether sufficient data and resources are currently available from underrepresented groups to develop this model, especially for those at higher risk of developing ADRD. The Council voted to defer this concept until there could be greater assurance (perhaps within the next 2 years) that sufficient resources are available. It was also suggested that program staff consider restructuring the proposal to broaden from preclinical to include mild clinical disease states.

Division of Geriatrics and Clinical Gerontology (DGCG)

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

Persons newly diagnosed with AD/ADRD typically have other chronic conditions or geriatric syndromes (e.g., frailty) that can confound interpretation of traditional disease assessments. Yet, current AD/ADRD studies of diagnostics and therapeutics have not adequately addressed differences by age and sex and have frequently excluded persons living with a variety of comorbidities. The proposed concept for a consortium to conduct transdisciplinary aging diagnostic biomarker and imaging research projects focused on AD/ADRD and MCCs to better align diagnostic testing with the needs and priorities of an aging population reflects a narrower focus than the earlier concept presented in September 2021 that had been deferred. This narrower focus might be increasingly important as new therapeutics turn out to be effective, and could provide valuable information for the Centers for Medicare & Medicaid Services (CMS) in considering coverage for diagnostic testing, which is currently extremely limited. The set-aside R24 mechanism was considered appropriate.

Division of Neuroscience (DN)

Precision Medicine Approaches in Addressing AD/ADRD Minority Health and Health Disparities

Although knowledge of the heterogeneity of AD/ADRD among minoritized populations has increased, some populations remain severely underrepresented in AD/ADRD research, and very little is known about AD/ADRD within most of these populations. This initiative aims to (1) support planning activities for the development or scale-up of research infrastructure and

resources to support studies of AD/ADRD in minoritized populations; (2) support pilot projects that utilize a multilevel, precision medicine approach and inform the scale-up of future research; and (3) support transformative multidisciplinary teams to address AD/ADRD disparities, burden, or resilience among minoritized populations. Council members considered this topic to be timely and noted that it addresses a number of important milestones and priorities. The cooperative UH2/UH3 phased mechanism, with a feasibility phase followed by a pilot data collection phase, is appropriate.

Neuronal Vulnerability to Proteinopathies in AD/ADRD
The goal of this proposed concept is to define and characterize neuronal and glial cell populations that are vulnerable to AD/ADRD proteinopathies. Specifically, a subsequent Funding Opportunity Announcement (FOA) would solicit applications to (1) establish a comprehensive set of data on neuronal and glial cells vulnerable to AD/ADRD proteinopathies based on single-cell transcriptomic or epigenetic signature; (2) identify intrinsic morphological, electrophysiological, and biochemical properties of neurons vulnerable to proteinopathies; and (3) identify neural circuits and/or large-scale networks that contribute to vulnerability to proteinopathies. This initiative will complement current NIA efforts aimed at a census of cells and circuits in the aging brain, the cellular scale connectome, and/or selective cell and network vulnerability in aging and Alzheimer's disease. Council members considered this proposed concept as targeting a very important question in the field, and unique in encouraging collaboration of investigators associated with the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative and Brain Map.

Demonstration Projects to Promote Use of Interoperable Health Records in Clinical Research in Older Adults
The 21st Century Cures Act Interoperability and Patient Access final rule (CMS-9115-F) created requirements for the health care industry to adopt standardized, interoperable, and secure downloadable, structured electronic health information at no cost. This concept is designed to provide evidence about the feasibility of utilizing the interoperability requirement to collect older research participants' EHRs. The proposed FOA will support 3-year demonstration projects to collect and analyze medical records from older adult research participants using downloaded health information. The projects will (1) create a digital infrastructure to collect EHRs donated by participants; (2) develop approaches to harmonize the data across patients and providers; and (3) develop informatic approaches to analyze medical records. This initiative will require involving EHR vendors who have traditionally not been NIA awardees.

NIA AD/ADRD SBIR/STTR Reissue: Advancing Research on AD/ADRD
The proposed initiative is a reissuance of PAS-19-316 and PAS-19-317, Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD) (R43/44 and R41/R42 respectively; Clinical Trial Optional), which expires in September 2022. It would support applications through NIA's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs to encourage research on and commercialization of novel therapies, devices, products, and health care programs and practices to prevent the onset of AD/ADRD and to reduce their burden on individuals, their families, and society at large. Research areas supported through these initiatives include AD/ADRD prevention, diagnosis, treatment, care, and tools. Council members voiced strong support for

reissuance and noted significant improvement in application quality. The WGOP members presented this initiative also as an opportunity to leverage small business grants to foster innovation and outreach to women and members of underrepresented groups.

V. COUNCIL GUEST SPEAKER

Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): NIH Researching COVID to Enhance Recovery (RECOVER) Initiative
Dr. Clinton Wright, Director, Immediate Office of the Director, Division of Clinical Research, National Institute of Neurological Disorders and Stroke (NINDS)

Dr. Wright's presentation outlined the barriers to studying PASC, emphasizing the need for a more organized, harmonized, and collaborative approach among researchers in different fields. PASC refers to the ongoing, relapsing, or other health effects that occur beyond the acute phase of SARS-CoV-2 infection, such as long COVID, multisystem inflammatory syndrome in adults and children, and other conditions. Dr. Wright provided a review of the literature, starting with a review of 57 studies of 250,351 COVID-19 survivors who were assessed for PASC at 30 days after acute COVID-19 and beyond that revealed enormous variability (and severity) of reported symptoms related to neurological disorders, cardiac disorders, respiratory disorders, and mobility impairment.

One study of COVID-19 survivors in the United Kingdom (n = 351,850) found that roughly 14% of people still experienced symptoms 12 weeks post-infection, leveling off at about 12% after 15 weeks post-infection. A study conducted by VA found that the burdens of PASC were consistently greater among people with poorer baseline health and with more severe acute infection, and varied by age. The overall burden of PASC (defined as at least one sequela in excess of a noninfected control group) at 6 months equaled 4.4% among non-hospitalized people, 21.7% among hospitalized people, and 36.5% among people admitted to intensive care.

A study by the Imperial College London measured the persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people; 19% self-reported COVID-19, and 38% reported symptomatic COVID-19 with at least one symptom lasting 12 weeks or more. Two distinct clusters emerged from this sample: (1) "tiredness cluster," which co-occurred with muscle aches, difficulty sleeping, and shortness of breath; and (2) "respiratory cluster," which included shortness of breath, tightness in the chest, and chest pain. A higher percentage of people in the respiratory cluster reported severe symptoms during acute COVID-19 illness (44%) than in the tiredness cluster (27%).

Another study compiled data from the VA health database to identify 6-month sequelae in survivors for at least 30 days after COVID-19 diagnosis (n = 74,000) vs. survivors of non-COVID-19 illnesses (n=~5,000,000). The researchers found that beyond the first 30 days, people with COVID-19 exhibited a greater risk of death (hazard ratio 1.59) and use of health resources. The study concluded that the risk gradient increases according to the severity of the acute COVID-19 infection.

A study measuring the risk factors and disease profile of post-vaccination SARS-CoV-2 in the United Kingdom found that fully vaccinated individuals who developed breakthrough infections were about half as likely as unvaccinated people to report symptoms of long COVID lasting at least 4 weeks after infection. Similarly, a VA database study found that individuals who developed breakthrough COVID-19 cases exhibited lower risks of death and post-acute sequelae than individuals with COVID-19 who were unvaccinated.

Dr. Wright explained that PASC is very likely a set of multiple conditions with varied underlying causes. Proposed causes include (1) persistence of SARS-CoV-2 virus in certain tissues stimulates ongoing and dysfunctional immune response and tissue damage; (2) viral infection sets in motion a dysregulated immune reaction that results in ongoing inflammation affecting various organs and tissues; and (3) viral infection and/or inflammatory responses cause damage to organs and tissues that results in dysfunction.

Multiple conditions with varied underlying causes will require a wide range of interventions. Examples of potential classes of treatments based on hypothesized pathogenic mechanisms include (1) persistence of SARS-CoV-2 virus stimulating an ongoing immune response (to be treated with antivirals); (2) viral infection setting in motion a dysregulated immune response affecting various organs and tissues (to be treated with immune modulators); and (3) viral infection and/or inflammatory responses causing damage to organs and tissues that result in dysfunction, to be treated by specific interventions targeting the host organ(s)/tissue(s). Dr. Wright emphasized a need for more robust epidemiological data to better understand the duration of PASC and its later effects, risk factors, underlying pathobiology, and more.

Dr. Wright then presented an overview of the NIH RECOVER Initiative, which aims to rapidly improve understanding of and ability to predict, treat, and prevent PASC. RECOVER's guiding principles are to be patient-centered, diverse and inclusive, multidisciplinary, and adaptive. RECOVER is separated into an acute infection cohort and a post-acute infection cohort, which will allow researchers to study and characterize the long-term effects of infection and the trajectory of recovery over time. RECOVER will enroll ~40,000 participants from more than 200 sites across all 50 states, who will then be divided into meta-cohorts based on a tiered assessment strategy. Investigators will aim to enrich the enrollment of disproportionately affected communities by leveraging community engagement, multidisciplinary partnerships across NIH, and collaborations with patient groups. RECOVER assessments relevant to AD/ADRD include Centers for Disease Control and Prevention disability screenings, comorbidity listings, physical function assessments, laboratory tests, brain magnetic resonance imaging (MRI), lumbar punctures, and in-depth cognitive testing. Finally, an autopsy cohort will include comprehensive examination of the central nervous system, nerve tissue sampling, and brain tissue histology.

Discussion

One Council member inquired about PASC's unique characteristics compared to other respiratory viruses. Dr. Wright commented that, although more data are needed, earlier variants of SARS-CoV-2 appear to have more severe outcomes than influenza and other prevalent pathogens. Another Council member asked whether gender is a differential factor in PASC cases, and Dr. Wright answered that women appear to have significantly more (and more varied) symptoms than men. Dr. Wright also confirmed that RECOVER's initial enrollment is 50% male

and 50% female, but that distribution might change as trends emerge. He also confirmed that RECOVER is leveraging all available funds and resources to expeditiously implement RECOVER intervention trials.

VI. NACA OPEN SESSION PRESENTATION

Reducing the Impact of Dementia in America: A NASEM Decadal Survey of the Behavioral and Social Sciences

Dr. Elena Fazio, Health Scientist Administrator, DBSR

Dr. Fazio explained that the goal of the National Academies of Sciences, Engineering, and Medicine (NASEM) Decadal Survey is to propose a 10-year research agenda in social and behavioral sciences through a process of information gathering, committee deliberation, and report development. The recent survey, supported by NIA and other federal agencies and nonprofits, was informed by four public workshops and six commissioned papers, as well as public comment and advisory panel input. The survey's committee identified five priorities for reducing the negative impacts of dementia: (1) improve the lives of people touched by dementia; (2) rectify inequalities and disparities; (3) develop innovations; (4) address costs, value, and outcomes; and (5) advance research capabilities.

The decadal report catalogs 150 recommendations, which Dr. Fazio classified into three groupings with sample recommendations: (1) *significant progress*—causal effects of social factors and health-related behaviors over the life course and expansion of data infrastructure; (2) *in progress*—non-pharmacologic prevention interventions, improved screening and diagnosis, end-of-life care for PLWD, and platforms to facilitate fielding pragmatic trials embedded in health care systems; and (3) *early stages*—approaches for integrating and coordinating care, characteristics of dementia-friendly communities, financing structure effects on quality of care and clinical outcomes, and improved measurement of exposures and outcomes. She also noted the convergence among multiple sources of input on DBSR AD/ADRD research priorities, including not only the NASEM Decadal Survey, but also NIA AD/ADRD Milestones, Dementia Care and AD Summits, and scientific workshops.

Discussion

In response to a question from a Council member, Dr. Lis Nielsen noted that ethics considerations stemming from the tension between investigators' desire to obtain evidence of earlier functional, psychological, or biological changes for research and potentially diagnostic purposes and the implications of sharing these data for research participants and patients has been a topic of interest for DBSR. In terms of specific examples of community-level outcomes, Dr. Fazio cited access and availability of services at the community level and infrastructure, such as the physical environment. She confirmed that housing is a structural determinant of health, particularly for PLWD. Investigators must collaborate with communities to better understand specific housing contexts and aspects, such as stock, quality, and cost.

VII. PROGRAM HIGHLIGHTS (DAB)

Clonal Hematopoiesis: Update and Future Challenges

Dr. Kenneth Walsh, Lockhart B. McGuire Professor; Director, Hematovascular Biology Center; Professor of Biochemistry and Molecular Genetics; Robert M. Berne Cardiovascular Research Center; University of Virginia School of Medicine

Clonal hematopoiesis is a condition in which a substantial proportion of mature blood cells are derived from a single dominant hematopoietic stem cell clone. Dr. Walsh shared an emerging view that clonal hematopoiesis is a causal risk factor for cardiovascular disease that appears to be as prevalent and consequential as traditional risk factors such as cholesterol, diabetes, hypertension, and smoking.

Advanced age is the greatest, yet least understood, risk factor in developing cardiovascular disease. An aspect of aging of interest to Dr. Walsh is somatic mosaicism, which is the occurrence of two genetically distinct populations of cells within an individual, derived from a postzygotic mutation. Researchers have estimated through ultra-deep error-corrected sequencing that by age 50 every cell in the body has acquired 1,000 to 10,000 somatic mutations. Because cells are in constant competition, somatic mutations can give rise to clonal events. Most somatic mutations are benign, but some can affect driver genes that give a selective advantage to the cell, resulting in a clonal expansion.

Clonal hematopoiesis occurs within the blood, making it likely to produce systemic consequences because white blood cells travel throughout the body and interact with a wide variety of cells and systems. Recent studies have associated mutant blood cells with accelerated aging. One study found that an aged immune system drives senescence and aging of solid organs, while another study found that T cells with dysfunctional mitochondria induce multimorbidity and premature senescence.

The hematopoietic system has exceptional turnover and is therefore subject to exceptional Darwinian selective pressures. Blood cells are tiny cells with a lifespan of 3 to 120 days, representing 90% of the body's cellular turnover. In contrast, large cells (e.g., fat and muscle) have a lifespan of 12 to 50 years. If large cells acquire a mutated driver gene, they lack the same ability to rapidly spread throughout the hematopoietic system. Over time, mutant cells with a selective advantage (i.e., the pre-cancerous state of hematopoiesis) will dominate the hematopoietic stem and progenitor cells pool. One advantage for the study of clonal hematopoiesis is its ready detection through sequencing of the mutant allele as it amplifies in white blood cells, which facilitates sample collection and access to many biobanks.

In 2014, two researchers reported that clonal hematopoiesis is more prevalent than previously understood, increases with age, and is associated with increased mortality perhaps due to hematologic cancer. However, secondary data analysis revealed that clonal hematopoiesis is associated with increased coronary heart disease and stroke—a finding that has since been observed in dozens of other studies, which expanded the association to chronic kidney disease, peripheral artery disease, chronic kidney disease, osteoporosis, and others. However, association

is not causation. Using a mouse model, Dr. Walsh and his team found that clonal expansion of TET2-deficient cells accelerated atherosclerosis, providing initial evidence for causality.

Clinical outcomes have validated experimental findings that clonal hematopoiesis is associated with elevations in IL-6 and IL-1ß. Individuals treated with anti-IL1ß therapy exhibit a superior response if they harbor TET2-mediated clonal hematopoiesis. In addition, therapies that inhibit IL-1ß/IL-6 signaling may more efficiently reduce risk for cardiovascular disease among individuals with clonal hematopoiesis.

To better understand the causes of clonal expansion, Dr. Walsh and colleagues have explored whether the mosaic loss of the Y chromosome (mLOY)—the most common cause of post-zygotic mutation in humans—is causally associated with morbidity and mortality, and if so, through what mechanism. They created a model of hematopoietic mLOY, involving bone marrow transplantation in male mice, which showed a causal connection between hematopoietic mLOY and fibrotic diseases. Finally, results from another mouse model suggest that mLOY promotes myeloid TGFß signaling. This NIA-funded research has been submitted for publication.

A Council member inquired about differences between the Y chromosomes in humans and mice, and whether those differences contribute to mLOY. Dr. Walsh responded that the analysis is imperfect because some of the losses on the human Y chromosome may not be replicable in mice (and vice versa). He and his team are employing CRISPR to isolate and identify the causative genes. He acknowledged the importance of comparing clonal hematopoiesis to more standard models of aging and of investigating the mechanisms for the cognitive decline that was also detected in the mouse model.

VIII. INTRAMURAL PROGRAM REPORT (OPEN SESSION)

Laboratory of Behavioral Neuroscience (LBN)
Dr. Susan Resnick

Dr. Resnick provided updates on LBN activities since the last report. LBN seeks to understand mechanisms of individual differences and age-associated cognitive variation from animal to human models, applying a multilevel approach (e.g., genes, molecules, physiology, neural systems) to promote successful cognitive outcomes. Within LBN, the STARRS (Successful Trajectories of Aging: Reserve and Resilience in RatS) installed an MRI machine and optimized phenotyping infrastructure and monitoring. Next steps are large-scale data collection and establishment of coordination and digital data center and a biospecimen repository.

After a 1-year COVID-related pause, Dr. Resnick's team has resumed collecting PET imaging data from Baltimore Study of Longitudinal Aging (BLSA) participants using ^{11}C-Pittsburgh compound B (PiB) and flortaucipir tracers. During the pause, the team performed plasma biomarker analyses on BLSA participant samples using the SIMOA Neurology 4-Plex platform; pTau analyses using the University of Gothenburg platform are expected soon. Biomarker analyses indicate that Aβ 42/40 ratios decline and both GFAP and NfL levels increase with

increasing age. Additional assessments identified that the Area Under the Curve for Aβ ratios to predict PiB-positivity is .692.

Using BLSA data, the Multimodal Imaging of Neurodegenerative Disease (MIND) Unit recently compared samples from people who reported prior symptomatic human herpesvirus (HHV) infection to those who did not and found greater longitudinal white matter loss in the former group, particularly in the temporal white matter. Along with external collaborators, investigators in the DREAM (Drug Repurposing for Effective Alzheimer's Medicines) study analyzed two, large, real-world clinical datasets with more than 2 million older individuals with clinical diagnoses and prescription data and identified several targets that warrant further investigation. Finally, WHIMS (Women's Health Initiative Memory Study) investigators are analyzing selected plasma biomarkers, olink proteomics, and biocrates metabolomics data from Women's Health Initiative baseline samples, to understand the biology of cognitive resilience in "APOE e4 escapees."

Laboratory of Epidemiology and Population Sciences (LEPS)
Dr. Lenore J. Launer

Dr. Launer provided an overview of the projects' collaborations, progress, challenges, and future directions. LEPS aims to understand the balance between maintaining and losing cognitive and physical function using integrative and translational models. LEPS follows a life course approach, and its cohorts are large, diverse, community-based, followed over time, and deeply phenotyped. The 2020 Board of Scientific Counselors review recommended rebuilding LEPS by naming a permanent Lab Chief, developing a strategic research plan, and assembling a full team of tenure-track investigators—as well as focusing on health disparities, new challenges to health, and bridging the gap between basic and population sciences. The current research landscape, particularly the substantial amounts of data now available through technology advances, poses challenges to understanding one disease. In response, LEPS plans to employ a whole person and systems biology approach. To foster translational science, LEPS will develop trainees for cross-discipline research and provide opportunities for collaborations with the Intramural Research Program. Future directions include study of the effects of disasters in accelerating aging and trajectories to dementia.

Translational Gerontology Branch (TGB)
Dr. Rafael de Cabo

Dr. de Cabo provided updates on the work of three TGB units. TGB, which continues to grow in terms of staffing, investigates and develops methods and interventions to support healthy aging and to prevent or delay the onset of functional decline and age-related diseases. Within TGB, the Translational Geroproteomics Unit has advanced efforts to develop the next generation of aging biomarkers with a focus on proteomics-driven approaches to quantify, target, and isolate senescent cells in humans/tissues. The Epigenetics & Stem Cell Aging Unit is pursuing additional research on the effects of NAD+ augmentation with nicotinamide riboside on the lymphoid potential of Atm-/- and old mice hematopoietic stem cells. Finally, the Helicases and Genomic Integrity Section is pursuing additional research on targeted inhibition of premature aging suppressor WRN to combat cancer.

Dr. Santora concluded the open session and invited the Council members to remain online for the closed session.

IX. REVIEW OF INTRAMURAL RESEARCH PROGRAM (CLOSED SESSION)

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[3]

X. ADJOURNMENT

The open session of the 145th meeting of the National Advisory Council on Aging adjourned at 2:13 p.m. on January 26, 2022. The next meeting is scheduled for May 10-11, 2022.

XI. CERTIFICATION

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

Richard J. Hodes -S Digitally signed by Richard J. Hodes -S Date: 2022.05.24 16:38:42 -04'00'

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

[4] These minutes will be approved formally by Council at the next meeting on May 10-11, 2022, and corrections or notations will be stated in the minutes of that meeting.