U.S. Department of Health and Human Services
National Institutes of Health (NIH)
Office of the Director (OD)
Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)

Council of Councils Meeting
September 7, 2018

Meeting Minutes

I. CALL TO ORDER AND INTRODUCTIONS

James M. Anderson, M.D., Ph.D., Director, DPCPSI, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The meeting began at 8:15 a.m. on Friday, September 7, 2018, in Building 60/Cloisters, Lecture Hall/Chapel, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson welcomed members and noted that Ms. Maria Acebal and Mr. Jorge Contreras were unable to attend, and Dr. Sachin Kheterpal was attending by phone. The meeting attendees are identified below.

Following introductions and announcements from Franziska B. Grieder, D.V.M., Ph.D., Executive Secretary for the NIH Council of Councils, Dr. Anderson reviewed the day's agenda.

A. Attendance

1. Council Members

Council Members Present
Chair: James M. Anderson, M.D., Ph.D., Director, DPCPSI
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI
Maria Rosario G. Araneta, Ph.D., M.P.H., University of California, San Diego, La Jolla, CA
Eric Boerwinkle, Ph.D., The University of Texas Health Science Center at Houston, Houston, TX
Melissa Brown, M.D., M.N., M.B.A., Thomas Jefferson University, Philadelphia, PA
Jonathan Epstein, M.D., Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
Rick Horwitz, Ph.D., Allen Institute for Cell Science, Seattle, WA
Patricia D. Hurn, Ph.D., R.N., University of Michigan, Ann Arbor, MI
R. Paul Johnson, M.D., Emory University School of Medicine, Atlanta, GA
Paul J. Kenny, Ph.D., Icahn School of Medicine at Mount Sinai, New York, NY
Sachin Kheterpal, M.D., M.B.A., University of Michigan Medical School, Ann Arbor, MI
Gary A. Koretzky, M.D., Ph.D., Weill Cornell Medical College, New York, NY
Michael D. Lairmore, D.V.M., Ph.D., University of California, Davis, Davis, CA
Jian-Dong Li, M.D., Ph.D., Georgia State University, Atlanta, GA
Terry Magnuson, Ph.D., The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC
Edith P. Mitchell, M.D., FACP, Thomas Jefferson University, Philadelphia, PA
Charles P. Mouton, M.D., M.S., The University of Texas Medical Branch, Galveston, TX

John Postlethwait, Ph.D., University of Oregon, Eugene, OR
Jean E. Schaffer, M.D., Washington University School of Medicine, St. Louis, MO
Scout, Ph.D., The Torvus Group, Beverly Hills, CA
J. Leslie Winston, D.D.S., Ph.D., Procter & Gamble Global Oral Care, Mason, OH
Nsedu Obot Witherspoon, M.P.H., Children's Environmental Health Network, Washington, DC
Gail Yokote, M.S., University of California, Davis, Davis, CA

Council Members Absent
Maria L. Acebal, J.D., Food Allergy Research & Education, Inc., Washington, DC
Jorge L. Contreras, J.D., The University of Utah, Salt Lake City, UT
Bruce Ovbiagele, M.D., M.Sc., M.A.S., University of California, San Francisco, San Francisco, CA

2. Liaisons

David M. Murray, Ph.D., Director, Office of Disease Prevention (ODP), DPCPSI
Barbara C. Sorkin, Ph.D., representing the Acting Director, Office of Dietary Supplements, ODP, DPCPSI
Elizabeth Spencer, R.N., representing **Janine A. Clayton, M.D.,** Director, Office of Research on Women's Health, DPCPSI
Karen L. Parker, Ph.D., M.S.W., Director, Sexual and Gender Minority Research Office (SGMRO), DPCPSI
Jay Radke, Ph.D., representing **Maureen M. Goodenow, Ph.D.,** Director, Office of AIDS Research, DPCPSI
William T. Riley, Ph.D., Director, Office of Behavioral and Social Sciences Research (OBSSR), DPCPSI
Marina Volkov, Ph.D., Director, Office of Evaluation, Performance, and Reporting, DPCPSI
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI
David R. Wilson, Ph.D., Director, Tribal Health Research Office, DPCPSI

3. *Ex Officio* Members Absent

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

4. Presenters

Gene Civillico, Ph.D., Program Leader, OSC, DPCPSI
Francis S. Collins, M.D., Ph.D., Director, NIH
Eric Dishman, Director, *All of Us* Research Program
Matthew Gillman, M.D., Director, Environmental influences on Child Health Outcomes (ECHO) Program
Lynn R. Goldman, M.D., M.S., M.P.H., Michael and Lori Milken Dean of the Milken Institute School of Public Health, Professor of Environmental and Occupational Health, The George Washington University, Chair, ECHO Scientific Board (Working Group of the Council of Councils)
Terry L. Powley, Ph.D., Distinguished Professor, Neuroscience, College of Health and Human Sciences, Purdue University
William T. Riley, Ph.D., Director, OBSSR, DPCPSI

5. NIH Staff and Guests

In addition to Council members, presenters, and Council Liaisons, others in attendance included NIH staff and interested members of the public.

B. Announcements and Updates

Dr. Grieder reviewed the following:

- Council members are Special Government Employees during the days of Council meetings and are therefore subject to the rules of conduct governing federal employees.

- Each Council member submitted a financial disclosure form and conflict-of-interest statement in compliance with federal requirements for membership on advisory councils. The financial disclosures are used to assess real and perceived conflicts of interest, and Council members must recuse themselves from the meeting during discussions of any items for which conflicts were identified.

- Time is allotted for discussion between the Council members and presenters, but time for comments from other meeting attendees is limited. The public may submit comments in writing; instructions are available in the *Federal Register* notice for the meeting, which was published on August 7, 2018.

- Minutes from the May 18, 2018 meeting are posted on the DPCPSI website. The minutes from this meeting also will be posted there.

C. Future Meeting Dates

Council meetings in 2019 are scheduled for January 24 and 25, May 16 and 17, and September 5 and 6. While these dates are reserved, the duration of each meeting is not yet confirmed.

II. NIH UPDATE

Francis S. Collins, M.D., Ph.D., Director of the NIH, commended retiring Institute and Center (IC) directors, Drs. Patricia Grady (NINR) and James Battey (NIDCD)and welcomed new directors, Drs. Helene Langevin (NCCIH) and Bruce Tromberg (NIBIB). Dr. Collins noted that current scientific excitement has enabled the NIH to recruit exceptional staff and take advantage of an increasing budget, which provides the sustained, predictable growth necessary to support exciting science and the next generation of investigators.

Dr. Collins updated the Council on several cutting-edge projects. Cancer research now can utilize genomics tools to identify the causes of individual tumors and look for a match between the mutations found and the available targeted therapeutics. Early results from the National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH) trial show a substantial portion, although not a majority, of participants responded to the targeted therapy and lived longer. Progress also has been made in cancer immunotherapy studies, which can be labor-intensive but often produce dramatic results. A recent 5-year public-private partnership to identify immunotherapy biomarkers, the Partnership for Accelerating Cancer Therapies (PACT), includes 12 companies, the NIH, and the U.S. Food and Drug Administration (FDA) and has the potential to produce exciting results if managed thoughtfully.

Another successful public-private collaboration is the Accelerating Medicines Partnership (AMP), which focuses on turning discoveries from basic science studies, including many genome-wide association studies (GWAS), into clear targets for therapeutic development. Dr. Collins emphasized the open-access nature of both MATCH and AMP. AMP includes four projects studying Alzheimer's disease, type 2 diabetes, rheumatoid arthritis and lupus, and Parkinson's disease. The Alzheimer's disease program ensures that the best biomarkers are utilized in all ongoing clinical trials; current projects include adding tau as a biomarker and studying brain samples for new targets. The type 2 diabetes project links human genetic and phenotypic data and integrates all data in the Knowledge Portal Network, and the Parkinson's disease study, which launched in January 2018, identifies biomarkers to predict progression. The rheumatoid arthritis and lupus program applies advances from single-cell biology to autoimmune diseases and uses biopsies of relevant tissues to conduct a census of immune cells. Dr. Collins noted that AMP's success has prompted a 1-year extension and discussions of continuing the research in its next phase.

Dr. Collins demonstrated several technology advances from the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, which is funded by both a base appropriation and the 21st Century Cures Act. The BRAIN Initiative's brain cell census has discovered a new type of human brain cell called the rosehip neuron. Dr. Collins noted that this single-cell census tracks with the Common Fund's Human Cell Atlas, which is performing similar studies for many human organs. He also commented on the expectation that the BRAIN Initiative would lead to improvements in deep brain stimulation. More than half of the funded principal investigators (PIs) in a recent round of grant awards are engineers, in line with the Initiative's foundational focus on circuitry and networks. A BRAIN 2.0 working group has begun assessing the Initiative's successes to revise the initial 10-year plan, including releasing a request for information (RFI) and conducting nationwide workshops, and an updated plan is expected around the fall of 2019.

Dr. Collins discussed the increasing use of artificial intelligence (AI) in medical applications, beginning with image-processing applications, such as skin and retinal exams, which AI often can assess more accurately than humans. Other terms associated with AI include "machine learning," which refers to a program that can learn as it is exposed to more data, and "deep learning," which applies to multilayered AI networks that learn from large amounts of data, often in ways that researchers do not yet understand. A recent workshop including both NIH grantees and experts from the private sector explored some of the potential applications and predictions about the future of this technology, and an advisory committee is being formed to ensure that this field is nurtured.

Dr. Collins commented on recent progress in gene editing, such as the ability to deliver a normal copy of the gene that causes spinal muscular atrophy. CRISPR/Cas9 therapeutic applications have become precise enough to change a single base with striking efficiency and safety, and Dr. Collins expressed hope that this technology would lead to a solution for sickle cell disease, the mechanisms of which have been understood for many years. For many conditions, CRISPR/Cas9 offers the promise of *ex vivo* treatment options without significant side effects and, eventually, a cure. Dr. Collins noted that the future of gene editing likely involves determining interventions for diseases in which *ex vivo* treatments are not an option, such as those involving the brain and requiring *in vivo* treatment. A new Common Fund program, Somatic Cell Genome Editing, offers the potential to develop a scalable approach for targeted gene editing.

<u>Discussion Highlights</u>

- When asked about risks in and lessons learned from public-private partnerships, Dr. Collins commented on two recent studies that were less objective than desired. The NIH learned from these challenges; a steering committee has been formed to carefully review new projects and determine their merit before sending each project to the Foundation for NIH, which ensures that

the firewall between donors and outcomes is sound. An additional working group is looking more carefully into the failed studies to prevent similar outcomes in future studies. Dr. Collins emphasized that many public-private partnerships have been successful.

- Dr. Collins confirmed that NCI's portfolio includes many cancer prevention strategies related to precision medicine, including partnerships with the National Institute for Environmental Health Sciences (NIEHS). Standards are required to determine levels of environmental risk associated with cancer; some risks are clear, but smaller risks are harder to confirm. Dr. Collins emphasized that continued efforts to reduce tobacco use remain one of the most important cancer prevention strategies. He also highlighted the TAILORx study, which used genomic analysis to identify a large percentage of women with breast cancer who would not benefit from adjuvant chemotherapy; this saves both pain for the patients and institutional cost, demonstrating that additional research does not always increase costs.

- When asked about stem cell models of diseases, Dr. Collins noted examples of disease-in-a-dish models that provide the opportunity to understand the basic cell biology and biochemistry of an illness. He added that the whole biochip program has successfully created organoids for a dozen human tissues.

- Dr. Collins emphasized the importance of NIH's reproducibility efforts and highlighted a number of efforts, including increasing requirements for grant applicants and partnering with journals to add questions to the submission process. He noted that although the consciousness has been raised about the importance of reproducibility, some areas, such as animal experiments that test therapeutics, require further efforts.

- In response to a question about trainees who leave research, Dr. Collins acknowledged the complexity of this issue. Although many trainees are led to believe that they should follow the same path as their mentor, they often produce exciting results in non-academic fields. The NIH must emphasize that academic research and non-academic career paths are equally valuable, so trainee programs have been expanded to allow trainees many opportunities to explore additional career paths. To support trainees who want to remain in research, the NIH now prioritizes applications from early-stage investigators applying for their first or second awards.

- Dr. Collins discussed the applicability of GWAS to autoimmune diseases and other diseases in which the immune system plays a role. Participants suggested investigating applications related to fibrosis, hyperinsulinemia, and other non-cancer arenas in which genetic therapy could be applied with support from the NIH.

- In response to a question about plans to extend new technology to populations with disparate disease burdens, Dr. Collins noted his regular discussions with Dr. Eliseo Pérez-Stable of the National Institute of Minority Health and Health Disparities and emphasized the centrality of health disparities to the goals of the *All of Us* program. Participants in *All of Us* also become more familiar with and available to other research studies. Dr. Collins emphasized the importance of reaching communities disparately affected by sickle cell disease and ensuring trust in the research enterprise; he reiterated that all IC directors prioritize health disparities research, and a strategic plan to address these issues is forthcoming.

- Dr. Collins commented on the necessity of supporting a health care system that learns from research and implements its discoveries quickly, for which *All of Us* will serve as a pilot. One potential strategy to increase this integration involves assessing reimbursement data from the Centers for Medicaid & Medicare Services to identify any inefficiencies.

III. *ALL OF US* RESEARCH PROGRAM UPDATE

Eric Dishman, Director of the *All of Us* Research Program, emphasized the participant-centric nature of the *All of Us* program, which has recruited a diverse group of participants, of all races and ethnicities, age groups, geographic regions, health statuses, etc. The program also developed several working groups of their Advisory Panel to provide input on several critical issues, including the Genomics, Child Enrollment Scientific Vision, and Tribal Collaboration groups. The fundamental mission of *All of Us* is to accelerate health research and enable individualized prevention, treatment, and care, and—although the program is focused on achieving its goal of enrolling 1 million participants—each component is being designed to act as part of a learning health system. *All of Us* plans to engage with participants for at least a decade and possibly even their entire life course; this will produce a large, rich biomedical resource that *All of Us* must make easy to access and secure. The program also must catalyze an ecosystem of funders, including those within NIH's 27 ICs and from the outside world, to support researchers from many scientific fields using this resource to make discoveries.

All of Us aims to recruit 70 to 75 percent of the initial 1 million participants from populations that are underrepresented in biomedical research, and 50 percent of those 1 million participants should be from underrepresented racial and ethnic communities. This will create a data set that better represents the wide range of people in the United States. *All of Us* is also exploring opportunities for collaborations and data linkages with other large cohort programs, including those in other countries, to make the data as valuable as possible for both common and rare diseases. Addressing diversity at the scale of 1 million participants is unique, and the successes of *All of Us* can inform how other researchers reach and build trust with diverse communities.

Although current data have been gathered primarily from surveys and clinical records, *All of Us* is working to add genomics, environmental, and social and behavioral data. Such diversity of data supports a holistic, thorough understanding of health conditions. *All of Us* also is committed to responsibly returning information to participants and ensuring that data are accessible to researchers and citizen scientists, though the data will be divided into several access tiers based on the reidentification risk, to protect participant privacy. The data support networks that have been created to curate and store data and samples, as well as enable access, are the foundation of the program's efforts.

Every partner health care provider organization (HPO) proved its ability to send electronic health records in a secure, standard format, so each participant recruited through these organizations has some baseline data. Participants are also invited to contribute physical measurements and biospecimens (PM&B) – blood and urine samples currently. In addition to partnering with HPOs, and *All of Us* has partnered with various organizations such as Walgreens, Quest, EMSI, and others to collect PM&B from "direct volunteer" partners – or individuals who do not sign up via an HPO. Some of these organizations can even facilitate at-home physicals for the most vulnerable participants. Pop-up events in collaboration with community partners can facilitate sample collection within a discrete time period. In addition to current recruitment and data collection strategies, wearable technology possibilities are in development. *All of Us* theoretically has the potential to reach 90 to 95 percent of the country within 20 to 30 minutes after all its capabilities have been scaled, and Mr. Dishman emphasized the significance of ensuring that health research can meet such a large number of people where they are.

As of September 1, 2017, *All of Us* had enrolled 2,500 participants at 12 sites; a year later, 106,000 participants have been enrolled at over 200 sites, and 77.2 percent of these participants are from populations underrepresented in biomedical research, which is more than the program's goal. Mr. Dishman emphasized that the program reached its diversity goals only through conscious effort from its inception, including specific messaging, community engagement, and trust strategies. Program materials currently are available in Spanish and English, with additional translations planned. Mr. Dishman

described the May 2018 national launch in seven communities across the country connected via webcast, which helped recruit participants from all 50 states.

To fully reach enrollment goals, the program must triple its rate of recruitment, and determining how to deliver value to participants at early stages remains a challenge. Additionally, many of the initial building stages are not yet finished, and the direct volunteer capacity has not yet been scaled up. In November, *All of Us* will launch regional campaigns at single-city and multi-state levels to explore the requirements for outreach in different markets. The program also is working to shift parts of the protocol toward at-home assessments to reduce the clinical encounter time for participants.

A funding opportunity announcement related to genetic counseling was released earlier this summer and the award recipients will be announced soon, and the program plans to include both genotyping and whole-genome sequencing, plus clinical validation when appropriate, on all 1 million core participants. Mr. Dishman noted the challenge of ensuring that the capacity for genetic counseling is sufficient for the participants' needs. *All of Us* also has been preparing to launch recruitment for children from birth to 6 years of age in the spring or summer of 2019. A family enrollment paradigm is likely to be part of this effort, but those details have not yet been determined.

The program also is working to build a centralized research portal that would allow researchers to apply once and receive credentials for a particular data security tier, rather than needing to reapply for each study. The computing model developed will allow most analysis capabilities researchers desire and can be accessed at www.researchallofus.org, which includes early scientific use cases and will facilitate the ability to submit additional use cases in the future. Mr. Dishman emphasized that building trust relationships and ensuring solid management for the many components of *All of Us* are the critical aspects to ensuring the program's ability to fulfill its goals.

Discussion Highlights

- In response to a question about counseling for both rare genetic conditions and more common health issues, Mr. Dishman explained that the program is developing a model to contextualize information for participants and ensure that sites have resources available to link a participant to additional help. The program also is exploring partnerships with provider outreach programs with specific expertise. Participants discussed the need to enhance training for genetic counseling across the NIH as genomics technology expands.

- When asked about participant control of data, Mr. Dishman commented on the access paradigms associated with various data types and suggested that electronic health records, which often contain errors that are difficult to alter, could be coupled with a tool that allows participants to provide context from their point of view.

- Socioeconomic diversity enrollment has been moderately successful; the appropriate community partners have been engaged, but more work is needed in rural areas.

- Materials may be translated into additional languages, which still need to be determined, following a thorough review of the lessons learned from making the program fully available in Spanish. Mr. Dishman also noted the aim to overrecruit from racial and ethnic minorities underrepresented in biomedical research and adjust flexibly as the program continues.

- Mr. Dishman explained that *All of Us* decided to start its data collection from scratch to meet its robust diversity goals, but linking to other data sets and specific ICs' cohorts could occur later.

- Mr. Dishman noted that recruitment of sexual and gender minorities has been promising within the community partners, thanks to careful demographic analysis and strong incentives. HPO partners also will soon begin gathering volunteer participants from families of their current patients.

IV. TOWARD INCORPORATING GENETICS IN THE ECHO-WIDE COHORT

Matthew Gillman, M.D., director of the ECHO program, explained that ECHO's mission is to enhance the health of children for generations to come by evaluating the effects of a broad range of early environmental exposures on child health and development. The ECHO-wide Cohort combines existing cohorts of mothers and children into a single data platform. Dr. Gillman commented on the importance of epigenetics and genetics to the science of ECHO, explaining that a recently formed working group will inform the protocol and scientific goals related to genetics and epigenetics and make recommendations for establishing and organizing a genetics core. The NIH Strategic Workshop on Epigenetics and Genetics occurred in February 2018, which produced additional recommendations. ECHO's External Scientific Board (ESB) is a working group of the Council of Councils, and its members use their diverse expertise to provide recommendations to the Council.

Lynn R. Goldman, M.D., M.S., M.P.H., chair of the ESB, explained that both the Epigenetics and Genetics Working Group and the workshop developed recommendations, and the ESB integrated these into a unified set of recommendations for consideration by the Council. ECHO's data set will include 50,000 or more children, most with biological samples from biological mothers and about 20 percent with information from the fathers. The cohort includes racial and ethnic diversity from the assembly of multiple existing data sets. Various 'omics might lead to greater understanding of the mechanisms through which genes, environments, and behavioral factors affect health and disease outcomes. These kinds of exposures are particularly important for children because epigenetics play a fundamental role in development.

The workshop recommendations include genome-wide characterization of genetic variation in all participants, array-based genotyping, making all genotypes available for downstream analysis, whole-genome sequencing of individuals from underrepresented ethnicities or races, epigenetic studies or single-cell sequencing to create reference panels and determine more accurate estimates of cell-specific expression, methods development for integrated analysis of 'omic data, and storage of maternal and cord plasma for future studies. Many recommendations from the working group were similar, but they specifically recommended using the Multi-Ethnic Gene Array (MEGA), which includes variants relevant to people with non-European ancestry, as the GWAS platform of choice. They also recommended sequencing child-parent trios and considering additional 'omics technologies in the future, given the longitudinal and environmental nature of ECHO.

The ESB was largely in agreement with many of the recommendations common to both groups. Whole-genome genotyping should be performed on all ECHO children and parents, and MEGA should be the platform of choice. Whole-genome sequencing on subsets of individuals based on ancestry would increase the validity of imputation calls, and whole-genome sequencing of parent-child triads could be performed for all 10,000 such triads. Epigenomics, transcriptomics, and metabolomics analyses should be added in the future, and 'omics should be integrated into the epidemiologic analyses of exposure-outcome hypotheses. However, the ESB recommended that single-cell sequencing would be better performed by a group other than ECHO. General advice included using the same platform for analyses whenever possible, instituting centralized quality control in imputation, making all data available to all investigators, and articulating policies on the return of individual results to participants—Dr. Goldman commented that regardless of the final decision on whether results should be returned, the issue should be examined carefully. ECHO needs to be open to validating and using new platforms that might be

developed in the future, rather than remaining anchored to the platform chosen now if it becomes less scientifically valid; ECHO also must decide whether to include extant sequencing data. Additionally, a sample repository should be supported, as should strong sharing principles for both samples and 'omics results. Dr. Goldman emphasized the need to standardize data collection enough so that the many large cohort studies being conducted around the world can share data more easily.

Discussion Highlights

- Council members with expertise in genetics commended the recommendations. Some suggested integrating with the intended cohort of children for *All of Us*. Dr. Gillman noted that this partnership is in progress; now that ECHO's protocol is running, its details can be shared with *All of Us* and further harmonization and bidirectional communication can occur.

- When asked what kinds of environmental exposures are studied, Dr. Gillman explained that the term "environment" is viewed broadly and can include physical and chemical exposures, societal factors, psychosocial factors, behaviors, and lifestyle; each of these is represented in the ECHO-wide Cohort data collection protocol. Primary data collection by parents includes these factors, and biosamples are collected in standardized ways, facilitated by a special task force on one of the working groups, and harmonized both between cohorts and longitudinally within cohorts by skilled data analysis centers.

- Dr. Gillman suggested that epigenetics could illuminate new information on the transmission of early environmental influences and noted that many ECHO investigators are interested in research on the placenta, including its epigenetics Dr. Goldman added that the difficulties associated with studying epigenetic mechanisms in a high-capacity format support the working group's recommendation for a strictly standardized sample repository and robust attention to future technologies.

- Dr. Gillman planned to relay a Council member's recommendation for whole-genome sequencing studies on twins. In response to a question, he noted that one cohort includes both biological and adoptive siblings.

- In response to a participant's question, Dr. Gillman noted that several cohorts collect stool samples, and a few collect breast milk. Metabolomics is part of the expertise of the Children's Health Analysis Exposure Resource, and metabolomics studies are planned for many types of biospecimens.

- Many cohorts track air pollution, and various measurements can be combined to estimate individual exposure. Dr. Gillman clarified, in response to a participant's question, that whether air pollution studies can include exposure from natural disasters depends on when cohorts are recruited. Dr. Goldman added that, because the cohorts are not synchronous, the ages at which participants were exposed to natural disasters will vary, and this would dramatically affect exposure.

- When asked whether ECHO's budget can support its vision, Dr. Goldman emphasized that organization is key to supporting those activities that ECHO as a whole can accomplish. She acknowledged that despite its size, ECHO will not be able to study many of the rarer outcomes that might interest investigators.

- Dr. Gillman noted that many cohorts are focusing on microbiome studies, including the nasal microbiome. The plans for data harmonization are particularly critical to such studies.

- When asked about prioritizing future ’omics studies, Dr. Gillman requested input from the Council in terms of members’ varied areas of expertise. ECHO relies on its experienced investigators to suggest research paths for which ECHO provides resource management. Dr. Gillman added that most existing samples consist of blood that is not appropriate for single-cell analysis, which affects the depth of information that can be gathered at this point. A participant recommended particular attention to how samples are prepared for RNA analysis, and Dr. Goldman explained that ECHO includes PI groups focused on ’omics and sample collection; the investigators writing sample collection protocols need to take into account what researchers need to use those samples.

- Dr. Anderson acknowledged the Council’s interest and guidance and confirmed its support for the ESB recommendations.

V. COMMON FUND PROGRAM—STIMULATING PERIPHERAL ACTIVITY TO RELIEVE CONDITIONS (SPARC)

Gene Civillico, Ph.D., program leader for the SPARC program, reviewed the circuitry of the nervous system and pointed out that nerves and the organs they target have become increasingly useful as therapeutic targets for electrical stimulation devices. Electroceutical or bioelectronic medicine devices can be implanted with minimal surgery and less risk than deep brain stimulation. Devices recently approved, cleared, or made available in the US via humanitarian device exemption include a treatment for sleep apnea, a leadless pacemaker, and a barometric blood pressure regulator; a vagus nerve stimulator to modulate the output of the spleen is in clinical trials; a new bioelectronic medicines company plans to build the next generation of nerve- and tissue-stimulation devices for nonbrain indications.

Dr. Civillico noted that unsuccessful devices often are founded on an incomplete understanding of target engagement. The SPARC program focuses on ensuring that devices are based on scientific evidence for target identification, characterization, and engagement measurement. SPARC collects data on how nerves map from the brain to the rest of the body’s electrical wiring and creates tools to fill gaps in these mapping technologies. Because the SPARC program is in a rapidly developing interdisciplinary area, it uses the Other Transactions (OT) mechanism, which utilizes Common Fund support to innovate within the standard NIH award life cycle. This mechanism allows SPARC to facilitate projects that are riskier than usual, and projects can be tuned to complement each other, resulting in highly multidisciplinary consortia. Comprehensive mapping awards targeted at SPARC’s organs of interest are supported by thorough technology development, all relying on a supportive data ecosystem and scientific management from multiple ICs.

Terry L. Powley, Ph.D., Distinguished Professor of Neuroscience at Purdue University, illustrated the abilities of SPARC’s OT award, the OT2. He emphasized that the stomach is an organ that can be stimulated very effectively, is highly innervated, and is implicated in a variety of diseases. The vagus nerve, which conveys signals between the brain and the gut, allows many opportunities for on-target stimulation. Dr. Powley noted that many early stimulation techniques for the vagus nerve are inadequate and nonspecifically implemented, and surgery options—such as bariatric surgery—are nonspecific, drastic, and irreversible.

The OT2 mechanism allows investigators to focus on both analysis and synthesis techniques and integrate pieces of a complex research puzzle to solve for the bigger picture. Dr. Powley’s interdisciplinary research team includes engineers, physiologists, electrophysiologists, and anatomists; the laboratories are studying basic questions that were bypassed in the first generation of stimulation technologies, developing functional maps of the system, and implementing the research in the clinic. The researchers

have developed new techniques to phenotype motor fibers innervated by the vagus nerve, identifying the patterns of input for relaxation and excitation and the mechanisms of peristalsis. Dr. Powley emphasized that these mixed motor fibers of the vagus nerve illustrate the challenge in stimulating the nerve in a way that avoids confusing either the brain or the stomach. On the sensory side, several different phenotypes were identified, including one that seems to be the stomach's stretch receptor, a good potential stimulation target.

In addition to the laboratories pursuing anatomical studies, Dr. Powley's team includes biomedical engineers working to increase the sophistication of stimulation techniques for the stomach, and these researchers have demonstrated that stimulation must be very precise to have the desired effect. Machine learning techniques can help develop algorithms for such precise stimulation. Dr. Powley also commented on experiments using magnetic resonance imaging (MRI) to explore these processes in four dimensions, including time. The OT2 mechanism has allowed Dr. Powley's team to collaborate with researchers who can move rat studies to pigs and then to humans and confirm the utility of noninvasive techniques for mapping the stomach and intestine. These studies can be expanded into a variety of indices and measurements or translated into techniques to stimulate the vagal nerve more precisely and regularly in the long term. Dr. Powley also demonstrated vagal stimulation experiments conducted in the clinic. Collaborators are working to map the ultrastructure in several animal models, as well as humans, and to translate existing two-dimensional maps to a three-dimensional dynamic scaffold. Dr. Powley predicted that the near future would include second-generation vagal nerve stimulation techniques to treat a variety of disorders and emphasized that a thorough understanding of basic questions is required to stimulate any organ effectively.

Discussion Highlights

- Participants suggested a number of avenues for future research, including the individual variability of vagus nerve stimulation, increased fMRI studies of brain stimulation, the effects of the microbiome on stimulation, and translation to other sphincters. Collaborations with additional programs, such as the BRAIN Initiative, could be explored if SPARC continues beyond its initial period.

- In response to a question, Dr. Powley explained that anesthesia was not used in the human experiment demonstrated, and animal research is conducted with careful attention to how relaxing agents affect smooth muscle and nerve activity, but unknown effects are possible.

- Dr. Anderson clarified that the OT mechanism is effective for some research questions, but is not appropriate for all, and the Research Project Grant (R01) remains the main grant mechanism at the NIH.

VI. REVIEW OF GRANT APPLICATIONS

This portion of the meeting was closed to the public, 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 Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[1] Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Council would represent a real or perceived conflict of interest. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect. The *en bloc* vote for concurrence with the initial review recommendations was

[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 applied only to applications that were discussed individually, not to *en bloc* actions.

affirmed by all Council members present. During the closed session, the Council concurred with the review of 91 ORIP applications with requested first-year direct costs of $22,387,506.

VII. COUNCIL OPERATING PROCEDURES

Dr. Anderson commented that the Council had received a letter noting the lack of input from early-stage investigators and asked Council members for input on how to increase the involvement of younger researchers without placing additional burdens on them during a demanding career stage. Early-stage investigators could be included as *ad hoc* members, regularly or on a single occasion, but they might not have the experience required to make certain decisions and might learn more by participating in study sections.

Dr. Anderson reviewed proposed changes to the Council's operating procedures, including changing the wording of the operating procedures so that the Common Fund projects presented to the Council for review and input are at a more developed stage and the Council can provide more specific guidance. The Council approved the update.

VIII. WORKSHOP REPORT ON CONTRIBUTIONS OF SOCIAL AND BEHAVIORAL RESEARCH IN ADDRESSING THE OPIOID CRISIS

William Riley, Ph.D., the director of OBSSR, explained that OBSSR works to enhance the impact of health-related behavioral and social sciences research, coordinate behavioral and social sciences research, and integrate this work within the larger biomedical research enterprise at the NIH. Implementation of research findings from basic and applied research is particularly difficult in the social and behavioral sciences, and one of OBSSR's strategic priorities is to foster adoption of social and behavioral sciences research. OBSSR also coordinates OppNet, a trans-NIH effort to support basic behavioral and social sciences research not funded by a specific IC. Behavioral and social sciences research related to AI also is underway, although Dr. Riley noted that scientific research in this area must catch up to what commercial entities have been able to do. A recently funded project will use sensor technology to gather a temporally dense set of behavioral phenomena and its context over time within individuals.

OBSSR held a workshop in March 2018 to explore knowledge and challenges related to the opioid crisis. The first panel, on the sociocultural and socioeconomic underpinnings of the crisis, explored how social contexts affect opioid use and "deaths of despair," a set of phenomena related to suicide, drug use, and alcohol abuse that are particularly prevalent in individuals from white populations without less than a college degree. Social and medical policy changes, such as France's 1995 opioid treatment program or improvements in the prescription of opioids compared to treatments, could help address these issues.

The second panel addressed behavioral and social factors related to preventing opioid initiation and mitigating the transition between acute and chronic opioid use. Dr. Riley pointed out that many communities and settings do not use substance abuse prevention programs that have been proven effective. Data also show that opioids and ibuprofen are equally effective for acute pain, yet implementation of this knowledge is lacking. Successful approaches have included asking prescribers to justify opioid prescriptions in the electronic health record, comparing prescription rates among peers, and countering survivor bias by sending letters to the prescribing physician for every opioid overdose death.

The third panel addressed ways to incorporate nonpharmacologic approaches in the treatment of opioid abuse and chronic pain management. Dr. Riley noted that successful psychosocial chronic pain treatments have been known for decades, but reimbursement for such interventions was reduced in the 1980s as opioid use was being promoted for chronic pain. Researchers also know that misusers of opioids are more

sensitive to opioids' rewards than nonusers, and they also have less sensitivity to the natural rewards in the environment.

The fourth panel examined challenges to implementation, including significant barriers in rural areas, the correctional system, and the legal system, as well as for particular groups, such as indigenous populations. Socioeconomic status also affects what types of treatment patients can access. Complicating factors include increases in rapid outbreaks of HIV related to injection drug use in rural areas and the lack of support for people leaving the criminal justice system, which leads to high rates of opioid overdose deaths in post-incarceration populations.

The final panel addressed integration approaches, such as a collaborative care model that better integrates primary care with mental health and substance abuse care. One participant was asked to speak particularly on a project in Vancouver that integrates not only primary care and mental health and substance abuse care, but also the public health system and community-based systems and care.

Next steps following this workshop include collaboration with other entities engaged in practice implementation. Dr. Riley noted that in this crisis, the NIH must ensure that its research is supported through the implementation stage. Proposals influenced by this workshop are in progress, and a trans-NIH planning group includes representatives from most ICs.

Discussion Highlights

- In response to a question about improving objective pain measurement, Dr. Riley noted that although pain scales have not improved, sensor technology has enabled better assessment of functional impairment related to pain. Council members discussed studies of pain measurement in animals, which capture large quantities of data and images to correlate with behavior and emphasized the benefit of learning across disciplines.

- Dr. Riley clarified that deaths correlated with the lack of a college degree are a proxy measurement for many underlying factors that require further study, such as shifts in economic capability, wage stagnation, or control over one's environment. The study data also do not reflect overdose deaths of people currently in high school or college because the birth cohort data is through 1980.

- A participant asked how to accelerate the uptake from data to implementation. Dr. Riley suggested that although some communities have experience in addressing substance abuse, shifting others' beliefs is difficult. In contrast to biomedical treatments, behavioral and social science interventions often lack a regulatory body and market-driven implementation system that would facilitate adoption of proven approaches. Council members suggested exploring partnerships with other agencies that could work on the state level.

- Dr. Riley explained that much is known about stigma and its influences, but less is known about how to intervene. These factors must be addressed on a societal level. HIV/AIDS and depression provide good models for addressing societal stigma, but opioid misuse stigma also comes from health care providers.

- Lessons could be learned from other ICs that have spurred dissemination and implementation work, such as the research core (P30) mechanism for diabetes research. Dr. Riley planned to take

this suggestion back to his team and explore additional dissemination and implementation strategies.

IX. RETIRING COUNCIL MEMBERS' PERSPECTIVES

Drs. Melissa Brown, Jonathan Epstein, John Postlethwaite, and Leslie Winston, Ms. Gail Yokote, and Ms. Nsedu Obot Witherspoon reflected on their experiences serving on the Council of Councils, offered suggestions, and provided advice to new Council members.

Ms. Yokote encouraged new members to attend the orientation and commended the networking opportunities, diverse expertise, and learning opportunities available through participation in the Council.

Dr. Epstein suggested that future meetings include additional analysis of how outcomes are measured for the NIH's flagship programs. Dr. Anderson commented that draft recommendations for High-Risk, High-Reward programs will be discussed at the January 2019 meeting. Dr. Epstein and Dr. Postlethwait both recommended increasing the time available for discussion after presentations.

Dr. Brown appreciated the learning and networking opportunities and encouraged additional assessment of cost and comparative effectiveness in Common Fund programs, particularly in relation to the increasing use of quality-of-life measurements.

Dr. Winston commented that she often was asked to share Council experiences with colleagues from the National Institute of Dental and Craniofacial Research, and this task helped her consider what she heard at each meeting in a different light. She noted that her particular expertise was not always relevant to the types of research presented at the meetings, and she would have liked to contribute more often. Dr. Anderson acknowledged the difficulty in utilizing the diverse expertise on the Council.

Ms. Witherspoon agreed with previous comments and commended the professionalism of the Council meetings and staff. She recommended that presenters include information on how the science will affect communities outside the NIH so that advocates can be better stewards, and she suggested that public health or policy advocates continue to be included on the Council.

X. CLOSING REMARKS

Dr. Anderson noted that planned discussions of a working group related to interoperable data sets and platforms had been postponed; the NIH Data Commons Pilot has made progress, but progress in *All of Us* and rapid technology development have complicated this issue. Discussions will occur after further assessment of the NIH's needs in this area.

Dr. Anderson thanked the Council members and speakers for their contributions at this meeting. He reminded the members that the next Council meeting is scheduled for January 24 and 25, 2019.

XI. ADJOURNMENT

Dr. Anderson adjourned the meeting at 3:16 p.m. on September 7, 2018.

XII. CERTIFICATION

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

James M. Anderson -S Digitally signed by James M. Anderson -S
Date: 2018.11.15 12:42:16 -05'00'

James M. Anderson, M.D., Ph.D.
Chair, NIH Council of Councils
Director, DPCPSI, OD, NIH

Date

Franziska B. Grieder -S Digitally signed by Franziska B. Grieder -S
Date: 2018.11.15 13:54:26 -05'00'

Franziska B. Grieder, D.V.M., Ph.D.
Executive Secretary, NIH Council of Councils
Director, ORIP, DPCPSI, OD, NIH

Date