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
January 26, 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, January 26, 2018, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson welcomed members and noted that Ms. Maria Acebal and Drs. Eric Boerwinkle, Melissa Brown, Molly Carnes, Sachin Kheterpal, Vivian Lee, Kimberly Leslie, Guillermina Lozano, and Keith Reimann were unable to attend, and Mr. Jorge Contreras and Dr. Jonathan Epstein were 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
Jorge L. Contreras, J.D., The University of Utah, Salt Lake City, UT
Jonathan Epstein, M.D., Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
Hakon Heimer, M.S., Schizophrenia Research Forum, Providence, RI
Patricia D. Hurn, Ph.D., R.N., University of Michigan, Ann Arbor, MI
Terry L. Jernigan, Ph.D., University of California, San Diego, La Jolla, CA
R. Paul Johnson, M.D., Emory University School of Medicine, Atlanta, GA
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
Scout, Ph.D., The Torvus Group, Beverly Hills, CA
Bruce J. Tromberg, Ph.D., University of California, Irvine, Irvine, 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
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
Molly Carnes, M.D., M.S., University of Wisconsin–Madison, Madison, WI
Rick Horwitz, Ph.D., Allen Institute for Cell Science, Seattle, WA
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
Vivian S. Lee, M.D., Ph.D., M.B.A., The University of Utah, Salt Lake City, UT
Kimberly K. Leslie, M.D., The University of Iowa Hospitals and Clinics, Iowa City, IA
Guillermina Lozano, Ph.D., The University of Texas MD Anderson Cancer Center, Houston, TX
Bruce Ovbiagele, M.D., M.Sc., MAS, Medical University of South Carolina, Charleston, SC
Keith Reimann, D.V.M., University of Massachusetts Medical School, Boston, MA
Jean E. Schaffer, M.D., Washington University School of Medicine, St. Louis, MO

2. Liaisons

Janine Clayton, M.D., Director, Office of Research on Women's Health (ORWH), DPCPSI
Paul M. Coates, Ph.D., Director, Office of Dietary Supplements, Office of Disease Prevention (ODP), DPCPSI
Maureen Goodenow, Ph.D., Director, Office of AIDS Research, DPCPSI
Christine Hunter, Ph.D., representing **William Riley, Ph.D.,** Director, Office of Behavioral and Social Sciences Research (OBSSR), DPCPSI
David M. Murray, Ph.D., Director, ODP, DPCPSI
Karen Parker, Ph.D., M.S.W., Director, Sexual and Gender Minority Research Office (SGMRO), DPCPSI
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI
David R. Wilson, Ph.D., Director, Tribal Health Research Office (THRO), DPCPSI

3. *Ex Officio* Members Present

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

4. Presenters

James M. Anderson, M.D., Ph.D., Director, DPCPSI
Olivier Blondel, Ph.D., Program Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Janine Clayton, M.D., Associate Director for Research on Women's Health, NIH; Director, ORWH, DPCPSI
Job Dekker, Ph.D., Professor, Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School

Matthew W. Gillman, Ph.D., Director, Environmental influences on Child Health Outcomes (ECHO) Program, NIH
Elizabeth L. Wilder, Ph.D., Director, OSC, DPCPSI
David R. Wilson, Ph.D., Director, THRO, DPCPSI
Nsedu Obot Witherspoon, M.P.H., Executive Director, Children's Environmental Health Network, Member of the ECHO Working Group of the Council of Councils

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 December 15, 2017.

- Minutes from the September 1, 2017 meeting are posted on the DPCPSI website. The minutes from this meeting also will be posted there.

C. Future Meeting Dates

Future Council meetings in 2018 will be held on May 17 and 18 and September 6 and 7; these dates are reserved, but the duration of each meeting is not yet defined. The September meeting will be held in the NIH Cloisters, rather than the current conference room, because of renovations to Building 31.

II. THE 4D NUCLEOME PROJECT: HOW THE GENOME WORKS IN SPACE AND TIME

Olivier Blondel, Ph.D., Program Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases at the NIDDK, explained that the 4D Nucleome (4DN) project aims, in the long term, to combine technologies to produce a three-dimensional structural and functional map of the human genome, which could provide critical new insights into human health and disease. 4DN prioritizes development of both early-stage and currently used technologies and has generated and shared many genome-wide omics data sets. An important collaborative project within 4DN called the "Joint Analysis" focuses on a small set of cell lines to ensure that all technologies in development can be combined and benchmarked, and standards for new and existing technologies also have been developed. 4DN also is the first large Common Fund Program at the NIH to require that investigators share their data and research

early through a preprint server (bioRxiv). In 2017, the project has added twelve new 2-year awards to increase its technology toolbox and the geographic diversity of its investigator pool. Collaborations with the worldwide community is also expected to increase in the future through the participation of 4DN in the International Human Epigenome Consortium. To further increase outreach and exchanges with non-4DN investigators, the annual meetings of the 4DN are now partially opened to the public, and 4DN is implementing an associate membership status to allow investigators outside the project to contribute data sets and analyses to existing 4DN's efforts.

At the halfway point of its initial 5-year funding period, 4DN's ongoing goals include continuation of technology validation, increased focus on combining technologies, and transition of omics technologies to single-cell resolution, which is the only way to explore the fourth dimension of the genome, or how its structure and organization change over time. Single-cell resolution also is necessary to study the variation in genome organization that occurs between individual cells. Tasks likely to remain after the initial funding period include completion of a first-generation 3D map of the human genome in a few cell types, refinement of structural and functional relationship models in live cells, and transition of technologies to live tissues, organs, and animals. Additionally, 4DN will need to begin exploring more broadly the relationship between genetic and epigenetic background, genome organization, and disease risk. Dr. Blondel added that the project must make its technologies, databases, and analytical and visualization tools useful not only for chromatin biology, but also for all areas of biomedical research.

Dr. Blondel introduced Job Dekker, Ph.D., a professor of Biochemistry and Molecular Pharmacology at the University of Massachusetts Medical School, who co-chairs 4DN's joint analysis program to collaboratively utilize new technologies and approaches. Dr. Dekker explained that a linear or two-dimensional map of the genome, such as that created by the Human Genome Project, does not fully explain function because regulatory elements often operate on target genes that are not close in linear space. Mapping the looped interactions between genes and their enhancers will allow scientists to relate each gene to its regulatory elements and understand how the genome operates in three dimensions. The three-dimensional structure of chromosomes also guides genome stability—the location of a chromosome in the nucleus can predispose the chromosome for rearrangement, which often is seen in cancer. Dr. Dekker explained that different cell types have different three-dimensional structures, and the genome must be refolded during cell division to facilitate accurate chromosome segregation, so structures must be studied in many types of cells and at different points in time to model the genome's movement in the fourth dimension and fully understand its function.

Although these processes have been studied for many years, complicating elements have made it difficult to accurately determine the three- and four-dimensional structure of the genome. One factor is that this is a highly interdisciplinary area, requiring expertise in imaging, genomics, and biophysics as well as communication between these historically siloed communities to both integrate existing knowledge and create the new technologies required. Dr. Dekker noted that the Common Fund is a mechanism well-suited to funding 4DN for this reason. Once the 4DN project has brought together data from disparate communities to outline dynamic three-dimensional structures of chromosomes, the team can determine the molecular mechanisms. Ultimately, the project aims to identify how the structures discovered relate to function and regulation of the genome and how these actions operate in disease.

Dr. Dekker explained that structural maps of chromosomes traditionally have been created through imaging; he believes the biggest innovation developed in 4DN will come from the imaging field. A number of imaging innovations have been developed recently, including CRISPR-based locus tagging used for engineering, live-cell imaging, and methods to increase throughput to see more loci, which often has been the major limitation for imaging. Dr. Dekker explained a new imaging and data-analysis pipeline that can visualize and locate many pairs of loci rather than one at a time, increasing the ability to visualize the entire structure of the genome. Another new technology within 4DN allows researchers to see

chromatin at a finer resolution than previously available, which is necessary to see small gene regulatory elements. Genomics also can be used to map interactions between loci near a particular sub-nuclear structure or chromosome interactions at sites bound by specific proteins. Chromosome conformation capture allows researchers to map genome-wide interactions between loci and use signal intensity to identify how frequently loci interact, which researchers can interpret as a looping interaction between the enhancer and the target gene. Such maps can illustrate compartments and associating domains and identify domains of self-interacting loci and precise looping interactions. New strategies also have been developed to label loci near a nuclear structure of interest to determine the genomic tracks of interactions between loci and sub-nuclear structures.

Dr. Dekker emphasized that facilitating collaboration between research communities is a major ongoing effort in 4DN and is required to build three-dimensional models that incorporate the many types of data gathered with many methods. However, 4DN first must generate and compare data with multiple methods for a limited set of cell lines to determine how to combine data gathered with disparate methods. Similar methods also must be conducted for imaging, because the many ways of labeling a locus have not yet been compared. Dr. Dekker pointed out that although this seems like a very technical endeavor, it is critical to identifying standard ways to interpret data. Because a genome is folded differently in every cell and because cells go through different states, time dynamics, cell-to-cell variations, and other dynamics during differentiation and the cell cycle all must be considered when comparing data. Dr. Dekker reiterated that 4DN aims to begin building realistic three-dimensional models of the human genome by the end of its initial funding period.

Dr. Dekker provided a specific example of what integrated imaging, genomics, and biophysical modeling can study. Genome folding in mitosis had been understudied because of the difficulty of conducting genomics on cells progressing synchronously, but 4DN researchers developed ways to release cells synchronously into mitosis and conduct imaging and genomics at very small time resolutions. Distances between sites of frequent interaction changed as the process progressed, and researchers determined that a helical structure in which the distance between loops changed over time would account for the changing distances between sites that interact. Dr. Dekker noted that this model explains the data, but the chromosome does not look like a helix under a microscope; however, a model with many closely packed loops similar to a spiral staircase would fit both a helical structure and a cylindrical appearance. This solves one of the longstanding problems in the field of mitotic chromosome formation and also shows an example of dynamic folding of the genome. Dr. Dekker emphasized that this is just one state of the genome, and 4DN must determine these kinds of problems for all states of interphase, different cell types, different disease states, and so forth. Generating four-dimensional nucleome maps for key cell types and states will allow 4DN researchers to continue identifying folding and structural regulatory mechanisms, and those data can be used to relate these mechanisms to disease.

Discussion Highlights

- In response to a question about the amount of noise in these processes, Dr. Dekker explained that conducting assays at single-cell resolution is critical because no two cells are the same and the structures are highly dynamic. Higher order structures probably are more stochastic by their nature, which may relate to cell-to-cell variation in gene expression, but these relationships have not yet been described. Dr. Dekker emphasized that any noisiness must be below the level at which it would affect the genome because most genomic processes function sufficiently well. When asked about the relationship between genomic structures and evolutionary rates, Dr. Dekker explained that chromosomes have structural units that remain intact when the genome is rearranged and may contain relevant enhancers for genes in the same domain. He noted that, in cancer, genomes do not obey this rule, and broken domains lead to misregulated genes.

- Dr. Dekker explained that single-cell genomics will include both imaging and genomic components, but the technology to combine imaging and genetic readout on the same cell does not yet exist. Data from a single cell might be sparse at current technological levels, and although researchers often can infer missing data for a chromosome folded in a certain way, the necessary resolution to study these processes is not yet available. Dr. Dekker noted that 4DN is particularly focused on developing this area because single-cell resolution is required to describe variation and compare data to imaging.

- Dr. Dekker explained that many variables—including sensitivity, specificity, and false positive rates—need to be described before methods can be integrated. One ongoing project is working to label a given locus with all strategies currently in use and compare the resulting position and dynamics. After methodologies within fields are integrated, the genomic and imaging groups must collaborate to determine how to compare data, but 4DN includes experts in both fields and works to encourage collaboration.

- When asked whether the same processes operate in meiosis, Dr. Dekker acknowledged that meiotic processes remain unexplored because of the increased technological difficulty in separating the four chromatids involved.

- Dr. Dekker recognized that team science can be challenging in such a large project, and he emphasized building the trust required to collaborate requires transparency from all parties. 4DN team members can review a list of all current projects within the network and contact team members working in related areas. He added that 4DN encourages openness at all levels and interactions with other communities, and methods developed to map the nucleome in four dimensions hopefully can be shared with other disciplines.

- In response to a question about the future of imaging, Dr. Dekker explained that although the genomics community has a long tradition of data-sharing, the imaging community has begun sharing its data only recently. He noted that a major challenge in imaging is finding ways to visualize the dynamics of loci in live cells without editing the locus every time, but researchers are working on cross-comparisons and hope to find ways to track loci at very small sizes.

III. NIH UPDATE

Lawrence A. Tabak, D.D.S., Ph.D., the principal deputy director of the NIH, reviewed NIH's budget history and noted that the continuing resolution through February 8 limits the ability to comment on future budgets. Dr. Tabak emphasized that although the NIH cannot control the level of resources it receives, it can control how these resources are used.

Updating the Council on the NIH response to the opioid crisis, Dr. Tabak provided background information on the prevalence of pain in U.S. adults and the overprescription of opioids despite their limited effectiveness for pain. Although research has improved the understanding of addiction and pain, treatments for addiction and overdose are limited, underutilized, and poorly understood, and non-addictive pain medications that can replace opioids are urgently needed. Dr. Tabak emphasized that opioid overdose deaths have increased dramatically in recent years, and a surge in 2016 is related to the extreme potency of synthetic opioids, particularly fentanyl and carfentanil.

One critical research area investigated by the NIH is pain management; Dr. Tabak explained that acute pain, an important defense mechanism, sometimes transitions to chronic pain through methods that are poorly understood. Advances in precision medicine should lead to unique interventions for heterogeneous pain. Dr. Tabak explained innovative potential strategies, including therapeutic intervention in particular

pain channels and non-pharmacological approaches to pain management, such as mindfulness-based stress reduction therapy and cognitive behavioral therapy. Both of these non-pharmacological approaches have been shown to manage chronic back pain more successfully than usual care, but Dr. Tabak noted the reluctance of many providers to embrace mindfulness despite these data. The NIH also is developing strategies for addiction treatment and overdose reversal, including an implant that provides a low-level dose of buprenorphine to stable patients, a nasal spray to reverse suspected overdose that is easier to use than an injection, and a medicine that blocks the effects of opioids and can be used as part of a treatment program.

Dr. Tabak explained that public-private partnerships to develop new interventions have strong support and may include partnership with companies specializing in extended-release medications or identification of new uses for existing medications. He noted that such partnerships also could focus on developing more potent opioid antagonists to reverse overdoses that involve highly potent synthetics. Additional collaborative projects could include working with the U.S. Food and Drug Administration to accelerate registration of non-addictive pain medications, developing data-sharing methods across the industry, and establishing a clinical research network to accelerate trials. The NIH also is working to identify causes of the conversion from acute to chronic pain, including by embedding research on the fundamental neurobiology of pain processing into the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative.

Dr. Tabak moved to the topic of data science, explaining that NIH's data science efforts began with the Big Data to Knowledge (BD2K) program, including the NIH Data Commons Pilot, which are the first trans-NIH efforts to create a virtual space where digital objects of biomedical research can be stored and computed upon. In response to NIH's evolving data needs, recruitment will soon begin to fill a new position: NIH Chief Data Strategist. This individual also will serve as the Director of the Office of Data Science, DPCPSI, and will develop a data ecosystem to maximize the utilization and extraction of knowledge from the data generated by and relevant to NIH research and promote coordination and harmonization of data use around the NIH. Other new data science programs include a data and technology advancement fellowship program.

In response to a federal directive to improve efficiency, the Reimagine HHS project, and a related NIH initiative known as Optimize NIH, has been developed to identify strategic shifts that can make the Department of Health and Human Services (HHS) a more responsive and innovative organization. The program includes objective assessment and process mapping to identify any disconnects between organizational function and mission. Dr. Tabak noted that the decentralization inherent in the NIH sometimes can lead to inefficiencies, and the reforms proposed through Optimize NIH will enhance the administrative functions that support NIH's scientific efforts and the centralized activities that coordinate NIH's disparate Institutes and Centers (ICs). Dr. Tabak emphasized that the NIH is approaching this effort as it does all projects—in a data-driven, scientific manner—and hopes to complete it during the 2018 calendar year.

Discussion Highlights

- Council members offered suggestions for additional areas to target in opioid research, including increased academic research and improved guidelines for practicing clinicians. Dr. Tabak emphasized that changes in prescription practice will be effected through outreach to many entities, including medical and dental schools, professional organizations, accrediting bodies, and additional governmental organizations. He added that public-private partnerships have been discussed with both pharmacological and medical device groups, and he theorized that successful strategies against the opioid crisis will involve collaboration across disciplines.

- When asked whether adding pain research to the BRAIN Initiative would divert funds from other projects or invite applications for unrelated projects, Dr. Tabak explained that funding for the BRAIN Initiative is robust and pain is closely related to the fundamental research discovery the initiative supports. He emphasized that other conditions cannot be viewed in the same way, so an increase in unrelated applications is unlikely, and the magnitude of the opioid crisis and the understudied nature of pain make the cost-benefit ratio very favorable for such research.

- In response to a question about data coordination, Dr. Anderson explained that the NIH Data Commons Pilot is working to develop standards to make data generated in specific areas interoperable, in part by working with existing data sets in cloud space. Dr. Tabak added that all NIH data eventually will be shared, but he acknowledged that an algorithm to incorporate legacy data has not yet been written. He agreed that the human element is a critical dimension; each discipline has a different tradition regarding data sharing, and Dr. Tabak suggested that human behavior, which cannot be solved by an algorithm, may be the last element to evolve in this process.

- Dr. Tabak explained that the Optimize NIH efforts to improve accountability relate to both the success of research efforts and NIH's responsibility to manage taxpayer money efficiently. Dr. Anderson noted the increased accountability within DPCPSI, but Council members wondered whether the time spent tracking accountability reduced the potential for innovation among senior NIH staff; members suggested developing a definition of accountability that would maintain the necessary balance in scientists' time.

IV. PIONEER AWARD GENDER DISCUSSION

Elizabeth Wilder, Ph.D., the director of OSC, provided background on the Pioneer Award, a larger grant that allows researchers who have proven their ability to conduct innovative research to start a new research path. This award focuses on the skills of the individual scientist rather than a particular project with the intent to identify investigators with creative ideas and the ability to manage a large project. In 2017, only one woman received an award—translating to 8 percent of the 12 winners—despite the 22 percent female applicant pool. The NIH conducted an investigation of the selection process to determine whether any bias had contributed to this result. Dr. Wilder explained that the Pioneer Award review process begins with an electronic review of all applications; a panel then interviews about 25 applicants at the NIH. The interview panel provides prioritized scores to the Council for concurrence, and NIH staff, including representatives from every IC, assess the diversity of science represented by the finalists and creativity relative to other projects in the NIH portfolio and generate the final pay list.

Dr. Wilder reviewed each year's percentages of women applicants, interviewees, and awardees; women represent an average of 23 to 28 percent of each stage. To identify whether 2017's percentage was the result of bias, the investigation team reviewed the language in the funding opportunity announcement (FOA), assessed the review criteria and instructions, reviewed the percentage of women on the interview panel, and communicated with the Center for Scientific Review, which manages the process. No substantial differences were found in the FOA language, review criteria, or review instructions, and 40 percent of the interview panelists were women. The percentage of women applicants also was consistent with other years. The team determined that these factors suggest no systematic bias in the review process; the 2017 outcome likely is a statistical fluctuation. Dr. Wilder emphasized that the diversity of applicants, finalists, and awardees must be monitored closely to ensure that this year remains an anomaly.

Dr. Wilder commented that although the gender balance of 2017's winners was unusual, the average percentage of women who apply to the Pioneer Awards, at 23 percent, is lower than the NIH average of

32 percent female applicants. Women might not self-identify as pursuing high-risk and innovative research as frequently as men or they might not be encouraged at the institutional level to apply for this type of award. Additionally, Pioneer Award applicants must demonstrate a history of innovative research and the capacity to run a large direct-cost project, which results in many applicants who are associate or full professors. Dr. Wilder's team assessed percentages of female faculty at institutions from which Pioneer applicants are likely to come and determined that, if 96 percent of Pioneer Award applicants are full or associate professors and women account for 17 to 26 percent of full professors and 30 to 33 percent of associate professors at these institutions, the Pioneer applicant pool is similar to the gender percentage of faculty overall.

This conclusion reinforces the idea that the Pioneer process does not include systematic bias, but Dr. Wilder emphasized that the low number of women among the senior faculty at major research institutions remains a problem. The review team will assess the two other high-risk, high-reward initiatives at the NIH to assess whether other factors contribute to the skewed percentage of female applicants to these awards. Dr. Wilder asked the Council to confirm that the existing review process is fair and unbiased.

Dr. Wilder introduced Janine Clayton, M.D., the director of ORWH, who explained that part of the mission of ORWH is to address issues related to promoting the recruitment, retention, and advancement of women. Career advancement for women scientists is a longstanding issue within the academic community, leading to fewer women applicants for NIH funding despite equal success rates for research program grants. Dr. Clayton emphasized that diversity affects the science produced and influences numerous organizational factors that lead to greater discovery and innovation. She commended the NIH for its investments in this area over many years, noting that long-term interventions are necessary to change the status quo and improving the attrition of women requires more active engagement and creative solutions.

Discussion Highlights

- The discussants, Terry Jernigan, Ph.D., University of California, San Diego, and Jonathan Epstein, M.D., Perelman School of Medicine at the University of Pennsylvania, concurred that no clear bias was shown in the 2017 result. Dr. Jernigan noted that, in most years, the percentage of women awardees is higher than the percentage of women applicants, but cautioned that awards like the Pioneer are subject to the vagaries of the scientific zeitgeist, so reviewers must monitor gender discrepancies in both the broader biomedical arena and particular fields that are exciting to reviewers at a certain moment in time. Dr. Epstein recommended that the review committee avoid reinforcing the status quo by implying that having a percentage of women awardees equal to the current percentage of senior faculty is acceptable. He suggested that the Council reinforce the need for bias training and review the 2018 Pioneer Award statistics to confirm that 2017 was a statistical aberration. Dr. Epstein also noted that more could be done to solicit applications from scientists at all levels who meet the other criteria of the award.

- In response to a question about expected outcomes from other groups of underrepresented minorities, Ravi Basavappa, Ph.D., the program leader for the high-risk, high-reward initiatives, explained that because few Pioneer Award applicants are from such groups, these statistics are subject to great fluctuations, but the percentage of awardees generally seems to reflect the percentage of applicants. Responding to a question about potential bias in review commentary, James Mack, Ph.D., the scientific review officer, explained that reviews for this award are typically short and straightforward, and although not every review has been analyzed, random samples suggest any significant degree of bias is unlikely.

- Council members suggested additional avenues for investigation and improvement, including comparison with other NIH grants that emphasize innovation, conveying to potential applicants that women are treated fairly in this award, and considering a structured review process. Council members also discussed whether students at medical and graduate schools, where women now are in the majority, are encouraged to participate in research. Dr. Anderson added that a working group will be formed to review all high-risk, high-reward programs at the NIH and Council members may be invited to participate.

V. 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 affirmed by all Council members present. During the closed session, the Council concurred with the review of 461 ORIP applications with requested first-year direct costs of $331,287,669.

VI. TRIBAL HEALTH RESEARCH OFFICE UPDATE AND INPUT

David Wilson, Ph.D., the director of THRO, explained that American Indian and Alaska Native (AI/AN) populations experience significant health disparities in such areas as cardiovascular disease, cancer, diabetes, and cirrhosis. Tribal communities have a unique status within the United States in that they are recognized as sovereign nations, and thus federal programs that benefit indigenous nations function as government-to-government relationships. Health research conducted in conjunction with tribes is subject to the HHS Tribal Consultation Policy, which uses the government-to-government relationship to require consultation with tribes about HHS programs and policies that affect them. Dr. Wilson noted that THRO works within HHS to provide a single point of contact for tribes and encourages HHS programs to take into consideration ways the tribal community can participate in work to address AI/AN health disparities.

Since its 2015 establishment, THRO has been working on numerous projects, including coordinating the NIH Tribal Advisory Committee (TAC) and the trans-NIH Tribal Health Research Coordinating Committee. Dr. Wilson emphasized the importance of the TAC but noted the challenge in communicating the science to tribal community members—many of whom do not have scientific backgrounds—in a way that keeps them engaged and ensures TAC continuity. Additionally, THRO works with the National Institute of Minority Health and Health Disparities to support epidemiological centers that handle data pertaining to tribal communities and with the National Institute for General Medical Sciences to enhance the Native American Research Centers for Health. THRO also is involved in several programs to engage AI/AN students and trainees, including developing a summer internship program with opportunities at multiple ICs to help students find their passion at the NIH.

Dr. Wilson explained that THRO's strategic plan was influenced by recommendations from tribes for ways the office can serve their communities. In service of the first strategic priority—to facilitate comfortable communication between tribes and THRO—the office soon will hold a national consultation with tribal representatives to develop strategies to combat the opioid crisis in tribal communities. THRO

[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.

also works with many ICs to enhance trans-NIH communication and coordination around tribal issues. In collaboration with the National Human Genome Research Institute, a genetic research conference was held to provide clarity on the risks and benefits of data sharing, an area in which past transgressions against tribes have occurred. Dr. Wilson explained that the Navajo Nation has seen a rise in cancer incidence, but a 2002 ban prevents genetics research; the conference assessed ways the community could benefit from recent advances in genetic research, and tribal legislation has since been presented that would lead to formally amending and ultimately lifting the ban.

THRO provides opportunities for student interns interested in biomedical research, which helps address the office's strategic priority related to building research capacity within tribal communities. THRO also aims to help expand and diversify NIH's research portfolio related to tribal health issues; this effort includes developing an institutional platform for understanding tribal research backgrounds, challenges, and needs, for which THRO is creating a document to help researchers and reviewers understand competencies associated with conducting research within tribal communities. The office also has partnered with the ECHO program to address community members' concerns related to involvement in large research programs.

Other priorities include establishing measurements to determine the effectiveness of THRO's efforts and incorporating cultural competency into every THRO activity. For example, an educational brief on basic genetics used for its cover a picture of Window Rock, a geographic feature of the Navajo Nation with great significance, as a way to engage with and relate to tribal communities. The community has since expressed an interest in having this document translated into the Navajo language—many medical terms do not have context in indigenous languages, so translation can help provide a starting point to discuss medical issues relevant to tribal communities. Dr. Wilson stressed that the strategic priorities must be considered holistically, because every element of the plan is necessary for THRO's efforts to succeed.

Discussion Highlights

- Council members suggested additional avenues for engaging students and communities, including leveraging NIH-funded institutions across the country to provide student opportunities that require less travel and embedding researchers in communities. Dr. Wilson commented that THRO has been working with local communities to develop student opportunities and with former NIH trainees now working in tribal communities to ensure that tribal needs are effectively addressed.

- Dr. Wilson noted that he is involved in the working group for the All of Us program and working to increase communication about tribal concerns around data sharing in this program. By emphasizing bidirectional communication, THRO can both prioritize community concerns and provide information to communities about ways current research could improve knowledge related to those concerns. Dr. Wilson noted that THRO's partnership with ECHO has helped increase awareness of potential tribal concerns in large research efforts. Council members suggested that education on the challenges faced by tribal communities could help scientists become more engaged in developing solutions, adding that many researchers are more aware of underserved settings in other countries.

VII. INTRODUCTION OF NEW WORKING GROUP TO COUNCIL OF COUNCILS

Dr. Anderson explained the need for a Council working group to assess the safety of relocating NIH's research chimpanzees, which have been an excellent model for some diseases and conditions and also have been instrumental in developing therapeutic strategies now used widely. NIH-owned chimpanzees have not been bred since before a 1995 moratorium, and a report in 2010 from the Institute of Medicine concluded that chimpanzees are unnecessary for most current biomedical research. The report offered

three principles to use in determining whether proposed research required chimpanzees: knowledge gained from the project must be necessary to human health, no other research model must be available, and the research must not be able to be ethically performed in humans. The report also required that animals used in NIH-funded research be maintained in appropriate physical and social environments. Although some chimpanzees were maintained for research meeting these recommendations, the Chimpanzee Research Use Panel created to assess whether a project was consistent with the recommendations brought no new applications to the Council during the subsequent 2 years. Additionally, the U.S. Fish and Wildlife Service declared captive chimpanzees an endangered species, further restricting potential research. In November 2015, the NIH director determined that NIH would no longer support biomedical research on chimpanzees, and all NIH chimpanzees were eligible for retirement and could be moved to a sanctuary.

The federal sanctuary for NIH-retired chimpanzees is run by Chimp Haven, Inc., in Louisiana, and since its inception in 2005 has accepted 352 NIH chimpanzees. Chimpanzees currently in research institutions in Texas and New Mexico are eligible to be moved to the federal sanctuary, but the decision to move a chimpanzee is based on an assessment of the animal's health and welfare, including its social grouping. Relocations can be stressful for the chimpanzees, many of which are older and have complicating health conditions. Dr. Anderson charged the working group with fulfilling NIH's commitment to protect the chimpanzees' health by providing advice and recommendations on factors to be considered by the attending veterinarian when deciding whether to relocate at-risk chimpanzees and presenting these recommendations to the Council. In response to a question, Dr. Anderson clarified that many complicating factors prevent options other than moving the chimpanzees; the NIH position is that every chimpanzee that can safely be moved with respect to its welfare will be transferred to the sanctuary.

VIII. THE ECHO PROGRAM AT YEAR ONE AND REPORT FROM THE ECHO WORKING GROUP TO THE COUNCIL

Matthew Gillman, Ph.D., director of the ECHO Program, explained that ECHO's mission is to enhance the health of children by evaluating the effects of a broad range of early environmental exposures on child health and development. The program assesses environmental exposures in the context of societal, medical, psychosocial, behavioral, and biological factors as it follows health outcomes throughout childhood and adolescence, focusing on high-impact pediatric conditions, as well as attributes that allow well-being. A cooperative U mechanism stipulates that the ECHO program office set a vision for the work that investigators conduct, but the investigators are encouraged to drive the science and create the policies. Dr. Gillman noted that ECHO's external scientific board is a working group of the Council charged with providing advice to ensure the long-term success of the program. Board members work in many scientific disciplines and with many communities at many levels.

ECHO's two components are observational cohort studies and intervention trials, the latter run by the Institutional Development Award (IDeA) States Pediatric Clinical Trials Network. The majority of ECHO's 83 cohorts began prenatally, allowing ECHO to follow *in utero* and prenatal determinants of child health, or within neonatal intensive care units. An eventual ECHO-wide cohort, harmonized and standardized on a single platform, would facilitate using large amounts of data to support changes in policies, programs, and practices. The IDeA Network, consisting of 17 clinical sites and a data coordinating and operation center, aims to provide state-of-the-art clinical trials for medically underserved and rural children and build pediatric research capacity. Dr. Gillman outlined some of the challenges faced by the program, which must balance its efforts to build a sustainable future with efficiency. Additionally, the differences between the cohort and clinical trials components make it difficult to coordinate funding, communication, expertise, and data sharing. Dr. Gillman emphasized that although ECHO's staff is small, the program is large and complex with many pressing demands.

Nsedu Obot Witherspoon, M.P.H., a member of the ECHO external scientific board, a Council working group, outlined the recommendations endorsed by the board. The U mechanism cooperative agreement was endorsed for its ability to combine strong scientific leadership from the NIH with engagement, transparency, and transdisciplinary team science, and the board recommended utilizing a mentoring leader to guide decision-making. Ms. Witherspoon noted that the ECHO-wide cohort effort must balance the power achieved by combining cohorts with the possibility of repeating past approaches deemed too expansive. To avoid this, the board recommended maintaining a manageable size and focusing on harmonization to support a small number of early successes, which will prove the program's benefits.

The external board recommended that the IDeA Network focus on a small number of home-grown clinical trial protocols with low participant burdens and the ability to deliver early results. Ms. Witherspoon encouraged realistic assessments of the network's resources, a strong but nimble leadership committee, and collaboration with experienced networks. The board also recommended that the data coordination and operations center receive guidance and support through the first clinical trial or longer. Ms. Witherspoon emphasized the importance of ensuring that this high-profile effort with significant NIH investment is successful.

Insufficient staffing has hindered ECHO's efforts to date, so although many programs are challenged to provide adequate staff in the current funding climate, the board recommended that the ECHO program's magnitude justified a hiring exemption based on public health need. Ms. Witherspoon added that ECHO also should begin communicating with the public at large and other advocacy organizations via the website, social media, and outreach to stakeholders.

Discussion Highlights

- Dr. Gillman explained that the Data Analysis Center coordinated by Johns Hopkins University and RTI International captures, curates, manages, and analyzes most of ECHO's data. In the future, this resource will be available for both ECHO and non-ECHO investigators. A public use data set with anonymized data also is planned, though its location has not yet been identified.

- Although investigators and the scientific board currently do not interact directly, Dr. Gillman acknowledged a desire for board members to be more informed about activities within the investigator community. Members are invited to attend meetings but often are unable to do so; Ms. Witherspoon added that the board's leadership recommendations incorporate current grantee coordination meetings.

- Ms. Witherspoon noted that the steering committee and mentor leaders are having extensive conversations to clarify the distinctions between their roles. Dr. Gillman commented that although steering committee meetings often include scientific discussions with program staff and project scientists, only recently have these groups been able to move beyond process discussions and toward scientific progress.

- Dr. Gillman acknowledged the challenge of organization and noted that the coordinating centers have helped to organize some of the program's innovative ideas. He emphasized that ECHO is working to institute a quality improvement cycle.

- In response to a question about staffing, Dr. Gillman explained that current staff are managing well but innovation and expansion are limited at current levels.

- When asked about the program's ability to encompass research with diverse communities given the current limitations, Dr. Gillman explained that the cohorts currently mirror the racial and ethnic diversity of U.S. children as a whole, and ECHO is working particularly hard to coordinate

with tribal nations. The Navajo Birth Cohort Study now is part of ECHO, and a stakeholder working group has developed principles of engagement with all peoples and communities for both the cohorts and the clinical trials network. Dr. Gillman emphasized that the IDeA Network is intended for underserved and rural populations, but the challenge is to maintain a view to diversity and disparities in future activities. On the investigator side, diversity is not ideal but could improve as younger investigators are added. Providers in the clinical trials network are more diverse, and a subgroup of the stakeholder working group is tasked with ensuring community engagement from both native and racial and ethnic minority communities.

- In response to a question about the U mechanism, Dr. Gillman clarified that the cohorts must pass certain milestones and metrics, but the program intends to arrange greater control for the investigators within the boundaries set by the NIH; the data sharing and policy documents, as well as the ECHO-wide data collection protocol, were created by the investigators. Council members encouraged the committee to rethink the level at which the U mechanism would operate given the desire to encourage research from the ground up, potentially in different ways for the two components of ECHO.

- When asked about mechanisms to incorporate information from related cohorts or literature, Dr. Gillman clarified that the current investigator purview includes some such efforts. He noted that the cohorts tend to be slightly ahead of the clinical trials, so information generally passes in that direction. Collaborative discussions with similar programs have occurred, and ECHO is monitoring activities at other ICs for ideas.

IX. UPDATE AND INPUT—OFFICE OF RESEARCH ON WOMEN'S HEALTH STRATEGIC PLAN

Dr. Clayton explained that among 16 peer high-income countries, the likelihood of women to reach the age of 50 is lowest in the United States by a significant margin, and the United States is the only one of those countries in which the rates are not increasing. She pointed out that the term "women's health" refers to everything that affects the health of women, including the many health conditions and health determinants that are specific to women, are more common or serious in women, have distinct causes or manifestations in women, or have different outcomes or treatments in women. ORWH's mission encompasses sex and gender influences in the context of biopsychosocial and life course factors at all life stages and across the biomedical research continuum.

Dr. Clayton proposed that ORWH's first vision statement emphasize that sex and gender influences should be integrated into the biomedical research enterprise; that every woman should receive evidence-based disease prevention and treatment tailored to her own needs, circumstances, and goals; and that women in science should reach their full potential. She noted that although this vision aligns with ORWH's past efforts, these goals have not yet been achieved. Dr. Clayton emphasized the importance of a multidimensional perspective to address the issues facing women, but she acknowledged that the complexity of such an approach has limited its application to date.

Within the NIH, integration of sex and gender considerations occurs differently in each IC, although each IC's area of focus includes research related to women's health. ORWH achieves its mission by partnering with ICs to co-fund relevant research rather than through independent grants. Dr. Clayton highlighted the success of the recent policy that sex as a biological variable (SABV) must be factored into research designs, analyses, and reporting for vertebrate animal and human studies. Administrative supplements offered by ORWH allow investigators to add the other sex or additional analyses of both sexes to their studies, and a new supplement program is available for understudied, underreported, and

underrepresented populations. ORWH has focused particular effort on the field of neuroscience, which historically included minimal consideration of SABV and a lack of transparency in reporting the sex of subjects. Dr. Clayton emphasized ORWH's early support for the BRAIN Initiative, which included consideration of both male and female animals prior to the institution of the official policy, and noted stipulations in the 21st Century Cures Act that affect women's health, including a requirement that Phase III trials report results from analysis for sex differences.

ORWH now is soliciting input from stakeholders about potential strategic priorities based on responses to an initial request for information (RFI) from a wide variety of entities and broad somatic categories. Dr. Clayton highlighted several points gathered from the RFI responses. Cardiovascular disease remains the leading cause of death for women in the United States, and issues both during and many years after pregnancy affect women's mortality and susceptibility to other conditions. Mental health is another critical issue to address, particularly related to how mental illness is integrated with other aspects of health. Additional RFI points include potential discovery areas, such as the microbiome and epigenetics, and public health considerations, such as health behaviors and the environment.

ORWH's primary strategic goal is to conduct and support relevant research, continuing and increasing its role as a facilitator of collaboration and communication with ICs across the NIH. Dr. Clayton emphasized the importance of multidimensional considerations, intentional integration, and interdisciplinary approaches as recurring themes in the draft strategic priorities. The office also will work to integrate sex and gender considerations throughout major NIH initiatives and develop and enhance research methods and resources, such as a new online course to educate scientists on SABV integration. Dr. Clayton pointed out that the majority of publications are not yet routinely disaggregating results by sex and gender or transparently reporting the sex of study animals, and ORWH will fulfill its strategic goal related to dissemination by working with journal editors, publishers, and other relevant parties to improve reporting of SABV. The office also will continue to advocate for women to achieve their full potential in biomedical careers. Critical to achieving these priorities is monitoring the success of NIH's investments in women's health research. Dr. Clayton explained that the draft strategic priorities next will be shared with leadership from all ICs and offices and distilled into feasible research priorities.

Discussion Highlights

- When asked whether ORWH would take a leadership role in publicizing clearer guidelines for personalized health care, particularly around breast cancer and cardiovascular disease, Dr. Clayton commented on the progress of the Women's Health Initiative in studying the effects of menopausal hormone therapy. ORWH will amplify the efforts of the National Heart, Lung, and Blood Institute, which has integrated these questions into its newest strategic vision to lead the work to fill this clear evidence gap.

- Council members commended the dual focus on women's health and careers of women in science. Dr. Clayton added that studies have shown a connection between the number of women on a research team and increased reporting of sex-specific results, emphasizing the integration of these two issues and the importance of both in efficiently achieving better science.

X. CLOSING REMARKS

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 May 17–18, 2018, noting that the actual length of the meeting has yet to be determined.

XI. ADJOURNMENT

Dr. Anderson adjourned the meeting at 3:52 p.m. on January 26, 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: 2018.03.06 11:50:57 -05'00'

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

Franziska B. Grieder 3.6.2018

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