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
May 20–21, 2021

Meeting Minutes

Day 1

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 and thanked Dr. Michael Lairmore for his service to the Council. The virtual meeting began at 11:00 a.m. on Thursday, May 20, 2021. The meeting attendees are identified below. Dr. Anderson then 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 L. Acebal, J.D., The Aspen Institute, Washington, DC
Maria Rosario G. Araneta, Ph.D., M.P.H., University of California, San Diego, La Jolla, CA
Kristin Ardlie, Ph.D., Broad Institute of MIT and Harvard, Cambridge, MA
Jeffrey R. Botkin, M.D., M.P.H., The University of Utah, Salt Lake City, UT
Linda Chang, M.D., FAAN, FANA, University of Maryland School of Medicine, Baltimore, MD
Graham A. Colditz, M.D., Dr.P.H., M.P.H., Washington University School of Medicine in St. Louis, St. Louis, MO
Andrew P. Feinberg, M.D., M.P.H., Johns Hopkins University, Baltimore, MD
Rick Horwitz, Ph.D., Allen Institute for Cell Science, Seattle, WA
Patricia D. Hurn, Ph.D., R.N., University of Michigan, Ann Arbor, MI
Kevin B. Johnson, M.D., M.S., Vanderbilt University Medical Center, Nashville, TN
Paul J. Kenny, Ph.D., Icahn School of Medicine at Mount Sinai, New York, NY
Gary A. Koretzky, M.D., Ph.D., Weill Cornell Medical College, New York, NY
Richard D. Krugman, M.D., University of Colorado School of Medicine, Aurora, CO
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
Edith P. Mitchell, M.D., FACP, Thomas Jefferson University, Philadelphia, PA
Charles P. Mouton, M.D., M.S., The University of Texas Medical Branch at Galveston, Galveston, TX
Megan O'Boyle, Phelan-McDermid Syndrome Data Network, Arlington, VA

Rhonda Robinson-Beale, M.D., Blue Cross of Idaho, Meridian, ID
Susan Sanchez, Ph.D., The University of Georgia, Athens, GA
Jean E. Schaffer, M.D., Joslin Diabetes Center, Boston, MA
Scout, Ph.D., National LGBT Cancer Network, Pawtucket, RI
Anna Maria Siega-Riz, Ph.D., M.S., University of Massachusetts Amherst, Amherst, MA
Russell N. Van Gelder, M.D., Ph.D., University of Washington, Seattle, WA

Council Members Absent

R. Paul Johnson, M.D., Emory University School of Medicine, Atlanta, GA
Sachin Kheterpal, M.D., M.B.A., University of Michigan Medical School, Ann Arbor, MI

2. Liaisons

Joseph M. Betz, Ph.D., Acting Director, Office of Dietary Supplements, DPCPSI
Janine A. Clayton, M.D., Director, Office of Research on Women's Health, DPCPSI
Maureen M. Goodenow, Ph.D., Director, Office of AIDS Research, DPCPSI
Susan K. Gregurick, Ph.D., Director, Office of Data Science Strategy (ODSS), DPCPSI
Franziska B. Grieder, D.V.M., Ph.D., Director, ORIP, DPCPSI
Christopher J. Lynch, Ph.D., Acting Director, Office of Nutrition Research, DPCPSI
George Santangelo, Ph.D., Director, Office of Portfolio Analysis (OPA), DPCPSI
David M. Murray, Ph.D., Director, Office of Disease Prevention (ODP), DPCPSI
Irene Avila, Ph.D., Assistant Director and **Karen L. Parker, Ph.D., M.S.W.,** Director, Sexual & Gender Minority Research Office (SGMRO), DPCPSI
William T. Riley, Ph.D., Director, Office of Behavioral and Social Sciences Research (OBSSR), DPCPSI
Marina L. 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* Member Absent

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

4. Presenters

Kristin Ardlie, Ph.D., Director of the GTEx Laboratory Data Analysis and Coordination Center, Broad Institute of Harvard and MIT
Ravi Basavappa, Ph.D., Program Leader, OSC, DPCPSI, NIH
Marie A. Bernard, M.D., Deputy Director, National Institute on Aging and Acting NIH Chief Officer for Scientific Workforce Diversity
Diana Bianchi, M.D., Director, *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), NIH
Laura Biven, Ph.D., Data Science Technical Lead, ODSS, DPCPSI, NIH
Graham A. Colditz, M.D., Dr.P.H., M.P.H., Council of Councils Member
Richard Conroy, Ph.D., M.B.A., Program Leader, OSC, DPCPSI, NIH
Susan Gregurick, Ph.D., Associate Director for Data Science, and Director, ODSS, DPCPSI, NIH
Adrienne Hallett, M.T.S., Associate Director for Legislative Policy and Analysis, NIH
Lyric Jorgenson, Ph.D., Acting Associate Director for Science Policy and Acting Director, Office of Science Policy (OSP), NIH

David M. Langenau, Ph.D., Associate Chief of Pathology for Research, Massachusetts General Hospital, Professor of Pathology and Atul K. Bhan Endowed Chair in Experimental Pathology, Harvard Medical School
Michael S. Lauer, M.D., Deputy Director for Extramural Research, NIH
Amy Lossie, Ph.D., Program Officer, National Institute on Drug Abuse, NIH
William T. Riley, Ph.D., Director, OBSSR, DPCPSI, NIH
Elizabeth Wilder, Ph.D., Director, OSC, DPCPSI, NIH

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

Franziska B. Grieder, D.V.M., Ph.D., the executive secretary for the NIH Council of Councils, 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 April 14, 2021.

- Minutes from the January 29, 2021, meeting are posted on the DPCPSI website. The minutes from this meeting also will be posted there.

C. Future Meeting Dates

The next Council meeting is scheduled to be held virtually on September 17, 2021.

II. ODSS CONCEPT CLEARANCE: ADDRESSING A WORKFORCE GAP IN DATA GOVERNANCE FOR AI AND BIOMEDICINE

Laura Biven, Ph.D., the Technical Lead for Data Science at ODSS, introduced a potential new program for workforce development titled, "Developing Experts for Better Biomedical and Behavioral Research Data: FAIR and AI and Machine Learning–Ready Data." The Artificial Intelligence (AI) Working Group of the Advisory Committee to the Director (ACD) developed a report outlining three areas—data, ethics, and people—in which the NIH could advance the use of AI and machine learning, as well as advance AI and machine learning itself. This program touches on all three areas, but focuses primarily on people. To make use of AI and machine-learning technologies for data-driven discovery across the NIH, data need to be of high quality and be findable, accessible, interoperable, and reusable (FAIR). Making data FAIR and AI and machine learning–ready requires special interdisciplinary skills. Skills likely needed are a combination of information sciences, computer science, AI and machine learning, and some expertise in

the biomedical and behavioral research fields. Experts with these skillsets will help the NIH develop new capabilities as they gain a better understanding of the specific needs of NIH researchers across projects and disciplines as they work with interdisciplinary teams to develop new tools and new capabilities. This program will weave ethical considerations throughout the data lifecycle and the development of AI and machine-learning technologies.

The program will be implemented with several interdisciplinary education and training centers and a coordinating center. The education and training centers will be funded for 5 years and will be expected to develop new curricula and training offerings, which must include ethical and culturally sensitive considerations. The centers also will develop outreach plans and partnerships to promote diversity among trainees, as well as assess diverse types of data. Ideally, these centers will catalyze long-lasting programs, and the centers will be asked to develop implementation plans for sustaining the workforce and incorporating expertise into the research culture. The centers also will assess the impact of their offerings, which will be used as part of an evaluation the program after 5 years. The education and training centers will reflect the interdisciplinary skills and competencies that are needed to reach these goals through such programs as multidisciplinary partnerships. Multi-institutional centers will increase the likelihood of gathering new and diverse talent and serve as a source of interesting data and use cases. The funding mechanism for the education and training centers is a U54 mechanism to allow flexibility in the types of trainees and the ways those trainees are supported. This funding mechanism supports linked awards in training, research projects, and administrative activities in a flexible way for the training and education centers. The coordinating center will connect the education and training centers into a network that also can share best practices, engage in cross-training, and align the community of experts and will be funded through a cooperative agreement.

The program overall will be funded for a total of $10 million per year through ODSS. Several NIH Institutes and Centers (ICs) are willing to partner with ODSS in support of this program, but those partnerships are not yet reflected in the budget. This budget will support 10 education and training centers for 5 years and one coordinating center. Approximately 125 students will be trained per year through this program. The solicitation is planned to be issued at the end of the current fiscal year, allowing awards in the summer of 2022. The first year of the program will be focused on establishing the education and training centers and a coordination center, arranging partnerships, developing the curricula, and determining communities of focus. The centers will begin training students in the second year, leading to operational centers in the fourth and fifth years. Throughout the process, the future of the centers will be considered, and evaluations will help determine whether to renew the program or develop new centers after the initial 5 years of the program.

Dr. Biven requested feedback on the potential sustainability and culture change aspects of this program. Although the initial investment is for 5 years, ODSS hopes this will establish training programs beyond those 5 years and catalyze culture change. The training and education program will need a sustainability plan, and the trainees who complete this program will need to be incorporated into the research culture. The NIH also will need to assess the program after the initial 5 years.

Discussion Highlights

- The discussants, Drs. Kevin Johnson and Graham Colditz, provided their comments. Dr. Johnson cautioned that the timeline is ambitious; he suggested developing a centralized set of resources, rather than requiring each center to develop its own programs in parallel. He expressed concern about several issues and noted the current lack of knowledgeable faculty in these areas and the lack of structure to leverage community partners. He suggested changing the structure to an initial phase of leveraging groups that already have training programs in place and that could focus on these areas to demonstrate their expertise in curriculum development, competency development,

and curriculum validation. Dr. Johnson emphasized that this is an important area, but this proposed program is not sufficient to produce meaningful change, trust, and useful byproducts.

- Dr. Colditz also noted the ambitious timeline and the high demands this would place on the coordinating center. He agreed that the goal is essential, but the concept is overly ambitious and might hinder progress. He added that the 5-year model does not provide adequate time for developing the curriculum, recruiting, training, and achieving success in the workforce.
- When asked if recruitment of underrepresented minorities would be a focus, Dr. Biven explained that some centers will specialize in certain activities, including potentially the recruitment of underrepresented minorities.
- Dr. Biven clarified that the program plans to make supplements to existing training awards this year to get a head start on the program. She also noted that the 5-year time period is flexible.
- Council members suggested including existing experts in the program and incorporating the private sector. They also noted that existing data on race and ethnicity are flawed, so efforts outside this initiative will be needed to improve how these data are gathered. Council members also suggested adding a formal requirement for collaboration with bioethics centers.
- Council members suggested a shorter award to develop a curriculum, an outline of the career path, and metrics of success and sharing those guidelines with the help of the coordinating center before the main component of the program is launched.
- In response to a question about this program's relationship to the Bridge2AI program, Dr. Biven explained that she works closely with that team. Several actions have been taken to ensure that this program would harmonize with Bridge2AI and move the community in a harmonized direction. Bridge2AI is focused on flagship data-generation efforts, and this proposal is broader and will reach more of the NIH community.
- Dr. Biven underscored that there is a need to change how data are managed to build a long-term ecosystem suitable for using AI and machine-learning technologies on research data. This culture change requires fostering experts who have knowledge in a mix of information and computer sciences and biomedical and behavioral sciences. She noted that this training program will benefit a broad range of data science, but it does include a special focus on AI and machine learning because that is an area with significant need for iterative dialogue between groups of data users.
- Council members expressed concern that making this an entire career path at this stage in the field's development is premature.
- Dr. Anderson noted that Congress has expressed some interest in beginning this project in 2022. He suggested that this could be a project with a pilot phase followed by a second phase based on success, or there could be a requirement that the program begin with a longer phase of curriculum development and engage relevant diverse communities with cultural competency. This change also should consider public–private partnerships and define what the program is trying to accomplish, whom they want to train, and the career paths of the trainees, as well as better defining success.

Vote

A modified motion to approve the Addressing a Workforce Gap in Data Governance for AI and Biomedicine concept—with changes to develop the curriculum, engage relevant communities, target

public–private partners, and develop a strategy of high-level success—was forwarded and seconded. The motion received 11 yes votes, 11 no votes, and one abstention. The concept was not approved.

III. NIH POLICY FOR DATA SHARING AND MANAGEMENT

Lyric Jorgenson, Ph.D., Acting Associate Director for Science Policy and Acting Director of OSP, outlined the NIH policy for data sharing and management. Data sharing and data accessibility benefits stewardship and trust as well as science. Access to data allows the validation of research results, and accessibility to high quality data sets removes the need to regenerate the data continually. Accessible data sets also accelerate future research directions and increase opportunities for collaborations, advancing high-quality research and the scientific enterprise. As the world's largest public funder of biomedical research, the NIH also must ensure public trust in its health research, and accessible data promote the purpose and accountability of NIH's use of taxpayer investments and good stewardship of taxpayer funds. Data stewardship goals also maximize research participant contributions and support appropriate protections of research participants' data.

The new NIH Policy for Data Management and Sharing requires all NIH-sponsored research to submit a data management and sharing plan. This policy replaces NIH's current data-sharing policy, which applies only to projects of more than $500,000 in a single year; the change shows that the NIH values data from projects of all sizes equally. After the data sharing plan is approved by the NIH, researchers must comply with their plan, so the plan is designed to be flexible to support changes in line with the data. The effective date of the Policy is January 25, 2023; until that date, OSP and OER are developing resources and working with the community to facilitate transitioning into the culture of data management and sharing. The Policy began development in 2016, and initial input was reflected in policy provisions released in 2018. The draft policy was released for public comment in 2019, and other stakeholder engagements were conducted, such as collaborating with the Secretary's Advisory Committee on Human Research Protections. The draft policy is currently undergoing Tribal Consultation.

The requirement to submit a plan will apply to research generating scientific data, which is defined as recorded factual material commonly accepted in the scientific community as of sufficient quality to validate and replicate research findings. This does not include laboratory notebooks, preliminary analysis, peer reviews, biospecimens, or physical objects. Data should be shared no later than the publication or end of the award, whichever comes first, but the length of time the data will be shared will depend on relevant requirements and expectations. Sharing should be the default practice for plans, and although sharing should fully be made available and accessible possible, plans may justify exceptions. Plans also should describe factors related to human subject protections, such as how privacy and confidentiality are protected and what existing laws, regulations, and policies are incorporated. Submitting a plan at time of application allows researchers to plan how they intend to use the data, which is a valuable tool in developing informed consent practices that incorporate potential future data sharing. Access to human participant data also should be controlled even if deidentified or lacking limitations on subsequent use. The plans should be submitted in the budget justification section of applications for funding reflecting the expenses associated with good sharing practices. Peer reviewers will comment only on the budget, but NIH program staff will assess data sharing plans for appropriateness. Researchers will be bound by the terms and conditions of the award, although plans can be updated over time with NIH program approval. Compliance will be monitored and factored into future funding decisions.

Reasonable costs associated with data sharing and management are allowed in the budget requests. Although typical costs of doing business (e.g., gaining access to data) are not considered data-sharing costs, these costs continue to be allowable elsewhere in budget requests. Flexibility in repository selection, except for repositories specified by the funding IC, is included to account for NIH's diversity of

data; established repositories are encouraged whenever possible, and criteria for identifying appropriate repositories, which are critical to shifting the culture, are included.

To consider implementation, the program convened approximately 1,700 people over a 2-day workshop to discuss best practices in data management and sharing, as well as challenges and solutions. Workshop participants determined that practices mindful of secondary data users are necessary for useful data sharing, metrics for assessing value must be developed, and costs associated with making data available are worth the return in advancing the scientific enterprise. The community continues to be engaged on these topics, and more resources are anticipated before implementation.

Discussion Highlights

- When asked about policies the NIH could advance to reduce the burden of data sharing, Dr. Jorgenson confirmed that OSP is exploring how to reduce burdens for institutions that have ensured appropriate mechanisms are in place.
- In response to a question about modular grants, Dr. Jorgenson explained that the goal is to make data sharing part of the research process, which requires larger overall budgets to accommodate data-sharing costs without affecting research budget cap.
- Council members pointed out that publication timelines often are long and suggested aligning data release with pre-print. Dr. Jorgenson confirmed that making data available as soon as possible, including at the time of pre-print, will be encouraged, especially when balanced with the need to ensure that data are robust and accurate.
- Dr. Jorgenson explained that the program is taking a holistic approach to compliance. Plans will be made publicly available, and data shared in established repositories should be easy to find and link. Data citation also will be included in the project report closeout.
- When asked about small business considerations, Dr. Jorgenson commented that patent protections on data sets will be acceptable justifications for limits on data sharing.
- Dr. Jorgenson explained that much of the work has been coordinated with other groups to ensure that consistent guidance is provided to the research community. She commented on the ideal of building a "one-stop shop" where data can be submitted and then shared as needed with any parties that can use them.
- In response to a question about the current ecosystem of personal data gathering and selling, Dr. Jorgenson agreed that participants should have a broader choice to share their data, and its life beyond the researchers' needs should be considered. Researchers must respect the needs of both participants who want their information used only for a specific study and those who want their data shared broadly to advance a cause.

IV. COMMON FUND PROGRAM REPORT: HIGH-RISK, HIGH-REWARD PROGRAM: IMPACT OF TARGETED OUTREACH AND ANONYMIZED REVIEW PILOT

Ravi Basavappa, Ph.D., a Program Leader in OSC, reported on the effects of targeted outreach conducted by the Common Fund's High-Risk, High-Reward Program. An ACD working group evaluated the High-Risk, High-Reward Program and found that—although the program is effective in supporting unusually innovative and impactful research and underrepresented groups are not adversely affected by the review processes—the applicant pool did not reflect the diversity of the biomedical research workforce. The group recommended that the program work to improve the diversity of the applicant pool by enhancing outreach efforts and piloting an anonymized review. Dr. Basavappa listed the outreach activities the

program engaged in or planned to engage in 2019 and 2020, such as conferences focused on underrepresented minorities, blog posts encouraging applicants, emails to officials at minority-serving institutions, and booths at NIH regional seminars. Efforts in 2019 did not result in a significant increase in applicant demographics as represented in the 2020 applicant pool, and the planned 2020 efforts were disrupted by the pandemic. The efforts will continue in 2021.

The anonymized review pilot was performed on the Transformative Research Award Initiative, one of four High-Risk, High-Reward Program initiatives but the only one focused on the project rather than the investigator, thus lending itself well to anonymization. Anonymity cannot be maintained for the entire review because the investigator and environment are required to be considered, but the program has been working closely with the Center for Scientific Review (CSR) to develop this pilot. The applicants were instructed on how to anonymize the specific aims and research strategies sections of their applications. The Transformative Research Awards were reviewed in three stages, beginning with the editorial board, which consisted of 25 scientists with diverse scientific backgrounds to provide broad scientific perspective. Only the anonymized specific aims page was made available to the editorial board, which included an overall description of the project, its innovative aspects, and how it is aligned with the spirit of the Transformative Research Awards program. The editorial board selected a subset of applications with transformative potential and sent them to the technical reviewers, who evaluated the specific aims page and the research strategies section, both of which were anonymized, and were asked to provide feedback on the innovation and impact in the form of comments delivered to the editorial board. The editorial board used this feedback to narrow the subset of applications further, then the full applications were made available to the board to review all five required review criteria. An internal NIH committee also reviewed the applications to ensure they were effectively anonymized.

The Science and Technology Policy Institute (STPI) has been commissioned to evaluate the process in near real time. In a survey of applicants with a 60 percent response rate, 25 percent agreed that an anonymized review process affected their decision to apply. More than 80 percent of the applicants said the instructions were adequate for anonymizing the applications; the primary suggestion was to provide additional examples, which the program will do for the next cycle. The editorial board also was surveyed, with a 44 percent response rate. None of the respondents was able to identify any participating individual or institution, and although 42 percent said the information provided in some anonymized specific aims sections was not sufficient to assess the transformative potential, this may have been related to the number of applications they had to review. More than 90 percent of respondents were somewhat or very confident in their assessments of the transformative potential. The technical reviewers responded at a 67 percent rate, with 81 percent of those indicating they could not identify individuals or institutions and that the materials provided were sufficient to assess the transformative potential. STPI also analyzed applicant diversity, finding a statistically significant lower proportion of male applicants, although there was no corresponding statistically significant increase in the proportion of female applicants. A significantly higher proportion of Black and African American applicants was identified, along with a significantly higher proportion of Hispanic and Latino applicants. Institutional diversity did not increase, but representation from Institutional Development Award (IDeA) state institutions and underserved institutions did. Overall, the trend is encouraging, and the High-Risk, High-Reward Program will continue outreach efforts and refine the Transformative Research Award anonymized review pilot process for 2 years.

Discussion Highlights

- When asked how the program might anonymize reviews for the awards more focused on candidates, Dr. Basavappa commented that in other awards, an anonymized component could be provided in earlier stages. Council members pointed out that increasing the diversity of the applicants would help.

- Dr. Basavappa confirmed that asking evaluators whether they could predict the gender or race and ethnicity of applicants is planned. Almost 20 percent of technical reviewers thought they could identify the applicant, so STPI will check if their guesses were correct. In such cases, the applicants were engaged in very distinctive research. How to keep such applications anonymous is an ongoing consideration.
- Dr. Basavappa commented on the year-to-year fluctuations in the rate of women applicants, noting that although the percentage of women finalists increased in the current year's cohort, no significant changes were made so this is likely due to statistical fluctuation. Broader programs to increase the success rates of women applicants may show effects over the remaining years of the program.
- Dr. Basavappa clarified that the survey response rates are considered robust.
- Although data on the numbers of Black and Latino applicants cannot be shared in a public forum, Dr. Basavappa commented that the CSR makes every effort to ensure that the reviewers include broad representation among underrepresented groups.

V. REPORT OF THE COUNCIL OF COUNCILS WORKING GROUP ON BASIC BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

William T. Riley, Ph.D., Associate Director for Behavioral and Social Sciences Research and the Director of OBSSR, explained that the basic behavioral and social sciences cover a range of fundamental mechanisms about behavioral and social functions relevant to health and well-being. In 2004, an ACD working group developed a report that led to the creation of OppNet, an NIH-wide effort to better identify and support NIH-wide basic behavioral and social sciences research (bBSSR). In 2020, a working group of the Council of Councils was convened to review how the bBSSR landscape has changed since that time, identify promising emerging areas and areas not adequately supported by the current NIH bBSSR portfolio, and determine whether any of those areas could be addressed by individual IC efforts or whether any would require NIH-wide efforts to address.

Research project grant funding for bBSSR was fairly flat at the NIH until 2014; from 2014 to 2019, it more than doubled in line with a 30 percent increase in overall NIH funding. This increase likely was strongly related to an increase in neuroscience-related bBSSR from the NIH Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, Alzheimer's research, and similar projects. Almost two-thirds of what is considered bBSSR also is coded as neuroscience; however, only about 15 percent of NIH grants coded as neuroscience also are coded as bBSSR. OPA classified bBSSR grants into 30 topic clusters, including large areas of specialty, such as neurobiology of behavior, and smaller areas, such as epigenetics. Some areas funded less often include sexual risk behaviors and sexual and gender minority health, neuroimmunology, neurocircuitry and receptors, and pain perception.

The working group identified eight promising areas of bBSSR. The first is in the behavioral, cognitive, and social neuroscience base, with a need to increase focus on event representation studies, some understudied brain regions, and integration of brain and periphery processes. This fits with areas that tend to be underfunded, such as pain perception and modulation or neuroimmunology and inflammatory processes. The second area is epigenetics, which is one of the more influential areas in terms of publication and citation rates despite being one of the smaller clusters in the bBSSR portfolio. Dr. Riley emphasized that interdisciplinary collaborations between the epigenetics field and the behavioral and social processes field should be increased.

Functions of sleep and sex stood out as areas that are important but underfunded, with no IC home for basic research on sleep and sexual function; sexual risk behaviors and sexual and gender minority issues also are one of the least-funded bBSSR topic areas. Dr. Riley noted that collaborations at the National

Center for Sleep Disorders Research and the SGMRO would help address some of those gaps. Another area of focus is infectious disease processes, which are particularly relevant in view of the COVID-19 pandemic. Little research was available on the social and behavioral processes that influence infectious disease transmission and mitigation, such as adherence to initiating and maintaining public health recommendations, risk communications, persuasion, decision-making under uncertainty by individuals at risk. The working group also noted a need to focus on social interactions and influences on health. Although research is available on intra-individual and population-level behavioral and social sciences, social interactions and influences connect those two domains and remain understudied. A funding opportunity announcement (FOA) recently released by OppNet focuses on social connectedness and isolation in health, so facilitating and expanding on that research could be an initial step forward.

Maintaining behavior change is another area of focus needing more research. The basic processes for initiating behavior change have been studied more than the factors that influence maintenance of those changes. Although some changes to behavior can be effective initially, some relapse tends to occur over time. Basic processes that are related include the shift from goal-directed to habitual learning and implicit learning processes. Another focus area is positive health processes. The NIH often focuses on disease processes, which is embedded in its organization, but this leaves limited attention to some of the basic processes that support improved health and well-being. Much of bBSSR has applications to how science itself is conducted, such as through open science efforts and replicability, or efforts around recruitment, retention, and ethics. Research is needed in areas like altruism, trust, and persuasion that are important components to build on adequate basic science base, so metascience is another important area that the NIH could focus on more.

The working group also took a comprehensive approach to how to address these focus areas. The first strategy is improving workforce diversity. Although the NIH has done significant work on that in recent years, it needs to be focused on in bBSSR efforts. Behavioral and social sciences research as a field has good gender diversity, although some senior leadership roles could be diversified more. However, the percentage of NIH grants given to Black and African American applicants is low; although some diversity is present in areas more related to field-based basic research on health disparities, community influences, and child development, the more laboratory-focused areas have very few awards. Work must be done both in addressing barriers and encouraging more diversity in those areas of research. The working group also discussed strengthening workforce capacity for data science. The working group also discussed the importance of fostering team science and transdisciplinary integration, which could be addressed in part by the newer Council of Councils Working Group on Behavioral and Social Sciences Integration. The working group also emphasized the need to strengthen research infrastructure and processes through encouraging more multilevel research. The group also suggested increasing coordination not only among NIH ICs, but also with the National Science Foundation, which is the other primary entity that funds bBSSR.

Discussion Highlights

- When asked whether the group discussed child abuse and maltreatment, Dr. Riley explained that the group did not focus on that, but it could fit under the population health-level efforts that were mentioned, as well as resilience. He noted that OBSSR also has been working on a broad program of violence prevention research.

Vote

A motion to accept the report of the bBSSR Working Group was forwarded and seconded. The motion passed with one abstention.

VI. COMMON FUND CONCEPT CLEARANCE: HUMAN BIOMOLECULAR ATLAS PROGRAM (HuBMAP) PRODUCTION PHASE—PROGRAM UPDATE AND CONCEPT CLEARANCE FOR TWO RFAS

Richard Conroy, Ph.D., M.B.A., a Program Leader in OSC, presented a concept to issue two new initiatives as a part of the Human BioMolecular Atlas Program (HuBMAP). HuBMAP is an integrated consortium that was established to catalyze the development of a framework for mapping the human body at single-cell resolution. Funding opportunities are organized around five steps: accelerating the development of next-generation tools and technologies, generating foundational 3D human tissue maps, establishing an open data platform, collaborating with the research community, and supporting pilot projects that demonstrate the value of HuBMAP resources. The program is divided into three phases—setup, scale up, and production—and is nearing the end of the scale-up phase. Many of the program awards will be carried over into the production phase.

A progress evaluation identified five areas for emphasis: (1) scaling up high-quality data generation; (2) ensuring data quality, reproducibility, and robustness; (3) integrating data across scales and molecular classes; (4) thinking broadly about what constitutes a map; and (5) engaging the community to determine needs. Areas 1 and 2 highlight the need to focus on generating high-quality data sets using validated assays. Areas 3 and 4 represent key challenges to address in the production phase. Area 5 is central to the role of HuBMAP in the wider ecosystem. Dr. Conroy emphasized that HuBMAP has made significant progress over the past 3 years. The principal investigators prepared a paper within 3 months of the first meeting, more than 57 papers have been published to date, and a series of additional publications are planned for the summer of 2021. Dr. Conroy outlined the workload for the components involved in HuBMAP. The first data set was generated in the summer of 2020, and the second data release is scheduled for the summer of 2021.

Dr. Conroy outlined potential applications of HuBMAP data, emphasizing that the central focus of HuBMAP is understanding spatial organization. HuBMAP is developing tools for analyzing data sets to build reference data sets for different organs. The Consortium has devoted time and effort to obtaining expert input on annotations to ensure consistency with current use, as well as the underlying common coordinate framework ontology. The HuBMAP Integration, Visualization, and Engagement (HIVE) Collaboratory presently is developing a range of tools to make these reference data sets more usable by the broader research community. HIVE manages data generated by the HuBMAP Consortium; coordinates internal and external Consortium activities; develops novel tools for visualizing, searching, and modeling data; and is building an atlas of tissue maps.

Two key challenges identified from the production phase focus groups were (1) the spatial and molecular integration of data onto 3D maps and (2) the construction of richer references and use cases in collaborating with the broader community. The identification and annotation of functional tissue units and clusters of cells associated with specific tissues and organs is an area of active study. Consideration of functional tissue units in 3D for 3D mapping is a long-term challenge. Additionally, the Consortium is working actively to prevent the different types from becoming siloed and to build a comprehensive atlas. Additional opportunities are available for developing richer references and use cases. The Consortium is leveraging partnerships and prior work to accomplish this task. Additional challenges include defining reference maps and ensuring that the data remain useful downstream. The two conditional initiatives are to reissue the HIVE request for applications (RFA) and to issue a new RFA for demonstration projects that will address well-defined biological challenges using HuBMAP-generated resources.

Discussion Highlights

- The discussants, Drs. Rick Horwitz and Jean Shaffer, provided their comments. Dr. Horwitz pointed out that a cell atlas extending beyond HuBMAP will require the early and aggressive coordination that HuBMAP offers. He theorized that this initiative would jumpstart a transformative use of maps and the tools that support them. Dr. Horwitz noted that the initiative plans to coordinate many types of data and suggested that focusing on a smaller set of standardized technologies would be a better first step. Dr. Conroy explained that a core set of assays have been defined that will be requested in the reissue of the tissue mapping centers, and assays will be adjusted based on performance.
- Dr. Shaffer asked whether target areas have been identified and what considerations related to the number of donors have been identified. Dr. Conroy commented that the focus of the production phase will be *in situ* mapping, adding that HuBMAP is interested not only in activities within cells but also in the extracellular environment, which must be studied *in situ*. The number of donors is an ongoing discussion with the consortium; some limitations surround acquisition of some tissues and from some groups. Over the past few years, HuBMAP has had more success studying more tissues from a smaller number of donors and exploring in detail the relationships within an individual than acquiring a large number of donors. The next phase likely will be an evolution of what has worked so far and an increased focus on mapping and generation of data sets that will be useful downstream. Additional development of tools likely will be required to open the work to the community.
- When asked how to ensure that a small number of donors reflects standard human biology, Dr. Conroy commented that many other programs are doing similar work with different outcomes, and HuBMAP collaborates with such programs to gather reference material for specific tissues.
- Dr. Conroy commented that the working groups have been thinking carefully about how to make clear that HuBMAP is actively engaging in the wider research community and communicating its opportunities available for researchers to participate. He noted that researchers involved with other mapping efforts will have the opportunity to collaborate with HuBMAP. Dr. Conroy also welcomed ideas for new ways to involve researchers who are not yet part of these efforts.

Vote

A motion to approve the HuBMAP Phase 3 Concept for reissue was forwarded and seconded. The motion passed with no abstentions.

VII. EXTRAMURAL RESEARCH IN THE ERA OF COVID-19

Michael S. Lauer, M.D., NIH Deputy Director for Extramural Research, presented a perspective on extramural research over the years and during the coronavirus disease 2019 (COVID-19) pandemic. Dr. Lauer began by presenting an overview of the NIH budget and highlighted trends in funding for research project grants (RPGs). The numbers of awards and awardees have increased in recent years, as has the number of early-stage investigators. Distribution of funding among racial and ethnic groups and genders has changed over time; the proportion of female awardees has increased, but disparities for Black investigators remain. Sharp payline decreases were observed for grantees in 2006 and 2013. Presently, the success rate is 20 percent to 21 percent, and the funding rate is nearly 30 percent. Dr. Lauer also discussed trends in the average cost of an RPG, which currently is about $560,000. He explained that the Biomedical Research and Development Price Index (BRDPI) is developed with the U.S. Bureau of Economic Analysis to account for inflation. In recent years, the BRDPI has approached the general rate of

inflation. Dr. Lauer also presented data demonstrating NIH's increased investment in both smaller and larger grants. He explained a greater proportion of funds is being spent on solicited projects.

The COVID-19 pandemic has had a significant impact on biomedical research. The Office of Extramural Research (OER) worked with the Scientific Workforce Diversity Office to assess the effects of the pandemic on researchers. The team released two surveys—one to vice presidents for research and one to researchers. Responses were received from 45,000 researchers and 224 research leaders. In the survey, about 55 percent of respondents expressed concern about the impact of the pandemic on career trajectories. About two-thirds of investigators stated that societal or political events negatively affect mental health. About 80 percent stated that the pandemic led to lower levels of research productivity. Postdoctoral researchers, particularly those conducting laboratory research, were more likely to express concern about career trajectories than more established investigators. Female early-stage investigators also were more likely to express concern about this topic; the NIH is offering deadline extensions and provided childcare allowances to provide support to research fellows with childcare responsibilities.

Dr. Lauer also emphasized the importance of maintaining a culture to promote ethical research practices, especially for COVID-19 research. He outlined several examples of misconduct over the years in the United States and in other parts of the world. Dr. Lauer affirmed that research institutions play a crucial role in this area. He stated that although scientific misconduct is relatively uncommon, the costs can be extremely severe. The OER has worked with various agencies and institutions to ensure that allegations are addressed in a parallel manner. Sexual harassment represents a major concern at research institutions; communication between institutions about allegations is crucial but often overlooked. Additionally, investigators can be dishonest in funding applications about various points, such as conflicts of interest. Dr. Lauer also emphasized the importance of honest and thoughtful research, expressing concern about anecdotal reports (e.g., on COVID-19) that cannot be verified.

Discussion Highlights

- In response to a question about NIH's stance on misinformation, Dr. Lauer commented that Drs. Francis Collins and Anthony Fauci have conveyed the best available scientific information to the public. Although the NIH is fundamentally a research agency, it is not unusual for IC directors to be witnesses at congressional hearings, particularly those related to priorities or budgeting.
- When asked about the ideal success rate, Dr. Lauer commented on the decrease in research that could be supported after the doubling period and noted that the NIH monitors investigators considered to be at risk, which includes those who are productive but losing funding in the hypercompetitive environment. The number of meritorious at-risk investigators who leave research could be 600 to 700 per year. Reports are distributed to ICs every 2 weeks identifying early-stage investigators and at-risk investigators who should be focused on.

VIII. PROPOSED NEW WORKING GROUP ON COMMON FUND DATA ECOSYSTEM

Elizabeth Wilder, Ph.D., the Director of OSC, outlined a proposed new working group to help with consideration of the Common Fund Data Ecosystem (CFDE) in its next iteration. The CFDE is unusual among Common Fund expenditures because it is an infrastructure investment intended to support and enhance the value of Common Fund programs, particularly those that generate large data sets. In 2018, the CFDE Coordinating Center Fund began working with several Common Fund Data Coordinating Centers to determine needs and opportunities for collaboration and to begin to create a data ecosystem. Each data-generating program within the Common Fund has its own data coordinating center, which works with the PIs who generate data to establish a harmonized data resource, but those centers

previously had been siloed. In 2020, the effort expanded to include Data Coordinating Center Engagement Awards, given to awardees who then collaborated with the CFDE Coordinating Center to establish an ecosystem of FAIR data sets. This exploratory phase will end in September 2022, at which time the Common Fund will determine the future scope and goals of the CFDE.

The proposed working group would review the vision established to date for the CFDE and the CFDE's progress to date and provide recommendations about its future. The principal goal of the CFDE is to enhance the value of the data sets, spur further discovery by fostering reuse of the data beyond its initial purpose and enable users to query multiple data sets simultaneously. The principal goal is to enhance the value of the Common Fund investment by enabling querying across data sets, which is a stewardship and infrastructure issue. Another goal is related to sustainability. Most Common Fund programs last for 10 years, during which time the data and tools they generate are available to the community, but building this ecosystem would ensure that what the programs develop remains available longer. Some data sets have been folded into existing repositories, but that is not always the case. The third primary goal is to train users to work with Common Fund data in a cloud environment, which is more secure and cost-effective. Although this is a shift in how people work, the CFDE aims to work actively with the user community to help transition to a cloud environment.

The proposed working group would review the current scope and goals of the CFDE, assess its status, and make recommendations about its future scope and goals. Particular focus areas include how the CFDE can enhance findability and accessibility, how it can support data harmonization and interoperability, how it can support computing in a cloud environment, how it can sustain access to data and tools after the program ends, and training and outreach. Ideally, the working group also would help consider the CFDE in the context of related NIH activities and ensure that the CFDE is aligned with best practices as the field moves forward.

Dr. Horwitz will chair the working group, which will last from June 2021 to May 2022. The working group would deliver a report to the Council at the May 2022 meeting, and if the Council accepts that report, it would be delivered to the NIH director; a response to the report would be developed and delivered at the September 2022 Council meeting.

Vote

A motion to approve the creation of the CFDE Working Group was forwarded and seconded. The motion passed with one abstention.

IX. ADJOURNMENT FOR THE DAY

Dr. Anderson adjourned the meeting at 4:02 p.m. on May 20, 2021.

Day 2

I. 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 meeting if they

[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.

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 44 ORIP applications with requested first-year direct costs of $14,682,851 and 1,254 Common Fund Applications with requested first-year direct costs of $2,075,026,551.

II. CALL TO ORDER

Dr. Anderson welcomed participants, NIH staff members, and members of the public to the second day of the meeting and reviewed the day's agenda. The virtual meeting began at 11:00 a.m. on Friday, May 21.

III. INTRODUCTION TO THE NEW CONGRESS

Adrienne Hallett, NIH Associate Director for Legislative Policy and Analysis, provided an introduction to the new Congress. The NIH has broad bipartisan support and has received substantial increases to its base funding in recent years. The President's Budget for FY 2022, although not released prior to the meeting, will include a $9 billion increase with a 2.5 percent general increase prorated across the ICs and $6.5 billion for a new proposal, the Advanced Research Projects Agency for Health (ARPA-H). NIH leadership is looking to take a leading role in combatting health disparities, including with the UNITE Initiative to end structural racism in research. COVID-19 research will continue, and the NIH is committed to focusing on the REsearching COVID to Enhance Recovery (RECOVER) Initiative, which will study the long-term effects of COVID-19, as well as mental and behavioral health related to COVID-19 mitigations, and general pandemic science to prepare for the next pandemic. The NIH also is focused on losses during the pandemic, particularly trainees and researchers who may be vulnerable because of the stage of their career or their caregiving responsibilities and the effects on clinical trials. As the NIH worked to coordinate the clinical trial networks to test as many therapeutic and vaccine candidates as possible during the pandemic, some networks had the capacity to join the effort even if they were not focused on virology and immunology, and making that transition easier and quicker in the next pandemic will be one focus. Rapid development of technologies was spurred by NIH's efforts, and lessons can be learned from that and applied to health technologies and diagnostics in general. Discussions also will occur about the proposed ARPA-H initiative.

Ms. Hallett explained that policymakers must be educated on relevant issues within scientific fields. One such issue is animal alternatives in research. Some members of Congress are pushing for the NIH to use alternatives to animals in research, particularly after the U.S. Environmental Protection Agency (EPA) announced that it would stop all mammal research by 2035. Ms. Hallett's team is educating members of Congress about how animal alternatives can be useful and in what fields alternatives are not possible. The diversity and inclusion conversation needs to be extended beyond vaccine trials into the broader research community, and partners will need to be engaged. Many members of Congress proactively offered to help promote NIH's issues in the previous year. Foreign influence in research is an important concern; those efforts should be supportive of transparency in research but not punitive or discriminatory. Gain-of-function research is in the press right now, with suggestions that this research could make a virus more transmissible or more virulent.

One of the main issues in Ms. Hallett's work is that many senior members of Congress who had worked closely with her office have retired or are retiring. A significant priority is to introduce the NIH to a new audience and develop new champions both for biomedical research in general and for specific areas, such as genomic privacy. Both new members and members who are now advancing into more senior roles in the near future will be included in these conversations.

Discussion Highlights

- When asked for additional information on the animal alternatives in research issue, Ms. Hallett explained that a small but vocal group of members of Congress long has been opposed to animal research; her office maintains a dialogue with them and ensures transparency regarding NIH's research. Recently, members have received the message from others that all benefits of research can be achieved without animal research. The belief is growing that the same level of research productivity can be maintained without animals because the alternatives exist and are ready to be scaled up. Although this is a myth, it is tempting for members to believe. Ms. Hallett emphasized the need to educate them on the differences between alternatives and the areas of science where alternatives never will be sufficient.
- Ms. Hallett clarified that developing expertise in specific subjects among members of Congress is a long process involving working with advocacy communities to identify a member who may have a personal interest, sending detailed articles and information on scientific advances, and offering briefings from experts to cultivate their interest.
- When asked about whether messages are coordinated between agencies, Ms. Hallett explained that agencies can only access members of committees that govern the issue they research—for example, EPA communicates with members of the Energy Committee, the National Science Foundation communicates with members of the Commerce Committee, and Ms. Hallett's office communicates with members of the Health Committee. More coordination may be encouraged by the Endless Frontiers Act and the President's Jobs Initiative.
- In response to a question about health disparities advocacy groups, Ms. Hallett explained that she has communicated with large advocacy groups on health disparities issues and with institutions that are engaged in health disparities across conditions. She added that this is a multifaceted conversation with many important stakeholders.
- When asked about ARPA-H, Ms. Hallett explained that although little information is available at this time, her team is reviewing related programs to identify components of success and challenges. More information will be available after the President's budget is released.

IV. NICHD UPDATE

Diana Bianchi, M.D., the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), presented an update on NICHD's new strategic plan, mission and vision. She began by emphasizing that NICHD is one of several ICs that contribute significantly to child health. NICHD formed the NIH Pediatric Research Consortium to provide a forum for program representatives from the NIH ICs to discuss important issues related to child health. NICHD also contributes significantly to NIH research on maternal health.

Previously, NICHD developed an extensive mission statement but lacked a strategic plan. The new strategic plan reflects a 2-year effort with input from multiple communities. NICHD's new mission is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all. The mission incorporates reproductive biology and health at large, and the phrase "optimizing abilities for all" refers to NICHD's role in coordinating the National Center for Medical Rehabilitation Research.

To develop the strategic plan, 270 scientific ideas were distilled into five research themes. The themes are (1) understanding the molecular, cellular, and structural basis of development in humans and animal models; (2) promoting gynecologic, andrologic, and reproductive health; (3) setting the foundation for healthy pregnancies and lifelong wellness; (4) improving child and adolescent health and the transition to

adulthood; and (5) advancing safe and effective therapeutics and devices for pregnant and lactating women, children, and people with disabilities.

Dr. Bianchi also outlined the Human Placenta Project. Outcomes of the project were highlighted recently at a 2-day workshop. These reports included detailed functional imaging of the placenta to track oxygen and blood flow, advances in circulating factors (e.g., mRNA, exosomes, microRNA), and how those molecules communicate among the fetus, the placenta, and the pregnant person. These data can serve as biomarkers to identify high-risk pregnancies. Additionally, the size and the shape of the placenta at the time of delivery predicts risk factors for cardiac disease, diabetes, and other conditions later in life. Dr. Bianchi emphasized that the placenta is the center of the chronic disease universe.

In the beginning of the COVID-19 pandemic, the Maternal–Fetal Medicine Units Network examined maternal and neonatal outcomes for pregnant people both with and without SARS-CoV-2 infection. A recent publication details results from these efforts, and pregnant and lactating people have participated in research to answer questions about complications related to COVID-19. With support from the Office of the NIH Director, NICHD also developed a program to leverage resources and existing networks from the National Institute of Allergy and Infectious Diseases; the National Heart, Lung, and Blood Institute; and NICHD to capture data on hospitalized children with multisystem inflammatory syndrome of childhood. The network has obtained funding for Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID).

The network also has obtained funding from the Rapid Acceleration of Diagnostics Radical (RADx-rad) Initiative for the Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds) study. NICHD has obtained funding for the Return to School Diagnostic Testing Approaches through RADx Underserved Populations (RADx-UP). NICHD also is participating in an NIH-wide effort to examine Post-Acute Sequelae of SARS-CoV-2 infection. The Implementing a Maternal health and Pregnancy Outcomes Vision for Everyone (IMPROVE) initiative is addressing social and biobehavioral research, as well as foundational biology. NICHD also is involved in the NIH-wide Maternal Morbidity and Mortality Task Force and the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) project. She concluded by emphasizing NICHD's vision of healthy pregnancies, healthy children, and healthy and optimal lives.

Discussion Highlights

- When asked about the opportunity to assess the prevalence of certain conditions and examine the placentas of women with COVID-19, Dr. Bianchi noted the high levels of interest in how COVID-19 affects the placenta, which appears to be very complicated. Gestational age is an important variable, and the placenta may provide a shielding effect, but it does not work in everyone. Several occurrences of vertical transmission to the fetus have occurred, and an increase in stillbirths was related to COVID-19. It is possible these were already high-risk pregnancies and patients did not visit their doctors as often because of the pandemic. Some reports suggest that the B.1.1.7. variant of SARS-CoV-2 is affecting the placenta in different ways. The pathology in the placenta associated with stillbirths is much more severe. She emphasized that the "whole story" is not yet known, but the difference in effects of the variants on the placenta is interesting.
- In response to a suggestion that reevaluating the mission and vision statements should be a regular part of strategic plan updates, Dr. Bianchi explained that the plan was developed following a 2-day workshop that included many stakeholders and a mission and vision subgroup. Some participants came from a marketing background. The 21st Century Cures Act now mandates that ICs update their strategic plans every 5 years, and each IC does have a mission

statement. She commented that mission and vision statements encourage an IC to define where it wants to lead and where it wants to partner. One achievement is that NICHD received no pushback on its statements.

V. PRECLINICAL CANCER MODELING USING ZEBRAFISH

David Langenau, Ph.D., a professor of pathology and Atul K. Bhan Endowed Chair in Experimental Pathology at the Harvard Medical School, shared aspects of his research on preclinical cancer modeling in zebrafish (*Danio rerio*). His laboratory studies the processes by which cancer stem cells (CSCs) relapse and progress to cancer to understand how rare cell types within the tumor drive tumor regrowth. Improved understanding of these processes can lead to targeted therapies to eradicate these tumors. In the Langenau laboratory, zebrafish are a discovery tool to better understand the biology of two pediatric cancers: rhabdomyosarcoma (RMS) and T-cell leukemia. RMS, a common pediatric cancer of the muscle, consists of two subtypes: embryonal or fusion-negative (FN) and alveolar or gene fusion–driven. Approximately 80 percent of RMS patients who relapse after treatment will succumb to the disease. The first exemplars Dr. Langenau developed, the transgenic zebrafish models of embryonal RMS (ERMS), enabled mapping the gene expression signatures to the human disease and illustrated the dominance of the *RAS* pathway as an oncogenic driver of 90% of human FN RMS. Transgenic approaches for labeling tumor compartments revealed insight into ways that CSCs drive RMS, including via ERMS pathways.

Although mouse xenografts are the most common for preclinical studies and U.S. Food and Drug Administration investigational new drug (IND) submissions, these models have limited imaging capability, are expensive, and lack high-throughput ability. In an ORIP-funded project over the past 8 years, Dr. Langenau and his laboratory have been developing immune-deficient zebrafish models that are optically clear for imaging and cost-efficient, allowing tumor growth visualization at a single-cell resolution. These data were published in the June 13, 2019, issue of *Cell*. The protein kinase DNA-activated catalytic subunit (*prkdc*) and interleukin 2 receptor gamma (*il2rga*) null model demonstrated that engraftment of a wide range of human tumors (e.g., sarcomas, triple-negative breast cancers, melanomas) and patient-derived xenografts (PDXs) grow similarly in zebrafish and genetically engineered mice. In addition, the *prkdc*, *il2rga* null zebrafish model has been used in preclinical drug discovery studies evaluating a new combination therapy (Olaparib plus Temozolomide or [OT]) for Ewing sarcoma. The model responded to drug therapy (i.e., tumor ablation) sustained for 28 days after treatment. Parallel studies in representative RMS cell lines (SMSCTR, RH41, and RH30) suggest the OT combination could be effective in these tumors. PDX ERMS generated in NSG mice, the current gold standard for human cancer engraftment, was used to validate combination therapies at doses currently used in the clinic. Collectively, these zebrafish pediatric cancer studies have informed the first-of-its kind, open clinical trial for pediatric cancer at Massachusetts General Hospital and the Dana–Farber Cancer Institute.

Unique to zebrafish models is the ability to image cell-cycle kinetics of RMS *in vivo* and at single-cell resolution. Leveraging the Fucci cell-cycle methodology, Dr. Langenau and his laboratory demonstrated similar cell proliferation in zebrafish and mice in both ERMS and alveolar RMS (ARMS) cell lines across the cell cycle phases. Combined with real-time *in vivo* imaging, experiments further showed a strong Gap 2 (G2) cell-cycle (i.e., gap between DNA synthesis and mitosis) arrest with the OT combination at 7 days after treatment. Because drug resistance to OT has been shown in a subset of adult RMS, the next step was to develop therapy-resistant xenograft mouse models to evaluate this further. In all eight of the models developed, the phosphoinositide 3-kinase (PI3K) pathway was upregulated and was consistent across RMS subtypes. This upregulation correlated to an increase in drug efflux pump proteins, including ATP binding cassette (ABC) transporters. This therapy resistance model approach allowed re-sensitizing the RMS to OT therapy using fluorescent-labeled PI3K and ABC transport inhibitors at single-cell resolution and cell division, which could then be quantified. Dr. Langenau envisions zebrafish xenografts

enabling new preclinical therapies advancing to mouse xenografts, followed by resistance models, thus building a new xenograft pipeline for identifying combination treatments for humans.

The Langenau laboratory recently developed a new immune-deficient zebrafish model for engrafting human cancer that fully ablates mature T- and B-cells and natural killer cells. This new model has been used to engraft human T-cells, with sufficient uptake into peripheral blood and kidney marrow, and also is used for assessing chimeric antigen receptor (CAR) T-cell and bi-specific T-cell engager function *in vivo* in similar imaging methods to those used in mouse xenografts. In addition, Dr. Langenau collaborated with Dr. Mark Cobbold at Massachusetts General Hospital to identify new immune-oncology therapies—specifically antibody peptide epitope conjugates (APECs). Using the zebrafish xenograft permitted medium-throughput *in vivo* screening of the best APEC eradicators in ovarian cancer. Dr. Langenau reiterated that the zebrafish xenograft is a new and powerful drug discovery model allowing single-cell imaging of drug responses for immunotherapy, pharmacokinetics, and treatment responses.

Discussion Highlights

- When asked about advice to the NIH on the future of the zebrafish preclinical model, Dr. Langenau called attention to NIH initiatives focusing on cancer mouse models and those supporting RFAs; similar opportunities for developing other relevant cancer models, including genetically engineered zebrafish and/or zebrafish xenograft models would be appropriate.
- In response to a question about a threshold in zebrafish discovery studies as adequate without confirmation in mouse xenografts, Dr. Langenau explained that his laboratory corroborates the zebrafish xenograft studies as a routine practice. Although pharmaceutical company partners were enthusiastic to support advancing his zebrafish studies to a clinical trial, he anticipates the field's gaining confidence in these models as more studies are conducted and data are published.
- Dr. Langenau commented that animal models (e.g., mouse, fruit flies, worms, zebrafish) within the ORIP R24 Animal Program have been transformative for improving the understanding of cancer and preclinical modeling and urged continued/expanded support. Although other models are significant discovery tools, the mouse model current remains the benchmark for assessing in vivo efficacies of drugs, in part due to lack of validation studies directly comparing the utility of other models with mouse xenograft studies. These hurdles are expected to be addressed as more people adopt the zebrafish xenograft approaches and examples of their utility in predicting clinical responses are published more widely.

VI. PRESENTATION ON THE UNITE INITIATIVE

Marie A. Bernard, M.D., the Deputy Director of the National Institute on Aging and Acting NIH Chief Officer for Scientific Workforce Diversity, presented an overview of the NIH UNITE Initiative, which was announced in a special meeting of the ACD and developed in response to the murder of George Floyd and the disproportionate impact of the COVID-19 pandemic on Black Americans, American Indians, and Hispanic Americans. IC Directors have expressed a shared commitment to address structural racism. The killings of six Asian women in March 2021, punctuated the need for such an initiative.

UNITE is committed to delineating elements that perpetuate structural racism in biomedical research, both within and external to the NIH, and to factors that lead to lack of personnel inclusiveness, equity, and diversity. UNITE represents five interacting workstreams: *understanding* stakeholder experiences through listening and learning; supporting *new* research on health disparities, minority health, and health equity; looking *internally* at improving the NIH culture and structure for equity, inclusion, and excellence; being *transparent* by communication and accountability for internal and external

stakeholders; and assessing the *extramural* research ecosystem to see what needs to be changed in policy, culture, and structure to promote workforce diversity.

The U committee is responsible for performing a broad systematic self-evaluation on structural racism. The N committee is addressing longstanding health disparities and issues related to minority health and advancing health equity by ensuring transparency, accountability, and sustainability of resources for health disparities, minority health, and health equity research. The I committee will examine the NIH internally to determine how the organizational culture and structure can be changed to promote diversity, equity, and inclusion throughout the workforce, regardless of job classification. The I committee also is interested in whether NIH employees encounter race-related barriers to career advancement. The team is developing a performance standard for every IC director to be accountable for diversity, equity, and inclusion activities in coordination with the Scientific Workforce Diversity Office and the Office of Equity, Diversity, and Inclusion. The E committee is responsible for developing strategies to address funding disparities and is examining career pathways, institutional culture, and NIH processes. The T committee will ensure communication, accountability, and sustainability. The committee led the development of the NIH UNITE website and is organizing a town hall meeting in coordination with the with Office of Communications and Public Liaison. It also is launching an internal awareness campaign to diversify portraiture on the NIH campus.

The UNITE committees have proposed the following measures at the 2/26/21 unveiling of the initiative: Publicly commit to identifying and correcting any NIH policies or practices that may have helped to perpetuate structural racism; aggressively implement approaches to address the "Ginther gap" to enhance portfolio diversity; launch a multiphase, tiered, and integrated Common Fund initiative focused on transformative health disparities research; ensure a robust NIH-wide commitment to a National Institute on Minority Health and Health Disparities (NIMHD) RFA focused on the effects of structural racism and discrimination on health; develop a sustainable process to systematically gather and make public the demographics of NIH's internal and external workforce; implement policy changes that promote antiracism and remove barriers to professional growth for staff from diverse backgrounds, including underrepresented groups; appoint a Diversity Equity, and Inclusion Officer in every IC with direct access to the Director to track, advance, and coordinate IC-specific diversity, equity and inclusion efforts and actively participate in NIH-wide diversity efforts; and expand the Distinguished Scholars Program.

Dr. Bernard concluded by summarizing the present status of UNITE activities and other NIH efforts. The NIH Common Fund Initiative to Address Health Disparities and Advance Health Equity was issued 1 month after the ACD meeting, and the NIMHD RFA was published on March 23. Additionally, the National Institute of General Medical Sciences issued a Notice of Special Interest in projects addressing the impact of structural racism and discrimination on biomedical career progression. The BRAIN Initiative recently issued a FOA that enables the consideration of a plan to enhance diverse perspectives in the scoring of grants. The OER recently amended its data book to include data by race, ethnicity, and disability status. The Office of Equity, Diversity, and Inclusion has posted data about the demographics by race and ethnicity for NIH staff and is developing an anti-racism steering committee to examine policies and procedures that lead to injustice. As noted, the recommendation of a Diversity, Equity, and Inclusion officer for every IC has been modified to a performance plan expectation for every IC director to be accountable for diversity, equity, and inclusion activities in coordination with the Scientific Workforce Diversity Office and the Office of Equity, Diversity, and Inclusion.

<u>Discussion Highlights</u>

- Council members emphasized the importance of youth outreach, noting the difficulty of obtaining NIH support for high school programs and "hands-on" opportunities to foster careers in science, especially biomedical research. Youth programs also benefit participating investigators, and many

smaller foundations are interested in participating in this area; centralized guidance from the NIH would be beneficial.

- Council members pointed out the importance of disaggregating data, particularly among Asian Americans. For example, Pacific Islanders display the highestSARS-CoV-2 infection rates but are overlooked in the national narrative on public health. This issue also is relevant to Hispanic and Black populations.
- When asked whether UNITE includes components focused on increasing the scientific workforce, Dr. Bernard responded that the team is approaching the issue from a holistic perspective, focusing on early stages of development through the senior level. They are interested in both individual and systematic issues, with an initial focus on NIH's internal environment. Partnerships with outside organizations will be crucial in the future.
- In response to a suggestion that the NIH consider incentives for institutions and public–private partnerships, Dr. Bernard noted that diversity supplements can be awarded as early as high school. UNITE launched internally in October 2020, and the Faculty Institutional Recruitment for Sustainable Transformation (FIRST) FOA was released in December 2020. The extramural community has expressed significant interest in the initiative, and the team is interested in partnerships and is exploring best approaches in that area. Additionally, the CSR is exploring ways to address elitism in grant review panels.
- When asked about the inclusion of measures related to sexual orientation and gender identity, Dr. Bernard explained that the initiative is working closely with the SGMRO to address this topic.

VII. UNITE INITIATIVE AND THE ROLE OF DPCPSI OFFICES

Dr. Anderson commented on the UNITE Initiative and the role of DPCPSI Offices. Several DPCPSI Offices are providing supportive data and analytics. Two NIH Common Fund projects were developed, and RFAs were released after approval as concepts by the ACD; the second RFA is limited in eligibility to minority-serving institutions. Responses to the RFAs are promising. Additionally, a group is planning an NIH-wide program; two of the four co-chairs are from DPCPSI. The ODP is interested in expanding research on health disparities and disease; IC directors have committed to developing an NIH-wide program to address this issue.

VIII. SEQUENCE READ ARCHIVE (SRA) DATA WORKING GROUP INTERIM REPORT

Kristin Ardlie, Ph.D., the Director of the GTEx Laboratory Data Analysis and Coordination Center at the Broad Institute of Harvard and MIT, and Susan Gregurick, Ph.D., the Associate Director for Data Science and Director of ODSS, presented the interim report of the SRA Data Working Group. The SRA is one of the largest and most diverse data sets and is essential for many areas of biomedical research. In 2019, the NIH migrated the SRA through the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative to two cloud service providers, Google Cloud Platform (GCP) and Amazon Web Services (AWS). The SRA is growing exponentially, and about 15 percent of users are working in the cloud. Data are retained in the original format, normalized format with base quality scores (BQS), and normalized format without BQS. Replication of these data formats across multiple cloud platforms benefits investigators, but it is costly for the NIH.

The prior SRA Data Working Group recommended a new model for SRA data storage and retrieval in the cloud. They suggested that the original and normalized formats be retained in "hot" (i.e., active) and "cold" (i.e., inactive) storage for both formats and usage. Based on these recommendations, the three data

formats are distributed across the two storage tiers in GCP and AWS. Data "thawing" and "re-freezing" costs are paid by the NIH. Researchers can use the SRA in the cloud through National Center for Biotechnology Information web resources, as well as a tabular query interface associated with AWS and GCP. Retrieval from hot and cold storage can be accomplished through a web-based or cloud data delivery service.

Responses from a request for information indicate that many users appreciate NIH's efforts to maximize efficiency in retrieval through the new formats and the new tier system. Concerns included the loss of BQS and original format and the need for more training in cloud computing. Most users do not use the SRA in the cloud. Dr. Gregurick stated that the NIH will update the hybrid storage model to address the respondents' concerns. In addition, the NIH will continue to host training sessions, code-a-thons, and workshops to help researchers use the SRA in the cloud. One of the key developments since late 2020 is the expansion of the AWS Open Data Program within the STRIDES Initiative. This program supports data storage at no cost to the NIH or users and researchers. Dr. Gregurick explained that this partnership creates significant cost savings for the NIH.

Dr. Ardlie next presented an overview of the new working group. The working group's charge is to provide recommendations to the Council regarding evaluation of SRA data storage, management, and access in cloud service provider environments. The working group also will continue to provide feedback as the NIH monitors the effectiveness of strategies for the SRA through data collection and analysis of the solutions implemented to maintain efficiency in the storage footprint of the SRA. The working group will focus on evaluation of the SRA as a resource and other related issues, including but not limited to (1) analysis and evaluation of strategies for and changes to SRA data storage, management, and access, including impact for the biomedical research community; (2) recommendations on data retention, data models, and/or data usage that will keep costs to the NIH within sustainable levels while maintaining community access to this large public data resource; and (3) vision for future needs or opportunities, including sustaining the SRA as a community resource.

The working group proposed the following recommendations: (1) reduce costs and ensure that data remain equitable and sustainable; (2) explore tolerance and frequency for data retrieval in cost models; (3) explore data usage, data types, search, and access; (4) consider more cloud vendors to host SRA data; (5) consider the needs of users who do not use GCP or AWS cloud platforms; (6) promote cloud computing with representative examples; (7) pursue training and user feedback (e.g., workshops, tutorials); (8) consider incentives for researchers using the SRA to develop tools and algorithms; and (9) evaluate the impact of the SRA. Dr. Ardlie emphasized the importance of understanding usage patterns and defining user communities; the working group suggests conducting user surveys, engaging with training efforts (e.g., partnering with cloud platforms to provide credits for workshops), and obtaining information on intended use (e.g., including a description field for downloads). Training and monitoring are needed to advance the adoption of the SRA in the cloud.

Discussion Highlights

- In response to a question about time limits on contracts with cloud vendors, Dr. Gregurick explained that the transactional agreements with AWS and GCP extend until 2022; renegotiations will be considered at that time. Council members cautioned that expansion of the SRA might create challenges for contract renegotiation.
- When asked about the working group's future directions, Dr. Gregurick stated that a draft working group report is in progress and will be finalized this summer. A presentation will be conveyed to the Council in September with final recommendations. At that time, the working group will be completed, and further steps will be considered.

IX. COMMON FUND CONCEPT CLEARANCE: SOMATIC MOSAICISM ACROSS HUMAN TISSUES (SMAHT)

Amy Lossie, Ph.D., Program Officer, National Institute on Drug Abuse, presented a concept clearance for the SMaHT Program. The primary objective of the two-phase, 10-year program is to illuminate somatic variation and capture the role that somatic mutations play in the formation of the personal genome that underlies biological processes in human health. The program's three major Phase 1 initiatives are to generate a catalog of somatic variants, develop new tools to optimize the identification of variants, and create data and analysis toolkits, as well as a FAIR data workbench that integrates with the current genome browsers. The team is seeking $150 million for the program. SMaHT would represent the first effort to document somatic variation systematically and to develop new molecular and data-driven tools to characterize the role that somatic variation plays in the establishment and function of the personal genome.

After soliciting input via a request for information and two think tanks, the development team identified five broad areas: (1) creating a catalog of somatic variants in different cell types, (2) building data analysis pipelines to detect and annotate structural variants and other somatic mutations, (3) developing new sequencing technologies to enhance the sensitivity and spatial resolution of somatic variations, (4) exploring the role of model systems to examine biological consequences, and (5) ensuring alignment with similar programs to build common data benchmarks and analytical tools. Identified challenges include sensitivity (i.e., for low-frequency variants), specificity (i.e., sources of technical variation), and repetitive areas of the genome (i.e., understudied regions).

Four target outcomes have been identified for Phase 1: (1) a developmental trajectory of somatic mutations (e.g., defining points that are sensitive to somatic mutations, identifying environmental components that contribute to somatic mutation), (2) a better understanding of cell lineage mapping throughout the human body, (3) mutational signatures, and (4) a better understanding of the "dark genome" (i.e., "junk DNA"). Phase 1 goals for the project are to build personal genomes via documentation of single-nucleotide changes, as well as structural variants and mobile DNA in humans to understand the biology of somatic mutations across the lifespan; develop next-generation tools and technologies to improve the sensitivity and resolution of somatic variants; and develop a FAIR and standards-driven data workbench to visualize, analyze, and model SMaHT data alongside data from other sources that integrates with current genome browsers. Initiative 1, the establishment of tissue mapping centers, will create a catalog of somatic variants in core tissues. The purpose of Initiative 2 is to develop, optimize, and implement tools and data analysis pipelines to improve the sensitivity and specificity of detection. The purpose of Initiative 3 is to create an organizational hub for the consortium that coordinates with other groups.

The first phase of the program would begin tentatively in fiscal year 2023. The projected outcomes of the final project are a better understanding of the repetitive genome and its contributions to development and aging; a better understanding of cellular connectivity (i.e., how cells "talk" to one another); insight on the genetics and genomics of rare and undiagnosed diseases (e.g., VEXAS syndrome); and insight on changes across the population level.

Dr. Lossie emphasized that the SMaHT Program is poised uniquely to uncover the personal genome. The project is synergistic—it builds upon other NIH programs—and fulfills a crucial community need. SMaHT will enable the development of tools, reference maps, and data analysis pipelines to catalyze future studies and potentially could transform the scientific community's understanding of the genetics of disease and other biological processes.

Discussion Highlights

- The discussants, Drs. Ardlie and Andrew Feinberg, provided their comments. Dr. Ardlie asked for clarification on whether the tissues are from a single individual; Dr. Lossie clarified that tissues must be collected from a single individual to provide insight on mosaicism. In response to Dr. Ardlie's concerns about clarity in the concept, she explained that sequencing technology is envisioned as a combination of long-range, short-range, and single-cell RNA sequencing. The program includes development of benchmarks, and all groups will receive standardized sets of data.

- Dr. Feinberg stressed the importance of including epigenetics systematically. Dr. Lossie noted that the program expects that people will collect long-read sequencing data, which includes DNA methylation information. Some pilot programs on epigenetics are in development.

- In response to a suggestion to consider smaller cohorts of individuals with specific diseases, Dr. Lossie explained that this would be possible in Phase 2—Phase 1 is focused on creating a reference map and functional analysis component.

- When asked how the initial cohorts will be selected, Dr. Lossie commented that they will be postmortem samples and although the entire lifespan should be studied, older individuals likely will be studied first to assess the prevalence of mutations. She added that the program hopes to attract donors of diverse genetic backgrounds.

Vote

A motion to approve the SMaHT concept was forwarded and seconded. The motion passed with no abstentions.

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 September 17, 2021, and it also will be virtual.

XI. ADJOURNMENT

Dr. Anderson adjourned the meeting at 3:24 p.m. on May 21, 2021.

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: 2021.06.28 12:48:52 -04'00'

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: 2021.06.28 11:50:43 -04'00'

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

Date