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, 2016

Meeting Minutes

I. WELCOME

James M. Anderson, M.D., Ph.D., Chair of the NIH Council of Councils, 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, May 20, 2016, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson welcomed members and noted that Molly Carnes, Jorge Contreras, Judy E. Garber, Lila M. Gierasch, Vivian S. Lee, John Postlethwait, Keith A. Reimann, J. Leslie Winston, and Nsedu Obot Witherspoon were unable to attend the day's meeting. The meeting attendees are identified below. Dr. Anderson also announced that Dr. Maureen M. Goodenow is the new Associate Director of the Office of AIDS Research (OAR), and he thanked Dr. Robert Eisinger for his service as OAR Acting Director.

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 and referred Council members to the Director's Report, included in their meeting books, which highlights upcoming meetings, funding opportunity announcements (FOAs), and other DPCPSI activities of interest.

A. Attendance

1. Council Members

Council Members Present

Chair: James M. Anderson, M.D., Ph.D., Director, DPCPSI, OD, NIH
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI, OD, NIH
Philip O. Alderson, M.D., Saint Louis University, St. Louis, MO
Sharon Anderson, M.D., Oregon Health & Science University, Portland, OR
Marlene Belfort, Ph.D., University of Albany, Albany, NY
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, Flourtown, PA
Joseph Buckwalter, M.D., University of Iowa College of Medicine, Iowa City, IA
Ana M. Cuervo, M.D., Ph.D., Albert Einstein College of Medicine, Bronx, NY
Jonathan Epstein, M.D., Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
Hakon Heimer, M.S., Schizophrenia Research Forum, Providence, RI
King K. Holmes, M.D., Ph.D., University of Washington, Seattle, WA

Terry L. Jernigan, Ph.D., University of California, San Diego, La Jolla, CA
Norma Sue Kenyon, Ph.D., University of Miami School of Medicine, Miami, FL
Kimberly K. Leslie, M.D., University of Iowa Hospitals and Clinics, Iowa City, IA
Guillermina Lozano, Ph.D., The University of Texas MD Anderson Cancer Center, Houston, TX
Terry Magnuson, Ph.D., University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC
Norbert J. Pelc, Sc.D., Stanford University, Stanford, CA
Gail Yokote, M.S., University of California, Davis, Davis, CA

Council Members Absent

Molly Carnes, M.D., M.S., University of Wisconsin–Madison, Madison, WI
Jorge Contreras, J.D., University of Utah, Salt Lake City, UT
Judy E. Garber, M.D., M.P.H., Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
Lila M. Gierasch, Ph.D., University of Massachusetts, Amherst, MA
Vivian S. Lee, M.D., Ph.D., M.B.A., University of Utah, Salt Lake City, UT
John Postlethwait, Ph.D., University of Oregon, Eugene, OR
Keith A. Reimann, D.V.M., University of Massachusetts Medical School, Boston, MA
J. Leslie Winston, Ph.D., D.D.S., The Procter & Gamble Company, Mason, OH Š
Nsedu Obot Witherspoon, M.P.H., Children's Environmental Health Network, Š Washington, D.C.

2. Liaisons

Janine A. Clayton, M.D., Director, Office of Research on Women's Health (ORWH), DPCPSI
Paul M. Coates, Ph.D., Director, Office of Dietary Supplements (ODS), ODP, DPCPSI
Robert W. Eisinger, Ph.D., Acting Director, OAR, DPCPSI
David M. Murray, Ph.D., Director, Office of Disease Prevention (ODP), DPCPSI, OD
William Riley, Ph.D., Director, Office of Behavioral and Social Sciences Research (OBSSR)
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI

3. *Ex Officio* Member

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

4. Presenters

Josephine Briggs, M.D., Director, National Center for Complementary and Integrative Health, and Interim Director, Precision Medicine Initiative® Cohort Program, NIH
Cristina Cassetti, Ph.D., Program Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID)
William A. Gahl, M.D., Ph.D., Director, Undiagnosed Diseases Network, and Clinical Director, National Human Genome Research Institute (NHGRI)
Eric D. Green, M.D., Ph.D., Director, NHGRI
Patricia Labosky, Ph.D., Program Leader, OSC
David O'Connor, Ph.D., Professor, University of Wisconsin-Madison
William Riley, Ph.D., Director, OBSSR
Barbara Spalholz, Ph.D., Chief, Cancer Cell Biology Branch, Division of Cancer Biology, National Cancer Institute (NCI)

Elizabeth L. Wilder, Ph.D., Director, OSC, DPCPSI
Carrie D. Wolinetz, Ph.D., Associate Director for Science Policy, and Director, Office of Science Policy, OD

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. Meeting Procedures

Dr. Grieder reviewed the following:

- Council members are Special Government Employees during the days of Council meetings and therefore are 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 have been identified.
- Time has been 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 8, 2016.
- Minutes from the January 29, 2016, meeting have been published on the DPCPSI website. The minutes from this meeting also will be published there.

C. Future Meeting Dates

The next Council meeting will be held on September 9, 2016. Council meetings in 2017 will be held on January 27, May 26, and September 1.

II. UNDIAGNOSED DISEASES NETWORK

William A. Gahl, MD, PhD, Co-Chair of the Undiagnosed Diseases Network Steering Committee and Clinical Director, NHGRI, described the Common Fund Undiagnosed Diseases Network (UDN) program. Dr. Gahl stated that nothing causes more anguish for patients, or for the physicians and family members caring for them, than a severe illness that cannot even be named. The UDN aims to provide care—and an accurate diagnosis—for patients with unknown disorders, as well as to facilitate research discoveries of new diseases and novel biochemical pathways that may provide new insights into human physiology and genetics. The UDN also works to foster a culture of data sharing that facilitates diagnosis, patient treatment, and basic research on these diseases.

The Undiagnosed Diseases Program (UDP), the precursor to the UDN, was founded in 2008 through a joint effort by NHGRI, the NIH Clinical Center, and the NIH Office of Rare Diseases Research. UDP investigations covered patient phenotyping to rule out known diseases and describe new ones; genetics studies, including commercial testing, SNP arrays, and exome sequencing; and functional studies. In 5 years, the UDP reviewed 3,500 medical records, and admitted and evaluated 1,000 patients of which

40 percent were children. Many patients have neurological conditions, and a diagnosis is made for approximately 25 percent of those admitted. Dr. Gahl noted that 70 publications have resulted from the UDP/UDN's work.

The UDN was established in 2013 with funding from the Common Fund for a nationwide network involving seven clinical sites (including the UDP), two sequencing centers, a metabolomics core, a coordinating center, a Model Organisms Screening Center, a coordinating center, a central data repository, and a central institutional review board (IRB) with reliance agreements. As the only NIH clinical site within the UDN, and the most experienced of the sites in coordinating multidisciplinary efforts in diagnosis (and, when possible, treatment) of unknown disorders, the UDP plays a key role in the UDN.

Dr. Gahl discussed four recent cases to highlight the challenges posed by these diseases and the strategies used by the UDN to address them. In the first case, diagnosis of the disease not only provided a solution to its treatment, but also led to the discovery of a previously unknown regulatory pathway. Five middle-aged siblings showed arterial calcification of their lower extremities, pain in their hands and feet, and leg pain due to impaired blood flow. Both parents were healthy, suggesting the involvement of a recessive mutation. The relatedness of the parents allowed geneticists to focus their search on the 1/128 of the genome shared by both parents, who were third cousins. Genome screening identified *NT5E* (a gene encoding the enzyme CD73, which catalyzes the production of adenosine from AMP) as a possible candidate. Skin biopsies demonstrated that CD73 was absent in fibroblasts of the affected siblings and that abnormal calcification could be inhibited in cultured skin cells by adding adenosine, alkaline phosphatase inhibitors, or lentivirus-delivered CD73. Discovery of a connection between adenosine and mineralization pathways not only facilitated treatment of this disease, but also demonstrated an unexpected relationship of CD73 to normal vascular function.

The second disease, congenital disorder of glycosylation type IIB (CDG-IIb), still eludes treatment, although its biochemical cause has been identified. As with the first case, unraveling its biochemical basis also has offered unexpected insights into other areas of human health. The UDP examined two young siblings with severe physiological and developmental abnormalities. Metabolic and genomic screening of these patients showed unusually high quantities of glucose-3-mannose-1 and deficiencies in glucosidase-I, both of which indicated abnormalities in processing of N-linked glycoproteins. Because immunoglobulins are glycoproteins, finding hypogammaglobulinemia in these patients was not surprising; however, neither sibling showed increased susceptibility to infection. Further research revealed that viral replication and secondary infection was much reduced in CDG-IIb T-cells because viruses are themselves dependent on their host's N-linked glycosylation processes for normal replication. This discovery has important potential implications for the development of novel treatments for viral infections.

Dr. Gahl described a third case involving a 25-year-old man with severe skin ulcerations and subcutaneous calcification. The disease so far has eluded diagnosis, but a promising treatment for the ulcers was developed from the insight that the skin ulcerations might be an inflammatory reaction to the extensive calcification below the skin. In this instance, progress occurred not from genomic or molecular breakthroughs, but through conversations among doctors who took the time to share perspectives.

A fourth case concerned a 21-year old woman with severe dystonia of unknown origin. In this instance, data sharing among different institutions proved crucial to diagnosis and treatment. Genomic analysis revealed a genetic variant of interest, but with no knowledge of the molecular cause, neurosurgeons were hesitant to try deep-brain stimulation as an approach to relieve the patient's dystonia. The UDP had posted the genetic and phenotypic data on the web, however, and recently learned that this woman's case was not unique. A neurologist in London informed the UDN that she had seen 19 identical cases, with similar genetic variants, and that five had improved after treatment involving deep-brain stimulation. This

international conversation is being used to persuade the NIH neurosurgeons that similar treatment might be useful for their own patient as well.

The 2013 expansion of the UDP into the nationwide UDN has introduced new analytic resources and expanded the program's clinical reach. Since the satellite clinical centers only started seeing patients in 2015, clinical and fiscal coordination between the NIH and the other centers is still evolving, as are plans for long-term sustainability of the UDN. The UDN IRB has approved the sharing of patient-identifying information within the network to facilitate diagnosis and treatment of these difficult diseases; satellite clinics already have started to collaborate on cases. Also interactions with international partners are increasing, including a newly formed international network, four international meetings, and encouragement of potential collaborations between the Model Organisms Screening Center and similar research efforts in Canada.

Discussion Highlights

- Efforts are ongoing to coordinate data sharing and research between NHGRI's Centers for Mendelian Genomics and the UDN's Model Organisms Genetic Screening Center.
- Insurers are becoming more open to the idea of covering the genome sequencing costs of family members as a means to speed diagnosis and avoid more expensive diagnostic tests.
- The UDN stores tissue, plasma, serum, and DNA samples, as well as other material for all patients who have been examined at the NIH. There is also follow-up on patients, including queries on new symptoms and subsequent management decisions.

III. INTRODUCTION OF AND UPDATES FROM THE DIRECTOR, NHGRI

Dr. Eric D. Green, Director, NHGRI, provided an overview of the progress in genomics and the activities of NHGRI. The term genomics was adopted in 1987 as the newly developing discipline of genome mapping and sequencing emerged. The NIH positioned itself to play a key role in the characterization of the human genome by establishing the Office for Human Genome Research in 1988, which was later named the National Center for Human Genome Research in 1989 until its designation as an NIH Institute in 1997. The major focus for NHGRI early on was the Human Genome Project, through which the United States led the efforts to map and sequence the human genome for the first time. The Institute has been in existence for 28 years and represents 1.7 percent of the NIH's budget. Following completion of the Human Genome Project, the Institute has re-envisioned its direction and now emphasizes team science applications, a rapidly disseminating footprint, a novel societal and bioethics component, support of Common Fund projects, and support of a large Intramural Research Program.

Sequencing the human genome has provided information to advance human health and provides an opportunity for changing the practice of medicine. A long-term goal of the Institute is to use genetic information to advance clinical care, moving toward the emerging medical discipline called "genomic medicine." Building on the strategy used to complete the Human Genome Project in 2003, the Institute developed a strategic vision that serves as a framework for building new programs that will move it closer to making genomic medicine a reality. Although seminal to the field of genomics, the high cost of sequencing the human genome made it less attainable for many; therefore, the Institute has led efforts to reduce the cost of sequencing a human genome from the starting point of $1 billion to approximately $1,000 over the last 13 years with the implementation of the next-generation platforms for DNA sequencing.

After reaching this pivotal milestone, the Institute shifted its focus to genomic variants and how they might play a role in health and disease. The 1,000 Genomes Project, a deep catalog of human variation, was launched in 2008 as an international research effort to determine the genetic variation in humans. These efforts have resulted in a landmark *Nature* paper, "A Global Reference for Human Genetic Variation." Accomplishments in genomic variants highlights the profound advances that have been made in understanding the function of the human genome. Other NHGRI programs and initiatives include the Encyclopedia of DNA Elements (ENCODE), Genotype-Tissue Expression (GTEx), and Knock-Out Mouse Program (KOMP) Common Fund projects. Together, these efforts have led the field of genomics to make significant advances in unraveling the genomic basis of human disease. The general categories of disease that have guided the programs are rare diseases, which involve single gene mutations and common diseases, which involve more complex genomics. The implementation of genome-wide association studies and the establishment of NHGRI Centers for Common Disease Genomics have helped to better understand individual genomic variants in common diseases such as cardiovascular disease and asthma.

Recent advances in genomics are bringing genomic medicine into focus, and NHGRI is heavily invested in stimulating the research. One leading clinical application of genomics is in cancer biology, which is partly fueled by the partnership with the NCI and The Cancer Genome Atlas (TCGA). Other areas of clinical applications of genomics and projects in which the Institute has vested interest include pharmacogenomics; the Electronic Medical Records and Genomics (eMERGE) network; rare genetic diseases diagnostics; newborn genome sequencing and the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program; and clinical genomics information systems and the Clinical Genome Resource.

Discussion Highlights

- The NHGRI has begun to establish an international consortium of genomic medicine practitioners to engage them intellectually, and to better understand the challenges associated with implementing genomic medicine in the clinical setting.

- Data science remains at the forefront of genomics activities, and discussions are ongoing at the highest level of NIH leadership about the topic. Investments in such programs as the Common Fund's Big Data to Knowledge (BD2K) Initiative, which was supported by the Directors of all 27 Institutes and Centers (ICs), and the establishment of a new leadership position in data science are among the steps taken to bring the NIH closer to solving the problems.

IV. INTRODUCTION TO ZIKA VIRUS

Zika Virus Outbreak and NIAID Research Response

Drs. Cristina Cassetti, Program Director, Division of Microbiology and Infectious Diseases, NIAID, and David O'Connor, Professor, University of Wisconsin-Madison, described NIAID's and ORIP's research on the Zika virus outbreak.

Dr. Cassetti provided a brief history of the Zika outbreak and the NIAID research response to that outbreak. Zika is a flavivirus related to the dengue, yellow fever, and West Nile viruses. It is transmitted by two mosquito species, *Aedes aegypti* and *A. albopictus*, which are common in several parts of the United States. Zika also can be transmitted through sexual contact, through blood transfusion, and between mother and fetus. Because most infected individuals are asymptomatic or experience only mild symptoms, Zika had been thought to be of little public health significance. The recent discovery of Zika-induced abnormalities in fetal brain development has changed that initial assessment to the realization that

the virus is a public health problem of utmost urgency. First isolated in 1947 from a monkey in Uganda and first detected in humans in Nigeria in 1952, the Zika virus has since spread to tropical regions worldwide. In the last 10 years, its rate of spread has accelerated markedly, and its pathogenicity also has increased. In 2015, Brazil and other Latin American countries experienced a sharp rise in Zika infections; among pregnant women, these infections were accompanied by a sudden rise in the number of babies born with microcephaly and an array of profound neurological abnormalities. Recent reports have emerged of Zika-infected adults experiencing acute symptoms, including Guillain-Barré syndrome.

Since January 2016, NIAID has funded 40 new projects on Zika that address the structure of the Zika virus; transmission mechanisms, pathophysiology, and immune responses in Zika infections, especially in fetuses and asymptomatic adults; development of vaccines; improvements in diagnostics and drug discovery; identification of the mosquito vectors; and new vector-control strategies. Development of several new animal models also is underway, including research in Dr. O'Connor's laboratory on non-human primate models.

Nonhuman Primate Models in the Zika Virus

Dr. O'Connor described his initiative to utilize rhesus macaques as models to understand Zika pathogenesis using supplemental funding from NIAID and pilot funds from the ORIP-supported Wisconsin National Primate Research Center. He stressed that this project is a large team effort, involving virologists, reproductive biologists, obstetricians, and collaborators in both the United States and Brazil. Using a macaque model allows researchers to investigate the dynamics of viral infections, including host immune response, over time. It enables invasive tissue sampling to understand the processes that generate fetal brain abnormalities; preclinical tests of vaccines and therapeutics; and overall acceleration of research progress, especially in investigating possible interactions between dengue and Zika infections in the areas where these viruses co-occur.

Dr. O'Connor reviewed preliminary data that highlight the promise of macaques as effective animal models for Zika research, and he noted the need for additional experimentation to confirm and extend the initial results. Macaques can be infected successfully with several Zika strains, using physiologically realistic doses that mimic virus concentrations delivered by mosquito bites. As in humans, most infected macaques remain asymptomatic, aside from a small rash in some animals. In the infected pregnant macaques, however, the fetal head size is smaller than normal though these observations are very preliminary. Furthermore, the Zika virus persists much longer in the blood of pregnant macaques than in non-pregnant macaques. Comparisons of infections with African and Asian strains of Zika virus suggest the possibility that Asian and African strains may differ in levels of pathogenicity. A third set of experiments indicates that Zika infection offers complete protection against reinfection for at least a few months after the original infection; this is promising news for the prospects of eventual development of an effective anti-Zika vaccine.

Finally, Dr. O'Connor emphasized the importance of collaborative approaches, online data sharing (http://zika.labkey.com), and rapid communication of results, especially in disease outbreaks such as Zika, where time is critical. He noted that similar approaches were helpful during the 2014 Ebola outbreak as well.

Discussion Highlights

- A participant commented that fetal abnormalities seen in Zika infections are much worse than microcephaly cases seen in toxoplasmosis and other infections.

- Because numbers are so small, it is not yet clear whether the timing of Zika infection in pregnant macaques with respect to gestational stage makes any difference in the severity of fetal abnormalities.

- There is no evidence of Guillain-Barré syndrome in macaques. The dynamics of Guillain-Barré in Zika-infected humans are not well understood, but may differ in several ways from classic Guillain-Barré syndrome.

- Although mouse models are not as physiologically relevant as primate models for Zika research, they offer the advantage of larger numbers and a history of use as models in studies of other viral diseases.

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 65 ORIP applications with requested first-year direct costs of $35,748,733. The Council also concurred with the review of 953 responsive Common Fund applications with first year direct costs of $1,650,632,518 and the review of 15 responsive Precision Medicine Initiative® applications with first year direct costs of $177,688,240.

VI. UPDATE ON AWARDS FOR THE NIH PRECISION MEDICINE INITIATIVE® COHORT PROGRAM

Drs. Josephine Briggs, Director, National Center for Complementary and Integrative Health, and Interim Director, Precision Medicine Initiative® Cohort program, and Carrie D. Wolinetz, Associate Director for Science Policy, and Director, Office of Science Policy, OD, provided an update on the Precision Medicine Initiative® Cohort program. Dr. Briggs stated that the new Precision Medicine Initiative® (PMI) Cohort Program Director, Eric Dishman, was announced in April, and she reviewed the ambitious timeline for both the data and grant activities. Vanderbilt University is heading the Direct Volunteer Pilot program, and two firms are providing communication support. Applications for cooperative agreements were received in February 2016, all of which the Council of Councils just reviewed in its closed session; the National Heart, Lung, and Blood Institute's Council will review two others in mid-June.

The PMI is committed to extracting research-quality data from electronic health records (EHRs), a task currently challenged by the lack of standardization, assessment of data quality, and/or interoperability. Two activities are being assessed for their capabilities in this area. The Data Sprint initiative is examining the ability for health care provider organization-enrolled PMI Cohort participants to share their EHR data. Sync for Science is focused on developing methods to facilitate individually controlled clinical data

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[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.

donations to the PMI Cohort, as well as accelerating and guiding the national ecosystem for patient-mediated data access through a set of application program interfaces.

The PMI Cohort Program Advisory Panel (the Panel) is providing oversight and includes two members of the Council of Councils: Dr. Jonathan Epstein and Dr. Terry Magnuson. The Panel is reviewing implementation papers on such topics as biobanks, EHRs, family engagement, participant-provided information, the physical and social environment, and physical evaluation. The documents are intended to represent a common store of knowledge and facilitate recommendations for implementation in the cohort. Dr. Briggs illustrated the level of detail and type of information included in the papers by describing the biobank's responsibilities, data flow, and overall workflow, as well as the measures, participant-provided information, and physical and social environment data compiled in the physical activity document. She also noted the intent to build a robust structure for EHR data extraction.

Dr. Wolinetz described the role of the PMI Cohort program's IRB, which is chaired by Dr. Nancy Kass, Johns Hopkins University, and has a roster of experts in ethics, privacy, genomics, bioinformatics, and other areas relevant to precision medicine, as well as a depth of IRB experience. The PMI Cohort program's IRB will serve as the IRB of record, charged with ensuring that risks to participants are minimized and do not outweigh anticipated benefits, that the selection of participants is diverse and that informed consent meets regulatory requirements. The Cohort IRB also will oversee data monitoring for the safety of participants, ensure that appropriate provisions are in place to protect participant privacy, and ensure protections for vulnerable populations. The PMI Cohort program's participant enrollment and research will occur at many sites, and the IRB will review initial protocols for establishing the Cohort program. This IRB's role in the review of future proposed research uses of the cohort data and specimens will be determined later.

Discussion Highlights

- A national dialogue about the return of results to patients is underway. The Advisory Committee to the Director stressed in its PMI review that providing patients access to their data should be done responsibly such as ensuring that adequate resources are available to help people understand the data. Structure and standard procedures are needed in order to confidentially provide access to accurate data The Steering Committee will first address a process for clearly actionable findings, such as pharmacogenomic determinants that indicate a patient with high blood pressure should not take a certain drug.

- EHRs make data more accessible than paper charts, but not necessarily significantly more accurate. PMI is supporting a variety of projects using EHR data extraction and considering measures to improve accuracy in the process. An effective infrastructure will allow concrete, question-focused cohort and sub-cohort development at a much lower cost than currently experienced. The PMI reflects an ambitious attempt to broaden the volunteerism and participation in clinical research in the United States.

- Members encouraged the IRB's conversations and decision-making process as much as possible. The IRB has convened formally twice, but it has been flexible and conducted expedited review of some revisions. The Board perceives itself as the initial guardian of the trust that is central to the PMI cohort and is sensitive to how decisions about each phase of the pilot program will ultimately affect later project directions and may interplay with governance decisions. It was noted that the Clinical and Translational Science Award program is engaged in developing standardized reliance agreements between IRBs and that the NIH is taking steps toward a mandate for centralized IRBs.

- The second phase of the PMI Cohort program will be expanded to include access to some imaging data that can be extracted at a reasonable cost.

- Recruitment sites include federally qualified health centers, which provide health services for many people with Medicaid. Health care for cohort members without insurance will need to be determined. Inclusion of minorities and individuals of low socioeconomic status is a high priority; the cohort should represent the distribution of races and socioeconomic status found across the Nation.

- The Council thanked Dr. Briggs for her work in leading the PMI Cohort to its current state.

VII. COUNCIL INPUT IN THE OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH (OBSSR) STRATEGIC PLAN

Dr. William Riley, Director, OBSSR, described the planning process and scientific priorities for the OBSSR's strategic plan. The OBSSR was established in 1995 to identify projects of behavioral and social sciences research that should be conducted or supported collaboratively across the NIH. Its activities aim to enhance the scientific and public health impact of behavioral and social sciences research (BSSR) and to communicate the research findings to stakeholders both within and external to the Federal Government.

Behavioral and environmental factors influence disease incidence and mortality. For example, one analysis showed a 40 percent contribution of behavioral patterns and 5 percent of environmental factors to premature death. Another study suggested a decline in colorectal cancer incidence as partly due to changing behavior, specifically those involving risk factors and screening. The OBSSR recognizes the multiple levels of influence on disease and has an interest in integrating social and behavioral sciences with effects seen at the biological levels, such as through cognitive behavioral neuroscience and behavioral genetics.

The guiding principles for the plan's development included integrating BSSR into the broader biomedical research efforts, consistent with the NIH mission, and coordinating and collaborating with the NIH ICs. Other emphases were identifying critical challenges that are barriers to BSSR advancement and focusing on those challenges that OBSSR is uniquely positioned to address. The process started in the fall of 2015 with the establishment of the Strategic Planning Workgroup and meetings at various levels within the NIH and with an expert panel. Stakeholder webinars occurred in May 2016 to inform the plan, which is expected to be finalized in June 2016.

Dr. Riley described three OBSSR scientific priorities in the strategic plan, provided examples of current relevant activities, and explained that the priorities are underpinned by four foundational processes: communication, program coordination and integration, training, and policy and evaluation. The first scientific priority is to improve the synergy of basic and applied BSSR by encouraging research with strong potential for applied translation relevant to health and by facilitating greater interaction among basic and applied BSSR researchers. Examples include OppNet initiatives on the basic processes of self-management of chronic disease and on complex dynamic modeling of resilience processes. The second scientific priority—which aims to enhance methods, measures, and data infrastructures to encourage more cumulative behavioral and social sciences—will emphasize data integration and replication, facilitate the development and testing of new measurement approaches, and expand the repertoire of methods available to social and behavioral researchers. The NIH Workgroup on Comparison Conditions in Behavioral Clinical Trials is supporting this area. To facilitate the adoption of BSSR findings in health research and practice, which is the third scientific priority, research that studies mechanisms and interventions in context will be encouraged, the relevance and scalability of social and behavioral interventions will be enhanced, and collaborations with stakeholder agencies and entities, including those that deliver research

findings and evaluate policy changes that influence adoption of effective approaches, will be fostered. Activities in this third area include dissemination and implementation research training, as well as collaboration with such organizations as the National Collaborative on Childhood Obesity Research.

Discussion Highlights

- Members suggested that the NIH encourage grantees to include information about their behavioral research findings on their websites to both better engage stakeholders in outcomes and communicate data on empirically based evidence for treatments of behaviors that influence health, such as tobacco, diet, and physical activity. The NIH was encouraged to continue working with professional societies and guilds to better disseminate effective research approaches and findings.

- Data sharing challenges will need to be addressed. OBSSR recognizes the myriad of behavioral ontologies, large data sets, and measurements used throughout the community and the need to integrate them. Cross-calibration can be a useful approach, but it does not replace the utility of a universal measurement standard.

- The PMI encompasses research on social and behavioral determinants of health, including the collection of location-based information, such as neighborhood and geolocation data. The Initiative also provides an opportunity to pilot test new technologies and identify new and improved measurement approaches.

- Better linkages between phenotypic characterization in animal models and translation for human health could help advance behavioral science.

- Behavioral scientists would benefit from easier screening measures for such diseases as depression, which is widespread and treatable. Different screening measures may be needed for different diseases.

VIII. COMMON FUND PROGRAM UPDATES

Dr. Elizabeth Wilder, Director, OSC, introduced an update session on two ongoing Common Fund programs that are midway through their funding cycles. The mid-cycle review provides an opportunity for the Council to review a project's goals and achievements, identify challenges, and participate in the decision-making process regarding future Common Fund investments in the program.

The following updates were provided:

Metabolomics

Dr. Barbara Spalholz, Chief, Cancer Cell Biology Branch, Division of Cancer Biology, NCI, discussed the progress and success of the Metabolomics program. Metabolomics is the systematic study of all the metabolites in a biological sample. Because metabolic profiles can provide direct signatures of the biochemical activities that correlate with health and disease, a metabolomics component has been included in many Common Fund projects, including the Human Microbiome Project, the Precision Medicine Initiative, Molecular Transducers of Physical Activity, and the Undiagnosed Disease Network. The Metabolomics program began in 2012 with the goal of increasing the national capacity in metabolomics research through infrastructure expansion, workforce development, technology enhancements, reference standard synthesis, and creation of a data repository.

Six Regional Comprehensive Metabolomics Resource Cores were established to expand access to affordable, high-quality metabolomics services that include providing at-cost analyses on a variety of platforms, technology development to improve methods, and collaborative opportunities for pilot studies. Expanding fee-for-service customer use has allowed the Resource Cores to continue working toward financial self-sufficiency. Training in metabolomics research consists of courses and workshops, mentored development in metabolomics, and collaborative supplements to promote metabolomics research. The courses and workshops were developed using the R25 funding mechanism and, since 2014, have trained 82 scientists in various aspects of metabolomics. In addition, Metabolomics in Medicine, an online learning portal, was started in 2015. The metabolomics technology development work, which uses the investigator-initiated research award (R01) vehicle, has improved the extraction, separation, detection, and identification of metabolites. Progress thus far in developing metabolite reference standards includes 18 synthesized standards and 26 standards in the process of being synthesized. The Data Repository and Coordinating Center (DRCC) houses the raw and processed metabolomics data, with 320 data sets uploaded to date, and has more than 400 registered users. In addition, the DRCC has developed metadata standards, designed a reference directory of metabolite names (RefMet), coordinated an inter-laboratory reproducibility exercise, prepared a directory of public data sets with international partners, and developed a website portal for consortium activities called the Metabolomics Workbench.

Dr. Spalholz, highlighting the accomplishments of the Metabolomics program in enabling untargeted metabolomics (i.e., global profiling), noted ongoing challenges in rigor and reproducibility, data analysis, and compound identification of unknown metabolites correlating with health or disease. The goals for continuing the Metabolomics program include coordinating community-wide identification and adoption of best practices for rigor, reproducibility, and data reuse; expanding support of metabolomics capacity building to meet increasing demand for data analysis and interpretation; and developing novel or more efficient methods or processes for compound identification.

Discussion Highlights

- The National Institute of Standards and Technology has an interest in metabolomics, has coordinated with the NIH on past metabolomics activities, and has been in discussion with the Common Fund Program recently on issues of mutual interest.

- Many of those who use data are not metabolite experts and will rely on software for interpretation. NIH leadership, in developing and disseminating such software, would greatly help the community. Similar -omics platforms and practices could be used as models.

- Because metabolomics is a new field, there is a need to identify and adopt best practices that would enable the community to do metabolite profiling well. Areas of challenge include the ability to apply rigor and reproducibility, as well as algorithms to support data analysis and interpretation. Better tools to support compound identification and elucidate biology by mapping specific metabolites to metabolic pathways would be useful.

Extracellular RNA Communication

Dr. Patricia Labosky, Program Leader, OSC, described the Extracellular RNA (exRNA) Communication Consortium, which aims to explore the potential for RNA in cell-to-cell communications, their role of exRNA in disease, and the therapeutic, and biomarker potential for exRNA. Five FOAs were released in 2012 under the cooperative agreement funding mechanisms and are aligned with the five initiatives of the program: a comprehensive reference profile of circulating human exRNAs; study of exRNA biogenesis, biodistribution, uptake, and effector function; clinical utility of exRNA for biomarker development;

clinical utility of exRNA for therapy development; and data management and resource repository (DMRR).

Dr. Labosky highlighted some of the findings in each of the program's initiatives. A comprehensive reference profile of circulating human exRNA has been defined using multiple body fluids (bile, cerebrospinal fluid, serum, saliva, plasma, etc) of healthy individuals and currently has 751 profiles. This reference profile will be used for future comparisons of healthy and disease-affected cohorts. In addition, through studies of exRNA biogenesis, biodistribution, uptake, and effector functions, the program provided the first demonstration that cell surface receptor signaling is linked to loading and uptake of specific miRNAs into recipient cells. For example, mutation of the KRAS signaling cascade inhibited phosphorylation on a specific site of the RNA-induced silencing complex component Argonaute 2 (AGO2)); this phosphorylation change resulted in alteration of RNA packaging into exosomes for secretion. The program also supported work on the clinical utility of exRNA for therapy development studies, which have shown that miRNA-containing exosomes promote the formation of myelin in animal models of multiple sclerosis (MS). Another study demonstrated the clinical utility of exRNA for biomarker development by verifying the presence of biomarkers in the saliva of gastric cancer patients and that were not present in non-gastric cancer control patients. The DMRR houses the data from all five initiatives and also includes the exRNA research portal, the protocol exchange, the exRNA Atlas, and other resources.

The Consortium-wide accomplishments include 197 publications in peer-reviewed journals, generation of highly standardized protocols, revisions of gene ontology terms relevant to exRNA, development of standards, and participation in a new Gordon Conference and a Keystone Symposia. The Consortium also has developed cell lines with mutations in the known components of vesicle biogenesis, as well as imaging tools. A remaining challenge is that the therapeutic goals may depend on a deeper understanding of the underlying biology, and much of the hypothesis-generating and broadly enabling work will need focused investments to reveal new paradigms over the next 4 to 5 years.

Discussion Highlights

- An opportunity exists to engage the neurodegeneration community to perhaps develop a joint workshop with RNA and protein experts. It would be highly productive as similar mechanisms of transport of vesicles for proteins are involved. This will also ensure that efforts are not duplicated.

- The audience was interested to know about relative abundance of non-human RNAs (i.e. viral sequences) in the biofluids of normal individuals. It was pointed out that this would be interesting data to analyze given the fact that many viral sequences are detected in healthy individuals.

- Discussion of whether the program needs additional investment was not decisive. The Council members appreciated how this program has developed; it has jump-started a whole new field and council members stated that the progress was impressive.

IX. CLOSING REMARKS

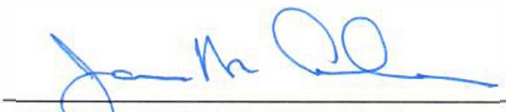
Dr. Anderson thanked the Council members and speakers for their contributions at this meeting.

X. ADJOURNMENT

Dr. Anderson adjourned the meeting at 4:08 p.m. on May 20, 2016.

XI. CERTIFICATION

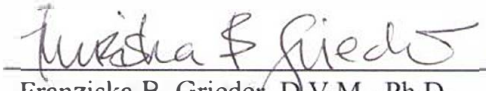
I hereby certify that, to the best of my knowledge, the foregoing summary minutes are accurate and complete.



6-26-2016

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

Date



6.26.2016

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

Date