National Diabetes and Digestive and Kidney Diseases Advisory Council
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Department of Health and Human Services

I. CALL TO ORDER
Dr. Rodgers

Dr. Griffin Rodgers, Director, NIDDK, called to order the 204th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m. on May 10, 2017, in Building 31, Conference Room 10, the NIH Campus, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Joseph Bonventre
Dr. David Brenner
Dr. Eugene Chang
Dr. David D'Alessio*
Dr. Mark Donowitz
Dr. Joel Elmquist
Dr. Caren Heller
Dr. Lee Kaplan
Dr. David Klurfeld
Mr. Richard Knight
Dr. Paul H. Lange*
Ms. Ellen Leake
Mr. Thomas Nealon*
Dr. Jeffrey Pessin
Dr. Craig Peters
Dr. Alan Saltiel
Dr. Jean Schaffer
Dr. Ian Stewart
Dr. Beverly Torok-Storb

*Served as an *ad hoc* member for this meeting.

In addition, serving as *ad hoc* members and attending only the Kidney, Urologic, and Hematologic Diseases subcommittee meeting via telephone:
Dr. Sharon Anderson
Dr. Mark Zeidel

Also Present:
Dr. Griffin Rodgers, Director, NIDDK and Chair of the NIDDK Advisory Council
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. Brent Stanfield, Executive Secretary, NIDDK Advisory Council

B. NIDDK STAFF AND GUESTS

Abbott, Kevin – NIDDK
Abraham, Kristin – NIDDK
Agodoa, Lawrence – NIDDK
Akolkar, Beena – NIDDK
Andersen, Dana – NIDDK
Arreaza-Rubin, Guillermo – NIDDK
Baker, Jenna – NIDDK
Barnard, Michele – NIDDK
Bavendam, Tamara – NIDDK
Begum, Najma – NIDDK
Berti-Mattera, Liliana – CSR
Best, Caroline – Am. Urol. Assoc.
Bishop, Terry – NIDDK
Blake, Lori – Fred Hutch Cancer Research
Blondel, Olivier – NIDDK
Boerboom, Lawrence – CSR
Bourque, Sharon – NIDDK
Bremer, Andrew – NIDDK
Burgess-Beusse, Bonnie – NIDDK
Byrd-Clark, Danita – NIDDK
Camp, Dianne – NIDDK
Castle, Arthur – NIDDK
Cerio, Rebecca – NIDDK
Chavez, Elizabeth – NIDDK
Chen, Hui – CSR
Cheng, Clara – CSR
Chowdhury, Bratati – NIDDK
Connaughton, John – NIDDK
Copeland, Randy – NIDDK
Cowie, Catherine – NIDDK
Curtis, Leslie – NIDDK
Davila-Bloom, Maria – NIDDK
Dayal, Sandeep – NIDDK
Densmore, Christine – NIDDK
Doherty, Dee – NIDDK
Doo, Edward – NIDDK
Drew, Devon – NIDDK
Eggerman, Thomas – NIDDK
Evans, Mary – NIDDK
Farishian Richard – NIDDK
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gamliel, Dee – NIDDK
Gansheroff, Lisa – NIDDK
Gossett, Danny – NIDDK
Greenwel, Patricia – NIDDK
Guo, Xiaodu – NIDDK
Haft, Carol – NIDDK
Hall, Sherry – NIDDK
Hanlon, Mary – NIDDK
Hoff, Eleanor – NIDDK
Hoffert, Jason – NIDDK
Hoofnagle, Jay – NIDDK
Hoover, Camille – NIDDK
Hoshizaki, Deborah – NIDDK
Hunter, Christine – NIDDK
Hyde, James – NIDDK
James, Stephen – NIDDK
Jenkins, Connie – NIDDK
Jerkins, Ann – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Ketchum, Christian – NIDDK
Kimmel, Paul – NIDDK
Kirkali, Ziya – NIDDK
Kranzfelder, Kathy – NIDDK
Kuczmarski, Robert – NIDDK
Kusek, John – NIDDK
Laakso, Joseph – Endocrine Society
Larkin, Jennie – NIDDK
Laughlin, Maren – NIDDK
Lee, Christine – NIDDK
Lee, Jessica – NIDDK
Leschek, Ellen – NIDDK
Linder, Barbara – NIDDK
Lynch, Christopher – NIDDK
Macpherson, Cora – Soc. & Sci. Sys., Inc.
Malfait, Anne-Marie – Rush University
Malik, Karl – NIDDK
Malozowski, Saul – NIDDK
Marchiolo, Eryn – Amer. College of Rheumatol.
Martey, Louis – NIDDK
Maruvada, Padma – NIDDK
Mastrangelo, Karin – NIDDK
Morris, Ryan – NIDDK
Moxey-Mims, Marva – NIDDK
Mullins, Christopher – NIDDK
Narva, Andrew – NIDDK
Newman, Eileen – NIDDK
Nguyen, Van – NIDDK
Niebylski, Charles – NIDDK
Osganian, Voula – NIDDK
Otradovec, Heidi – NIDDK
Parsa, Afshin – Univ. of Maryland
Pawlyk, Aaron – NIDDK
Payne, January – NIDDK
Perrin, Peter – NIDDK
Perry-Jones, Aretina – NIDDK
Pike, Robert – NIDDK
Pileggi, Antonello – CSR

Ramani, Rathna – NIDDK
Rankin, Tracy – NIDDK
Rasouli, Beeta – Lewis-Burke Associates
Reiter, Amy – NIDDK
Rivers, Robert – NIDDK
Roberts, Tibor – NIDDK
Rojas, Raul – CSR
Rosenberg, Mary Kay – NIDDK
Roy, Cindy – NIDDK[+]
Rushing, Paul – NIDDK
Rys-Sikora, Krystyna – NIDDK
Sanovich, Elena – NIDDK
Saslowsky, David – NIDDK
Sechi, Salvatore – NIDDK
Serrano, Jose – NIDDK
Shelness, Gregory – CSR
Shepherd, Aliecia – NIDDK
Sherker, Averell – NIDDK
Sierra-Rivera, Elaine – CSR
Silva, Corinne – NIDDK
Singh, Megan – NIDDK
Smith, Jaime – NIDDK
Smith, Philip – NIDDK
Spain, Lisa – NIDDK
Star, Robert – NIDDK
Tatham, Thomas– NIDDK
Teff, Karen – NIDDK
Thornton, Pamela – NIDDK
Tilghman, Robert – NIDDK
Torrance, Rebecca – NIDDK
Tuncer, Diane – NIDDK
Turner, Linda – NIDDK
Unalp-Arida, Aynur – NIDDK
Utama, Herman– NIDDK
Van Raaphorst, Rebekah – NIDDK
Vinson, Terra – NIDDK
Wallace, Julie – NIDDK
Wang, Xujing – NIDDK
Weiner, Jeff – NIDDK
Yang, Jian– NIDDK
Yanovski, Susan – NIDDK

[+]*Attended only the Kidney, Urologic and Hematologic Diseases subcommittee meeting and this was via telephone.*

C. ANNOUNCEMENTS

Dr. Rodgers

***Ad Hoc* Council Member**

Dr. Rodgers introduced and welcomed a new *ad hoc* member joining the meeting.

Dr. David D'Alessio joined the meeting representing the Department of Veterans Affairs. Dr. D'Alessio earned his M.D. at the University of Wisconsin, and completed his residency in internal medicine at Temple University. He then went on to do a research fellowship within the Division of Metabolism, Endocrinology, and Nutrition at the University of Washington. Dr. D'Alessio is currently a professor within the Department of Medicine at Duke University and the director of the Division of Endocrinology. He is also an attending physician at Duke University Hospital in the Durham Veterans Administration's Medical Center. Dr. D'Alessio's research focuses on the regulation of insulin secretion and glucose tolerance in Type II diabetes. He is especially interested in the peptide GLP-1 and its role in healthy individuals and those with diabetes. He also focuses on the mechanisms underpinning the impact of bariatric surgery on insulin secretion dynamics. Dr. D'Alessio has an impressive peer review and editorial service record, with over 150 peer-reviewed articles to his credit.

In Memoriam

Dr. Rodgers reported with sadness the deaths of several persons important to the NIDDK scientific community:

- Former Council member ***John Walsh*** passed away on March 7. He had served on NIDDK's Advisory Council from 2011 to 2015, and on the NIH Council of Councils from 2009 to 2012. In 1989, Mr. Walsh was diagnosed with Alpha-1 antitrypsin deficiency, or

Alpha-1, a genetic condition that can result in serious lung and/or liver disease. Learning that there was no organized effort to promote research and find a cure for Alpha-1, he focused his talents and efforts to help fill that void. In 1995, he cofounded the Alpha-1 Foundation, a not-for-profit corporation dedicated to providing the leadership and resources to increase research, improve health, promote detection, and find a cure for Alpha-1. Mr. Walsh served as the president and CEO of Alpha-1 Foundation for more than 20 years. He also co-founded AlphaNet, a nonprofit disease management service company providing comprehensive care exclusively to individuals with Alpha-1. His efforts directly helped thousands of Alpha-1 patients through AlphaNet, and many more indirectly through the tens of millions of dollars that his efforts have helped to raise over the years for research.

- ***Dr. Thomas E. Starzl***, a long-time grantee who was 90 years old, passed away on March 4. Dr. Starzl was a pioneer in transplantation surgery and medicine. He joined Northwestern University as a faculty member in 1958 and then moved to the University Colorado School of Medicine in 1962, before joining the University of Pittsburgh School of Medicine in 1981. Dr. Starzl performed the world's first successful liver transplantation in 1967 while he was at the University of Colorado, then went on to develop various immunosuppressive and antirejection strategies that helped establish transplantation as an accepted treatment for patients with end-stage disease of the liver and other organs. His honors were numerous, but most recently they included receiving he Lasker-DeBakey Clinical Medicine Research Award and the Presidential National Medal of Science.
- Long-time grantee, ***Dr. Sushil Sarna***, passed away on February 27. Dr. Sarna was most recently the Charlotte Warmoth Professor of Internal Medicine and a professor of neuroscience and cell biology at the University of Texas Medical Branch at Galveston. As a leading authority on gastrointestinal motility disorders, Dr. Sarna's research interests included cell signaling and gene expression in gut inflammation, functional bowel disorders, and in response to chronic psychological stress.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 203rd COUNCIL MEETING

Dr. Rodgers

The Council approved, by voice vote, the Summary Minutes of the 203rd Council meeting, which had been sent to them in advance for review.

III. FUTURE COUNCIL DATES

2017

September 6-7 (Wednesday and Thursday)
Natcher Conference Center (Building 45)
Conference Rooms E1/E2, D and F1/F2

2018

January 24-25 (Wednesday and Thursday)
Natcher Conference Center (Building 45)
Conference Rooms E1/E2, D and F1/F2

May 16-17 (Wednesday and Thursday)
Natcher Conference Center (Building 45)
Conference Rooms E1/E2, D and F1/F2

September 7 (Friday)
Tentative

Most meetings are expected to be a single day. However, the NIDDK asks Council members to reserve two days for each meeting should a situation arise where a longer meeting is required.

Dr. Rodgers noted that the NIH conference space in Building 31, where the NIDDK Council meetings have been held the past few years will be closed for renovations for at least a year. For at least the next three sessions, the Council will meet at the Natcher Conference Center. People attending those meetings that will be held in the Natcher Building should allow extra time to pass through the additional security checks if they will be driving onto the NIH Campus and parking in the garage underneath the Natcher Building. He noted that plans for the September 2018 meeting remain tentative.

IV. ANNOUNCEMENTS
Dr. Brent Stanfield

Confidentiality

Dr. Stanfield reminded the Council Members that material furnished for review purposes and discussion during the closed portion of the meeting is considered confidential. The content of discussions taking place during the closed session may be disclosed only by the staff and only under appropriate circumstances. Any communication from investigators to Council Members regarding actions on an application must be referred to the Institute. Any attempts by Council Members to handle questions from applicants could create difficult or embarrassing situations for the Members, the Institute, and/or the investigators.

Conflict of Interest

Dr. Stanfield reminded the Council Members that advisors and consultants serving as Members of public advisory committees, such as the NIDDK Advisory Council, may not participate in situations in which any violation of conflict of interest laws and regulations may occur. Responsible NIDDK staff shall assist Council Members to help ensure that a Member does not participate in, and is not present during, the review of applications or projects in which, to the Member's knowledge, any of the following has a financial interest: the Member, or his or her spouse, minor child, or partner (including close professional associates), or an organization with which the Member is connected.

To ensure that a Member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. A statement is provided for the signature of the Member, and this statement becomes a part of the meeting file. Dr. Stanfield directed each Council Member to a statement in his or her meeting folder regarding the conflict of interest in review of applications. He asked each Council Member to read it carefully, sign it, and return it to NIDDK before leaving the meeting.

Dr. Stanfield pointed out that at Council meetings when applications are reviewed in groups without discussion, also called "*en bloc*" action, all Council Members may be present and may participate. The vote of an individual Member in such instances does not apply to applications for which the Member might be in conflict.

Regarding multi-campus institutions of higher education, Dr. Stanfield said that an employee at one campus may participate in any particular matter affecting another campus, if the employee's financial interest is solely at one campus and the employee has no multi-campus responsibilities.

V. REPORT FROM THE NIDDK DIRECTOR

Dr. Rodgers

Budget Update

Dr. Rodgers reported that, on May 5, the President signed into law the Consolidated Appropriations Act of 2017, funding government agencies through September 30, 2017. This law provides the NIH with an additional $2 billion over the 2016 appropriation, an increase of 6.2 percent.

Of this additional $2 billion, $400 million will be designated for research on Alzheimer's Disease through the National Institute on Aging. Additionally, the National Institute of Allergy and Infectious Diseases has been designated to receive $152 million for Zika response and preparedness, and $50 million for antibiotic resistance research.

The NIDDK's portion included an additional $52.24 million, or a 2.9-percent increase, compared to 2016, bringing the Institute's total budget to $1.87 billion for Fiscal Year 2017. Dr. Rodgers reminded Council members this amount does not include the Special Diabetes Program, which is a separate appropriation that requires periodic authorization. The current authorization expires at the end of the 2017 fiscal year. In anticipation of the program's reauthorization, NIDDK recently held a planning meeting to discuss potential funding opportunity announcements that could be released early next fiscal year if the funds are renewed. During the two-day meeting, nonfederal experts provided input on proposals developed by NIDDK and other institutes within the NIH.

Dr. Rodgers also reminded Council that the December 6th continuing resolution provided an additional $352 million to the NIH from the 21st Century Cures Act. The NCI will receive $300 million of that for the Beau Biden Cancer Moonshot and $40 million will go to the Office of the

Director for the Precision Medicine Initiative. Additionally, $10 million has been allocated for the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, and $2 million has been allocated for Regenerative Medicine.

The President's fiscal year 2018 budget blueprint was released on March 16. It reflects a $5.8 billion decrease for NIH compared to fiscal year 2016. The 2017 budget had not been signed at that point. The detailed budget proposal was scheduled to be submitted to Congress on May 22, and specifics related to NIH were embargoed until then.

Dr. Rodgers reported that NIH is the subject of two upcoming congressional hearings. On May 17, NIH was scheduled to testify before the Labor/HHS/Education subcommittee of the House Committee on Appropriations. Since that hearing was to precede the planned May 22 release of the President's 2018 budget, the hearing's focus was science in general and scientific opportunities. Additionally, NIH will testify on June 22 before the Senate counterpart of this subcommittee, the Labor/HHS/Education subcommittee of the Senate Committee on Appropriations. Dr. Rodgers said that he expects to be able to give the Council more information about appropriations for fiscal year 2018 at the September meeting.

VI. ALL OF US RESEARCH PROGRAM

Mr. Eric Dishman

Dr. Rodgers introduced Mr. Eric Dishman, Director of the All of Us Research Program, part of the Precision Medicine Initiative. Prior to joining NIH last year, Mr. Dishman was an Intel fellow and vice president of Health and Life Group at Intel Corporation, where he was responsible for Intel's cross-business strategies, research, and development and policy initiatives for health and life science solutions. Trained as a social scientist, he pioneers innovative techniques that incorporate anthropology, ethnography, and other social science methods into the development of new technologies.

Dr. Rodgers also provided some background on the NIH's All of Us Research Program. This is an historic effort to gather data over many years from 1 million or more people living in the United States, with the goal of accelerating research and improving health. Unlike research studies that are focused on a specific disease or population, All of Us will serve as a national resource to inform thousands of studies covering a wide variety of health conditions. Researchers will use data from the program to learn more about how individuals' different lifestyles, environment, and biological makeup can influence health and disease. Participants will be able to learn more about their own health and contribute to an effort that may advance the health of generations to come.

Before Mr. Dishman started his presentation, he outlined some of his own experiences as a patient with kidney disease and how this has affected his professional involvement with the health care system and health care innovation. He commended NIDDK for its research into diabetes and kidney disease.

Mr. Dishman explained that the All of Us Research Program is designed to address some of the challenges of implementing precision medicine on a wider scale. From the patient and provider perspective, he pointed out that few patients have access to—or even awareness of—precision medicine today. Clinicians may be wary of unfamiliar clinical domains like precision medicine. Pertinent research/data to draw from may be limited. One patient at a time analysis is often inconsistent with the time available to professional providers and compute times and analytics needed may in some cases exceed the time patients have available to benefit from the results – they may succumb to their disease before the computer time needed has transpired. From the research perspective, there is often enormous time and financial burden associated with building IT systems and tools rather than actually performing research and data resources and funding opportunities are often not broadly disseminated. Researchers also face challenges acquiring large and diverse sample sizes. Finally, incentives are not currently aligned for data sharing and large-scale collaboration.

He then explained that the mission of All of Us is to accelerate health research and medical breakthroughs to enable individualized prevention, treatment, and care for all persons. Specifically, All of Us has three strategic objectives:

1. Nurture relationships with 1 million U.S. participant partners, from all walks of life, for decades.
2. Deliver a rich and large biomedical dataset that is easy, safe, and free to access.
3. Catalyze a robust ecosystem of diverse researchers and funders, who are "hungry" to use and support the All of Us dataset.

Mr. Dishman outlined the core values of All of Us for the Council:

- Participation in the All of Us Research Program will be open to interested individuals.
- The Program will reflect the rich diversity of America.
- Participants will be partners in the Program.
- Trust will be earned through robust engagement and full transparency.
- Participants will have access to information and data about themselves.
- Data from the Program will be broadly accessible to empower research.
- The Program will adhere to the Precision Medicine Initiative Privacy and Trust Principles and the Precision Medicine Initiative Data Security Policy Principles and Framework.
- The Program will be a catalyst for innovative research programs and policies.

Mr. Dishman explained the program's emphasis on diversity of all kinds. For example, All of Us will reflect the broad diversity of the U.S.—all ages, races/ethnicities, genders, socioeconomic status, geography, and health and disease status. The plan is to achieve this multifaceted diversity by over-recruiting those who have been underrepresented in biomedical research. The goal is to have at least 50 percent of the 1 million people, or 500,000, from groups that are underrepresented in biomedical research based on race and ethnicity. The program will also recruit women, sexual and gender minorities, as well as people with disabilities, people from rural areas and of lower socioeconomic status so that 75 percent of subjects are those who have been underrepresented in

traditional biomedical research.

Mr. Dishman outlined the six program building blocks for All of Us.

- The **Data and Research Center (DRC)** will act as the data repository to capture, clean, curate, and share data in a secure environment. It will also be the responsible party for developing, licensing, and obtaining research tools. The award for this portion of the project went to Vanderbilt University, Verily, and the Broad Institute.
- The **Biobank** will be the repository for processing, storing, and sharing the estimated 35 million biosamples. This contract has gone to Mayo Clinic, where building construction has been completed, including robot installation.
- The **Participant Center**, which will direct volunteer participant enrollment, digital engagement innovation, and consumer health technologies, including wearables. This award has gone to Scripps Research Institute (with multiple partners).
- The **Participant Technology Systems Center**, awarded to Vibrent Health, is tasked with building out the participant-facing platforms, including web-based, Apple, and Android apps.
- A robust network of **Health Provider Organizations (HPOs)** includes more than 20 regional medical centers, federally qualified health centers, and VA facilities that will be responsible for enrolling and retaining participants. One example is Geisinger Health Systems in Pennsylvania, which is collaborating with the VA to recruit All of Us participants from the Million Veterans program and then expand recruitment to include active-duty military personnel, as well. Other HPO partners include Northwestern University, University of Arizona, the California Precision Medicine Consortium, the New England Precision Medicine Consortium, and others. Additional HPOs will be added to the network soon.
- **Communications and engagement** is the last component. Two contractors, Wondros and HCM, will provide communications, marketing, and design expertise to coordinate engagement and develop a community partners network.

Mr. Dishman emphasized to the Council that participants will also be able to enroll directly, without going through a physician. Accordingly, the All of Us community partners network will be important for expanding the geographic and demographic reach. The goal is to develop 31,000 evaluation and specimen collection sites that will cover 97 percent of where people in America live.

Mr. Dishman outlined direct volunteer and HPOs associated with components of the V1 protocol for All of Us including:

- Branding and content;
- Education and awareness;
- Outreach and recruitment;
- Enrollment and informed consent;
- Baseline evaluation and biospecimen collection; and
- Sustained engagement

He also described a general schedule that involves launching a beta phase of All of Us in May 2017 pending testing results and IRB approval of the Version 1 protocol. The national launch should follow in October 2017.

Mr. Dishman outlined use cases for how the program would assist research and treatment of cardiovascular disease, cancer, and kidney disease. For example, the breadth of data from All of Us should help the clinical community better understand the root causes, pathways, and patient experiences of chronic kidney disease. The richness of the dataset will allow clinicians to leverage -omics data to understand risk factors more deeply, including immune cell profiling, epigenomics, metablomics, proteomics, and microbiomics. The hope is that these data will lead to precision therapeutics for disease and that the diversity and scale of All of Us will allow for the detection of differential responsiveness (e.g. off-target effects).

Mr. Dishman emphasized that this is just the first version of the All of Us program; subsequent versions will build on this foundation. This first version will include a set of surveys to establish basic information like patient demographics, family history, and electronic health record (EHR) consent. (All HPOs have demonstrated their ability to send patient EHR data in the necessary format.) Additionally, the baseline assessment will include physical measurements like height, weight, waist circumference, and blood pressure. Blood and urine samples will also be obtained.

Mr. Dishman reminded the Council that both the Advisory Council and the larger NIDDK community will be able to influence many aspects of All of Us. He asked Council members to help identify issues that would have a multi-area impact even beyond any clinical expert's own field.

The All of Us Research Program plans to hold a series of national workshops in March or April 2018. Experts, patient advocacy groups, and outside funders will all be invited and asked to envision and brainstorm about how the power of the full cohort program can advance the state of scientific knowledge in their own area of interest and expertise. What short-term, medium-range and long-range hypotheses would they want to test for which the power of one million patients is adequately suited? What would they need to do to capture their relevant data? These workshops will cover a variety of disciplines and therapeutic arenas to develop projects with multi-field impact.

Mr. Dishman closed by emphasizing the need to envision precision medicine as a new, broader ecosystem that embraces the clinical and financial ecosystems with which it interacts. Data and innovations will be shared freely and improvements evaluated holistically.

Council Questions and Discussion

Is there an intervention that will be part of the All of Us program?

Mr. Dishman emphasized that the All of Us Program is just one part of the Precision Medicine Initiative. While it is primarily seen as a data collection research project, he is hopeful that, through the VA, CMS, and the CMS Innovation Center, intervention studies and tests on comparative

methods will be possible. Participating HPOs may propose their own intervention studies as data accumulate from their sites.

How will you ensure that children are adequately represented among participants, given the increasing evidence that what happens in childhood defines adulthood?

Mr. Dishman answered that, at the time of its launch, the All of Us Research Program will be able to include only adults ages 18 and over, due to informed consent requirements. However, a committee is currently being assembled to address the challenges of including children. A key consideration in this is navigating all relevant state laws. Mr. Dishman stated that he has been conferring with Dr. Matthew Gillman as the Environmental Influences on Child Health Outcomes (ECHO) Program Director for NIH, as well as Dr. Diana W. Bianchi, director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Mr. Dishman also noted that, for similar legal and informed consent reasons, the program will not be able to include incarcerated persons at the time of its launch.

Who will curate the incoming samples? What quality controls will be in place?

Mr. Dishman stated that the Biobank and the Data & Research Center will operate according to current best practices. For example, the Biobank at the Mayo Clinic will be able to receive participant samples from anywhere in the U.S. within 24 hours. All sites must have evening and weekend hours to increase participation among people who are not available during regular business hours.

As far as data curation, Mr. Dishman explained that all data will be stored in its original state as well as being cleaned and de-identified so that researchers and the public can have access to it. This dual storage system will ensure that researchers will be able to study and refine the data curation algorithm itself, as well as the actual dataset. He is conferring with the National Science Foundation and others regarding this issue.

Given that prevention is a critical aspect of many chronic conditions like cardiovascular disease and diabetes and other metabolic conditions, how will prevention and other longitudinal issues be represented in the dataset?

Mr. Dishman replied that there have been some conversations and debate about how to accelerate and standardize prevention research, but no consensus has emerged. He emphasized that this has been and will continue to be one of the greatest challenges involved in shifting researchers' focus from specific disease states to a holistic approach.

How will All of Us ensure and protect participants' confidentiality?

Mr. Dishman emphasized that All of Us will operate with privacy and security principles developed in consultation with ethicists, patient advocacy groups, industry partners, and government agencies. Mr. Dishman explained that the dataset will operate using a three-tiered security system. The first tier, which will contain only de-identified data, will be completely open

to the public. No login or institutional affiliation will be required. For the second tier of data, users will have to adhere to a set of principles that are still being developed in conjunction with ethicists and others. The third tier of data will require a login and affiliation with an institution that can perform validation. This tiered data system will ensure that no identifying data will be in the public domain. There will need to be an extensive educational outreach to ensure that all participants understand what protections certificates of confidentiality covey and how the 21st Century Cures Act has enhanced some protections.

Will All of Us have an industry-based component?

Mr. Dishman answered that he expects that the program will develop public-private partnerships as issues and interests develop. The hope is that the pharmaceutical and medical device industries will use the dataset to develop needed devices and interventions. The necessary rules of engagement and policies are starting to be worked through.

VII. COFFEE BREAK

VIII. UPDATE FROM THE DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

Dr. Joshua Gordon

Dr. Rodgers introduced Dr. Gordon, who earned his M.D. and Ph.D. in a dual degree program at the University of California at San Francisco, and then went to Columbia University for his psychiatry residency and research fellowship. He joined the faculty of Columbia in 2004 as an assistant professor in the Department of Psychiatry. He was also a research psychiatrist at the New York State Psychiatric Institute and a psychiatrist at New York Presbyterian-Columbia. He was associate director of the Columbia University New York State Psychiatric Institute psychiatry residency program, where he directed the neuroscience curriculum and administered research programs for residents. Dr. Gordon's research is focused on the analysis of neural activity in mice carrying mutations of relevance to psychiatric diseases, and his lab studies genetic models of these diseases from an integrative neuroscience perspective focusing on understanding how a given disease mutation leads to a behavioral phenotype across multiple levels of analysis. His research has direct relevance to schizophrenia, to anxiety disorders, and to depression.

Dr. Gordon started by sharing some background about NIMH, the NIH's principal institute concerned with research regarding mental illness and its underlying neurobiology. NIMH envisions a world in which mental illnesses are prevented and cured, and the Institute's mission is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. NIMH supports about 3,000 research grants and contracts at universities and institutions around the U.S. and overseas. Additionally, the Institute's intramural research program supports approximately 600 scientists working on the NIH campuses.

As Dr. Gordon has been with NIMH for less than a year, he has no immediate plans to launch rapid

and dramatic changes in direction. He identified his first task as being to listen to the perspectives of the people who are invested in what the Institute does.

Dr. Gordon supports the widely held view that this is a time of unprecedented possibilities for better understanding the brain, thanks largely to basic neurobiology research that is funded by a variety of NIH agencies, as well as the BRAIN Initiative. Technology is advancing rapidly, genetic clues are being deciphered, and new approaches are emerging for characterizing and observing the connection between circuits and behavior.

Complex challenges remain. These include diagnostic heterogeneity and a lack of correspondence between psychiatrists' diagnoses and the underlining biology that has limited the profession's ability to make advances. Also, psychiatric treatment options remain limited in their efficacy and in their reach.

Dr. Gordon believes that the key to addressing those challenges is to create a balanced research portfolio that supports diversity in scientific workforce, study participants, subject matter, and research approaches. He also seeks balance between short-, medium-, and long-term objectives. Examples include:

- **Short-Term Goal: Suicide Prevention -** According to CDC data, age-adjusted suicide rates in the U.S. have steadily increased since at least 1999 for both men and women. Through partnerships with the VA and with private health care agencies, NIMH has been able to develop algorithms to detect individuals who are at risk for suicide and refer them for treatment. Additionally, researchers have amassed modest evidence that some treatment programs successfully prevent suicide, and the novel drug ketamine has been shown to acutely lower suicide risk. These advances and others made over the last five years have the potential to address suicide prevalence.
- **Medium-Term Goal: Understanding of Neural Circuits** – Circuit neuroscience is foundational to improving our understanding the neural circuitry underlying the devastating symptoms of mental illness. Current understanding holds that etiological factors such as genes or experiences result in molecular or structural pathology to create circuit dysfunction, which in turn leads to neuro-functional disability, which affects behavior. Research using animal models shows that it is possible to identify circuits involved in dysfunction and to manipulate them to repair or mediate that dysfunction. Translating these findings to humans is an intriguing prospect but much more concerted effort is needed. NIMH can take an active role by directing psychiatric neuroscientists to explore ways to identify, label, and manipulate these circuits in human beings, whether that be through traditional pharmacological approaches or novel circuit therapeutics.
- **Long-Term Goal: Develop Computational Psychiatry** – Dr. Gordon believes that bringing computational and theoretical skills to psychiatry has the potential to change both research and treatment in the field. The most familiar application of this is to use data mining of large datasets to explore more effective ways of diagnosing individuals or identifying their precise behavioral abnormalities. Dr. Gordon envisions additional uses for computational psychiatry to include biophysical modeling, computational modeling, and computational phenotyping, and to model how a defect at the cellular level might affect

behavior. This approach may make it possible to test links across multiple levels of analyses, including genetic, molecular, cellular, circuit, and behavioral. Computational psychiatry could also formalize behavioral analysis by defining underlying algorithms and facilitating neurobiological and clinical studies, and providing quantitative assessments of the utility of specific biomarkers. Ultimately, this would lead to an enhanced and integrative nosology.

Dr. Gordon also provided insights into well-known controversies and emerging initiatives within psychiatry, including the research domain criteria initiative, the concept of experimental therapeutics, and the notion of how much support NIMH should offer "big science" and "small science," and what the policy ramifications are for each.

- **Research Domain Criteria (RDoc)** – The aim of this initiative is to refocus and align clinical research in psychiatry with current developments in biological, cognitive, and social science research. In this approach, researchers focus on a behavioral domain rather than a diagnosis, as is currently done. For example, a researcher interested in learning about psychosis would recruit subjects who display that behavior, rather than subjects who have been diagnosed with a specific diagnosis, such schizophrenia, bipolar disorder 1, or major depression. The goal would be to try to understand psychosis as a domain of behavioral function at multiple levels of analysis: the behavioral level, the neurocircuit level, the cellular level, the molecular level and gain an understanding of the underlying neurobiology of psychosis. The hope would be to conduct large-scale behavior experiments to drive a bottom-up approach to parsing out the domains of human behavior.
- **Experimental Therapeutics Approach** – This is a new—and currently unproven—two-phase approach to clinical trials. In the approach, the hypothesis regarding the target of the intervention is first tested to verify that the intervention engages the target *in vivo* and in humans. If this early stage produces negative results it is an indication that the proposed mechanism underlying the disease may need reconsideration and suggests that attention should be redirected. Only after verifying that the intervention engages the target hypothesized to be pertinent to the underlying mechanism of the disease would the trial move forward. In this approach, the testing of the intervention provides information about both the mechanism underlying the disorder as well as the intervention's potential for therapeutic utility.
- **Genomics** – The new National Advisory Mental Health Council (NAMHC) Genomics Workgroup will offer advice on future directions in psychiatric genetics and functional genomics, including how best to address the gap in knowledge between gene discovery and mechanistic models of disease that transcend categorical DSM disease classification. Some of NIMH's efforts associated with genomics research includes a recent workshop focused on leveraging electronic medical records for psychiatric genetic research and establishing a Psychiatric Genomics Consortium that uses an NIMH repository to conduct meta-analysis of Gene Wide Association Study data.
- **"Big Science" Versus "Small Science"** – Dr. Gordon's view is that big science should build infrastructure that allows small scientists to pose hypotheses and mine data for meaning and significance.

Dr. Gordon concluded his presentation by sharing his vision of the future at NIMH. This includes prioritizing excellent science and within that realm diversity of science. NIMH will focus on learning and working closely with other NIH components to gain insight that can help inform the direction of future research programs. Finally, he encouraged broader thinking about neuroscience, psychiatry, and public health to build momentum towards treatments that can transform the lives of individuals, families, and communities affected by mental disorders.

Council Questions and Discussion

How can we create mental health research programs that acknowledge and address the interactions between physiology and behavioral sciences?

Dr. Gordon agreed that this is a key area of research. Using multiple sclerosis (MS) as an example, Dr. Gordon explained that originally the high rate of depression in people with MS was explained by the stress of having a debilitating disease. However, quantitative studies showed that people with MS had higher rates of depression than people with other disabling diseases. Later researchers found that the immune mediators of MS affect mood and brain function and could result in psychiatric symptoms. This research has decreased the stigma of depression and opened-up new possibilities for treatment.

Scientific research has long operated in a climate where the currency of success was an independent award. How will NIMH reconcile this as more disciplines are applying big data solutions and methods that often don't square with an independent award mindset?

Dr. Gordon emphasized the need for a funding focus that favors the creation of very large datasets, which can then be analyzed by a large number of independent researchers. This would require substantial investment and an evolving paradigm that moves away from the idea that publicly funded individual researchers can lay claim to the data they generate, which rightfully belong to the public. He suggested that a value measure in a scientific community is the science performed and papers produced. It is important to get credit for contributions to a paper. When someone uses a dataset that is not theirs, the data source should be cited in the references and this contribution can be valued in a way that is comparable to the way the paper itself is valued. If we establish standards for this valuation it can be tied into, for example, demonstration of progress associated with grants.

Dr. Gordon's vision is that data from NIMH-funded studies should become available as soon as they are acquired. Multiple individual investigators can then be funded to use that data to test their hypotheses, to construct the models of how the data are shaped, and to explore competing ideas about what knowledge can be gleaned from that data. In this way, innovative young investigators and small groups of investigators would have access to datasets that will allow them to move beyond reliance on small, poor-quality datasets that do not advance science. This should be accompanied by a clear message to trainees that strong data science and quantitative reasoning abilities will be crucial for building successful careers.

What work is NIMH currently doing to investigate the gut-brain axis and gut microbiome? Are there opportunities for NIMH and NIDDK to work in partnership in this area?

Dr. Gordon responded that NIMH has begun to fund microbiome studies. The Institute is still determining whether initial research should focus more on model systems or human-based studies, with the same caveats seen in other areas: human-based studies need very large datasets and findings from animal models may or may not transfer to humans. He sees the microbiome as an important avenue of pursuit to understand some psychiatric disorders. Data and samples from NIDDK studies may aid in this process.

As an Institute that's focused on a specific disease and biology area, how has NIMH addressed the issues of trying to ensure that the kinds of data and biological samples gathered from big data initiatives will be relevant for that disease area?

Dr. Gordon is very optimistic about the All of Us cohort and believes that it will support a data-driven approach to analyzing human behavior. NIMH is preparing for the advent of the Precision Medicine Initiative and the All of Us cohort by developing a broad panel of behavioral tests that can be shared with the research community. The goal is to be able to use the All of Us web portal to reach enough participants to yield a well-powered body of data. Similarly, the All of Us electronic medical records link may provide access to a large body of data. NIMH will participate enthusiastically and fund innovative ways to gather, use, and store relevant data from All of Us.

When you get all this data from an individual, do you pool it or does it stay linked to the individual?

Dr. Gordon said that his understanding was that all data from the All of Us cohort will be anonymized in the public database, but researchers will be able to access the information—electronic health record, behavior panel, blood sample, etc.—to get the full profile of an individual, unidentified patient. Microbiome samples will be stored and available for researchers to analyze.

Should this type of research be done by individual institutes like NIMH or should many institutes at the NIH be involved?

Dr. Gordon answered that this is an important question and that NHGRI and Mr. Dishman of All of Us are aware of it and will continue to discuss it.

How will researchers be able to demonstrate target engagement when tissue samples must be shared between, say, brain biologists and kidney biologists?

Dr. Gordon responded that, for drug development, PET scan is one way to show whether the drug being administered binds to the appropriate receptor. Another method is functional imaging, which has been used in a few NIMH trials to date. Researchers are asking whether psychotherapy engages a particular neural circuit, and they use imaging during sessions to determine the answer.

Can you elaborate on your earlier comment that ketamine is an example of developing better

treatments for people with existing disease? And can you talk about other physical methods that researchers are using to stimulate various portions of the brain?

Dr. Gordon explained that infusing the anesthetic ketamine at a lower dose than causes the usual psychometric effects can dramatically decrease depression symptoms after just hours, as opposed to the weeks it takes using antidepressants. Ketamine also reduces suicidal ideation for several days to a week, and then another infusion can reproduce the effect. Researchers are still studying how to maintain that effect, especially when infusions are impractical. They are also attempting to create orally bio-available forms and ketamine knockoffs that can be patented, so it's an area of great interest.

As far as other methods of stimulating the brain, Dr. Gordon mentioned transcranial magnetic stimulation, in which an induced magnetic field that will cause an electrical field within the brain and activate or inhibit neurons. Researchers have shown that it's modestly effective for depression and maybe for some other disorders. Work now is focused on developing better, more personalized targeting. They also want to understand more about the brain circuits that are being engaged to achieve better therapeutic outcomes and, perhaps, bigger effect sizes.

Dr. Gordon also described the use of deep brain stimulation for resistant depression as a promising area of exploration, as well as the even more speculative transcranial direct current stimulation and transcranial alternating current. They may be promising early stage treatments or they may be worthless, he noted. NIMH is funding some studies in this area.

Dr. Gordon also mentioned circuit-level interventions that are trying to harness the technologies being used to manipulate brain circuits in animals for use in humans. The goal would be to engineer ways to deliver proteins to human neurons. Theoretically, those neurons could be manipulated in specific ways to benefit patients.

IX. UPDATE FROM THE DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
Dr. Tabak

Dr. Rodgers introduced Dr. Lawrence A. Tabak, Principal Deputy Director of NIH. Before assuming his current post, Dr. Tabak was the director of the National Institute of Dental and Craniofacial Research from 2000 to 2010. Prior to joining NIH, Dr. Tabak was a senior associate dean for research and professor of dentistry and biochemistry and biophysics at the School of Medicine and Dentistry at the University of Rochester in New York. Dr. Tabak continues to run an active research program focused on structure, biosynthesis, and the function of glycoproteins. Among his many honors, he was elected a member of the National Academy of Medicine.

Dr. Tabak’s presentation focused on NIH’s efforts to promote a stronger and more stable biomedical research workforce. He began by noting that NIH is entrusted to maximize the impact of research dollars that it expends. Similarly, the NIH is committed to develop and sustain the most qualified workforce possible.

Dr. Tabak quoted from a perspective paper in PNAS by Dr. Bruce Alberts and colleagues: "The long-held but erroneous assumption of never-ending rapid growth in biomedical science has created an unsustainable hypercompetitive system that is discouraging even the most outstanding students from entering our profession... This is a recipe for long-term decline... It is time to confront the dangers at hand and rethink some fundamental features of the U.S. biomedical research system."

Dr. Tabak illustrated this hypercompetitive atmosphere by sharing data showing that, while the number of NIH awardees has remained stable since 2003, the number of people applying for grants has risen substantially. Additionally, he noted that Dr. Judith Kimble and colleagues held workshops at the University of Wisconsin-Madison that identified two core problems -- too many researchers vying for too few dollars, and too many postdocs competing for too few faculty positions.

Dr. Tabak also shared data showing the percent of funded investigators stratified by age over time from 1990 to 2015. The proportion of early career investigators (up to age 45) was in a free fall from 1990 until about 2005 which coincides with NIH instituting an early stage investigator policy which has stabilized but not yet increased the percentage of funded investigators in this cohort. Mid-career investigators (age 46-60) compose the greatest percentage of NIH grantees, but their success has been eroding since 2005. Late-career investigators (age 60+) are the smallest number of grantees, but they have been successfully outcompeting younger colleagues since around 2005. Dr. Tabak emphasized that the proportional increase in the Late-career investigators is not sufficiently explained by simple demographic trends associated with the population surge wave associated with the Baby Boom cohort moving through the workforce.

Dr. Tabak then explained the uneven distribution of NIH resources. He said that 1 percent of scientists receive 11 percent of the total dollars, 10 percent of scientists receive 40 percent of the dollars, and 20 percent receive 56 percent of total research dollars. The concentration of resources among the most senior investigators challenges NIH's ability to maintain a future biomedical research workforce. But, does this skewed distribution of resources yield optimal productivity? The NIH is concerned with what Dr. Tabak described as this maldistribution among the different cohorts.

In its search for appropriate surrogates to measure investigator productivity in near-real time, NIH is exploring whether bibliometrics can be used to compare the influence of publications or productivity of an award. Commonly used measures and some considerations include:

- Publication Counts: field-dependent, use-independent
- Impact Factor: journal-level not article-level
- Citation Rates: field- and time-dependent –h-index: field-dependent and time-dependent
- Relative Citation Ratio: article level and field independent

Of these, NIH prefers the relative citation ratio (RCR), which it developed and has the advantage over these commonly used measures of being able to describe things at the article level in a field-

independent way. Hutchins et al., 2016, *PLOS Biology,* lays out in great detail how the RCR was developed and how it has been validated using the so-called gold standard of investigators actually providing their independent review of publications that are then matched up against the RCR index. There has been remarkable correspondence between them.

Dr. Tabak shared data showing the incremental research output according to the extent of grant support. In plotting the weighted RCR per year of 71,493 principal investigators funded from 1996 to 2014 against the funded R01 grant equivalents per year, one sees the law of diminishing returns. The NIH sees a substantial incremental return for investigators receiving their first or second NIH grant, but, on average, the returns diminish gradually after about the third grant.

The NIH is currently funding less than 20 percent of its applications. According to Dr. Tabak, the optimal funding rate would be at least 30 percent of the applications. Given the quality of many applications, a great deal of promising science is being left unfunded.

Dr. Tabak also addressed the widespread perception that only well-funded labs produce high-performing early stage investigators. According to agency data, early stage investigators who are successful at obtaining an NIH RPG are no more likely to come from a well-funded lab than one that is not well-funded. Other research has shown that increases in funding did not predictably increase scientific impact and productivity does not increase proportionally in larger research groups.

Dr. Tabak turned to the 21st Century Cures Act, which directs the NIH to promote policies that will promote earlier independence and increased funding for new investigators. The language included in the Act reads as follows:

> **404M.Next generation of researchers** (a)Next Generation of Researchers Initiative - There shall be established within the Office of the Director of the National Institutes of Health, the Next Generation of Researchers Initiative (referred to in this section as the Initiative), through which the Director shall coordinate all policies and programs within the National Institutes of Health that are focused on promoting and providing opportunities for new researchers and earlier research independence.

Dr. Tabak stated that he has visited many of the NIH's National Advisory Councils to gain input on three important questions. How can the NIH:

- Increase the number of early career funded scientists?
- Stabilize the career trajectories of all scientists, particularly this group?
- Maximize the impact of its funding?

NIH is considering several different approaches. He pointed to recommendations outlined by Judith Kimble et al at the University of Wisconsin in a June 30, 2015 journal article, including a policy of redistributing funds to support both junior investigators and pioneering projects. The authors of that article observed, "That redistribution will be painful, especially for established senior investigators, but necessary to support the next generation and cutting edge research."

He also pointed out that the Federation of American Societies in Experimental Biology (FASEB) has published a report on sustaining discovering in biological and medical sciences that recommends limiting the amount of funding awarded to any individual scientist or laboratory to enable more people to be actively engaged in research. Evidence suggests that limiting the amount of funding might enhance productivity of the portfolio overall.

NIH solicited public input on this issue in 2015, and the most common suggestion was to cap the number of NIH grants or amount of funds a principal investigator can receive.

Dr. Tabak emphasized that the NIH is committed to implementing efforts to address these funding disparities and welcomes the Council's input on how to achieve this goal.

Institutes, Centers and Offices within the NIH will continue to use a variety of mechanisms to make funding decisions. These include:

1. Adhering to the early stage investigator policy to the extent that they're able.
2. Expanding R01 investigator-initiated research at the expense of institute-solicited FOAs, again to the extent possible.
3. Encouraging R56 Bridge Awards for early stage investigator to increase R01 resubmission success rates.
4. Targeting the so-called R35 award for mid-career emerging investigators, patterned after the so-called Maximizing Investigators' Research Award (MIRA) that NIGMS has adopted.
5. Continuing to carefully track funding patterns across all career stages

However, none of these approaches directly address the issue of diminishing returns in the research groups of highly funded investigators. Because the highly funded investigators, for the most part, are supported by two or more Institutes, Centers or Offices, Dr. Tabak called for a trans-NIH approach to address this.

Dr. Tabak said that NIH is considering a new measure, the grant support index (GSI). This number will attempt to capture a measure of a PI's grant support as a way to estimate investigator bandwidth. The measure takes into account that some types of research are inherently more expensive—and more time-consuming— than others, but that expense and time are not directly associated.

The plan is to benchmark the GSI to the R01, at a value of 7 points per grant. The R21 will be fewer points and the R35 will be more.

The proposed GSI plan will:

- Institute a new trans-NIH policy that resets expectations for support provided to any single investigator. NIH will use the GSI to monitor levels of PI bandwidth and automatically calculate GSI for every PI.

- Work with the applicant to limit the bandwidth of any single PI to a GSI of 21 (roughly equivalent to 3 R01s). Applications with investigators above a GSI of 21 will submit a plan with any new or competing application to mitigate any increase to the investigators' GSI.
- Begin with applications being submitted this fall (2017). Application of the policy will be rolling with submission of a new application or a competitive renewal. No current studies will be defunded.

Dr. Tabak emphasized that, in 2016, 33,472 scientists received NIH funding. Of these, 65 percent have a GSI of less than or equal to 7. Only 5 percent have a GSI of more than 21. So nearly all current investigators will be below the 21-point threshold.

Additionally, there will be a rigorous exceptions process that the lead Institute, Center, or Office can initiate. It will consider the unique research requirements of the lead agency to support investigators at all career stages and the need to maximize productivity of grant resources. The final decisions will be made centrally in the NIH Director's office because of the trans-NIH nature of the funding patterns that these investigators enjoy.

Dr. Tabak emphasized that implementing the GSI program will allow NIH to redirect resources for about 1,600 new awards over the next several years.

NIH will also develop an analogous program for its intramural research program. Comparable metrics have not yet been developed.

Several major issues with the GSI program remain to be resolved. These include:

- How can NIH best account for complex clinical trial networks and other complex infrastructure programs?
- How can NIH account for team science?
- Are special considerations required to account for the need to attract highly talented investigators into new fields of science?
- Where should the locus of decision making occur: at the first or second level of peer review, or will it be post-Council decisions by ICOs?

Dr. Tabak concluded by reiterating NIH's commitment to assuring the robustness and stability of the next generation of biomedical scientists and optimizing the use of resources for maximum impact. Achieving this goal will require a variety of approaches and each ICO will use a different mix of these methods. He called again for input from the research community and the Advisory Council members to help work through the details of implementation of this strategy.

Council Questions and Discussion

Science is moving toward more cooperative activities, with pooled and shared data, but an R01 is generally focused on individuals. Using the R01 as the currency of success may defeat the GSI process and may discourage senior investigators from participating in collaborative or program

projects because the proposed system would not be in accordance with institutions' expectations of effort and reward regarding PIs. The system asks senior investigators to prioritize being a multi-PI versus doing an independent investigation.

Dr. Tabak replied that his expectation is that large, collaborative program projects would receive a point schedule commensurate with their scale. Under the proposed system, multiple PIs on the same R01would not each be charged 7 points. Rather, they would be charged some proportion of the total, say, 5 points. He calculated that the proposed points system would allow for four multi-PI applications, (4 x 5 = 20), plus take the lead on a T32, and still be in the cap. He agreed that the proposed system would ask senior investigators to prioritize their applications. But, from a faculty retention perspective, he reiterated that the GSI system should help institutions stabilize their younger faculty members' careers.

Will the NIH share the models and methodology used in the analysis used to develop the GSI to help better anticipate any unintended consequences that may develop?

Dr. Tabak said the NIH is happy to share the dataset upon request. The study explaining the RCR was published in PLOS in 2016. There is also a public website that allows people to calculate RCRs themselves. Anticipating unintended consequences is part of the motivation for meeting with Advisory Councils to get their input.

One unintended consequence may be that this system will be very discouraging for scientists with center grants or program grants to take on the responsibility of resource development in the community.

Dr. Tabak called that an "absolutely fair point" and something the NIH will take into consideration when finalizing the policy.

Are we training too many people?

Dr. Tabak noted that many people who just miss getting funding are excellent researchers. Currently, the most senior group of investigators are the only group that continues to be highly successful. Considering the best way to distribute resources, especially at the margin, so that we can get things back into better balance is appropriate. Eventually the Baby Boomer generation will fade. When this happens who will be left in the workforce if all these people drop out of the system?

Training grants like T-32s and T-35s can be onerous if you're a PI, because you don't get any salary support for them. You spend a lot of time on them, and you don't get any recognition for it. Have you considered how this change may discourage investigators from pursuing them?

Dr. Tabak responded that the NIH has come to understand that T-32s are very time-consuming and a service function. This realization has caused them to reconsider what point value to assign.

How often will this point system be re-evaluated?

Dr. Tabak reiterated that the GSI program is an experiment. The outcomes will determine how rapidly the NIH revisits and adjusts the program that was originally laid out.

With regard to the GSI methodology, you said that 10 percent of researchers commandeer nearly 40 percent of the resources, but isn't that because all of that money gets assigned to the PI, especially in larger groups? Will this system put us in the trap of legislating how researchers spend their time?

Dr. Tabak said that the PI does have a very strong role and a considerable amount of power when it comes to money distribution among a research team. He agreed that the amount of time different people require to do the same task always varies, but then reiterated that the uneven distribution of grants among investigators requires new approach.

What if you set a pay line so that an investigator who received three or more grants would have meet more stringent standards? To not tell an investigator upfront that he wouldn't get the money is very demoralizing.

Dr. Tabak said the new proposal would let investigators know upfront whether they were eligible, based on that 21-point cap. The proposed exceptions process should also allow a certain degree of flexibility in exceptional circumstances.

Won't applicants look for ways around the 21-point cap?

Dr. Tabak stated that the proposed system, with its stated cap, will be open and fair. He emphasized that successfully exceeding the points cap will require adjudication and will not automatically be granted, so applicants should prioritize their applications based on that knowledge.

One unintended consequence may be a potential loss of spontaneity in pursuing new projects. Some "U" grants come to mind, which the NIH has promoted to researchers and have been effective, but carry little money with them. The points system could discourage researchers from pursuing such grants.

Dr. Tabak replied that the evaluation for several types of grants—including T-32s, core, and network grants—will be reviewed to ensure that their service-oriented natures are considered when assigning points.

What will the GSI system do to grant-making foundations who provide funding to junior investigators who need support to apply to the NIH for their first R01 grant? It's possible that savvy investigators who get rejected by the NIH could then apply for foundation support, in effect siphoning off support from investigators trying to get their first R01? Additionally, foundations may endure political consequences if they push back on the more senior investigators.

Dr. Tabak pointed out that non-NIH funds will not be factored into the GSI system. He agreed that more senior investigators could seek foundation support, changing the applicant mix for those

grants. However, foundations have within their purview the ability to continue with their mission, however it is articulated, and in some ways, may enjoy more flexibility than the NIH in this regard. He agreed that concern about political consequences for foundations is a fair point.

If we really do see that the fifth and sixth R01 are not as productive, that suggests that our study sections are not taking that kind of productivity into adequate consideration. Shouldn't productivity become part of the consideration at the Institute level when the funding decisions are made?

Dr. Tabak responded that this should not become a study section issue, but should remain one at the level of secondary review and/or decision-making by the Institute director and his or her staff. The NIH has tried with the so-called million-dollar policy to adjudicate this in some ways, but there were some shortcomings to that approach. The current belief is that, once an optimal scoring system is established, the GSI will yield a better way going forward than the previously tried million-dollar discussion that most, if not all, Councils have had.

With the heterogeneous portfolio of science, grants of the same size but different structures may result in differences in opportunities for training and development of trainees who go on to get their own support. Do you see the same diminishing returns associated with trainee outputs if you compare similar grant structures, such as comparing preclinical R01s against preclinical R01s?

Dr. Tabak responded that, to his knowledge, NIH has not looked at the data using, for example, just comparably structured R01s, to consider outputs of the trainees and investigators that they produce. Dr. Tabak indicated that he felt this was a good idea and will look into it.

X. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1368 grant applications (440 primary and 928 dual), requesting support of $501,368,358 were reviewed for consideration at the May 10, 2017 meeting. An additional 1120 Common Fund applications requesting $1,575,860,327 were presented to Council. Funding for all but one of these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, 1142 applications requesting $376,400,723 received second-level review through expedited concurrence. All of the expedited concurrence applications were recommended for funding at the Scientific Review Group recommended level. The expedited concurrence actions were reported to the full Advisory Council at the May 10, 2017 meet

XI. ADJOURNMENT

Dr. Rodgers

Dr. Rodgers expressed appreciation on behalf of the NIDDK to the Council members, presenters, and other participants. He thanked the Council members for their valuable input. There being no other business, the 204th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m.

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

Griffin P. Rodgers, M.D., M.A.C.P.
Director, National Institute of Diabetes and Digestive and Kidney Diseases, and
Chairman, National Diabetes and Digestive and Kidney Diseases Advisory Council