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

The NIDDK Director, Dr. Griffin P. Rodgers, called to order the 198th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m. on May 13, 2015, in Building 31 of the NIH campus, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Sharon Anderson
Dr. Gopal Badlani
Dr. Joseph Bonventre
Dr. David Brenner
Dr. Eugene Chang
Dr. Mark Donowitz
Dr. Lee Kaplan
Dr. Kenneth Kaushansky
Dr. David Klurfeld
Ms. Ellen Leake
Dr. Jerry Palmer
Dr. Craig Peters
Dr. Alan Saltiel
Dr. Jean Schaffer
Dr. Alan Shuldiner
Dr. Irving Smokler
Dr. Bruce Spiegelman
Ms. Pamela Taylor
Dr. Robert Vigersky

Also Present:
Dr. Griffin Rodgers, Director, NIDDK
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, Guillermo – NIDDK
Barnard, Michele – NIDDK
Bavendam, Tamara – NIDDK
Begum, Najma – NIDDK
Best, Carolyn – American Urol. Assoc.
Bleasdale, John – CSR
Blondel, Olivier – NIDDK
Bourque, Sharon – NIDDK
Bremer, Andrew – NIDDK
Buchanan, Sarah – NEFCARE
Calvo, Francisco – NIDDK
Camp, Dianne – NIDDK
Carrington, Jill – NIDDK
Cerio, Rebecca – NIDDK
Cheng, Clara – CSR
Chen, Hui – CSR
Cho, Jennifer – NIDDK
Choporis, Louis – NIDDK
Chowdhury, Bratati – NIDDK
Copeland, Randy – NIDDK
Cowie, Catherine – NIDDK
Curtis, Leslie – NIDDK
Dayal, Sandeep – NIDDK

Densmore, Christine – NIDDK
Dirks, Dale – NEFCARE
Doherty, Dee – NIDDK
Donohue, Patrick – NIDDK
Doo, Ed – NIDDK
Drew, Devon – NIDDK
Duggan, Emily – NIDDK
Evans, Mary – NIDDK
Farishian, Richard – NIDDK
Feld, Carol – NIDDK
Flessner, Michael – NIDDK
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gallivan, Joanne – NIDDK
Gansheroff, Lisa – NIDDK
Goter-Robinson, Carol – NIDDK
Guo, Xiaodu – NIDDK
Haft, Carol – NIDDK
Hall, Sherry – NIDDK
Hamilton, Frank – NIDDK
Hoff, Eleanor – NIDDK
Hoffert, Jason – NIDDK
Hoofnagle, Jay – NIDDK
Hoover, Camille – NIDDK
Hoshizaki Deborah – NIDDK
Ivins, Jonathan – CSR
Jerkins, Connie – NIDDK
Stephen, James – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Karimbakas, Joanne – NIDDK
Ketchum, Christian – NIDDK
Kimmel, Paul – NIDDK
Kirkali, Ziya – NIDDK
Kranzfelder, Kathy – NIDDK
Kuaban, Alice – Amer. Soc. Heme.
Kuczmarski, Robert – NIDDK
Laakso, Joseph – Endocrine Society
Laughlin, Marin – NIDDK
Leschek, Ellen – NIDDK
Li, Yan – NIDDK
Linder, Barbara – NIDDK
Malik, Karl – NIDDK
Malozowski, Saul – NIDDK
Maruvada, Padma – NIDDK
Margolis, Ronald – NIDDK
Martey, Louis – NIDDK
McBryde, Kevin – NIDDK
Menke, Andy – Social and Sci. Systems
Miller, David – NIDDK
Moxey-Mims Marva – NIDDK
Mullins, Christopher – NIDDK
Mullsteff, Clairisse – NIDDK
Narva, Andrew – NIDDK
Nguyen, Van – NIDDK
Nurik, Jody – NIDDK
Olan, Grant – Amer. Soc. Neph.
Olumi, Aria – Mass. Gen. Hosp.
Pawlyk, Aaron – NIDDK
Perrin, Peter – NIDDK
Perry-Jones, Aretina – NIDDK
Pike, Robert – NIDDK
Pileggi, Antonello – CSR
Podskalny, Judith – NIDDK
Ramani, Rathna – NIDDK
Rankin, Tracy – NIDDK
Rasooly, Rebekah – NIDDK
Reiter, Amy – NIDDK
Riber, Morgan – NIDDK
Rivers, Robert – NIDDK
Roberts, Tibor – NIDDK
Rosenberg, Mary Kay – NIDDK
Rosendorf, Marilyn – NIDDK
Roy, Cindy – NIDDK
Ruhl, Constance –Social and Sci. Systems
Rushing, Paul – NIDDK
Rys-Sikora, Krystyna – NIDDK
Saslowsky, David – Boston Child. Hosp.
Sato, Sheryl – NIDDK
Savage, Peter – NIDDK
Sechi, Salvatore – NIDDK
Serrano, Jose – NIDDK
Sheets, Dana – NIDDK
Shelness, Gregory – CSR
Sherker, Averell – NIDDK
Shepherd, Aliecia – NIDDK
Sierra-Rivera, Elaine – CSR
Silva, Corinne – NIDDK
Singh, Megan – NIDDK
Smith, Philip – NIDDK
Spain, Lisa – NIDDK
Star, Robert – NIDDK
Stoeckel, Luke – NIDDK
Tuncer, Diane – NIDDK
Tatham, Thomas– NIDDK
Teff, Karen – NIDDK
Tilghman, Robert – NIDDK
Torrance, Rebecca – NIDDK
Unalp-Arida, Aynur – NIDDK
Van Raaphorst, Rebekah – NIDDK
Wellner, Robert – NIDDK
Wilkerson, Anita – NIDDK
Woynarowska, Barbara – NIDDK
Wright, Elizabeth – NIDDK
Yang, Jian – NIDDK
Yanovski, Susan – NIDDK

C. ANNOUNCEMENTS

Dr. Rodgers and Dr. Germino

In Memoriam

Dr. William D. Steers, a former NIDDK Council member, passed away in April 2015. He had served on the Kidney, Urologic, and Hematologic Diseases (KUH) Subcouncil. Dr. Steers was Professor and Chairman of the Department of Urology at the University of Virginia Health System, and Editor of *The Journal of Urology*. He was a faculty member at the University of Virginia since 1988, became Chair of the Department of Urology in 1995, and was awarded the Hovey Dabney Professorship in 2003. With more than 300 basic research and clinical publications, his diverse clinical interests spanned urinary incontinence, benign prostatic hyperplasia, neurogenic bladder and robotic surgery for prostate cancer. In addition to serving on the NIDDK Advisory Council, he had been a member of the FDA's Reproductive Medicine Advisory Panel. He also chaired the NIH's Urinary Incontinence and Interstitial Cystitis Clinical Trials. He was a Principal Investigator on the original clinical trials on the use of Viagra for erectile dysfunction. Among his many honors for contributions to urology, Dr. Steers received the American Urological Association's (AUA) Gold Cystoscope Award in 1994 and the Hugh Hampton Young Award in 2011. He was also selected to receive a Presidential Citation in May 2015 for years of service to the AUA.

Dr. Russell Chesney, a long-serving Chair of the Department of Pediatrics at the University of Tennessee Health Science Center and a pediatric nephrologist at Le Bonheur Children's Hospital, passed away in April 2015. Among his many research endeavors, Dr. Chesney chaired the Steering Committee of the NIDDK-funded Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial, and was a leader of the Pediatric Pharmacology Research Unit, funded by the NIH's *Eunice Kennedy Schriver* National Institute of Child Health and Human Development. He also served as President of the American Pediatric Society and Chairman of the American Board of Pediatrics. Dr. Chesney was a committed physician to children and mentor to trainees and colleagues alike.

NIDDK Staff

Dr. Wei Yang, Senior Investigator in the NIDDK Intramural Laboratory of Molecular Biology, was elected to the American Academy of Arts and Sciences. Founded in 1780, the Academy is one of the nation's most prestigious honorary societies. Current membership includes more than 250 Nobel laureates and more than 60 Pulitzer Prize winners. In a recent *Nature* paper, Dr. Yang and her team reported the crystal structure of the RAG1-RAG2 protein complex, which initiates DNA rearrangement to generate millions of antibodies and T-cell receptors that defend against infection.

Dr. Judith Podskalny is retiring from the NIDDK after more than 40 years of service. Dr. Podskalny made major contributions as Program Director for the Career Development and Research Fellowship programs in the Division of Digestive Diseases and Nutrition (DDN). She was also responsible for trans-NIDDK medical student training, involving both short-term training of medical students, and the Medical Student Research Training Program. In addition, Dr. Podskalny served as a Program Director for the Digestive Diseases Centers Programs. She is widely recognized both at NIH and in the extramural community as an extraordinarily dedicated and talented administrator.

Samuel J. Heyman Service to America Medals

Dr. Germino announced that Dr. Rodgers has been honored as a Finalist in the 2015 Samuel J. Heyman "Service to America Medals" – often called the "Sammies." These prestigious awards are presented annually by the nonprofit, nonpartisan Partnership for Public Service to celebrate excellence in the federal civil service. Awards will be announced this Fall. Dr. Rodgers' nomination is based on his research in sickle cell disease. He and colleagues developed the first effective drug treatment--hydroxyurea--for sickle cell disease. This treatment has decreased the need for blood transfusions and lessened pain and suffering for patients. He has also collaborated on a stem cell transplant clinical trial reported last year, which reversed the illness in a majority of patients.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 197th COUNCIL MEETING

Dr. Rodgers

The Council approved, by voice vote, the Summary Minutes of the 197th Council meeting, which had been sent to them in advance for review.

III. FUTURE COUNCIL DATES

Dr. Rodgers

Dr. Rodgers reminded the Council of upcoming Council dates. Most meetings are expected to be a single day. However, Council members were asked to hold both days to ensure flexibility should a situation arise where a longer meeting is required.

2015
September 9-10 (Wednesday and Thursday)

2016
January 27-28 (Wednesday and Thursday)
May 18-19 (Wednesday and Thursday)
September 7-8 (Wednesday and Thursday)

2017
February 1-2 (Wednesday and Thursday)
May 10-11 (Wednesday and Thursday)
September 6-7 (Wednesday and Thursday)

III. ANNOUNCEMENTS
Dr. Stanfield

Confidentiality

Council members were reminded 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 that advisors and consultants serving as members of public advisory committees, such as the NIDDK National 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, partner (including close professional associates), or an organization with which the member is connected.

To ensure that a Council 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 noted that each Council member's folder contained a statement regarding conflict of interest in his or her review of applications. He said that each Council member should read it carefully, sign it, and return it to the NIDDK before leaving the meeting.

Dr. Stanfield said that, at Council meetings when applications are reviewed in groups without discussion, that is, "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.

With respect to multi-campus institutions of higher education, Dr. Stanfield said that: An employee may participate in any particular matter affecting one campus of a multi-campus institution of higher education if the employee's financial interest is solely employment in a position at a separate campus of the same multi-campus institution, and the employee has no multi-campus responsibilities.

IV. REPORT FROM THE NIDDK DIRECTOR

Dr. Rodgers

FY 2015 Operating Budget

Dr. Rodgers reminded the Council that the NIDDK is currently operating on its FY 2015 budget, which provides a 0.8 percent increase over the preceding fiscal year. This is an increase of about $15 million, which includes mandatory funds for the Special Statutory Funding Program for Type 1 Diabetes Research.

FY 2016 President's Budget Request

On February 2, 2015, the President submitted his Fiscal Year 2016 budget request for federal agencies. His budget calls for a $1 billion increase for NIH, of which an increase of $39 million is requested for the NIDDK. These amounts include the special funds for type 1 diabetes research. The President's budget proposes to eliminate sequestration and to use other alternatives to reduce spending over the next decade.

The House and Senate held hearings on the President's budget for the NIH on March 3 and April 30, respectively. Both hearings went well, with Members of Congress expressing strong support for NIH budget increases. The Chairs of the full House and Senate Appropriations Committees have said their goal is to pass all Fiscal Year 2016 spending bills before the end of Fiscal Year 2015 on September 30. However, if the bills are not passed and signed by the President by then, one or more Continuing Resolutions would likely be enacted. Such measures provide stop-gap funding for those agencies whose regular appropriations have not yet been enacted.

House Budget Resolution

One potential impediment to an NIH funding increase in Fiscal Year 2016 is the Budget Resolution passed by the House on May 5. This is not a bill and it does not go to the President for signature and enactment into law. Rather, it is intended to guide appropriations for the entire government. This blueprint assumes that the Congress would cut spending by more than $5 trillion over the next decade, eliminate the deficit, and create a surplus in 2024. The new Budget Resolution continues the practice of imposing caps on discretionary spending. There is an expectation that the House and Senate appropriations sub-committees will operate within these caps, and each committee is given a target spending ceiling. The President has proposed a legislative change to raise these caps.

Special Statutory Funding Program for Type 1 Diabetes Research

On April 16, 2015, the President signed the *Medicare Access and CHIP Reauthorization Act of 2015*. One provision extended the Special Statutory Funding Program for Type 1 Diabetes Research for two additional years--Fiscal Years 2016 and 2017--at a funding level of $150

million each year. The NIDDK will continue to administer the program on behalf of the HHS Secretary.

The NIDDK recently convened a workshop to discuss ideas and receive input on research opportunities in type 1 diabetes that could be pursued with unobligated funds during the current fiscal year. Now that the program has been extended, the NIDDK can use these ideas to plan new and expanded initiatives for Fiscal Years 2016 and 2017.

Due to the timing of this Program's extension, it will not be subject to a reduction in its Fiscal Year 2016 funding through sequestration. Prospects for sequestration of the program's funds in Fiscal Year 2017 are uncertain at this time.

V. PRECISION MEDICINE FOR ADVANCING HUMAN HEALTH

Dr. Eric Green, Director, National Human Genome Research Institute (NHGRI)

Dr. Rodgers introduced Dr. Eric Green, who has been the Director of the National Human Genome Research Institute (NHGRI) since late 2009. Dr. Green earned his M.D. and Ph.D. degrees from Washington University in 1987. During his residency training in clinical pathology, he launched his career in genomics research. In 1992, he was appointed Assistant Professor of Pathology and Genetics, as well as a co-investigator, in the Human Genome Center at Washington University. In 1994, Dr. Green joined the newly established Intramural Research Program of the National Center for Human Genome Research, later renamed the NHGRI. There, he held a number of positions, including Scientific Director from 2002 to 2009, before succeeding Dr. Francis Collins as Institute Director. While directing an independent research program for almost two decades, Dr. Green has been at the forefront of efforts to map, sequence and understand eukaryotic genomes. His work included significant, start-to-finish involvement in the Human Genome Project. These efforts eventually blossomed into a highly productive program in comparative genomics that has provided important insights about genome structure, function and evolution. Dr. Green has authored and co-authored nearly 350 scientific publications.

Dr. Green focused his remarks on the origin, vision, and planning of a new Presidential Initiative on Precision Medicine. He noted that President Obama is very interested in and supportive of biomedical research--particularly genomics. When he was a Senator, the President introduced a bill entitled the Genomics and Personalized Medicine Act of 2006, and strongly advocated for the idea of advancing medical care using genomic information. Although the bill did not move forward, it was indicative of his views. As President, his interest in genomics is reflected in his selection of two leaders in the field for top posts--Dr. Francis Collins as NIH Director, and Dr. Eric Lander as Co-Chair of the President's Council of Advisors on Science and Technology. Moreover, key White House positons are held by individuals with knowledge of biomedical research generally.

In June 2014, the President asked a small group of experts to meet in the Oval Office to strategize regarding opportunities to launch a bi-partisan initiative that would be part of his

legacy. It became clear that he was interested in including genomics in a broader vision. The President decided on the concept of precision medicine, which encompasses extending knowledge about genomics, lifestyle, environmental exposure, and other areas to improve individualized medical care for the advancement of human health. One factor in the President's decision was reportedly a National Research Council publication that put the phrase "precision medicine" on the map, and provided a conceptual foundation for a major U.S. initiative (*Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* National Academies Press, 2011). Dr. Green elaborated on the concept of precision medicine. He said that the physicians and healthcare providers understand that current medical care is based on the expected response of the average patient; however, future medical care will be based more on the uniqueness of individuals. This concept has existed for many years; for example, in the use of prescription eyeglasses precisely tailored to an individual's vision needs.

The President concluded that the time is right to undertake a large, bold initiative to propel this field forward with rigorous, multidisciplinary research. The NIH was assigned the lead role, with the involvement of several other agencies, to develop a planning document that was presented to the President in October 2014 at a meeting that included Francis Collins, Eric Lander, Secretary Burwell, and others. On January 28, the President named and briefly described the Initiative in his State of the Union Address. On January 30, he formally announced and provided details about the Initiative in the East Room of the White House. During a visit to the NIH that same day, Secretary Burwell underscored the President's commitment. Also on January 30, *The New England Journal of Medicine* posted an online article by Drs. Francis Collins and Harold Varmus describing the rationale and general plans for the Initiative.

Since the Initiative's announcement, there have been indications of bi-partisan support in the Congress, which would be essential for funding. The scientific community has responded favorably, and coverage by the lay press has been positive. Moreover, the private sector is showing great interest in partnering with the scientific community. For example, Apple is promoting a "research kit" that provides apps and opportunities for people to participate directly in biomedical research by using their iPhones. The term "precision medicine" is becoming more widely known and used.

Vision for the Precision Medicine Initiative

Dr. Green described the vision for the Initiative. The objective of the Initiative's near-term component is to achieve research successes with regard to cancer, which is a model disease for precision medicine. The objective of the longer-term component is creation of a National Research Cohort of at least one million volunteers to generate a knowledge base for precision medicine. Some policy changes will likely be needed to remove barriers to clinical implementation. Federal rules regarding the protection of research participants will need updating. Also, changes will be needed to advance FDA oversight of precision medicine products. Regarding policy changes, Dr. Green directed the Council's attention to Dr. Eric

Lander's article: "Cutting the Gordian Helix: Regulating Genomic Testing in the Era of Precision Medicine" (*The New England Journal of Medicine*, February 17, 2015).

Dr. Green elaborated on the vision for a blended National Cohort of Volunteers, which would include not only new participants, but also cohorts already funded by the NIH. Genomic data, lifestyle information, and biological samples would be linked to electronic health records. A new model of "doing science" would be developed, with an emphasis on engaging participants; providing for open, responsible data sharing; and ensuring strong privacy protections. The health care system would be not only a system for delivering health care, but also a "learning system."

Dr. Green said that the need for a National Research Cohort has been recognized for many years. For example, in 2004, when Dr. Collins was the Director of the National Human Genome Research Institute, he wrote a commentary entitled: "The Case for a U.S. Prospective Study of Genes and Environment" (*Nature* 429**:**475-477, May 27, 2004). Dr. Collins said: "Information from the Human Genome Project will be vital for defining the genetic and environmental factors that contribute to health and disease. Well-designed case-control studies of people with and without a particular disease are essential for this, but rigorous and unbiased conclusions about the causes of diseases and their population-wide impact will require a representative population to be monitored over time (prospective cohort study). The time is right for the United States to consider such a project."

Dr. Collins' 2004 commentary laid out many of the ideas now being pursued, and the years since its publication have produced changes that enable the transformation of those concepts into the Precision Medicine Initiative. For example, knowledge has rapidly accumulated about the workings of the human genome and the role of genomic variances in disease states. Today, over 95 percent of health care providers use electronic health records, which provide a wealth of data for analysis. Technologies for monitoring physiology and lifestyle have advanced enormously--providing a rich source of health-related information. Over 50 percent of Americans now use Smartphones, which could easily be used by a National Research Cohort to capture and transmit information to enrich scientific data about human health and disease. At the same time, the field of data analytics is exploding. Importantly, more people want to participate in biomedical research than in the past--a change that may be related to social media. However, individuals want to participate as partners in research, not just subjects or patients. Citizen-science and crowdsourcing movements reflect these energies. These are some of the factors that have helped moved Dr. Collins' 2004 concept into a 2015 reality.

As the Initiative moves forward, early signs of success would likely emerge. For example, rigorous testing of pharmacogenomics could be undertaken to identify the right drug at the right dose for the right patient. New therapeutic targets could be developed by identifying loss-of-function mutations protective against common diseases. Examples of such new targets already include identification of the *PCSK9* gene for cardiovascular disease and the *SLC30A8* gene for type 2 diabetes. New insights about prevention could be gained from studying the currently

unexplained resistance of some individuals to a disease for which they have a genetic vulnerability. New methods could be developed to advance and evaluate the use of mobile health (mHealth) technologies for the prevention and management of chronic diseases. These are just some possible early successes one can think of for the Initiative.

Planning and Implementation – Next Steps

In February 2015, the NIH convened a meeting to strategize about the directions of the Initiative and to identify issues associated with building the National Research Cohort. Over 1,700 individuals joined the meeting remotely through live videocasts, and the social media coverage was extensive. This type of brainstorming will continue. Upcoming events, including workshops, will be posted on the NIH website (www.nih.gov/precisionmedicine).
There is also a White House website for the Initiative.
https://www.whitehouse.gov/precision-medicine

To help guide the Initiative, Dr. Collins has established a Working Group under the Advisory Committee to the Director, NIH (ACD). The Group is tri-chaired by Richard Lifton, M.D., PhD., Bray Patrick-Lake, M.F.S., and Kathy Hudson, Ph.D. The Working Group is slated to present an interim report to the full Advisory Committee in September 2015, including a plan and strategic vision for developing the National Research Cohort. A Request for Information has already gathered input regarding existing cohorts that could be incorporated into the larger effort. To draw upon broad expertise and input from stakeholders, meetings and workshops are helping to inform this highly transparent planning process. Coordination with other relevant agencies is continuing. Dr. Green noted that detailed plans for the Precision Medicine Initiative will likely evolve over time as new insights are gained, in much the same way as the Human Genome Project developed. It will be important for the scientific community to remain nimble as the Initiative moves forward and details are worked out.

Regarding implementation, the near-term, cancer-focused part of the Initiative will be directed by the National Cancer Institute, which has its own advisory process and will begin by ramping up ongoing efforts. Longer-term efforts will be implemented in a trans-NIH model involving a group of Institute Directors, including the NIDDK Director. The group will be chaired by Dr. Green and the Director of the National Heart, Lung and Blood Institute, Dr. Gibbons.

Contingent on congressional appropriations, the first funding opportunities are slated to be announced in the Fall of 2015. Funding is expected to begin in Fiscal Year 2016, in coordination with other U.S. government agencies. The estimated budget for starting the Initiative is $215 million.

Council Questions and Discussion

Is $215 million sufficient for this Initiative? Dr. Green responded that $215 million is the amount estimated to start the Initiative, with about $130 million of that going toward first steps in creating a National Research Cohort. He said that he did not want to get ahead of the advisory and planning process, but that he would imagine some pilot studies might be undertaken. Answers would likely be sought to fundamental questions about how to build new cohorts and integrate existing ones into the Initiative. Future budget estimates will need to be developed as the Initiative moves forward.

How does this U.S. Initiative compare with similar efforts abroad? Dr. Green said that several other countries have already invested in this type of initiative. The Precision Medicine Initiative is important to the enablement of U.S. science.

What impact will the Initiative have on health disparities? If steps are not taken to ensure that participation in the Initiative is representative of diversity in the U.S., could it unintentionally increase health disparities? Dr. Green responded that there are five groups of NIH staff from multiple Institutes who are looking at major issues, including ways to achieve diversity in the National Research Cohort.

How will the role of the environment in health and disease be included in the Initiative? Dr. Green said that the development and application of technologies will likely be the key to providing new insights about environmental factors. There is a great opportunity for public-private partnerships in this area. It is possible, for example, that the development of biosensors may parallel the process by which achievements have been made in gene sequencing technologies. The NIH will make strategic investments in technologies that will further science and human health.

Is there an effort underway to encourage companies that market systems for electronic medical records to increase the quality of the data, and also obtain information from patient-reported outcomes, including glucose levels? Dr. Green replied that this is an incredibly complicated area that is one of several being addressed by the Office of the National Coordinator for Health Information Technology within the Department of Health and Human Services. The support of the President may further progress in this area. The activism of patients who want input into the management of their own medical data may also contribute to progress.

VI. COUNCIL FORUM: NIDDK Physician-Scientist Workforce Review
Dr. Gregory Germino, NIDDK Deputy Director

Dr. Rodgers began the Forum by commenting on the important, central role that physician-scientists have traditionally had in the biomedical research enterprise. For decades, concerns have been voiced about declining MD participation in biomedical research. In September 2013, NIDDK Deputy Director, Dr. Gregory Germino, presented data associated with the aging of the cohort of MDs holding NIDDK R01 research grants, and the entry of MDs into the NIDDK Research Career Award program--the K Award Program. The purpose of the Council Forum was to provide the Council with an update on these issues, as well as some findings and recommendations of a Physician-Scientist Workforce Working Group of the Advisory Committee to the Director, NIH. Dr. Rodgers encouraged the Council to suggest ways the Institute might enhance physician-scientist representation in the NIDDK portfolio.

Dr. Germino began his presentation by describing the unique and valuable perspective that physician-scientists bring to research. They combine experience in understanding and caring for patients with the analytic skills of basic research. MDs can speak the language of both clinical medicine and basic science, and can thus effectively facilitate the translation and integration of fundamental discoveries into medical practice. Dr. Germino noted that a recent report of the Advisory Committee to the Director, NIH, pointed out that 37 percent of Nobel Laureates in Physiology or Medicine over the last 25 years had an MD degree; as do 69 percent of the current NIH Institute Directors and 70 percent of the Chief Scientific Officers at the top 10 pharmaceutical companies. Clearly, the role of MDs in conducting and leading research endeavors has been and is significant.

Update on Trends

Dr. Germino recounted the long-term trends he presented in data to the Council in September 2013. Over time, a decline had occurred in the proportion of NIDDK Principal Investigators with an MD. Fewer MDs had entered the basic science research track. A decline had occurred in the participation of MDs in K08 career development awards, which are oriented toward basic research. This decline was only partially offset by an increase of MDs receiving the clinically oriented K23 research career award. Furthermore, short term trends in Early Stage Investigator (ESI) awards made to MDs showed signs of decline. Additional investigation showed that the median age of MD Principal Investigators in the NIDDK portfolio was rising faster than that of MD/Ph.Ds. and Ph.Ds. Together these data left little room for doubt that the number MD scientists in the pipeline and entering the NIDDK R01 workforce is not sufficient to replace those who are exiting.

Dr. Germino presented data showing that the trends he identified in 2013 have continued over the past two years. For example, the total number of NIDDK K08 awards to MDs has continued to decline from 2012 to 2014. This decline has not been offset to any great degree by the number of K23 awards to MDs. The percentage of ESIs who are MDs remains relatively low and only modestly outpaces the percentage of ESIs who are MD/Ph.D.s. In addition, the median age of MD recipients of R01 awards has continued to increase, which is a strong indication that the

cohort of MD research investigators within the NIDDK portfolio is not being replenished. Dr. Germino emphasized that the major underlying problem appears to be the drop-off in the number of MDs who apply for K awards, which are an important precursor of R01 grant activity. Dr. Germino emphasized that the issue is the pipeline for K awards, not the competition for R01 grants. MDs compete favorably for NIH funding when they do apply, so there is no systematic bias against them in peer review.

Deeper Analysis of MD and MD/PhD Trends

The continuation of long-term trends suggests that, absent some intervening action, MD representation in the NIDDK workforce may continue to decline further. The Institute continues to collect and analyze data to gain a better understanding of the dynamics underlying these trends, and where adjustments may be needed in the career development pipeline. To that end, Dr. Germino presented a new analysis of physician-scientists in the NIDDK R01 portfolio based on whether or not their activities are coded by NIH as involving "human subjects research" (a surrogate for clinical research). Activities not so coded can be viewed as oriented toward basic research.

Dr. Germino said that there are two categories of NIDDK investigators whose median age has risen over the past decade: MDs and MD/PhDs whose research does not involve human subjects. In contrast, the median age for other categories of researchers has remained relatively stable, which suggests that those individuals are entering and leaving the NIDDK research enterprise at approximately the same rate. These age-related data suggest a problem with the replacement rate for MDs and MD/PhDs involved in basic research in the NIDDK portfolio. The issue is not only the proportional representation of MDs, but also their absolute numbers. In 2013, across the entire Institute, there were only five MDs involved in basic research who received (new/competing) New Investigator R01 awards.

Using involvement in non-human subjects research as a surrogate for basic research, Dr. Germino presented the following points regarding the long-term representation of MDs in NIDDK R01 grant activity:

- The median age of MDs submitting unsolicited R01 grant applications oriented toward basic research is rising faster than for other groups.

- The median age of MDs receiving unsolicited R01 awards oriented toward basic research is rising faster than for other groups.

- The number of MDs receiving one or more unsolicited R01 awards oriented toward basic research in a fiscal year has trended down since fiscal year 2004. In contrast, the number of MDs receiving one or more unsolicited R01 award(s) involving more clinically oriented research (human subjects research) has trended up.

- The average age of MDs receiving an R01 award oriented toward basic research has

trended up much faster and consistently than the average age of MDs receiving an R01 award involving clinically oriented research (i.e., human subjects research).

Collectively, these data suggest that there may be a problem associated with entry into the NIDDK R01 biomedical research workforce of early career-stage MDs focused on basic research. Further analysis has shown that these trends in R01 grants appear linked to the annual number of new NIDDK Research Career Development awards--K awards--going to MDs from 2004-2014. The overall number of K applications from MDs has decreased by about 40 percent, and the overall number of competing K awards to MDs has also declined by about 40 percent. Applications from and awards to MDs are down for basic-research focused K08s and up for clinically focused K23s. Thus, fewer MDs are applying for K awards, and those who actually do apply tend to focus on clinically oriented research. These trends in K08 and K23 applications from and awards to MDs are also reflected in the training background of NIDDK new Principal Investigators. Moreover, they are evident in a shift in research focus--from a basic to a more clinical focus--among MDs who receive their first R01 award.

Working Group of Advisory Committee to the Director, NIH (ACD)

Dr. Germino said that the NIDDK trends align with some of the findings of the Physician-Scientist Workforce (PSW) Working Group, which was established under the Advisory Committee to the Director, NIH (ACD). He emphasized, however, that the Working Group defined physician-scientists very broadly to include nurse-scientists, veterinarian-scientists, and dental-scientists. In the NIDDK portfolio, physician scientists are mostly MDs and MD/PhDs. Furthermore, the charge to the Working Group was very broad. The Group was asked to develop approaches that can inform decisions about the development of the U.S. physician- scientist workforce; analyze the size and composition of the workforce and consider the impact of NIH funding policies; assess needs and career opportunities for physician-scientist trainees; and identify incentives and barriers to entering the physician-scientist workforce.

Dr. Germino noted that the Working Group presented a report on its findings and recommendations to the full ACD in June 2014 (http://acd.od.nih.gov/reports/PSW_Report_ACD_06042014.pdf).
Some of the major findings included the following. The physician-scientist pool is stagnating. The total number of physician-scientists engaged in research has been unchanged over the past decade. The physician-scientist pool is aging in a similar but more pronounced way than the biomedical workforce pool. Major challenges for physician-scientists are the availability of research funding, average educational debt, increased length and complexity of training, striking a work-life balance, competing clinical vs. research responsibilities, and requirements regarding credentialing, work hours, and other activities.

Dr. Germino highlighted the following nine Working Group recommendations, and commented on related NIDDK efforts and goals.

1. ***Sustain strong support for MD/PhD programs.*** Dr. Germino said that in contrast to NIH

wide data that show that ~50% of the Physician-Scientist workforce are MD/PhDs, only 31% of the physician-scientists involved in NIDDK research are MD/PhDs. This has important implications since the focus by the ACD committee on MD/PhDs may not address NIDDK's workforce problem. When queried, MD/PhDs have said that their career choices were made as early as middle school or high school, often based on models provided by family members and educators. While individuals who enter MD/PhD training programs have a strong interest in and commitment to science, they are unlikely to engage with NIDDK investigators and programs until they have completed that training. Therefore, to sustain or increase the representation of MD/PhDs in the NIDDK portfolio would probably require the Institute to reach out to these individuals early in their scientific careers, or to link into their MD/PhD training period. The NIDDK also will have to direct more effort on training and retaining MD physician-scientists given the high proportion they make of the NIDDK workforce.

2. ***Shift National Research Service Award (NRSA) postdoctoral training awards to support proportionally more individual fellowships (F Awards) vs. institutional training grants (T Awards).*** The NIDDK had shifted the focus of its NRSA programs toward fellowships prior to the Working Group's recommendation. The Fellowship Program is viewed as being the more successful of the two awards in terms of outcomes. Its success may relate to the relatively young age and prior research exposure of the Fellows. Dr. Germino emphasized, however, that Institutional Training Grants are still an important research training mechanism for individuals who are not exposed to science until quite late in their careers.

3. ***Continue to address the gap in R01 grant award rates between new and established investigators.*** The NIDDK has established an automatic five percentile point payline advantage for ESIs. NIDDK Program Staff also identify for possible support those meritorious applicants who have missed the payline but have promising projects.

4. ***Develop more effective tools for assessing the strength of the biomedical workforce and tracking career progress.*** The NIDDK is enhancing its own analytic capabilities, and taking advantage of those available through central NIH. The NIDDK's data analyses have revealed a pipeline problem in the Institute's K08 Program for MDs, especially in basic research. The NIDDK has shown that its K08 recipients fare as well as any other comparable K group (e.g., K01 or K23 awardees) in obtaining R01 grant awards--if they apply.

5. ***Establish physician-scientist specific K99/R00-equivalent granting mechanism.*** The NIDDK has the largest K award program for physician-scientists at the NIH. Moreover, MD recipients of the Institute's K awards have high rates of applying for and receiving regular research grants. Discussions are under way in the Institute as to whether a new K99/R01 award is needed to recruit and retain physician-scientists in the NIDDK portfolio, or whether other mechanisms should be explored.

6. ***Expand loan repayment programs and increase dollar amounts of loan forgiveness.*** The NIDDK recognizes that difficulties exist in expanding the funding levels for these programs. However, there may be opportunities to restructure the programs to increase loan limits for investigators and make eligibility more flexible to include groups like MDs that work in basic science.

7. ***Support pilot grant programs to test existing and novel approaches to improve and/or shorten research training.*** Opportunities may exist for pilot programs to shorten the research training period, especially for MDs and MD/PhDs. It may be possible to shorten clinical research training for individuals who have already developed and maintained clinical and/or research capabilities. Dr. Germino said that some academic institutions have already established successful models.

8. ***Intensify efforts to increase diversity in the physician-scientist workforce.*** The NIDDK seeks to promote diversity in the physician-scientist workforce, and other areas of its portfolio. Institutional research training grants are one of several avenues the NIDDK uses for increasing diversity of the workforce.

9. ***Leverage the existing resources of the CTSA Program to obtain maximum benefit for training and career development.*** A major NIDDK goal is to leverage existing investments in all its programs.

Dr. Germino elaborated further on the success of the investigators who complete the Institute's K award program. Over three-quarters of K awardees apply for R01 grants, and have high success rates. Moreover, an NIDDK analysis of cohorts of awardees has shown that a very high percentages of K awardees have remained in research careers over relatively long periods of time. Likely factors that contribute to the K Program's success in transitioning investigators to long-term research careers include the shepherding of awardees by NIDDK Program Directors; NIDDK conferences for K awardees regarding the workings of the NIH; and an R03 small grant program that enables awardees to receive a modest additional amount of funds to develop their research activities during their K award period. On the other hand, it is troublesome that almost a quarter of the K awardees never apply for an R01 grant and the attrition rate for those who apply and fail to get an award after one failed submission is relatively high. Dr. Germino emphasized that the NIDDK invests substantial resources in its K Program, and would like to reduce this drop-out rate of highly skilled research investigators.

The NIDDK recognizes that some of the reasons that K awardees may drop out of research include: inability to redirect a faulty hypothesis, slow start-up period, fear of failure, misperception of career risk, and change in personal circumstances. Possible corrective actions to reduce drop-outs might be to provide for improved mentoring and a better safety net of bridge funding so that an investigator has time to gather more data or redirect an idea. It may be helpful to have a better strategy to communicate to K awardees their excellent likelihood of a productive research career based on the success rates of their peers in obtaining NIH regular research grants. Regarding a safety net, Dr. Germino noted that the NINDS has established a K02 program that

provides up to three years of support to investigators who complete a K08 or K23 award. The only requirement is that they must apply for an R01 grant by the third year of support. Data on the NINDS K02 recipients show a significant improvement in R01 application numbers and success rates.

Dr. Germino closed his presentation by suggesting some ideas for discussion. He asked the Council to suggest ways the NIDDK could improve the pipeline for and retention rate of MDs performing research--especially basic research. Three ideas consistent with recommendations of the Working Group of the Advisory Committee to the NIH Director are: (a) continue to focus on Fellowship training awards; (b) continue/enhance investment in the Loan Repayment Program; and (c) continue support of New Investigators. Other ideas are to highlight diversity of the workforce and a commitment to basic research in NIDDK core values. The NIDDK could also consider Special Emphasis awards for MDs engaged in basic research; creation of a new "bridge" award for K08 awardees, similar to the K02 used by the NINDS; or creation of a K99/00 award for MDs. Dr. Germino asked Council members to consider these ideas and suggest others. He asked for feedback on the Working Group's recommendations so that the NIDDK can convey ideas to the NIH level before implementation decisions are made.

Council Questions and Discussion

Council members generally agreed that the data regarding the representation of MDs and MD-PhDs in NIDDK basic research is sobering. The data underscore the importance of early exposure to research. Lifestyle, debt, lack of mentoring, inadequate monetary support and other factors are all disincentives that may influence the decision of MDs to pursue a career as a physician-scientist.

Regarding institutional support, it was noted that institutions and subspecialty professional organizations could help increase funding, especially salary levels for early stage investigators. It might be helpful for the NIDDK to develop a pilot with a few institutions. One Council member noted that some institutions are simply unable to provide the support required by NIH for K99 awards, and they struggle with the programmatic expectation that the awardee change institutions when transitioning from the K99 to R00 phase of the award. This could hinder rather than help career development if investigators lose the networks they have established, particularly MDs who are often well-networked within their training home. It was noted that the commitment of academic research institutions goes beyond financial support of investigators.

Regarding the possible creation of a K99/R00 award for physician-scientists, Dr. Germino said that such an award would likely involve some co-investment by institutions. Perhaps as an alternative, the NIH and the institution would accept some shared risk in supporting a highly promising K awardee who just missed getting an R01. The program would provide a bridge award like the K02 to give candidates time to refine their concepts for independent research before re-submitting their R01 grant application. The K02 award is an interesting concept that appears to be working well for NINDS, and it could be modified by the NIDDK to incorporate institutional commitment.

Other approaches were discussed, including making the R03 award more robust. The R03 might be restructured to include a requirement for submitting an R01 application that could be funded at a lower level and for a shorter period of time than a traditional R01 grant. The institution could play a role in selecting promising candidates. Additionally, there may be new ways of incentivizing physician-scientists to work in teams early in their careers in order to promote a nurturing environment and a commitment to science.

VII. SCIENTIFIC PRESENTATION:

Origin and Fate of Myofibroblasts in Liver Fibrosis

David Allen Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the School of Medicine, University of California, San Diego (UCSD)

A leader in gastroenterological research, and a widely recognized clinician and teacher, Dr. Brenner specializes in liver diseases. He is widely respected as a translational scientist whose work bridges the laboratory and clinical settings. He has focused on understanding the molecular pathogenesis of fibrotic liver disease and the genetic basis of liver disorders as the foundation for improving prevention and treatment of liver disease. Dr. Brenner served for five years as Editor-in-Chief of the journal Gastroenterology, and currently serves on a number of editorial boards. Dr. Brenner earned his M.D. from the Yale University School of Medicine. After completing his residency at Yale-New Haven Medical Center, he served as a research associate in the Genetics and Biochemistry Branch at NIH. Dr. Brenner first went to UC San Diego in 1985 as a gastroenterology fellow. He later joined the medical school faculty, and served as a physician at the Veterans Affairs San Diego Healthcare System. In 1993 he became Chief of the Division of Digestive Diseases and Nutrition, University of North Carolina at Chapel Hill. Then, from 2003 to 2007 he served at the Columbia University Medical Center College of Physicians and Surgeons, as Samuel Bard Professor and Chair of the Department of Medicine, a Member of the Herbert Irving Comprehensive Cancer Center, a Member of the Columbia University Institute of Nutrition, and Physician-in-Chief of New York Presbyterian Hospital/Columbia. He returned to UCSD in 2007.

VIII. CONSIDERATION OF APPLICATIONS

A total of 1884 grant applications (704 primary and 1180 dual), requesting support of $510,391,181 were reviewed for consideration at the May 13, 2015 meeting. An additional 1030 Common Fund applications requesting $1,383,850,634 were presented to Council. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, 1218 applications requesting $ 362,632,400 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 13, 2015 meeting.

IX. 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 198th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m. on May 13, 2015.

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