221st Meeting of the
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

Hybrid Meeting
Held in-person NIH Main Campus (Bethesda, MD)
Building 31, C-Wing 6th Floor Conference Center
and virtually using web-based collaboration/meeting tools

I. CALL TO ORDER
Dr. Griffin Rodgers

Dr. Griffin Rodgers, Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), called to order the 221st meeting of the NIDDK Advisory Council at 8:33 a.m. on January 25, 2023, live and via Zoom videoconference. Advisory Council members and NIDDK staff members met in person for the first time since 2020. In addition, some Council members and staff attended virtually. The meeting was conducted using a two-tiered webinar format. The panelist tier consisted of NIDDK's Advisory Council members and NIDDK staff members attending virtually. The audience tier was available to members of the public via a livestream, which allowed them to view and listen to the meeting.

ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. John Carethers
Dr. Iain Drummond
Dr. Penny Gordon-Larsen
Dr. Debra Haire-Joshu
Ms. Davida Kruger
Dr. Jacquelyn Maher
Dr. Mark Nelson
Dr. Keith Norris
Dr. David Penson
Ms. Ceciel Rooker
Ms. Ricky Safer
Dr. Kathleen Sakamoto
Dr. Philipp E. Scherer
Dr. Elizabeth Seaquist
Dr. Michael Snyder
Dr. Gary Wu

Subject Matter Expert:
Dr. Aylin Rodan

Ex-officio members:
Dr. David A. D'Alessio
Dr. Cindy Davis
Dr. Ian Stewart

Also Present:
Dr. Griffin Rodgers, Director, NIDDK and Chair of the NIDDK Advisory Council
Dr. Karl F. Malik, Executive Secretary, NIDDK Advisory Council

Dr. Gregory G. Germino, Deputy Director, NIDDK
Dr. William Cefalu, Director, Division of Diabetes, Endocrinology and Metabolic Diseases, NIDDK
Dr. Stephen P. James, Director, Division of Digestive Diseases and Nutrition, NIDDK
Dr. Robert A. Star, Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK

Panelists and Speakers:
Dr. William Herman, Chair, National Clinical Care Commission
Dr. Pamela Thornton, NIDDK
Dr. Olivier Blondel, NIDDK
Dr. Teresa Jones, NIDDK

II. ANNOUNCEMENTS
Dr. Griffin Rodgers

Dr. Rodgers announced that NIDDK will continue to hold hybrid Council meetings for the foreseeable future, although there might be an occasional fully-virtual meeting as the need arises or circumstances change. Further details about the May 2023 Council meeting, as well as future meeting dates, will be posted on the Council website.

Recognition of Subject Matter Experts

Dr. Rodgers welcomed subject matter expert Dr. Aylin Rodan and thanked her for her time and participation in the Council process.

- **Dr. Aylin Rodan** is an Associate Professor of Internal Medicine and Adjunct Associate Professor of Human Genetics at the University of Utah. She will participate in the Kidney, Urologic, and Hematologic Diseases (KUH) Subcommittee.

Council Member News

Dr. Rodgers recognized four current Council members who have agreed to extend their term of service: **Drs. Iain Drummond, Penny Gordon-Larsen, Michael Snyder,** and **Gary Wu.** He thanked them for their exemplary service over their terms and added that their agreement to extend their membership is yet another example of how they have been willing to step up throughout their tenure on Council.

NIDDK Staffing News

Dr. Rodgers announced recent staffing news from NIDDK's Intramural Program:

- **Dr. Christopher Koh** has been named the new NIDDK Clinical Director in the Division of Intramural Research. Dr. Koh previously served as Deputy Clinical Director before becoming Acting Clinical Director in 2020.
- **Dr. Behdad Afzali** was elected as a Fellow of the Royal College of Physicians, an honor that recognizes innovative and exceptional physicians for their ongoing

contributions to medicine. A Stadtman Tenure-Track Investigator, Dr. Afzali oversees the Immunoregulation Section in NIDDK's Kidney Diseases Branch, which focuses on understanding the mechanisms and resolution of tissue inflammation.

- **Dr. Kenneth Jacobson** was awarded the American Chemical Society's 2023 E.B. Hershberg Award for Important Discoveries in Medicinally Active Substances. Dr. Jacobson's decades of research have led to the development of promising therapies for many diseases. His laboratory has produced more than 35 compounds that are commercially available as research tools and used in hundreds of laboratories.

- **Dr. Jürgen Wess** was selected as a Fellow of the American Society for Pharmacology and Experimental Therapeutics. Dr. Wess is recognized for his outstanding contributions to the pharmacology field, particularly through pioneering research on G protein-coupled receptors, as well as his longstanding commitment to mentoring young scientists of diverse backgrounds.

- The **NIDDK Green Labs team** received the 2022 Honorable Mention Award for Communications and Education of Green Labs Strategies from the International Institute of Sustainable Laboratories.

Dr. Rodgers announced recent staffing news in NIDDK's Extramural Program:

- **Dr. Chen Liang** of the NIH Data and Technology Advancement (DATA) Scholar National Service Program will be assisting the Division of Kidney, Urologic, and Hematologic Diseases (KUH) in the Kidney Precision Medicine Project, especially with integration of clinical consortium data. He will also be working on other data science projects at NIH. Dr. Liang is an Assistant Professor at the University of South Carolina. His research focuses on the development and application of data science, informatics, and artificial intelligence, leading to safe and intelligent health systems.

- **Dr. Rajatava Basu** joined the Division of Diabetes, Endocrinology, and Metabolic Diseases (DEM) as a Program Director. Dr. Basu will oversee programs focused on the physiologic contribution of the immune system to the development, severity, and resolution of nonautoimmune diabetes, obesity, and associated metabolic syndromes. Prior to joining NIDDK, Dr. Basu was an Assistant Professor in the Division of Molecular and Cellular Pathology, Department of Pathology, at the University of Alabama, Birmingham. Dr. Basu earned a Ph.D. collaboratively from the Indian Institute of Chemical Biology, India, and the Charité Medical School, Humboldt University, Germany.

- **Dr. Raphael Gorospe** joined DEM as a Program Director. Dr. Gorospe will oversee programs focused on translational research on improving outcomes for adults with or at risk of developing type 2 diabetes and diabetes in older adults. Prior to joining NIH in 2007, Dr. Gorospe was an Assistant Professor of Pediatrics at the Center for Genetic Medicine, Children's National Medical Center, George Washington University School of Medicine. While at NIH, Dr. Gorospe has had significant experience serving as Senior Science Advisor and Physician in the

Office of AIDS Research. He also served as Project Scientist for the Institutional Development Awards (IDeA) States Pediatric Clinical Trials Network, and as an IDeA Program Official. The IDeA program is managed through the National Institute of General Medical Sciences.

- **Ms. Ginger Webb** joined NIDDK's Division of Extramural Activities (DEA) as a Program Analyst Team Lead in the Office of Research Evaluation and Operations (OREO). Ms. Webb comes to NIDDK from the National Institute on Deafness and Other Communication Disorders. She will be managing NIDDK's Funding Opportunity Announcement process, Electronic Council Book activities, and assisting with OREO process coordination.

- **Dr. Tori Stone** joined DEA's Scientific Review Branch as a Scientific Review Officer. Dr. Stone comes to NIDDK from the Yale School of Medicine and the John B. Pierce Research Institute, where she completed a postdoctoral fellowship. Dr. Stone served on the Executive Board of the Yale Postdoctoral Association as Committee Chair, leading outreach activities targeting the Yale and New Haven communities. At the Pierce Institute, Dr. Stone investigated mechanisms of blood pressure regulation in women with polycystic ovary syndrome. She received her Ph.D. at the University of Alabama.

Dr. Rodgers announced retirements among NIDDK staff members and congratulated them on their public service and remarkable careers.

- **Dr. Kristin Abraham**, Program Director in DEM, retired after 22 years of service to NIH and 14 years of service to NIDDK. Dr. Abraham oversaw a diverse research portfolio consisting of studies that defined the role of the immune response in metabolic dysfunction and type 2 diabetes, and projects that developed and validated the utility of new animal models for basic and preclinical research in diabetes, endocrinology, and metabolic diseases. Dr. Abraham served as Chair and led the major basic science working group within DEM for the past 2 years.
- **Dr. Teresa Jones**, Program Director in DEM, retired at the end of December after 22 years of service to NIDDK. Dr. Jones served as Program Director for the Diabetes Complications Program that includes basic, translational, and clinical research on diabetic neuropathy, diabetic wound healing, and diabetic ketoacidosis. Dr. Jones served as Project Scientist for the Diabetic Foot Consortium and as DEM's Program Director for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) research on diabetes complications.

Drs. Jones and Abraham will serve during the coming year as re-employed annuitants to continue assisting DEM.

- **Mr. Robert Pike,** NIDDK's Chief Grants Management Officer (CGMO), will retire on January 31st after 31 years of federal service, 16 of which were at NIDDK as CGMO. Mr. Pike began his ascent up the Grants Management ladder at the National Institute on Aging. In 2001, he joined the National Heart, Lung, and Blood Institute as a Grants Management Section Chief, serving as Team Leader on the Lung Team. He joined NIDDK in 2007 as CGMO. Mr. Pike led the transition from a paper to an electronic grants environment; helped the Institute navigate the

grants policy, reporting, and workload challenges associated with American Recovery and Reinvestment Act funding; and managed transitions to remote work environments first because of renovations to the Democracy II building and then as a result of work environment changes due to COVID-19.

NIDDK's *Recent Advances and Emerging Opportunities* (2023)

Dr. Rodgers announced the publication of the 2023 edition of NIDDK's *Recent Advances and Emerging Opportunities*, now in its 23rd year. The report highlights examples of NIDDK-supported research advances published in Fiscal Year 2022. It also includes "Personal Perspectives" of people who have given time and effort to support NIDDK-sponsored clinical research, and special features, such as one describing NIDDK's efforts to address health disparities, advance health equity, and promote workforce diversity. The report and a companion Executive Summary are posted on the "Strategic Plans and Reports" section of the NIDDK website.

Dr. Rodgers noted that production of the report was an Institute-wide effort. He acknowledged the efforts of the Office of Scientific Program and Policy Analysis for developing the content and managing this project, and the Extramural Divisions and Offices, as well as the Division of Intramural Research, for providing input and guidance. Dr. Rodgers welcomed comments on the report.

NIH Proposed Simplified Framework for Peer Review Criteria

Dr. Rodgers described an NIH effort to develop a revised, simplified framework for peer review of research project grant applications.

NIH proposes to reorganize the five review criteria (Significance, Innovation, Approach, Investigator, and Environment) into three factors, with Factors 1 and 2 receiving a numerical score. Reviewers will be instructed to consider all three factors in arriving at their Overall Impact Score (scored 1-9), reflecting the overall scientific and technical merit of the application. The proposed factors are:

- Factor 1: Importance of the Research (which will be scored 1-9)
- Factor 2: Feasibility and Rigor (which will be scored 1-9)
- Factor 3: Expertise and Resources (which will be evaluated but not individually scored)

NIH believes that these changes will help peer reviewers focus on the critical task of assessing scientific merit and will improve those assessments by reducing bias. There is currently a Request for Information (RFI) on the Proposed Simplified Review Framework with a 90-day comment period that will be open through March 10, 2023. Dr. Rodgers encouraged Council members and the research community at large to review the information within the RFI and submit comments. The proposal can be found at NIH Notice Number NOT-OD-23-034, which includes a link to the webpage to submit comments.

Update: Implementation of the NIH Data Management and Sharing Policy at NIDDK

Dr. Gregory Germino, Deputy Director, NIDDK

Dr. Rodgers announced that the NIH Data Management and Sharing Policy (DMS Policy) takes effect January 25, 2023. He noted that NIH has a long-standing commitment to the sharing of research results, and the new policy represents an evolution of this principle for the agency and research community. NIH and NIDDK have been developing resources to help support the research community as they implement this policy. He introduced Dr. Gregory Germino to provide a short orientation on some of these resources.

Dr. Germino began by stating that the DMS Policy will create a consistent minimum expectation for all research supported by NIH. It applies to all NIH funding mechanisms with an effective date on or after January 25, 2023, including extramural grants, contracts, intramural projects, and other funding agreements.

The Policy applies to all research, funded or conducted in whole or in part by NIH, that results in the generation of scientific data. The term "scientific data" is defined as "the recorded factual material commonly accepted in the scientific community as of sufficient quality to validate and replicate research findings, regardless of whether the data are used to support scholarly publications."

The Policy requires submission of a Data Management and Sharing Plan (DMS Plan) with all applications for funding submitted beginning January 25, 2023. It also requires compliance with the DMS Plan that has been approved by the funding NIH Institute, Center, or Office. An NIH Scientific Data Sharing website provides NIDDK-specific guidance for writing a DMS Plan, aids for repository selection, example plans, data and metadata standards, a glossary of terms, and FAQs.

NIDDK activities subject to the DMS Policy include all research-generating scientific data, including but not limited to: research projects, certain career development (K) Awards, SBIR/STTR awards, and research centers. It does not pertain to research projects not generating scientific data or nonresearch projects, including but not limited to: training (T) awards, fellowships (F) awards, construction (C06) awards, conference grants (R13 awards), resources (G awards), or research-related infrastructure programs (S06 awards).

Elements of a DMS Plan include data type; related tools, software, and code; standards; data preservation, access, and timelines; access, distribution, and reuse considerations; and oversight of data management and sharing.

Allowable costs include curating data and developing supporting documentation; preserving and sharing data through repositories; and local data management considerations. Costs must be incurred during the performance period. Unallowable costs include infrastructure costs typically included in indirect costs and costs associated with the routine conduct of research (e.g., costs of gaining access to research data).

NIDDK has created a resource on the Research Resources section of its website that includes guidance, tools, and resources for developing a DMS Plan. Sample DMS Plans are provided and are intended to assist researchers by providing examples for educational

purposes to demonstrate NIDDK's expectations for submitted DMS Plans. DMS Plan content will differ based on the type of research being conducted, inclusion of human participants, and methods used to collect data.

Council Questions and Discussion
Dr. Germino, moderator

Comment from Council: *The challenge is not so much getting people to propose data sharing plans, but rather, getting them to share their data. There has to be a "stick" as well as a "carrot" approach. In addition, sharing of data often occurs after the work has been published.*

Dr. Germino responded that NIH is pursuing both a carrot and a stick approach. The hope is that investigators will see an amplified impact of their work when their data are shared. NIH is also building systems to track compliance with the sharing policies, which is a condition of the award. There is an expectation that what is proposed in the plan will be executed over the course of the award. There is a clear expectation in the scientific community as well as in the White House that data sharing should be promoted. It will take some time to work through this new policy.

Comment from Council: *An additional incentive (carrot) might be to promote examples of successful data sharing on the website.*

Dr. Germino agreed and noted that the challenge is to lower the barriers to sharing. Because this is a new policy, it will take time to develop roadmaps for achievement, including the development of data standards and data repositories. NIDDK is considering how to use its Central Repository to help people link with the data.

Comment from Council: *Sharing is made easier by well-organized repositories. The goal is gathering all of the terabytes of data into one place so they can be searched. Some foreign repositories are more developed than those in the United States.*

Comment from Council: *Although this is important, there are associated costs. Will applicants be expected to roll this into their total costs for an R01, or will there be additional funding available? If it is the former, it might make it more difficult for investigators.*

Dr. Germino replied that investigators can request funds to cover the costs of curating and depositing the data, and for repository costs of hosting the data. Because this would go beyond the extent of the award and need to be paid up front, it will be a chargeable cost on grants that are nonmodular. This will become more challenging for R01s closer to the $500,000 direct cost limit, an issue that is under consideration and will be addressed.

III. CONSIDERATION OF SUMMARY MINUTES OF THE 220th COUNCIL MEETING
Dr. Griffin Rodgers

The Council approved, by electronic poll, the Summary Minutes of the 220th Council

meeting, which had been sent to members in advance for review.

IV. FUTURE COUNCIL DATES
Dr. Griffin Rodgers

As noted previously, Dr. Rodgers told Council that future meeting will be held using a hybrid format to accommodate both virtual and in-person attendance. The next meeting of the NIDDK Advisory Council is scheduled for May 17-18, 2023. Although the plan is to meet May 17, Council was asked to hold both days open to maintain flexibility. Updates about future meetings will be posted on the Council website.

V. CONFIDENTIALITY/CONFLICT OF INTEREST
Dr. Karl Malik

Confidentiality

Dr. Karl Malik reminded 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. Malik reminded 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.

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 with which he/she has a 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. Malik 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. Malik pointed out that when the Council reviews applications in groups without discussion—also called "en bloc" actions—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. Malik 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.

VI. ANNUAL APPROVAL OF THE COUNCIL OPERATING PROCEDURES

Dr. Karl Malik

During its winter meeting each year, the NIDDK Council approves the Council Operating Procedures, which were included for Council review in the pre-meeting materials in the Electronic Council Book. The Council Operating Procedures proposed for 2023 include minor updates from last year reflecting the changes to the NIH Special Council Review Policy, in which the threshold for Special Council Review was revised from $1 million in direct costs per year to $2 million in total costs (inclusive direct and indirect) per year.

Dr. Malik asked for questions or comments regarding the Council Operating Procedures for 2023, and there being none, called for a motion for concurrence. The Council concurred, by electronic poll, with the Council Operating Procedures for 2023.

VII. REPORT FROM THE NIDDK DIRECTOR

Dr. Griffin Rodgers

<u>Budget Update</u>

Dr. Rodgers updated the Council on the current budget cycle and the NIH and NIDDK appropriations for Fiscal Year 2023 (FY 2023).

The FY 2023 budget cycle began with the release of the President's Budget Request in April 2022. Between May and August 2022, the House and Senate Appropriations Labor, Health and Human Services, and Education Appropriations Subcommittees held budget hearings and released appropriations bills, and the House Subcommittee held a bill markup.

The new fiscal year began shortly after the last Council meeting. Since a full appropriations package had not been passed, on September 30, President Biden signed into law a Continuing Resolution to keep the government open through December 16. Two additional Continuing Resolutions kept the government open through December 23 and December 30, respectively, while Congress negotiated topline budget numbers and passed an Omnibus Appropriations bill. On December 29, President Biden signed the FY 2023 Omnibus Appropriations bill into law. The President's FY 2024 Budget Request is likely to be released in early spring.

The President's FY 2023 Budget Request, released in March, included $50.228 billion for NIH, or $5.3 billion over the FY 2022 enacted funding level. The request also included a proposed $2.206 billion for NIDDK. On June 22, the House released its FY 2023 Labor-HHS-Education Appropriations bill. The bill included $47.459 billion for NIH, which is $2.5 billion, or about a 5.6 percent increase, over the 2022 enacted budget. This included a

3.6 percent increase for NIDDK, from $2.204 billion to $2.283 billion.

The Senate FY 2023 bill released in July included $47.959 billion for NIH, which is a $3 billion, or 6.7 percent, increase over 2022. The bill provided NIDDK with $2.291 billion, which is an $87 million, or 3.9 percent, increase over the previous year. The Senate bill also contained $8.55 million to restore cuts to the mandatory Special Diabetes Program that resulted from Budget Control Act sequestration.

As noted, President Biden signed the FY 2023 appropriations bill into law on December 29, 2022. NIH received $47.459 billion in the FY 2023 Omnibus Appropriations bill, a $2.6 billion increase, or 5.5 percent, over the FY 2022 level. NIDDK received $2.301 billion in the Omnibus bill, which is a $97 million increase over last year's budget, or a 4.4 percent increase. As in the Senate bill, this includes $8.55 million to restore cuts to the mandatory Special Diabetes Program that resulted from sequestration. It also includes $5 million for pain research at NIDDK, which will allow the Institute to support additional pain management research this year.

Next, Dr. Rodgers provided an update on funding of the Advanced Research Projects Agency for Health, or ARPA-H. In the FY 2022 appropriations cycle, ARPA-H received $1 billion in funding. The FY 23 President's Budget Request included an additional $5 billion for the agency as a component of NIH. Of note, both the House and Senate bills include FY 2023 funds for ARPA-H, but less than the $5 billion requested by the President. The FY 2023 Omnibus Appropriations bill provided ARPA-H with $1.5 billion in the Office of the HHS Secretary, but the bill allows for funds transfer to NIH.

Dr. Rodgers then discussed leadership changes following the November 8, 2022, midterm elections for the 118th Congress. Democrats added one seat to their majority in the Senate, while Republicans narrowly regained the majority in the House.

Of particular interest to NIH is leadership changes to the House and Senate Committees with jurisdiction over the agency. In the Senate, Senators Patty Murray and Susan Collins will be the top appropriators following the retirements of Senators Richard Shelby and Patrick Leahy. Replacing Senator Murray on the Senate Committee on Health, Education, Labor and Pensions is Senator Bernie Sanders, with Senator Bill Cassidy as Ranking Member. On the House side, the leadership for the House Appropriations Committee and the House Energy and Commerce Committee will remain the same as the previous Congress, except that the majority and minority are flipped.

NIDDK is working to enhance outreach efforts to Congress through NIH's Office of Legislative and Policy Analysis. These efforts include information on NIDDK research contributions to recent drug or device approvals; news, press releases, and other exciting research advances; announcements of large NIDDK programs; and patient education materials that Members may want to distribute to their constituents. NIDDK will share these items with Members of Congress, including the leadership of the House and Senate Labor-HHS appropriations subcommittee that oversees the NIH budget, as well as NIH Authorizing Committee leadership, leaders of Congressional caucuses focused on specific diseases or research areas, and other members identified by staff in the Office of Scientific Program and Policy Analysis as champions and advocates of particular diseases.

Congressional Activities

On September 27, Dr. Sue Yanovski and the other members of the NIH Obesity Research Task Force, including representatives from NHLBI and NICHD, briefed staff in the office of Representative Mark Pocan on weight stigma and treatment.

VIII. WORKING GROUP PROPOSAL: HETEROGENEITY OF DIABETES

Dr. William Cefalu, Director, NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases

Dr. Rodgers began the session by noting that an important way for NIDDK to receive and digest input and perspective from its external community is through the Council working group process. Once Council working groups develop their recommendations in a report, the report is then presented to Council for consideration and discussion. He then introduced Dr. William Cefalu to propose establishment of a Council Working Group on the Heterogeneity of Diabetes.

Dr. Cefalu proposed that the Council convene a working group to support NIDDK's activities in the area of heterogeneity of diabetes. The rationale is that the field is evolving toward more precise diagnostic, preventive, and management strategies for diabetes and its complications (i.e., precision medicine). Current diabetes classifications, especially for type 2 diabetes, are very broad. Further, the significant heterogeneity of the disease, the current understanding of the pathophysiology of diabetes, and the contributions of multiple metabolic pathways are not captured in current definitions.

The current classifications of diabetes are dated. One of the first reports to suggest differences in diabetes was in 1939 when it was suggested that diabetes be divided into "insulin sensitive" and "insulin insensitive" categories based on the oral glucose challenge test. In 1979, the American Diabetes Association issued its recommended classifications, which were confirmed by the World Health Organization and now referred to as "Type 1" and "Type 2" diabetes Those two categories remain as the major categories, but many types of diabetes have been recognized over time.

For example, monogenic diabetes was first described in the literature in the mid-1970s, but the molecular underpinnings were not understood until the 1990s. It is now known that there are at least 12 classes of monogenic diabetes. In addition, latent autoimmune diabetes subtypes of adults, cystic-fibrosis related diabetes, post-transplantation related diabetes, pancreatic diabetes, and diabetes resulting from lipodystrophy are all recognized. Further, current efforts are focusing on diabetes occurring post-onset post-COVID.

Another concern is the blurring of lines between type 1 and type 2 diabetes due to conditions of obesity, auto-immunity, etc. For example, an individual in their late 20s or early 30s may have autoimmunity, obesity, inflammation, or insulin resistance that confounds a diagnosis. Even when narrowly focusing on type 2, data show a difference in type 2 diabetes between youth and adolescents and adults, with a different pathophysiology and treatment response. Moreover, evolving data suggest there are subtypes within type 2 diabetes. While monogenic diabetes results from mutations in a single gene, type 2 diabetes is much more complex and involves multi-tissue dysfunction, including contributions from insulin secretion deficits, hepatic glucose production, inflammation, insulin resistance, obesity, the environment, and social determinants of

health. These factors all influence progression and development of complications. Yet, diabetes is still classified based on one biomarker: glucose. Even treatment recommendations like anti-hypoglycemic therapy remain based on average glucose effects from clinical trials. This evolving understanding of the complexity of the disease has prompted research on clustering of variables to define the subtypes.

An example of one such effort is a landmark study in a Scandinavian cohort reported in 2018, where they examined the following variables: GAD antibody positivity, glycemic control with A1C, age, body mass index, and measures of insulin secretion and resistance. The investigators defined at least five subtypes of diabetes-Severe Autoimmune Diabetes, Severe Insulin Deficient Diabetes, Severe Insulin Resistant Diabetes, Moderate Obesity-Related Diabetes, and Moderate Age-Related Diabetes. Importantly, they were able to show that these subtypes when followed over time relate to specific clinical outcomes. They demonstrated that this clustering approach, considering all of these other factors, was superior to the measurement of glucose alone.

These subtypes and this approach have since been validated in many other populations around the world. Some cardiovascular studies have looked at the clustering subtypes and shown relationship to cardiovascular disease. This heterogeneity was also described in individuals considered at "high risk" and in prediabetes. A study published by Dr. Robert Wagner and colleagues looked at numerous variables—estimates of insulin secretion and resistance, visceral body fat and hepatic fat content, genetic risk, and high-density cholesterol—and defined six clusters; three clusters were defined as having low risk of progression to diabetes and three clusters were moderate or high diabetes risk, with increased risk of cardiovascular disease, nephropathy, and mortality. Thus, if individuals could be stratified at an early age based on diabetes heterogeneity, clinicians could recommend more tailored monitoring or intervention.

The charge of this Council Working Group would be to conduct a detailed overview of the current state of knowledge on the heterogeneity of diabetes and inform NIDDK scientific staff of evolving concepts in this field from a global perspective. Its composition will reflect a diversity of interests and scientific disciplines that will facilitate a comprehensive assessment of the current and evolving state of the field. The format will be similar to that of the Health Disparity Health Equity Working Group, with regular meetings, ad hoc seminars, and subgroups to address specific interests. Interim and final reports will be submitted to Council. The goal is to ensure NIDDK scientific staff are better equipped with a clear understanding of the needs of the field in order to stimulate research efforts to develop more discrete definitions of subtypes of diabetes.

The overarching goal of developing a robust program to reclassify diabetes will take years. This would require initiatives to enhance understanding of heterogeneity in preclinical research at the molecular, cellular, and tissue levels, perhaps even identifying new biomarkers. The clinical program would continue to promote understanding of heterogeneity and disease development across the lifespan, which requires advances in precision diagnostics and therapeutics to understand the heterogeneity of therapeutic response. Finally, the results of these efforts will have to be disseminated and translated to healthcare settings, communities, and populations on a global scale. This will be a long-term effort, as heterogeneity needs to be evaluated at the preclinical, translational, and clinical stages and findings disseminated.

Council Questions and Discussion
Dr. Cefalu, moderator

Comment from Council: *There might be additional subtypes to consider.*

Dr. Cefalu agreed and said the proposed subtypes are just a template and starting point.

Comment from Council: *This is so badly needed in clinical practice, where every day clinicians see patients who don't meet the criteria and need more precise and appropriate disease management strategies.*

Another Council member also addressed this issue and suggested that the proposed working group assess newer therapies to determine how they might fit into the emerging hierarchy of categories.

Comment from Council: *Breaking down the disease into subtypes offers new opportunities for genomics and basic understanding of segregation of genes and different diseases. Looking forward and backward, is there a way to take these classifications of diabetes and extract genomic data from other existing cohort studies, to further look for genetic determinants of the different subtypes?*

Dr. Cefalu noted that the RADIANT trial is studying atypical diabetes. Additional available cohorts could be studied for genetics, biomarkers, social and behavioral phenotyping, nutrition, and environment factors, which could be the focus of a subgroup of the Council Working Group. NIDDK has representation on All of Us but that effort is not diabetes-specific. The goal of this program would be to dig deeper into behavioral, clinical and molecular phenotyping of diabetes, but it will be important to do so without duplicating efforts, such as those that already exist in precision nutrition.

Comment from Council*: The timing of this effort is particularly good because it can benefit and build on the work done by the Working Group of Council on Health Disparities and Health Equity.*

Comment from Council*: The research cited by Dr. Cefalu was conducted in a Scandinavian cohort and subsequent validation studies have been performed in European and East Asian cohorts. There is a need to make this a global investigation because even though diabetes is a global problem, the genetic and environmental differences among cohorts deserve study.*

Dr. Cefalu responded that NIDDK is proposing to put together a coalition of colleagues in Europe, Canada, and South Asia and planning to first convene an initial meeting of global leaders in the field at the American Diabetes Association meeting in June to share information about their programs and discuss how to work together to share information and advance the filed.

Comment from Council*: In addition to thinking about global factors, thought should be given to subtyping that might take place across the lifespan. In addition, there will be a need for methodological expertise to inform statistical analysis and bioinformatics when working with large, high-volume, complex data.*

Dr. Cefalu said that the Working Group will include that expertise and will consider a subgroup be formed on this issue.

***Comment from Council**: The working group should aim to limit the complexity of the proposed classification system in order to be clinically practical.*

IX. NATIONAL CLINICAL CARE COMMISSION: REPORT TO CONGRESS ON LEVERAGING FEDERAL PROGRAMS TO PREVENT AND CONTROL DIABETES AND ITS COMPLICATIONS

Dr. William Herman, Chair, National Clinical Care Commission

Dr. Rodgers introduced the session by stating that diabetes is an epidemic, in which the health impacts for individuals can be overwhelming. Further, the economic burden on the health care system and society is great. Diabetes is one of the costliest chronic conditions in the United States.

In 2017, Congress passed the National Care Commission Act, which directed the U.S. Department of Health and Human Services to convene a committee to evaluate and make recommendations to Congress and the HHS Secretary regarding federal programs that impact diabetes and its complications. The National Clinical Care Commission (NCCC) included 23 members: 12 nonfederal members representing diverse disciplines and views and 11 ex-officio federal members. The nonfederal members include primary care physicians, clinical endocrinologists, nonphysician health care professionals, clinical pharmacists, patient advocates, and public health experts.

The federal members represented the Centers for Medicare and Medicaid Services (CMS), the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), the Indian Health Service (IHS), the Department of Veterans Affairs (VA), NIH, the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), the Department of Defense (DoD), the U.S. Department of Agriculture (USDA), and the Office of Minority Health. NIH was represented on the Commission by Dr. Barbara Linder from NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases.

From 2018 to 2021, the Commission conducted meetings and in-depth interviews with stakeholders across the diabetes ecosystem. In January 2022, the NCCC submitted its final report to Congress, which consists of a series of 39 recommendations to leverage federal programs to prevent type 2 diabetes and control diabetes complications. The report contains evidence-based recommendations for: reducing diabetes-related risks and preventing type 2 diabetes in the general population, preventing type 2 diabetes in targeted populations at high risk for its development, and treating and managing diabetes and its complications to improve the health outcomes of individuals with the disease.

Dr. Rodgers welcomed Dr. William Herman, NCCC Chair, to give an overview of the report and its recommendations. Dr. Herman is a Professor of Internal Medicine and Epidemiology at the University of Michigan and Director of the Michigan Center for Diabetes Translational Research.

Dr. Herman reviewed the NCCC mandate and membership, as described by Dr. Rodgers.

NCCC is a Federal Advisory Committee established by Public Law 115-80 and charged "to evaluate and make recommendations to the Congress regarding improvements to the coordination and leveraging of programs within the Department of Health and Human Services and other Federal agencies related to awareness, prevention, and clinical care for diabetes." The NCCC framework for diabetes prevention and control is: "Diabetes is both a societal problem and a complex medical problem. Prevention and control must address social determinants of health and health care delivery."

Accordingly, the Commission adopted a framework for diabetes prevention and control that incorporated elements of both a socioecological model and a chronic care model. The socioecological model suggests that population health outcomes are impacted by diverse sectors of influence, such as food systems, environment, housing, labor, and transportation. These factors work through behavioral settings, where people live, work, and play. They are also affected by individual-level factors, but it is the productive interactions in relationships among these factors, including informed and activated populations, supportive policies, social conditions, and environments, that influence population health outcomes.

The chronic care model postulates that health systems that incorporate organizational support, clinical information systems, delivery system design, decision support, self-management support, and community resources are better able to influence chronic disease outcomes. Again, it is the interaction between informed and activated patients and prepared proactive health systems and practice teams that affect population health outcomes, patient-level functional and clinical outcomes, and health equity.

Subcommittees of the NCCC focused on three major themes:

- Reducing diabetes-related risk and preventing type 2 diabetes in the general population
- Preventing type 2 diabetes in targeted populations at high risk
- Treating and managing diabetes and its complications to improve the health outcomes of individuals with diabetes

The NCCC collected information on federal policies and programs relevant to diabetes through data calls, literature searches, key informant and stakeholder discussions, public comment, and from health-related and non-health-related federal agencies.

As described by Dr. Rodgers, Dr. Herman said the Commission held 12 public meetings between October 2018 and September 2021, as well as numerous subcommittee meetings, and meetings with key informants and stakeholders. Its report was completed in September 2021 and transmitted to Congress on January 6, 2022.

The NCCC was only the second congressional commission addressing diabetes. The first was the National Commission on Diabetes, chaired by Dr. Oscar Crawford. It was convened in 1974 and issued its report 45 years ago, in 1976. It was a transformational report at the time. It established the NIH program for diabetes research and training centers. It recommended the conduct of the Diabetes Control and Complications Trial and the Diabetic Retinopathy Study, and it established the Diabetes Mellitus Interagency

Coordinating Committee. It also recommended the formation of the diabetes control programs through the CDC, VA, and IHS diabetes programs. However, it took a fairly narrow view on diabetes, viewing it as a medical condition requiring biomedical solutions. As such, the NCCC report differs in its recognition of diabetes as a societal problem, noting that to improve prevention and treatment and to prevent complications, social determinants of health must also be addressed.

Dr. Herman reviewed NCCC's recommendations for diabetes prevention in the general population:

- Updating and increasing funding to the USDA's nutrition assistance programs to promote both food security and dietary quality
- Increasing breastfeeding rates through effective federal programs and paid maternity leave
- Implementing federal strategies to encourage the consumption of water over sugar-sweetened beverages
- Updating FDA's food labeling policies and practices
- Providing the Federal Trade Commission (FTC) with the authority and resources to regulate the food and beverage industry's marketing and advertising to children
- Expanding housing opportunities in health-promoting environments for low-income individuals and families through the Department of Housing and Urban Development (HUD) and Internal Revenue Service (IRS) programs. The Moving to Opportunity Study in the 1970s showed that providing public housing in environments that were more favorable to low-income individuals actually reduced the rate of obesity and diabetes in families and their children. Currently, only about 20 percent of people who are eligible for public housing are able to receive it because of limitations in funding to the program. Increasing funding for the program would allow more people to live in healthful environments.
- Modifying federal policies to reduce toxic environmental exposures and improve the built environment. The Commission focused on $PM_{2.5}$ air pollution, heavy metals in water, and the importance of safe drinking water, as well as bisphenols and phthalates and PFASs, where emerging literature is showing that they are associated with risks of obesity and type 2 diabetes.

Dr. Herman then reviewed NCCC's recommendations for diabetes prevention in people at high risk:

- Increasing awareness of prediabetes and availability of effective lifestyle intervention programs, in particular the National Diabetes Prevention Program (NDPP). Currently, about 90 million Americans have prediabetes. Only 17 percent of them are aware of the diagnosis, and of the 90 million people with prediabetes, fewer than one million have enrolled in the NDPP.
- Promoting better coverage of HbA1c as a screening test for prediabetes
- Adopting clinical quality measures that support screening for prediabetes and targeted interventions to delay or prevent type 2 diabetes
- Facilitating FDA review and approval of metformin for diabetes prevention. Metformin is a generic medication that has been shown to be safe and effective for the delay or prevention of diabetes. However, no manufacturer holds the new drug

application (NDA), so an alternative strategy is required to get it submitted for FDA review and approval.
- Providing adequate insurance coverage for all effective delivery modalities for diabetes prevention (in-person, telehealth, and virtual). Currently, CMS only covers in-person programs, which have limited enrollment.
- Approving the Medicare Diabetes Prevention Program (MDPP) as a permanent covered benefit.
- Continuing efforts to streamline the recognition and payment processes for type 2 diabetes prevention programs. There are differences between the NDPP and the MDPP in terms of recognition and payment.
- Incentivizing state Medicaid programs to provide coverage for the NDPP

Recommendations for treatment of diabetes and its complications include:

- At the patient level, reducing barriers and streamlining administrative processes to facilitate diabetes self-management training and access to diabetes technologies and devices, expanding access to virtual care, and ensuring that medications are affordable and accessible
- At the practice level, enhancing programs that support team-based care and developing capacity to support technology-enabled interventions
- At the health system level, aligning programs funded by the Department of Health and Human Services (HHS) with health care workforce needs. Currently, HHS provides funds for training programs but does not specify who should be trained. Workforce needs in diabetes prevention and treatment are largely unmet and better alignment between HHS funding and health care workforce needs could begin to address this problem.
- At the health policy level, ensuring pre-deductible insurance coverage for insulin and high-value diabetes treatments and services. Currently, services for primary prevention that are approved or recognized as being Level A or Level B by the U.S. Preventative Services Task Force are mandated for coverage under the Affordable Care Act. There is no similar provision, though, for secondary and tertiary interventions in diabetes, like ACE inhibitors for kidney disease or retinal laser therapy for diabetic proliferative retinopathy. A formal review and approval system would provide better access to secondary and tertiary preventative services.

NCCC also developed overarching recommendations, as follows:

- Diabetes must be addressed as a societal problem and not simply as a medical problem
- Federal policies and programs should ensure that people at risk for or with diabetes have access to comprehensive, high-quality, and affordable health care
- Health equity should be considered in every new or existing federal policy and program that impacts people at risk for or with diabetes to eliminate any unintended, adverse impacts those policies and programs may have on health disparities
- To coordinate and monitor federal efforts to prevent and control diabetes and to ensure trans-agency collaboration, an Office of National Diabetes Policy should be created and given responsibility to develop and implement a national diabetes

strategy across health and non-health-related federal agencies

Dr. Herman then described the Commission's recommendations to support research across the three themes, identifying potential federal actors where relevant. He noted that challenges will arise in getting the health-related agencies to work with nontraditional partners to address the societal and environmental determinants of diabetes.

Recommendations to support research to reduce risk in the general population include the following:

- Elucidate the associations between social and environmental factors and diabetes risk and complications; study the impact of interventions to change these factors; modify, implement, and evaluate changes in agency policies and programs to address social and environmental conditions to prevent and control diabetes (NIH, CDC, USDA, Department of Transportation [DoT], FDA, FTC, Environmental Protection Agency [EPA])
- Conduct natural experiments to evaluate the impact of changes in social and environmental policies and programs to prevent and control diabetes
    - Focus on non-clinical policies/non-health-related federal agencies
    - Health-in-all policies
    - Health impact assessments
    - Cost-effectiveness analyses (NIH, CDC, Centers for Medicare and Medicaid Services (CMS)/Center for Medicare and Medicaid Innovation, USDA, HUD, DoT, EPA)
- Expand precision nutrition research to address:
    - Foods, beverages, and additives that promote and prevent type 2 diabetes
    - Targeted marketing and communication interventions that promote and prevent type 2 diabetes for at-risk populations
    - Development, implementation, and evaluation of neighborhood-level (culture- and geography-focused) precision nutrition interventions
    - Water consumption and health across the lifespan (NIH)
- Study the impact of exposure to life course trauma and environmental pollutants/endocrine disrupting chemicals on diabetes risk and the impact of interventions to reduce exposure on outcomes (NIH)

Recommendations to support research addressing high-risk populations include:

- Barriers to participation in targeted diabetes prevention interventions (health systems/providers/patients)
- Barriers to long-term weight loss maintenance (health systems/providers/patients)
- Optimal lifestyle intervention program design
- Effectiveness of combined lifestyle and medication interventions
- Causes, screening, and prevention for type 1 diabetes including increased support for the Special Diabetes Program
- Implementation and dissemination research (NIH, CDC, CMS, HRSA, IHS, VA, DOD, AHRQ)

The last set of recommendations focused on supporting research to address diabetes treatment and its complications:

- Elucidate barriers to Diabetes Self-Management Education and Support and Training (DSME/S/T) and develop, implement, and evaluate interventions to address barriers that are feasible and acceptable to diverse populations (health systems, providers, patients, families)
- Assess the feasibility and impact of implementing quality measures, incentives, and system redesign (collaboration with community providers) to address social determinants of health (SDOH) and disparities in DSME/S/T
- Develop, implement, and evaluate strategies to facilitate team-based care and address barriers to the uptake of effective interventions, models of care delivery, and payment systems
- Implementation and dissemination research (NIH, CDC, CMS, HRSA, IHS, VA, DoD, AHRQ)
- Encourage collaboration among federal agencies to investigate digital connectivity as a super SDOH and identify types of digital services and levels of adoption needed to impact health (HHS, NIH, Federal Communications Commission [FCC])

Council Questions and Discussion
Dr. Rodgers, moderator

Comment from Council: *Although the report is very comprehensive, it seems to be a bit outdated already, for example, with its focus on HbA1c for screening when there are new measures that are going to be less expensive and provide more information. Those types of advances should be considered. In addition, perhaps the NDPP should be updated.*

Dr. Herman responded that the recommendation was focused on CMS coverage of HbA1c screening for prediabetes or diabetes. The NDPP should be assessed for all effective measures.

Comment from Council/Staff: *Where would the Office of National Diabetes Policy reside?*

Dr. Herman said the NCCC envisioned it being above the HHS, perhaps as a Presidential commission, involving HHS but with the authority to coordinate across all federal department and agencies.

Comments from Council*: Did the Commission prioritize interventions or discuss milestones? How would it track the outcome of an intervention to determine whether it is providing benefit?*

Dr. Herman said the NCCC chose not to prioritize the interventions, recognizing that readers will focus on different recommendations according to their mission and agency perspective.

As for measuring impact, one focus would be on population health (e.g., reduction in the incidence of type 2 diabetes or improvements in diabetes care). Despite new, safe, and

effective treatments for diabetes, improvement in performance measures, such as A1C, blood pressure, and non-HDL cholesterol levels, have remained low over the past 10 years; the proportion of patients with diabetes achieving those goals has decreased. In addition, there has been an uptick in the incidence of diabetic complications. So, outcome measures would focus on population data.

Comment from Council: *Given that there are 90 million people with prediabetes, is there any information about which of those individuals are likely to progress? Could the different subtypes provide information about who to target for interventions given the low uptake for prevention programs?*

Dr. Herman replied that existing data suggest that there are different levels of risk of progression of people based on current criteria (e.g., fasting glucose, oral glucose tolerance test, A1C). There is a need to tailor interventions to those who can benefit most.

Comment from Council: *With 90 million people with prediabetes and another 30 million with a diagnosis, roughly a third of the U.S. population is at risk, emphasizing that it is a societal disease. Has the Commission considered the factors that make this a societal problem and how research initiatives on this topic could be funded?*

Dr. Herman said that the Commission recognized that the resources within the non-health-related agencies, such as USDA's school lunch and SNAP programs, are much larger than the budget of NIDDK. The impacts of changes in those agencies could be substantial.

Comment from Council: *More than $300 billion is spent each year on diabetes-related care. Did the NCCC conduct an economic analysis to determine what full implementation of its recommendation might mean with respect to health or the economy?*

Dr. Herman replied that that was beyond the scope of its mandate.

X. CONCEPT CLEARANCE

Dr. Rodgers then turned to Concept Clearance by Council, a step required before ICs can publish funding opportunity announcements, or FOAs. To streamline this process, summaries of the concepts were supplied to Council members for their review in ECB before the meeting. Cleared concepts will be made publicly available on the NIDDK website. He then introduced each speaker.

Human Islet Research Network (HIRN) – On Beta Cell Death and Survival (CBDS)
Dr. Olivier Blondel

This concept will solicit new applications to the Consortium on Beta Cell Death and Survival (CBDS) that propose to use human pancreatic cells and tissues for the discovery of defective signaling or processing pathways that contribute to the asymptomatic phase of type 1 diabetes, the discovery of early biomarkers of type 1 diabetes pathogenesis, and/or the identification of therapeutic targets for the development of preventative or early

treatment strategies. CBDS is part of the Human Islet Research Network (HIRN) and this concept would represent the second renewal of the CBDS effort. In the past 7 years, the consortium has made significant progress toward its long-term goal of better understanding the triggers of type 1 diabetes initiation in humans. Renewed support is needed to better understand this (still) understudied phase of human type 1 diabetes with the long-term goal of developing innovative strategies for protecting the residual beta cell mass in type 1 diabetes patients as early as possible in the disease process and preventing the progression to autoimmunity in at-risk individuals.

Council Questions and Comments

Dr. Rodgers invited Council members to ask any questions related to this concept. There were no questions or comments.

Continuous Ketone Monitoring for the Safe Use of Sodium-Glucose Cotransporter-2 Inhibitors in Type 1 Diabetes (R01 Clinical Trial Required)
Dr. Teresa Jones

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) that were developed for the treatment of type 2 diabetes have significant protective effects for cardiac and renal diseases for people with and without diabetes. However, the benefits of SGLT2i are not available to individuals with type 1 diabetes because of the increased risk of diabetic ketoacidosis (DKA) for this population and they are not currently approved for use in this population. Despite this concern, these drugs are increasingly being prescribed off-label for people with type 1 diabetes. Continuous ketone monitoring (CKM) is a rapidly advancing technology that could be leveraged to prevent DKA by an early warning of ketone elevations. The purpose of this proposal is to develop and test risk mitigation strategies that integrate CKM for the safe use of SGLT2i for people living with type 1 diabetes so that they may benefit from the cardiac and renal protection and glucose-lowering effects of this drug class. The funding opportunity will support short-term, clinical trials to test DKA risk mitigation strategies for the use of SGLT2i in people with T1D using CKM technology in an out-patient setting. Possible topics include testing optimal insulin delivery in closed loop systems or multiple daily injections and developing clinical protocols to control or ameliorate elevated ketone levels. Research studies will be conducted through individual R01 grants to accelerate the execution and increase the flexibility of trial design with coordination of efforts among the investigators and NIDDK program staff through regular meetings.

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Council Questions and Comments

Dr. Rodgers invited Council members to ask any questions related to this concept.

Comment from Council: *Would subjects wear a CGM as well as CKM patch?*

Dr. Jones said that the device is being developed as one patch, with both CGM and CKM capabilities.

Comments from Council*: Given the controversy about possible effects on ischemic*

stroke and the fact that these transporters are highly expressed in the brain, how long would the patch be worn and what are the possible long-term consequences for stroke or small vessel diseases of the brain? Safety, timing, and length of use should be studied in addition to efficacy.

Dr. Jones answered that these are widely prescribed drugs and data are being collected on both type 1 and 2 diabetes for efficacy and effects. The benefit appears to outweigh the risk.

Comment from Council*: These drugs have been studied in tens of thousands of people with type 2 diabetes and now in randomized clinical trials. The bulk of the evidence is that, for the most part, they prevent mortality and cardiovascular events. There are fewer studies in type 1 diabetes, so the emphasis on safety in this trial is important. Existing studies have focused on glucose lowering. Ketone monitoring seems important in that the drugs have been shown to be very effective in people with type 1 diabetes and in limiting the amount of insulin needed, showing less hypoglycemia. However, people are fearful about using them because of diabetic ketoacidosis (DKA). There are two concerns about this study. First, it is rare to develop DKA, so a relatively large sample size will be needed to answer the question. Second, this seems more like an industry trial because whoever makes the sensors is likely to gain financially from their use. Prescribing SLGT2 inhibitors to patients with type 1 diabetes who use CKM would significantly benefit the maker of the monitors. Freestyle Libre is offering investigator-initiated grants for this type of work, which NIDDK should consider when deciding which initiatives to fund.*

Dr. Jones responded that industry has shown little interest in SGLT2 inhibitors and type 1 diabetes. Although industry would likely develop the sensors, it is important to conduct unbiased studies on their use without industry funding and then quickly disseminate the findings. It is also not clear whether industry would invest in the smaller market for SGLT2 inhibitors, especially when there is potentially life-threatening complication.

Dr. Cefalu added that while there could be a role for industry, right now these drugs are being used off-label and DKA is a serious adverse event and can be life threatening. The goal would be to test the mitigation strategy as a first step toward using these drugs safely, which will set the stage for longer-term efficacy studies.

Comment from Council*: What are the plans for getting some preliminary efficacy data, perhaps based on the near- or short-term endpoint?*

Dr. Jones replied that the project could include obtaining some short-term data on glucose and ketone levels. Once an efficacy study is designed, it would be a larger and longer trial, but it would likely provide more data on kidney disease, heart failure, and other comorbidities and complications.

Comment from Council*: In a trial testing SGLT2 inhibitors in patients with type 1 diabetes, several patients developed DKA, but it is challenging to get emergency department staff to test for DKA. In addition, cardiologists and nephrologists might be prescribing SGLT2 inhibitors for patients with type 1 diabetes without their endocrinologist's awareness, so there is concern that the patients are not*

appropriately monitored for DKA. Having a sensor for ketones is important because these patients may be at risk for DKA, as their ketone test strip prescriptions might have expired, never been filled, or used inappropriately. This is an important study because as new medications are being developed for type 2 diabetes, there are a lot of questions about whether they can also be used safely in type 1 diabetes.

***Comment from Council**: Will these studies be conducted across all of the available SGLT2 inhibitors for comparison? Are there concerns about heterogeneity?*

Dr. Jones responded that meta-analyses have shown that SGLT2 inhibitors are fairly similar in their effects. Investigators will have to provide a rationale for which ones they are using.

There being no further questions or comments from Council, Dr. Rodgers proceeded to request a motion for concurrence with the two concepts presented. The motion was made, seconded, and approved by electronic vote.

XI. REPORT OF THE WORKING GROUP OF COUNCIL ON HEALTH DISPARITIES AND HEALTH EQUITY RESEARCH

Dr. Pamela Thornton and Dr. Gregory Germino

Dr. Rodgers began his introduction of the final presentation of the open session by reminding Council that an outcome of its Council Forum on Underrepresented Investigators and Underrepresented Science was the establishment of a Working Group on Health Disparities and Health Equity (HD/HE Working Group). Council has been kept abreast of the Working Group's activities and has heard updates from all five of its subgroups. The Working Group has now completed its report. Dr. Rodgers introduced Drs. Germino and Thornton to lead an overview of the Working Group's report and discussion with Council.

Dr. Germino provided a brief overview of the history of the Working Group, which was assembled as the result of the three-part Council Forum mentioned by Dr. Rodgers. The Forum launched in September 2020 with an initial focus on the lack of Black investigators in NIDDK's extramural workforce and with a review of efforts taken to rectify the problem and consideration of promising new strategies. At the January 2021 Council meeting, discussion focused on the related but distinct issue of health disparities research. One factor identified as contributing to the lower success rate for Black researchers was that they tend to propose research on topics with lower award rates, such as health disparities, and these topics are favored by Institutes with smaller budgets and lower award rates.

A review of NIDDK programs found some important work in these areas but investments in and support of health equity research is modest. In May 2021, efforts focused on what was happening elsewhere at NIH to address these issues. After reflection, it was decided that input from external researchers and community experts would guide planning. Council was asked to establish a working group to work with staff to develop a health disparities, health equity research implementation plan that would be linked to the Institute's Strategic Plan.

The Working Group's deliberations were informed by NIDDK's December 2021 Strategic Plan for Research, which states: "NIDDK is committed to empowering a multidisciplinary research community; engaging diverse stakeholders; and leveraging discoveries of connections among diseases across NIDDK's mission to improve prevention, treatment, and health equity— pursuing pathways to health for all."

The Working Group Report and Implementation Plan is a complement to the NIDDK Strategic Plan and embeds equity-focused principles and tips in research activities. It promotes multilevel approaches to target root causes of disparities and provides specific actionable research recommendations to help the Institute coordinate and prioritize activities to eliminate disparities and advance health equity within NIDDK's mission.

The Working Group was asked to become familiar with and consider the NIDDK context for health disparities and equity research, using the NIDDK Strategic Plan and the Strategic Plan and Research Framework of the National Institute of Minority Health and Health Disparities (NIMHD) as resources. The Working Group was charged with establishing a set of actionable high-impact research activities to address disparities and promote equity, as well as high-impact research opportunities within the NIDDK mission. It was also asked to help define measures of progress over time and with consideration of the resources, partnerships, and workforce training required to execute the plan.

The Working Group was organized according to five scientific themes and subgroups, each tasked with addressing the topic from complementary perspectives:

1. Engaging communities and building sustainable partnerships
2. Understanding social determinants of health (SDOH) effects on the biology of health and disease
3. Intervening to impact SDOH to improve health and eliminate disparities
4. Addressing upstream causes of SDOH and health disparities from an NIDDK perspective
5. Listening to community perspectives

There was considerable overlap in discussions and recommendations among the five subgroups, as the underlying themes are interconnected. One particular feature of this Working Group was its central focus on individuals who live with, are at risk of developing, or are caring for someone with NIDDK mission diseases and conditions. Subgroup Five was fully composed of community members and their input was solicited at all stages of the process.

The Working Group was comprised of community members, patients, and caregivers, leaders of major not-for-profit organizations, and external researchers from across the country with expertise in multidisciplinary research fields related to health disparities and health equity. Many of the members have conducted foundational work in the field, including some Council members. In order to ensure that the voice of the community was present throughout the entire process, each subgroup had at least one community member who also participated on the Steering Committee of the full Working Group. The Working Group received extensive input from members of the Institute, including numerous individuals from across the three extramural programmatic divisions, the Division of Extramural Activities, the Office of Minority Health Research Coordination, the Office of

Scientific Program and Policy Analysis, and the Office of Communications and Public Liaison.

Over the past year, 11 individual subgroup meetings and 3 steering committee meetings were held. Periodic updates were provided to Council at its meetings. The final report, presented to Council, is written in the voice of the Working Group with recommendations from the Working Group to Council. The order of the recommendations does not necessarily directly correlate with subgroup structure. Text boxes throughout the report highlight insights from community members reflecting their critical input in the process.

Dr. Germino then asked Dr. Pamela Thornton, his Co-Chair, to review highlights of the report and its recommendations.

Dr. Thornton first reviewed the Introduction and its various components. It includes a general framing of the report and discusses the utility of the recommendations for NIDDK and its broader research communities. It includes definitions of key terms and NIDDK's commitment to this area of science, as highlighted in the Institute's Strategic Plan, and now through the Guiding Principles for Embedding Equity into Research, which is outlined for the first time in this report. The Introduction also contains an overview of NIDDK's accomplishments and programs in health disparities research and a brief discussion of how the report was developed.

Dr. Thornton then discussed the individual components and recommendations in more detail. She presented an abbreviated version of the Guiding Principles, which the Working Group believed were necessary to better enable staff to consistently adopt an equity lens to inform the Institute's relevant research efforts. The principles align with and build on the Institute's overarching principles that were set by Dr. Rodgers, and are intended to: (1) maintain a robust health disparities and health equity research portfolio across the spectrum of sciences that NIDDK supports; (2) partner with diverse communities, which include patients, family members, caregivers, and other community members affected by the Institute's diseases and conditions; (3) include diverse populations in research and promote diverse perspectives in research by supporting multidisciplinary and community research teams; (4) nurture a diverse world-class research workforce; (5) support appropriate consideration of race, ethnicity, and gender in research (this entails acknowledging that these categories are social constructs, not biological variables, and encouraging appropriate use of the social categories in research); and (6) promote transparency and accountability by regularly communicating the Institute's progress to diverse audiences.

The report features five major research recommendations with multiple opportunities under each that reflect robust deliberations across the subgroups.

The first recommendation focuses on a cross-cutting theme to, whenever possible, strengthen community engagement through partnership, sharing power or influence in decision-making and capacity-building to improve research. One opportunity is to build and sustain trusted collaborations with communities. This sometimes means researchers need to carefully plan how to address mistrust that may predate their study, as well as future challenges regarding issues of trust. An essential goal is to pursue mutually beneficial and effective research to ultimately improve health.

The next opportunity under this recommendation is to partner and engage with trusted community entities, such as community-based organizations (CBOs) and people that community members rely on as trusted brokers of information about health and well-being. A third opportunity is to build capacity and infrastructure to make it easier for community members and entities such as CBOs to engage in research. For example, research data could be made more accessible to the community by providing the data and appropriate training in how to access and interpret it. Additionally, enhanced guidance and technical assistance could be provided on how to apply for research funding. Finally, it is important to identify collaboration models between investigators and various groups that can provide care and foster healing from trauma and injustice as needs arise. An example of this is simply bringing resource guides when collecting data from participants in the community.

Recommendation 1 also includes practical tips for investigators planning to conduct health disparities and health equity research. The Working Group thought providing guidance would be a good strategy to start building competency in the scientific workforce, particularly for investigators who are new to the field, and to set expectations for NIDDK-funded projects to collectively begin or continue to nurture high-quality science. The tips provide general guidance on identifying the health disparity problem and contributing factors with input from affected communities. It also includes tips on initializing and sustaining engagement of key stakeholders and participants beyond the recruitment phase and developing plans for using appropriate research methods and disseminating the findings. These tips leverage effective practices developed by experts in the field of public health and community-engaged research.

Dr. Thornton re-emphasized the community insight callout boxes that appear throughout the report. One included under Recommendation 1 concerns community involvement in the research process. Community members said that they want to be involved in the research activities and stay engaged beyond the study period. They also expressed interest in being part of the research design and developing research questions that are important to them.

Recommendation 2 is to advance research on the mechanisms by which biological, behavioral, environmental, and structural factors interact to affect health, disease, and resilience. The first opportunity for this recommendation is to explore how experiences of psychosocial trauma affect biology and behavior—in this context, trauma specifically relates to the negative effects of structural racism, discrimination, and stigma. This type of research could include investigating the impact of such external conditions and how they interact with and impact changes in biology such as: allostatic load; neuroendocrine processes; and communication between the brain and other organs like the gut and even the microbiome, and understanding how they interact with physiological changes.

The next opportunity under Recommendation 2 focuses on research to understand the relationships among structural factors, SDOH, and epigenetics and their effects on health disparities and heterogeneity. For example, the APOL1 gene is a risk factor for kidney disease in some people with West African ancestry, but a stressor or “second hit” is required to trigger pathologic processes that result in renal injury. Social and environmental factors may be important contributors to triggering kidney disease, which

need to be better understood in order to improve prevention and treatment. Another opportunity is to determine promoters and mechanisms of resilience that prevent or lessen disease severity. Finally, under this recommendation, the Working Group believed that it is critically important to explore whether biopsychosocial precision medicine approaches to disease and conditions could identify unique sociobiological phenotypes. Knowing these specific phenotypes could help provide a more complete picture of disease pathways so that targeted and superior treatments can be developed.

Recommendation 3 is to advance research on interventions and studies that address the effects of racism, unmet health-related social needs and the social determinants of health. One way to advance this area of research is for multidisciplinary and multisectoral research teams to test strategies that integrate social and medical care interventions. This type of research involves healthcare and community settings that provide resources to patients and families, such as medical care, food banks, pharmacies, and places for regular and safe exercises. The strategies could be tested at the local community level or go further upstream by testing regional level approaches that target population health outcomes.

Another opportunity is to test interventions to address harmful implicit biases and structural racism in healthcare delivery. This could involve testing training models to advance good communication and other skillsets for both providers and patients. The next research opportunity is to expand equity-centered dissemination and implementation research to accelerate the development, adoption, communication, and sustainability of equitable and effective interventions for diverse healthcare and community settings. The last opportunity under this recommendation highlights advancing policy-oriented research through the expanded use of flexible research opportunities to evaluate health outcomes of policy, particularly community policy changes. For example, NIDDK's Rapid Grant Program, which accepts and reviews applications on a monthly basis, could be expanded to support policy and program evaluation research on a broad range of health equity topics.

A community member insight under this recommendation concerns bias in medical care. Community members said that training healthcare providers to recognize and address racism, as well as other "isms" and their effects on patients is important. Some healthcare providers may not realize or may deny that racism exists in their communities and those beliefs may be perpetuated intentionally or unintentionally by physicians or other healthcare providers.

Recommendation 4 focuses on promoting new methods, measures, tools, and technologies. One research opportunity highlights the need to develop and apply standardized methods and measures for social determinants of health and upstream structural exposure, such as psychosocial trauma, healthcare bias, and other variables that were discussed under Recommendations 2 and 3. In addition, efforts to broaden and optimize use of technologies that lessen participant burden in research participation and data collection were considered important. Examples of technologies that could be leveraged include home-based tools, such as wearable devices that track physical activity, glucose levels, and biologic metrics such as heartbeat, body temperature, and fluctuation of hormones over time. The plan also describes the need to leverage data science approaches and tools to achieve health equity research goals, such as linking to big data from health and social services sectors. The last opportunity under this recommendation discusses the need to address bias in predictive algorithms and lack of diversity in their source datasets so that

healthcare teams have accurate information to help medical decision making.

The community member insight under this recommendation focuses on medical records and hidden data. Community members said that individual identities such as cultural preferences, sexual and gender identity, and disability status are not always accurately or completely documented in clinical data, and race may be assumed based on appearance or not recorded at all. They also recognize that some people may be reluctant to share this information due to fear of discrimination or differential treatment. However, they also said when these patients' characteristics are not included in clinical data, the ability to draw insights from data linkages that could benefit these populations is hindered and healthcare guidance and interventions will not be tailored to reflect the full picture of the patient.

Recommendation 5 focuses on approaches to enhance NIDDK collaboration, structures, and programs to support robust research in health equity. The Working Group recommends that NIDDK create a new integrative guiding framework or conceptual model to support its health disparities and health equity research. Numerous research frameworks currently exist that have been valuable to the field, such as the NIMHD Research Framework, and these resources could be leveraged or adapted for NIDDK-specific science.

The Working Group also encouraged the Institute to provide ongoing training to NIDDK staff and external scientific communities to enhance knowledge and skills in core health equity concepts and community-engaged research. Another opportunity is to promote multidisciplinary efforts by sharing resources and pursuing collaborations across NIH and other federal agencies that are making investments and progress in this area. This final recommendation relates to the guiding principle of transparency and accountability, which is to conduct ongoing monitoring and evaluation activities to track NIDDK's progress and adjust priorities and approaches as needed.

The report concludes with direct quotes from the community members. Overall, they expressed hope that NIDDK-funded research will incorporate their perspectives, ideas, and suggestions to improve health outcomes. One community member said, "It made me feel proud and honored that my opinion was valued, and it made me want to go out and do research in the community to see what is missing or where we can help or fill the void to respond to the community's voice or the community's calling." Another community member said, "I believe participating in this group will facilitate change for us that feel we have been left behind. Another said, "I hope [NIDDK] will take our ideas to help better serve our communities to help us live a healthier life and hopefully prevent disease."

Dr. Thornton's closing remarks about the report included an overview of the Appendix section containing information such as new and expanded definitions of terms; examples of research frameworks being used in the field; acknowledgement of the Working Group members and additional contributors; and a portfolio analysis to begin benchmarking NIDDK's research investments and progress in this area. Dr. Thornton expressed appreciation to Council for their attention before transitioning to Dr. Germino.

Dr. Germino then described next steps. The goal is to prepare the report to be published online for public comment in early February for a period of 30 days. Council members were encouraged to share it with their various committees and networks to promote broad

input and response. After receipt of public comments and final editing, the report will be finalized. Several members of the Working Group's Steering Committee have expressed interest in continuing their involvement to assist the Institute in implementing and manifesting one of the opportunities (5.1), which is to develop a new framework to support health equity research as part of NIDDK's mission. The Institute plans to identify a small working group of additional experts and community voices for that effort. Finally, the Institute is looking internally to examine its organizational structures and resources to see how they can be realigned, or perhaps deploy additional resources to support health equity research in the future.

Dr. Germino then invited Council members who were members of the Working Group to offer their thoughts on the Working Group process and report.

Dr. Carethers co-chaired the efforts for the second subgroup. He said the subgroup engaged in robust discussions with input from the community. He noted that this report is likely to transform NIDDK and NIH with regard to health disparities research because it is a forward-thinking plan. He said that although it might not address all concerns, it will be an enduring document for research going forward.

Dr. Gordon-Larsen agreed that this is an extraordinary and important document providing a lot of definitional and foundational information. People are often confused about what health disparities and health equity mean and what can be done to address them. The report contains a great deal of useful information, particularly fundamentals on how one can conceive, think about, and tackle some very thorny issues. It includes many actionable ideas and implementable solutions for research to actually effect change. The engagement of the community was a good model of how this can be done productively with scientists and community members work alongside each other.

Dr. Haire-Joshu agreed that the report is outstanding and that she felt privileged to serve on the Working Group. Equity is the central feature of this report and it permeates all of the recommendations. The report is going to redefine team science and team approaches. The community involvement informs the report in a unique and visionary way. Another important contribution of the report is its foundational and actionable approach. What gets measured gets done, and there needs to be consistency when collaborating with the community, which promotes accountability.

Dr. Norris said that this report is a tour-de-force in that it pulls together something that many who work in community partner research have been waiting to see. Its focus on equity and bringing the patient and community voices forward has been outstanding. The outline and framework intersects nicely with many of the basic mechanisms and pathways currently being studied by NIDDK. Much of the work that is critical for health equity and the distribution of life-affirming resources and opportunities may have a direct impact on health, but they also have an indirect impact on health through many of the different signaling and neural hormonal pathways that ultimately affect many of the organs that are a focus of NIDDK's research mission. However, it is going to take several generations before we see some level of significant health equity. Therefore, we still have to take care of patients and optimize their health and not expect them to wait until society becomes more equitable. This document puts forward a proposal that allows that to happen.

Dr. Germino noted that Ms. Edwards, also a member of the Working Group, was unable to attend the meeting but has been a supportive and outspoken proponent throughout the entire process.

Council Questions and Comments

Dr. Germino asked for questions from other members of Council or additional comments from Working Group members. He asked two specific questions: (1) How could NIDDK sustain momentum and transparency—for example, should there be a smaller subgroup of the Working Group to serve as a continuing Working Group of Council? and (2) Would Council like to receive an annual progress report?

Comment from Council: *Does the report address Native Americans and sovereignty issues?*

Dr. Germino replied that it does not, but it does recognize that different communities have different opportunities and challenges and those must be addressed. Dr. Norris added that this question reinforces the need for an ongoing effort to address issues that the Working Group could not address in great depth.

Comment from Council*: This is a report that investigators can use as a roadmap, recognizing that one size does not fit all. For example, Digestive Disease Centers would have to customize what they do best and then figure out how to sustain movement forward to advance these goals. Perhaps Center Directors could meet on an annual or biannual basis to discuss what they are contemplating or actually doing to promote these equity goals.*

Comment from Council*: Immigration status might affect health disparities when people are hesitant to share health immigration and reveal their status. Did the Working Group address immigration status?*

Dr. Thornton said the Working Group expanded the current NIH definitions for populations who experience health disparities and immigration status is included. Whether people feel safe disclosing health information depends on local context, but the community members made clear that if a community engages with researchers in an authentic and meaningful relationship, transformational questions can be asked and solutions can be found.

Comments from Council*: Several members agreed that the report is transformational and has implications beyond NIDDK and NIH that will require a broader effort. Several members agreed an annual report to Council is a good way to measure progress and that metrics of success need to be developed.*

Comment from Council*: Are there plans for filtering this into grant applications, perhaps with a section on community partnerships?*

Dr. Germino said NIDDK is looking at different levers to do this that are under its control, for example, through language or requirements in Requests for Applications or Funding Opportunity Announcements.

There being no further questions or comments from Council, Dr. Rodgers requested a motion for concurrence with the recommendations of the draft Working Group report, noting that pending final edits for clarity, it will be posted by NIDDK for public comment. The motion was made, seconded, and approved by electronic vote.

In closing, Dr. Germino thanked Council for standing up the Working Group, the many experts and community members who generously gave of their time and shared their expertise, and the NIDDK staff who met regularly for two years to draft the plan. Dr. Germino thanked Ms. Reaya Reuss, his Chief of Staff and Executive Secretary for this effort, Ms. Emily Callahan and the Scientific Consulting Group for writing and logistics support, Dr. Thornton for her masterful leadership and expert input, and Dr. Rodgers for his generous and unwavering support.

XII. OPEN SESSION OF SUBCOMMITTEE MEETINGS

See Minutes posted on NIDDK Council Minutes Website.

XIII. CLOSED SESSION OF THE SUBCOMMITTEE MEETINGS

A portion of the meeting was closed to the public in accordance with the determination that it concerned matters exempt from mandatory disclosures under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C. and Section 10(d) of the Federal Advisory Committee Act as amended (5 U.S.C. Appendix 2).

Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

XIV. CLOSED SESSION OF THE FULL COUNCIL

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the 31 Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

CONSIDERATION OF REVIEW OF GRANT APPLICATIONS.

A total of 1,025 grant applications (208 primary and 817 dual), requesting support of $405,728,140 were reviewed for consideration at the January 25, 2023 meeting. An additional 247 Common Fund applications requesting $147,996,323 were presented to Council. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, 1,199 applications

requesting $447,106,750 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 January 25, 2023 meeting.

XIV. ADJOURNMENT

Dr. Griffin 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 221st meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m. on January 25, 2023.

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

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Date

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