228th 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

Meeting held virtually using web-based collaboration/meeting tools

I. CALL TO ORDER and ANNOUNCEMENTS
Dr. Griffin Rodgers

Dr. Griffin Rodgers, Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), called to order the 228th meeting of the NIDDK Advisory Council at 10:01 am on May 14, 2025. The meeting was held virtually and conducted using a two-tiered webinar format. The panelist tier included NIDDK Advisory Council members and NIDDK staff members who presented during the meeting. The audience tier was available via a live stream to the public, allowing them to view and listen to the meeting.

Dr. Rodgers noted that not all summary statements for applications received for the May Council round were available for the May 14th meeting. Because of this, an additional short Council meeting was planned for June 17th, 2025, from 3 to 5 pm EDT. More information would be made available once the logistics for the meeting were complete.

ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Jamy Ard
Dr. Richard Blumberg
Dr. Arthur Burnett
Dr. John Carethers
Dr. Lilia Cervantes
Dr. Peng Ji
Ms. Neicey Johnson
Dr. Davida Kruger
Dr. Jacquelyn Maher
Dr. Keith Norris
Dr. Aylin Rodan
Dr. Philipp Scherer
Dr. Elizabeth Seaquist
Dr. Hunter Wessels

Ex-officio Members:
Dr. David D'Alessio
Dr. Cindy Davis

Also Present:
Dr. Griffin Rodgers, Director, NIDDK and Chair of the NIDDK Advisory Council
Dr. Karl Malik, Executive Secretary, NIDDK Advisory Council
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. William Cefalu, Director, Division of Diabetes, Endocrinology and Metabolic Diseases, NIDDK
Dr. Stephen James, Director, Division of Digestive Diseases and Nutrition, NIDDK
Dr. Robert Star, Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK

Speakers:
Dr. Paul Franks
Dr. Stephen Rich

Awards

Dr. Rodgers recognized two NIDDK-supported investigators for their groundbreaking and impactful work:

- **Dr. Joel Habener** and **Dr. Svetlana Mojsov**, both NIDDK grantees, won the 2024 Lasker-DeBakey Clinical Medical Research Award for their discovery of glucagon-like peptide-1 (GLP-1), a molecule that has revolutionized treatments for diabetes and obesity. They share this prize with fellow researcher Lotte Bjerre Knudsen, of Novo Nordisk. Their collective efforts have led to the design of groundbreaking new pharmaceuticals and to a new era of medical science. A lead researcher in the fields of diabetes and endocrinology, Dr. Habener has been researching the role of the hormone glucagon in blood sugar regulation since the 1970s, and NIDDK has been supporting his work for nearly 40 years. NIDDK funded Dr. Mojsov's research on glucagon-like peptides (GLPs) in the 1980s and 1990s.

In Memoriam

Dr. Rodgers noted recent losses for the NIDDK research community:

- **Dr. Alison Field**, a long-time NIDDK awardee. Dr. Field served as professor and chair of epidemiology at the Brown University School of Public Health and professor of pediatrics at Brown's Alpert Medical School. Dr. Field earned her Doctor of Science in epidemiology from the Harvard T.H. Chan School of Public Health. She had been continually funded by multiple NIH institutes for studies using observational data to better understand the relationships between environmental, behavioral, and psychosocial factors leading to development of eating disorders and obesity across the lifespan. Most recently, Dr. Field expanded her work to incorporate extensive phenotyping of children in longitudinal studies collecting behavioral, psychological, metabolic, familial, and genetic data to better understand the heterogeneity of the development of obesity and eating disorders in youth, with a goal of identifying subtypes to advance precision approaches to their prevention and treatment. Dr. Field was one of the few investigators who, from the start of her career, recognized the intrinsic connection between obesity and eating disorders, and that prevention or treatment of one does not mean ignoring the devastating health consequences of the other.
- **Dr. Bruce Ames**, who worked at NIH from 1953 to 1967, first as a postdoc, then as a biochemist, and then as chief of the Microbial Genetics Section in the Laboratory of Molecular Biology in what is now NIDDK. Dr. Ames famously created the Ames test, a widely used tool to determine the mutagenic potential of chemical compounds.

II. FUTURE COUNCIL DATES

Dr. Griffin Rodgers

As previously noted, the next meeting of the NIDDK Advisory Council is scheduled for June 17, 2025, as a virtual meeting. The next regularly scheduled meeting of the NIDDK Advisory Council is scheduled for September 17-18, 2025. Updates about future meetings will be posted on the Council website.

III. ANNOUNCEMEMNTS

Dr. Karl Malik

Confidentiality

Dr. Malik said that Council members are reminded that material furnished for review purposes and discussion during the closed portion of this 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

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

To ensure that a member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. A statement is provided for the signature of the member, and this statement becomes a part of the meeting file.

After today's meeting, Council members will be sent a statement regarding conflict of interest in their review of applications. Each Council member should read the statement carefully, electronically sign it, and then return the signed statement by email to Devon Drew (Committee Management Officer) or to Dr. Malik within one day.

At Council meetings when applications are reviewed in groups without discussion, that is, by "*en bloc*" action, all Council members may be present and may participate. The vote of an individual member in such instances does not apply to applications for which the member might be in conflict.

Multi-campus institutions of higher education: An employee may participate in any particular matter affecting one campus of a multi-campus institution of higher education,

if the employee's financial interest is solely employment in a position at a separate campus of the same multi-campus institution, and the employee has no multi-campus responsibilities.

IV. REPORT: HETEROGENEITY of DIABETES WORKING GROUP

Dr. William Cefalu, Dr. Paul Franks, and Dr. Stephen Rich

Dr. William Cefalu, Director of NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases, provided an update on the activities of the Heterogeneity of Diabetes Working Group.

Dr. Cefalu explained that in order to fully achieve a stratified diabetes medicine approach for future applications, it would require a thorough understanding of the interactions between the exposome (all non-genetic elements to which we are exposed) and the physiome (genome, epigenome, transcriptome, proteome, metabolome, and metagenome) in relation to the environment in which we live. The objective of precision diabetology is to develop stratified prevention and treatment for subgroups of people with different risk profiles, aiming to reduce adverse events from pharmacotherapy, delay the onset of diabetes and its complications, decrease morbidity and mortality, and lower the cost of care. The challenge right now is really finding the right drug for the right patient at the right time to obtain the best clinical outcome.

The current diabetes classification system, which categorizes diabetes into type 1 and type 2, is outdated, as we now recognize numerous forms of diabetes with different genetic and pathophysiological mechanisms. Despite understanding this complexity, glucose remains the only diagnostic and treatment biomarker in 2025, highlighting the need for more precise approaches to diabetes management. Dr. Cefalu stated that current research efforts are attempting to identify diabetes subtypes by clustering variables from different pathogenic mechanisms to advance more precise diagnosis and treatment approaches.

Previous research has identified several diabetes subtypes by analyzing multiple physiological variables beyond glucose levels, revealing that these subtypes correlate with different clinical outcomes. Another study found distinct risk clusters even in pre-diabetic individuals, suggesting potential for more targeted prevention and intervention approaches based on specific risk profiles rather than treating all at-risk patients the same way.

Research gaps and opportunities include the fact that the clinical utility of subtypes may be limited by the nature of the variables, as many variables may change with disease progression and treatment; and the use of simple clinical phenotypes as continuous traits may outperform subtypes for disease progression and treatment. It is also unknown if the subtypes can be used for specific therapeutic decisions and what are the precise molecular etiologies of subtypes.

NIDDK plans to continue to develop a Heterogeneity of Diabetes Program that would serve as an umbrella program to oversee all research at NIDDK that relates to the heterogeneity of diabetes and all prior research programs that could inform the topic. In January 2023, a new NIDDK Working Group of Council was formed to create a blueprint

to inform on the heterogeneity of diabetes research and address gaps and opportunities. The Committee published a manuscript outlining their goals (Franks PW, et al. *J Clin Endocrinol Metab*. 2025;110(3):601-610. doi:10.1210/clinem/dgae844). The research roadmap to address the heterogeneity of diabetes aims to move toward the goal of precision medicine and inform significantly on re-classification of diabetes.

Dr. Paul Franks provided background on the heterogeneity of diabetes initiative. The American Diabetes Association and the European Association for the Study of Diabetes Precision Medicine in Diabetes Initiative contributed to the heterogeneity of the diabetes initiative. In 2020, a consensus report was released, laying the groundwork for further work. This was followed by a 3-year effort published in a consensus report (Tobias DK, et al. *Nat Med*. 2023;29(10):2438-2457. doi:10.1038/s41591-023-02502-5) as well as 16 systematic evidence reviews that underpin the consensus report. Monogenic diabetes shows the most practical progress in precision medicine, while promising opportunities exist in gestational diabetes for diagnostics and treatment. Type 1 diabetes benefits from combining polygenic risk scores with islet antibodies for prediction, and type 2 diabetes is advancing through various subclassification methods and simple precision approaches.

The report recommends ensuring precision medicine for diabetes is developed using population-specific data to promote healthcare for all, as solutions may not transfer well between different populations. It advises against over-relying on single technologies like genetics, instead favoring multimodal approaches to model diabetes heterogeneity. Clear communication with patients is crucial when redirecting treatments based on prediction algorithms. The recommendations emphasize the importance of striking a balance between commercialization and accessibility through public-private partnerships. The importance of standardized reporting in precision medicine research was emphasized, with a focus on the need for early engagement with regulators to ensure that approaches are suitable for clinical translation. Finally, while existing trials provide value, new trial designs specifically for precision medicine hypotheses are needed to distinguish between individual variations in treatment responses, alongside consistent biomarker analysis and appropriate AI/machine learning applications.

Dr. Stephen Rich provided an overview of the Heterogeneity of Diabetes report. The Executive Committee established content-specific subgroups chaired by experts who assembled diverse academic teams to evaluate the current state of knowledge on diabetes heterogeneity in their assigned domains, identify gaps and opportunities, and provide recommendations to guide NIDDK staff in developing funding proposals that could be approved or modified by Council members. The chairs were assisted by NIDDK Program Leads and the subgroups also has NIDDK program participation. An Executive Summary of the report was provided to the Advisory Council prior to the meeting. There were five separate subgroups: engagement, preclinical, clinical, lifestyle, and innovation, along with two cross-cutting themes: health for all and data science, There are planned cross cutting teams for cost-effectiveness and partnerships. Each subgroup provided research recommendations, rationale for recommendations, and research opportunities to address the recommendations. Dr. Rich provided two to three example recommendations from each subgroup:

The preclinical subgroup had the following recommendations:

- Increase the genetic diversity of animal (strain) and human (ancestry) cell/organoid models deployed to study diabetes and make them widely available through a central repository that is accessible to the community
- Standardize and benchmark the assays that are widely deployed for metabolic phenotyping to enable data synthesis across models
- Characterize diabetes-relevant tissues from the same individuals and benchmark against human induced pluripotent stem (iPS) cell models (e.g., Human Pancreas Atlas Program) and Genotype-Tissue Expression (GTEx) Portal)

The clinical subgroup had the following recommendations:

- Promote generation of new datasets in under-represented groups across ancestry, geography, gender, socioeconomic status, and age
- Support international collaboration to enable dataset harmonization, linkage, and sharing across existing sources and amalgamation of multi-population datasets
- Elucidate distinct diabetes subtypes to develop appropriate diagnostic and therapeutic guidelines with new longitudinal datasets containing clinical information, environmental exposures, and multi-omic biomarkers

The lifestyle subgroup had the following recommendations:

- Support clinical trials targeting key life-course periods to define heterogeneity of individual responses to lifestyle interventions that prevent and treat diabetes
- Support research to study how lifestyle contributes to heterogeneity of the pathophysiology of diabetes and pre-diabetes across life period transitions

The innovation subgroup had the following recommendations:

- Advance research to increase understanding of the diagnostic, prognostic, and therapeutic value of individual continuous glucose monitoring profiles in individuals with or at risk of dysglycemia
- Develop strategies to elucidate the clinical relevance of molecular biomarkers for understanding type 2 diabetes heterogeneity
- Promote research using wearable technologies for real-time monitoring of behavioral and physiological parameters to understand diabetes heterogeneity

The engagement subgroup had the following recommendations:

- Investigator teams must demonstrate engagement with people with lived experience and communities impacted by diabetes
- Future funding opportunities should delineate an expectation for engagement with distinct communities that can be interrelated but distinct from engagement with individuals from within communities
- Investigators should adequately compensate and provide necessary resources for community members and people with lived experience to participate in research engagement activities

Diabetes is a global disease with varying pathophysiology across regions, reflecting heterogeneity in exposures and risk factors. Multiple data sources and biomarkers exist, each with varying costs and scalability. Research must integrate clinical features, environmental drivers, and behavioral factors, while leveraging human population variety

to understand diabetes heterogeneity. Advanced data integration tools and interpretable AI models are improving research capabilities, though point-of-care decision support systems remain necessary. Standardization across regions is essential, and diabetes must be understood throughout the entire developmental continuum. NIDDK is initiating and facilitating a bottom-up global partnership effort rather than directing or funding it, while actively helping to define sustainability approaches for this collaborative initiative (Cefalu WT et al. *Nat Med*. 2024;30(7):1819-1822. doi:10.1038/s41591-024-03032-4).

The NIDDK Working Group of Council Report is expected to be issued by the next regularly scheduled Council meeting.

Council Questions and Discussion
Dr. Rodgers, moderator

Comment from Council: *What are the top priorities that would be most feasible to implement and would deliver the greatest impact relative to the resources invested?*

Dr. Cefalu said that while the working group initially categorized initiatives by timeline (short, intermediate, and long-term feasibility), this categorization was removed from the Executive Report. NIDDK program staff will internally evaluate the feasibility and prioritization of opportunities after receiving the report, while respecting the scientific recommendations from the subgroups. The implementation will involve global partnerships, with some opportunities applicable across multiple countries. Overall, the report outlines a 10-to-15-year vision for long-term implementation.

Comment from Council: *Has there been specific discussion about the critical role of early life events in shaping the exposome, in addition to the broader environmental aspects being examined by the working group?*

Dr. Rich replied that several subgroups made specific recommendations related to the life-course approach. New studies are needed to track how the exposome changes throughout early life, as existing research from the 1990s does not capture these day-to-day variations. This will require decade-long studies with early data collection and long-term follow-up.

Dr. Franks added that life-course studies were supported by experts in the subgroups and advocated strongly for this approach in precision medicine contexts. A key insight is that "children are not small adults." This is particularly relevant for type 2 diabetes, as cases with adolescent onset show significantly different risk factor profiles compared with adult-onset cases. Future research must consider the entire life course, including conception and in utero development, despite the challenges this approach presents.

Comment from Council: *How will you incorporate ongoing changes in the rapidly evolving landscape of risk factors and available treatments as this initiative moves forward?*

Dr. Franks responded that as the field moves towards precision medicine, epidemiological methods will change. A citizen science approach using mobile apps to

collect data allows for flexibility and increased frequency in data collection. Dynamic and innovative epidemiological methods will be needed.

Dr. Rich suggested using multiple smaller studies across age ranges instead of single, long-term cohort studies to create a more flexible "synthetic cohort."

Comment from Council: *Could you explain how diabetic complications are addressed within the heterogeneity framework of precision medicine, given their limited coverage in earlier research papers?*

Dr. Franks discussed diabetes clinical subtyping research, highlighting a landmark 2018 study that used machine learning clustering to identify patterns in diabetes complications trajectories. The importance of understanding why some patients with diabetes develop severe, costly complications while others live relatively unaffected lives was emphasized. Precision prognostics are a major focus of precision medicine. Future advances will come from combining different data types, including time series analysis and repeated measures analysis. Type 2 diabetes and its complications manifest differently across ancestral groups worldwide, presenting important unanswered questions for research.

V. CONCEPT CLEARANCE

Dr. Rodgers then turned to Concept Clearance by Council, a step required before Institutes and Centers can publish notices of funding opportunities. To streamline this process, summaries of the concept were supplied to Council members for their review prior to the meeting. Cleared concepts will be made publicly available on the NIDDK website. He then introduced each speaker.

Engineering Improved Stem Cell-Derived Islet Cells for Replacement Therapies
Dr. Albert Hwa

This initiative aims to support research on understanding how to engineer improved stem cell-derived islet cell products, which can lead to enhanced cell replacement therapy outcomes. Unlike cadaveric human islets, stem cell-derived islet cell products are generated from well-defined and highly controlled cell bank sources. Their banking, manufacturing, and quality control processes can be utilized to instill optimized cell characteristics, leading to more durable graft viability and function. This proposed concept aims to stimulate studies on targets and pathways amenable to such engineering approaches and to encourage preclinical testing and validation of such strategies.

Accelerating Medicines Partnership in Type 2 Diabetes (AMPT2D) – Renewal
Dr. Norann Zaghloul

The Accelerating Medicines Partnership (AMP) is a pre-competitive collaboration among government, academia, and industry to improve the ongoing efforts to develop new therapies for complex, heterogeneous diseases (https://www.niddk.nih.gov/about-niddk/research-areas/diabetes/accelerating-medicines-partnership-type-2-diabetes). The overarching goal of AMP-Common Metabolic Diseases (CMD) is to use human genetics as a powerful approach to obtain human-data derived disease understanding and biomarker/therapeutic opportunities. This is being accomplished through systematic

aggregation of existing genotype-phenotype data for CMD, related traits, and its complications as well as the generation of a large amount of new -omic data which are being deposited in the portal. The goal of the NIDDK-funded component of the consortium will be to continue to build on the current capabilities of the Common Metabolic Diseases Knowledge Portal (CMDKP) and harmonize with other NIDDK resources.

Council Questions and Comments

Comment from Council: *Is there inspirations from other cell adoptive therapy methods, particularly CAR-T, for overcoming challenges related to cell loss, destruction, or dysfunction?*

Dr. Hwa replied that cell therapies in regenerative medicine often utilize allogeneic sources, employing established methods to inactivate human leukocyte antigen and add immunoregulatory proteins. For type 1 diabetes, there is a lack of good clinical models with autoimmune components. Since beta cells actively participate in autoimmunity, mitigating endoplasmic reticulum stress and antigen presentation could improve cell function. From neurodegenerative and cancer research, much research has shown specific pathways to modify to make cells more accessible to the body.

Comment from Council: *Regarding the AMP concept, are both academic investigators and pharmaceutical companies contributing to the data?*

Dr. Zaghloul replied that there is currently a limited amount of data from pharmaceutical companies, and it's mostly sourced from academic investigators. Pharmaceutical company data contributions are typically incorporated once they reach the point at which the data can be released, as this timing depends on the type and phase of each study.

Comment from Council: *Is the harmonization of data occurring at the level of those depositing data, or is NIDDK taking the data as it comes and then harmonizing and standardizing it?*

Dr. Zaghloul indicated that the CMDKP team is developing various tools to integrate diverse data types from different studies, even when investigators haven't integrated the data themselves.

Comment from Council: *How is data sharing regulated, if at all, and how many groups have utilized this data sharing framework?*

Dr. Zaghloul responded that access to the portal is currently free for users through an individual application process. There are thousands of users and many publications utilizing the data. A key goal for the upcoming term is to increase user numbers while making the process more sustainable by having users contribute to the portal's ongoing operations.

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

VI. 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.

VII. 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 1101 grant applications (492 primary and 609 dual), requesting support of $523,892,643 were reviewed for consideration at the May 14, 2025, meeting. An additional 657 Common Fund applications requesting $1,283,015,773 were presented to Council. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, 822 applications considered in the Expedited Concurrence process requesting a total of $314,082,015 in direct year one costs. All Expedited Concurrence applications were recommended for funding at the Scientific Review Group recommended level. The expedited concurrence actions were reported to the full Advisory Council at the May 14, 2025, meeting.

VIII. ADJOURNMENT

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 228th meeting of the NIDDK Advisory Council was adjourned at 2:00 p.m. on May 14, 2025.

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

_____
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